Albuminuria as a Biomarker of the Renal Disease

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Abstract

Albuminuria is an early and sensitive marker of kidney damage in diabetic patients, a good predictor of kidney outcome and cardiovascular disease. Screening for albuminuria is important to identify individuals at risk for renal outcome, i.e., developing end-stage renal disease, acute kidney injury, and progressive chronic kidney disease as well as cardiovascular disease and all-cause mortality in both general and high-risk population (diabetes, cardiovascular disease, hypertension, and older patients). Also, it is the most widely used clinical marker of diabetic nephropathy. The terminology of "early diabetic nephropathy" indicated diabetic subjects with albuminuria. In this early phase of diabetic

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nephropathy, the glomerular filtration rate is usually well preserved. In patients with several cardiovascular risks, albuminuria is predicting outcome, even below the level to be taken as normal. It seems that the pathophysiologic mechanisms linking albuminuria to cardiovascular and renal risk are generalized loss of vascular endothelial function in organs. Furthermore, albuminuria can be used as a target for treatment for primary and secondary prevention of renal and cardiovascular disease development. ACE inhibition in subjects with nondiabetic albuminuria may prevent future cardiovascular events. Measurement of albuminuria can help to determine whether or not the patient with hypertension should be treated, how aggressively they should be treated, and what medications we should treat them with.

Keywords

Albuminuria • Healthy subject • Diabetic nephropathy • Screening of chronic kidney disease • Prediction of renal progression • Cardiovascular mortality • Target for treatment • Hypertension

Abbreviations

ACR	Albumin-to-creatinine ratio
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
RAAS	Renin–angiotensin–aldosterone system
RRT	Renal replacement therapy
UAER = UAE	Urinary albumin excretion rate

Key Facts of Kidney Function

- Healthy kidneys regulate the body's fluid levels and filter wastes and toxins from the blood into the urine. Also, they release a hormone that regulates blood pressure, activate vitamin D to maintain healthy bones, release the hormone that directs production of red blood cells, and keep blood minerals in balance (sodium, phosphorus, potassium).
- Patients at risk for kidney disease should have simple blood and urine tests to check if their kidneys are working properly. These include diabetes, high blood pressure, family history of kidney failure and being age 60 or older, kidney stones, smoking, obesity, and cardiovascular disease.
- The glomerular filtration rate is a measure of kidney work to remove wastes from the blood. To assess the glomerular filtration rate is necessary to determine the concentration of creatinine in the serum. Reduction of glomerular filtration rate and increased serum creatinine show renal failure.
- The presence of high albumin concentration in urine indicates renal damage most probably at an early stage. The presence of high protein in the urine may indicate the kidney disease.

- Part of routine health screening is urinalysis. Urine sample is collected from the patient in a specimen cup (about 50 ml). It is evaluated by its physical appearance (color, cloudiness, odor, clarity); macroscopic, chemical, and molecular properties; or microscopic assessment.
- Urine is used to diagnose a urinary tract or kidney infection, to evaluate causes of kidney failure, and to screen for progression of some chronic conditions such as diabetes mellitus and high blood pressure (hypertension).
- Patients with decreased glomerular filtration rate or proteinuria should be evaluated to determine its cause(s).

Definitions

Acute kidney injury (AKI) Acute kidney injury (AKI) is the sharp loss of kidney function, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes.

Albumin-to-creatinine ratio (ACR) Expression of albuminuria from the ratio of albumin to creatinine in urine, determined in individual sample of urine.

Angiotensin-converting enzyme inhibitors Are drugs that block the production of angiotensin II. The latter is a hormone that circulates in the blood and has many effects on the cardiovascular system; angiotensin II is a strong vasoconstrictor.

Angiotensin II receptor antagonists Are the drugs that modulate the renin–angiotensin–aldosterone system by blocking angiotensin II receptors.

Chronic kidney disease (CKD) Chronic kidney disease, also called **chronic kidney failure**, describes the gradual loss of kidney function. Its stages are based on the patient's level of glomerular filtration rate (GFR) which is a measure of filtering capacity of the glomeruli.

Diabetic nephropathy Is a slow progressive kidney disease that occurs in patients with diabetes.

End-stage renal disease (ESRD) Means glomerular filtration rate below 15 ml/min/1.73 m^2.

Estimated glomerular filtration rate (eGFR) Describes how much fluid filtered through the kidney. It is usually measured with creatinine clearance rate: it is the volume of plasma that is cleared of creatinine per unit time. Nowadays, glomerular filtration rate is estimated using different formulas based on creatinine or other markers such as cystatin C.

Framingham score for assessment of cardiovascular risk It gives an estimate of the probability that a person will develop cardiovascular disease within a specified amount of time, usually 10–30 years. It also indicates who is most likely to benefit from prevention.

Glomeruli and tubule Both represent part of the nephron, the basic structural and functional unit in the kidney.

Immunochemistry assays (Immunonephelometry, immunoturbidimetry, radioimmunoassay, enzyme-linked immunosorbent assay) Are based on the interaction of the urinary albumin with anti-albumin antibodies in the reagents.

Insulin resistance A decreased sensitivity to the action of insulin. Conditions in which the increased amount of insulin is inadequate to induce normal insulin responses in insulin-sensitive tissues (liver, skeletal muscles, adipose tissues).

Likelihood ratios Tell us how much we should shift our suspicion for a particular test result. The "positive likelihood ratio" (LR+) tells us how much to increase the probability of disease if the test is positive, while the "negative likelihood ratio" (LR−) tells us how much to decrease it if the test is negative.

Nonsteroidal anti-inflammatory drugs It is a group of medication with antipyretic, analgesic, and anti-inflammatory effects.

Progression of chronic kidney disease Worsening of kidney function, usually slow, which is determined by measuring glomerular filtration rate and albuminuria and/or proteinuria.

Renal replacement therapy (RRT) Refers to the three ways of replacing the lost kidney function: dialysis (hemo- or peritoneal) and kidney transplant.

Renin–angiotensin–aldosterone system Is a hormone system that regulates blood pressure and water balance in the body.

Sensitivity vs. specificity Sensitivity (the true positive rate) measures the proportion of actual positives which are correctly identified (the percentage of sick people who are correctly identified as having the condition). Specificity (the true negative rate) measures the proportion of negatives which are correctly identified (the percentage of healthy people who are correctly identified as not having the condition).

Type 1 diabetes mellitus It is a type of glucose control disturbance that results from the autoimmune destruction of insulin-producing cells in the pancreas. There is absolute lack of insulin. Type 2 diabetes mellitus It is characterized by hyperglycemia due to insulin resistance and relative lack of insulin.

Urinary albumin excretion (UAE) The presence of albumin in the urine as a consequence of high permeable glomerular membrane and inhibition of tubular cell reabsorption.

Introduction

Albuminuria refers to abnormal loss of albumin in the urine. Albumin is one fraction of plasma protein found in the urine in normal subjects but in larger quantity in patients with kidney disease. Although the measurement of urinary proteins has been a standard tool for nephrologists to diagnose kidney diseases for more than two centuries, the introduction of novel methods in 1980s enabled the measurement of small quantities of albumin in the urine. This triggered a series of investigations showing that increased urinary albumin excretion was an early and sensitive marker of diabetic nephropathy (Viberti 1982; Parving 1982), and an independent risk factor for cardiovascular disease in patients with hypertension and diabetes, cardiovascular and peripheral vascular disease (Parving 2001; Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000) and in the general population (Hillege 2002; Romundstad 2003).

All these statements derived from the screening studies, which have shown that there are signs of kidney disease in apparently healthy individuals (Kiberd 2006; Levey 2007). Thus renal disease became epidemic worldwide. The overall prevalence of albuminuria in the general population has been reported to be 7.2 % in the PREVEND cohort from the Netherlands ($n = 40{,}548$) (Hillege 2002) and 10.7 % in the more racially diverse United States National Health and Nutrition Examination Survey (NHANES III) study ($n = 15{,}939$) (Mattix 2002). About 8 % of adults have microalbuminuria (30–300 mg of albumin per 24 h), and 1 % have macroalbuminuria (i.e., excretion of more than 300 mg of albumin per 24 h). Furthermore, albuminuria was detected in one of every three persons with diabetes, one of every seven persons with high blood pressure but no diabetes, and one of every six persons older than 60 years (Collins 2009; Levey 2009). Also, assessment of urinary albumin excretion rather than plasma creatinine or estimated glomerular filtration rate (eGFR) seems the utmost tool for recognizing the chronic kidney disease especially in the early stages (Brantsma 2008; de Jong 2008; van der Velde 2009). Finally, in the majority of guidelines, albuminuria as a marker of kidney damage joined the glomerular filtration rate (GFR) as a measure of kidney function for definition of chronic kidney disease stages in order to evaluate chronic kidney disease (CKD) (National Kidney Foundation 2002; NICE clinical guideline 73 http://guidance.nice.org.uk/cg73, American Diabetes Association 2014).

In this review, the etiology and physiologic mechanisms of albuminuria in renal disease are highlighted. Also, clinical impact of albuminuria as a factor in renal disease compromises and establishes the link toward cardiovascular diseases, diabetes, and hypertension is shown. Therapeutic possibilities influencing on albuminuria and consequences of this are shown, too. Finally, a few dilemmas will be set up as a proposal for further investigation.

Mechanisms of Albuminuria

Mechanisms underlying increased urinary albumin excretion are complex. Plasma albumin filtered in the glomeruli is considered to be the major source of urinary albumin. Most albumin passing (intact-unprocessed albumin) through the glomerular membrane is reabsorbed by proximal tubular cells (known as the *retrieval pathway*). The small amount of albumin not taken up by this pathway is destined for excretion through the *degradation pathway* in tubular cell lysosomes. Thus, normal protein excretion in humans is now recognized to involve the excretion of 1–3 g/day of albumin-derived fragments in combination with less than 25 mg/day of intact albumin (Greive 2001). In pathological states, the glomeruli may become increasingly permeable to circulating albumin due to disturbances in endothelial cell function, basement membrane abnormalities, or podocyte disorders. In addition, inhibition in proximal tubule reabsorption of filtered albumin can also contribute to albuminuria (Russo 2009).

Data suggest that the excreted albumin itself and/or bound ligands, such as fatty acids, initiate a series of events that eventually leads to fibrosis (Chen 2000; Thomas 2002; Arici 2002). In vitro studies have shown that albumin induces changes in tubular cells stimulating the expression of inflammatory and fibrogenic mediators (Wang 1997; Tang 2003; Zoja 1995; Yard 2001). Although inflammation appears to be an important pathogenic factor in a number of renal diseases characterized by albuminuria, the possible pathogenic role of albumin itself is not yet fully elucidated in humans.

Values and Categories of Albuminuria

Previously, the presence of albumin in the urine is called microalbuminuria. This name was changed in albuminuria, because this is not a small molecule of plasma albumin, but a low quantity of albumin present in the urine that could not be detected by standard dipstick test. The current definition of proteinuria, albuminuria, and microalbuminuria is shown in Table 1. Lately, albuminuria is categorized into the following stages: normal or <30 mg albumin/g creatinine (<3.4 mg/mmol), moderately increased (formerly called *microalbuminuria*) from 30 to 299 mg/g (3.4–34.0 mg/mmol), and severely increased (formerly called *macroalbuminuria* or nephrotic range) at ≥300 mg/g (>34.0 mg/mmol) (Levey UpToDate last visit 2015) (Table 2).

Urinary albumin excretion (UAE) can be measured in the urine collected during 24 h or overnight (8–12 h). As UAE changes throughout the day, the amount of albumin excreted over 24 h has been considered the "gold standard." Nevertheless,

Table 1 The terminology and the difference between albuminuria and microalbuminuria

Proteinuria	Abnormal excretion of protein by the kidney including any or all proteins excreted
Albuminuria	Abnormal excretion rate of albumin
Microalbuminuria	Abnormally increased excretion rate of albumin in the urine in the range of 30–299 mg/g creatinine

Table 2 Categories of albuminuria

Categories	UAER mg/24 h	Overnight UAER μg/min	ACR mg/mmol	ACR mg/g
Normal	<30	<20	<3	<30
			Male: <2.5	<17
			Female: <3.5	<25
Moderately increased (previous name *microalbuminuria*)	30–300	20–200	3–30	30–300
Severe increased (previous name *macroalbuminuria*)	>300	>200	>30	>300

Derived from KDIGO (2012) Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease 2013; Joint Specialty Committee of the Royal College of Physicians of London and the British Renal Association (2005, 20–3; Mattix 2002; and The CARI guidelines. Caring for Australasians with Renal Impairment. Sydney: Australian and New Zealand Society of Nephrology http://www.cari.org.au/guidelines.php
Levin 2008 http://www.cmaj.ca/cgi/data/179/11/1154/DC1
UAER urinary albumin excretion rate, *ACR* albumin-to-creatinine ratio

24-h urine collection is a cumbersome procedure. In daily practice albumin can be determined in any urine sample: first morning urine specimens or random spot urine collections. In such cases, its excretion can be estimated by measurement of the albumin alone or albumin-to-creatinine ratio (ACR). Comparisons among all albuminuria measurements and 24-h albuminuria showed that albuminuria from first morning voids is a more reliable alternative to 24-h urinary albumin excretion than spot urine samples for diagnosis of albuminuria and to monitor it over time. If it is decided to collect the first morning sample, then measurement of the ACR is to be preferred over urinary albumin concentration alone (Witte 2009; Jafar 2007).

The cutoff value that traditionally indicates the presence of albuminuria is considered to be albumin excretion equal or greater than 30 mg/24 h. For the diagnosis of kidney disease, guidelines suggest diverse values as the limit of normal albuminuria (Table 2). Some of them recommend different threshold values depending on the individual's sex, so albuminuria is defined as an ACR greater than 2.5 g/mmol creatinine for men and 3.5 g/mmol creatinine for women (Joint Speciality Committee of the Royal College of Physicians of London and the British Renal Association. Guidelines for identification, management and referral of adults with chronic kidney disease. London: Department of Health for England 2005;20–3. http://www.rcplondon.ac.uk/pubs/books/kidney/), or 17 mg/g creatinine for men and 25 mg/g creatinine for women (Mattix 2002), while a threshold value for albuminuria of 30 mg/g (3.4 mg/mmol) regardless of the sex of the patients is recommended by others (National Kidney Foundation 2002 http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm

The CARI guidelines. Caring for Australasians with Renal Impairment. Sydney: Australian and New Zealand Society of Nephrology n.d.. http://www.cari.org.au/guidelines.php Levin 2008 http://www.cmaj.ca/cgi/data/179/11/1154/DC1). Individual laboratories express the ACR in milligrams of albumin per gram of creatinine, while others use albumin in milligrams per millimole of creatinine, so specified limit values are expressed in several units.

There are some limitations that must be considered to maximize the reliability of the ACR. Many conditions can cause a false-positive value for albuminuria. Thus, urine samples should not be collected during: marked acute hyperglycemia; urinary tract infection; marked hypertension; congestive cardiac failure; heavy exercise (due to increased protein catabolism and altered renal circulation); fever, immediately after surgery or after an acute fluid overload; and contamination with seminal or menstrual fluid (which contains more albumin). Also, the value of the ACR depends on the rate of urinary creatinine excretion that, in turn, reflects interindividual differences in muscle mass. Therefore, persons with low muscular mass often have the moderate ACR elevation used to define albuminuria in the absence of a true elevation in absolute albuminuria. That contributes to the difference in values for albuminuria between men and women (Joint Speciality Committee of the Royal College of Physicians of London and the British Renal Association. Guidelines for identification, management and referral of adults with chronic kidney disease. London: Department of Health for England 2005, 20–3. http://www.rcplondon.ac.uk/pubs/books/kidney/, Mattix 2002).

Furthermore, due to variability in urinary albumin excretion, two out of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have developed increased UAE or to have exhibited progression in albuminuria.

Methods of Albuminuria Assessment

Collection of the urine sample is very important when albuminuria is measured, as many factors can alter the value and errors may occur due to inadequate aseptic precautions or improper storage and handling. After collection it is preferable to measure on the same day, but if urine albumin is not estimated immediately, then the urine can be stored at 4 °C. Specimens are stable for at least 2 weeks at 4 °C and 5 months at −70 °C. Freezing samples may decrease the albumin result but mixing immediately before assay eliminates this effect (David et al. 1999).

There are two types of assay used for assessment of albuminuria: colorimetric test strips (semiquantitative) and immunochemistry-based assays (quantitative) (Table 3). Traditionally, detection of albuminuria starts with the dipstick test. These test strips have been used in some countries for screening program of kidney damage (Iseki

Table 3 Methods of albuminuria assessment

Semiquantitative colorimetric assays
Dipstick test: Micral microalbumin urine test strip, CLINITEK Microalbumin
Quantitative immunochemistry-based assays
Immunoturbidimetry
Nephelometry
Radioimmunoassay (RIA)
Chemiluminescent immunoassay (CLIA)
Enzyme-linked immunosorbent assay (ELISA)

Derived from Martin (2011)

1996; Ležaić 2011). Some disadvantages are recognized. The test is semiquantitative and insensitive for reliable detection of albumin in concentration ranges around 300 mg/day. Furthermore, concentrated urines may give a color change in the positive range of a reagent strip device even though protein loss remains normal and vice versa. False-positive results may occur if the urine is alkalinized (e.g., due to urinary tract infection) or in the presence of quaternary ammonium compounds that alter the urine pH. The performance of reagent strips is operator dependent (Rumley 2000) and affected by the presence of colored compounds such as bilirubin and certain drugs (e.g., ciprofloxacin, quinine, and chloroquine) (Scotti da Silva-Colombeli 2007).

Immunochemical assays (immunonephelometry, immunoturbidimetry, radioimmunoassay, enzyme-linked immunosorbent assay) are based on the interaction of urinary albumin with anti-albumin antibodies in the reagents. With these methods it is possible to detect very small concentrations of albumin in the urine. Each method has advantages and disadvantages, and the choice depends on local experience and technical support. All methods have similar precision, sensitivity, and range. Currently urinary albumin is predominantly measured in diagnostic laboratories using immunoturbidimetric assays (Martin 2011). Radioimmunoassay (RIA) and chemiluminescent immunoassay (CLIA) are highly sensitive, specific, and reproducible methods. Disadvantages are unavailability, the cost factor, proper infrastructure needed, and radioactive hazards (Agarwal 2002).

Measuring albumin in the urine is complex, especially as multiple species of intact albumin (immunoreactive albumin and immuno-unreactive albumin) and albumin-derived fragments have been reported (Comper 2003). Albumin fragments are not detected by conventional immunoassays commonly used to measure urinary albumin. At present there is no diagnostic tool available to measure albumin fragments in urine routinely.

Potential Applications to Prognosis, Other Diseases, or Conditions

Albuminuria (ACR more than 3 mg/mmol) is a marker for kidney disease in apparently healthy subjects as well as in patients with different comorbidities such as diabetes, hypertension, or obesity and is widely used in clinical practice (Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. NICE guidelines [CG182] Published date: July 2014). It may precede the appearance of type 2 diabetes mellitus, being present in the insulin resistance syndrome. Also albuminuria is considered to be a marker of cardiovascular risk in the general population (Mykkanen 1998; MacIsaac 2004; Thomas 2011). In addition, albuminuria has predictive significance, i.e., the higher the albuminuria the higher the risk for mortality (cardiovascular and all cause), progression of chronic kidney disease (CKD), and end-stage renal disease (ESRD) independent of eGFR as a measure of kidney function. No apparent threshold value was found in the general population and a population at high risk for kidney disease (Matsushita 2010; Gansevoort 2011; van der Velde 2011). All this derives from the results of large studies conducted over the last three decades.

Screening for Chronic Kidney Disease in the General Population

Screening for chronic kidney disease in the general population is usually performed using eGFR and albuminuria. Recent data have shown a positive correlation between UAE and rate of decline in eGFR, i.e., patients with higher levels of UAE had a more rapid decline in eGFR, especially beyond a UAE of above 150 mg/24 h. The average rate of renal function decline in the UAE category above 300 mg/24 h was four times more rapid than that for UAE less than 15 mg/24 h (van der Velde 2009). In Table 4 the predictive cutoff albuminuria values for renal replacement therapy (RRT) start during 6 years of follow-up was shown. During follow-up a UAE concentration above 20 mg/L identified individuals with the risk of RRT with 58 % sensitivity and 92 % specificity. The likelihood ratio of a positive test result showed that an individual at risk, i.e., with a history of hypertension or diabetes and a UAC >20 mg/L, has 24.3 times the previous odds to start RRT during follow-up; for a UAC >200 mg/L, this odds to start RRT is 118.7. These data suggest that screening for albuminuria might be effective to identify individuals at risk for developing ESRD (van der Velde 2009).

Albuminuria is a risk factor not only for ESRD but also acute kidney injury and progressive CKD in both general and high-risk populations (Gansevoort 2011). Hazard ratios for renal outcomes at different ACR presented in Table 5 show similarity between general population and high-risk cohorts. The patterns for ESRD were less steep in the high-risk cohorts compared with the general population, whereas the patterns for acute kidney injury and progressive CKD were similar in the general population cohorts and high-risk cohorts. These associations are independent of other cardiovascular risk factors (Gansevoort 2011) (Table 6).

Lower eGFR and higher albuminuria were each independently associated with mortality and ESRD as it was shown in the meta-analysis of 13 cohorts, including 21,688 individuals selected because of CKD (Astor et al. 2011). This risk increased progressively with every higher level of albuminuria: an eightfold higher ACR was

Table 4 Various cutoff values of albumin excretion rate in a single first morning void urine to identify individuals who started RRT during follow-up

AER category mg/L	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR−
General population						
>20	58	92	0.8	99.9	7.43	0.46
>200	36	99	5.7	99.9	54.44	0.65
With known HTA/DM						
>20	44	98	2.6	99.9	24.3	0.57
>200	31	99	11.6	99.9	118.7	0.69
Age >55 years						
>20	44	96	1.3	99.9	12.1	0.58
>200	27	99	7.1	99.9	68.9	0.74

Derived from van der Velde (2009)
AER albuminuria excretion rate, *LR+* likelihood ratio of a positive test, *LR−* likelihood ratio of a negative test, *NPV* negative predictive value, *PPV* positive predictive value
HTA arterial hypertension, *DM* diabetes mellitus

Table 5 Pooled hazard ratios for renal outcomes, i.e., end-stage renal disease, acute kidney injury, and progressive chronic kidney disease by albuminuria categories for the general and high-risk population

	Albumin-to-creatinine ratio 30–299 mg/g	Albumin-to-creatinine ratio ≥300 mg/g
General population		
ESRD	12 (7.9–18.1)	72.1 (64.3–121)
AKI	2.5 (1.7–3.7)	6.0 (4.5–8.0)
Progressive CKD	3.1 (2.5–3.8)	11.2 (5.8–21.5)
High-risk patients		
ESRD	4.3 (2.6–7.1)	38.1 (15.6–93.5)
AKI	2.7 (2.2–3.4)	7.4 (5.5–9.8)
Progressive CKD	2.2 (1.9–2.7)	9.9 (6.7–14.5)

Derived from Gansevoort (2011)
Pooled adjusted hazard ratios (95 % confidence interval) for ESRD and acute kidney injury and pooled adjusted odds ratios (95 % confidence interval) for progressive CKD
ESRD end-stage renal disease, *AKI* acute kidney injury, *CKD* chronic kidney disease

Table 6 Adjusted hazard ratio (95 % confidence interval) for mortality, by albuminuria category

	HR	95 % confidence interval
Albumin-to-creatinine ratio, mg/g		
30–299	1.5	1.28–1.75
300–999	1.85	1.08–3.16
>1,000	2.7	1.74–4.26
Estimated glomerular filtration rate, ml/min/1.73 m^2		
30–44	1.35	1.23–1.49
15–29	2.25	1.81–2.79
<15	3.74	2.69–5.20

Derived from Astor et al. (2011)
Adjusted for age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol concentration

associated with an estimated 40 % higher risk of death and an estimated threefold higher risk of ESRD after adjustment for eGFR (Astor et al. 2011).

For evaluation of chronic kidney disease, albuminuria as a marker of kidney damage is combined with eGFR as a measure of kidney function. Both markers were used in the classification of chronic kidney disease (CKD) (National Kidney Foundation 2002; NICE clinical guideline 73 http://guidance.nice.org.uk/cg73, American Diabetes Association. Standards of Medical Care in Diabetes 2014). That is why regular screening for albuminuria is of utmost importance, especially at stages 1 and 2 of CKD, where therapeutic interventions may be of benefit to prevent or delay the development of renal injury.

Albuminuria is the most widely used clinical marker of diabetic nephropathy and has been recognized as a predictor of progression to ESRD in both type 1 and type 2 diabetes (Perkins 2010; Adler 2003). It is one of the earliest markers of diabetic

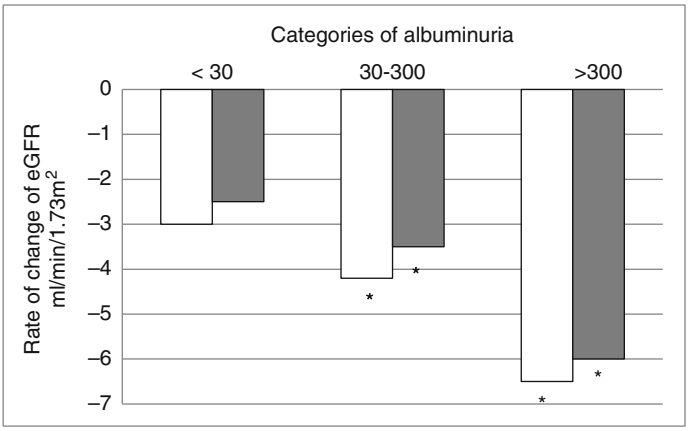

Fig. 1 Comparison of the rate of the change in estimated glomerular filtration rate (*eGFR*) monitored at least 5 years, adjusted for age and baseline eGFR in diabetic women and men, and classified according to the average urinary albumin excretion at baseline. *White* (women) and *gray* (men) bars; *$p < 0.001$ versus normal albuminuria value (Derived from Babazono (2009))

nephropathy that precede severely increased albuminuria (>300 mg/24 h). The impact of elevated UAE in predicting future renal function loss in subjects with diabetes was emphasized in the 1980s (Mogensen 1986; Parving 1982). During these years, the terminology of "early diabetic nephropathy" was introduced to indicate diabetic subjects with albuminuria. In this early phase of diabetic nephropathy, eGFR is usually well preserved. Early nephropathy contrasts with the later phase of overt nephropathy in which albuminuria increases into overt proteinuria and the eGFR falls below 60 ml/min finally progressing to the level of ESRD. Documentation of the early phase of kidney damage with albuminuria but still normal eGFR has helped us to understand better the impact of albuminuria during the loss of renal function in diabetes. Moreover, it led to the demonstration that early intervention by interfering in the renin–angiotensin–aldosterone system (RAAS) slows the progression of nephropathy in diabetic patients (Parving 2001; Ruggenenti 2004). The changes between these albuminuria states represent a hallmark of disease progression or regression (American Diabetes Association 2014). More recent studies have shown that an increase in albuminuria, even within the range that is currently considered normal, indicates higher renal risk (Babazono et al. 2009; Gansevoort 2011). In patients with type 2 diabetes monitored for at least 5 years, higher albuminuria at baseline was associated with a faster decline in renal function (Fig. 1), according to the data of Babazono T and coworkers' study (Babazono 2009). Importantly, although within the normal range, it was calculated that albuminuria of ×10 mg/g in women or ×5 mg/g in men was associated with a significantly greater rate of renal function decline (Babazono 2009). Not only the albuminuria level itself but also changes in albuminuria (ACR within 30–300 mg/g) over time predict renal or cardiovascular risk changes. In patients with type 2 diabetes and ACR 30–300 mg/g, those subjects in whom albuminuria decreased by more than

50 % over 2-year follow-up had a subsequent renal function decline of −1.8 ml/min per year. In contrast, in subjects without a 50 % reduction in albuminuria, long-term renal function decline was significantly greater, being −3.1 ml/min per year (Araki 2007).

During the 1990s, there was growing evidence that albuminuria is important for progressive reduction of renal function in nondiabetic renal disease. The findings from large clinical trials showed the beneficial effect of lowering albuminuria by using agents that interfere with the RAAS to prevent progression to ESRD (The Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN) Group 1997; Jafar 2003). This focused attention on treatment of renal patients for albuminuria and not only for high blood pressure (De Jong 1999).

Albuminuria as a Cardiovascular Disease Marker

Some evidence suggested that high albuminuria is associated with cardiovascular risk. Three large studies conducted in the general population showed that high albuminuria predicts cardiovascular risk (Hillege 2001; Romundstad 2003; Yuyun 2004). The predictive power of albuminuria on cardiovascular risk is independent of other known cardiovascular risks. Hence the idea that albuminuria should be combined with Framingham scores for assessment of cardiovascular risk is suggested as a primary prevention strategy with higher efficiency (Asselbergs 2004b). In patients with several cardiovascular risk factors, albuminuria predicts outcome, even below the level taken as normal (Mann 2004).

Albuminuria and Hypertension

Albuminuria may not only be the consequence of but it may also precede the development of hypertension (Forman 2008; Scheven 2013). Albuminuria is found in 11–40 % of persons with hypertension, the prevalence increasing with age and the duration of hypertension (Rossa 2000; Özyilmaz 2013). According to the PREVEND study results, in subjects with elevated albuminuria and newly discovered hypertension or hypercholesterolemia, the cardiovascular risk exceeded by 20 % the risk in normoalbuminuric hypertensive patients. Thus, detecting albuminuria might also help the clinician decide when to initiate antihypertensive therapy. In addition, identification of target organ damage is an indication for treatment in patients with lower blood pressure (European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension 2003).

Link Between Albuminuria and Increased Cardiovascular and Renal Risk

The pathophysiological mechanisms linking albuminuria to cardiovascular and renal risk are still not fully understood, but much evidence appears to connect any level of

UAE to generalized loss of vascular endothelial function in many organs including kidneys (Solbu 2009; Foster 2008).

Albuminuria as a Target for Treatment

Albuminuria can be used as a target for treatment for primary and secondary prevention of renal and cardiovascular disease development. Previous studies showed that the degree of albuminuria reduction was associated with a more beneficial renal outcome in long-term follow-up (Apperloo 1994; Rossing 1994). Therefore, several measures were introduced in clinical practice in order to reduce albuminuria, such as dietary protein restriction (El Nahas 1984), nonsteroidal anti-inflammatory drugs (Vriesendorp 1986), angiotensin-converting enzyme inhibitors, and angiotensin II receptor antagonists (Gansevoort 1994). Thus far, no trials have shown that lowering albuminuria in the early phase (i.e., microalbuminuria with a GFR >60 ml/min, namely, stage 1 or 2 CKD) slows the progressive decline of renal function. On the other side, there is some evidence that ACE inhibition in subjects with nondiabetic albuminuria may prevent future cardiovascular events (Asselbergs 2004). Also, measurement of albuminuria can help to determine whether or not a patient with hypertension should be treated, how aggressive should the therapy be, and what medications should be used (European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension 2003).

Not Resolved Questions

Although the strong association between age and kidney function is well established, the clinical significance of CKD in older asymptomatic people remains disputable. In addition, it is unclear what portion of this decline is due to the higher prevalence of risk factors for kidney disease at older ages, such as hypertension, diabetes, and vascular disease. It seems to be worth investigating:

- The cutoff value of albuminuria that contribute to the accurate diagnosis of CKD in the elderly
- The introduction of standardized laboratory tests that will clearly separate the whole molecule, antibodies' recognizable molecules, and fragments of albumin in the urine

Summary Points

- This chapter focuses on albuminuria: definition, classification, importance in renal disease detection, prognostic significance, mechanism of occurrence, and methods of estimation.

- Currently, albuminuria categorizes into the following stages: normal, less than 30 mg/g (<3.4 mg/mmol); moderately increased, 30–299 mg/g (3.4–34.0 mg/mmol); and severely increased albuminuria, ≥300 mg/g (>34.0 mg/mmol).
- Albuminuria is a marker for kidney disease in apparently healthy subjects and in patients with different comorbidities.
- Screening for albuminuria is important to identify individuals at risk for developing end-stage renal disease, acute kidney injury, and progressive chronic kidney disease, as well as cardiovascular disease and all-cause mortality in both general and high-risk population (diabetes, cardiovascular disease, hypertension, and older patients).
- Albuminuria is the most widely used clinical marker of early stage of diabetic nephropathy when the glomerular filtration rate (GFR) is usually well preserved.
- The predictive power of albuminuria on cardiovascular risk is independent to other known cardiovascular risks.
- Albuminuria can be used as a target for treatment for primary and secondary prevention of renal and cardiovascular disease development.

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