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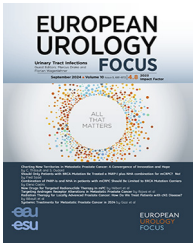

Mini Review

Interleukins in Urine and Blood as Markers of Infection and as Risk Factors for Systemic Conditions

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Abstract

Interleukins are a diverse group of cytokines that play a crucial role in controlling immune responses and have potential as biomarkers. This mini review evaluates 12 recent papers linking urinary interleukins to both urinary infection and systemic diseases. While measurement of serum interleukins can indicate systemic inflammation, urinary interleukins provide more specific insights into renal or urinary tract inflammation. Urinary interleukins such as IL-8, IL-18, and IL-1β show promise for diagnosing urinary tract infections and other conditions. However, their diagnostic utility is complicated by their wide distribution in the body and patient-related factors. Advances in analytical techniques have enhanced the sensitivity and speed of interleukin measurement, improving their clinical utility.

Patient summary: This review highlights research showing that measurement of molecules associated with the immune system in urine samples can help in diagnosing and monitoring disease affecting the urinary tract and kidneys. These urine tests can provide more specific information about infections than blood tests can.

1. Background

Interleukins, a diverse group of cytokines that control immune responses, have attracted significant attention as potential biomarkers. Elevated levels of specific interleukins in urine and blood have been correlated with various infectious agents and inflammatory conditions, offering the potential for early detection and monitoring. For this mini review we selected 12 papers that reflect recent findings showing that urinary interleukins are associated with not only urinary tract disease but also systemic disease. While serum interleukin levels provide information about systemic inflammation, the correlation between urinary and serum levels depends on the specific interleukin and the pathology. Thus, for certain systemic diseases and renal pathologies, measurement of urinary interleukins can offer more specific insight into localised renal or urinary tract inflammation with greater clinical utility than serum interleukins. Traditionally, urinary tract inflammation has been inferred from results of urine dipstick tests and microbiological investigations. Table 1 summarises studies on the use of different interleukins.

Interleukins enter the bloodstream from sites of inflammation or infection, where they circulate throughout the body to exert their effects on target cells. Interleukins found in urine are from three main sources. (1) Low-molecular-

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Table 1 – Summary of studies on the use of urinary interleukins

IL	Mw (kDa)	Assay technique	NUC (pg/ml)	Trial and reference	Sample size and outcome
IL-6	24	ELISA	10–19	Differentiation of AP from LUTI in children [10]	n = 43 trial; n = 38 control p = 0.03; AP vs LUTI NS
IL-8	11.1	ELISA	50–130	Differentiation of AP from LUTI in children [10]	n = 43 trial; n = 38 control p = 0.05 AP; p = 0.03 LUTI AP vs LUTI NS
		ELISA		Urine biomarkers associated with PCR-positive UTI [11]	n = 1132 PCR^+ samples p < 0.0001
		ELISA		Urine biomarkers associated with rUTI in postmenopausal women [12]	n = 57; p < 0.0001
IL-9	14	Luminex assay [a]	<0.5	IL-9 as a marker of podocyte injury in diabetes type 1 [2]	n = 53; inversely relationship between IL-9 and extracellular vesicles (p = 0.003)
		ECL		AIN prognosis and prediction of corticosteroid responsiveness [8]	n = 55; IL-9 could be used to test ISTx efficacy in AIN patients
IL-10	37	Cytometric bead array	0–3	Role of IL-10 in gestational diabetes [3] Compared NG-C, NG-UI, GDM-C, and GDM-I groups	NG-C: n = 28; NG-UI: n = 28; CDM-C: n = 20; GDM-I: n = 21
IL-15	14-15	ELISA	1.6–4.6	Use of IL-15 in children with idiopathic nephrotic syndrome [6]	n = 30 test; n = 44 control p < 0.0001
IL-16	15.5	ELISA	<0.5	IL-16 evaluation as a biomarker for proliferative LN and differentiation from active and inactive nrSLE [5]	LN: n = 84; active nrSLE n = 63; inactive nrSLE: n = 73; MPC: n = 48; p < 0.0001
IL-18	24	CLIA	0–163	Assay development for IL-18 [1]	n = 62 test; n = 162 control Detection limit 0.0044 ng/ml Linear range 0.01–2.7 ng/ml
		ELISA		Children and adolescents with hyperuricaemia [4]	n = 48 test; n = 25 control p < 0.01
		ELISA		Prediction of kidney injury in acute paediatric sepsis [7]	n = 40 trial; n = 73 control p < 0.001
		ELISA		Changes in IL-18 in patients treated with vancomycin [9]	26 patients before and after vancomycin; p = 0.015
		ELISA		Urine biomarkers associated with rUTI in postmenopausal women [12]	n = 57; p < 0.0001

AIN = acute interstitial nephritis; AP = acute pyelonephritis; CLIA = chemiluminscence immunoassay; ECL = electrochemiluminescence; ELISA = enzyme-linked immunosorbent assay; GDM-C = gestational diabetes mellitus continent; GDM-I = gestational diabetes mellitus with pregnancy-specific urinary incontinence; IL = interleukin; ISTx = immunosuppressive therapy; LN = lupus nephritis; LUTI = lower urinary tract infection; MPC = matched population control; M_w = molecular weight; NG-C = normoglycemic continent; NG-UI = normoglycemic with pregnancy-specific urinary incontinence; NS = not significant; NUC = normal urinary concentration; PCR = polymerase chain reaction; UTI = urinary tract infection; rUTI = recurrent UTI; SLE = systemic lupus erythematosus; nrSLE = nonrenal SLE.

[a] Cytokine/chemokine panel.

weight interleukins present in the bloodstream are filtered by the kidneys and subsequently excreted in urine. (2) Interleukins are locally produced within the urinary tract in response to inflammation or infection. Immune cells present in the urinary tract, such as macrophages and lymphocytes, release interleukins as part of the immune response to pathogens or tissue damage. (3) Kidney diseases that lead to an increase in the permeability of the glomerular filtration membrane can result in greater leakage of interleukins from the bloodstream into urine, resulting in abnormally high concentrations in urine.

2. Review of papers

The immunological techniques used to measure interleukins have become increasingly sensitive, improving from ng/ml to pg/ml levels. The assay speed has also improved. For example, in 2023 Fu et al [1] described a new chemiluminescence immunoassay that is simple to operate and has a wide dynamic range (0.01–2.7 ng/ml) and a low detection limit (0.0044 ng/ml) with an assay time of 30 min. In comparison, traditional enzyme-linked immunosorbent assay methods can take many hours to perform.

A number of papers have reported that measurement of urinary interleukins is beneficial in detecting or monitoring systemic disease. For example, in type 1 diabetes, urinary IL-9 is associated with early podocyte injury, indicating its potential role in diabetic kidney damage. It was noted that there was a negative relationship between urinary IL-9 and podocyte-derived extracellular vesicles, with similar findings in females and males. The results indicate that IL-9 has a protective effect on podocytes in diabetic patients [2].

Elevated urinary levels of IL-18 were observed in patients with diabetic nephropathy, indicating kidney inflammation [1]. In a study ofgestational diabetes cases, pregnant women with urinary incontinence had elevated urinary IL-10 levels and IL-10 was associated with high serum viscosity [3]. In hyperuricemia, a systemic condition prevalent among children and adolescents that can lead to kidney damage due to deposition of uric acid crystals and a subsequent inflammatory response, patients had elevated IL-18 levels. Interestingly, there was no increase in serum levels of IL-18, suggesting that the IL-18 in urine was a result of local renal inflammation [4].

Other systemic conditions, such as chronic inflammation associated with autoimmune disease, can result in kidney damage, as in patients with systemic lupus erythematosus (SLE) and the associated complication of lupus nephritis (LN). Elevated urinary IL-16 levels were associated with LN. Urinary IL-16 concentrations could differentiate between LN and non-renal SLE [5]. Serum IL-16 did not differentiate between lupus classes, suggesting that urinary measurements may provide better discrimination of renal involvement. In a study developing a sensitive method for measurement of urinary IL-18, elevated urinary IL-18 concentrations were detected in a number of systemic conditions, including multiple myeloma, Sjogren's syndrome, SLE, allergic purpura nephritis, nephrotic syndrome, chronic renal failure, and diabetic nephropathy, and after cardiac surgery [1].

Urinary interleukins are typically elevated in kidney diseases, reflecting inflammation or infection. In children with idiopathic nephrotic syndrome, elevated IL-15 levels were observed in both serum and urine during the active phase of the disease, but the elevation was greater in urine [6]. Elevated urinary IL-18 levels were detected in patients with chronic renal failure, indicating ongoing inflammation. Elevated urinary IL-18 also predicted the onset of acute kidney injury in paediatric patients with sepsis, and had better sensitivity than KIM-1 and IGFBP7 [7].

Measurement of urinary interleukins also seems to be beneficial in monitoring responses to certain drugs. In a study by Moledina et al [8] in patients with acute interstitial nephritis, elevated urinary IL-9 was associated with lower kidney function. Patients with higher urine IL-9 concentrations and better kidney function before disease onset appeared to benefit from corticosteroid treatment [8]. In another study, a significant increase in urinary IL-18 after vancomycin therapy was associated with potential kidney damage [9].

3. Urinary tract infection

Measurement of interleukins for the diagnosis and prognosis of urinary tract infection (UTI) has been studied for many years. A recent study showed that urinary IL-6 and IL-8 levels were elevated during the acute phase of a UTI, but they did not differentiate between upper and lower UTIs. IL-8 was particularly good at discriminating between the acute and convalescent phases of infection [10].

A study on urine samples measured positive for infection by polymerase chain reaction (PCR), compared IL-8 to two other markers, neutrophil gelatinase-associated lipocalin and IL-1β. IL-8 positivity was greater in the PCR^{+} group than in the PCR^{-} group, and a greater number of samples were positive for IL-8 than for the other two biomarkers. The authors also investigated 30 causative organisms of UTI, of which *Escherichia coli* was the most prevalent and *Pantoea agglomerans* was the least prevalent. Levels of these biomarkers increase in urine as resident and recruited immune cells rapidly mount a pro-inflammatory response to pathogens detected in the urinary tract. The study results strongly indicate that urinary biomarker levels, especially IL-8, are strong predictors of an inflammatory response associated with UTI [11].

A study by Ebrahimzadeh et al [12] provided further evidence that urinary inflammatory cytokines have potential as diagnostic biomarkers of UTI. The authors found that postmenopausal women with UTI had elevated levels of IL-8, IL-18, and IL-1β, while women without UTI had higher levels of the anti-inflammatory interleukins IL-13 and IL-4. The findings indicated that IL-8 and IL-18 seem to be the main candidate biomarkers for UTI diagnosis.

4. Conclusions

Urinary interleukins provide better clinical sensitivity and specificity than serum interleukins for certain systemic conditions involving the kidneys and urinary tract, and indicate localised inflammation. However, the technology is still at a stage that is too early for implementation in clinical practice. Additional efforts are needed to establish which biomarkers have potential for use in routine practice. A recent publication suggests that various biomarkers, includ-

ing IL-16, can improve the diagnostic accuracy in identifying UTI versus asymptomatic bacteriuria in older women with pyuria [13]. Once the most appropriate biomarkers are identified, technology for rapid, reliable, and affordable measurement will be needed.

The papers we reviewed suggest that measurement of urinary interleukins could be an effective method for differentiating lupus nephritis, diabetic nephropathy, and acute kidney injury. While serum interleukins reflect systemic inflammatory responses, their levels do not always correlate with the severity of localised kidney disease.

Conflicts of interest: The authors have nothing to disclose.

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