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LETTER TO EDITOR

Microalbuminuria detection: Analytical challenges and future directions

Kamal Kishor Maru[1], Deepak Kumar[2], Rajasri Bhattacharyya[1], and Dibyajyoti Banerjee[1*]

[1]Department of Experimental Medicine and Biotechnology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[2]School of Bioengineering and Food Technology, Faculty of Applied Sciences and Biotechnology, Shoolini University, Bajhol, Himachal Pradesh, India

Dear editor,

The clinical recognition and detection of urinary albumin excretion (albuminuria) has deep historical roots. Ancient texts such as the Charak Samhita describe urine inspection for diagnostic purposes, but systematic qualitative and quantitative analysis emerged only in the modern era.[1,2]

By the 15th century, European physicians had observed that frothy or cloudy urine could indicate disease, providing an early empirical basis for the field of nephrology. A breakthrough came in 1836, when Richard Bright demonstrated the association between proteinuria and renal pathology, establishing urinary protein analysis as a key tool in clinical medicine.[3]

However, the detection methods available then—boiling, heat coagulation, and nitric acid testing—were nonspecific and detected only gross proteinuria, failing to identify low but clinically significant levels of albumin.[4]

True progress occurred in the late 20th century with the introduction of immunochemical assays such as immunoturbidimetry and immunonephelometry, which enabled sensitive detection of low levels of albumin (i.e., microalbuminuria).[4]

Microalbuminuria refers to the excretion of 30–300 mg/g of creatinine in a spot urine sample or 30–300 mg of albumin per day in a 24-h urine collection, a level below the detection threshold of conventional dipstick or heat coagulation tests.[5,6]

Detecting such low concentrations marked a milestone in preventive nephrology and metabolic disease monitoring, such as diabetic kidney disease and cardiovascular diseases. The evolution of albumin detection, from gross proteinuria using classical methods to microalbuminuria using modern ultrasensitive immunoassays, illustrates growing analytical sophistication in medicine. However, analytical and conceptual challenges persist, necessitating improved, more specific, and clinically meaningful detection strategies.

Albuminuria, particularly in its earliest detectable form—microalbuminuria—is a key marker of glomerular injury. Glomerulopathy underlies not only primary renal diseases but also systemic conditions such as diabetes mellitus, hypertension, obesity, sickle cell anemia, heavy metal toxicity, and vasculopathies, all characterized by disruption of the glomerular filtration barrier and subsequent albumin leakage.[7,8]

Among these, diabetic kidney disease represents a major global health challenge,

***Corresponding author:**
Dibyajyoti Banerjee
(dibyajyoti5200@yahoo.co.in)

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contributing substantially to morbidity and mortality.[9] The detection of microalbuminuria has shifted diabetic kidney disease management from reactive to proactive care. Early identification allows timely interventions—glycaemic control, lifestyle changes, and pharmacologic therapies—that can slow or even reverse glomerular damage. Thus, microalbuminuria functions not only as a biomarker of renal injury but also as a prognostic tool that guides clinical decision-making.

For the detection of microalbuminuria, immunochemical methods have become the mainstay in clinical laboratories, particularly due to their superior specificity compared to dye-binding techniques (e.g., bromocresol green and bromocresol purple assays) and traditional methods (e.g., heat coagulation, boiling, and nitric acid testing).[6,10]

Current immunochemical methods provide significantly greater specificity by relying on antigen–antibody interactions to quantify urinary albumin. Immunoturbidimetric assays measure turbidity from immune complex formation, while immunonephelometry detects scattered light from these complexes. Although both methods improve upon dye-based techniques, they have limitations.

One notable issue is the Hook effect (also termed the prozone phenomenon), where very high antigen concentrations saturate antibodies and prevent measurable immune complex formation, paradoxically producing falsely low readings in cases of overt albuminuria.[11] Although the Hook effect is primarily a concern in high-range albuminuria rather than microalbuminuria, no systematic study has conclusively evaluated its prevalence or impact in early-stage disease. Instrument and kit manufacturers typically implement design safeguards to reduce this risk, yet empirical verification remains limited.

Due to limitations of dye-based and immunochemical methods, high-performance liquid chromatography (HPLC) has been explored as an alternative for urinary albumin detection. Size-exclusion HPLC often reports higher albumin levels than immunoassays, with mass spectrometry and electrophoresis confirming the presence of immune-unreactive albumin, a form of albumin not detected by immunochemical-based assay.[4,12]

On the other hand, reverse-phase HPLC improves separation and specificity but is technically demanding, resource-intensive, and unsuitable for routine clinical use, particularly in low- and middle-income settings. A further limitation is the risk of co-elution of structurally similar proteins or peptides, which can compromise analytical accuracy.[13]

Despite its limitations, HPLC-based methods have been instrumental in confirming the presence of immune-unreactive albumin. Several studies have shown that HPLC detects higher urinary albumin levels in diabetic patients compared to immunochemical assays, with some samples classified as normoalbuminuric by immunoassays falling within the microalbuminuria range by HPLC.[14] This highlights a limitation of immunochemical methods—the inability to detect structurally modified albumin that no longer binds antibodies—potentially leading to underestimation of clinically significant albuminuria.

In summary, while HPLC is impractical for routine diagnostics due to cost and complexity, it has confirmed that immune-unreactive albumin is real, biochemically verified, and clinically important. This fraction likely represents early molecular changes such as post-translational modifications or conformational shifts that reduce antibody binding. Detecting this hidden pool is crucial for developing diagnostic methods that identify both immunoreactive and immune-unreactive albumin, enabling earlier and more accurate detection of kidney damage. Overcoming this analytical gap requires techniques that assess albumin based on functional or structural properties, moving beyond antibody dependence and addressing limitations that have persisted for decades in nephrology.

Conflict of interest

The authors declare no conflict of interest.

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