INTRODUCTION

Uremic pruritus or chronic kidney disease-associated pruritus (CKD-aP) remains a frequent and compromising symptom in patients with advanced or end-stage renal disease, strongly reducing the patient's quality of life. The pathogenesis of CKD-aP remains obscure. Parathormone and histamine as well as calcium and magnesium salts have been suspected as pathogenetic factors. Newer hypotheses are focusing on opioid-receptor derangements and microinflammation as possible causes of CKD-aP, although until now this could not be proven. Pruritus may be extremely difficult to control, as therapeutic options are limited ***(Mettang and Kremer, 2014).***

Many inflammatory substances take part in the pathogenesis of pruritus and are produced by mast cells during degranulation: histamine, tryptase, endothelin, acetylcholine, prostaglandins, and cytokines ***(Mirosław et al., 2013).***

Mast cells are found in many tissues, but are present in greater numbers along the epithelial linings of the body, such as the skin, respiratory tract and gastrointestinal tract. Mast cells are also located in the perivascular tissue surrounding small blood vessels. They are involved in a

variety of physiological and pathophysiological states, including immediate hypersensitivity, delayed-type hypersensitivity, cell growth regulation, defense against neoplasia and the sensations of pain and itch. Mast cells have also been implicated in chronic inflammatory states and are involved in neuroimmune interactions, mast cells are best known for their potent effector functions in allergic disorders. Also, mast cells have been identified to be involved in a surprisingly complex range of immune functions that go far beyond allergies and include the development of autoimmune disorders and peripheral tolerance, and the initiation and maintenance of adaptive and innate host responses ***(Metz and Maurer, 2007).***

Interactions between dermal mast cells (MC) and afferent C neuron terminals may play an important role in the mediation of pruritus since these structures sit very close together. The skin of chronic renal failure patients with pruritus has a greater number of mast cells. There are various substances released from mast cells including histamine, IL2, TNF-α and proteases such as tryptases ***(Ghazal et al., 2009).***

There is no relationship between plasma histamine and pruritus score in patients undergoing dialysis. In addition, antihistamines are relatively ineffective in treating uraemic itch. Therefore, it was hypothesized that probably

other mediators released from mast cells are responsible for chronic renal failure associated pruritus; tryptase being one of these mediators ***(Ghazal et al., 2009).***

Mast cells make and secrete an abundance of peptidases "proteases", which are stored in such large amounts in granules that they comprise a high fraction of all cellular protein. For many years after the main peptidases were first described, they were best known as markers of degranulation, for they are released locally in response to mast cell stimulation and can be distributed systemically and detected in blood. The principal peptidases are tryptases, chymases, carboxypeptidase A3, and dipeptidylpeptidase I (cathepsin C). Numerous studies suggest that these enzymes are important and even critical for host defense and homeostasis ***(Trivedi and Caughey, 2010).***

Tryptase, a 135kDa tetrameric serine protease, is stored in and released from mast cells granules upon activation, mast cell tryptases are a somewhat eclectic group of secreted, serine-class peptidases with trypsin-like target preferences, which is to say that they cleave peptide and protein substrates after lysine and arginine. In comparison with trypsin, however, they can exhibit major physical and behavioral differences, such as intracellular pre-activation prior to secretion, membrane anchorage, and formation of a proteasome-like oligomers that resist circulating anti-peptidases such as α_1-antitrypsin and α_2-

macroglobulin. Although the functions of mast cell tryptases remain to be fully explained, they are hard to ignore if only because of their abundance ***(Caughey, 2006).***

Because tryptases are present in an activated form inside of mast cells granules, they have potential intracellular roles, including self-activation. On the other hand, the soluble tryptases and mastins as a class are secreted and protect themselves from circulating inhibitors by forming proteasome-like oligomers, with active sites facing into a central cavity in which large inhibitors do not fit. Thus, tryptases have the opportunity to hydrolyze extracellular peptides and proteins ***(Trivedi and Caughey, 2010).***

Unlike histamine, the measurement of serum tryptase levels selectively indicates the extent of mast-cell activation, since negligible amounts of this enzyme are present in other cell types, such as basophils ***(Kawakami et al., 2006)***.

There is a significant correlation between the intensity of pruritus and serum tryptas levels in hemodialysis patients. Mast cell tryptase activates protease-activated receptors (PAR) on sensory neurons, causing neuronal excitation and release of substance P ***(Dugas-Breit et al., 2005).***

Steinhoff et al. (2003) have shown in their experiment that neuronal PAR-2 is involved in pruritus of human skin and that a histamine-independent, protease-dependent, PAR-2 mediated itch pathway may provide a link to novel therapies for pruritus and cutaneous inflammation.

AIM OF THE WORK

The aim of this study is to evaluate the possible role of mast cell tryptases (MCT) enzyme in the pathogenesis of uremic pruritus by measuring its level in the serum of chronic hemodialysis patients with pruritus and to correlate its level with the severity of pruritus.

REVIEW OF LITERATURE

1. UREMIC PRURITUS

Chronic renal failure (CRF), is a progressive loss of renal function over a period of months or years. Chronic kidney disease is divided into 5 stages of increasing severity. Each stage is a progression through an abnormally decreasing and deteriorating glomerular filtration rate (GFR), which is usually determined indirectly by the serum creatinine level. All individuals with either kidney damage or a GFR < 60 ml/min/1.73 m2 for 3 months are classified as having chronic renal disease. End-stage renal disease (ESRD) is considered the fifth stage of CRF, and can lead to uremic syndrome, which can cause death in patients with this condition if toxins accumulate in the body ***(Beheshti et al., 2013).***

Patients with CRF on hemodialysis (HD) experience many dermatological symptoms during treatment. Complete and precise examination of skin, hair, nails, and mucosal membranes may reveal a wide variety of the following symptoms including hyperpigmentation, xerosis, ichthyosis, pruritus, onychomycosis, onycholysis, splinter hemorrhages, subungual hyperkeratosis, brittle hair, and sparse body scalp hair These diseases are sometimes related to underlying renal illness but are more often associated, directly or indirectly, with uremia in its broadest sense ***(Beheshti et al., 2013).***

1.1. Cutaneous Manifestations of ESRD

1.1.1. Non-specific disorders

1. Pruritus

It will be discussed later.

2. Xerosis

Referring simply to dry or roughened skin, xerosis occurs in 50-75% of dialysis patients. It manifests as poor skin turgor with scaling, dryness and fissuring of the skin, particularly affecting extensor surfaces of extremities. This condition can be very uncomfortable as it may promote the development of fissures, ulcers, lichen simplex chronicus and irritant or allergic contact dermatitis. It also predisposes patients to infections (e.g. cellulitis) because it compromises the normal skin barrier (Figure 1) ***(Lynde and Kraft, 2007).***

3. Pigmentary disorder

Pigmentary changes to the skin are very common in ESRD it's estimated that 25-70% of dialysis patients are affected to some degree. Incidence increases with the duration of renal disease. The spectrum of pigmentary changes ranges from hyperpigmentation to yellowish discoloration and pallor. Hyperpigmentation is often photo distributed and is the result of an increase in melanin in the basal layer of the epidermis (Figure 2). The yellow skin

colour in ESRD patients is caused by lipochrome and carotenoid deposition in the dermis and subcutaneous tissues. Pallor is a result of anemia associated with chronic disease and is widespread ***(Lupi et al., 2011)***.

4. Half-and-half nails

Half-and-half nails (Lindsay's nails) are found in roughly 33% of patients with azotemia and in up to 40% of those on dialysis. In this condition, the proximal half of the nail is white due to edema of the nail bed and capillary network. The distal portion appears normal or even brown due to increased melanocyte stimulating hormone in patients with ESRD. The nail plate is unaffected (Figure 3). The likeliness of these changes may increase with the time a patient's been on dialysis, but there most likely isn't a correlation with the severity of uremia. Half-and-half nails tend to disappear after successful transplantation ***(Lupi et al., 2011).***

5. Elastosis

In sun-exposed areas, elastosis is often seen as elastin is broken down. The relationship to ESRD is unclear, but it's possible that this acceleration of cutaneous aging is a function of the time a patient has been on dialysis. Elastosis refers to yellow, atrophic plaques with wrinkling of the skin ***(Lynde and Kraft, 2007).***

6. Uremic frost

Uremic frost, superficial white deposits of crystallized urea excreted from sweat, can be a late feature of severe ESRD ***(Lynde and Kraft, 2007).***

7. Ecchymoses

Ecchymoses is a skin condition results from platelet dysfunction (Figure 4) ***(Lupi et al., 2011)***.

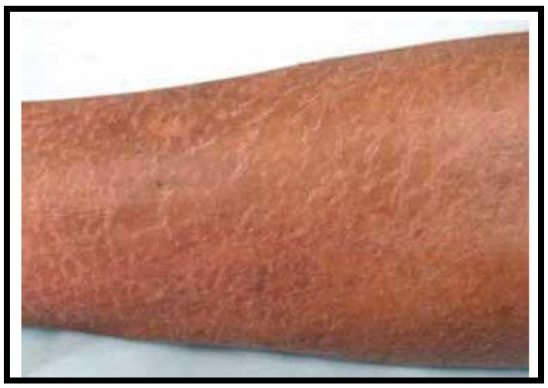

Figure (1): Skin xerosis evolving with ichthyosiform appearance in the lower limb of a chronic renal patient ***(Lupi et al., 2011)***.

Figure (2): Hyperchromic macules with a reticulated aspect in the frontal region of a patient with chronic renal failure undergoing hemodialysis ***(Lupi et al., 2011)***.

Figure (3): Light-colored proximal region and brownish distal region of the nail, characterizing half and half nail ***(Lupi et al., 2011)***.

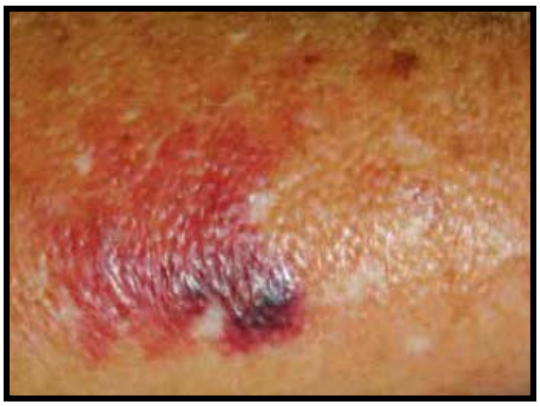

Figure (4): Spontaneous ecchymotic injury on the upper limb of a patient with chronic renal failure ***(Lupi et al., 2011)***.

1.1.2 Specific disorders

1. Metastatic calcification

- ***Calcinosis cutis***

This refers to calcium deposition in the skin and is a subtype of calcinosis, a condition describing calcification in vessels and organs. Patients with calcinosis cutis get painless flexural infiltrating plaques and nodules at periarticular sites. The size and number of plaques corrolate with degree of hyperphosphatemia. Unlike calciphylaxis

this disorder does not cause skin necrosis (Figure 5). Risk factors include low albumin, high phosphate, high alkaline phosphatase and morbid obesity. It occurs in about 1% of dialysis patients. There is no gold standard treatment but normalisation of calcium and phosphate can cause lesions to regress ***(Markova et al., 2012).***

- ***Calciphylaxis***

In this disorder calcification of the small vessels of the dermis and subcutaneous tissues occurs. This leads to vessel thrombosis, tissue infarction and skin necrosis. It occurs in 1-4% of dialysis patients. Risk factors include hyperparathyroidism, an elevated calcium-phosphate product (>70 mg^2/dl^2), diabetes mellitus, female sex, obesity, warfarin use, and protein C or S deficiency. 1-year survival after the diagnosis of calciphylaxis is about 50%. In calciphylaxis patients get very painful violaceous reticulated plaques that are well defined and deep. These lesions develop into deep non-healing ulcers that can become gangrenous (Figure 6). Sepsis is the most common cause of mortality. Treatment options include a low phosphorous diet, normalizing calcium and phosphate with non-calcium based phosphate binders and low-calcium dialysate. Sodium thiosulphate 25g IV over 30 minutes three treatments per weeks has been shown to improve lesions and should be continued for 2 months beyond the resolution of lesions ***(Markova et al., 2012).***

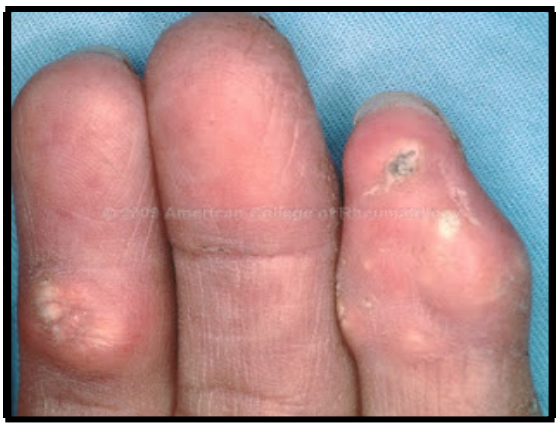

Figure (5): Calcinosis cutis ***(Markova et al., 2012).***

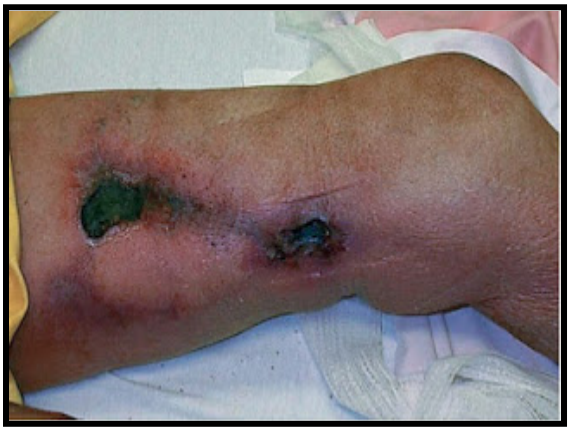

Figure (6): Calciphylaxis ***(Markova et al., 2012).***

2. Bullous dermatoses

- ***Porphyria cutanea tarda***

Porphyria cutanea tarda (PCT) is a vesiculobullous skin disease with a prevalence of 1-18% in patients receiving HD. It's a disorder of the hepatic heme biosynthesis pathway associated with uroporphyrinogen

decarboxylase deficiency. The symptoms of the disorder associated with ESRD are similar to those of sporadic PCT induced by other agents. The blistering photosensitive rash is composed of tense vesicles and bullae distributed on the dorsa of the hands, face and sometimes feet. The skin is fragile. Secondary features include erosions and crusts. Blisters heal with scarring and milia formation. Other cutaneous findings of PCT include hyperpigmentation of sun-exposed skin with hypertrichosis and sclerodermoid plaques (Figure 7) ***(Lynde and Kraft, 2007).***

- ***Pseudoporphyria***

Patients may also present with pseudoporphyria, which has clinical and histologic features similar to PCT, but without abnormal porphyrin levels. Most do not show hypertrichosis or sclerodermoid plaques (Figure 8) ***(Markova et al., 2012).***

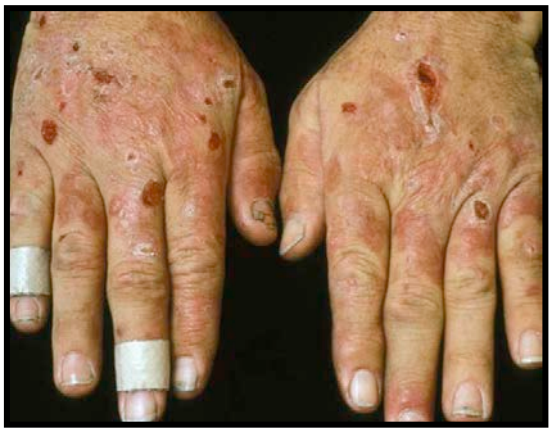

Figure (7): Porphyria cutanea tarda ***(Markova et al., 2012).***

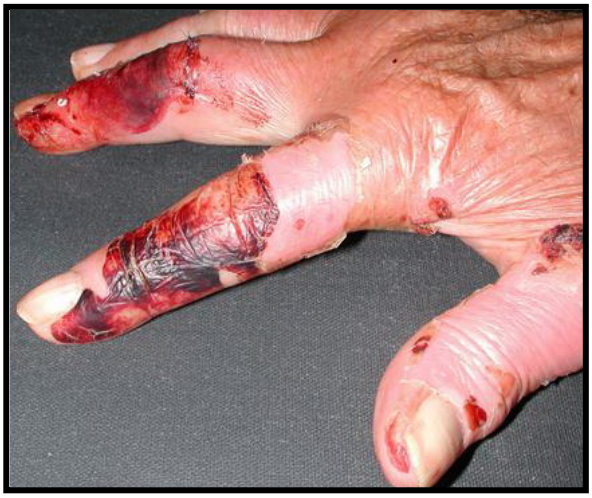

Figure (8): Pseudoporphyria ***(Markova et al., 2012).***

3. Acquired perforating dermatosis

Between 4 and 10% of people receiving HD develop acquired perforating dermatosis (APD). When presenting with APD, people often complain of severe pruritus. The disease shows features of primary perforating dermatosis and is the result of altered connective tissue within the dermis being eliminated through the epidermis, with little damage to surrounding structures ***(Lynde and Kraft, 2007).***

Clinically, APD manifests as keratotic, dome-shaped, grouped papules and nodules, 1-10 mm in diameter. Papules may be umbilicated with a central keratotic plug. They appear pink in lighter skin, while in darker-skinned patients, they are brown or hyperpigmented. In some cases