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ORIGINAL RESEARCH

Comparative diagnostic utility of different urinary biomarkers during pre-albuminuric stages of non-hypertensive type 2 diabetic nephropathy

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Abstract
Background: Pre-albuminuria DN may be defined by the activation of the renin-angiotensin system and the development of tubulointerstitial injury. In non-hypertensive people with type 2 diabetes, we analyzed the ability of four urine biomarkers to predict the development of albuminuria: angiotensinogen (Angio), interleukin-18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), and cystatin (Cys). An indicator of nephropathy in persons with type 2 diabetes was a low albumin-to-creatinine ratio (ACR). The eGFR of these individuals was less than 120 ml/min." At one year, they were split into three groups based on whether they had hyperfiltration, normoalbuminuria, or microalbuminuria. Fifty more T2DM patients who did not have nephropathy served as controls. All of them were also evaluated for ACR, HbA1 C, eGFR, and a panel of urine biomarkers (IL-18, cystatin-C, NGAL, and AGT). Both correlation and logistic regression were used to evaluate the accuracy of each diagnostic tool across subgroups. The results showed that IL-18/Cr, cystatin/Cr, and AGT/Cr were all elevated in the urine of those with hyperfiltration, normoalbuminuria, and microalbuminuria compared to controls, whereas NGAL/Cr remained unchanged. According to multivariate logistic regression, the chances ratio for developing nephropathy increased by a factor of eight with increasing log Angio/Cr ratios.
Conclusions: Urinary AGT was more useful than ACR and eGFR, then IL-18 and cystatin, for identifying DN before albuminuria developed.
Key words: pre-albuminuric stage, non-hypertensive type 2 diabetic nephropathy, urinary biomarkers, diagnostic.

Introduction

Chronic kidney disease (CKD) due to diabetic nephropathy (DN) often results in end-stage renal disease (ESRD). Neuropathy is a common complication of diabetic mellitus (DM). Forty percent or more of those with a diagnosis of type I or type II DM also have a diagnosis of DN [1]. End-stage renal disease (ESRD) and the need for chronic renal replacement therapy (RRT) are both significantly increased by diabetes [2,3]." In light of the rising prevalence of both DM and DN, it is crucial to identify the condition at its earliest stages so that proper treatment may be instituted to halt or decrease the progression to end-stage renal disease.In the early diagnosis of DN, biomarkers are crucial. The most well-known of them is called microalbuminuria. Furthermore, microalbuminuria is a sign of the systemic endothelial dysfunction seen in diabetes, connecting the kidneys to cardiovascular and cognitive damage.
The inflammatory and oxidative processes that occur in tandem with DM and DN are also being evaluated at this time. We chose to focus on early DN since there is already a wealth of data on markers showing renal failure in later DM stages.Cystatin-C, NGAL, and kidney injury molecule-1 (KIM-1) are early indicators of renal damage that may be detected by testing [3,4]. The purpose of this research was to determine whether or not four urine biomarkers (Angio, IL-18, NGAL, and cystatin) might be utilized to detect non-hypertensive individuals with type 2 diabetes before the onset of albuminuria.

Method

Each participant signed an informed assent form, and the Organization's ethics committee approved of the research. Analyzing and evaluating data: Inclusion criteria were an estimated glomerular filtration rate (eGFR) of 120 ml/min/1.73 m2 and an unlimited ACR esteem, as well as an eGFR of 60-120 ml/min/1.73 m2 and an ACR of 30-300 mg. UTIs, kidney stones, hypertension, pregnancy, genitourinary or primary diseases, thyroid infections, nephrotoxic medicines or steroids, and dialysis or post-renal transplant were all grounds for rejection. Anyone who fit these parameters was turned away as a patient. As previously, patients without microalbuminuria and with an eGFR between 90 and 120 ml/min were utilized as controls.

A total of 120 patients were included, and subgroups were established according to urine ACR and eGFR using the MDRD4 algorithm, with patients falling into either glomerularhyperfiltration, normoalbuminuria, microalbuminuria, or the designated control categories. After collecting 7 ml of venous blood from each participant, standard natural chemistry was performed, including a haemogram, renal capacity test, liver function tests, HbA1c, plasma glucose, and lipid panel. In addition, an electrocardiogram, an echocardiogram, a fundus examination, and a microalbumin pee (spot pee for protein and Cr rate) were carried out. Tests were performed at the 3-, 6-, and 12-month marks to establish the presence of nephropathy.

Additional urine samples for the analysis of urinary biomarkers were obtained in Eppendorf tubes at month 12 and stored at 20 degrees Celsius until analysis. Fifty healthy individuals were recruited from the same outpatient clinics as the patients for the purpose of comparing clinical, biochemical, and biomarker measurements. A fully automated dry clinical science analyzer was also used to conduct further testing.

All data was imported into Excel before being analyzed statistically using SPSS version 23 (IBM Corp., 2015). IBM's statistical analysis program, SPSS, version 23.0 for Windows. Location: Armonk, New York A Mann-Whitney U-Test The median biomarker was compared using a U test.ACR, and urine albumin levels. On the basis of their eGFR and ACR, the subjects were categorized as cases or controls using logistic regression analysis.

Results

Comparison of ACR, eGFR, and numerous biomarkers to the urine Cr ratio after 12 months is shown in Table III. Both AGT/Cr and AGT had AUCs of 0.93, whereas AGT had an AUC of 0.95. Area under the curve (AUC) values for other biomarkers also decreased following AGT; this was the case for IL-18, IL-18/Cr, cystatin, cystatin/Cr, NGAL, and NGAL/Cr.(Table 1)."

Table 1: Diabetic nephropathy after 12 months: the role of urine creatinine and other indicators

Biomarkers	Sensitivity(%)	Specificity(%)	AUC	*P*
Angiotensinogen/Ur.Creat.(mg/g)	89	84	0.93	0.00
Cystatin/Ur.Creat.(mg/g)	65	51	0.59	0.00
IL-18/Ur.Creat.(mg/g)	64	50	0.60	0.00
NGAL/Ur.Creat.(mg/g)	65	45	0.50	0.60
ACR(mg/g)	55	90	0.70	0.00
e-GFR(ml/min)	34	85	0.65	0.02
Cystatin-C (ug/ml)	59	45	0.55	0.03
IL-18 (pg/ml)	71	60	0.65	0.00
NGAL(ng/ml)	60	30	0.35	0.41
Angiotensinogen(ng/ml)	85	75	0.95	0.00

In addition to age, BMI, mean BP, cholesterol, and hemoglobin A1c, all log-transformed biomarker ratios with Cr were included as independent factors in a multivariate logistic regression analysis. Compared to those who did not have nephropathy, individuals whose log AGT/Cr and IL-18/Cr ratios were low were 1.5 times more likely to acquire DN.

(Table 2)

Table2: Univariateandmultivariatelogisticregressionanalysisoutcome

Parameters	Oddsratio	*P*Univariate	Oddsratio	*P*multivariate
Age	0.945	0.745	0.955	0.340
BMI	0.989	0.285	0.991	0.955
MBP(mmHg)	1.000	0.834	1.015	0.745
HbA_{1c}(%)	1.450	0.121	1.029	0.805
Cholesterol (mg/dl)	0.891	0.450	0.895	0.150
Logcystatin-C/Ur.creat.(mg/g)	1.654	0.001	0.498	0.078
LogIL-18/Ur.creat.(mg/g)	2.175	0.002	1.586	0.275
LogNGAL/Ur.creat.(mg/g)	1.140	0.401	0.985	0.898
Logangiotensinogen/Ur.creatinine(mg/g)	6.745	0.000	6.515	0.000

Discussion

Using an evaluation of glomerular injury markers (IgG), Higher potential gains of NGAL, H-FABP, and urinary irritation were documented in normoalbuminurics compared to controls, as were distal tube-shaped injury indicators (urinary KIM-1, Trouble, NGAL, and cystatin) and proximal adjusted injury signals (urinary H-FABP, KIM-1, and NGAL). However, cystatin C levels in the urine were rather low [5]. In the present investigation, pre-albuminuria nephropathy was substantially correlated with elevated levels of AGT and IL-18, as well as a greater AUC in patients compared to controls. The sensitivity and specificity of AGT were higher than those of the standard ACR, urine albumin, and eGFR. There was a correlation between nephropathy and diabetes status, with microalbuminuria patients having considerably higher levels of uncontrolled blood glucose. Similarly, Chowta et al. [6] found that 37%

of people had microalbuminuria. Microalbuminuria was not associated with body mass index or gender in this research, although there was a strong association between microalbuminuria and diabetes duration. Significant increases in urine microalbumin levels were associated with both the duration of diabetes and poor glycemic management, Kundu et al. [7].

Although ACR was greater than in the control group, it did not progress to the next stage in the same way that increased GFR occurred without worsening of albuminuria in a prior study. "Our results showed that between the hyperfiltration and microalbuminuria groups, there was a statistically significant difference in AGT and IL-18 at a single time point, but not in cystatin or NGAL. Urine NGAL was shown to increase from the normoalbuminuria group to the macroalbuminuria group after a one-year follow-up, contrary to our results [8]. However, a few other studies [9,10] Despite our results, others have shown that diabetic normoalbuminuric patients had higher NGAL levels than healthy controls.

Sueud et al. [11] likewise observed a poor AUC (0.54) and low specificity (0.30%) for NGAL in their DN patients. Renal damage may be predicted more accurately by measuring urine ACR levels than by measuring NGAL levels. Compared to NGAL and IL-18, they discovered that NAG in the diabetic urine was the most sensitive marker for early kidney injury. When it comes to keeping tabs on renal impairment, serum cystatin-C has been found to be the most sensitive and specific biomarker of damage development [12].

Microalbuminuric T2DM patients exhibited an AUC of 0.85 for urine AGT-Cr, whereas macroalbuminuric T2DM patients had an AUC of 0.96.Microalbuminuria diagnostic sensitivity was 80-90% and macroalbuminuria diagnostic specificity was 75-80%. Urinary albumin to creatinine ratio (AGT/ACR) is a useful diagnostic for detecting DN in its earliest stages. The non-haemodynamic effects of angiotensin II on the progression of tubulointerstitial fibrosis may account for the increased AGT and AUC values seen in our instances.[13]

Due to their early nature, the results presented here cannot be used in clinical practice. Additional research with bigger sample sizes and longer follow-up times for diabetes controls and cases is needed to confirm the results of the present study.

Conclusion

When comparing the four biomarkers used to make the diagnosis of EDN, The AGT/Cr ratio outperformed the ACR in terms of sensitivity and specificity. Pre-albuminuric EDN may be diagnosed by measuring AGT and IL-18 levels in the urine. Non-proteinuric DN patients at high risk of progression may be identified by these indicators who would have been overlooked by traditional ACR."

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