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# Evaluation of the Role of Some Cytokines and Biochemical Parameters in Patients With Uremic Pruritus in Diyala Governorate

A Thesis

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**By**

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## 1.Introduction

Itch (also known as pruritus) is an irritating sensation that induces a desire to scratch. Itch is classified as acute or chronic based on its persistence, with the latter one lasting for more than six weeks in an affected individual (Weisshaar *et al*., 2019). Uremic pruritus (UP), also known as "chronic kidney disease-associated pruritus" (CKD-aP), is a common, troubling and in some cases debilitating problem for patients with chronic kidney disease (CKD), end-stage renal disease (ESRD) as well as those maintained on dialysis, including hemodialysis (HD) or peritoneal dialysis (PD) (Verduzco and Shirazian, 2020).

The prevalence of UP varies widely among research studies. It has been reported that it can range between 20% and 90% among CKD and ESRD patients and has a significant clinical impact associated with poor sleep, depression, reduced quality of life, and increased mortality among these patients (Pisoni *et al*., 2006; Rayner *et al*., 2017; Shirazian *et al*., 2017). CKD-aP can develop without any associated diagnosable skin disorders or primary skin lesions, although, over time, secondary skin alterations such as excoriations may occur as a result of intense scratching. Symptoms can be either localized, affecting symmetrical areas of the body, or generalized, affecting the whole body (Swarna *et al*., 2019; Kremer and Mettang, 2019; Ragazzo *et al*., 2020).

The pathogenesis of CKD-aP is complex and not fully understood, and many hypotheses have been proposed regarding its development. Multiple biomarkers have been reported to be associated with CKD-aP. Conventionally, it was assumed that efficiency of dialysis and metabolism biomarkers such as phosphorus, calcium, and parathyroid hormone are associated with an increased risk of UP (Ramakrishnan *et al*., 2013; Verduzco and Shirazian, 2020).

The involvement of immune system dysfunction in the pathogenesis of CKD-aP has been discussed in the past, but it remains unclear. In a study by Kimmel *et al*., (2006) an association was discovered between the serum interleukin-6 (IL-6) level and the occurrence of pruritus in 171 HD patients. Similar findings were recently reported by German researchers (N= 39 HD patients), who observed an increase in serum IL-6 level in patients with uremic pruritus compared to those who did not have pruritus (Schricker *et al*., 2019). In a recent study published in 2021, researchers discovered that serum levels of interleukin-31 (IL-31) were elevated in patients with UP compared to the control group. The same study found that interleukin-13 (IL-13) had a statistically significant correlation with severity of pruritus in UP patients (Oweis *et al*., 2021).

Tumor necrosis factor-alpha (TNF-α) is commonly elevated in patients with ESRD, and it is thought to play a key role in the pathophysiology of UP. TNF-α has been shown to sensitize the itch-recording nerve endings (c-fibers) in the skin, resulting in a more intense signal in response to a specific stimuli (Yosipovitch *et al*., 2003; Gupta *et al*., 2015). In a recent study published in 2020, the authors discovered that serum levels of interleukin-2 (IL-2) were elevated in patients with CKD-aP compared to those without CKD-aP (Rusyati *et al*., 2020).

It is important to highlight that complement activation can occur during hemodialysis (HD), which can lead to chronic inflammation in patients with ESRD (Melchior *et al*., 2021). Overactivation, deficiency, or abnormality of the control proteins of the complement system are often related to several skin diseases, such as psoriasis, lupus erythematosus, and urticaria (Giang *et al*., 2018). In HD patients, activation of the complement system may also induce an allergic response, hence many patients experience pruritus (Poppelaars *et al*., 2018a).

Since CKD is an immune-deficient disease, the prevalence of blood-borne viral infections among HD patients is considerably higher than in the general population. As

result, patients with CKD receiving HD are more susceptible to hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) (Ali *et al*., 2019; Kamal and Mahdi, 2018). The high incidence of these infections among HD patients is due to the existence of common risk factors such as improper or no vaccination, patients are not tested for HBV and HCV before starting HD therapy, inadequate disinfecting of dialysis machines, spreading the infection from one patient to another, and repeated blood transfusions (Roushan *et al*., 2016).

## Aims of the study:

According to previous studies, the immunological and uremic toxin hypotheses may be the main contributors to chronic kidney disease-associated pruritus (CKD-aP). Furthermore, with an increasing number of supporters and opponents of these hypotheses, the high incidence of CKD-aP, the psychological and physical difficulties that CKD-aP patients face, and the high prevalence of blood-borne viral infections among these hemodialysis patients, we decided to investigate this disease and its immune hypothesis by measuring the following parameters:

1- Detection of the prevalence of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) among hemodialysis patients attending Ibn Sina Dialysis Center in Diyala.
2- Evaluation of the serum interleukin-6 (IL-6), interleukin-13 (IL-13), and tumor necrosis factor-alpha (TNF-α) levels among hemodialysis patients with uremic pruritus attending Ibn Sina Dialysis Center in Diyala.
3- Assessment of serum complement 3 (C3) and complement 4 (C4) levels in patients with chronic kidney disease-associated pruritus (CKD-aP).
4- Evaluation of urea, creatinine, phosphorus, and albumin levels in hemodialysis patients with uremic pruritus.

## الخـــلاصـــة

الحكة اليوريمية (UP) هي مشكلة شائعة، مزعجة، وفي بعض الأحيان تكون منهكة للأشخاص الذين يعانون من مرض الكلى المزمن (CKD) والفشل الكلوي في مراحله النهائية (ESRD) وكذلك أولئك الذين يخضعون لغسيل الكلى الدموي (Hemodialysis) أو البريتوني (Peritoneal Dialysis). آلية نشوء وتطور الحكة اليوريمية غير مفهومة تماما الى الان وقد تم اقتراح العديد من الفرضيات فيما يتعلق بتطور هذا المرض.

تهدف هذه الدراسة للتحري عن انتشار فيروسات التهاب الكبد B و C (HBV, HCV)، الى جانب فيروس نقص المناعة البشرية (HIV)، و لتقييم مستوى الـ إنترلوكين 6 (IL- 6)، إنترلوكين 13 (IL- 13)، عامل نخر الورم ألفا (TNF-α)، المتمم 3 (C3)، والمتمم 4 (C4)، بالإضافة إلى بعض المؤشرات الكيموحيوية لدى المرضى الخاضعين للغسيل الكلوي والمصابين بالحكة اليوريمية.

أجريت هذه الدراسة في الفترة ما بين 4 أكتوبر 2021 و 5 مارس 2022 على 90 شخصا من المرضى الخاضعين للغسيل الكلوي الدموي والذين يعانون من الحكة اليوريمية وعلى 30 من الأشخاص الأصحاء (السيطرة) في مركز ابن سينا للغسيل الكلوي في مستشفى بعقوبة التعليمي. تم تقييم شدة الحكة وقياسها باستخدام مقياس تناظري بصري (VAS). حيث، طُلب من المريض تحديد شدة الحكة التي يشعر بها على خط أفقي بطول 10 سم (1-2 حكة خفيفة، 3-7 حكة متوسطة، 8-10 حكة شديدة). بعد ذلك، تم سحب ما يقرب الـ 4 مل من دم المرضى الذين يعانون الحكة اليوريمية خلال الدقائق العشر الأولى من بدأ عملية الغسيل الكلوي، وتم الحصول على نفس كمية الدم من الأشخاص الأصحاء في ظل ظروف معقمة تمامًا. تم فصل عينات الدم باستخدام جهاز الطرد المركزي وقسمت الأمصال التي تم الحصول عليها من كل عينة إلى أربع أنابيب إيبندورف وخزنت عند درجة حرارة (20−) درجة مئوية لتحليلها لاحقًا للكشف عن الـ HBV، HCV، وHIV بالإضافة إلى قياس مستوى الـ IL- 6، IL- 13،