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Leveraging the South African Diabetes Prevention Programme to screen for chronic kidney disease: an observational study

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ABSTRACT

Objective To evaluate the viability of leveraging an existing screening programme (the South African Diabetes Prevention Programme (SA-DPP)) to screen for chronic kidney disease (CKD), by assessing the yield of CKD cases among those participating in the programme.

Design Observational study conducted between 2017 and 2019.

Setting 16 resource–poor communities in Cape Town, South Africa.

Participants 690 participants, aged between 25 and 65 years, identified as at high risk for type 2 diabetes mellitus (T2DM) by the African Diabetes Risk Score.

Primary outcome measure The prevalence of CKD among those participating in the SA-DPP.

Results Of the 2173 individuals screened in the community, 690 participants underwent further testing. Of these participants, 9.6% (n=66) and 18.1% (n=125) had screen-detected T2DM and CKD (defined as an estimated glomerular filtration rate (eGFR) of<60 mL/min/1.73 m^2 and/or albumin-to-creatinine ratio >3 mg/mmol), respectively. Of those with CKD, 73.6% (n=92), 17.6% (n=22) and 8.8% (n=11) presented with stages 1, 2 and 3, respectively. Of the participants with an eGFR <60 mL/min/1.73 m^2, 36.4% had no albuminuria and of those with normal kidney function (eGFR ≥90 mL/min/1.73 m^2), 10.2% and 3.8% had albuminuria stages 2 and 3, respectively. Of those with T2DM and hypertension, 22.7% and 19.8% had CKD, respectively.

Conclusion The fact that almost one in five participants identified as high risk for T2DM had CKD underscores the value of including markers of kidney function in an existing screening programme. By using an opportunistic approach to screen high-risk individuals, those with CKD can be identified and appropriately treated to reduce disease progression.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The strength of our study is that both estimated glomerular filtration rate (eGFR) and albuminuria were used to define chronic kidney disease (CKD), unlike most other population-based CKD prevalence studies in South Africa and Africa in general which rely on eGFR only.
⇒ Due to the self-selection approach of recruitment and the disproportionate female participation, our study findings may not be generalisable.
⇒ The small proportion of participants with chronic kidney disease (CKD) in this study resulted in reduced statistical power when analysis was stratifying by CKD stage.
⇒ CKD was defined based on a single time point serum and urinary creatinine and albumin assessment and not on repeated measurements, at least 3 months apart, as per guidelines.

INTRODUCTION

Chronic kidney disease (CKD) is a leading cause of morbidity and mortality globally,[1] affecting more than 840 million individuals worldwide.[2] The increasing burden of CKD is demonstrated by its ascent in ranking among the global causes of disability-adjusted life-years, rising from 29th in 1990 to 18th in 2019 overall, and from 14th to 8th in the older aged groups (aged ≥50 years).[3] However, despite being a global problem, the prevalence of CKD is increasing most rapidly in low-income and middle-income countries (LMICs) where the burden of disease is more pronounced.[4] This is worrisome as the healthcare systems in most LMICs are already under pressure, and options for kidney replacement therapy are not frequently available or affordable.[5 6] Given the inequity in access to healthcare services, which disproportionally affects disadvantaged populations, and the costs of kidney replacement therapies, early detection of CKD followed by low-cost treatments should be encouraged.[7]

Early-stage CKD presents with no or non-specific symptoms and is commonly diagnosed opportunistically from screening tests for other diseases, or when the disease has progressed, and symptoms appear.[8] Therefore, screening for CKD plays an important role in early detection, as implementing treatment on diagnosis can slow the rate of kidney function loss and reduce morbidity

and mortality.[9 10] However, there is often a strong argument against community-based CKD screening due to the potential harm arising from screening and the cost implications of such an undertaking. According to a recent study, community-based CKD screening is unlikely to be effective or cost-effective anywhere in the world.[11] In contrast, community-based screening for CKD risk factors like hypertension and type 2 diabetes mellitus (T2DM) are deemed effective. Community-based screening programmes for hypertension and T2DM provide an opportunity to incorporate screening for CKD. Certainly, using the screening of hypertension and T2DM, which are common risk factors for CKD, as a gateway for CKD screening in clinical settings will involve minimal additional costs. Furthermore, (1) the yield of screen-detected cases is likely to be high, considering the high prevalence and incidence of CKD in the presence of these risk factors; (2) awareness of the presence of CKD with hypertension or T2DM can prompt the intensification or modification of treatments to enhance kidney protection and prevent CKD progression and (3) a large proportion of people with CKD likely have a combination of suboptimal risk factors with raised levels of blood pressure and/or glucose that fall below the threshold for disease classification. These individuals with pre-diabetes and/or prehypertension are not generally targeted for CKD screening in routine practice but may already have CKD. The opportunistic incorporation of CKD testing in hypertension or T2DM screening programmes can therefore identify CKD that may otherwise be missed if only those with established hypertension or T2DM are screened for the condition.

The aim of this study was to evaluate the viability of CKD screening when incorporated into an existing disease screening programme. The yield of CKD cases in the South African Diabetes Prevention Programme (SA-DPP) was determined by assessing markers of kidney function (serum and urinary creatinine levels and urinary albumin) among participants at high risk for T2DM.

MATERIAL AND METHODS

Study population and setting

The SA-DPP is a 'real-world' randomised implementation trial, of a structured lifestyle intervention programme, adapted from programmes previously shown to be effective in Finland,[12] Australia[13] and India.[14] The SA-DPP uses an open-labelled cluster randomised control design, conducted across 16 resource–poor communities in Cape Town, South Africa. Participants were recruited by self-selection approaches, by raising awareness of the study with flyers distributed in the community or through local councillors' offices, churches and schools. Interested participants were invited to predetermined venues in their community for community-based risk screening. In the current study, baseline data were obtained from black and mixed ancestry participants, aged between 25 and 65 years, who were at high risk for T2DM.[15] The data included in this study were collected between 2017 and 2019 and the details have been previously described.[15]

Community-based screening to identify high-risk individuals

For the community-based risk screening, the African Diabetes Risk Score (ADRS),[16] which is a validated African screening tool comprising non-laboratory-based variables including age, waist circumference (WC) and the presence of hypertension, was used to identify adults at high risk for T2DM. Trained fieldworkers administered a brief questionnaire, which included age, gender, population group, and measured anthropometry and blood pressure. Standard anthropometric methods were used to measure weight, height and WC.[17] Body weight (nearest 0.1 kg) was measured with a calibrated Omron digital scale, with the participant in light clothing and without shoes. A stadiometer was used to measure the participant height (nearest cm), with the participant standing in an upright position, on a flat surface. WC was measured using a non-elastic tape measure at the level of the umbilicus. Blood pressure measurements were taken in a seated position after 5 min of rest. The systolic and diastolic blood pressures (SBP and DBP, respectively) were recorded three times at 2 min intervals, using an appropriately sized cuff and an automated blood pressure monitor (Omron 711, Omron Health Care, Hamburg, Germany). An average of the last two readings was used in the analyses.

Clinic-based assessments of high-risk participants

Participants deemed at high risk, based on the ADRS, were invited for further clinical and biochemical assessments. At the clinic, trained fieldworkers administered questionnaires to obtain information on participant sociodemographic and personal and family medical history. Anthropometric and blood pressure measurements were repeated using standardised techniques as described above.

As per the WHO's guidelines,[18] blood samples were collected after a 10-hour overnight fast by a qualified nurse for the oral glucose tolerance test (OGTT). Following the administration of 75 g anhydrous glucose dissolved in 250 mL, blood samples were taken 2 hours later. Biochemical analyses were conducted at an ISO accredited laboratory (PathCare Laboratories, Cape Town, South Africa). Plasma glucose was determined by the glucose oxidase method (Glucose Analyzer 2, Beckman Instruments, Fullerton, California, USA), serum insulin, determined by a Microparticle Enzyme Immunoassay (AxSym Insulin Kit, Abbot, Illinois, USA) and glycated haemoglobin (HbA1c) was analysed with high-performance liquid chromatography (Biorad Variant Turbo, BioRad, Johannesburg, South Africa). Vitamin D (25(OH)D3) was measured using liquid chromatography mass spectrometry and enzymatic colorimetric methods were used to measure serum calcium, phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT). Full blood counts, including total red blood cells (RBC), total white blood

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cells, haemoglobin, haematocrit and platelets, were measured on a Coulter LH 750 haematology analyser (Beckman Coulter, South Africa).

For the current study, we used the blood and urine samples in the SA-DPP biobank to conduct secondary laboratory analyses. To determine the levels of serum and urinary creatinine, the modified Jaffe-Kinetic method (calibrated to isotope dilution mass spectrometry standards) (Beckman AU, Beckman Coulter, South Africa) was used, and the colorimetric (using bromocresol purple) method (Beckman AU, Beckman Coulter, South Africa) was used to determine the level of urine albumin.

Classification of kidney function and comorbidities

Kidney function was estimated using the serum creatinine-based CKD Epidemiology Collaboration 2009 equation[19], with the race correction factor omitted. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 and/or urinary albumin-to-creatinine ratio (uACR) >3 mg/mmol. CKD staging was based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[20] as, stage 1 (eGFR ≥90 mL/min/1.73 m^2 and uACR >3 mg/mmol), stage 2 (eGFR 60–89 mL/min/1.73 m^2 and uACR >3 mg/mmol) and stage 3 (eGFR<60 mL/min/1.73 m^2). Albuminuria (stage 2) was defined as uACR between 3 and 30 mg/mmol and albuminuria (stage 3) as >30 mg/mmol.[21]

Given that GFR declines with healthy ageing without any overt signs of kidney damage, CKD was also defined by an age-adapted definition, as an eGFR <75 mL/min/1.73 m^2 for participants younger than 40 years, eGFR <60 mL/min/1.73 m^2 for participants aged between 40 and 65 years and eGFR <45 mL/min/1.73 m^2 for participants aged greater than 65 years.[22] Additionally, the age-standardised prevalence of CKD was calculated, using the standard world population distribution as projected by the WHO for 2000–2025.[23]

Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared (kg/m^2). This was categorised as normal weight (BMI ≤24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2). Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg,[24] or taking antihypertensive medications. We further categorised our study participants into four groups related to the level of blood pressure control, namely, (1) normotensive (defined as no use of antihypertensive medication and SBP/DBP <140/90 mm Hg), (2) treated and controlled blood pressure (defined as use of antihypertensive medication and SBP/DBP <140/90 mm Hg), (3) treated but uncontrolled blood pressure (defined as use of antihypertensive medication but SBP/DBP ≥140/90 mm Hg) and (4) newly detected hypertension (defined as no use of antihypertensive medication and SBP/DBP ≥140/90 mm Hg). Normal and dysglycaemia categories, based on the OGTT, were defined according to WHO criteria[18] as: (1) normal glucose tolerance (fasting glucose (FG) <6.1 mmol/L and 2-hour glucose <7.8 mmol/L) or (2) pre-diabetes including impaired FG (6.1≤FG<7.0 mmol/L and 2-hour glucose <7.8 mmol/L), impaired glucose tolerance (FG <7.0 mmol/L and 7.8≤2 hours glucose<11.1 mmol/L) and (3) T2DM (FG ≥7.0 mmol/L and/or 2 hours glucose ≥11.1 mmol/L). High GGT was defined as levels >38 IU/L, and based on the laboratory (PathCare, South Africa) reference standards. Liver fibrosis was classified based on the fibrosis-4 (FIB-4) index, where FIB-4 index was calculated using the formula: (age (years) × AST (IU/L))/ (platelet (10^9/L) × √ALT (IU/L)).[25] Low risk for advanced fibrosis was defined a FIB-4 score <1.30, intermediate risk as a value between 1.30 and 2.67, and high risk as FIB-4 >2.67.[26] Anaemia was defined using the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines as haemoglobin level <135 g/L for men and <120 g/L for women.[27]

Statistical analysis

The SA-DPP sample size was calculated based on the following assumptions: (1) a cumulative incident diabetes rate of 13.6% at 2–3 years, as observed in our Bellville South cohort,[28] (2) an expected relative risk of 0.51, which is the pooled effect estimate of efficacy trials comparing lifestyle intervention to usual care in diabetes prevention studies,[29] (3) an intracluster correlation coefficient for FG of 0.02,[30] (4) a significance level of 5% with a type II error risk of 20% and (5) an estimated 36 months lost to follow-up of 20–25%.

Due to the non-Gaussian distribution of most variables, the participant characteristics were summarised as median (25–75th percentile) or counts and percentages. Group comparisons were analysed by χ^2 tests, Wilcoxon rank-sum and Kruskal-Wallis tests. The Dunn's test was used as non-parametric pairwise multiple-comparison post hoc test when the Kruskal-Wallis test was rejected. All statistical analyses were performed using STATA V.17 (Statcorp) and statistical significance was based on a $p<0.05$.

Patient and public involvement

Participants and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

RESULTS

Of the 2173 individuals screened in the community, 690 participants, deemed at high risk of T2DM based on the ADRS, presented at our research clinic for an OGTT and other assessments (online supplemental file). The sociodemographic, clinical and biochemical characteristics are summarised by CKD status in table 1. Among the 690 participants included in this study, 80.9% were female, with a group median age of 52 years. Of these participants, 9.6% had screen-detected T2DM and 18.1% had CKD, with 2.2% presenting with both CKD and T2DM. A similar CKD prevalence rate was observed with age-adapted eGFR thresholds (18.1%); however, the

Table 1 Sociodemographic, clinical and biochemical characteristics presented in the overall sample and by CKD status

Sociodemographic variables	Total (n=690)	Without CKD (n=565)	CKD (n=125)	P value
Age (years)	52 (45–59)	52 (45–59)	53 (47–60)	0.241
Gender (n,% female)	558 (80.9)	460 (81.4)	98 (78.4)	0.438
African Diabetes Risk Score	2.3 (1.7–3.4)	2.3 (1.7–3.4)	2.4 (1.8–3.4)	0.882
Anthropometry				
Weight (kg)	91.0 (79.6–103.6)	92.2 (80.4–104.6)	88.0 (76.1–101.3)	0.050
Waist circumference (cm)	102.7 (95.3–111.1)	103.4 (95.7–111.1)	101.3 (93.4–111.1)	0.242
Hip circumference (cm) (n=632)	112.6 (103.2–121.7)	113.0 (104.3–122.4)	111.3 (102.1–118.3)	0.067
Body mass index (kg/m^2)	35.6 (30.5–40.5)	35.7 (30.6–40.6)	33.9 (29.4–39.9)	0.185
Body mass index categories (n, %)				0.316
Normal	29 (4.2)	23 (4.1)	6 (4.8)	
Overweight	129 (18.7)	100 (17.7)	29 (23.2)	
Obese	532 (77.1)	442 (78.2)	90 (72.0)	
Blood pressure (BP)				
Systolic blood pressure (mm Hg)	124.5 (113.5–137.0)	123.5 (113.5–135.0)	128.0 (116.0–145.5)	0.004
Diastolic blood pressure (mm Hg)	83.0 (77.0–91.5)	83.0 (77.0–90.3)	86.0 (78.5–94.5)	0.014
Hypertension	379 (55.0)	304 (53.9)	75 (60.0)	0.215
Among participants with hypertension (n=379):				<0.0001
Treated and controlled BP	143 (37.7)	127 (41.8)	16 (21.3)	
Treated and uncontrolled BP	103 (27.2)	71 (23.4)	32 (42.7)	
Screen-detected HPT	133 (35.1)	106 (34.9)	27 (36.0)	
Biochemical				
Fasting blood glucose (mmol/L)	5.0 (4.6–5.5)	5.0 (4.6–5.5)	5.0 (4.6–5.6)	0.691
2-hour glucose (mmol/L) (n=688)	6.0 (4.9–7.4)	6.0 (4.9–7.3)	6.3 (5.1–7.6)	0.205
Glucose categories (n, %) (n=688)				0.600
Normoglycaemia	520 (75.6)	428 (76.0)	92 (73.6)	
Pre-diabetes (IFG/IGT)	102 (14.8)	84 (14.9)	18 (14.4)	
Type 2 diabetes	66 (9.6)	51 (9.1)	15 (12.0)	
HbA1c (%) (n=685)	5.8 (5.6–6.1)	5.8 (5.6–6.1)	5.9 (5.6–6.2)	0.740
Fasting insulin (IU/L)	8.8 (6.2–12.6)	8.5 (5.9–12.1)	11.1 (7.2–14.8)	0.144
Vitamin D (ng/mL)	6.1 (5.0–7.8)	6.0 (5.0–7.7)	6.2 (5.1–8.1)	0.222
Calcium (mmol/L) (n=688)	2.3 (2.3–2.4)	2.3 (2.3–2.4)	2.4 (2.3–2.4)	0.644
Phosphate (mmol/L) (n=688)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	0.981
Gamma-glutamyl transferase (IU/L) (n=688)	36.0 (24.0–61.0)	35.0 (24.0–55.0)	47.0 (26.0–78.0)	0.008
High gamma-glutamyl transferase (n=688)	315 (45.8)	245 (43.4)	70 (56.5)	0.008
Aspartate aminotransferase (IU/L) (n=688)	24.0 (20.0–29.0)	23.0 (20.0–29.0)	26.0 (21.0–34.0)	0.004
Alanine aminotransferase (IU/L) (n=646)	22.0 (16.0–32.0)	22.0 (16.0–32.0)	22.0 (17.0–33.0)	0.372
AST/ALT ratio	1.1 (0.9–1.4)	1.1 (0.9–1.4)	1.2 (0.9–1.5)	0.110
Fibrosis-4 index (n=644)	0.9 (0.7–1.3)	0.9 (0.7–1.3)	1.0 (0.8–1.4)	0.016
Liver fibrosis (n, %)				0.065
No risk	497 (77.2)	413 (78.4)	84 (71.8)	
Intermediate risk	138 (21.4)	109 (20.7)	29 (24.8)	
High risk	9 (1.4)	5 (0.9)	4 (3.4)	
Red blood cells (×10^{12}/L)	4.6 (4.2–4.9)	4.6 (4.3–4.9)	4.5 (4.2–4.8)	0.046

Continued

Table 1 Continued

Sociodemographic variables	Total (n=690)	Without CKD (n=565)	CKD (n=125)	P value
White blood cells (×10^9/L)	23.0 (18.0–28.0)	23.0 (18.3–28.0)	23.0 (17.0–28.0)	0.270
Platelet count (×10^9/L)	276 (235–325)	276.0 (234.5–322.5)	276.0 (235.0–333.0)	0.705
Haematocrit (volume %)	0.4 (0.4–0.4)	0.4 (0.4–0.4)	0.4 (0.4–0.4)	0.442
Haemoglobin (g/L)	135 (126–143)	135 (127–143)	134 (124–144)	0.491
Anaemia, n (%)	103 (14.9)	77 (13.6)	26 (20.8)	0.042

Data are presented as median (25–75th percentiles) or count and percentages.
AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio; CKD, chronic kidney disease; HbA1c, glycated haemoglobin; HPT, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

age-standardised prevalence of CKD was lower, at 14.6%. Furthermore, there were high rates of obesity (77.1%), hypertension (55.0%), raised GGT levels (45.8%), intermediate risk of advanced liver fibrosis (21.4%) and anaemia (14.2%) among participants in this study. There were no significant differences in the sociodemographic and anthropometric variables between participants with and without CKD. However, SBP (128.0 vs 123.5 mm Hg; p=0.004) and DBP (86.0 vs 83.0 mm Hg; p=0.014) were higher in participants with CKD compared with those without. Although hypertension prevalence was not significantly different by CKD status (p=0.215), uncontrolled hypertension on treatment was significantly higher in those with than without CKD (42.7% vs 23.4%). The median levels of GGT (47.0 vs 35.0 IU/L; p=0.008), AST (26.0 vs 23.0 IU/L; p=0.004) and FIB-4 index (1.0 vs 0.9; p=0.016), were higher in participants with CKD compared with those without CKD, while RBC count (4.5 vs 4.6×10^{12}/L; p=0.046) was lower in CKD compared with those with normal kidney function. The prevalence of high GGT (p=0.008) and anaemia (p=0.042) were significantly higher in participants with CKD compared with those without CKD. All other biochemical variable were similar between groups.

The prevalence of CKD in the overall sample and grouped by glucose and blood pressure categories are shown in figure 1. In those with pre-diabetes, T2DM and hypertension, 17.6%, 22.7% and 19.8% had CKD, respectively. Of the participants with hypertension, the prevalence of CKD was highest in those on antihypertensive treatment but with uncontrolled blood pressure (31.1%), while 20.3% of those newly identified with hypertension and 11.2% of those on treatment with controlled blood pressure had CKD.

The stages of CKD according to eGFR and albuminuria following KDIGO classification are presented in figure 2. Of the 11 participants with an eGFR <60 mL/min/1.73 m^2, 4 (36.4%) had no albuminuria, with 36.4% (n=4) and 27.3% (n=3) presenting with moderate (uACR: 3–30 mg/mmol) and severe albuminuria (uACR: >30 mg/mmol), respectively. Furthermore, of the those with normal kidney function (eGFR ≥90 mL/min/1.73 m^2), 67 (10.2%) and 25 (3.8%) had moderate and severe albuminuria, respectively.

Table 2 describes the participant characteristics by CKD stage. The majority of individuals with CKD presented with stage 1 CKD (73.6%), with 17.6% and 8.8% presenting with stages 2 and 3, respectively. Participants with stage 3 CKD were older than those with normal kidney function and stage 1 CKD (p=0.030 for both). Levels of AST were significantly higher with stage 2 CKD compared with stage 3 CKD (p=0.042). SBP and DBP did not differ by stages of CKD but differed between those with normal kidney function and those with CKD as follows: normal kidney function vs CKD stage 1 (SBP: p=0.007 and DBP: p=0.010), stage 2 (SBP: p=0.039) and stage 3 (DBP: p=0.013).

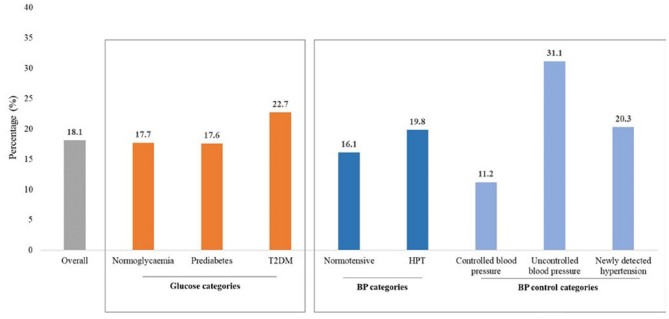

Figure 1 Prevalence (%) of chronic kidney disease overall and by glucose and blood pressure categories. Data presented as percentages. BP, blood pressure; HPT, hypertension; T2DM, type 2 diabetes mellitus.

CKD stages	eGFR (ml/min/1.73m^2)	Albuminuria A1 (<3 mg/mmol)	A2 (3-30 mg/mmol)	A3 (>30 mg/mmol)	Total
G1	≥90	565 (86.0%)	67 (10.2%)	25 (3.8%)	657 (95.2%)
G2	60–89	0 (0%)	15 (68.2%)	7 (31.8%)	22 (3.2%)
G3 (a and b)	<60	4 (36.4%)	4 (36.4%)	3 (27.3%)	11 (1.6%)
Total		569 (82.5%)	86 (12.5%)	35 (5.1%)	690 (100%)

Figure 2 Stages of chronic kidney disease according to estimated glomerular filtration rate and albuminuria following Kidney Disease Improving Global Outcomes (KDIGO) classification. displayed are number of patients (%) within each category. The colour code indicates risk category according to KDIGO[20]: green 'low risk', yellow 'moderate risk', orange 'high risk' and red 'very high risk'. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 2 Sociodemographic, clinical and biochemical characteristics in participants by CKD stages

Sociodemographic variables	No CKD (n=565)	Stage 1 (n=92)	Stage 2 (n=22)	Stage 3 (n=11)	P value
Age (years)	52 (45–59)*	52 (45–59)*	56 (51–61)	57 (52–63)	0.029
Gender (n,% female)	460 (81.4)	75 (81.5)	15 (68.2)	8 (72.7)	0.408
African Diabetes Risk Score	2.3 (1.7–3.4)	2.4 (1.8–3.1)	2.2 (1.7–4.8)	2.8 (1.9–3.9)	0.865
Kidney function					
Serum creatinine (µmol/L)	57.0 (48.0–67.0)	54.0 (46.5–62.0)	78.5 (72.0–88.0)	122.0 (96.0–160.0)	0.0001
eGFR (ml/min/1.73 m^2)	103.0 (95.0–114.0)	106.0 (98.0–117.5)	79.5 (75.0–83.0)	49.0 (32.0–57.0)	0.0001
uACR (mg/mmol)	0.6 (0.4–1.0)	6.0 (4.1–14.1)	6.5 (3.6–17.3)	3.9 (0.8–43.2)	0.0001
Anthropometry					
Weight (kg)	92.2 (80.4–104.6)	89.1 (77.8–101.7)	84.4 (70.6–95.3)	78.7 (63.2–102.4)	0.117
Waist circumference (cm)	103.4 (95.7–111.1)	101.6 (93.9–111.4)	97.2 (93.1–109.7)	100.6 (93.4–107.0)	0.497
Hip circumference (cm) (n=632)	113.0 (104.3–122.4)	112.7 (102.3–120.9)	110.4 (99.4–117.9)	108.6 (96.4–108.9)	0.085
BMI (kg/m^2)	35.7 (30.6–40.6)	34.7 (30.5–40.7)	31.6 (26.9–39.5)	31.9 (27.2–36.9)	0.121
BMI categories (n, %)					0.039
Normal	23 (4.1)	2 (2.2)	2 (9.1)	2 (18.2)	
Overweight	100 (17.7)	19 (20.7)	8 (36.4)	2 (18.2)	
Obese	442 (78.2)	71 (77.2)	12 (54.5)	7 (63.6)	
Blood pressure (BP)					
SBP (mm Hg)	123.5 (113.5–135.0)	129.5 (115.0–145.5)†	126.5 (123.5–153.0)‡	127.5 (106.5–156.0)	0.031
DBP (mm Hg)	83.0 (77.0–90.3)	86.5 (78.3–94.0)§	80.8 (75.0–94.5)	90.5 (82.5–105.5)¶	0.017
Hypertension	304 (53.9)	54 (58.7)	12 (54.5)	9 (81.8)	0.263
Among participants with hypertension (n=379):					0.010
Treated and controlled BP	127 (41.8)	10 (18.5)	3 (25.0)	3 (33.3)	
Treated and uncontrolled BP	71 (23.4)	23 (42.6)	5 (41.7)	4 (44.4)	
Screen-detected HPT	106 (34.9)	21 (38.9)	4 (33.3)	2 (22.2)	
Biochemical					
FBG (mmol/L)	5.0 (4.6–5.5)	5.0 (4.6–5.6)	4.9 (4.4–5.6)	4.8 (4.7–5.3)	0.886
2-hour glucose (mmol/L) (n=688)	6.0 (4.9–7.3)	6.3 (5.1–7.6)	6.3 (4.7–8.5)	6.4 (5.6–7.2)	0.624
Glucose categories (n, %) (n=688)					0.543
Normoglycaemia	428 (76.0)	70 (76.0)	13 (59.1)	9 (81.8)	
Pre-diabetes (IFG/IGT)	84 (14.9)	11 (12.0)	6 (27.3)	1 (9.1)	
Type 2 diabetes	51 (9.1)	11 (12.0)	3 (13.6)	1 (9.1)	
HbA1c (%) (n=685)	5.8 (5.6–6.1)	5.9 (5.6–6.2)	5.7 (5.3–6.2)	5.7 (5.6–6.2)	0.591
Fasting insulin (IU/L)	8.5 (5.9–12.1)	11.1 (6.4–15.5)	11.0 (8.7–13.2)	–	0.334
Vitamin D (ng/mL)	6.0 (5.0–7.7)	6.2 (5.0–7.8)	6.7 (5.9–8.1)	6.8 (5.2–10.6)	0.361
Calcium (mmol/L) (n=688)	2.3 (2.3–2.4)	2.3 (2.3–2.4)	2.4 (2.3–2.4)	2.3 (2.3–2.4)	0.794
Phosphate (mmol/L) (n=688)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.2 (0.9–1.3)	0.777
GGT (IU/L) (n=688)	35.0 (24.0–55.0)	45.0 (26.0–81.0)	46.5 (25.0–64.0)	49.0 (24.0–122.0)	0.071
High GGT (n=688)	245 (43.4)	51 (56.0)	13 (59.1)	6 (54.5)	0.071
AST (IU/L) (n=688)	23.0 (20.0–29.0)	26.0 (21.1–34.0)	26.5 (22.0–34.0)**	21.0 (20.0–28.0)	0.009
ALT (IU/L) (n=646)	22.0 (16.0–32.0)	23.0 (17.0–33.0)	21.0 (18.0–31.0)	18.5 (15.5–37.5)	0.799
AST/ALT ratio	1.1 (0.9–1.4)	1.2 (0.9–1.5)	1.3 (1.1–1.4)	1.3 (0.9–1.5)	0.413
Fibrosis-4 index (n=644)	0.9 (0.7–1.3)	1.0 (0.8–1.3)	1.1 (0.9–1.5)	1.3 (0.7–1.6)	0.063

Continued

Table 2 Continued

Sociodemographic variables	No CKD (n=565)	Stage 1 (n=92)	Stage 2 (n=22)	Stage 3 (n=11)	P value
Liver fibrosis (n, %)					0.124
No risk	413 (78.4)	66 (75.0)	14 (66.7)	4 (50.0)	
Intermediate risk	109 (20.7)	19 (21.6)	6 (28.6)	4 (50.0)	
High risk	5 (0.9)	3 (3.4)	1 (4.8)	0 (0)	
Red blood cells ($\times10^{12}$/L)	4.6 (4.3–4.9)	4.5 (4.2–4.9)	4.5 (4.2–4.6)	4.7 (4.5–5.1)	0.071
White blood cells ($\times10^{9}$/L)	23.0 (18.3–28.0)	22.0 (17.0–28.0)	26.0 (16.0–31.9)	25.0 (19.0–26.0)	0.550
Platelet count ($\times10^{9}$/L)	276.0 (234.5–322.5)	276.5 (235.0–333.5)	271.0 (244.0–335.0)	261.0 (217.0–325.0)	0.956
Haematocrit (volume %)	0.4 (0.4–0.4)	0.4 (0.4–0.4)	0.4 (0.4–0.4)	0.4 (0.4–0.5)	0.433
Haemoglobin (g/L)	135 (127–143)	133 (123–145)	135 (133–144)	137 (129–158)	0.390
Anaemia, n (%)	77 (13.6)	22 (23.9)	2 (9.1)	2 (18.2)	0.063

Data are presented as median (25–75th percentiles) or count and percentages.
*p=0.030 (CKD stage 3 vs no CKD; CKD stage 3 vs CKD stage 1).
†p=0.007 (no CKD vs CKD stage 1).
‡p=0.039 (no CKD vs CKD stage 2).
§p=0.010 (no CKD vs CKD stage 1).
¶p=0.013 (no CKD vs CKD stage 3).
**p=0.042 (CKD stage three vs CKD stage 2).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GGT, gamma-glutamyl transferase; HbA1c, glycated haemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; SBP, systolic blood pressure; uACR, urinary albumin-to-creatinine ratio.

DISCUSSION

To our knowledge, this is the first study to show that by using an opportunistic approach, CKD can be detected early, allowing for timely referral for specialised testing to confirm diagnosis and subsequent care. This was achieved through leveraging the information already collected in an existing screening programme that targeted individuals at high risk for T2DM and included a few additional kidney-related biochemical markers to the variables for testing. The yield of screen-detected cases was high for a low investment which cost ZAR237.80 (US$14.59) per person and highlights the potential cost-effectiveness of such a strategy.

By including a minimal number of markers of kidney function (namely serum and urinary creatinine, and urinary albumin) to the scope of markers already collected, we found that 18.1% of those at high risk for developing T2DM had CKD with the majority (73.6%) having mild CKD (CKD stage 1). The CKD burden, at 22.7%, was even higher in participants with newly diagnosed T2DM, which underscores the need for frequent screening of individuals at high risk for T2DM to avoid T2DM presenting with complications at diagnosis. Therefore, using T2DM as a gateway for CKD screening through existing screening programmes is justified as such an approach, together with diagnosing new T2DM, simultaneously identified those with complications, that is, CKD. The newly diagnosed T2DM may receive comprehensive care with tight control of both their T2DM and CKD. This intensification of treatment could contribute to a delay in CKD progression and consequently help reduce the risk of developing end-stage kidney disease (ESKD) or CVD-related complications.[31] Further support for CKD screening in individuals at high risk for T2DM was the substantial CKD burden in pre-diabetes (17.6%). Notably, if screening for CKD was initiated only after the development of T2DM, the identification of CKD in individuals with pre-diabetes, which generally fall below the threshold for disease management in clinical practice, would have been missed. This would then have been a lost opportunity to identify and manage CKD early and delay progression of the disease in this high-risk group.

Our study also highlights the importance of screening for albuminuria as 91.2% of those with CKD would have gone undetected if CKD were based on eGFR alone. Guidelines recommend albuminuria testing using ACR, like we did in our study, however, this is not always possible in many low-resource settings. In these instances, low-cost semiquantitative methods, like urinary dipsticks, can be used to measure albuminuria with subsequent confirmation of positive dipstick result with a quantitative laboratory test to confirm CKD diagnosis.[20] Or repeated dipstick assessments can be employed to reduce the possibility of false-negative results as this could delay the timely diagnosis and management of CKD.

Given that this is the first study to report the prevalence of CKD in people at high risk for developing T2DM, based on the ADRS, the prevalence estimates cannot be directly compared with other studies as no similar data have been published. Nevertheless, at a similar median age (52 vs 53 years), the prevalence of CKD in those with pre-diabetes in our study was comparable to that reported in a large representative sample in the USA (17.6% vs 17.7%, respectively).[32] Also, although an older population (median age of 68 years) with a higher prevalence of advanced CKD (stages 3–5), a South African study found

that the prevalence of CKD in those with pre-diabetes was 19.8%.[33] The similarly high CKD prevalence in pre-diabetes across several studies suggests that perhaps there should be regular CKD screening for all individuals with pre-diabetes.

A likely contributor to the substantial CKD burden in this study is the high prevalence of hypertension, which at 55% is higher than the 44%–46% reported for South Africa.[34] While the high reported prevalence of hypertension is consequent to the score used to identify high-risk individuals, a larger proportion of the participants with hypertension had CKD compared with those with normal blood pressure (19.8% vs 16.1%, respectively). The prevalence of CKD may be related to the delayed detection of hypertension or the suboptimal control of blood pressure in treated hypertension, as reported in the current study and in several South African studies.[34 35] Indeed, a high proportion of participants with treated but uncontrolled hypertension had CKD (31.1%) in this study as did participants with newly detected hypertension (20.3%). This further highlights the benefit of screening high-risk individuals for CKD. Notably, adequate blood pressure control is fundamental to slowing the progression of CKD[36 37] and timeous treatment with antihypertensive medication can improve both kidney and cardiovascular outcomes[38 39] thereby preventing the progression to ESKD and reducing the risk of all-cause and cardiovascular mortality.[38 40 41]

Elevated GGT and the FIB-4 index, which are commonly used markers of liver injury and non-alcoholic fatty liver disease,[42] have been linked to increased CKD risk in various populations.[43–46] In our study, 56.5% of the participants with CKD presented with higher-than-normal GGT levels, compared with 43.4% of participants without CKD. Also, a significant proportion of people with CKD presented with intermediate and high risk for advanced liver fibrosis, based on the FIB-4 index, compared with those without CKD (28.2% vs 21.6%). Early recognition and interventions directed at reducing the risk of liver injury among individuals with CKD could reduce CKD progression.

Anaemia was prevalent in our study population (14.9% of total sample), with nearly twice as many participants with CKD having anaemia compared with those without CKD, as shown in other studies as well.[47 48] Although the overall prevalence of anaemia in this study was not uncommon for South Africa,[49] the prevalence in participants with CKD is concerning. While erythropoiesis stimulating agents and iron supplementation to treat anaemia are unlikely to be prescribed to people in the early stages of CKD, anaemia can accelerate the decline in kidney function by causing kidney haemodynamic alterations and tissue hypoxia.[8] It is strongly predictive of all-cause and cardiovascular mortality,[50 51] and should thus be closely monitored.

Although lifestyle interventions addressing unhealthy diets, physical inactivity, tobacco smoking and alcohol misuse are advocated to reduce the growing global burden of non-communicable diseases,[52 53] little is known about the impact of reducing unhealthy lifestyle behaviours on kidney health. The SA-DPP intervention, implemented in individuals with pre-diabetes, will provide a unique opportunity to examine the effects of improving lifestyle behaviours on changes in CKD status.

This is the first study to show that using an opportunistic approach, through leveraging the information already collected in an existing screening programme is advantageous to screen for CKD. However, our study does have limitations. The SA-DPP study included participants at high risk of T2DM and our findings might not be reproducible across other non-communicable diseases screening programmes. The small number of participants identified with CKD in this study reduced the statistical power of our analyses when stratifying by CKD stage. Based on the self-selection approaches used to recruit participants, the disproportionate greater number of females, the varying socioeconomic status, lifestyle behaviours and disease prevalence (hypertension and T2DM) across provinces and by urban–rural residence in South Africa,[34] our study findings cannot be generalised. Another limitation is that CKD was defined based on a single time point serum and urinary creatinine and albumin assessment and not on repeated measurements, at least 3 months apart, as per KDIGO guidelines.[20] However, a strength of our study is that both eGFR and albuminuria were used to define CKD, unlike most other population-based CKD prevalence studies in South Africa and Africa in general which rely on eGFR only for CKD classification. Finally, as for all studies using eGFR to characterise CKD, instead of the gold standard of measured GFR, the overestimation or underestimation of the estimate cannot be excluded.

CONCLUSION

The fact that almost one in five participants identified as high risk for T2DM had CKD underscores the value of including markers of kidney function in existing disease screening programmes. Our findings provide support for key stakeholders and policy makers to adapt current strategies for hypertension and T2DM screening to include screening for CKD. Indeed, by using an opportunistic approach to screen high-risk individuals, those with early-stage CKD can be identified and appropriately managed to reduce disease progression. Existing cardiovascular or non-communicable disease screening programmes should perhaps explore including markers for CKD evaluations to maximise limited resources without compromising on effectiveness.

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