A simple estimation of glomerular filtration rate in diabetes patients from serum creatinine

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Abstract:

Serum creatinine level is frequently used to estimate the renal function; however, some diabetes patients can have significantly decreased glomerular filtration rates (GFR) despite normal range serum creatinine values, making the recognition of early stage chronic renal dysfunction more difficult. This retrospective study recruited all type 2 diabetes patients attending the primary care unit medicine practice, Amphoe Muang, Surin Province in 2014, their serum creatinine, urine micro and macro-albumin and the GFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation were collected to estimate the kidney function. Of 3,231 diabetes patients screened, 1,484 (45.9%) of them met the inclusion criteria of chronic kidney disease (CKD). Among them, renal failure stage 3 or more (GFR <60 ml/min) was present in 45.5% and severe renal failure stage 4 or more (GFR <30 ml/min) was present in 3.9%. The old criterion of kidney failure, serum creatinine >2.0 mg/dl, had a sensitivity of 45.8% and the specificity of 99.9% for detecting CKD stage 3 or more and the sensitivity of 4.1% for general CKD. Only 322 (47.6%) of the 676 diabetes patients with renal failure had albuminuria more than 30 mg%. It was concluded that earlier stages of CKD could be early detected for planning of management based on the combination of kidney damage by using albuminuria and decreased calculated GFR.

Key words: Chronic kidney disease, Diabetes, Renal failure, Albuminuria

บทคดย่อ: การประเมินอัตราการกรองผ่านไตอย่างง่ายโดยการคำนวณจากค่าซีรั่มครีอะตินินในผู้ป่วยเบาหวาน

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ปัจจุบันโรงพยาบาลส่วนใหญ่ใช้ผลการตรวจค่าซีรั่มครีอะตินินในการประเมินการทำงานของไต แต่ผู้ป่วยเบาหวานส่วนหนึ่งมีการทำงานของไตลดลงโดยที่ค่าซีรั่มครีอะตินินยังอยู่ในเกณฑ์ปกติทำให้มีการวินิจฉัยโรคไตวายเรื้อรังระยะแรก ๆ ได้ยาก การศึกษานี้เลือกใช้ข้อมูลซีรั่มครีอะตินินค่าไมโครอัลบูมิน แมคโครอัลบูมินในปัสสาวะ จากกลุ่มตัวอย่างผู้ป่วยเบาหวานชนิดที่ 2 ที่รับยาที่หน่วยปฐมภูมิ ในโรงพยาบาลส่งเสริมสุขภาพตำบล ในเขตอำเภอเมือง จังหวัดสุรินทร์ ในปี 2557 ควบคู่กับค่าอัตราการกรอง ผ่านไตโดยประมาณ ซึ่งได้จากการคำนวณโดยใช้สมการ CKD-EPI ในการประเมินการทำงานของไต ผลการศึกษาพบว่าการใช้เกณฑ์ใหม่ในการวินิจฉัยภาวะไตวายเรื้อรังนั้น พบผู้ป่วยเบาหวานที่มีภาวะไตวายระยะแรกจำนวนมาก จากคนไข้ทั้งหมด 3,231 ราย เข้าเกณฑ์การวินิจฉัย 1,484 (45.9%) โดยมีไตวายระยะที่ 3 ขึ้นไป ถึง 45.5% และไตวายระยะที่ 4 ขึ้นไป 3.9 % เปรียบเทียบกับการใช้เกณฑ์ดั้งเดิมในการวินิจฉัย ซีรั่มครีอะตินิน >2.0 มก/ดล มีความไว 45.8% และความจำเพาะ 99.9% ในการวินิจฉัยไตวายระยะรุนแรง ส่วนในภาวะไตวายเรื้อรังทั่วไป มีความไวเพียง 4.1% เท่านั้น โดยในกลุ่มไตวายเรื้อรังนั้น พบโปรตีนในปัสสาวะมากกว่า 30 มก% ตามเกณฑ์ โรคไตจากเบาหวาน 47.6% จึงสรุปได้ว่าการเปลี่ยนแปลงกฎเกณฑ์การวินิจฉัยโรค ทำให้วินิจฉัยได้รวดเร็วมากขึ้น โดยเฉพาะภาวะไตวายเรื้อรังในระยะแรก ทำให้สามารถวางแผนการดูแลผู้ป่วย เพื่อชะลอการเสื่อมของไตได้อย่างเหมาะสม

คำสำคัญ: โรคไตเรื้อรัง, เบาหวาน, ไตวาย, โปรตีนในปัสสาวะ

Introduction

Diabetes mellitus and chronic kidney disease (CKD) are common and exhibit synergistic associations with premature mortality. Current diabetes guidelines in the UK recommend annual urinary albumin and serum creatinine determinations to screen for diabetic kidney disease. CKD is now recognized as a common condition that elevates the risk of cardiovascular disease as well as kidney failure and other complications[1-3]. The number of patients with kidney failure treated with dialysis and transplantation (the end stage of CKD) has increased dramatically in the United States from 209,000 in 1991 to 472,000 in 2004[4]. The age, sex, and race-adjusted incidence of end stage renal disease increased by 43 % during the decade following 1991[4]. Estimation of the prevalence of earlier stages of CKD in the US population and ascertainment of trends over time are central to disease management and prevention planning, particularly given the increase in the prevalence of obesity, diabetes[5-6] and hypertension,[7-8] the leading risk factors for CKD[5].

Earlier stages of CKD are defined based on the combination of kidney damage (most often quantified by albuminuria) and decreased kidney function (quantified by glomerular filtration rate or GFR) estimated from the serum creatinine concentration)[2].

Unfortunately, serum creatinine alone may be misleading when evaluating renal dysfunction. For instance, patients with a relatively lower muscle mass, such as women and/or elderly persons, can have a serum creatinine level within the laboratory-reported normal range although their renal function is severely compromised[9-14]. More accurate estimates of renal function can be obtained in clinical practice by measuring creatinine clearance from a timed urine collection or by using formulae,

such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) to calculate the GFR[15].

The renal failure in diabetes patients could be under-detected because their serum creatinine levels fall within or only slightly above the laboratory-reported normal range, so these patients should deserve an appropriate evaluation. A study was, therefore, designed to detect the renal failure in diabetes patients at the primary care setting.

Patients and Methods

This study, approved by the Research Ethics Board of Surin Hospital, is a retrospective medical record review between March 1 and July 1, 2014. All diabetes patients in a primary care unit medicine practice at Surin Hospital, a tertiary care teaching hospital, were identified using a computer-generated list obtained from the main practice database. Patients would be excluded from the study for the following reasons: a serum creatinine and urine microalbumin level had never been documented in the medical record, or the medical record was not available for review during the study period. The following data were colleted for each patient: age, sex, most recent serum creatinine level, and urine microalbumin. The CKD-EPI was used to calculate the GFR. This formula has been validated in diabetes populations to accurately predict the measured creatinine clearance and the GFR. The CKD-EPI GFR has also been shown superior to the measured creatinine clearance as a predictor of GFR in several studies. The improved outcomes for people who were reclassified to a proper CKD stage using the CKD-EPI formula were also seen for mortality, renal progression and cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study and for mortality in the Australian Diabetes, Obesity and Lifestyle study[15].

Renal failure was defined as a CKD-EPI GFR of <60 ml/min. This value was chosen to represent a decreased GFR that would not be attributable to normal aging alone. Severe renal failure was defined as a CKD-EPI GFR of <30 ml/min. At this level of renal function, prompt referral to a nephrologist for ongoing management has been proved beneficial. Additional urine microalbumin data were sought in the renal failure category: (1) <30 mg/dl, (2) 30-300 mg/dl and (3) >300 mg/dl.

The serum creatinine is generally used to evaluate renal function in a diabetes primary care population. The creatinine level of 2.0 mg/dl was selected as a clinically relevant cutoff value, and any higher value was considered a positive test result for renal failure. This conservative cutoff value was selected based on previous studies which demon-strated that physicians would diagnose chronic kidney disease when the serum creatinine was 2.0 mg/dl or more. The serum creatinine level was compared with the CKD-EPI GFR to demonstrate its characteristics as a test for renal failure. Secondary outcomes were the prevalence of renal failure in this population, the pattern of kidney damage by using microalbuminuria and macroalbuminuria. And finally the validity of the tests was calculated.

Results

There were 3,231 diabetes patients with active medical records, only 1,484 of them were available for review, 1,747 were excluded (11 had not a documented creatinine level, and 1,736 had not documented albumin in urine). Renal failure

(CKD-EPI GFR <60 ml/min) was present in 45.5 % of the patients while severe renal failure (CKD-EPI GFR <30 ml/min) was present in 3.9 % of the patients (Table 1). The prevalence of renal failure was significantly higher in stage 2 CKD and stage 3a than severe renal failure stage. Of the participants, 627 (42.25 %) were tested positive for microalbuminuria and 322 (47.63 %) had GFR <60 ml/min/1.73 m^2. Importantly, only 28 (1.8 %) of participants reported a history of CKD at screening.

For the detection of renal failure, a serum creatinine level of 2.0 mg/dl had an overall low sensitivity, only 4.1 % (Table 2), so CKD awareness was low but high specificity among individuals with moderately decreased GFR. Awareness was higher among patients with lower kidney function and higher albuminuria levels. Also, chart review of patients suggested that CKD was often undiagnosed. The serum creatinine could better detect severe renal failure; however the sensitivity was only 45.76% (Table 3). A lower GFR cutoff compromises the sensitivity and gives a larger number of false-negative results, 95.86 % in renal failure and 54.24 % in severe renal failure, which would underestimate the true prevalence of CKD, and too many patients would not be appropriately recognized as being at probable increased risk for progression to ESRD and treated accordingly.

Table 2 Diagnostic screening test for renal failure of serum creatinine 2.0 mg% or more

Diagnostic test	%
Sensitivity	4.14
Specificity	100
Positive predictive value	100
Negative predictive value	55.49
False positive rate	0
False negative rate	95.86

Table 1 Stages of chronic kidney disease

Stage	Definition	Estimated GFR (ml/min per 1.73 m2)	Albuminuria >30 mg/g	Albuminuria >30-300 mg/g	Albuminuria >300 mg/g	Total 1484
1	Kidney damage with normal or increased GFR	≥90	98 (6.60%)	53 (3.57%)	8 (0.54%)	159 (10.71%)
2	Kidney damage with mild decreased GFR	60 to 89	405 (27.29%)	225 (15.16%)	19 (1.28%)	649 (43.73%)
3a	Mildly to moderately decreased GFR	45 to 59	197 (13.27%)	145 (9.77%)	17 (1.14%)	359 (24.19%)
3b	Moderately to severely decreased GFR	30-44	131 (8.82%)	102 (6.87%)	25 (1.68%)	258 (17.39%)
4	Severely decreased GFR	15 to 29	26 (1.75%)	23 (1.55%)	8 (0.54%)	57 (3.84%)
5	Kidney failure	<15	0 (0%)	1 (0.07%)	1 (0.07%)	2 (0.14%)

Table 3 Diagnostic screening test for severe renal failure of serum creatinine 2.0 mg% or more

Diagnostic test	%
Sensitivity	45.76
Specificity	99.92
Positive predictive value	96.42
Negative predictive value	97.80
False positive rate	0.07
False negative rate	54.24

Discussion

Chronic kidney disease (CKD) is common and harmful but treatable and it is recognized as a world-wide public health problem. Kidney failure and cardiovascular disease (CVD) are generally consi-dered to be its most important outcomes but the risks for each outcome vary widely among patients, and clinicians need the guidance to prioritize their clinical decisions.

"Chronic kidney disease" is a general term for heterogeneous disorders of kidney structure and function. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines define CKD as follows, regardless of clinical diagnosis:[17-18] kidney damage (usually defined as an albumin creatinine ratio (ACR) ≥30 mg/g) or a GFR < 60 ml/min/1.73 m^2 (usually estimated from the serum creatinine level) for at least 3 months. Severity is traditionally classified according to GFR but several landmark studies have shown that a higher level of proteinuria (ascertained by ACR or dipstick protein testing) is a risk factor for CKD progression and mortality independent of estimated GFR. The Organization Kidney Disease: Improving Global Outcomes (KDIGO) recently sponsored a collaborative meta-analysis and international conference that examined these studies, as well as others that confirmed and extended their findings. These data convincingly demonstrate the poor sensitivity of serum creatinine alone for the detection of renal failure in early stage CKD patients. The goal of a medical screening program is to recognize a disease in its preclinical phase so that intervention can occur at earlier stages, hopefully leading to better outcomes. Screening programs may also promote public awareness and education, encourage physician adherence to clinical practice guidelines. We per-formed our sensitivity analysis based on a serum creatinine level of 2.0 mg/dl although the selection of a lower cutoff value would have increased the sensitivity of the test for the detection of renal failure. The goal of this study was to evaluate the validity of the serum creatinine level in its clinical context so primary care practitioners could apply it and plan to manage their patients. In addition, a high-risk population may be more motivated to participate a screening program and more likely to follow recommendations if the screening is positive.

Treatment of comorbid conditions, inter-ventions to slow progression of kidney disease, and measures to reduce the risk for CVD should begin during stage 1 and stage 2. Hypertension is both a cause and a complication of CKD and should be carefully controlled in all patients. Evaluation and treatment of other complications of the decreased GFR, such as anemia, malnutrition, bone disease, neuropathy and decreased quality of life, should be undertaken during stage 3, as the prevalence of these complications begins

to rise when GFR declines to < 60 ml/min/1.73 m^2. Preparation for kidney replacement therapy should begin during stage 4 well before the stage of kidney failure. Initiation of dialysis and transplantation are triggered by the onset of uremic symptoms. Preparations for these treatments should begin when GFR declines to <15 ml/min/1.73 m^2 (stage 5). The clinical action plan for each stage should include the actions begun in preceding stages[17-18]. Patients with CKD should be referred to a specialist for consultation and co-management if the patient's personal physician cannot adequately evaluate and treat the patient. And a nephrologist should participate in the care of patients with a GFR < 30 ml/min/1.73 m^2.

Conclusion

In an attempt to decrease the national burden of kidney disease and reduce the morbidity and mortality associated with CKD, detection of CKD, particularly at early stages, is essential because therapeutic interventions are likely to be effective if they are implemented early in the course of the disease. My study shows that serum creatinine is not the best test to screen diabetes populations. In contrast, the estimation or measurement of GFR with urine albumin is the more accurate screening method for the detection of renal failure in diabetes patients.

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