Interstitial nephritis; a rising threat with different aspects

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Abstract
Interstitial nephritis is gradually becoming a common cause of acute renal failure (ARF) and chronic kidney disease (CKD). In order to prevent interstitial nephritis, it is necessary to observe some modalities; understanding risky conditions, detecting patients at risk, and discontinuing the harmful drugs are the main preventive and therapeutic strategies which can be adopted to control interstitial nephritis. Administration of a short course of oral or intravenous glucocorticoids has also been proposed. On the other hand, delayed diagnosis impairs the final recovery.

Keywords: Acute interstitial nephritis, Chronic interstitial nephritis, Drug hypersensitivity, Chronic kidney disease, Acute renal failure, Interstitial nephritis, Interstitial inflammation

Introduction
Interstitial nephritis is gradually becoming a common cause of acute renal failure (ARF) and chronic kidney disease (CKD). In order to prevent interstitial nephritis, it is necessary to observe some modalities; understanding risky conditions, detecting patients at risk, and discontinuing the harmful drugs are the main preventive and therapeutic strategies which can be adopted to control interstitial nephritis. Administration of a short course of oral or intravenous glucocorticoids has also been proposed. On the other hand, delayed diagnosis impairs the final recovery.

Materials and Methods
In order to conduct this mini-review, we collected and used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO, and directory of open access journals (DOAJ). We searched a combination of the following keywords and/or their equivalent terms; acute interstitial nephritis, chronic interstitial nephritis, drug hypersensitivity, interstitial inflammation, chronic kidney disease, acute renal failure, and interstitial nephritis. First we investigated and assessed the titles and abstracts of review articles, clinical trials, cohort studies, case-control studies, and reports related to the studied topic.

Interstitial nephritis; a rising issue
In a recent comprehensive registry report in Spain, a total of 17680 kidney biopsies were investigated and the prevalence of AIN among all the cases of ARF was about 13% which showed a large increase in the prevalence of the disease as compared with the previously reported prevalence which was 3.6% in 1994–1998 report (1). AIN occurs in extremely diverse conditions and most cases of the disease emerge in a similar form. However, if diagnosed on time, the patients show an appropriate response to treatments (1,2). The common clinical manifestations are hematuria, leukocyturia, and non-nephrotic range proteinuria. Eosinophiluria may also occur in the patients, however it is not considered as a good symptom for discriminating AIN (4). Sometimes this disease may result in symptoms similar to those of IgA nephropathy. In some cases of AIN,
Core tip
Understanding risky conditions, detecting patients at risk, and discontinuing the harmful drugs are the main preventive and therapeutic modalities, which can be adopted to control of interstitial nephritis.

Interstitial nephritis as a combination of different issues
About 100 drugs are considered in hypersensitivity related AIN and CIN. The number of agents contributing to the initiation of the disease is increasing. Cell-mediated immunity is probably the most common mechanism. Apart from the characteristics of contributing agents, patients’ immune system and diversities in drug pharmacodynamics can affect the risk of AIN development (11,12). For example, some recent common drugs such as rosuvastatin, linezolid, and clindamycin are also added to the list of AIN etiology (12,13). Proton pump inhibitors are among the newly listed risk factors. According to being exposed to a high blood flow and the need for oxygen supply, kidney is an organ vulnerable to minute hemodynamic changes and is affected by the concentration of circulating substances. Hence, drugs and toxins may reach a high concentration in the nephrons where water is reabsorbed; such a condition results in higher concentration of substances and makes nephrons more vulnerable to toxins (1-3).

Endogenous, environmental, and pharmacological compounds could act as damaging agents. Moreover, in some conditions, they could act synergistically and damage the body organ. Among such conditions and agents, we may note the following conditions; radiocontrast-induced hemodynamic alternations, non-steroidal anti-inflammatory drugs (NSAIDs), induced regional perfusion changes, and antimicrobials acting in a synergetic way (14,15). Furthermore, toxins that affect other major organs also have some harmful effects on kidney. In this condition, severe volume depletion and muscle breakdown also indirectly can affect renal function. Other endogenous nephrotoxins such as muscle breakdown agents and even necrotic material could act as potential nephrotoxins (5,16,17).

Distant organ inflammation can indirectly affect renal function and results in intrarenal hemodynamic changes and interstitial inflammation (18,19).

A latent and asymptomatic decline of glomerular hyperfiltration happens in those who regularly consume large amounts of protein. This condition may frequently happen in bodybuilders. Accordingly, excessive protein consumption can induce hyperfiltration and glomerulosclerosis. It is a finding that has been confirmed by various experimental studies (17-19). Therefore, a balanced diet that contains antioxidants and natural vasodilators may ameliorate the nephrotoxicity caused by high-protein diet and other toxins. The risk of concurrent acute tubular necrosis and interstitial nephritis is high in several situations, particularly in diabetic patients who are taking different medicines; in such a condition, nephrotoxicity and superimposed interstitial nephritis could emerge concurrently (20-22).

Prevalence of AIN
It is difficult to estimate the real prevalence of AIN. Schwarz et al reviewed more than 1000 renal biopsies and found that of all cases, 6.5% had AIN. Moreover, 85% were drug-induced, and NSAIDs were the major group of drugs involved in development of the disease (23). It is possible to recover renal function through eliminating the risk factor, but renal function never returns to its previous normal state and unfortunately 60% of NSAID-induced AIN are left with some degrees of permanent renal damage and chronic renal insufficiency (2,23).

Recent studies have reported a sharp increase in the prevalence of interstitial nephritis and toxic nephropathy which may be due to increased administration of synthetic substances (24,25). In view of that, dietary supplementation of antioxidants should be reconsidered as a potential preventive modality (26,27).

Especial features of AIN
The excessive risk of kidney disease among disadvantaged and poor populations could be due to their environmental and occupational exposure to nephrotoxins. The exposure to lead, cadmium, and mercury is higher among people who are living in slums and consuming unhealthy drinking water (28). Chronic hyperuricemia leads to chronic interstitial nephritis; when this disease coexists with gout, the possibility of lead intoxication should be considered (18).

The first case of aristolochic-induced CIN was reported in Belgium in 1990. Patients had rapidly progressive renal dysfunction and all of them had a history of Chinese herb consumption (29). Sarcoidosis is a rare cause of interstitial nephritis and non-caseation. Additionally, caseation granuloma of tuberculosis, silicosis, and histoplasmosis are the other etiologies for granulomatous interstitial nephritis (30).

Meso-American nephropathy (MeN) is a recently defined condition observed among sugarcane workers who are working long hours in humid conditions and high temperature. The cause of MeN remains uncertain; however, several potential causes are proposed including the followings; episodes of heat stress, loss of water and solutes and fast repletion probably in combination with NSAID administration, the presence of some probable nephrotoxins, heavy infestation of rodents that exist in that environment (31). The patients often have fever, nausea and vomiting, myalgia, and back pain, a condition very similar to hemorrhagic fever with renal syndrome (6,32).

Likewise, familial Mediterranean fever (FMF) is an auto-inflammatory condition that often leads to painful joints and episodes of abdominal pain. The high prevalence of analgesic and NSAID administration together with FMF-induced renal amyloidosis are the major pre-
disposing conditions for the disease. Thus, it is of great importance to conduct a genetic study of this condition particularly in regions with high prevalence of this condition (33).

Iodinated contrast agents, which are mainly used for cardiovascular imaging, are the leading cause of ARF particularly in those with an underlying CKD. It is manifested with a rapid increase in creatinine level mainly after 24-48 hours after exposure to the agents; it reaches its peak within 3-5 days and resolves within a week. Sodium phosphate bowel purgation and gadolinium are the newly proposed nephrotoxins (14).

Studies on lithium administration showed that end-stage renal disease and a decline in GFR mainly occurred in patients with a prolonged exposure to lithium and those who had episodes of acute lithium intoxications. Physician should manage other risk factors such as hypertension, smoking, diabetes, and weight gain; they also should avoid the administration of other nephrotoxins and non-steroidal anti-inflammatory drugs (34).

Conclusion
As a brief conclusion it is necessary to observe the following modalities to avoid interstitial nephritis; understanding risky conditions, detecting patients at risk, and discontinuing the harmful drugs are the main preventive and therapeutic strategies which can be adopted to control interstitial nephritis. Administration of a short course of oral or intravenous glucocorticoids has also been proposed. On the other hand, delayed diagnosis impairs the final recovery.

Authors’ contribution
All authors contributed equally to this work.

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The authors declared no competing interests.

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