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Hypoglycemic agents and prognostic outcomes of chronic kidney disease patients with type 2 diabetes

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ABSTRACT

Introduction: Chronic kidney disease (CKD) poses a financial burden on most patients from low/middle income countries. Glycaemic control with affordable hypoglycemic agents may influence on the prognosis of diabetic nephropathy.

Objectives: We aimed to compare the rates of CKD progression and proteinuria in the type 2 diabetic population in response to the use of various hypoglycemic agents.

Patients and Methods: A retrospective cross-sectional study of a total of 250 patients of Afro-Caribbean descent at the University hospital of the West Indies between 2018 and 2019 was conducted. The use of hypoglycaemic agents and changes in albuminuria were calculated as odds ratios with a 95% confidence interval (CI). A P value<0.05 was considered statistically significant.

Results: Of 250 patients with diabetic nephropathy, the number of rapid CKD progression was highest in patients on insulin (26.3%). In comparison, number of rapid progressions in patients receiving metformin, dipeptidyl peptidase 4 (DPP-4 inhibitors), sulfonylurea and pioglitazone were 19.1%, 22.2%, 21.9% and 20%, respectively. After eliminating confounding factors, comparison within the group analysis on DPP-4 inhibitors (n= 171) demonstrated 62.6% significant improvement in quantitative proteinuria with reduction of mean spot urine albumin creatinine ratio (ACR) from 362.1 ± 338.9 mg/g to 303 ± 300.1 mg/g (ORs, 0.77; 95% CI 0.41 to 0.97; P = 0.03).

Conclusion: Type 2 diabetic patients requiring insulin were found to have progression of CKD than patients on oral hypoglycaemic agents. Among the affordable oral hypoglycaemic agents, DPP-4 inhibitors had an association with reduction in albuminuria.

Implication for health policy/practice/research/medical education:
The finding on prognostic outcomes of affordable hypoglycemic agents among Afro-Caribbean people, who are recognized as a high-risk racial group for CKD progression, requires further assessment. Our study will influence the development of guidelines for selecting appropriate hypoglycemic agents to treat diabetic nephropathy in the limited-resource setting.

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Original Article

Introduction

The burden of advanced chronic kidney disease (CKD) is financially intolerable to most people of low/middle income countries (1,2). Diabetes is the leading cause of CKD and end-stage renal disease (ESRD) worldwide (3,4). Several previous studies have proven that targeted glycemic control plays a pivotal role in retarding the progress of diabetic nephropathy. The options for hypoglycemic agents in CKD stage 3 and above are very limited (5). All patients who are at risk for fast CKD progression need a strict control of modifiable known risk factors (6). Although there are possibilities of various unknown risk factors for CKD progression, by far, diabetes, hypertension, black race, proteinuria, obesity and male gender are known to be major risk factors for rapid progression of CKD and, as such, require maximum attention (7). Of note, persons of African descent are known to be at higher risk for developing ESRD in association with genetic variants (APOL1), while some studies have demonstrated that variable declining renal

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function has been observed in persons of African descent with or without the APOL1 gene (8,9). Diabetes mellitus is a well-known risk factor for the development of CKD and progression to ESRD (10). Hyperglycemia is the most common underlying aetiology for the progression of CKD and the development of ESRD (11).

Pathophysiology of diabetic kidney disease

In diabetic kidney disease, thickening of glomerular basement membrane is the earliest anatomical changes and capillary and tubular basement membrane thickening changes may be seen at the same time. These changes progress to loss of endothelium fenestration, mesangial matrix expansion, loss of podocytes with effacement of foot process, formations of Kimmelstiel-Wilson nodules (nodular glomerulosclerosis) and fibrotic changes in advanced cases (12). Intensive glycemic control is vital for delaying progression of CKD to ESRD. Similarly, control of hypertension and proteinuria are also essential to retard the progression of CKD. A few studies have shown that some newer hypoglycaemic agents may improve proteinuria and/or blood pressure (13,14).

Management of diabetes in CKD

Management of diabetes mellitus in patients with diabetic kidney disease is challenging because of progression of renal failure-related changes in insulin signalling, glucose transport and metabolism. Additionally, impairments of the clearance and metabolism of antidiabetic agents and insulin cause hypoglycemia and sides effects more frequently. The Reduction of Atherothrombosis for Continued Health (REACH) Registry (2004) suggested decreased mortality in patients with moderate kidney disease who use metformin (15).

Dipeptidyl peptidase-4 (DPP-4) inhibitors may have nephroprotective effects. Evidence suggests renoprotective effects of linagliptin. DPP-4 inhibitors also increase stromal cell derived factor-1 levels which ameliorate endothelial dysfunction and display antioxidant property (16). The SGLT 2 inhibitors, empagliflozine and canagliflozin, have been shown to be renoprotective. SGLT 2 inhibitors cause vasoconstriction of the afferent arterioles and decreasing the hyper-filtration in the glomerulus and giving renoprotective effect by reducing rate of progression of proteinuria (17).

The Kidney Diagnostic Initiative Global Outcomes guidelines on CKD defines CKD as abnormalities of kidney structure or function, such as: albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities on histology, structural abnormalities on imaging and history of kidney transplantation, present for more than three months, with implications for health, either of the more than three months, or decreased glomerular filtration rate (GFR) (<60 mL/min/1.73 m^2). In general, CKD progression is defined by a decrease in the estimated GFR by more than 4 mL/min/1.73 m^2 per or by a change in CKD stage.

Objectives

We conducted this study to correlate the CKD progression including albuminuria and the use of common hypoglycemic agents in the Afro-Caribbean type 2 diabetic population with nephropathy. We aim to recognize affordable hypoglycemic agents that may retard CKD progression and reduce proteinuria.

Patients and Methods

Study design

This is a retrospective cross-sectional study of medical outpatient clinics at the University hospital of the West Indies, Kingston public hospital, St. Ann Bay hospitals and Edgeport medical centre between January 2018 and December 2019. All participants were of Afro-Caribbean decent with background type 2 diabetes who had been diagnosed with diabetic nephropathy for more than one year by at least one certified nephrologist at the designated hospitals and offices.

Data collection

Demographic, diagnostic and laboratory variables were extracted by chart review and from the electronic data system. Cases with diabetic nephropathy were recruited by recruiters at renal clinics of three hospitals and two private offices in Jamaica which include the University hospital of the West Indies, Kingston public hospital, St. Ann Bay hospital, Hughenden medical centre in Kingston and Edgeport medical centre in Portmore. Patient's age, gender, duration of diabetes, blood pressure, list of hypoglycemic agents being used, results of previous serum creatinine in the past one to two years, the most recent serum creatinine conducted in 2019, previous spot urine albumin creatinine ratio (ACR) in past one to two years, the most recent spot urine ACR conducted in 2019, and the most recent HbA1c were collected from the results of routine blood and urine tests ordered to follow-up patients with diabetic nephropathy. The medication lists were reviewed and the names of the hypoglycemic agents that the patient had been taking for more than a year were recorded. Overall data collection was carried out by research staff assigned for recruitment (including department of medicine research nurses or research students assisting and under the supervision of the research nurses) who were not involved in the direct care of these patients. Cases in this study were selected by the presence of CKD secondary to diabetic nephropathy that required

long-term renal follow up under specialist clinics and not by easy availability, diminished autonomy, or social bias. The confidentiality of the collected data was ensured by the investigators.

Participants selected were type 2 diabetic patients over the age of 16 years, had been on angiotensin-converting enzyme inhibitors (ACEIs) and an angiotensin receptor blockers (ARBs) and had not been on any form of dialysis. Demographic variables including age, gender, laboratory variables such as serum creatinine at presentation, eGFR, repeated serum creatinines and eGFRs, baseline level of albuminuria, repeated level of albuminuria and hypoglycaemic agents employed for individual patients were obtained from the dockets.

Sample size

The required number of cases with diabetic nephropathy was calculated by the Cochran's sample size formula. Based on the population of CKD secondary to diabetes mellitus in Jamaica (18), the minimum required sample size to validate this study was 241.

Statistical analysis

Continuous numerical variables are expressed as mean ± SD, and categorical data are expressed as numbers and percentages. We used one-way ANOVA descriptive analysis to analyze the data set and adjusted for gender, age, stages of CKD, rate of CKD progression and changes in serum creatinine. Simple descriptive analysis was applied to identify the rate of CKD progression based on serum creatinine and eGFR changes based on the use of hypoglycemic agents, duration of diabetes and gender. Odds ratios (ORs) and association between changes in albuminuria and the hypoglycaemic agents used were analysed using Pearson's chi square or phi test, as appropriate. The data of correlation between progress of CKD in sample populations and glycemic control with single or dual hypoglycaemic agents (e.g., metformin plus DPP-4 inhibitor or metformin plus sulfonylurea) was applied by means of a 95% confidence interval (95% CI) and the *P* value. A *P* value <0.05 is considered statistically significant. All statistical analysis was carried out by using IBM SPSS version 22.

The primary outcome measures were the rate of CKD progression in Afro-Caribbean patients with diabetic nephropathy on hypoglycaemic agents and the correlation between the progression of diabetic nephropathy, albuminuria and commonly administered hypoglycemic agents. The secondary outcome measures were the effect of glycaemic control over the progress of diabetic nephropathy and the effect of commonly used hypoglycemic agents on the eGFR changes in Afro-Caribbean patients in Jamaica with CKD.

Key inclusion criteria were type 2 diabetic patients ≥16 years old, a diagnosis of diabetic nephropathy for more than one year by at least one certified nephrologist, all patients with diabetic nephropathy on either ACEI or ARB and attendance to the designated renal clinics between January 1, 2018, and December 31, 2019. Exclusion criteria were age <16 years, (because minors are under care of pediatric nephrology), a diagnosis of diabetic nephropathy for less than one-year, diabetic nephropathy with no previously documented serum creatinine result and estimated GFR, patients who had not been on ACEIs or ARBs at the time of previous investigations and patients with diabetic nephropathy who are on more than two hypoglycemic agents.

Results

Of the randomly selected 250 patients with diabetic nephropathy patients from the different institutions in Jamaica, 102 were male and 148 were female. Mean age of the sample population was 65.4 years with a standard deviation of ±15.1 years. Hypoglycemic agents taken by the participants for longer than a year were grouped as insulin, metformin, DPP-4 inhibitors (sitagliptin, vildagliptin, linagliptin), sulfonylureas (gliclazide, glibenclamide, glimepiride) and pioglitazone (Avandia). No patient in the study was on SGLT2 (sodium-glucose co-transporter-2) inhibitors (empagliflozin/dapagliflozin/canagliflozin) and only three patients were on an α-glucosidase inhibitor (Acarbose). Among the patients on DPP-4 inhibitors, 137 (80.1%) were on vildagliptin, 17 (9.9%) were on sitagliptin and 17 (9.9%) were on linagliptin. Three cases (1.2%) were on dual hypoglycemic therapy with insulin and metformin, 40 (16%) with insulin and DPP-4 inhibitors, 10 (4%) with insulin and sulfonylurea, 9 (3.6%) with metformin and DPP-4 inhibitors, 7 (2.8%) with metformin and sulfonylurea, 8 (3.2%) with DPP-4 inhibitors and sulfonylurea, and 3 (1.2%) with sulfonylurea and pioglitazone. All these patients had been on either ACEIs or ARBs at the time of previous blood and urine investigations. Mean duration of diabetes for individual hypoglycemic agents were insulin 22.9±6.3 years, metformin 10.7±6.9 years, DPP-4 inhibitors 15.5±9.1 years, sulfonylureas 10.4±7.5 years and pioglitazone 11.9±8.3 years (Table 1).

Rate of CKD progression, changes in serum creatinine and eGFR

Rate of rapid CKD progression was highest in patients required insulin (26.3%). In comparison, the rate of rapid progression in patients receiving metformin, DPP-4 inhibitors, sulfonylurea, and pioglitazone were 19.1%, 22.2%, 21.9% and 20%, respectively (Table 2).

Table 1. Baseline characteristics of Afro-Caribbean type 2 diabetic patients with nephropathy on hypoglycemic agents at the renal clinics in Jamaica between 2018-2019 [n (%)]

Characteristic	Insulin	Metformin	DPP-4I	SU	Glitazones	Total
No. of patients	95 (38)	115 (46)	171 (68.4)	105 (42)	45 (18)	250 (100)
Age (y)	63.9±18.1	63.1±11.6	68.1±12.2	62.2±12.8	64.4±11.9	65.4±15.1
Gender, No. (%)						
Male	40 (16)	44 (17.6)	68 (27.2)	40 (16)	20 (8.0)	102 (40.8)
Female	55 (22)	71 (28.4)	103 (41.2)	65 (26)	25 (10)	148 (59.2)
Lab Findings						
Previous sCr, M±SD	278.7±114	159.8±65.2	217.6±102.3	165.1±60.3	173.6±57.6	198.96±79.8
Repeat sCr, M±SD	332.7±117	170.5±89.8	245.9±139.9	178.8±99.3	186.0±89.6	222.78±107
Previous eGFR, M±SD	26.3±18.6	43.7±18	32.7±17	42.1±15.7	38.8±13.6	32.9±19.2
Repeat eGFR, M±SD	23.6±19.2	42.0±18.3	30.4±16.8	40.4±16.5	37.2±14.2	31.3±19.3
Previous ACR (mg/g)	442.7±402	345.1±355	362.1±338.9	388.8±398.4	327.4±433	373.22±384
Repeat ACR (mg/g)	467.8±466	376.2±401	303.0±300.1	420.0±440	329.9±332	379.38±384
Test interval (mth)	12.1	12.2	12.1	12.4	12.0	12.16
Systoloic BP, M±SD	132±21	129±18	130±20	130±19	131±23	130±22
Diastolic BP, M±SD	79±12	77±11	78±12	80±14	82±14	79±13
Pre-admission medications						
ACEI/ARBs	95 (38)	115 (46)	171 (68.4)	105 (42)	45 (18)	NA
Diuretics	3 (.2)	12 (4.8)	11 (4.4)	14 (5.6)	17 (6.8)	NA
β-blockers	33 (13.2)	36 (14.4)	29 (11.1)	30 (12.0)	15 (6.0)	NA
CCB	79 (31.6)	82 (32.8)	80 (32.0)	45 (18.0)	33 (13.2)	NA
Pre-admission morbidity						
Duration of DM (y)	22.9 ±6.3	10.7±6.9	15.5±9.1	10.4±7.5	11.9±8.3	NA
Hypertension	85 (34.0)	93 (37.2)	151 (60.4)	81 (32.4)	34 (13.6)	NA

DPP-4I= dipeptidyl peptidase inhibitor, SU= sulfonylurea, sCr = serum creatinine, ACR = albumin creatinine ratio, ACEI= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, BP= blood pressure, M±SD= mean ± standard deviation, CCB= calcium channel blocker, NA = not applicable due to effect of multi-drug therapies, DM= diabetes mellitus.

Table 2. Correlation between use of individual hypoglycemic agents and the rate of CKD progression in Afro-Caribbean type 2 diabetic patients in Jamaica 2018-2019 n (% within exposed group)

Agent used	Rate of CKD Progression			95% CI
	Progressed	No change	Improved	
Insulin	25 (26.3)	63 (66.3)	7 (7.3)	0.63, 0.92
Metformin	22 (19.1)	67 (58.2)	26 (22.6)	1.5, 6.7
DPP-4I	38 (22.2)	110 (64.3)	23 (13.4)	0.6, 1.8
Sulfonylurea	23 (21.9)	61 (58.0)	21 (20.0)	1.0, 2.6
Pioglitazone	20 (20.0)	31 (68.8)	9 (11.1)	0.92, 1.42

Progressed= rapid progression either by changing the stage of CKD or declined in eGFR >5ml/annum, No change= No change in CKD stage, Improved= downgraded in CKD stage, CKD= Chronic Kidney Disease, DPP-4 I= Dipeptidyl peptidase-4

Previous serum creatinine (mean ± SD) for the patients required insulin was 278.7 ± 114 µmol/L and repeated serum creatinine ≥6 months after was 332.7 ± 117.7 µmol/L. The average eGFR decline in that group was from 26.3 ± 18.6 mL/min/1.73 m^2 to 23.6 ± 19.2 mL/min/1.73 m^2 which occurred within average duration of 12.1 months. In the group with patients on metformin, worsening of serum creatinine from 159.8 ± 65.2 µmol/L to 170.5 ± 89.8 µmol/L indicated that the eGFR (mean ± SD) declined from 43.7 ± 18 mL/min/1.73 m^2 to 42 ± 18.3 mL/min/1.73 m^2 in the average duration of 12.2 months. In the other remaining groups, eGFR changes on DPP-4 inhibitors was from 32.7 ± 17 mL/min/1.73 m^2 to 30.4 ± 16.8 mL/min/1.73 m^2 in the average 12.1 months duration as mean serum creatinine was increased from 217.6 ± 102.3 µmol/L to 245.9 ± 139.9 µmol/L. In the group on sulfonylureas, eGFR decline was from 42.1 ± 15.7 mL/min/1.73 m^2 to 40.4 ± 16.5 mL/min/1.73 m^2 in the average 12.4 months duration while changes in serum creatinine was from 165.1 ± 60.3 µmol/L to 178.8 ± 99.3 µmol/L and in the pioglitazone group, eGFR decline was from 38 ± 13.6 mL/min/1.73 m^2 to 37.2 ± 14.2

mL/min/1.73 m^2 in average 12 months with increased mean serum creatinine from 171.6 ± 57.6 µmol/L to 186 ± 89.6 µmol/L. Overall, mean eGFR fall in the entire sampled population was 1.6 ± 19.3 mL/min/1.73 m^2 and serum creatinine increment was from 198.98 ± 79.8 mL/min/1.73 m^2 to 222.78 ± 107.2 µmol/L in average 12.16 months (Table 3, Figures 1-3).

On the other hand, significant improvement in eGFR with downgrading of CKD stages was observed the least in insulin group (7.3%) and the most in patients who received metformin (22.6%). Median improvement outcomes were found in the groups placed on DPP-4 inhibitors, sulfonylureas and pioglitazone (13.4, 20 and 11.1%, respectively). Most of the study population had no significant changes in eGFR in the mean duration of 12.1 months. Around 66.3% of participants on insulin, 58.2% on metformin, 64.3% on DPP-4 inhibitors, 58% on sulfonylureas and 68.8% on pioglitazones were observed to have stable CKD stage in the average 12.16 months.

Gender and rapid CKD progression

On descriptive analysis, rapid progression was observed more in males as 35 (34.3%) had rapid progression of CKD while only 26 (17.5%) females had rapid progression of CKD (Figure 4).

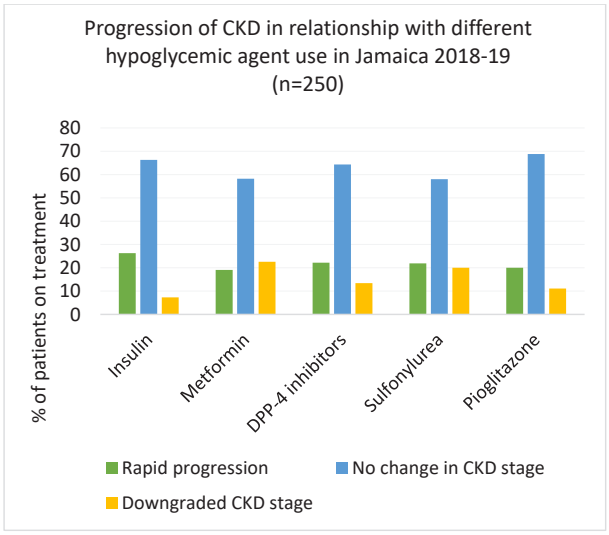

Figure 1. CKD progression in the study population with Diabetic nephropathy on different hypoglycemic agents.

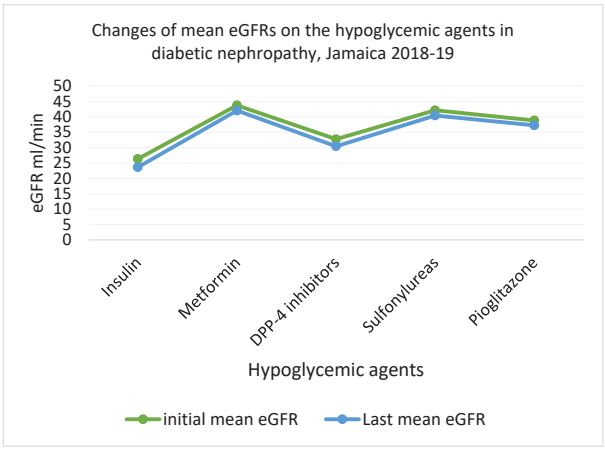

Figure 2. Changes in eGFR according to the hypoglycemic agents use, Jamaica 2018-2019 (n = 250).

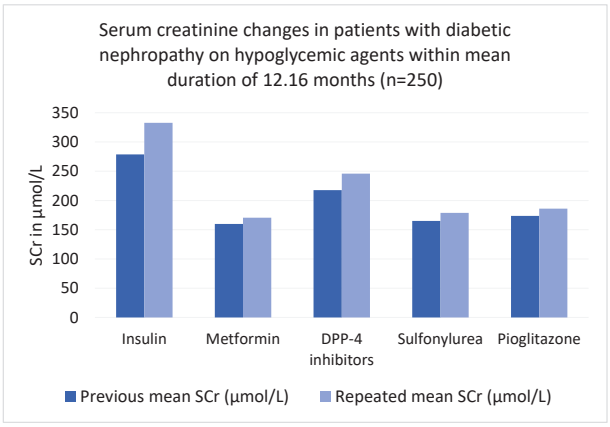

Figure 3. Relationship between changes in serum creatinine and hypoglycemic agents use in Jamaica, 2018-2019.

Changes in albuminuria on administration of hypoglycemic agents

After eliminating confounding factors by selecting patients who had already been on either ACEIs or ARB, comparison within the group analysis on DPP-4 inhibitors (n= 171) demonstrated that 62.6% of patients had a

Table 3. Hypoglycemic agents use and changes in eGFR among 250 type 2 Diabetic patients with CKD in Jamaica

Hypoglycemic agent	No. (%)	Previous eGFR, M±SD	Repeat eGFR, M±SD
Insulin	95 (38)	26.3±18.6	23.6 ±19.2
Metformin	115 (46)	43.7±18	42.0±18.3
DPP-4I	171 (68.4)	32.7±17	30.4±16.8
Sulfonylurea	105 (42)	42.1±15.7	40.4±16.5
Pioglitazone	45 (18)	38.8 ±13.6	37.2±14.2

eGFR= estimated Glomerular Filtration Rate, M±SD = mean ± standard deviation, DPP-4I = DPP4 inhibitor.

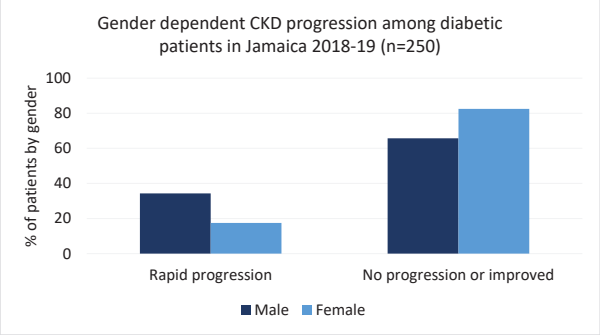

Figure 4. Progression of CKD according to gender in selected type 2 diabetic patients with nephropathy in Jamaica 2018-2019.

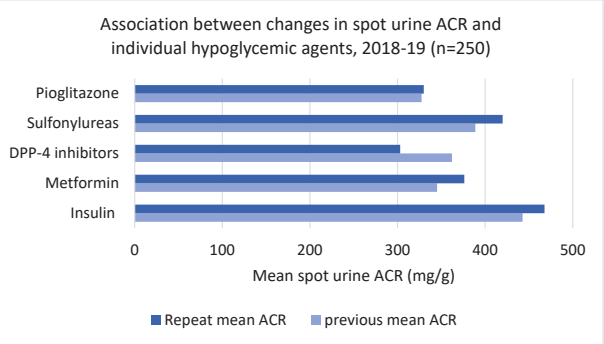

Figure 5. Changes in quantitative proteinuria in relationship with hypoglycaemic agents use in Jamaica, 2018-2019 (n=250).

significant improvement in the level of proteinuria with reduction of mean spot urine ACR from 362.1 ± 338.9 mg/g to 303 ± 300.1 mg/g (ORs, 0.77; 95% CI 0.41 to 0.97; *P*=0.03). In contrast, comparison analysis within the group on insulin (n= 95) showed that spot urine ACR showed no improvement or worsening in 77.9% with declining of mean ACR from 442.7 ± 402.8 mg/g to 467.8 ± 446.7 mg/g (ORs, 2.23; 95% CI, 1.47 to 3.42; *P*=0.002).

Although the spot urine ACRs worsened from 345.1 ± 355.4 mg/g to 376.2 ± 401.8 mg/g in metformin group (n= 115), from 388.8 ± 398.4 mg/g to 420±440 mg/g in sulfonylurea group and from 327.4 ± 433.6 mg/g to 329.9±332.9 mg/g in pioglitazone group, no statistically significant associations were found between these three agents and spot urine ACR (OR, 0.98; 95%CI, 0.33 to 1.75; *P*=0.12, OR, 1.65; 95%CI, 0.77 to 2.45; *P*=0.25 and OR, 1.99; 95% CI, 0.46 to 3.34; *P*=0.5, respectively; Table 4, Figures 5 and 6).

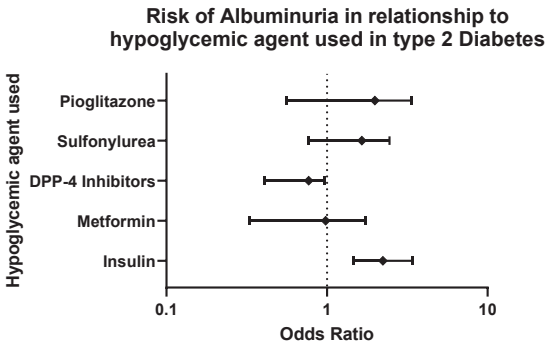

Figure 6. Comparison in Odds ratio of the albuminuria on hypoglycemic agents used among type 2 diabetic patients with nephropathy in Jamaica 2018-2019 (n=250).

Discussion

Although a few newer hypoglycemic agents have been shown to be beneficial in CKD, previous hypoglycemic agents cause significantly serious adverse effects, such as hypoglycemia. However, studies on the influence of individual hypoglycemic agents on the progression of diabetic nephropathy are scarce. In advanced CKD, some hypoglycemic agents are contraindicated. The expectation to reduce the incidence of ESRD mainly depends on the achievement of targeted treatment goals in CKD patients. We observed progression of CKD in association with worsening serum creatinine and proteinuria in the group of type 2 diabetic patients who received insulin treatment (insulin sensitization and insulin provision). Previous studies on the relationship between insulin and renal function were limited. One study by Aneliya et al, demonstrated that insulin resistance was associated with an increase in the rate of albuminuria in type 2 diabetes patients (19), since almost every type 2 diabetes patient is insulin resistant. The patients who were receiving insulin therapy in that study were elderly and/or had long-standing type 2 diabetes mellitus and/or were in late

Table 4. Correlation between albuminuria and individual hypoglycaemic agents in Afro-Caribbean patients with type 2 diabetic nephropathy in Jamaica 2018-2019 n (%)

Hypoglycaemic agent	Improved UAE	Worsened UAE	Odds ratio	95% CI	*P* value
Insulin	21 (22.1)	74 (77.9)	2.23	1.47, 3.42	0.002
Metformin	58 (50.4)	57 (49.6)	0.98	0.33, 1.75	0.12
DPP-4 inhibitors	107(62.6)	64 (37.4)	0.77	0.41, 0.97	0.03
Sulfonylurea	51 (48.5)	54 (51.5)	1.65	0.77, 2.45	0.25
Pioglitazone	22 (48.8)	23 (51.2)	1.99	0.56, 3.34	0.5

stages (stage 4 or 5) of diabetic nephropathy. A previous study published as early as in 1981 mentioned that insulin resistance could result in kidney damage by activation of the sympathetic nervous system (20), sodium retention, decreased Na-K^+ ATPase activity and increased GFR by changing of renal hemodynamics (hyperfiltration and hyperperfusion). On the molecular level, insulin signalling is suppressed via phosphorylation of the insulin receptor substrate (IRS-1) caused by activation of c-Jun N-terminal kinases (JNKs) and the causation of endoplasmic reticulum (ER) stress which has been proven to have a strong relationship with insulin resistance. The underlying factor causing proteinuria is podocyte damage which is significantly attributable to alterations of nephrin N-glycosylation in podocytes and renal endoplasmic reticulum stress (21). Insulin resistance may also cause the overproduction of very low-density lipoprotein leading to hypertriglyceridemia. Hypertriglyceridemia is a risk factor for proteinuria. One animal study demonstrated the double-edge effect of insulin on the kidneys as although insulin prevents hyperfiltration and proteinuria, it does not prevent glomerular growth and induces mesangial expansion (22). These structural changes also explain partly the increased ACR ratio or persistent albuminuria in the late stages of diabetic nephropathy patients. The nature of CKD itself is progressive and its progression is accelerated by poor glycemic control, blood pressure control, dyslipidemia, obesity and hyperuricemia. All these factors may contribute directly or indirectly to the finding of progressive proteinuria in patients requiring insulin.

Another important finding in our study is the compliance of previous animal trials which have shown that DPP-4 inhibitors reduce albuminuria (both micro and macro) in type 2 diabetic patients and prevent the progression of diabetic kidney disease. The effect of DPP-4 inhibition on kidneys was thought to be direct inhibition via reduction of oxidative stress, pro-inflammatory cytokines and chemokines, and improvement of endothelial dysfunction. DPP-4 inhibitors increase GLP1 (glucagon like peptide 1) level. GLP 1 receptors are expressed not only in the pancreas, but also in glomerular endothelial cells, mesangial cells, podocytes and proximal tubular cells (23). GLP1 can decrease AGEs production by activation of protein kinase A and it also has anti-inflammatory effects. A GLP independent effect of DPP-4 inhibitors is the inhibition of the breakdown of other enzymes and/or proteins such as high mobility group protein (HMGB1), meprin B, neuropeptide Y, peptide YY by DPP-4 which contributes to reduction of proteinuria (24,25). There is no question that good glycaemic control prevents the progression of CKD. The beneficial effect of DPP-4 inhibitors in reducing proteinuria found in our study and other animal studies should be routinely applied in retardation of CKD progression in diabetic nephropathy among Afro-Caribbean patients. We believe that the understanding of both good and bad outcomes of hypoglycemic agents in the diabetic population with impaired renal function would play a pivotal role in handling diabetic nephropathy. Retarding CKD progression is always the principal target for clinicians while managing CKD patients regardless of their underlying causes. It is extremely important to apply all affordable and readily available treatment to achieve our goal; to retard the progression of CKD in diabetic population. Reducing the incidence of ERSD in countries with disadvantages should be the priority in significantly reducing the healthcare burden.

Conclusion

Type 2 diabetic patients requiring insulin were found to have an association with rapid progression of CKD than patients who were on oral hypoglycemic agents only. Among the commonly used affordable oral hypoglycemic agents, DPP-4 inhibitors had a significant association with reduction of albuminuria.

Limitations of the study

The sample population in this study was mainly Afro-Caribbean patients. Hence, the findings may not be representative of all patients with diabetic nephropathy. The sample size was also relatively small compared to the total number of patients with diabetic nephropathy in the region. Patient compliance to medications, diet, lifestyles changes, which have some influence on the progression of CKD might interfere the accuracy of drug effect. Co-morbidities such as heart failure, dyslipidemia and nutritional status which were not included in this study might also influence the renal outcomes. Patients who need three or more hypoglycemic agents hypothetically also have difficulties in glycaemic control and are more likely to have a higher risk of diabetic complications and adverse outcomes. However, for statistical reasons, such patients were excluded in this study. Renal patients are usually on polypharmacy to control other renal complications which might affect their renal function and subsequently, might have interfered with the study outcome. The kidney function of selected patients might have also been affected by environmental factors, lifestyle factors and infections. The period of observation of patient outcomes was also relatively short. Patient populations should have been standardized by location, education level, environment, and social status. Additionally, none of the participants in our study had a sufficient exposure time to SGLT-2 inhibitors which have been shown to be beneficial in combating early stages of diabetic nephropathy by most recent studies.

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Authors' contribution
Conceptualization: KKH and TLH.
Formal analysis: KKH, TLH and THSH.
Resources: KKH, TLH and THSH.
Methodology: KKH.
Data curation: KKH and THSH.
Validation: KKH and THSH.
Visualization: KKH.
Writing-original draft: KKH and TLH
Writing–review and editing: KKH and THSH
Supervision: KKH.
Investigation: TLH.
Funding acquisition: TLH.

Availability of data and materials
The datasets in this study from the corresponding authors can be available upon reasonable request.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. Ethical approval for the study was granted by the Ethics Committee of the Faculty of Medical Sciences, University of the West Indies/University Hospital of the West Indies, Mona, Jamaica EC 197 (18/19). The institutional ethical committee at the University of the West Indies approved all study protocols. The study was conducted as a fulfilment to complete the Internal Medicine Residency program of Tin Lynn Han. Besides, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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