"A STUDY OF CUTANEOUS MANIFESTATIONS IN PATIENTS OF CHRONIC KIDNEY DISEASE STAGE 5 UNDERGOING HEMODIALYSIS AND THEIR CORRELATION TO PARATHYROID HORMONE LEVELS AT A TERTIARY CARE HOSPITAL IN BELGAUM, A CROSS SECTIONAL STUDY"

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This is to certify that the dissertation entitled "**A STUDY OF CUTANEOUS MANIFESTATIONS IN PATIENTS OF CHRONIC KIDNEY DISEASE STAGE 5 UNDERGOING HEMODIALYSIS AND THEIR CORRELATION TO PARATHYROID HORMONE LEVELS AT A TERTIARY CARE HOSPITAL IN BELGAUM, A CROSS SECTIONAL STUDY**" is a bonafide research work done by **REG NO. : BT0111001.**

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LIST OF ABBREVIATIONS USED

APD – Acquired Perforating Disorder

B_2M – Beta-2-microglobulin

CKD – Chronic Kidney Disease

CREST – Calcinosis, Raynaud's syndrome, Esophageal dysmotility, Sclerodactyly, Telangiectasia

DOPPS – Dialysis Outcomes and Practice Patterns Study

ESRD – End Stage Renal Disease

GABA – gamma Aminobutyric acid

GFR – Glomerular Filtration Rate

HD – Hemodialysis

MSH – Melanocyte Stimulating Hormone

NFD – Nephrogenic Fibrosing Dermatopathy

PCT – Porphyria Cutanea Tarda

PTH – Parathyroid hormone

RBC – Red Blood Cell

SLE – Systemic Lupus Erythematosus

SNRI – Selective Neuroepinephrine Re-uptake Inhibitors

ABSTRACT

Background and objectives

Chronic kidney disease stage 5 patients who are on hemodialysis present with an array of cutaneous manifestations. There have been some reports of raised parathyroid hormone levels associated with some conditions like pruritus. The aim of this study was to study the cutaneous manifestations seen in patients of chronic kidney disease stage 5 undergoing hemodialysis and to correlate them with parathyroid hormone.

Materials and Methods

64 patients of chronic kidney disease stage 5 who were undergoing hemodialysis and who gave an informed consent to participate in the study were included. The study period was for 1 year. A pretested pro-forma was used which had a list of all the skin changes seen in patients of chronic kidney disease stage 5 undergoing hemodialysis. In addition to this, blood was drawn from all patients and the serum parathyroid hormone levels were tested. Other pre-existing laboratory results were also noted down. A skin biopsy was done for a patient suffering from a perforating disorder. It was sent in 10% formalin to Pathology lab and was stained with Haematoxylin and eosin.

Results

There were 14 females and 50 males. The dialysate used was bicarbonate solution. 59% had elevated parathyroid hormone levels. 65% had pallor, 47% had edema, 28% had itching before dialysis, 41% had itching post dialysis, 22% complained of generalized darkening post dialysis, 52% had abnormal skin turgor, 16% had 1/2 and 1/2 nail, 35% had koilonychia, 23% had Terry's nail, 8% had Muehrcke's lines, 39% had hairloss, 95% had xerosis, 28% had coated tongue.

Among the specific disorders seen in patients of chronic kidney disease stage 5 undergoing hemodialysis, only acquired perforating dermatosis was seen. It was seen in 3 (4.7%) patients. Other specific changes like bullous disease of hemodialysis, calciphylaxis, calcinosis cutis and nephrogenic systemic fibrosis were not observed. None of the cutaneous manifestation's correlation with parathyriod hormone levels was statistically significant. The parathyroid hormone levels were consistently low among the patients who were undergoing hemodialysis between 6 months to 36 months. It was statistically significant. (p=0.037)

Conclusion

The cutaneous manifestations seen in patients of chronic kidney disease stage 5 undergoing hemodialysis do not seem to have any correlation with parathyroid hormone levels. Thus parathyroid hormone cannot be used as a marker for cutaneous manifestations seen in these patients. Most of the conditions seen in the study were non-specific like pruritus, xerosis and pallor. Among the specific manifestations only acquired perforating dermatosis was seen. This too was seen in only 3 (4.7%) patients. It did not have any statistically positive correlation with parathyroid hormone levels. Perhaps the bicarbonate diasylate has properties to filter calcium salts and porphyrins due to which neither calcific disorders nor bullous changes were seen. Otherwise the other specific manifestations may be more relevant to western population.

Key words

Hemodialysis; Parathyroid Hormone; Kidney failure, chronic; Skin manifestations

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INTRODUCTION

Skin diseases are a common occurrence in patients with chronic kidney disease. Due to recent shift in demographic profile of India, the average lifespan of Indians has increased. Thus more and more people are getting diagnosed with chronic kidney disease. Chronic kidney disease has various stages depending on the severity ranging from stage 1 to stage 5. Chronic kidney disease stage 5 is the last stage of chronic kidney disease. At this stage life is not possible without dialysis or renal transplantation. Due to legal and infrastructural issues renal transplantation is not possible on a routine basis in India. Thus most of the patients are surviving on maintenance dialysis.

Dialysis is of 2 types: hemodialysis and peritoneal dialysis. Hemodialysis is the preferred modality in most centres and in our hospital it is the only kind of dialysis offered to the patients. Since most of the patients of chronic kidney disease are on dialysis there is an overlap of skin manifestations found in them. It has been estimated in various studies that the frequency of skin manifestations in patients undergoing dialysis varies from 80-100%.

Since no such study had been done in this institute, it was decided to study the skin manifestations in patients undergoing hemodialysis. On reviewing literature we found that there were already many studies on this topic in other centers. There was a need to do something more. There were a few articles relating parathyroid hormone to pruritus and calcific disorders but there was no conclusive evidence for it. It was decided to check parathyroid hormone levels in all patients and to study if there is any correlation between the skin findings and parathyroid hormone. The idea was that if

any correlation existed between them then parathyroid hormone levels may act as a marker for the cutaneous manifestation. Also, if a correlation existed with a skin manifestation then treatment of the raised parathyroid hormone could lead to improvement in the skin manifestation too.

OBJECTIVES

1. To study the cutaneous manifestations seen in patients of chronic kidney disease stage 5 undergoing hemodialysis.

2. To study the relation between these cutaneous manifestations and parathyroid hormone.

REVIEW OF LITERATURE

Skin conditions are very common in patients with chronic kidney disease. It is estimated that 80% of patients with chronic kidney disease have at least one skin manifestation. The term chronic renal failure is no longer used. It is referred to as chronic kidney disease. It has 5 stages. Stage 5 is the end stage renal disease defined by GFR < 15 mL/min per 1.73 m^2.[1] Stage 5 is the end stage requiring intervention of some kind for survival. It may be dialysis or renal transplantation. Dialysis is of 2 types, hemodialysis and peritoneal dialysis. In hemodialysis movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate.[2] Peritoneal dialysis is another type of dialysis in which dextrose containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time. The peritoneal membrane is used as the filtering membrane across which the substances are filtered. In our hospital hemodialysis is done on a routine basis. Peritoneal dialysis is not done and renal transplantation is done infrequently.

Since most of the patients of chronic kidney disease stage 5 are invariably on some form of renal replacement therapy there is an overlap between the skin manifestations due to chronic kidney disease and skin manifestations seen in hemodialysis patients. No study has been done on the skin manifestations in hemodialysis patients in our hospital so that was the basis of starting this study. On a look through literature there were numerous studies describing skin manifestations in dialysis patients[3] so a need was felt to explore things further. There are some studies which have correlated some skin manifestations to Parathyroid hormone. Massry et al postulated that itch associated with chronic kidney disease was due to secondary hyperparathyroidism and that it could even respond to parathyroidectomy.[4] There also

seems to be correlation between dry skin and hyperparathyroidism.[5] Also there is an obvious correlation with the calcemic manifestations seen in chronic kidney disease patients and parathyroid hormone levels.[6] However this is not true in all cases and in other studies no such correlation has been found between Parathyroid hormone levels and these conditions. In addition Pubmed search at the time of starting this study did not show any result for cutaneous changes in hemodialysis and their correlation to parathyroid hormone. With this backdrop this study was initiated.

Parathyroid hormone is produced from parathyroid glands. It is an 84-amino-acid single chain peptide. It causes calcium resorption from bones, and calcium resorption from the kidneys. This hormone maintains extracellular fluid calcium concentrations within a narrow normal range. Increased level of parathyroid hormone is known as hyperparathyroidism. This can be primary or secondary. Primary hyperparathyroidism is due to excess secretion from either an adenoma or hyperplasia of the parathyroid glands. Secondary hyperparathyroidism occurs due to an adaptive response to an underlying pathology causing increase in the parathyroid hormone levels. Patients with secondary hyperparathyroidism may develop bone pain, ectopic calcification and pruritus. The bone disease in patients with secondary hyperparathyroidism and renal failure is termed renal osteodystrophy. In patients on long-term dialysis especially who have excess aluminium in their dialysis regimen, aluminum intoxication may occur. Aluminium starts to deposit in the bones and causes severe osteomalacia, acute dementia and unresponsiveness. Prevention is by avoiding aluminium excess in the dialysis regimen.

Various studies done on cutaneous changes in hemodialysis patients have shown that about 80% of patients have at least one cutaneous manifestation[7].

The cutaneous manifestations of patients undergoing dialysis can be arbitrarily divided into 2 types, non-specific and specific skin lesions.

Table 1: Cutaneous manifestations of patients undergoing hemodialysis

Non- specific changes	Specific changes
Pruritus	Uremic fetor
Xerosis	Tongue sign of uremia
Pallor	Uremic frost
Pigmentary changes	Dialysis related amyloidosis
Hair abnormalities	Uremic neuropathy
Nail changes e.g. Koilonychia, subungual hyperkeratosis, Mees' lines	Nail changes e.g. Half and half nail
Purpura	Acquired perforating dermatosis
Lesions at the site of cannula insertion	Nephrogenic systemic fibrosis
Oral mucosal changes – xerostomia	Bullous disease of hemodialysis
	Calciphylaxis

Non-specific findings

1) **Pruritus** - The prevalence of pruritus in hemodialysis patients in various studies varies from 50-90%.[8] The largest study done so far analyzed data from 18,801 patients undergoing hemodialysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS) from 1996 to 2004 and indicated that 42% of hemodialysis patients experienced moderate to severe pruritus.[9] It is the most characteristic and annoying symptom of chronic kidney disease.[10] It is also referred to as 'uremic pruritus' which literally means pruritus secondary to uremia which is untrue. The pruritus does not have relation with gender, age or duration of dialysis. The pruritus seems to be less in patients on ambulatory peritoneal dialysis than on hemodialysis patients. Pruritus also depends on the type of dialysis machine e.g. the ones with high permeability of dialysis membrane have been thought to have decreased pruritus.[11] In those patients on regular dialysis the pruritus seems to be maximum 2 days after the last dialysis session and least on the day following dialysis. Also itching is relatively high during the dialysis procedure.[6]

Clinical characteristics of itch

The intensity of itch associated with chronic kidney disease ranges from sporadic discomfort to complete restlessness during the day and night. It could be intermittent or persistent.[12] It can be generalized in 25-50% of patients, and it predominantly affects the back (70%), abdomen (46%), head (46%), and arms (43%).

Uremic pruritus is absent in acute renal failure.[13] Exact cause for itching in chronic renal failure is not known. It is multifactorial in origin. The common causes are uremic xerosis, secondary hyperparathyroidism, hypervitaminosis A, uremic

neuropathy, elevated serum histamine levels and iron deficiency anemia. Of these, uremic xerosis is perhaps the most important cause as it is the most common cutaneous manifestation in chronic kidney disease patients. It is present in 90-100 % patients having pruritus.[14] The level of uremic pruritus is directly proportional to the xerosis. Xerosis is due to dehydration of skin resulting from atrophy of eccrine glands and loss of lipids on skin due to atrophy of sebaceous glands however, Yosipovitch et al did not find any evidence between the severity of pruritus and objective parameters of xerosis.

Endogenous opioids are important players in the pathogenesis of itch. An increased ratio of serum beta-endorphin to dynorphin A was reported in hemodialysis patients compared with healthy controls and the ratio increased with increased intensity of itch.[15]

Some studies have reported significant association between serum parathyroid hormone and itching whereas others have not found any association. Kidney failure, hyperphosphatemia, hypocalcemia and decreased levels of calcitriol (vitamin D) are factors which increase parathyroid hormone levels.[16] Thus the raised parathyroid hormone level in kidney failure is actually a type of secondary hyperparathyroidism.[17] It has been reported that pruritus in some patients can completely disappear after parathyroidectomy.[18] Hyperparathyroidism can stimulate mast cells to release histamine. This can promote micro precipitation of calcium and magnesium salts in the skin. On the other hand all patients with severe hyperparathyroidism do not have pruritus. Also there is no difference in the number of mast cells in patients with hyperparathyroidism in patients who are having and not having pruritus.[19] In experimental studies, intradermal injections of parathyroid hormone failed to produce

pruritus. In the same study, immunohistochemistry was negative for parathyroid hormone in skin biopsies of patients undergoing hemodialysis.[20] In a recent Iranian study, there was a significant correlation between itching score and serum intact parathyroid hormone in hemodialysis patients.[21]

Impact on the quality of life

It was found in Dialysis Outcomes and Practice Patterns Study, that patients undergoing hemodialysis with pruritus were more likely to feel drained and have poor sleep quality, depression and lower mental and physical composite scores of quality of life than patients with no or mild pruritus. Moreover, pruritus in hemodialysis patients is associated with 17% higher mortality rate than the patients on hemodialysis who are not having pruritus.[9]

The difficulty which an investigator faces with pruritus is the subjectivity of the symptom. It is a purely subjective symptom and each patient may have a different threshold for what he or she finds bothersome. There are a few ways of objectively measuring pruritus. One way is to ask the patient to rate his or her pruritus on a scale of one to ten, one being 'no itching' and ten being the 'most severe' itching which the patient is unable to tolerate. Another scale is the modified scoring system proposed by Duo.[22] The total scoring of pruritus is calculated as follows:

(severity of pruritus x distribution of pruritus) + sleep disorder.

Table 2: The severity of pruritus is assessed as:

1 point	Slight itching
2 points	Itching with scratching
4 points	Itching and scratching with excoriations
5 points	Itching causing total restlessness

Table 3: The distribution of pruritus is scored as

1 point	Pruritus maximum in 2 areas of the body
2 points	Pruritus maximum in more than 2 areas of the body
3 points	Generalized pruritus

Table 4: The sleep disorder is monitored as

2 points (maximum of 10 points)	Every episode of waking up due to itching
1 point (maximum of 5 points)	Each episode of scratching

The cause of itching is not known. There may be some sort of pruritogen which is not adequately filtered through the dialysis membrane, thus accumulating in the body under the skin and cause itching. The type of dialysate may also have a role in pruritus. Lower levels of Magnesium in the dialysate have been correlated with lower levels of pruritus.[23]

Treatment of pruritus

There are various treatment modalities which have variable efficacy for treatment of pruritus.

Wang et al have proposed a therapeutic ladder for management of pruritus in end stage renal disease.[24]

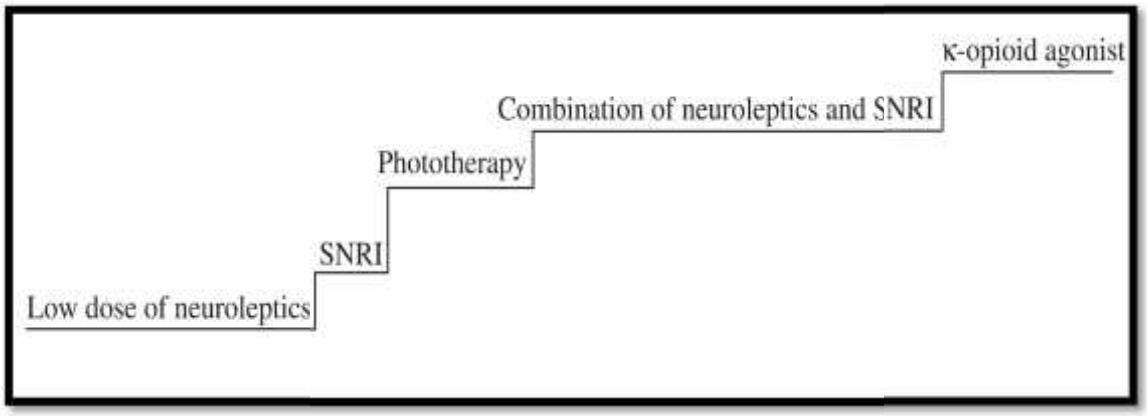

Figure 1 – Therapeutic ladder of the treatment of pruritus in end stage renal disease (SNRI, selective neuroepinephrine re-uptake inhibitors)

The first line of management is with neuroleptics. Gabapentin and pregabalin are structural analogs of the neurotransmitter GABA. The exact mechanism of their mechanism is not clear. They probably inhibit the central itch pathways just like in neuropathic pain.[25] In a placebo controlled double blinded study by Gunal et al in 25 patients with end stage renal disease associated pruritus found that 300 mg of oral

gabapentin given after each hemodialysis session was a safe and effective regimen.[26] Gabapentin is a neurotoxic drug. In another study, it was suggested that a starting dose of 100 mg initially with a slow upward titration can reduce this side effect.[27]

The second line of management is SNRI (Selective neuroepinephrine re-uptake inhibitors). They relieve the itching probably by reducing central sensitization to itch. Mirtazapine has been found to be effective in treatment of nocturnal pruritus.[28] It has also been found to be effective in renal pruritus.[29]

The third line of management is phototherapy. UVB therapy is effective in severe intractable pruritus.[30] It is considered the treatment of choice in many centers. UVA therapy without psoralens is also said to be just as effective.[31] The exact mechanism of action is not known. Probably it works via chemical modification of pruritogens in the skin or an alteration of skin sensitivity to pruritogens. It may also work by reducing post inflammatory cytokines. It is important to inform the patient that the in the first 2 weeks the itch may worsen and the reduction in pruritus may take 1-2 months.

If itching is not controlled by the above measures, the fourth line management is using a combination of neuroleptics like Gabapentin and selective neuroepinephrine re-uptake inhibitors like Mirtazapine.

If itching is still not controlled then the fifth line of management is kappa-Opioid agonists. A recent kappa receptor agonist, nalfurafine (TRK-820) has shown antipruritic effect in the treatment of ESRD associated pruritus. However it is not available commercially.[32]

Other alternatives are activated charcoal, cholestyramine, erythropoietin, ondansetron and naltrexone.[33] Sedating antihistaminic like hydroxyzine have some role in control of pruritus. Other antihistaminics do not help much because histamine does not play a significant role in uraemic pruritus.[34] Various topical therapies can also be used. Emollients help to a certain extent as xerosis is one of the most common causes of pruritus. In a double blinded placebo controlled study 0.025% capsaicin was found to significantly reduce pruritus in comparison to placebo.[19] Pramoxine 1% lotion was found to be efficient in treatment of uremic pruritus in a recent study.[35]

Renal transplantation is curative for uremic pruritus.

2) **Xerosis** - Uremic patients tend to have a very dry skin. It is the most common cutaneous manifestation seen in patients undergoing hemodialysis.[36] It is seen in up to 90% of patients. This is thought to be due to reduction in the eccrine sweat glands which reduces water content of the skin and also reduction in size of pilosebaceous units due to which there are decreased lipids on skin surface.[37] High dose diuretics may lead to iatrogenic dehydration leading to dryness of skin.[38] Xerosis is also a manifestation of Diabetes Mellitus and since it is the most common cause of chronic kidney disease in most centers, xerosis may be attributed to it. Also uraemia has been known to cause peripheral neuropathy which could also affect peripheral autonomic nerves thus leading to decreased sweating secondary to autonomic nervous dysfunction. This could in turn cause xerosis.

Treatment – Emollients can help only to a certain extent.

3) **Pallor** - Kidneys are the sites for erythropoietin production, which is essential for normal erythropoiesis. Thus in chronic kidney disease there is reduced erythropoietin

production which causes decreased RBC production leading to anemia. Udayakumar et al. reported pallor in 60% of uremic patients.[39] Pallor may be difficult to appreciate in some patients due to development of diffuse pigmentation all over body.

Treatment – Erythropoietin injections can help in RBC synthesis to a certain extent.

4) **Pigmentary changes** - Two different types of pigmentation patterns may be seen. First one is diffuse hyperpigmentation present all over the body but more so in sun exposed areas. The prevalence for this has been estimated as around 20-25%.[40] The diffuse hyperpigmentation has been attributed to increased melanin in the basal layer of epidermis and upper region of dermis due to failure kidneys to excrete beta-melanocyte stimulating hormone (β-MSH).[41] Hyperpigmented macules over palms and soles have also been reported.

The second type of pigmentation pattern seen is yellowish discoloration of skin. This has been reported in as many as 40% of patients. This has been attributed to accumulation of carotenoids and nitrogenous pigments like urochromes in the dermis.[42]

There might be a third kind of skin colour change, the pale skin due to severe pallor. This is described more so in western literature as it is difficult to ascertain in Indian skin.

5) **Hair abnormalities** - Sparse body hair and diffuse alopecia have been described.[43] The exact cause is not known. One of the causes can be severe anemia which is very common in these patients. The second hypothesis is that these patients are under a lot

of stress which can precipitate telogen effluvium. The hair in these patients is dull and lustreless. This is so because of decreased sebum secretion.[44]

6) **Nail changes**– Nail changes may be specific or non-specific.

Specific nail changes

Half and Half Nails- The classical nail change described is Lindsay's nails (half and half nails). These nails are red or pink in the distal half and white in the proximal half. A distinct line appears to separate the two zones. The red colour in the distal half does not fade with pressure.[45] Studies have shown prevalence from 16-50%.[46] The pathogenesis is not known. Stimulation of nail bed melanocytes by increased levels of plasma melanotrophic hormones and vascular changes have been suggested as possible causes.[47] They have also been reported after cancer chemotherapy; in a breast cancer patient after androgen use; after exposure to paraquat.[48] Erythematous crescent is a reddish discoloration of the distal nail involving less than 40% of distal nail bed. It is also seen in chronic renal failure.[49] They may also be present in normal healthy adults. Once present these changes may remain permanently even after hemodialysis.

Non-specific nail changes

A) **Koilonychia** – There is loss of convex curvature of the nails. The nails either become flat or truly concave or 'spoon like nails'. It affects fingernails more than toenails. It can be acquired or heredity. The acquired form is much more common and associated with iron deficiency anemia. They may even be present in normal individuals and may be a racial characteristic in Ladhakhi and Tibetan populations.[50] It has also been described in post renal transplant patients and after hemodialysis.

B) **Subungual hyperkeratosis** - It refers to hyper proliferation of keratinous debris under the nails)

C) **Onycholysis**–It is breakage in the distal end of nail plate.

D) **Mees' lines** – These are white transverse bands seen on nail plate. Generally there is a single band but multiple bands may occur. They result from focal parakeratosis of the nail matrix. They have a contour similar to the distal edge of lunula. They are seen in a variety of systemic disorders. Some of them are

a. Arsenic, thallium or heavy metal poisoning

b. Carbon monoxide poisoning

c. Drug induced – due to chemotherapeutic agents like cyclophosphamide, vincristine

d. Psoriasis

e. Renal allograft rejection

f. Chronic renal failure

E) **Muehrcke's lines** –These are also narrow white transverse bands parallel to the lunula. Like Mees' lines they span the entire width of the nail. They occur in pairs and they represent abnormality in the nail bed. They frequently occur on the second, third and fourth finger nails. Unlike in Mees's lines squeezing the distal digit will make the lines temporarily disappear. Hypoalbuminemia is an important cause of these lines. They have been reported in various conditions. Some of them are

A. Chemotherapy
B. Hypoalbuminemia (nephrotic syndrome, glomerulonephritis, liver disease, malnutrition)
C. Malnutrition
D. Heart transplant recipients[51]

F) **Terry's nails** – There is leukonychia affecting the entire nail plate except the distal 20% or 2 mm distal margin. The distal margin corresponds to the onychodermal band, which is characteristic.[52] Terry's nails are a result of changes in nail bed vascularity, a decrease in the proximal portion and an increase at the distal edge. All nails are affected uniformly. They are generally seen in cirrhosis of liver, heart diseases or diabetes mellitus.

G) **Splinter hemorrhages** – They have also been described which are seen more commonly than in normal population.[53] They are present as longitudinal red colored streaks beneath the nail plate due to extravasation of red blood cells from the damaged capillaries.

7) **Purpura** - Purpurae are reddish non-blanchable lesions due to extravasation of red blood cells into the skin or mucosa. Dialysis patients are often on heparin which may increase the incidences of bleeding. Also in hemodialysis patients arteriovenous shunt is formed which may lead to extravasation of blood due to trauma during the dialysis process.[54]

8) **Lesions at site of cannula insertion** - The cannula is inserted into the arteriovenous fistula during dialysis procedure. There might be extravasation of blood, phlebitis due to repeated manipulation of cannula during multiple sittings per

week. Eczema may develop at the site of shunt formation either due to cleaning of the area with betadine or secondary to extravasation of blood. There may also be infections which may be local or rarely cause dangerous septicemia.[55]

9) **Oral mucosal changes** - Oral changes are very common in patients undergoing hemodialysis. [56]They may be specific or non-specific.

Specific signs - Teeth marking is seen along with macroglossia which is known as the '**tongue sign of uremia**'. This finding was first described by Mathew in Chronic kidney disease patients.[57] When urea levels are more than 200 mg/100 ml, a condition known as '**uraemic fetor**' is described. This is an ammoniacal odor produced secondary to high urea concentration in the saliva which breaks down to release ammonia which has a pungent odor. These patients have fewer fungiform taste buds which may cause impairment of taste.[58]

Non-specific signs - Xerostomia (dry mouth) has been reported which may be due to dehydration. Ulcerative stomatitis has been described classically in patients with high urea levels (>150 mg/100 ml) but fortunately this condition is now rarely seen.

10) **Acantholytic dermatosis**–A case of persistent acantholytic disease (Grover's disease) has been described since 6 months in a patient who was on hemodialysis since 9 years.[59] Grover first described this disorder.[60] It is also known as Grover's disease. It is characterized by pruritic, edematous papules or papulovesicles with excoriations. The lesions occur mainly on the upper trunk and histologically show epidermal acantholysis that resemble Darier's disease. The lesions may be transient in which case the condition is called transient acantholytic dermatosis. There is a variant of this disease in which the lesions are persistent. It this case it is called persistent

acantholytic dermatosis. The cause is unknown but actinic damage has been implicated as an initiating factor.

Treatment – There are reports of good response to systemic retinoids. For persistent small lesions surgical excision can deliver excellent results.[61]

Specific findings

1) **Uremic frost**- This is seen in those people whose urea levels are very high (>200 mg/100 ml). The frost consists of white/yellow coating of urea crystals on the beard or on the trunk. It occurs due to urea secretion through the sweat glands which deposits as beads on surface as it cannot evaporate.[62] It is more commonly seen in acute renal failure.

In erythema papulatum uremicum, large papules and nodules on an erythematous base are seen over palms, soles and face. In a few weeks they desquamate and form fissures. This change is also not seen in the present era.

2) **Dialysis related amyloidosis** - It is a type of secondary systemic amyloidosis in which there is deposition of beta 2-microglobulin. It is frequently associated with musculoskeletal and joint complaints. Deposits in the wrist area leads to carpal tunnel syndrome, deposits in bones lead to bone cysts.[63] Heart is the most common extra-articular organ involved followed by the gastrointestinal tract. This visceral form βeta-2-Microglobulin amyloidosis is a major complication of chronic renal failure and occurs mainly in patients who have been on dialysis for more than 10 years. Lingual deposits of amyloid on the tongue have been described as multiple white-yellow and red coloured non-tender, firm nodules of different size.[64] It is closely related to use of low flux, bioincompatible cellulose membranes, which can cause tissue deposition of

beta-2-microglobulin as amyloid fibrils.[65] Other visceral deposits of beta-2-microglobulin amyloid include large masses in subcutaneous tissues, especially in the gluteal region, which is also a rare manifestation of dialysis related amyloidosis.[66] The treatment of dialysis related amyloidosis is limited to the management of symptoms and surgical removal of amyloid deposits. New high flux, biocompatible dialysis membranes are available which are more permeable to beta 2-microglobulin which might delay the onset of dialysis related amyloidosis.[67]

3) **Uremic neuropathy** affects about 60% of patients with chronic kidney disease or patients on long term hemodialysis. This appears to be a predominantly sensorimotor neuropathy.[68] This is a manifestation of uremia.

4) **Acquired perforating dermatosis** – There is lot of ambiguity regarding this terminology. Perforating disorders are a group of disorders, which are characterized by transepidermal elimination of amorphous material. Currently there are 4 disorders, which are recognized as primary perforating disorders. They are elastosis perforans serpiginosa, Kyrle's disease, perforating folliculitis and reactive perforating collagenosis. These perforating dermatosis can occur in diabetes mellitus and in patients with chronic renal failure, many of whom are undergoing hemodialysis.[69] The distinction between these four dermatosis is not clear-cut especially in the case of hemodialysis patients; the conditions may overlap. Thus the name 'acquired perforating disorder' has been proposed for the perforating dermatosis occurring in the setting of chronic kidney disease/ hemodialysis. Gracia Bravo et al have used the term 'uremic follicular hyperkeratosis' for it.[70] When these conditions occur outside the setting of diabetes mellitus or chronic kidney disease they occur as separate entities. This dermatosis occurs in up to 10% of patients undergoing hemodialysis.[71]

Clinically the patients present with hyperkeratotic papules with a central crust filled crater on the trunk and on extensor surfaces often in a linear distribution.[72] The extensor surface of limbs is more commonly involved.

The histologic features may resemble any of the four primary perforating dermtosis.

Chang et al studied 9 Guatemalan patients with acquired perforating disease associated with chronic kidney disease.[73] Out of these 9 patients, 6 were on hemodialysis. Out of these 6 patients, in 5 patients the lesions appeared after starting hemodialysis. In lesions resembling Kyrle's disease there is a keratotic plug showing parakeratosis and basophilic cellular debris filling an epidermal invagination. There is acanthosis in the surrounding area.[74] In perforating folliculitis, a widely dilated follicle is seen which is filled with a keratotic plug containing parakeratosis, suppurative inflammation and basophilic necrotic debris. In reactive perforating collagenosis there is broad cup-shaped epidermal invagination containing parakeratotic debris, inflammatory cells, vertically oriented degenerated basophilic collagen.[75]

The exact etiology for the disorder is not known. Possible explanations are diabetic microangiopathy, dysregulation of vitamin A or D metabolism, inflammation and connective tissue degradation caused by dermal deposition of substances like uric acid or calcium salts which are accumulated in excess during renal failure.[76] It is also thought that this is a reaction pattern to constant itching and scratching in chronic kidney disease.

Treatment options consist of topical and intralesional corticosteroids, topical and systemic retinoids, cryotherapy and ultraviolet therapy. Oral vitamin A (1, 00,000 U/day) has also been tried.

5) **Nephrogenic fibrosing dermopathy -** Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis (NFD/NSF) is a recently recognized fibrosing disorder of the skin that occurs in patients with renal insufficiency. NFD was originally described in 1997 in 15 patients receiving hemodialysis, who developed lesions on their extremities and trunk, characterized by thickening and hardening of the skin, papules and nodules with hyperpigmentation, and flexion contractures.[77] In this condition on examination the lesions are well defined and may have finger like projections. The plaques may be erythematous, yellow or skin coloured. Patients describe pain, paresthesias and pruritus but are most bothered by the limitations in the mobility resulting from flexion contractures. On examination of eyes most patients have scleral plaques. Clinically the lesions resemble scleroderma or morphea but they have distinct biopsy findings correlating with scleromyxoedema. Scleromyxoedema is a condition characterized by mucin deposition in the viscera and immunoglobulin G (IgG) lambda paraproteinemia. However these 2 conditions are lacking from the patients of nephrogenic fibrosing dermopathy. Scleromyxoedema tends to involve the head and neck area. These areas are spared in nephrogenic systemic fibrosis.

There seems to be no correlation between ethnic background, sex or the cause of chronic kidney disease. This condition occurs in patients on end stage renal disease most of whom are on hemodialysis.[78]. The histopathology of Nephrogenic fibrosing dermopathy is similar to scleromyxoedema. There is proliferation of fibroblasts in the

dermis and subcutaneous septae, along with deposition of collagen and mucin.

It has been recently discovered that this condition occurs in people who have had a magnetic resonance scan using gadolinium. Gadolinium is a radiocontrast media. Such contrast media are not recommended if the glomerular filtration rate is less than 30 ml/min. It is hypothesized that the retention of Gadolinium in patients with kidney disease is profibrotic. In some studies it has been shown by skin biopsies that Gadolinium has been retained in the skin of patients with chronic kidney disease even more than 2 years after intake.[79] These patients have also been shown to have abnormal scintigraphy with increased uptake of ^{99mTc}-hydroxymethylene diphosphonate in the skeletal muscle underlying the involved skin, demonstrating an abnormal process extending deeper than the dermis.[80,81] The disease process can involve the underlying organs also so a new terminology "Nephrogenic systemic fibrosis" has been proposed. Involvement of the diaphragm can even lead to death. 10% of the patients with nephrogenic systemic fibrosis have a fatal course.

Recently a classification scheme was proposed for the clinical subtypes seen based on data from published reports and the NFD registry organized through Yale University, United States of America.[82]

Table 5: Clinical subtypes of nephrogenic fibrosing dermopathy (NFD): a proposed classification scheme[83]

Subtypes	Description	% Of previously reported patients (n = 100)	% of patients from case series (n = 9)	NFD progression
1	New onset acute renal failure or acute decompensation from chronic renal failure	25	22	May be transient
2	Pneumonia like disorder followed by renal failure	6	0	Usually transient
3	Surgical procedure or acute blood loss followed by acute renal failure	18	22	May be transient
4	Kidney transplant	34	55	May be transient
5	Chronic renal failure, unknown trigger	3	11	Usually chronic
6	Thrombotic event, renal failure may predate or follow the event	12	11	May be transient

Treatment – Since there are very few cases described in literature no definitive therapy exists. The most dramatic improvement was seen in 3 patients who were treated with plasmapheresis.[84] Other therapies tried with variable success are UV-A1 phototherapy, prednisone, extracorporeal photopheresis and methotrexate.[85]

6) **Bullous disease of hemodialysis** - It is a well known entity with an incidence of 2-18% in patients undergoing hemodialysis. It is also known as pseudoporphyria of hemodialysis. Korting first reported it in 1975 as a bullous dermatosis resembling porphyria cutanea tarda undergoing maintainance hemodialysis. All these patients had normal porphyrin levels. In chronic kidney disease, the normal porphyrin excretion is retarded so it may be confusing to distinguish between Porphyria cutanea tarda and pseudoporphyria. However in pseudoporphyria the porphyrin levels are only moderately elevated so accurate assays of porphyrin levels are of prime importance.[86] Pseudoporphyria may also develop in association with medications like furosemide, nalidixic acid, tetracycline, naproxen, pyroxidine or amiodarone.

The clinical presentation of pseudoporphyria is similar to sporadic porphyria cutanea tarda. Clinically there are tense vesicles and bullae distributed on the dorsal hands, face and occasionally the feet. Secondary changes include erosions and crusts. The bullae heal with scarring and milia formation. The skin is fragile and easily traumatized. Hyperpigmentation of sun exposed skin is seen. Hypertrichosis is also observed.

Laboratory findings: All types of porphyria cutanea tarda have increased serum iron, ferritin and hepatocellular iron. Those patients who are not anuric excrete increased uroporphyrin I, which is greater than uroporphyrin III and7-carboxyl porphyrins in the urine. Anuric patients demonstrate markedly elevated plasma levels of uroporphyrin.[87]

Histopathology: Porphyria cutanea tarda in characterized by subepidermal vesiculation with little or no inflammation. The base of bulla is corrugated and lined by well preserved dermal papillae (festooning). There is mild thickening of basement

membrane zone and vessel walls, which can be highlighted with periodic acid-Schiff stain. The findings in pseudoporphyria are similar although periodic acid-Schiff stain reveals less vessel wall thickening.

Management: In both the scenarios sun protection is vital. Broad-spectrum physical blockers such as zinc oxide or titanium dioxide are preferred. Unfortunately, standard hemodialysis does not effectively remove uroporphyrin. High flow rate dialysis with a high-flux polysulfate dialyzer can reduce plasma porphyrin levels by up to 37%,[88] however this is insufficient to induce clinical remission. N-acetyl cysteine, which is an antioxidant, may help in reducing the blistering.[89] Treatment of true Porphyria cutanea tarda in the patients is limited as antimalarials work by forming complexes with porphyrins and getting excreted in urine. In chronic kidney disease patients the urine production is reduced. Further the porphyrin-antimalarial complexes cannot pass through the dialysis membrane. For patients without renal problem phlebotomy is the treatment of choice. In this procedure, 500 ml of blood is removed every fortnightly. However this procedure is limited in patients with chronic kidney disease stage 5 as these patients already have low hemoglobin due to reduced erythropoietin formation. Small volume phlebotomies (50-100 ml) every week over 1 year have been reported to induce remission. These patients are also treated with erythropoietin along with small volume phlebotomies. This has been shown to mobilize hepatic iron stores. Complete resolution may require several months of therapy. Desferoxamine may also lower porphyrin levels in some patients but it has side effects and so can be used only for limited time. Renal transplantation provides complete resolution of symptoms.[90]

7) **Calciphylaxis** - It is characterized by progressive cutaneous necrosis associated with small and medium vessel calcification. It occurs in the setting of end stage renal disease, diabetes and hyperparathyroidism. Many of these patients are also on hemodialysis. The exact cause is not known. Vascular calcifications are common in patients with chronic kidney disease and generally they are asymptomatic. In calciphylaxis there is sudden thrombosis in the calcified vessels. It is a type of induced systemic hypersensitivity in which tissues respond inappropriately to certain challenging substances with calcium deposition. The challenging agents include glucocorticoids, albumin infusions, intramuscular tobramycin, iron dextran complex, calcium heparinate, immunosuppresive agents and vitamin D. It occurs closely following initiation of hemo- or peritoneal dialysis.

It is a very painful condition. Initially there is a preinfarct stage. In this stage there is mottling of skin or it may have a livedo reticularis like pattern. The skin may appear dusky red or violaceous. Later bullae may start forming over the ischaemic area. These bullae eventually become necrotic and progresses to the infarct stage. The central infarcted site becomes black or yellowish. This infarcted area keeps becoming larger. When this is debrided, deep ulcers are seen which may even reach up till the fascia. This ulcer can become secondarily infected and may take a sinister course like cellulitis or septicemia. The calciphylactic skin changes are mostly seen on distal extremities, especially over the lateral and posterior calves, abdomen, buttocks, fingers and glans penis. On investigation uremia is present. The calcium x phosphate product is elevated. Parathyroid hormone levels are elevated in these patients.

For histopathology deep incisional biopsy should be taken. There is calcification of small to medium sized blood vessels in the dermis and subcutaneous

tissue. Intraluminal fibrin thrombi are present. If the ischemia is severe lobular or septal fat necrosis may take place along with lymphohistiocytic infiltrate. Radiographs of affected extremities show calcium deposition outlining small and medium sized vessels.

The differential diagnosis includes panniculitis, necrobiosis lipoidica with ulceration, dystrophic calcification, disseminated intravascular coagulation, pyoderma gangrenosum and warfarin necrosis.

Overall the prognosis is bad and mortality rate is very high. Treatment of renal failure helps in improving the condition. Aggressive debridement of wound helps in preventing secondary infection and in wound healing. Subtotal or total parathyroidectomy may help as this condition is related to hyperparathyroidism. Phosphate binding agents may also help.

In addition to vascular calcification and calciphylaxis, nodular calcification may occur in the skin and fat of patients with chronic kidney disease. These deposits are identical to calcinosis cutis of CREST syndrome. The involved skin may ulcerate here also but this is without the severe pain and livedo reticularis like lesions.

Discussion

64 patients were examined in the study. No controls were taken in the study. In an Egyptian study by Attia et al total of 206 uremics were taken. They were then compared with controls which were age and gender matched. This is a limitation of the present study which is a cross sectional study. A case control study would have helped to eliminate the confounding errors.

Table 24: Sample size of various studies

Study	Sample size
Present study	64
Eyptian study by Attia et al	206
Indian study by Udayakumar et al	100
Indian study by Tawade et al	35

Larger the sample size greater is the power of the study. However due to time restriction only 64 patients were examined. Increasing the sample size would have increased the power of the study.

The criteria for choosing the patients in the present study was that the patient should be having chronic kidney disease stage 5. It is defined as the end stage renal disease with Glomerular filtration rate < 15 mL/min per 1.73 m^2 In the study by Attia et al predialysis lab parameters were taken to include patients into the study. They were

Serum creatinine - >4 mg/dl

Blood urea >100 mg/dl

Serum potassium > 6.5 meq/l

Serum bicarbonate <15 meq/l.

In the study by Makhlough et al all the patients who were undergoing hemodialysis were taken into study. All the patients having skin pathologies were excluded.

In the present study out of 64 patients 50 were men and 14 were women. Thus men constituted 78.12% of cases. This value is much higher than those seen in other studies. In an Israel study conducted by Dyachenko et al men constituted 60% of the cases.[91] In an Egyptian study by Attia et al men constituted 53% of cases. (add end note). The kidney disorders are not known to affect the different sexes differentially. The result in our study is probably due to the fact that increased numbers of men seek treatment for their disorders probably due to socioeconomic reasons.

Table 25: Comparison of the number of males and females taking part in various studies

Study	**Men**	**Women**
Present study	50 (78.12%)	14 (21.87%)
Tawade et al	30 (85.71%)	5 (14.28%)
Udayakumar et al	70 (70%)	30 (30%)
Attia et al	110 (53.39%)	96 (46.60%)
Makhlough et al	80 (52.3%)	73 (47.7%)

Cause of renal failure–In the present study hypertension was the most common cause of renal failure, followed by diabetes and chronic tubulointerstitial disease. This differed from the study by Attia et al where diabetes was the most common cause followed by hypertension.

Table 26: Comparison of etiology of chronic kidney disease in various studies

Cause of renal failure	Present study (in %)	Attia et al (in %)
Diabetes Mellitus	32.8	11.6
Hypertension	70.3	9.8
Renal stones	1.5	9
Chronic pyelonephritis	1.5	3
SLE	1.5	2.4
Chronic tubulointerstitial disease	18.75	-
Others	20.31	60

Duration of dialysis– Patients of chronic kidney disease stage V were taken into the study irrespective of the duration of dialysis. The range varied from less than 3 months to more than 5 years. The duration of dialysis were categorically divided and correlated with PTH levels. In all these categories the least abnormal values were found between 6 months to 36 months. There was a statistically positive correlation with normal parathyroid hormone levels during this period. This means that on an average it takes 6 months of hemodialysis for the parathyroid hormone levels to

become normal. They remain normal till 36 months and after that they start to rise abnormally even after continuing hemodialysis.

Pruritus:

In the present study 28.1% patients complained of itching prior to dialysis where as 40.6% patients complained of itching post dialysis.. Thus there was an increase in the incidence of itching post dialysis. No objective criteria were used to measure the intensity of pruritus. Patients were asked only two questions regarding pruritus. They were

1) Was there pruritus prior to dialysis?

2) Has the itching increased after dialysis?

In the study by Maklough et al the prevalence of pruritus was 61.4%. In the study by Dyachenko et al prevalence of pruritus was 74.3% at the time of dialysis

Table 27: Comparison of prevalence of pruritus in various studies

Study done	Prevalence of pruritus
Present study	28.1%
Makhlough et al	61.4%

Dyachenko et al	74.3%

In the study by Makhlough et al an elaborate scoring system proprosed by Duo et al (insert reference AD)was used to quantify pruritus and then the intensity of itch was compared with various parameters.[22] The total scoring of pruritus is calculated as follows:

(Severity of pruritus x distribution of pruritus) + sleep disorder.

The severity of pruritus is assessed as:

1 point	Slight itching
2 points	Itching with scratching
4 points	Itching and scratching with excoriations
5 points	Itching causing total restlessness

The distribution of pruritus is scored as

1 point	Pruritus maximum in 2 areas of the body
2 points	Pruritus maximum in more than 2 areas of the body
3 points	Generalized pruritus

The sleep disorder is monitored as

2 points (maximum of 10 points)	Every waking up due to itching
1 point (maximum of 5 points)	Each scratching

The drawback of this scoring system is that pruritus is a subjective symptom and the perception of itch may vary from person to person even if the same level of pruritus exists in two individuals. Thus the resultant score is prone for errors. The advantage of this method is that pruritus is quantified and so correlational studies can be easily carried out.

Dyachenko et al studied hemodialysis related pruritus and associated cutaneous manifestations.[92] In their study the patients were considered to have pruritus if they had either of the two conditions

1) At least 3 episodes of itching during a period of 2 weeks or less, with the symptom appearing several times during the day, lasting for at least a few minutes, and troubling the patient

2) The appearance of itch on a regular pattern in a regular pattern during a period of 6 months.

To be defined 'uremic' the pruritus had to appear shortly before the onset of dialysis, or at any time thereafter, without evidence of any other active disease, which could explain it.

In the present study pruritus was considered only as either present or absent. This was probably an oversimplification and the scoring system by Duo et al could have given more statistically relevant results.

The etiology of pruritus is still unknown. The hypothesis of the present study was to see if there was a correlation between pruritus and parathyroid hormone levels. In the present study there was no correlation between pruritus and parathyroid hormone. In the study by Makhlough et al there was a statistically positive correlation between pruritus and parathyroid hormone.

Table 28: Comparison between parathyroid hormone and pruritus in different studies

Subgroup		Hyperparathyroidism present	Hyperparathyroidism absent	P value
Present study				
	Pruritus present	17 (43.58%)	14 (56%)	P = 0.546
	Pruritus absent	22 (56.42%)	11 (44%)	
Makhlough et al (males)				
	Pruritus present	37 (64.3%)	19 (61.3%)	P = 0.001
	Pruritus absent	15 (35.7%)	12 (38.7%)	
Makhlough et al (females)				
	Pruritus present	27 (64.3%)	19 (61.3%)	P = 0.18
	Pruritus absent	15 (35.7%)	12 (38.7%)	

Makhlough et al had divided the patients into males and females. As can be seen from table 27 that the statistically significant correlation between pruritus and parathyroid hormone levels was obtained only for males and not for females. Neither pruritus nor parathyroid hormones are known to affect the different sexes differentially so there seems to be some fallacy in the above results in the above study. In the present study the patients were not divided on the basis of sex. Thus there is still not clear consensus whether hyperparathyroidism is the cause for uremic pruritus. According to the present study pruritus seen in hemodialysis has no relation to parathyroid hormone.

Also in the present study the prevalence of itching prior to dialysis was 28.1% whereas after starting dialysis the prevalence of itching was 40.6%. So there was 12.5% increase in the prevalence of pruritus. Thus this increase in pruritus can be attributed to the dialysis procedure. It might either be that the pruritogens are not filtered through the dialysis membrane. The constituents of the diasylate fluid may be causing increase in pruritus.

In the present study the sample was collected before starting the dialysis procedure as during the dialysis procedure many patients are administered heparin. This could possibly alter the laboratory results. This was similar to the study by Makhlough et al in which blood was withdrawn prior to starting the dialysis procedure.

Analysis was done in various studies between pruritus and duration of dialysis. In the study by Makhlough et al there was no relation between pruritus and duration of dialysis. In the study by Dyachenko et al also there was no relation between the two. Our study also had a similar finding.

Pallor

In the present study prevalence of pallor was 65.62%. This was slightly less than that seen in the study by Dyachenko et al (75.7%). In an Egyptian study by Attia et al, the patients were divided into adults and children among adults the prevalence of pallor was 48.5%. In children the prevalence of pallor was only 18%. They hypothesized that in Egypt there is free supply for erythropoietin in their health programs which accounted for the low prevalence of pallor. Udayakumar et al studied 100 patients undergoing hemodialysis in India. The prevalence of pruritus in their study was 60%. They hypothesized that the prevalence of pallor was low in their study due to darker complexion of the patients. Thus the figures in the present study correlate with the Indian study by Udayakumar et al. Pallor did not have a statistically positive correlation with parathyroid hormone.

Table 29: Comparison of pallor between various studies

Study	Prevalence of pallor
Present study	65.62%
Attia et al	48.5%
Udayakumar et al	60%
Dyachenko et al	75.7%

Skin colour changes post dialysis

In the present study 21.87% patients complained of darkening post dialysis. This differed from other studies. In the study by Udayakumar et al 40% of patients experienced darkening post dialysis. In the study by Dyachenko et al the 75.7% patients complained of hyperpigmentation post dialysis. In the study by Attia et al hyperpigmentation was seen in 17.8% of their cases but only in 3% of controls. In contrast to all the other studies which showed pigmentation more in a photodistributed area, in the present study patients complained of generalized diffuse pigmentation. The earlier studies had suggested that the increased pigmentation was due to the inability of kidneys to excrete beta-melanocyte stimulating hormone but that does not explain why the pigmentation would occur more in a sun distributed area. The present study does not have that discrepancy as the pigmentation was seen in a diffuse pattern. There was no statistically positive correlation between hyperpigmentation and parathyroid hormone.

Table no 30: Comparison between skin darkening post dialysis in various studies

Study	Prevalence of skin darkening
Present study	21.87 %
Udayakumar et al	40 %

Attia et al (cases)	17.8%
Attia et al (controls)	3 %
Dyachenko et al	78.7%

Half and half nail

Half and half nail is a specific feature of patients with chronic kidney disease stage 5. Even among these patients it is seen more commonly in patients undergoing hemodialysis.[92] In the present study it was seen in 15.62% of cases. It was similar to the prevalence seen in study by Dyachenko et al (18.6%). In an Indian study by Tawade et al the prevalence was 17%. Thus the prevalence of half and half nail was more or less similar in various studies. In the present study there was no correlation was found between this nail change and parathyroid hormone. No similar studies were found which compared the two variables.

Table 31: Comparison of half and half nail in various studies

Study	**Prevalence of half and half nail**
Present study	15.62%
Dyachenko et al	18.6%

Tawade et al	17%
Udayakumar et al	21%

Terry's nail

In the present study Terry's nail was found in 23.44% of patients. This is unusual because none of the literature pertaining to nail changes in hemodialysis patients mentions this finding. Terry's nails are usually seen in cirrhosis of liver, heart failure and in diabetes mellitus. In the present study the patients with Terry's nails were not suffering from this disorder. Thus Terry's nails can be also be considered as one of the cutaneous manifestations of patients undergoing hemodialysis. In the present study there was no statistically relevant correlation between Terry's nail and parathyroid hormone levels.

Muehrcke's lines

In the present study the prevalence of Muehrcke's lines was 7.8%. This was similar to study by Udayakumar et al who reported prevalence of 5% in their study. In the present study there was no correlation between Muehrcke's lines and parathyroid hormone. In our knowledge no other study has compared these 2 variables.

Hair changes

In the present study 39.1% patients reported that they had lost hair post dialysis.in the study by Udayakumar et al 30% of patients had sparse body hair whereas 11% had sparse body hair at the time of inspection. They did not mention whether these changes were present before the hemodialysis or they appeared after starting it. In the Egyptian study by Attia et al, among adults the prevalence of pruritus was 33.7% cases whereas in children the prevalence of hair loss post dialysis was 34.9%. Thus our study has similar findings. The hair loss in dialysis patients may be due to stress of the disease per se or the dialysis procedure due to which the hair enter into telogen effluvium. Another cause can be anaemia in these patients, which may cause hair loss.

Table 32: Comparison of hair loss after dialysis in various studies

Study	Prevalence of hair loss
Present study	39.1
Udayakumar et al	41%
Attia et al (adults)	33.7%
Attia et al (children)	34.9%

Xerosis

In the present study prevalence of xerosis was 95.31%. Xerosis has been known to be the most common manifestation of patients undergoing hemodialysis. Our study also found similar result. It was the most common manifestation seen in our study. However it did not have a statistically positive correlation with parathyroid hormone.

Acquired perforating disorder

In our study it acquired perforating disorder was seen in 3(4.7%) of cases. Out of these 3 cases 2 were diabetic. Out of the 3 one patient consented for skin biopsy. The skin biopsy did not reveal any evidence of altered elastin material, nor was there any evidence of folliculitis. Thus it was neither elastosis perforans serpinginosa nor perforating folliculitis. In the study by Dyachenko et al they did not find any case of perforating disorder in their study. Tawade et al reported a prevalence of 17% in their study on 35 patients on hemodialysis. Udayakumar et al reported a prevalence of 21% in their study of 100 patients on haemodialysis. Attia et al reported a prevalence of 2.5% among their patients.

Table 33: Comparison of prevalence of acquired perforating dermatosis among various studies

Study	**Prevalence of APD**
Present study	4.7%

Dyachenko et al	0%
Tawade et al	17%
Udayakumar et al	21%
Attia et al	2.5%

Bullous disease of hemodialysis

This was not seen in the present study. This was because it is a rare disorder and the sample size of the present study was small. Attia et al reported a single case (0.6%) of bullous dermatosis. Udayakumar et al did not report any case of bullous dermopathy in their study. Dyachenko et al also did not report any case of bullous dermopathy in their study.

Nephrogenic systemic fibrosis

No case of nophrogenic systemic fibrosis was found in the present study. This was probably because is a very rare disorder and the sample size was small.

Calciphylaxis

In the present study no case was found to have calciphylaxis. This was so because it is also a rare disorder and the sample size was small. It was not reported by Attia et al, Dyachenko et al, Udayakumar et al.

Thus parathyroid hormone was not statistically significant to any of the cutaneous changes seen in patients undergoing hemodialysis.

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Methodology

Skin conditions are very common in patients with chronic kidney disease. It is estimated that 80% of patients with chronic kidney disease have at least one skin manifestation. The term chronic renal failure is no longer used. It is referred to as chronic kidney disease. It has 5 stages. Stage 5 is the end stage renal disease defined by GFR < 15 mL/min per 1.73 m^2.[1]Stage 5 is the end stage requiring intervention of some kind for survival. It may be dialysis or renal transplantation. Dialysis is of 2 types, hemodialysis and peritoneal dialysis. In hemodialysis movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate.[2] Peritoneal dialysis is another type of dialysis in which dextrose containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time. The peritoneal membrane is used as the filtering membrane across which the substances are filtered. In our hospital hemodialysis is done on a routine basis. Peritoneal dialysis is not done and renal transplantation is done infrequently.

Since most of the patients of chronic kidney disease stage V are invariably on some form of renal replacement therapy there is an overlap between the skin manifestations due to chronic kidney disease and skin manifestations seen in hemodialysis patients. No study has been done on the skin manifestations in hemodialysis patients in our hospital so that was the basis of starting this study. On a look through literature there were numerous studies describing skin manifestations in dialysis patients[3] so a need was felt to explore things further. There are some studies which have correlated some skin manifestations to Parathyroid hormone. Massry et al postulated that itch associated with chronic kidney disease was due to secondary hyperparathyroidism and that it could even respond to parathyroidectomy.[4] There also seems to be correlation between dry skin and hyperparathyroidism[5]. Also there is an obvious correlation with the calcemic manifestations seen in chronic kidney disease patients and Parathyroid hormone levels.[6] However this is not true in all cases and in other studies

no such correlation has been found between Parathyroid hormone levels and these conditions. In addition Pubmed search at the time of starting this study did not show any result for cutaneous changes in hemodialysis and their correlation to Parathyroid hormone. With this backdrop this study was initiated and to our knowledge no such study has been done in India so far.

Parathyroid hormone is produced from parathyroid glands. It is an 84-amino-acid single chain peptide. It causes calcium resorption from bones, and calcium resorption from the kidneys. This hormone maintains extracellular fluid calcium concentrations within a narrow normal range. Increased level of parathyroid hormone is known as hyperparathyroidism. This can be primary or secondary. Primary hyperparathyroidism is due to excess secretion from either an adenoma or hyperplasia of the parathyroid glands. Secondary hyperparathyroidism occurs due to an adaptive response to an underlying pathology causing increase in the parathyroid hormone levels. Patients with secondary hyperparathyroidism may develop bone pain, ectopic calcification and pruritus. The bone disease in patients with secondary hyperparathyroidism and renal failure is termed renal osteodystrophy. In patients on long-term dialysis especially who have excess aluminium in their dialysis regimen, aluminum intoxication may occur. Aluminum starts to deposit in the bones and causes severe osteomalacia, acute dementia and unresponsiveness. Prevention is by avoiding aluminum excess in the dialysis regimen.

Various studies done on cutaneous changes in hemodialysis patients have shown that at least 80% of patients have at least one cutaneous manifestation[7].

The cutaneous manifestations of patients undergoing dialysis can be arbitrarily divided into 2 types, non-specific and specific skin lesions.

Table 1: Cutaneous manifestations of patients undergoing hemodialysis

Non- specific changes	**Specific changes**
Pruritus	Uremic fetor
Xerosis	Tongue sign of uremia
Pallor	Uremic frost
Pigmentary changes	Dialysis related amyloidosis
Hair abnormalities	Uremic neuropathy
Nail changes e.g. Koilonychias, subungualhyperkeratosis, Mees' lines	Nail changes e.g. Half and half nail
Purpura	Acquired perforating dermatosis
Lesions at site of cannula insertion	Nephrogenic systemic fibrosis
Oral mucosal changes – xerostomia	Bullous disease of hemodialysis
	Calciphylaxis

Non-specific findings

1) **Pruritus** - The prevalence of pruritus in hemodialysis patients in various studies varies from 50-90 %.[8]The largest study done so far analyzed data from 18,801 patients undergoing hemodialysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS) from 1996-2004) and indicated that 42% of hemodialysis patients experienced moderate to severe pruritus.[9]It is the most characteristic and annoying symptom of chronic kidney disease.[10] It is also referred to as 'uremic pruritus' which literally means pruritus secondary to uremia which is untrue. The pruritus does not have relation with gender, age or duration of dialysis. The pruritus seems to be less in patients on ambulatory peritoneal dialysis than on hemodialysis patients. Pruritus also depends on the type of dialysis machine e.g. depending on the permeability of the dialysis membranes the ones with high

permeability have been thought to have decreased pruritus. [11] In those patients on regular dialysis the pruritus seems to be maximum on 2 days after the last dialysis session, least on the day following dialysis. Also itching is relatively high during the dialysis procedure.[6]

Clinical characteristics of itch

The intensity of itch associated with chronic kidney disease ranges from sporadic discomfort to complete restlessness during the day and night. It could be intermittent or persistent.[12] It can be generalized in 25-50% of patients, and it predominantly affects the back (70%), abdomen (46%), head (46%), and arms (43%).

Uremic pruritus is absent in acute renal failure.[13] Exact cause for itching in chronic renal failure is not known. It is multifactorial in origin. The common causes are uremicxerosis, secondary hyperparathyroidism, hypervitaminosis A, uremic neuropathy, elevated serum histamine levels and iron deficiency anemia. Of these uremic xerosis is perhaps the most important cause as it is the most common cutaneous manifestation in chronic kidney disease patients. It is present in 90-100 % patients having pruritus.[14] The level of uremic pruritus is directly proportional to the xerosis. Xerosis is due to dehydration of skin resulting from atrophy of eccrine glands and loss of lipids on skin due to atrophy of sebaceous glands however Yosipovitch et al did not find any evidence between the severity of pruritus and objective parameters of xerosis.

Endogenous opioids are important players in the pathogenesis of itch. An increased ratio of serum beta-endorphin to dynorphin A was reported in hemodialysis patients compared with healthy controls and the ratio increased with increased intensity of itch.[15]

Some studies have reported significant association between serum parathyroid hormone and itching whereas others have not found any association. Kidney failure, hyperphosphatemia, hypocalcemia and decreased levels of calcitriol (vitamin D) are factors which increase parathyroid hormone levels.[16] Thus the raised parathyroid hormone level in kidney failure is actually a type of secondary

hyperparathyroidism.[17] It has been reported that pruritus in some patients can completely disappear after parathyroidectomy.[18] Hyperparathyroidism can stimulate mast cells to release histamine. This can promote micro precipitation of calcium and magnesium salts in the skin. On the other hand all patients with severe hyperparathyroidism do not have pruritus. Also there is no difference in the number of mast cells in patients with hyperparathyroidism in patients having and not having pruritus.[19] In experimental intradermal injections of parathyroid hormone failed to produce pruritus. Also in the same study immunohistochemistry was negative for parathyroid hormone in skin biopsies in patients undergoing hemodialysis.[20] In a recent Iranian study there was a significant correlation was found between itching score and serum intact parathyroid hormone in hemodialysis patients.[21]

Impact on the quality of life

It was found in Dialysis Outcomes and Practice Patterns Study that patients undergoing hemodialysis with pruritus were more likely to feel drained and have poor sleep quality, depression and lower mental and physical composite scores of quality of life than patients with no or mild pruritus. Moreover pruritus in hemodialysis patients is associated with 17% higher mortality rate than the patients on hemodialysis who are not having pruritus. (insert end note AA)

The difficulty which an investigator faces with pruritus is the subjectivity of the symptom. It is a purely subjective symptom and each patient may have a different threshold for what he or she finds bothersome. There are a few ways of objectively measuring pruritus. One way is to ask the patient to rate his or her pruritus on a scale of one to ten, one being ‘no itching’ and ten being the ‘most severe’ itching which the patient just can’t tolerate. Another scale is the modified scoring system proposed by Duo.[22] The total scoring of pruritus is calculated as follows:

(Severity of pruritus x distribution of pruritus) + sleep disorder.

Table 2: The severity of pruritus is assessed as:

1 point	Slight itching
2 points	Itching with scratching
4 points	Itching and scratching with excoriations
5 points	Itching causing total restlessness

Table 3: The distribution of pruritus is scored as

1 point	Pruritus maximum in 2 areas of the body
2 points	Pruritus maximum in more than 2 areas of the body
3 points	Generalized pruritus

Table 4: The sleep disorder is monitored as

2 points (maximum of 10 points)	Every waking up due to itching
1 point (maximum of 5 points)	Each scratching

There may be some sort of pruritogen which is not adequately filtered through the dialysis membrane thus accumulating in the body under the skin and cause itching. The type of dialysate

may also have a role in pruritus. Lower levels of Magnesium in the dialysate have been correlated with lower levels of pruritus.[23]

Treatment of pruritus

There are various treatment modalities which have variable efficacy for treatment of pruritus. Wang et al have proposed a therapeutic ladder for management of pruritus in end stage renal disease.[24]

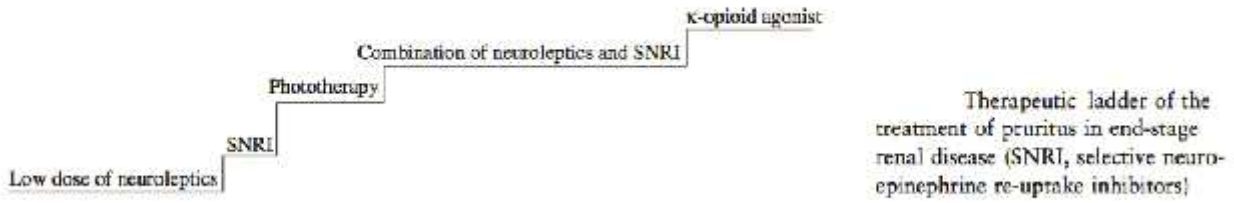

Figure 1 – Therapeutic ladder of the treatment of pruritus in end stage renal disease (SNRI, selective neuroepinephrine re-uptake inhibitors)

The first line of management is with neuroleptics. Gabapentin and pregabalin are structural analogs of the neurotransmitter GABA. The exact mechanism of their mechanism is not clear. They probably inhibit the central itch pathways just like in neuropathic pain.[25] In a placebo controlled double blinded study by Gunal et al in 25 patients with end stage renal disease associated pruritus found that 300 mg of oral gabapentin given after each hemodialysis session was safe and effective

regimen.[26] Gabapentin is a neurotoxic drug. In another study it was suggested that starting 100 mg initially with a slow upward titration can reduce this side effect.[27]

The second line of management is SNRI (Selective neuroepinephrine re-uptake inhibitors). They relieve the itching probably by reducing central sensitization to itch. Mirtazapine has been found to be effective in treatment of nocturnal pruritus.[28]It has also been found to be effective in renal pruritus.[29]

The third line of management is phototherapy.UVB therapy is effective in severe intractable pruritus.[30] It is considered the treatment of choice in many centers. UVA therapy without psoralens is also said almost just as effective.[31] The exact mechanism of action is not known. Probably it works via chemical modification of pruritogens in the skin or an alteration of skin sensitivity to pruritogens. It may also work by reducing post inflammatory cytokines. It is important to inform the patient that the in the first 2 weeks the itch may worsen and the reduction in pruritus may take 1-2 months.

If itching is not controlled by the above measures the fourth line management is using a combination of neuroleptics like Gabapentin and selective neuroepinephrine re-uptake inhibitors like Mirtazapine.

If itching is still not controlled then the fifth line of management is Opioid agonists. A recent kappa receptor agonist, nalfurafine(TRK-820) has shown antipruritic effect in the treatment of ESRD associated pruritus. However it is not available commercially.[32]

Other alternatives are activated charcoal, cholestyramine, erythropoietin, ondansetron and naltrexone.[33] Sedating antihistaminic like hydroxyzine have some role in control of pruritus. Other antihistaminics do not help much because histamine does not play a significant role in uraemic pruritus.[34]Various topical therapies can also be used. Emollients help to a certain extent as xerosis is one of the most common causes of pruritus. In a double blinded placebo controlled study 0.025% capsaicin was found to significantly reduce pruritus in comparison to placebo.(insert reference

AB)Pramoxine 1% lotion was found to be efficient in treatment of uremic pruritus in a recent study.[35]

Renal transplantation is curative for uremic pruritus.

2) **Xerosis** - Uremic patients tend to have a very dry skin. It is the most common cutaneous manifestation seen in patients undergoing hemodialysis.[36] It is seen in up to 90% of patients. This is thought to be due to reduction in the eccrine sweat glands which reduces water content of the skin and also reduction in size of pilosebaceous units due to which there are decreased lipids on skin surface.[37] High dose diuretics may lead to iatrogenic dehydration leading to dryness of skin.[38]Xerosis is also a manifestation of Diabetes Mellitus and since Diabetes mellitus is the most common cause of chronic kidney disease in most centers, xerosis may be attributed to it. Also uraemia has been known to cause peripheral neuropathy which could also affect peripheral autonomic nerves thus leading to decreased sweating secondary to autonomic nervous dysfunction. This could in turn cause xerosis.

Treatment – Emollients can help only to a certain extent.

3) **Pallor** - Kidneys are the sites for erythropoietin production, which is essential for normal erythropoiesis. Thus in chronic kidney disease there is reduced erythropoietin production which causes decreased RBC production leading to anemia. Udayakumar et al. reported pallor in 60% of uremic patients.[39] Pallor may be difficult to appreciate in some patients as they start developing diffuse pigmentation all over body.

Treatment – Erythropoietin injections can help in RBC synthesis to a certain extent.

4) **Pigmentary changes** - Two different types of pigmentation patterns may be seen. First one is diffuse hyperpigmentation present all over the body but more so in sun exposed areas. The

prevalence for this has been estimated as around 20-25%.[40] The diffuse hyperpigmentation has been attributed to increased melanin in the basal layer of epidermis and upper region of dermis due to failure kidneys to excrete beta-melanocyte stimulating hormone (β-MSH).[41] Hyperpigmented macules over palms and soles have also been reported.

The second type of pigmentation pattern seen is yellowish discoloration of skin. This has been reported in as many as 40% of patients. This has been attributed to accumulation of carotenoids and nitrogenous pigments like urochromes in the dermis.[42]

There might be a third kind of skin colour change which may be described that is the pale skin due to severe pallor. This is described more so in western literature and difficult to ascertain in Indian skin.

5) **Hair abnormalities** - Sparse body hair and diffuse alopecia have been described.[43] The exact cause is not known. One of the causes can be severe anaemia which is very common in these patients. The second hypothesis is that these patients are under lot of stress which can precipitate telogen effluvium. The hair in these patients is dull and lusterless. This is so because of decreased sebum secretion.[44]

6) **Nail changes**– Nail changes may be specific or non-specific.

Specific nail changes

Half and Half Nails- The classical nail change described is Lindsay's nails (half and half nails). These nails are red or pink in the distal half and white in the proximal half.A distinct line appears to separate the two zones. The red colour in the distal half does not fade with pressure.[45] Studies have shown prevalence from 16-50%.[46]The pathogenesis is not known. Stimulation of nail bed melanocytes by increased levels of plasma melanotrophic hormones and vascular changes have

been suggested as possible causes.[47] They have also been reported after cancer chemotherapy; in a breast cancer patient after androgen use; after exposure to paraquat.[48] Erythematous crescent is a reddish discoloration of the distal nail involving less than 40% of distal nail bed. It is also seen in chronic renal failure.[49] They may also be present in normal healthy adults. Once present these changes may remain permanently even after hemodialysis.

Non-specific nail changes

A) **Koilonychia** – There is loss of convex curvature of the nails. The nails either become flat or truly concave or'spoon like nails'. It affects fingernails more than toenails. It can be acquired or heredity. The acquired form is much more common and associated with iron deficiency anemia. They may even be present in normal individuals and may be a racial characteristic in Ladhakhi and Tibetan populations.[50] It has also been described in post renal transplant patients and after hemodialysis.

B) **Subungual hyperkeratosis** - It refers to hyper proliferation of keratinous debris under the nails)

C) **Onycholysis**–It is breakage in the distal end of nail plate.

D) **Mees' lines** – These are white transverse bands seen on nail plate. Generally there is a single band but multiple bands may occur. They result from focal parakeratosis of the nail matrix. They have a contour similar to the distal edge of lunula. They are seen in a variety of systemic disorders. Some of them are

   a. Arsenic, thallium or heavy metal poisoning

b. Carbon monoxide poisoning
c. Drug induced – due to chemotherapeutic agents like cyclophosphamide, vincristine
d. Psoriasis
e. Renal allograft rejection
f. Chronic renal failure

E) **Muehrcke's lines** –These are also narrow white transverse bands parallel to the lunula. Like Mees' lines they are span the entire width of the nail. They occur in pairs and they represent abnormality in the nail bed. They frequently occur on the second, third and fourth finger nails. Unlike in Mees's lines squeezing the distal digit will make the lines temporarily disappear. Hypoalbuminemia is an important cause of these lines. They have been reported in various conditions. Some of them are

a) Chemotherapy

b) Hypoalbuminemia (nephrotic syndrome, glomerulonephritis, liver disease, malnutrition)

c) Malnutrition

d) Heart transplant recipients[51]

F) **Terry's nails** – There is leukonychia affecting the entire nail plate except the distal 20% or 2 mm distal margin. The distal margin corresponds to the onychodermal band, which is characteristic.[52]Terry's nails are a result of changes in nail bed vascularity, a decrease in the proximal portion and an increase at the distal edge. All nails are affected uniformly. They are generally seen in cirrhosis of liver, heart diseases or diabetes mellitus.

G) **Splinter hemorrhages** – They have also been described which are seen more commonly than in normal population.[53] They present as longitudinal red colored streaks beneath the nail plate due to extravasation of red blood cells from the damaged capillaries.

7) **Purpura** - Purpurae are reddish non-blanchable lesions due to extravasation red blood cells into the skin or mucosa. Dialysis patients are often on heparin which may increase the incidences of bleeding. Also in hemodialysis patients arteriovenous shunt is formed which may lead to extravasation of blood due to trauma during the dialysis process.[54]

8) **Lesions at site of cannula insertion** - The cannula is inserted into the arteriovenous fistula during dialysis procedure. There might be extravasation of blood, phlebitis due to repeated manipulation of cannula during multiple sittings per week. Eczema may develop at the site of shunt formation either due to cleaning of the area with betadine or secondary to extravasation of blood. There may also be infections which may be local or rarely cause dangerous septicemia.[55]

9) **Oral mucosal changes** - Oral changes are very common in patients undergoing hemodialysis.[56]They may be specific or non-specific.

Specific signs - Teeth marking is seen along with macroglossia which is known as the '**tongue sign of uremia**'. This finding was first described by Mathew in Chronic kidney disease patients.[57]When urea levels are more than 200 mg/100 ml, a condition known as '**uraemic fetor**' is described. This is an ammoniacal odor produced secondary to high urea concentration in the saliva which breaks down to release ammonia which has a pungent odor. These patients have fewer fungiform taste buds which may cause impairment of taste.[58]

Non-specific signs - Xerostomia (dry mouth) has been reported which may be due to dehydration. Ulcerative stomatitis has been described classically in patients with high urea levels (>150 mg/100 ml) but fortunately this condition is now rarely seen.

10) **Acantholytic dermatosis**–A case of persistant acantholytic disease (Grover's disease) has been described since 6 months in a patient who was on hemodialysis since 9 years.[59]Grover first described this disorder.[60] It is also known as Grover's disease. It is characterized by pruritic, edematous papules or papulovesicles with excoriations. The lesions occur mainly on the upper trunk and histologically show epidermal acantholysis that resemble Darier's disease. The lesions may be transient in which case the condition is called transient acantholyticdermatosis. There is a variant of this disease in which the lesions are persistent. It this case it is called persistant acantholytic dermatosis.The cause is unknown but actinic damage has been implicated as an initiating factor.

Treatment – There are reports of good response to systemic retinoids. For persistent small lesions surgical excision can deliver excellent results.[61]

Specific findings

1) **Uremic frost-** This is seen in in those people whose urea levels are very high (>200 mg/100 ml). The frost consists of white/yellow coating of urea crystals on the beard or on the trunk. It occurs due to urea secretion through the sweat glands which deposits as beads on surface as it cannot evaporate.[62] It is more commonly seen in acute renal failure.

In erythema papulatumuremicum, large papules and nodules on an erythematous base are seen over palms, soles and face. In a few weeks they desquamate and form fissures. This change is also not seen in the present era.

2) **Dialysis related amyloidosis** - It is a type of secondary systemic amyloidosis in which there is deposition of beta 2-microglobulin. It is frequently associated with musculoskeletal and joint complaints. Deposits in the wrist area leads to carpal tunnel syndrome, deposits in bones lead to bone cysts.[63] Heart is the most common extra-articular organ involved followed by the gastrointestinal tract. This visceral form β_2M amyloidosis is a major complication of chronic renal failure and occurs mainly in patients who have been on dialysis for more than 10 years. Lingual deposits of amyloid on the tongue have described presenting as multiple white-yellow and red coloured non-tender, firm nodules of different size.[64]It is closely related to use of low flux, bioincompatible cellulose membranes, which can cause tissue deposition of beta 2 microglobulin as amyloid fibrils.[65] Other visceral deposits of β2M amyloid include large amyloid protein masses in subcutaneous tissues, especially in the gluteal region, which is also a rare manifestation of dialysis related amyloidosis.[66] The treatment of dialysis related amyloidosis is limited to the management of symptoms and surgical removal of amyloid deposits. New high-flux, biocompatible dialysis membranes are available which are more permeable to beta 2-microglobulin which might delay the onset of dialysis related amyloidosis.[67]

3) **Uremic neuropathy** affects about 60% of patients with chronic kidney disease or patients on long term hemodialysis. This appears to be a predominantly sensorimotor neuropathy.[68] This is a manifestation of uaemia.

4) **Acquired perforating dermatosis**–There is lot of ambiguity regarding this terminology. Perforating disorders are a group of disorders, which are characterized by transepidermal elimination of amorphous material. Currently there are 4 disorders, which are recognized as primary perforating disorders. They are elastosis perforans serpiginosa, Kyrle's disease, perforating

folliculitis and reactive perforating collagenosis. These perforating dermatoses can occur in diabetes mellitus and in patients with chronic renal failure, many of who are undergoing hemodialysis.[69] The distinction between these four dermatoses is not clear-cut especially in the case of hemodialysis patients; the conditions may overlap. Thus the name 'acquired perforating disorder' has been proposed for the perforating dermatoses occurring in the setting of chronic kidney disease/ hemodialysis. Gracia Bravo et al have used the term 'uremic follicular hyperkeratosis' for it.[70] When these conditions occur outside the setting of diabetes mellitus or chronic kidney disease they occur as separate entities. This dermatosis occurs in up to 10% of patients undergoing hemodialysis.[71] Clinically the patients present with hyperkeratotic papules with a central crust filled crater on the trunk and on extensor surfaces often in a linear distribution.[72] The extensor surface of limbs are more commonly involved.

The histologic features may resemble any of the four primary perforating dermtosis. Chang et al, where they studied 9 Guatemalan patients with acquired perforating disease associated with chronic kidney disease.[73] Out of these 6 were on hemodialysis. Out of these 6 in 5 patients the lesions started after starting hemodialysis. In lesions resembling Kyrle's disease there is a keratotic plug showing parakeratosis and basophilic cellular debris filling an epidermal invagination. There is acanthosis in the surrounding area.[74]In perforating folliculitis, a widely dilated follicle is seen which is filled with a keratotic plug containing parakeratosis, suppurative inflammation and basophilic necrotic debris. In reactive perforating collagenosis there is broad cup-shaped epidermal invagination containing parakeratotic debris, inflammatory cells, vertically oriented degenerated basophilic collagen.[75]

The exact etiology for the disorder is not known. Possible explanations are diabetic microangiopathy, dysregulation of vitamin A or D metabolism, inflammation and connective tissue degradation caused by dermal deposition of substances like uric acid or calcium salts which are

accumulated in excess during renal failure.[76] It is also thought that that this is a reaction pattern to constant itching and scratching in chronic kidney disease.

Treatment options consist of topical and intralesional corticosteroids, topical and systemic retinoids, cryotherapy and ultraviolet therapy. Oral vitamin A (1,00,000 U/day) has also been tried.

5) **Nephrogenic fibrosing dermopathy** – Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis (NFD/NSF) is a recently recognized fibrosing disorder of the skin that occurs in patients with renal insufficiency. NFD was originally described in 1997 in 15 patients receiving hemodialysis, who developed lesions on their extremities and trunk, characterized by thickening and hardening of the skin, papules and nodules with hyperpigmentation, and flexion contractures.[77]On examination the lesions are well defined and may have finger like projections. The plaques may be erythematous, yellow or skin coloured. Patients describe pain, paresthesias and pruritus but are most bothered by the limitations in the mobility resulting from flexion contractures. On examination of eyes most patients have scleral plaques. Clinically the lesions resemble scleroderma or morphea but they have distinct biopsy findings correlating with scleromyxoedema. Scleromyxoedema is a condition characterized my mucin deposition in the viscera and immunoglobulin G (IgG) lambda paraproteinemia. However these 2 conditions were lacking from the described patients. Scleroderma tends to involve the head and neck area. These areas are spared in nephrogenic systemic fibrosis.

There seems to be no correlation between ethnic background, sex or the cause of chronic kidney disease. This condition occurs in patients on end stage renal disease most of whom are on hemodialysis.[78]. The histopathology of Nephrogenic fibrosing dermopathy is similar to scleromyxoedema. There is proliferation of fibroblasts in the dermis and subcutaneous septae, along with deposition of collagen and mucin.

It has been recently discovered that this condition occurs in people who have had a gadolinium scan magnetic resonance procedures. Gadolinium is a radiocontrast media. Such contrast media are not recommended if the glomerular filtration rate is less than 30 ml/min. It is hypothesized that the retention of Gadolinium in patients with kidney disease is profibrotic. In some studies it has been shown by skin biopsies that Gadolinium has been retained in the skin of patients with chronic kidney disease even more than 2 years after the intake of Gadolinium.[79]These patients have also been shown to have abnormal scintigraphy with increased uptake of ^{99mTc}-hydroxymethylene diphosphonatein the skeletal muscle underlying the involved skin, demonstrating an abnormal process extending deeper than the dermis.[80,81]The disease process can involve the underlying organs also so a new terminology "Nephrogenic systemic fibrosis" has been proposed. Involvement of the diaphragm can even lead to death. 10% of the patients with nephrogenic systemic fibrosis have a fatal course.

Recently a classification scheme was proposed for the clinical subtypes seen based on data from published reports and the NFD registry organized through Yale University, United States of America.[82]

Table 5: Clinical subtypes of nephrogenic fibrosing dermopathy (NFD): a proposed classification scheme[83]

Subtypes	**Description**	**% Of previously reported patients (n = 100)**	**5 of patients from case series (n = 9)**	**NFD progression**
1	New onset acute renal failure or	25	22	May be transient

	acute decompensation from chronic renal failure			
2	Pneumonia like disorder followed by renal failure	6	0	Usually transient
3	Surgical procedure or acute blood loss followed by acute renal failure	18	22	May be transient
4	Kidney transplant	34	55	May be transient
5	Chronic renal failure, unknown trigger	3	11	Usually chronic
6	Thrombotic event, renal failure may predate or follow the event	12	11	May be transient

Treatment – Since there are very few cases described in literature no definitive therapy exists. The most dramatic improvement was seen in 3 patients who were treated with plasmapheresis.[84] Other therapies tried with variable success are UV-A1 phototherapy, prednisone, extracorporeal photopheresis, methotrexate.[85]

6) **Bullous disease of hemodialysis** - It is a well known entity with an incidence of 2-18% in patients undergoing hemodialysis. It is also known as pseudoporphyria of hemodialysis.Korting first reported it in 1975 as a bullous dermatosis resembling porphyria cutanea tarda undergoing maintainance hemodialysis. All these patients had normal porphyrin levels. In chronic kidney disease the normal porphyrin excretion is retarded so it may be sometimes confusing to distinguish between Porphyria cutanea tarda and pseudoporphyria. However in pseudoporphyria the porphyrin levels are only moderately elevated so accurate assays of porphyrin levels are of prime importance.[86] Pseudoporphyria may also develop in association with medications like furosemide, nalidixic acid, tetracycline naproxen, pyroxidine or amiodarone.

The clinical presentation of pseudoporphyria is similar to sporadic porphyria cutanea tarda. Clinically there are tense vesicles and bullae distributed on the dorsal hands, face and occasionally the feet. Secondary changes include erosions and crusts. The bullae heal with scarring and milia formation. The skin is fragile and easily traumatized. Hyperpigmentation of sun-exposed skin is seen. Hypertrichosis is also observed.

Laboratory findings. All types of porphyria cutanea tarda have increased serum iron, ferritin and hepatocellular iron. Those patients who are not anuric excrete increased uroporphyrin I greater than uroporphyrin III, 7-carboxyl porphyrins in the urine. Anuric patients demonstrate markedly elevated plasma levels of uroporphyrin.[87]

Histopathology. Porphyria cutanea tarda in characterized by subepidermal vesiculation with little or no inflammation. The base of bulla is corrugated and lined by well preserved dermal

papillae (festooning). There is mild thickening of basement membrane zone and vessel walls, which can be highlighted with periodic acid-Schiff stain. The findings in pseudoporphyria are similar although periodic acid-Schiff stain reveals less vessel wall thickening.

Management. In both the scenarios sun protection is vital.Broad-spectrum physical blockers such as zinc oxide or titanium dioxide are preferred. Unfortunately, standard hemodialysis does not effectively remove uroporphyrin. High flow rate dialysis with a high-flux polysulfate dialyzer can reduce plasma porphyrin levels by upto 37%[88], however this is insufficient to induce clinical remission. N-acetyl cysteine, which is an antioxidant, may help in reducing the blistering.[89] Treatment of true Porphyria cutanea tarda in the patients is limited as antimalarials work by forming complexes with porphyrins and getting excreted in urine. In chronic kidney disease patients the urine production is reduced. Further the porphyrin antimalarial complexes cannot pass through the dialysis membrane. For patients without renal problem phlebotomy is the treatment of choice. In this procedure 500 ml of blood is removed every fortnightly. However this procedure is limited in these patients as these patients already have low hemoglobin due to reduced erythropoietin formation. Small volume phlebotomies (50-100 ml) every week over 1 year have been reported to induce remission. These patients are treated with erythropoietin along with small volume phlebotomies. This has been shown to mobilize hepatic iron stores. Complete resolution may require several months of therapy. Desferoxamine may also lower porphyrin levels in some patients but it has side effects and so can be used only for limited time. Renal transplantation provides complete resolution of symptoms.[90]

7) **Calciphylaxis** - It is characterized by progressive cutaneous necrosis associated with small and medium vessel calcification. It occurs in the setting of end stage renal disease, diabetes and hyperparathyroidism. Many of these patients are also on hemodialysis. The exact cause is not known. Generally vascular calcifications are common in patients with chronic kidney disease and

most of the times they are asymptomatic. In calciphylaxis there is sudden thrombosis in the calcified vessels. It is a type of induced systemic hypersensitivity in which tissues respond inappropriately to certain challenging substances with calcium deposition. The challenging agents include glucocorticoids, albumin infusions, intramuscular tobramycin, iron dextran complex, calcium heparinate, immunosuppresive agents and vitamin D. It occurs closely following initiation of hemo- or peritoneal dialysis.

It is a very painful condition. Initially there is a preinfarctic stage. In this stage there is mottling of skin or it may have a livedoreticularis like pattern or skin may appear dusky red or violaceous. Later bullae may start forming over the ischaemic area. These bullae eventually become necrotic. The central infarcted site becomes black or yellowish. This infarcted area keeps becoming larger. When this is debrided deep ulcers are seen which may even reach up till the fascia. This ulcer can become secondarily infected and may take a sinister course like cellulitis or septicemia. The calciphylactic skin changes are mostly seen on distal extremities, especially over the lateral and posterior calves, abdomen, buttocks, fingers and glans penis. On investigation uremia is present. The calcium x phosphate product is elevated. Parathyroid hormone levels are elevated. For

Histopathology deep incisional biopsy should be taken. There is calcification of small to medium sized blood vessels in the dermis and subcutaneous tissue. Intraluminal fibrin thrombi are present. If the ischaemia is severe lobular or septal fat necrosis may take place along with lymphohistiocytic infiltrate. Radiographs of affected extremities show calcium deposition outlining small and medium sized vessels.

The differential diagnosis includes panniculitis, necrobiosis lipoidica with ulceration, dystrophic calcification, disseminated intravascular coagulation, pyoderma gangrenosum and warfarin necrosis.

Overall the prognosis is bad and mortality rate is very high. Treatment of renal failure helps in improving the condition. Aggressive debridement of wound helps in preventing secondary infection and in wound healing. Subtotal or total parathyroidectomy may help as this condition is related to hyperparathyroidism. Phosphate binding agents may also help.

In addition to vascular calcification and calciphylaxis, nodular calcification may occur in the skin and fat of patients with chronic kidney disease. These deposits are identical to calcinosis cutis of CREST syndrome. The involved skin may ulcerate here also but this is without the severe pain and livedo reticularis like lesions.

METHODOLOGY

A cross-sectional study design is suited for estimating prevalence of disease and traits. It can be used to describe participants' attributes as well. We adopted a ***cross-sectional design*** for this study. The details of the study methodology are described below:

a) Study site: The study was conducted in the Department of Nephrology, KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum as a part of the MD academic curriculum

b) Study duration – The study was done between January 2012 to December 2012

c) Ethical clearance: It was granted by the J.N.M.C. Institutional Ethics Committee on Human Subjects Research, 2011-12.

d) Inclusion criteria: Patients of chronic kidney disease stage 5 undergoing hemodialysis in the department of Nephrology at KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum between January to December 2012, who were willing to provide written informed consent, were to be considered for inclusion in the study.

e) Exclusion criteria: Cases of acute renal failure or those who were having chronic kidney disease other than stage 5 were excluded from the study. Patients of chronic kidney disease stage 5 who were not willing to be a part of the study were also excluded from the study

f) Sample size - The formula used for sample estimation was $4PQ/D^2$. In this formula 'P' is the prevalence. 'Q' is 100-P. D is disallowable error which can vary from 5-20% of 'P'. Based on previous studies the prevalence of skin

manifestations in patients of chronic kidney disease stage 5, it was seen that 80% of the patients had at least one cutaneous manifestation. So 'P' became 80, 'Q' became 20 and 'D' was taken as 10% of 'P' that is 8. The resultant sample size was 64.

g) Data collection - A predesigned and pretested pro-forma was used. An informed and signed consent was taken first which was also signed by the principal investigator and a witness who wasn't related to either the patient or the principal investigator. The pro-forma contained patient's basic demographic data like name, age and sex. Various relevant laboratory parameters like hemoglobin, creatinine, blood urea, serum potassium, serum calcium and serum phosphate levels were noted down from patient's records. Serum parathyroid hormone levels were measured in all patients. In apart from this any other relevant investigation was carried out like skin biopsy for acquired perforating disorder, or 10% potassium hydroxide mount for superficial fungal infections. Cause of chronic kidney disease, duration of dialysis was noted. Then general physical examination was done. Various skin, hair and nail manifestations seen in chronic kidney disease stage 5 undergoing hemodialysis were looked for. Later enquiry was made about any other illness related to cardiovascular, respiratory and nervous system. In the end the pro-forma was signed by the principal investigator, the guide and the co-guide.

h) Procedure - Parathyroid hormone levels analysis was done using IMMULITE®/ IMMULITE® 1000 Intact PTH Analysers. The kit is intended for in vitro diagnostic use for quantitative measurement of intact parathyroid

hormone in EDTA plasma or serum. In this study serum sample was used in all the patients. This kit is a solid phase two site chemiluminescent enzyme labelled immunoassay.[91]

BD vacutainer™ with gel was used to collect the sample. The specimen was allowed to clot at room temperature. Serum was separated from the cells using centrifuge machine. Anticoagulant therapy may delay the clotting process. The patients undergoing hemodialysis are administered heparin therapy to prevent blockage of the arteriovenous shunt so the sample was collected in all cases before the dialysis process started. When the analysis was delayed the samples were stored at 2-8 ºC for not more than 8 hours as per the instructions on the kit. According to the manufacturers of the kit the reference range for intact parathyroid hormone samples was 11-67 pg/ml. The median value was 31pg/ml.

Limitations of the kit - Heterophile antibodies present in the human serum can react with the immunoglobulins present in the assay components causing false reading of the test.

Specificity - the IMMULITE Intact parathyroid hormone assay is highly specific for intact parathyroid hormone with particularly low cross reactivity to most parathyroid hormone fragments, as well as to other naturally occurring compounds which may be present in the patient samples.

Skin biopsy was performed in one case that consented for biopsy to be taken. Prior history of allergy to lignocaine was asked which was negative. The area was cleaned with 70% alcohol. 1 ml of plain lignocaine 2% injection was given intralesionally and a disposable punch of 4 mm was used to do

punch biopsy following which the wound was sealed with antibiotic ointment and dressing. The biopsy specimen was sent to pathology lab in 10% formalin for histopathologic examination. No other special tests were done in the study

***i*) *Statistical analysis* -** Percentages were used for categorical outcomes. The prevalence of abnormal parathyroid hormone level values between groups was compared by chi square test

Discussion

64 patients were examined in the study. No controls were taken in the study. In an Egyptian study by Attia et al total of 206 uremics were taken. They were then compared with controls which were age and gender matched. This is a limitation of the present study which is a cross sectional study. A case control study would have helped to eliminate the confounding errors.

Table 24: Sample size of various studies

Study	Sample size
Present study	64
Eyptian study by Attia et al	206
Indian study by Udayakumar et al	100
Indian study by Tawade et al	35

Larger the sample size greater is the power of the study. However due to time restriction only 64 patients were examined. Increasing the sample size would have increased the power of the study.

The criteria for choosing the patients in the present study was that the patient should be having chronic kidney disease stage 5. It is defined as the end stage renal disease with Glomerular filtration rate < 15 mL/min per 1.73 m^2 In the study by Attia et al predialysis lab parameters were taken to include patients into the study. They were

Serum creatinine - >4 mg/dl

Blood urea >100 mg/dl

Serum potassium > 6.5 meq/l

Serum bicarbonate <15 meq/l.

In the study by Makhlough et al all the patients who were undergoing hemodialysis were taken into study. All the patients having skin pathologies were excluded.

In the present study out of 64 patients 50 were men and 14 were women. Thus men constituted 78.12% of cases. This value is much higher than those seen in other studies. In an Israel study conducted by Dyachenko et al men constituted 60% of the cases.[91] In an Egyptian study by Attia et al men constituted 53% of cases. (add end note). The kidney disorders are not known to affect the different sexes differentially. The result in our study is probably due to the fact that increased numbers of men seek treatment for their disorders probably due to socioeconomic reasons.

Table 25: Comparison of the number of males and females taking part in various studies

Study	**Men**	**Women**
Present study	50 (78.12%)	14 (21.87%)
Tawade et al	30 (85.71%)	5 (14.28%)
Udayakumar et al	70 (70%)	30 (30%)
Attia et al	110 (53.39%)	96 (46.60%)

Makhlough et al	80 (52.3%)	73 (47.7%)

Cause of renal failure–In the present study hypertension was the most common cause of renal failure, followed by diabetes and chronic tubulointerstitial disease. This differed from the study by Attia et al where diabetes was the most common cause followed by hypertension.

Table 26: Comparison of etiology of chronic kidney disease in various studies

Cause of renal failure	Present study (in %)	Attia et al (in %)
Diabetes Mellitus	32.8	11.6
Hypertension	70.3	9.8
Renal stones	1.5	9
Chronic pyelonephritis	1.5	3
SLE	1.5	2.4
Chronic tubulointerstitial disease	18.75	-
Others	20.31	60

Duration of dialysis– Patients of chronic kidney disease stage V were taken into the study irrespective of the duration of dialysis. The range varied from less than 3 months to more than 5 years. The duration of dialysis were categorically divided and

correlated with PTH levels. In all these categories the least abnormal values were found between 6 months to 36 months. There was a statistically positive correlation with normal parathyroid hormone levels during this period. This means that on an average it takes 6 months of hemodialysis for the parathyroid hormone levels to become normal. They remain normal till 36 months and after that they start to rise abnormally even after continuing hemodialysis.

Pruritus:

In the present study 28.1% patients complained of itching prior to dialysis where as 40.6% patients complained of itching post dialysis.. Thus there was an increase in the incidence of itching post dialysis. No objective criteria were used to measure the intensity of pruritus. Patients were asked only two questions regarding pruritus. They were

1) Was there pruritus prior to dialysis?

2) Has the itching increased after dialysis?

In the study by Maklough et al the prevalence of pruritus was 61.4%. In the study by Dyachenko et al prevalence of pruritus was 74.3% at the time of dialysis

Table 27: Comparison of prevalence of pruritus in various studies

Study done	Prevalence of pruritus
Present study	28.1%
Makhlough et al	61.4%
Dyachenko et al	74.3%

In the study by Makhlough et al an elaborate scoring system proprosed by Duo et al (insert reference AD)was used to quantify pruritus and then the intensity of itch was compared with various parameters. (insert reference AC) The total scoring of pruritus is calculated as follows:

(Severity of pruritus x distribution of pruritus) + sleep disorder.

The severity of pruritus is assessed as:

1 point	Slight itching
2 points	Itching with scratching
4 points	Itching and scratching with excoriations
5 points	Itching causing total restlessness

The distribution of pruritus is scored as

1 point	Pruritus maximum in 2 areas of the body
2 points	Pruritus maximum in more than 2 areas of the body
3 points	Generalized pruritus

The sleep disorder is monitored as

2 points (maximum of 10 points)	Every waking up due to itching
1 point (maximum of 5 points)	Each scratching

The drawback of this scoring system is that pruritus is a subjective symptom and the perception of itch may vary from person to person even if the same level of pruritus exists in two individuals. Thus the resultant score is prone for errors. The advantage of this method is that pruritus is quantified and so correlational studies can be easily carried out.

Dyachenko et al studied hemodialysis related pruritus and associated cutaneous manifestations.(insert reference AE) In their study the patients were considered to have pruritus if they had either of the two conditions

1) At least 3 episodes of itching during a period of 2 weeks or less, with the symptom appearing several times during the day, lasting for at least a few minutes, and troubling the patient
2) The appearance of itch on a regular pattern in a regular pattern during a period of 6 months.

To be defined 'uremic' the pruritus had to appear shortly before the onset of dialysis, or at any time thereafter, without evidence of any other active disease, which could explain it.

In the present study pruritus was considered only as either present or absent. This was probably an oversimplification and the scoring system by Duo et al could have given more statistically relevant results.

The etiology of pruritus is still unknown. The hypothesis of the present study was to see if there was a correlation between pruritus and parathyroid hormone levels. In the present study there was no correlation between pruritus and parathyroid hormone. In the study by Makhlough et al there was a statistically positive correlation between pruritus and parathyroid hormone.

Table 28: Comparison between parathyroid hormone and pruritus in different studies

Subgroup		Hyperparathyroidism present	Hyperparathyroidism absent	P value
Present study				
	Pruritus present	17 (43.58%)	14 (56%)	P = 0.546
	Pruritus absent	22 (56.42%)	11 (44%)	
Makhlough et al (males)				
	Pruritus present	37 (64.3%)	19 (61.3%)	P = 0.001
	Pruritus absent	15 (35.7%)	12 (38.7%)	
Makhlough et al (females)				
	Pruritus present	27 (64.3%)	19 (61.3%)	P = 0.18
	Pruritus	15 (35.7%)	12 (38.7%)	

	absent			

Makhlough et al had divided the patients into males and females. As can be seen from table 27 that the statistically significant correlation between pruritus and parathyroid hormone levels was obtained only for males and not for females. Neither pruritus nor parathyroid hormones are known to affect the different sexes differentially so there seems to be some fallacy in the above results in the above study. In the present study the patients were not divided on the basis of sex. Thus there is still not clear consensus whether hyperparathyroidism is the cause for uremic pruritus. According to the present study pruritus seen in hemodialysis has no relation to parathyroid hormone.

Also in the present study the prevalence of itching prior to dialysis was 28.1% whereas after starting dialysis the prevalence of itching was 40.6%. So there was 12.5% increase in the prevalence of pruritus. Thus this increase in pruritus can be attributed to the dialysis procedure. It might either be that the pruritogens are not filtered through the dialysis membrane. The constituents of the diasylate fluid may be causing increase in pruritus.

In the present study the sample was collected before starting the dialysis procedure as during the dialysis procedure many patients are administered heparin. This could possibly alter the laboratory results. This was similar to the study by Makhlough et al in which blood was withdrawn prior to starting the dialysis procedure.

Analysis was done in various studies between pruritus and duration of dialysis. In the study by Makhlough et al there was no relation between pruritus and duration

of dialysis. In the study by Dyachenko et al also there was no relation between the two. Our study also had a similar finding.

Pallor

In the present study prevalence of pallor was 65.62%. This was slightly less than that seen in the study by Dyachenko et al (75.7%). In an Egyptian study by Attia et al, the patients were divided into adults and children among adults the prevalence of pallor was 48.5%. In children the prevalence of pallor was only 18%. They hypothesized that in Egypt there is free supply for erythropoietin in their health programs which accounted for the low prevalence of pallor. Udayakumar et al studied 100 patients undergoing hemodialysis in India. The prevalence of pruritus in their study was 60%. They hypothesized that the prevalence of pallor was low in their study due to darker complexion of the patients. Thus the figures in the present study correlate with the Indian study by Udayakumar et al. Pallor did not have a statistically positive correlation with parathyroid hormone.

Table 29: Comparison of pallor between various studies

Study	Prevalence of pallor
Present study	65.62%
Attia et al	48.5%
Udayakumar et al	60%
Dyachenko et al	75.7%

Skin colour changes post dialysis

In the present study 21.87% patients complained of darkening post dialysis. This differed from other studies. In the study by Udayakumar et al 40% of patients experienced darkening post dialysis. In the study by Dyachenko et al the 75.7% patients complained of hyperpigmentation post dialysis. In the study by Attia et al hyperpigmentation was seen in 17.8% of their cases but only in 3% of controls. In contrast to all the other studies which showed pigmentation more in a photodistributed area, in the present study patients complained of generalized diffuse pigmentation. The earlier studies had suggested that the increased pigmentation was due to the inability of kidneys to excrete beta-melanocyte stimulating hormone but that does not explain why the pigmentation would occur more in a sun distributed area. The present study does not have that discrepancy as the pigmentation was seen in a diffuse pattern. There was no statistically positive correlation between hyperpigmentation and parathyroid hormone.

Table no 30: Comparison between skin darkening post dialysis in various studies

Study	Prevalence of skin darkening
Present study	21.87 %
Udayakumar et al	40 %
Attia et al (cases)	17.8%
Attia et al (controls)	3 %
Dyachenko et al	78.7%

Half and half nail

Half and half nail is a specific feature of patients with chronic kidney disease stage 5. Even among these patients it is seen more commonly in patients undergoing hemodialysis.[92] In the present study it was seen in 15.62% of cases. It was similar to the prevalence seen in study by Dyachenko et al (18.6%). In an Indian study by Tawade et al the prevalence was 17%. Thus the prevalence of half and half nail was more or less similar in various studies. In the present study there was no correlation was found between this nail change and parathyroid hormone. No similar studies were found which compared the two variables.

Table 31: Comparison of half and half nail in various studies

Study	**Prevalence of half and half nail**
Present study	15.62%
Dyachenko et al	18.6%
Tawade et al	17%
Udayakumar et al	21%

Terry's nail

In the present study Terry's nail was found in 23.44% of patients. This is unusual because none of the literature pertaining to nail changes in hemodialysis patients mentions this finding. Terry's nails are usually seen in cirrhosis of liver, heart failure and in diabetes mellitus. In the present study the patients with Terry's nails were not suffering from this disorder. Thus Terry's nails can be also be considered as one of the cutaneous manifestations of patients undergoing hemodialysis. In the present

study there was no statistically relevant correlation between Terry's nail and parathyroid hormone levels.

Muehrcke's lines

In the present study the prevalence of Muehrcke's lines was 7.8%. This was similar to study by Udayakumar et al who reported prevalence of 5% in their study. In the present study there was no correlation between Muehrcke's lines and parathyroid hormone. In our knowledge no other study has compared these 2 variables.

Hair changes

In the present study 39.1% patients reported that they had lost hair post dialysis.in the study by Udayakumar et al 30% of patients had sparse body hair whereas 11% had sparse body hair at the time of inspection. They did not mention whether these changes were present before the hemodialysis or they appeared after starting it. In the Egyptian study by Attia et al, among adults the prevalence of pruritus was 33.7% cases whereas in children the prevalence of hair loss post dialysis was 34.9%. Thus our study has similar findings. The hair loss in dialysis patients may be due to stress of the disease per se or the dialysis procedure due to which the hair enter into telogen effluvium. Another cause can be anaemia in these patients, which may cause hair loss.

Table 32: Comparison of hair loss after dialysis in various studies

Study	Prevalence of hair loss
Present study	39.1

Udayakumar et al	41%
Attia et al (adults)	33.7%
Attia et al (children)	34.9%

Xerosis

In the present study prevalence of xerosis was 95.31%. Xerosis has been known to be the most common manifestation of patients undergoing hemodialysis. Our study also found similar result. It was the most common manifestation seen in our study. However it did not have a statistically positive correlation with parathyroid hormone.

Acquired perforating disorder

In our study it acquired perforating disorder was seen in 3(4.7%) of cases. Out of these 3 cases 2 were diabetic. Out of the 3 one patient consented for skin biopsy. The skin biopsy did not reveal any evidence of altered elastin material, nor was there any evidence of folliculitis. Thus it was neither elastosis perforans serpinginosa nor perforating folliculitis. In the study by Dyachenko et al they did not find any case of perforating disorder in their study. Tawade et al reported a prevalence of 17% in their study on 35 patients on hemodialysis. Udayakumar et al reported a prevalence of 21% in their study of 100 patients on haemodialysis. Attia et al reported a prevalence of 2.5% among their patients.

Table 33: Comparison of prevalence of acquired perforating dermatosis among various studies

Study	Prevalence of APD
Present study	4.7%
Dyachenko et al	0%
Tawade et al	17%
Udayakumar et al	21%
Attia et al	2.5%

Bullous disease of hemodialysis

This was not seen in the present study. This was because it is a rare disorder and the sample size of the present study was small. Attia et al reported a single case (0.6%) of bullous dermatosis. Udayakumar et al did not report any case of bullous dermopathy in their study. Dyachenko et al also did not report any case of bullous dermopathy in their study.

Nephrogenic systemic fibrosis

No case of nophrogenic systemic fibrosis was found in the present study. This was probably because is a very rare disorder and the sample size was small.

Calciphylaxis

In the present study no case was found to have calciphylaxis. This was so because it is also a rare disorder and the sample size was small. It was not reported by Attia et al, Dyachenko et al, Udayakumar et al.

Thus parathyroid hormone was not statistically significant to any of the cutaneous changes seen in patients undergoing hemodialysis.

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RESULTS

All the patients in the present study were cases of chronic kidney disease stage 5.

All the manifestations seen were statistically correlated with parathyroid hormone. Statistical value (p) of <0.05 was considered significant.

Demographic data: The youngest person to receive dialysis was 14 years old whereas the oldest person in the study was 76 years old. The average age of all the patients enrolled in the study was 49.14. Out of 64 patients 50 were males and 14 were females.

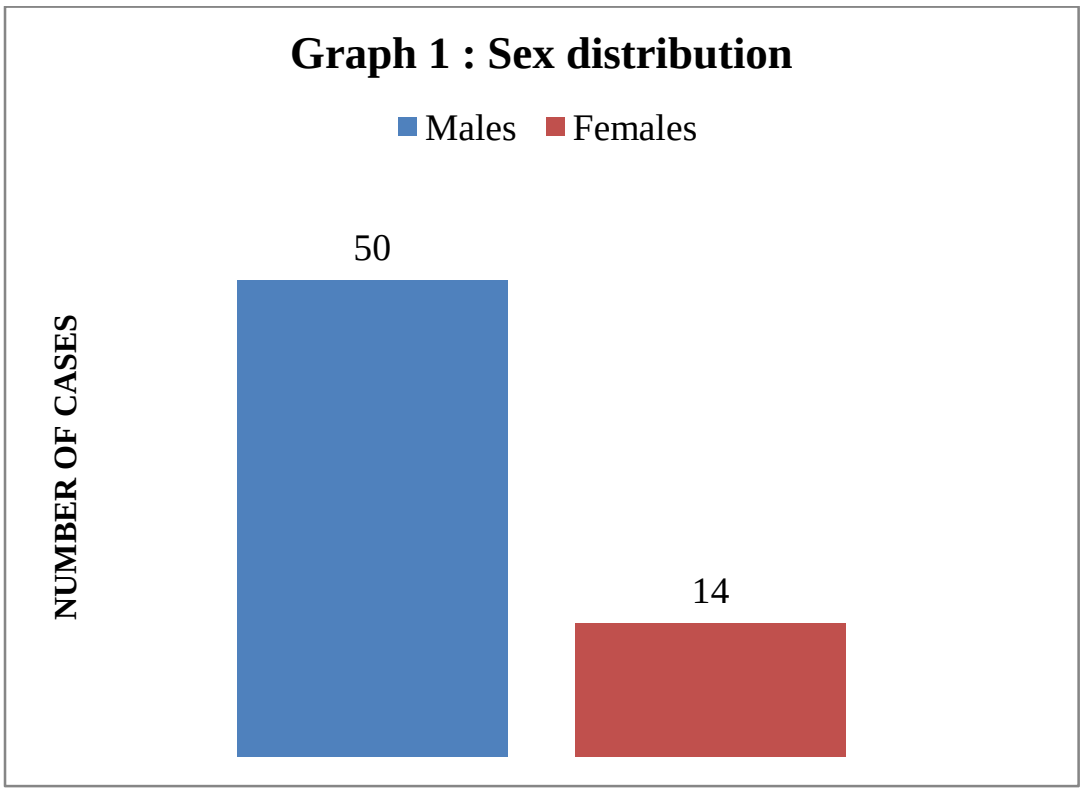
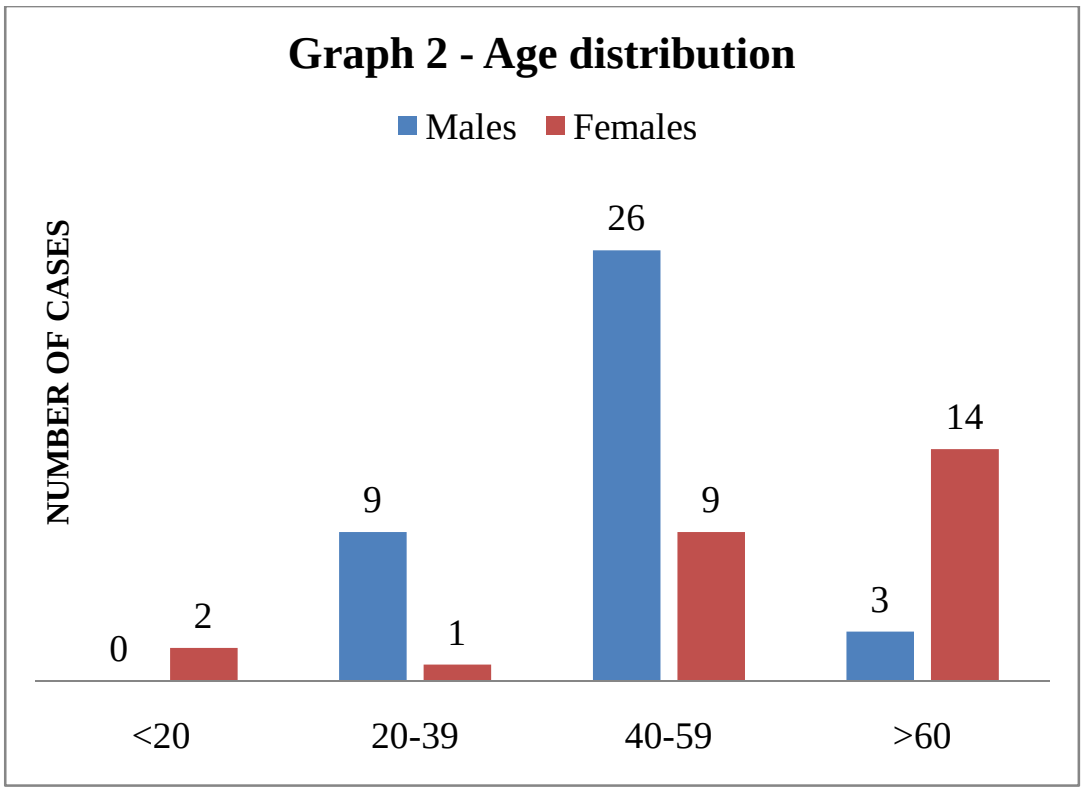


Table 6: Age distribution of patients

Age group (years)	Number of cases	Percentage out of total number of cases
<20	2	3
20-39	10	16
40-59	35	55
>60	17	26

The mean Hemoglobin levels were 8.84 g/dl. The mean Creatinine levels were 9.19 mg/mL. The average urea levels of the patients were 106.6 mg/dL. 38 (59.37%) patients had increased parathyroid hormone levels. The mean parathyroid hormone levels were 240.6 pg/mL(normal 10-69 pg/ml).



Cause of Chronic Kidney Disease stage 5

The most common cause of chronic kidney disease was hypertension followed by diabetes mellitus and chronic tubulointerstitial disease.

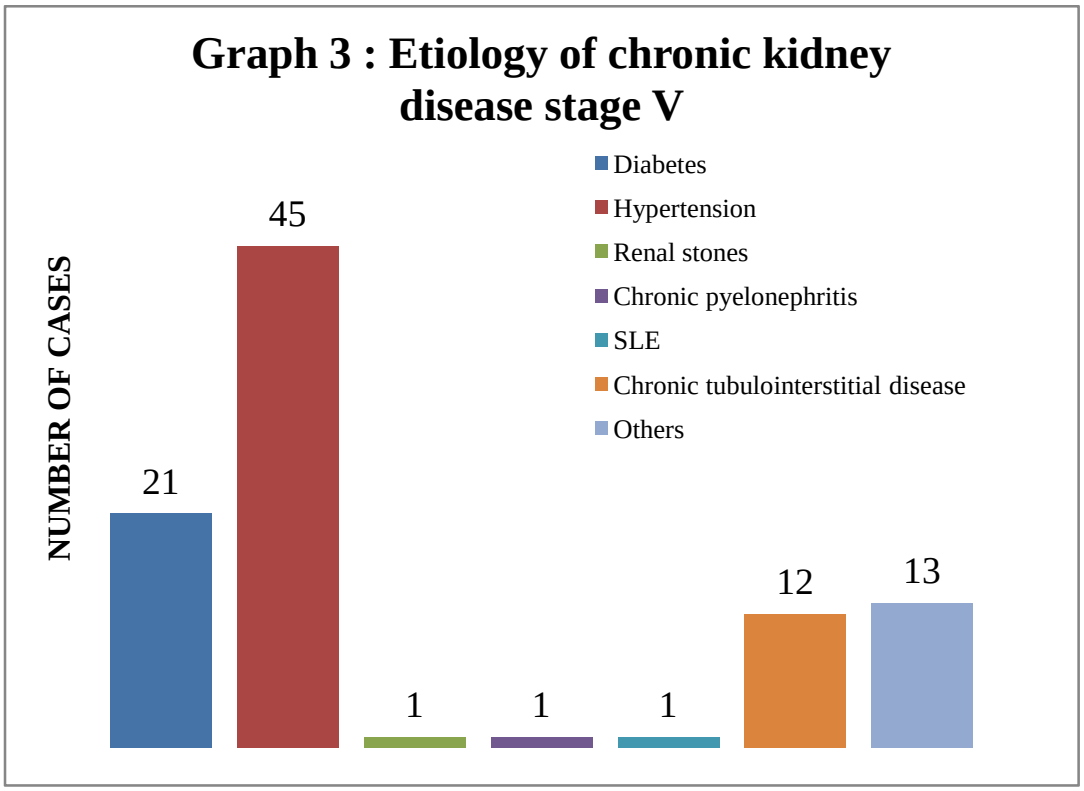


Table 7: Etiology of chronic kidney disease stage 5

Etiology	Diabetes	Hyper-tension	Renal stones	Chronic pyelonephritis	SLE	Chronic tubuloint-erstitial disease	Others
Number of cases	21	45	1	1	1	12	13

Duration of dialysis

Patients were divided into 6 categories based on how long they were receiving dialysis.

Table 8: Duration of dialysis and its correlation to parathyroid hormone

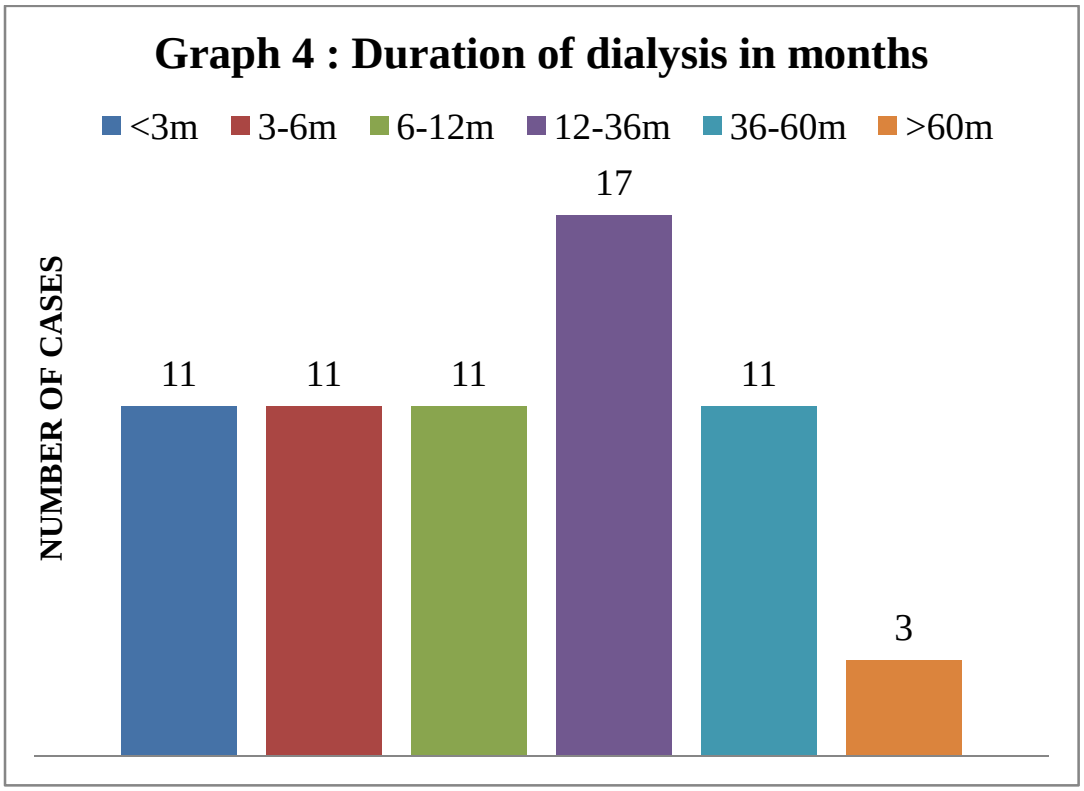
Duration of hemodialysis (in months)	PTH raised	PTH normal	Total no. of patients	Percentage of total cases
<3	9 (81.8)	2 (18.2%)	11	17.9
3-6	8 (72.7%)	3 (27.3%)	11	17.9
6-12	3 (27.3%)	8 (72.7%)	11	17.9
12-36	8 (47.1%)	9 (52.9%)	17	26.56
36-60	8 (72.7%)	3 (27.3 %)	11	17.9
>60	3 (100%)	0	3	4.69

$X^2 = 11.835$

Degrees of freedom – 5

P = 0.037

This means that the parathyroid hormone levels were consistently normal between 6 to 36 months. It was statistically significant (p=0.037). Another inference which can be drawn is that it takes 6 months of dialysis to get the parathyroid hormones to normal. It remains normal till the period of 36 months while the patient is on dialysis but starts to rise abnormally after this period irrespective of continuation of dialysis.

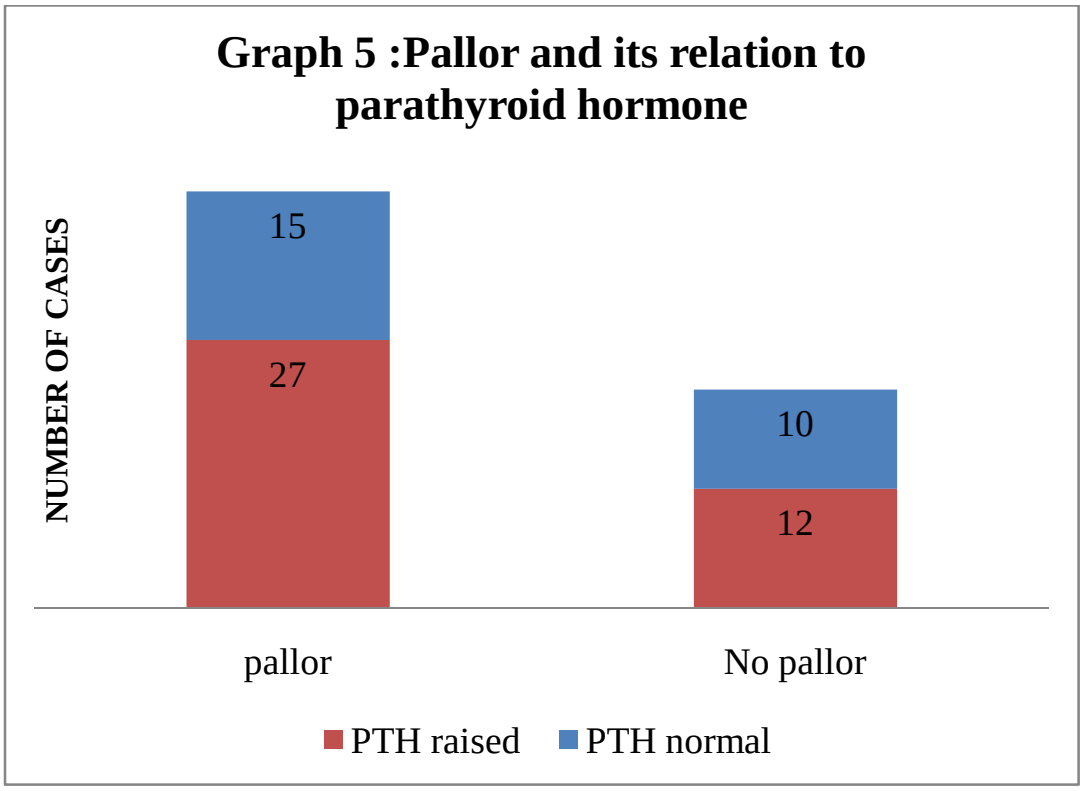


General physical examination

Pallor - Pallor was present in 65.62% patients. It did not have a statistically significant correlation with parathyroid hormone levels.

Table 9: Pallor and its relation to parathyroid hormone

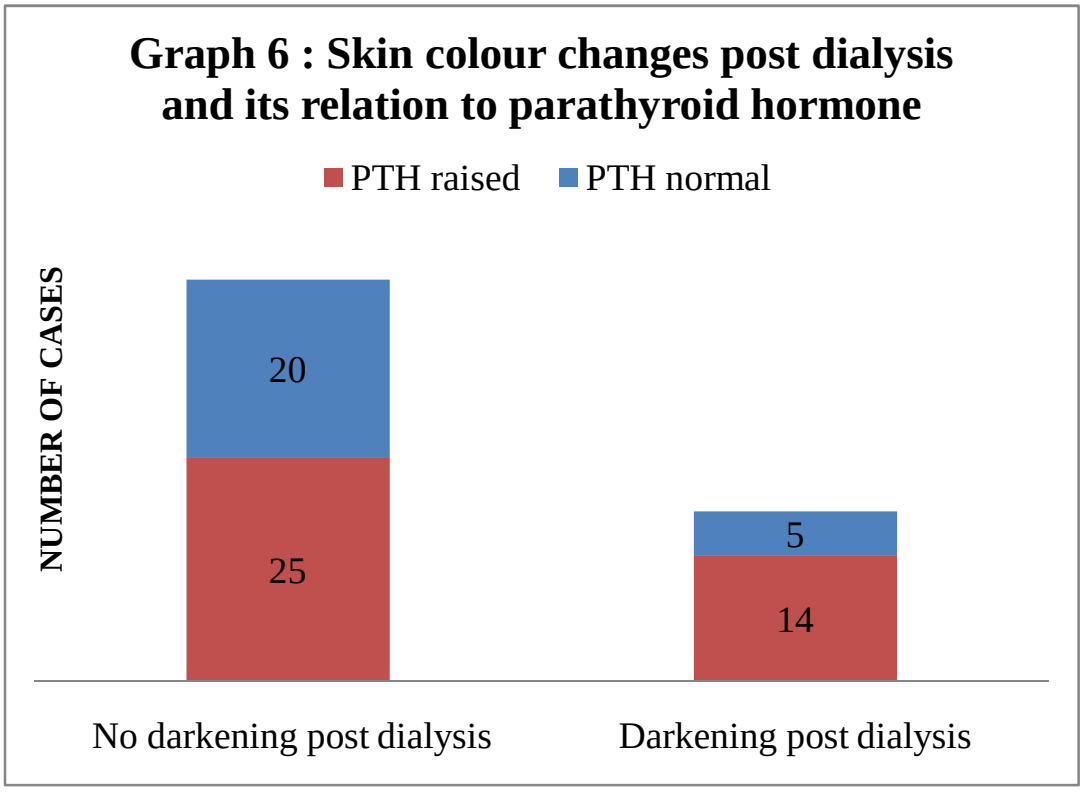
	PTH raised	**PTH normal**	**Total**	
Pallor	27 (64.28%)	15 (35.71%)	42	P = 0.448
No pallor	12 (54.54%)	10 (45.45%)	22	



Skin colour changes: 19 patients (21.87%) complained that they developed darkening of skin post dialysis. According to most of them, the darkening was diffuse in nature and was not in sun-exposed areas. It did have a statistically significant correlation with parathyroid hormone levels.

Table 10: Skin colour and its relation to parathyroid hormone

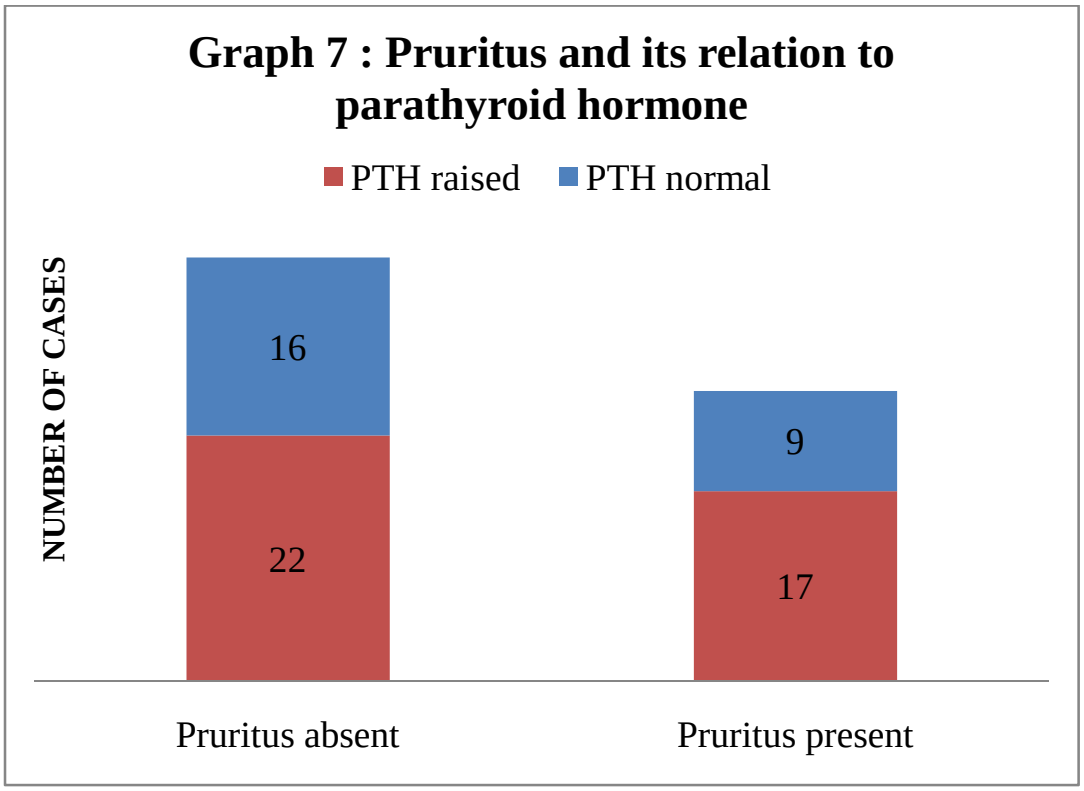
Colour change	PTH raised	PTH normal	Total	
No darkening post dialysis	25 (55.55%)	20 (44.44%)	45	P = 0.174
Darkening post dialysis	14 (73.68%)	5 (26.31%)	19	



Pruritus: 18 patients (28.1%) complained of itching prior to dialysis and 26 patients (40.6%) complained of itching after starting dialysis. So the incidence of pruritus had increased post dialysis. Pruritus at the time of dialysis did not have a positive correlation with PTH levels.

Table 11: Pruritus and its relation to parathyroid hormone

Pruritus	PTH raised	PTH normal	Total	
Absent	22 (57.89%)	16 (42.11%)	38	P = 0.546
Present	17 (65.38%)	9 (34.61%)	26	

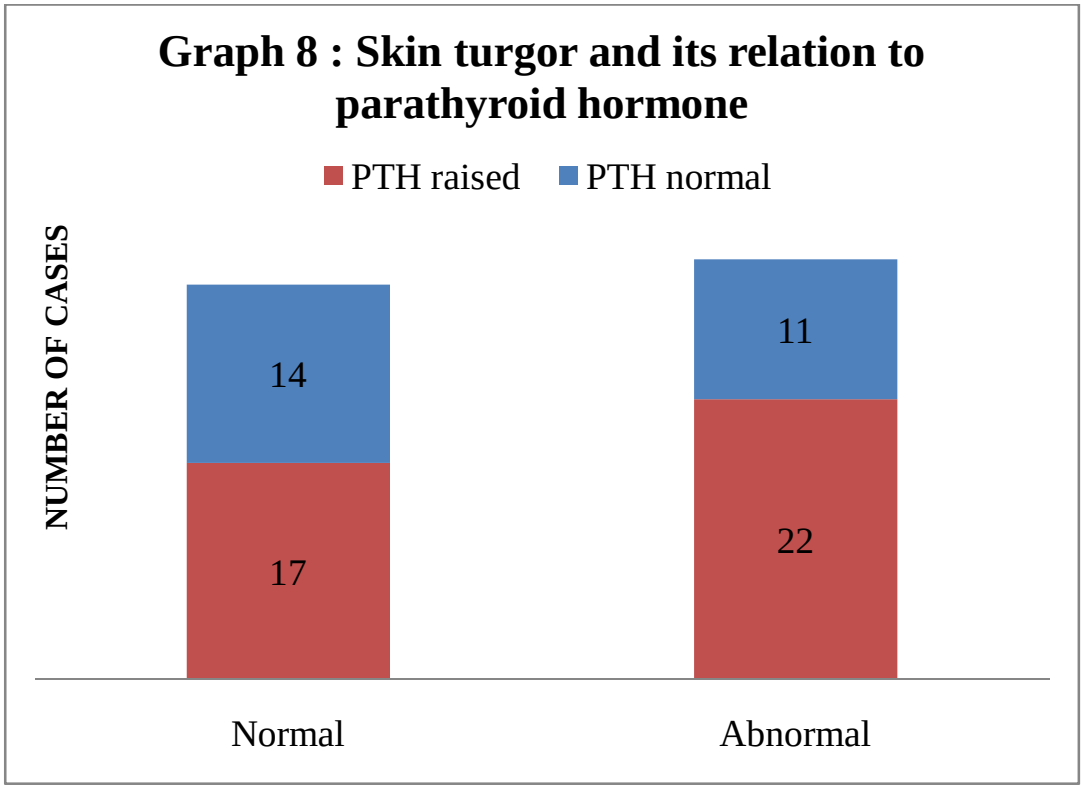


Skin turgor

33 (51.6%) patients had abnormal skin turgor and 31 patients had normal skin turgor. It did not have a statistically significant correlation with parathyroid hormone levels.

Table 12: Skin turgor and its relation to parathyroid hormone

Skin turgor	PTH raised	PTH normal	Total	
Normal	17 (54.83%)	14 (45.16%)	31	P = 0.332
Abnormal	22 (66.66%)	11 (33.33%)	33	

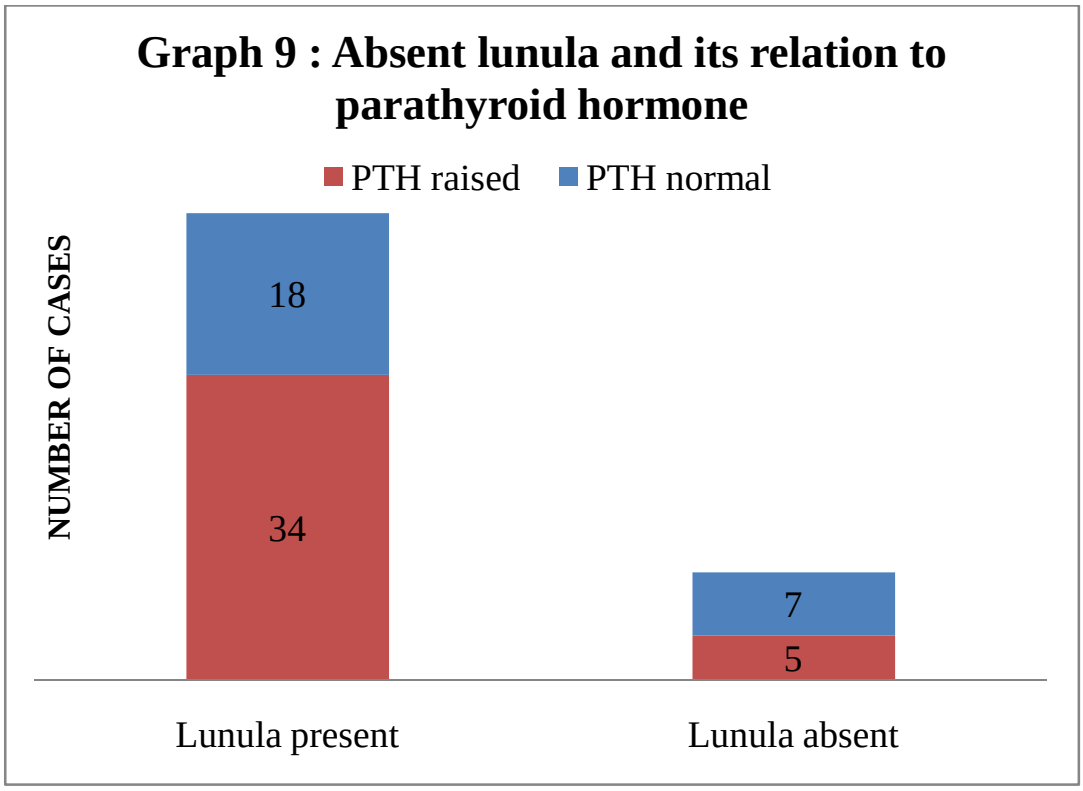


Absent lunula

12 patients (18.75%) did not have lunulae in their nails. It did not have a statistically significant correlation with parathyroid hormone levels.

Table 13: Absent lunula and its relation to parathyroid hormone

Lunula	PTH raised	PTH normal	Total	
Present	34 (65.38%)	18 (34.61%)	52	P = 0.234
Absent	5 (41.66%)	7 (58.33%)	12	

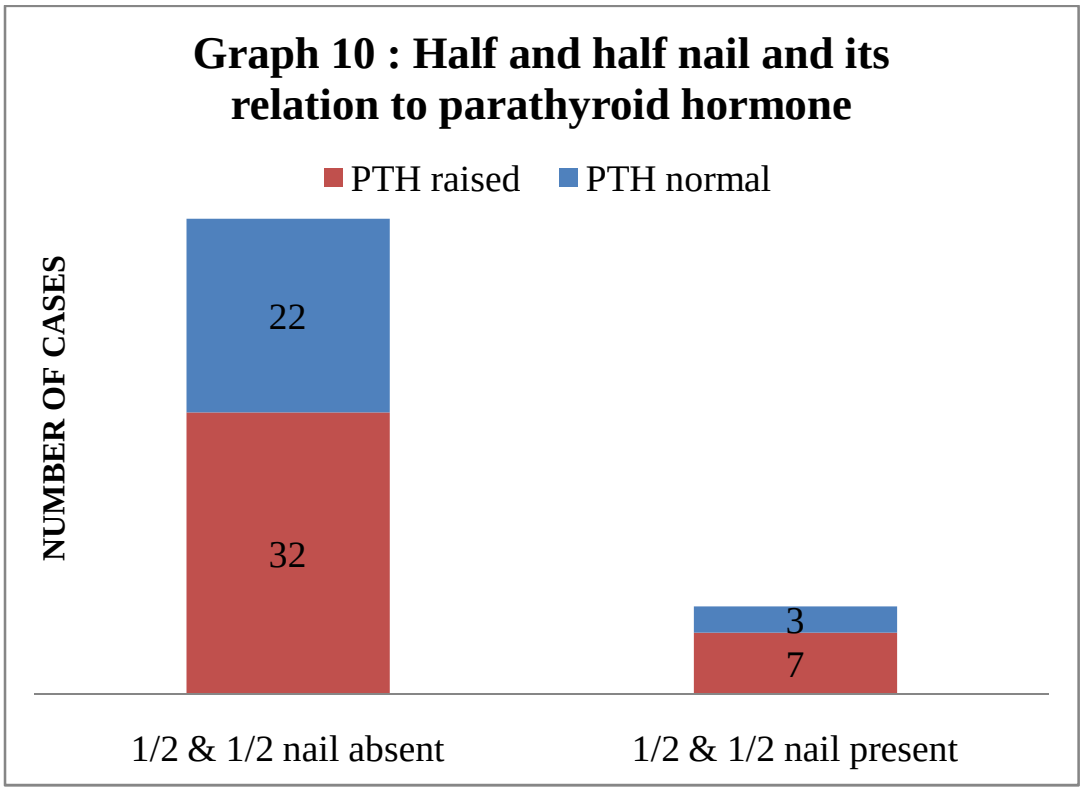


Half and half nails

10 patients (15.62%) had half and half nail. It did not have a statistically significant correlation with parathyroid hormone levels.

Table 14: Half and half nail and its relation to parathyroid hormone

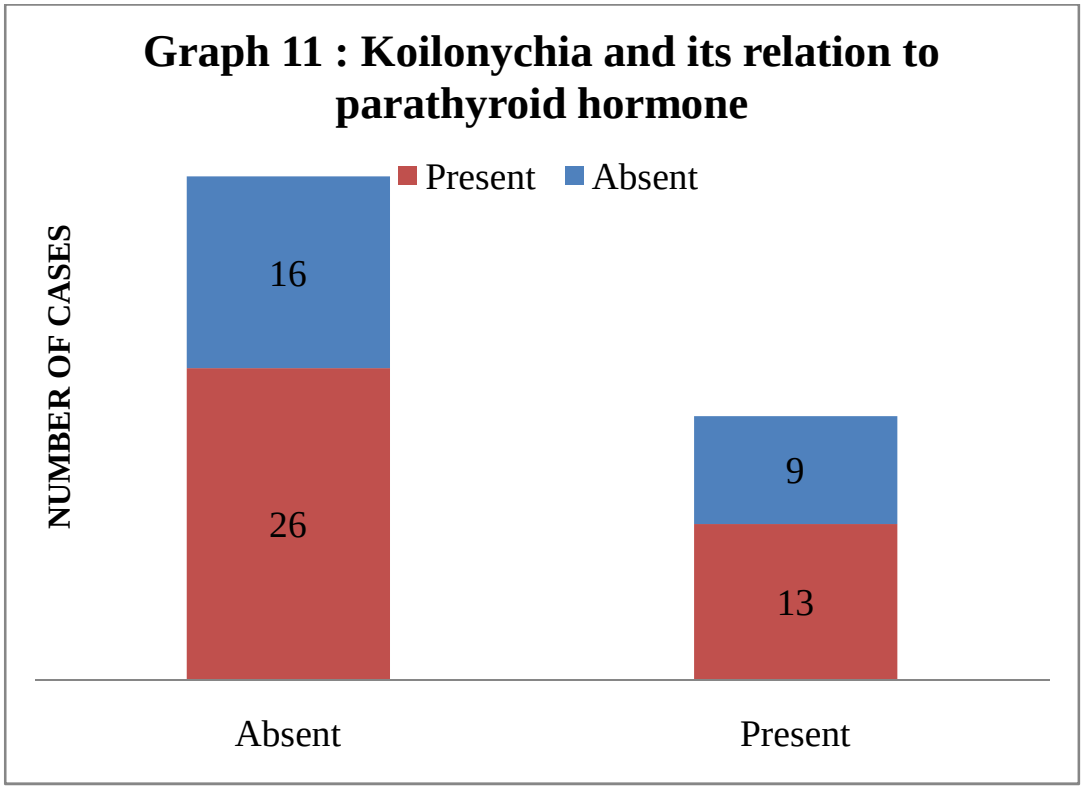
Half and half nail	PTH raised	PTH normal	Total	
Absent	32 (59.25%)	22 (40.74%)	54	P = 0.774
Present	7 (70%)	3 (30%)	10	



Koilonychia It refers to spoon shaped nails in which the normal convexity of the nail is lost. 22 patients (34.75%) had koilonychias. This was probably due to the coexistent anemia in these patients. It did not have a statistically significant correlation with parathyroid hormone levels.

Table 15: Koilonychia and its relation to parathyroid hormone

Koilonychia	**PTH raised**	**PTH normal**	**Total**	
Absent	26 (61.90%)	16 (38.09%)	42	P = 0.827
Present	13 (59.09%)	9 (40.91%)	22	

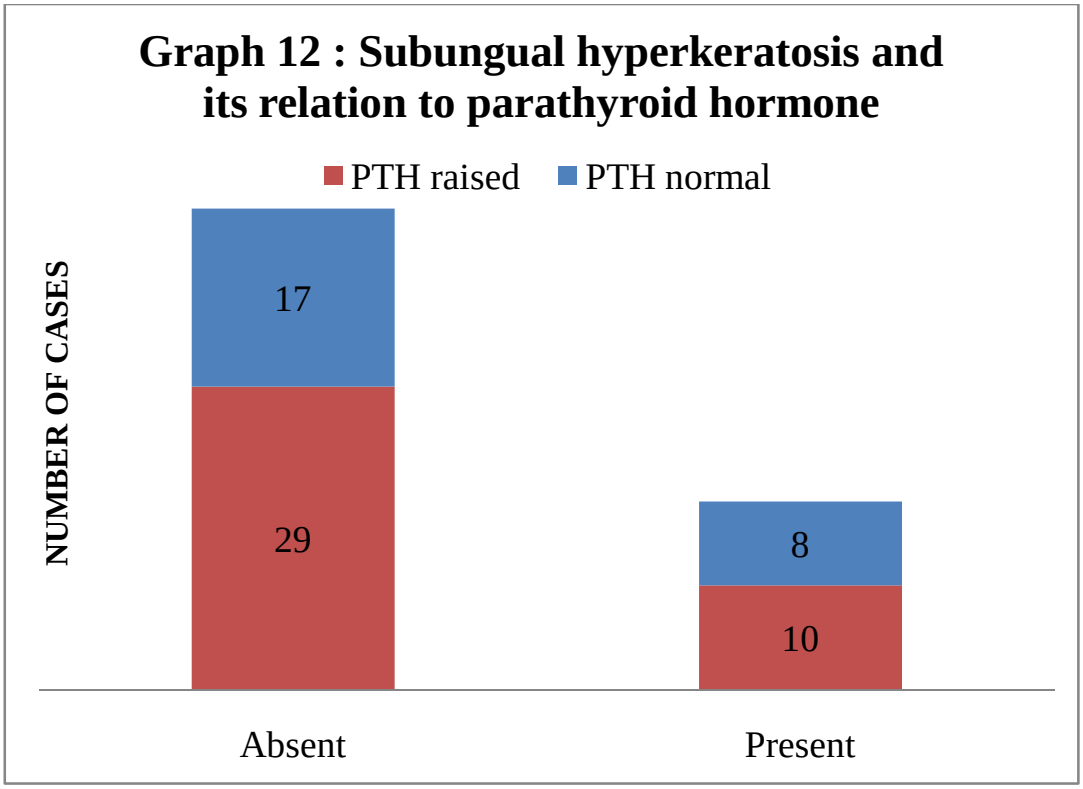


Subungual hyperkeratosis

It was seen in 18 patients (28.12%). It did not have a statistically significant correlation with parathyroid hormone levels.

Table 16: Subungual hyperkeratosis and its relation to parathyroid hormone

Subungual hyperkeratosis	PTH raised	PTH normal	Total	
Absent	29 (63.04%)	17 (36.95%)	46	P = 0.581
Present	10 (55.55%)	8 (44.44%)	18	



Onycholysis

Onycholysis was not seen in any patient.

Mees' lines

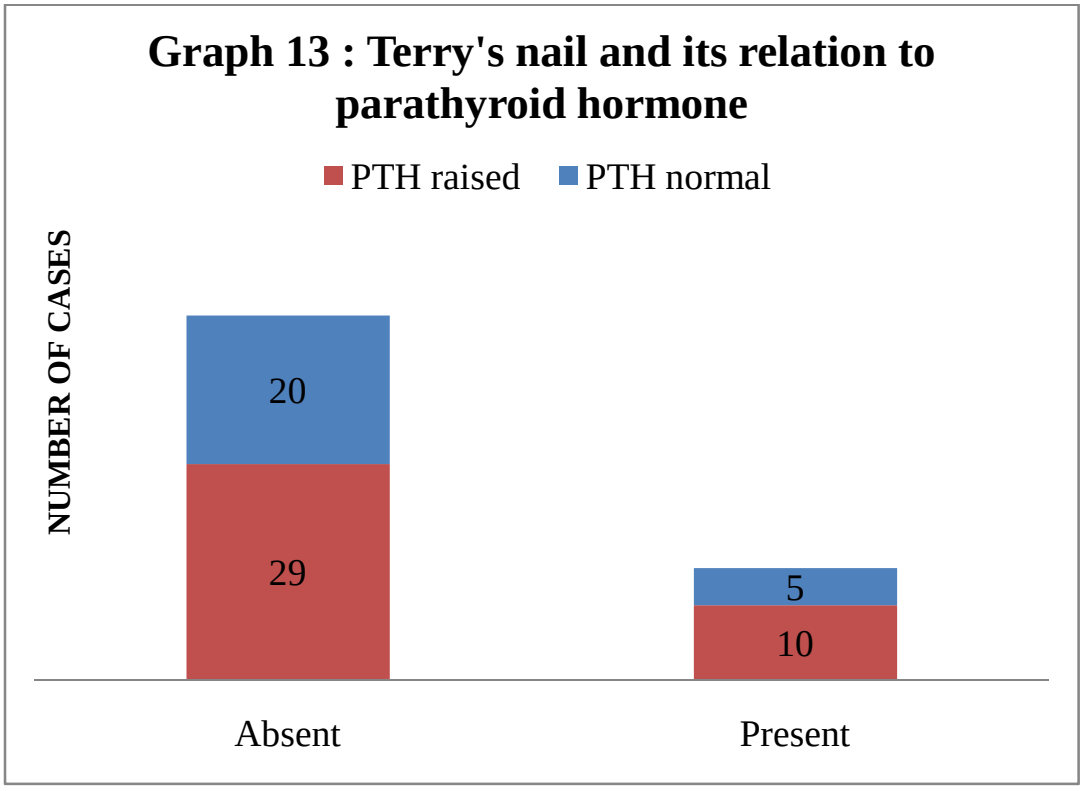
Mees lines were not found in any patient.

Terry's nails

It was seen in 15 cases (23.44%). It did not have a statistically significant correlation with parathyroid hormone levels.

Table 17: Terry's nails and its relation to parathyroid hormone

Terry's nails	PTH raised	PTH normal	Total	
Absent	29 (59.18%)	20 (40.81%)	49	P = 0.603
Present	10 (66.66%)	5 (33.33%)	15	

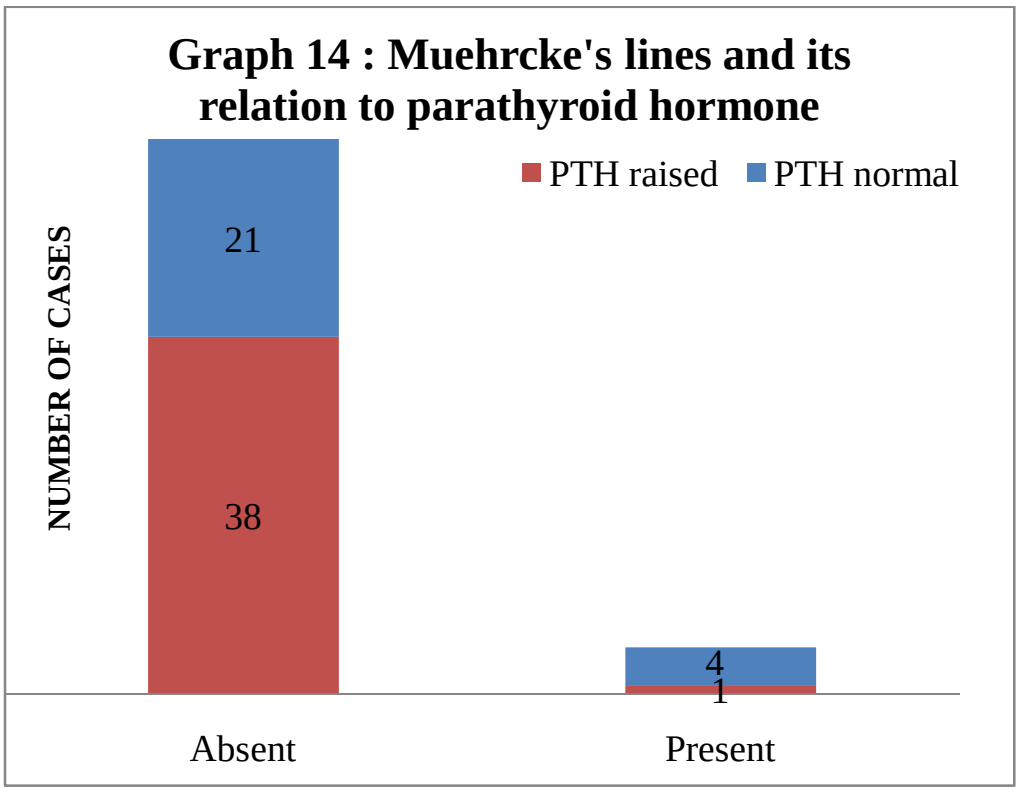


Muehrcke's lines

These were seen in 5 cases (7.8%). It did not have a statistically significant correlation with parathyroid hormone levels.

Table 18: Muehrcke's lines and its relation to parathyroid hormone

Muercheke's lines	PTH raised	PTH normal	Total	
Absent	38 (64.40%)	21 (35.59%)	59	P = 0.140
Present	1 (20%)	4 (80%)	5	

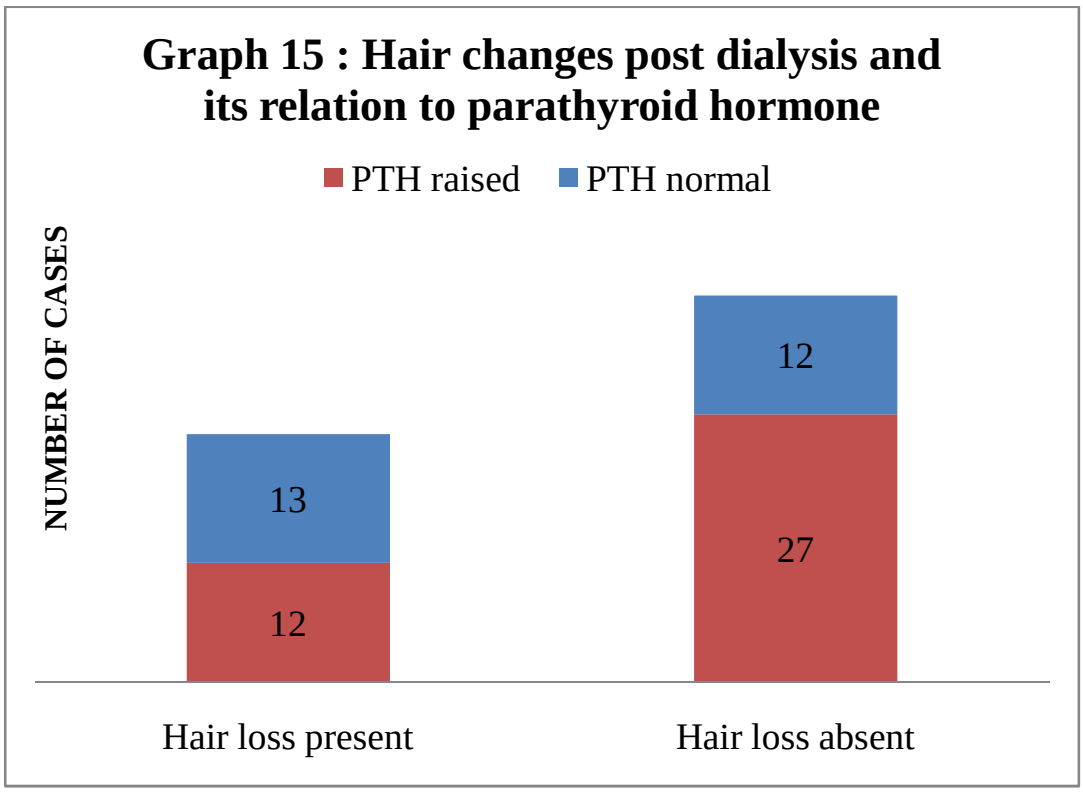


Hair changes

25 cases (39.06%) complained of hair loss post dialysis. They did not have a statistically significant correlation with parathyroid hormone levels.

Table 19: Hair changes and their relation to parathyroid hormone

Hair changes	PTH raised	PTH normal	Total	
Hair loss post dialysis	12 (48%)	13 (52%)	25	P = 0.089
No hair loss	27 (69.23%)	12 (30.77%)	39	

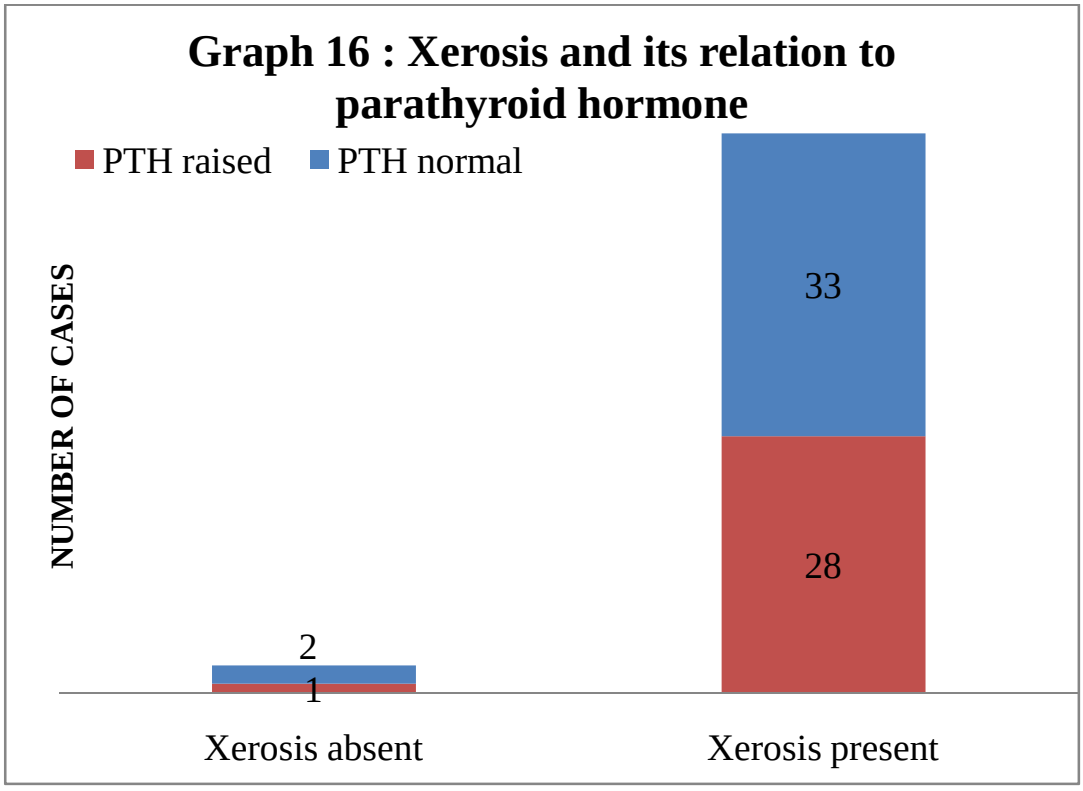


Xerosis

61 patients (95.31%) had xerosis. It did not have a statistically significant correlation with parathyroid hormone levels.

Table 20: Xerosis and its relation to parathyroid hormone

Xerosis	PTH raised	PTH normal	Total	
Absent	1 (33.33%)	2 (66.66%)	3	P = 0.691
Present	28 (45.90%)	33 (54.09%)	61	

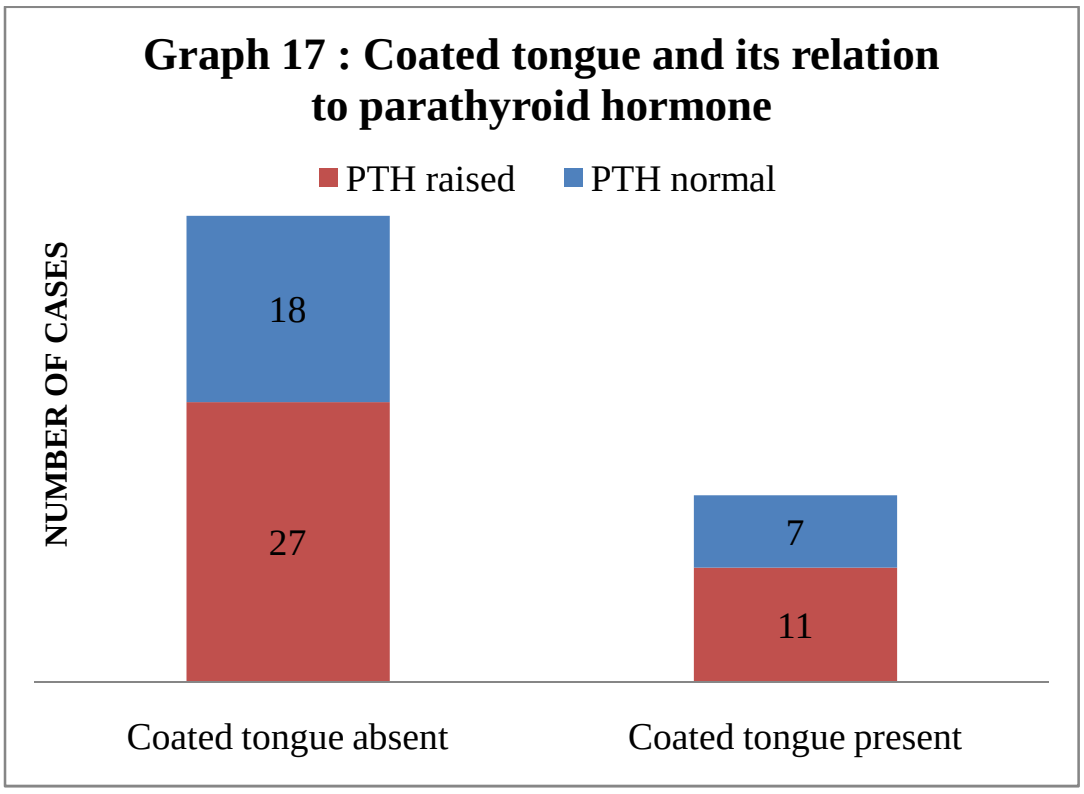


Coated tongue

18 patients (28.12%) were found to have coated tongue. It did not have a statistically significant correlation with parathyroid hormone levels.

Table 21: Coated tongue and its relation to parathyroid hormone

Coated tongue	PTH raised	PTH normal	Total	
Absent	27 (60%)	18 (40%)	45	P = 0.935
Present	11 (61.11%)	7 (38.88%)	18	

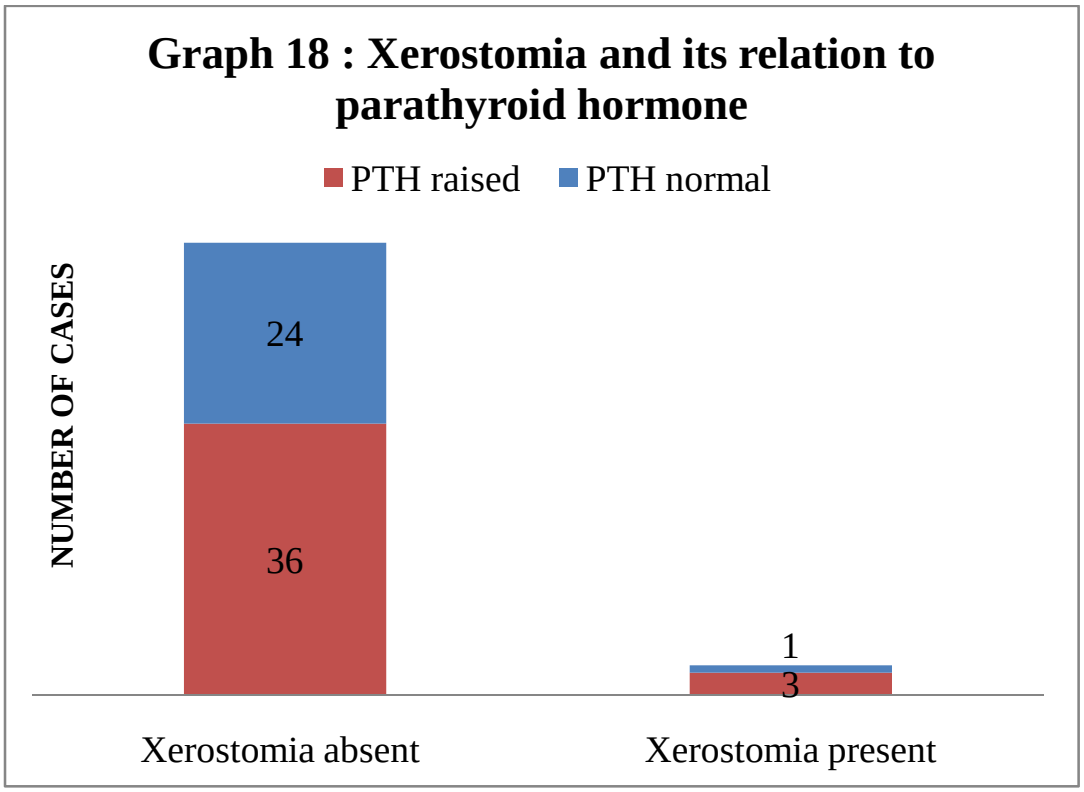


Xerostomia

Only 4 patients (6.25%) had xerostomia. It did not have a statistically significant correlation with parathyroid hormone levels.

Table 22: Xerostomia and its relation to parathyroid hormone

Xerostomia	PTH raised	PTH normal	Total
Absent	36 (60%)	24 (40%)	60
Present	3 (75%)	1 (25%)	4



Uremic fetor

Only one patient had uremic fetor.

Tongue sign of uremia

No patient had the tongue sign of uremia.

Allergic contact dermatitis

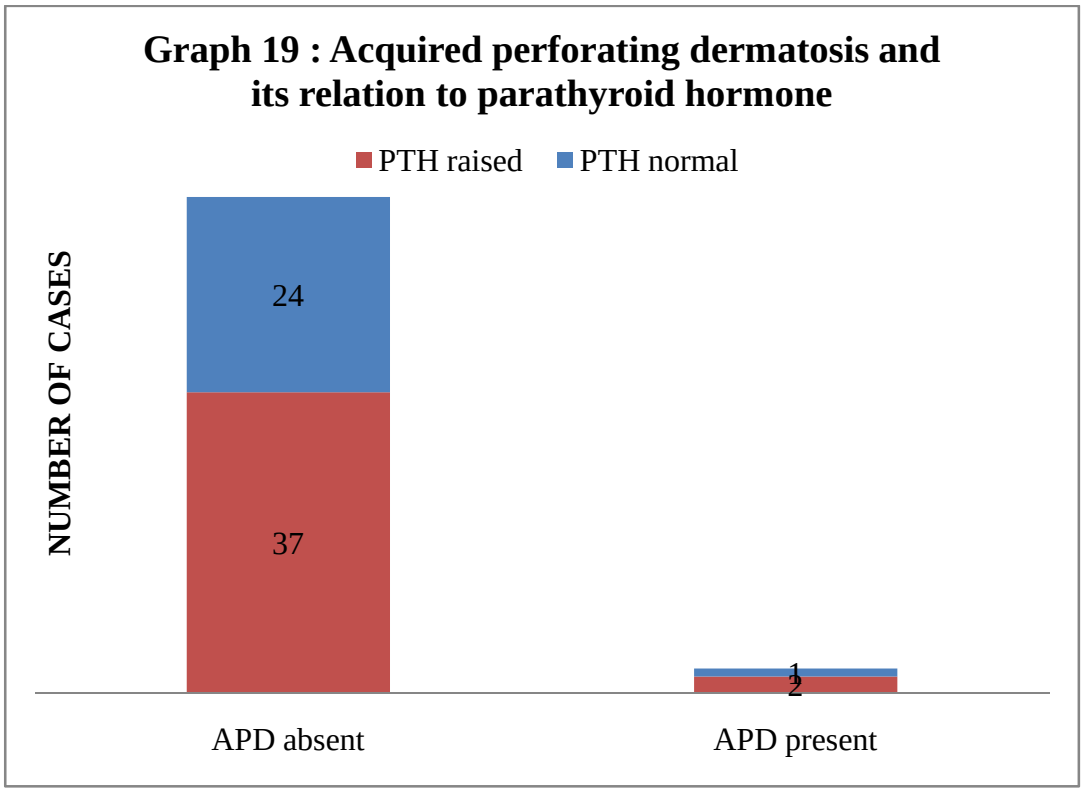
2 patients were having eczematous changes at the site of cannula insertion.

Acquired perforating dermatosis

It was seen in 3 patients (4.69%). It did not have a statistically significant correlation with parathyroid hormone levels.

Table 23: Acquired perforating dermatosis and its relation to parathyroid hormone

APD	PTH raised	PTH normal	Total	
Absent	37 (60.65%)	24 (39.34%)	61	P = 1
Present	2 (66.66%)	1 (33.33%)	3	



Out of the three patients, one patient was willing for a skin biopsy. The specimen was taken from a perforating lesion over the right knee. It was sent to pathology lab in 10% formalin and staining was done with Haematoxylin and Eosin stain. The epidermis showed acanthosis with hyperkeratosis. Epidermal invagination was present with formation of a cornified plug containing degenerated basophilic staining debris from neutrophils. The invagination was surrounded by degenerated collagen bundles. Hair shaft was not seen in the biopsy specimen. These findings were suggestive of a perforating dermatosis as suspected clinically.

Nephrogenic systemic fibrosis

No patient had thickened indurated plaques suggestive of nephrogenic systemic fibrosis.

Calciphylaxis

No patient had any evidence of calcific deposits on inspection. There were no symptoms of ulceration or rapidly developing anaphylaxis.

Bullous disease of hemodialysis

None of the patients had any bulla formation at present or in the recent past.

Skin conditions are very common in patients with chronic kidney disease. It is estimated that 80% of patients with chronic kidney disease have at least one skin manifestation. The term chronic renal failure is no longer used. It is referred to as chronic kidney disease. It has 5 stages. Stage 5 is the end stage renal disease defined by GFR < 15 mL/min per 1.73 m^2.[1]Stage 5 is the end stage requiring intervention of some kind for survival. It may be dialysis or renal transplantation. Dialysis is of 2 types, hemodialysis and peritoneal dialysis. In hemodialysis movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate.[2] Peritoneal dialysis is another type of dialysis in which dextrose containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time. The peritoneal membrane is used as the filtering membrane across which the substances are filtered. In our hospital hemodialysis is done on a routine basis. Peritoneal dialysis is not done and renal transplantation is done infrequently.

Since most of the patients of chronic kidney disease stage V are invariably on some form of renal replacement therapy there is an overlap between the skin manifestations due to chronic kidney disease and skin manifestations seen in hemodialysis patients. No study has been done on the skin manifestations in hemodialysis patients in our hospital so that was the basis of starting this study. On a look through literature there were numerous studies describing skin manifestations in dialysis patients[3] so a need was felt to explore things further. There are some studies which have correlated some skin manifestations to Parathyroid hormone. Massry et al postulated that itch associated with chronic kidney disease was due to secondary hyperparathyroidism and that it could even respond to parathyroidectomy.[4] There also seems to be correlation between dry skin and hyperparathyroidism[5]. Also there is an obvious correlation with the calcemic manifestations seen in chronic kidney disease patients and Parathyroid hormone levels.[6] However this is not true in all cases and in other studies no such correlation has been found between Parathyroid hormone levels and these conditions. In addition Pubmed search at the time of starting this study did not show any result for cutaneous changes in hemodialysis and their correlation to Parathyroid hormone. With this backdrop this study was initiated and to our knowledge no such study has been done in India so far.

Parathyroid hormone is produced from parathyroid glands. It is an 84-amino-acid single chain peptide. It causes calcium resorption from bones, and calcium resorption from the kidneys. This hormone maintains extracellular fluid calcium concentrations within a narrow normal range. Increased level of parathyroid hormone is known as hyperparathyroidism. This can be primary or secondary. Primary hyperparathyroidism is due to excess secretion from either an adenoma or hyperplasia of the parathyroid glands. Secondary hyperparathyroidism occurs due to an adaptive response to an underlying pathology causing increase in the parathyroid hormone levels. Patients with secondary hyperparathyroidism may develop bone pain, ectopic calcification and pruritus. The bone disease in patients with secondary hyperparathyroidism and renal failure is termed renal osteodystrophy. In patients on long-term dialysis especially who have excess aluminium in their dialysis regimen, aluminum intoxication may occur. Aluminum starts to deposit in the bones and causes severe osteomalacia, acute dementia and unresponsiveness. Prevention is by avoiding aluminum excess in the dialysis regimen.

Various studies done on cutaneous changes in hemodialysis patients have shown that at least 80% of patients have at least one cutaneous manifestation[7].

The cutaneous manifestations of patients undergoing dialysis can be arbitrarily divided into 2 types, non-specific and specific skin lesions.

Table 1: Cutaneous manifestations of patients undergoing hemodialysis

Non- specific changes	**Specific changes**
Pruritus	Uremic fetor

Xerosis	Tongue sign of uremia
Pallor	Uremic frost
Pigmentary changes	Dialysis related amyloidosis
Hair abnormalities	Uremic neuropathy
Nail changes e.g. Koilonychias, subungualhyperkeratosis, Mees' lines	Nail changes e.g. Half and half nail
Purpura	Acquired perforating dermatosis
Lesions at site of cannula insertion	Nephrogenic systemic fibrosis
Oral mucosal changes – xerostomia	Bullous disease of hemodialysis
	Calciphylaxis

Non-specific findings

1) **Pruritus** - The prevalence of pruritus in hemodialysis patients in various studies varies from 50-90 %.[8]The largest study done so far analyzed data from 18,801 patients undergoing hemodialysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS) from 1996-2004) and indicated that 42% of hemodialysis patients experienced moderate to severe pruritus.[9]It is the most characteristic and annoying symptom of chronic kidney disease.[10] It is also referred to as 'uremic pruritus' which literally means pruritus secondary to uremia which is untrue. The pruritus does not have relation with gender, age or duration of dialysis. The pruritus seems to be less in patients on ambulatory peritoneal dialysis than on hemodialysis patients. Pruritus also depends on the type of dialysis machine e.g. depending on the permeability of the dialysis membranes the ones with high permeability have been thought to have decreased pruritus. [11] In those patients on regular dialysis the pruritus seems to be maximum on 2 days after the last dialysis session, least on the day following dialysis. Also itching is relatively high during the dialysis procedure.[6]

Clinical characteristics of itch

The intensity of itch associated with chronic kidney disease ranges from sporadic discomfort to complete restlessness during the day and night. It could be intermittent or persistent.[12] It can be generalized in 25-50% of patients, and it predominantly affects the back (70%), abdomen (46%), head (46%), and arms (43%).

Uremic pruritus is absent in acute renal failure.[13] Exact cause for itching in chronic renal failure is not known. It is multifactorial in origin. The common causes are uremicxerosis, secondary hyperparathyroidism, hypervitaminosis A, uremic neuropathy, elevated serum histamine levels and iron deficiency anemia. Of these uremic xerosis is perhaps the most important cause as it is the most common cutaneous manifestation in chronic kidney disease patients. It is present in 90-100 % patients having pruritus.[14] The level of uremic pruritus is directly proportional to the xerosis. Xerosis is due to dehydration of skin resulting from atrophy of eccrine glands and loss of lipids on skin due to atrophy of sebaceous glands however Yosipovitch et al did not find any evidence between the severity of pruritus and objective parameters of xerosis.

Endogenous opioids are important players in the pathogenesis of itch. An increased ratio of serum beta-endorphin to dynorphin A was reported in hemodialysis patients compared with healthy controls and the ratio increased with increased intensity of itch.[15]

Some studies have reported significant association between serum parathyroid hormone and itching whereas others have not found any association. Kidney failure, hyperphosphatemia, hypocalcemia and decreased levels of calcitriol (vitamin D) are factors which increase parathyroid hormone levels.[16] Thus the raised parathyroid hormone level in kidney failure is actually a type of secondary hyperparathyroidism.[17] It has been reported that pruritus in some patients can completely disappear

after parathyroidectomy.[18] Hyperparathyroidism can stimulate mast cells to release histamine. This can promote micro precipitation of calcium and magnesium salts in the skin. On the other hand all patients with severe hyperparathyroidism do not have pruritus. Also there is no difference in the number of mast cells in patients with hyperparathyroidism in patients having and not having pruritus.[19] In experimental intradermal injections of parathyroid hormone failed to produce pruritus. Also in the same study immunohistochemistry was negative for parathyroid hormone in skin biopsies in patients undergoing hemodialysis.[20] In a recent Iranian study there was a significant correlation was found between itching score and serum intact parathyroid hormone in hemodialysis patients.[21]

Impact on the quality of life

It was found in Dialysis Outcomes and Practice Patterns Study that patients undergoing hemodialysis with pruritus were more likely to feel drained and have poor sleep quality, depression and lower mental and physical composite scores of quality of life than patients with no or mild pruritus. Moreover pruritus in hemodialysis patients is associated with 17% higher mortality rate than the patients on hemodialysis who are not having pruritus. (insert end note AA)

The difficulty which an investigator faces with pruritus is the subjectivity of the symptom. It is a purely subjective symptom and each patient may have a different threshold for what he or she finds bothersome. There are a few ways of objectively measuring pruritus. One way is to ask the patient to rate his or her pruritus on a scale of one to ten, one being 'no itching' and ten being the 'most severe' itching which the patient just can't tolerate. Another scale is the modified scoring system proposed by Duo.[22] The total scoring of pruritus is calculated as follows:

(Severity of pruritus x distribution of pruritus) + sleep disorder.

Table 2: The severity of pruritus is assessed as:

1 point	Slight itching
2 points	Itching with scratching
4 points	Itching and scratching with excoriations
5 points	Itching causing total restlessness

Table 3: The distribution of pruritus is scored as

1 point	Pruritus maximum in 2 areas of the body
2 points	Pruritus maximum in more than 2 areas of the body
3 points	Generalized pruritus

Table 4: The sleep disorder is monitored as

2 points (maximum of 10 points)	Every waking up due to itching
1 point (maximum of 5 points)	Each scratching

There may be some sort of pruritogen which is not adequately filtered through the dialysis membrane thus accumulating in the body under the skin and cause itching. The type of dialysate

may also have a role in pruritus. Lower levels of Magnesium in the dialysate have been correlated with lower levels of pruritus.[23]

Treatment of pruritus

There are various treatment modalities which have variable efficacy for treatment of pruritus. Wang et al have proposed a therapeutic ladder for management of pruritus in end stage renal disease.[24]

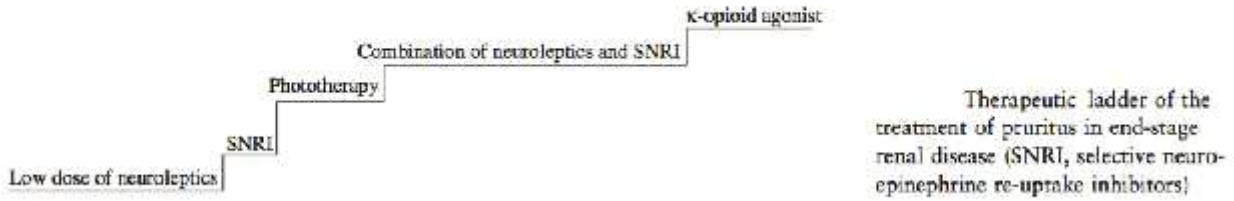


Figure 1 – Therapeutic ladder of the treatment of pruritus in end stage renal disease (SNRI, selective neuroepinephrine re-uptake inhibitors)

The first line of management is with neuroleptics. Gabapentin and pregabalin are structural analogs of the neurotransmitter GABA. The exact mechanism of their mechanism is not clear. They probably inhibit the central itch pathways just like in neuropathic pain.[25] In a placebo controlled double blinded study by Gunal et al in 25 patients with end stage renal disease associated pruritus found that 300 mg of oral gabapentin given after each hemodialysis session was safe and effective regimen.[26] Gabapentin is a neurotoxic drug. In another study it was suggested that starting 100 mg initially with a slow upward titration can reduce this side effect.[27]

The second line of management is SNRI (Selective neuroepinephrine re-uptake inhibitors). They relieve the itching probably by reducing central sensitization to itch. Mirtazapine has been found to be effective in treatment of nocturnal pruritus.[28]It has also been found to be effective in renal pruritus.[29]

The third line of management is phototherapy.UVB therapy is effective in severe intractable pruritus.[30] It is considered the treatment of choice in many centers. UVA therapy without psoralens is also said almost just as effective.[31] The exact mechanism of action is not known. Probably it works via chemical modification of pruritogens in the skin or an alteration of skin sensitivity to pruritogens. It may also work by reducing post inflammatory cytokines. It is important to inform the patient that the in the first 2 weeks the itch may worsen and the reduction in pruritus may take 1-2 months.

If itching is not controlled by the above measures the fourth line management is using a combination of neuroleptics like Gabapentin and selective neuroepinephrine re-uptake inhibitors like Mirtazapine.

If itching is still not controlled then the fifth line of management is κ–Opioid agonists. A recent kappa receptor agonist, nalfurafine(TRK-820) has shown antipruritic effect in the treatment of ESRD associated pruritus. However it is not available commercially.[32]

Other alternatives are activated charcoal, cholestyramine, erythropoietin, ondansetron and naltrexone.[33] Sedating antihistaminic like hydroxyzine have some role in control of pruritus. Other antihistaminics do not help much because histamine does not play a significant role in uraemic pruritus.[34]Various topical therapies can also be used. Emollients help to a certain extent as xerosis is one of the most common causes of pruritus. In a double blinded placebo controlled study 0.025% capsaicin was found to significantly reduce pruritus in comparison to placebo.(insert reference AB)Pramoxine 1% lotion was found to be efficient in treatment of uremic pruritus in a recent study.[35]

Renal transplantation is curative for uremic pruritus.

2) **Xerosis** - Uremic patients tend to have a very dry skin. It is the most common cutaneous manifestation seen in patients undergoing hemodialysis.[36] It is seen in up to 90% of patients. This is thought to be due to reduction in the eccrine sweat glands which reduces water content of the skin and also reduction in size of pilosebaceous units due to which there are decreased lipids on skin surface.[37] High dose diuretics may lead to iatrogenic dehydration leading to dryness of skin.[38]Xerosis is also a manifestation of Diabetes Mellitus and since Diabetes mellitus is the most common cause of chronic kidney disease in most centers, xerosis may be attributed to it. Also uraemia has been known to cause peripheral neuropathy which could also affect peripheral autonomic nerves thus leading to decreased sweating secondary to autonomic nervous dysfunction. This could in turn cause xerosis.

Treatment – Emollients can help only to a certain extent.

3) **Pallor** - Kidneys are the sites for erythropoietin production, which is essential for normal erythropoiesis. Thus in chronic kidney disease there is reduced erythropoietin production which causes decreased RBC production leading to anemia. Udayakumar et al. reported pallor in 60% of uremic patients.[39] Pallor may be difficult to appreciate in some patients as they start developing diffuse pigmentation all over body.

Treatment – Erythropoietin injections can help in RBC synthesis to a certain extent.

4) **Pigmentary changes** - Two different types of pigmentation patterns may be seen. First one is diffuse hyperpigmentation present all over the body but more so in sun exposed areas. The prevalence for this has been estimated as around 20-25%.[40] The diffuse hyperpigmentation has been attributed to increased melanin in the basal layer of epidermis and upper region of dermis due to failure kidneys to excrete beta-melanocyte stimulating hormone (β-MSH).[41] Hyperpigmented macules over palms and soles have also been reported.

The second type of pigmentation pattern seen is yellowish discoloration of skin. This has been reported in as many as 40% of patients. This has been attributed to accumulation of carotenoids and nitrogenous pigments like urochromes in the dermis.[42]

There might be a third kind of skin colour change which may be described that is the pale skin due to severe pallor. This is described more so in western literature and difficult to ascertain in Indian skin.

5) **Hair abnormalities** - Sparse body hair and diffuse alopecia have been described.[43] The exact cause is not known. One of the causes can be severe anaemia which is very common in these patients. The second hypothesis is that these patients are under lot of stress which can precipitate telogen effluvium. The hair in these patients is dull and lusterless. This is so because of decreased sebum secretion.[44]

6) **Nail changes–** Nail changes may be specific or non-specific.

Specific nail changes

Half and Half Nails- The classical nail change described is Lindsay's nails (half and half nails). These nails are red or pink in the distal half and white in the proximal half.A distinct line appears to separate the two zones. The red colour in the distal half does not fade with pressure.[45] Studies have shown prevalence from 16-50%.[46]The pathogenesis is not known. Stimulation of nail bed melanocytes by increased levels of plasma melanotrophic hormones and vascular changes have been suggested as possible causes.[47] They have also been reported after cancer chemotherapy; in a breast cancer patient after androgen use; after exposure to paraquat.[48] Erythematous crescent is a reddish discoloration of the distal nail involving less than 40% of distal nail bed. It is also seen in chronic renal failure.[49] They may also be present in normal healthy adults. Once present these changes may remain permanently even after hemodialysis.

Non-specific nail changes

A) **Koilonychia** – There is loss of convex curvature of the nails. The nails either become flat or truly concave or'spoon like nails'. It affects fingernails more than toenails. It can be acquired or heredity. The acquired form is much more common and associated with iron deficiency anemia. They may even be present in normal individuals and may be a racial characteristic in Ladhakhi and Tibetan populations.[50] It has also been described in post renal transplant patients and after hemodialysis.

B) **Subungual hyperkeratosis** - It refers to hyper proliferation of keratinous debris under the nails)

C) **Onycholysis–**It is breakage in the distal end of nail plate.

D) **Mees' lines –** These are white transverse bands seen on nail plate. Generally there is a single band but multiple bands may occur. They result from focal parakeratosis of the nail matrix. They have a contour similar to the distal edge of lunula. They are seen in a variety of systemic disorders. Some of them are

a. Arsenic, thallium or heavy metal poisoning
b. Carbon monoxide poisoning
c. Drug induced **–** due to chemotherapeutic agents like cyclophosphamide, vincristine
d. Psoriasis
e. Renal allograft rejection
f. Chronic renal failure

E) **Muehrcke's lines –**These are also narrow white transverse bands parallel to the lunula. Like Mees' lines they are span the entire width of the nail. They occur in pairs and they represent abnormality in the nail bed. They frequently occur on the second, third and fourth finger nails. Unlike in Mees's lines squeezing the distal digit will make the lines temporarily disappear.

Hypoalbuminemia is an important cause of these lines. They have been reported in various conditions. Some of them are

a) Chemotherapy

b) Hypoalbuminemia (nephrotic syndrome, glomerulonephritis, liver disease, malnutrition)

c) Malnutrition

d) Heart transplant recipients[51]

F) **Terry's nails –** There is leukonychia affecting the entire nail plate except the distal 20% or 2 mm distal margin. The distal margin corresponds to the onychodermal band, which is characteristic.[52]Terry's nails are a result of changes in nail bed vascularity, a decrease in the proximal portion and an increase at the distal edge. All nails are affected uniformly. They are generally seen in cirrhosis of liver, heart diseases or diabetes mellitus.

G) **Splinter hemorrhages –** They have also been described which are seen more commonly than in normal population.[53] They present as longitudinal red colored streaks beneath the nail plate due to extravasation of red blood cells from the damaged capillaries.

7) **Purpura** - Purpurae are reddish non-blanchable lesions due to extravasation red blood cells into the skin or mucosa. Dialysis patients are often on heparin which may increase the incidences of bleeding. Also in hemodialysis patients arteriovenous shunt is formed which may lead to extravasation of blood due to trauma during the dialysis process.[54]

8) **Lesions at site of cannula insertion** - The cannula is inserted into the arteriovenous fistula during dialysis procedure. There might be extravasation of blood, phlebitis due to repeated manipulation of cannula during multiple sittings per week. Eczema may develop at the site of shunt formation either due to cleaning of the area with betadine or secondary to extravasation of blood. There may also be infections which may be local or rarely cause dangerous septicemia.[55]

9) **Oral mucosal changes** - Oral changes are very common in patients undergoing hemodialysis.[56]They may be specific or non-specific.

Specific signs - Teeth marking is seen along with macroglossia which is known as the '**tongue sign of uremia**'. This finding was first described by Mathew in Chronic kidney disease patients.[57]When urea levels are more than 200 mg/100 ml, a condition known as '**uraemic fetor**' is described. This is an ammoniacal odor produced secondary to high urea concentration in the saliva which breaks down to release ammonia which has a pungent odor. These patients have fewer fungiform taste buds which may cause impairment of taste.[58]

Non-specific signs - Xerostomia (dry mouth) has been reported which may be due to dehydration. Ulcerative stomatitis has been described classically in patients with high urea levels (>150 mg/100 ml) but fortunately this condition is now rarely seen.

10) **Acantholytic dermatosis–**A case of persistant acantholytic disease (Grover's disease) has been described since 6 months in a patient who was on hemodialysis since 9 years.[59]Grover first described this disorder.[60] It is also known as Grover's disease. It is characterized by pruritic, edematous papules or papulovesicles with excoriations. The lesions occur mainly on the upper

trunk and histologically show epidermal acantholysis that resemble Darier's disease. The lesions may be transient in which case the condition is called transient acantholyticdermatosis. There is a variant of this disease in which the lesions are persistent. It this case it is called persistant acantholytic dermatosis.The cause is unknown but actinic damage has been implicated as an initiating factor.

Treatment **–** There are reports of good response to systemic retinoids. For persistent small lesions surgical excision can deliver excellent results.[61]

Specific findings

1) **Uremic frost**- This is seen in in those people whose urea levels are very high (>200 mg/100 ml). The frost consists of white/yellow coating of urea crystals on the beard or on the trunk. It occurs due to urea secretion through the sweat glands which deposits as beads on surface as it cannot evaporate.[62] It is more commonly seen in acute renal failure.

In erythema papulatumuremicum, large papules and nodules on an erythematous base are seen over palms, soles and face. In a few weeks they desquamate and form fissures. This change is also not seen in the present era.

2) **Dialysis related amyloidosis** - It is a type of secondary systemic amyloidosis in which there is deposition of beta 2-microglobulin. It is frequently associated with musculoskeletal and joint complaints. Deposits in the wrist area leads to carpal tunnel syndrome, deposits in bones lead to bone cysts.[63] Heart is the most common extra-articular organ involved followed by the gastrointestinal tract. This visceral form β_2M amyloidosis is a major complication of chronic renal failure and occurs mainly in patients who have been on dialysis for more than 10 years. Lingual deposits of amyloid on the tongue have described presenting as multiple white-yellow and red coloured non-tender, firm nodules of different size.[64]It is closely related to use of low flux, bioincompatible cellulose membranes, which can cause tissue deposition of beta 2 microglobulin as amyloid fibrils.[65] Other visceral deposits of β2M amyloid include large amyloid protein masses in subcutaneous tissues, especially in the gluteal region, which is also a rare manifestation of dialysis related amyloidosis.[66] The treatment of dialysis related amyloidosis is limited to the management of symptoms and surgical removal of amyloid deposits. New high-flux, biocompatible dialysis membranes are available which are more permeable to beta 2-microglobulin which might delay the onset of dialysis related amyloidosis.[67]

3) **Uremic neuropathy** affects about 60% of patients with chronic kidney disease or patients on long term hemodialysis. This appears to be a predominantly sensorimotor neuropathy.[68] This is a manifestation of uaemia.

4) **Acquired perforating dermatosis–**There is lot of ambiguity regarding this terminology. Perforating disorders are a group of disorders, which are characterized by transepidermal elimination of amorphous material. Currently there are 4 disorders, which are recognized as primary perforating disorders. They are elastosis perforans serpiginosa, Kyrle's disease, perforating folliculitis and reactive perforating collagenosis. These perforating dermatoses can occur in diabetes mellitus and in patients with chronic renal failure, many of who are undergoing hemodialysis.[69] The distinction between these four dermatoses is not clear-cut especially in the case of hemodialysis patients; the conditions may overlap. Thus the name 'acquired perforating disorder' has been proposed for the perforating dermatoses occurring in the setting of chronic kidney disease/

hemodialysis. Gracia Bravo et al have used the term 'uremic follicular hyperkeratosis' for it.[70] When these conditions occur outside the setting of diabetes mellitus or chronic kidney disease they occur as separate entities. This dermatosis occurs in up to 10% of patients undergoing hemodialysis.[71] Clinically the patients present with hyperkeratotic papules with a central crust filled crater on the trunk and on extensor surfaces often in a linear distribution.[72] The extensor surface of limbs are more commonly involved.

The histologic features may resemble any of the four primary perforating dermtosis. Chang et al, where they studied 9 Guatemalan patients with acquired perforating disease associated with chronic kidney disease.[73] Out of these 6 were on hemodialysis. Out of these 6 in 5 patients the lesions started after starting hemodialysis. In lesions resembling Kyrle's disease there is a keratotic plug showing parakeratosis and basophilic cellular debris filling an epidermal invagination. There is acanthosis in the surrounding area.[74]In perforating folliculitis, a widely dilated follicle is seen which is filled with a keratotic plug containing parakeratosis, suppurative inflammation and basophilic necrotic debris. In reactive perforating collagenosis there is broad cup-shaped epidermal invagination containing parakeratotic debris, inflammatory cells, vertically oriented degenerated basophilic collagen.[75]

The exact etiology for the disorder is not known. Possible explanations are diabetic microangiopathy, dysregulation of vitamin A or D metabolism, inflammation and connective tissue degradation caused by dermal deposition of substances like uric acid or calcium salts which are accumulated in excess during renal failure.[76] It is also thought that that this is a reaction pattern to constant itching and scratching in chronic kidney disease.

Treatment options consist of topical and intralesional corticosteroids, topical and systemic retinoids, cryotherapy and ultraviolet therapy. Oral vitamin A (1,00,000 U/day) has also been tried.

5) **Nephrogenic fibrosing dermopathy –** Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis (NFD/NSF) is a recently recognized fibrosing disorder of the skin that occurs in patients with renal insufficiency. NFD was originally described in 1997 in 15 patients receiving hemodialysis, who developed lesions on their extremities and trunk, characterized by thickening and hardening of the skin, papules and nodules with hyperpigmentation, and flexion contractures.[77]On examination the lesions are well defined and may have finger like projections. The plaques may be erythematous, yellow or skin coloured. Patients describe pain, paresthesias and pruritus but are most bothered by the limitations in the mobility resulting from flexion contractures. On examination of eyes most patients have scleral plaques. Clinically the lesions resemble scleroderma or morphea but they have distinct biopsy findings correlating with scleromyxoedema. Scleromyxoedema is a condition characterized my mucin deposition in the viscera and immunoglobulin G (IgG) lambda paraproteinemia. However these 2 conditions were lacking from the described patients. Scleroderma tends to involve the head and neck area. These areas are spared in nephrogenic systemic fibrosis.

There seems to be no correlation between ethnic background, sex or the cause of chronic kidney disease. This condition occurs in patients on end stage renal disease most of whom are on hemodialysis.[78]. The histopathology of Nephrogenic fibrosing dermopathy is similar to scleromyxoedema. There is proliferation of fibroblasts in the dermis and subcutaneous septae, along with deposition of collagen and mucin.

It has been recently discovered that this condition occurs in people who have had a gadolinium scan magnetic resonance procedures. Gadolinium is a radiocontrast media. Such contrast media are not recommended if the glomerular filtration rate is less than 30 ml/min. It is hypothesized that the retention of Gadolinium in patients with kidney disease is profibrotic. In some studies it has been

shown by skin biopsies that Gadolinium has been retained in the skin of patients with chronic kidney disease even more than 2 years after the intake of Gadolinium.[79] These patients have also been shown to have abnormal scintigraphy with increased uptake of ^{99mTc}-hydroxymethylene diphosphonatein the skeletal muscle underlying the involved skin, demonstrating an abnormal process extending deeper than the dermis.[80,81] The disease process can involve the underlying organs also so a new terminology "Nephrogenic systemic fibrosis" has been proposed. Involvement of the diaphragm can even lead to death. 10% of the patients with nephrogenic systemic fibrosis have a fatal course.

Recently a classification scheme was proposed for the clinical subtypes seen based on data from published reports and the NFD registry organized through Yale University, United States of America.[82]

Table 5: Clinical subtypes of nephrogenic fibrosing dermopathy (NFD): a proposed classification scheme[83]

Subtypes	**Description**	**% Of previously reported patients (n = 100)**	**5 of patients from case series (n = 9)**	**NFD progression**
1	New onset acute renal failure or acute decompensation from chronic renal failure	25	22	May be transient
2	Pneumonia like disorder followed by renal failure	6	0	Usually transient
3	Surgical procedure or acute blood loss followed by acute renal failure	18	22	May be transient
4	Kidney transplant	34	55	May be transient
5	Chronic renal failure, unknown trigger	3	11	Usually chronic
6	Thrombotic event, renal failure may predate or follow the event	12	11	May be transient

Treatment – Since there are very few cases described in literature no definitive therapy exists. The most dramatic improvement was seen in 3 patients who were treated with plasmapheresis.[84] Other therapies tried with variable success are UV-A1 phototherapy, prednisone, extracorporeal photopheresis, methotrexate.[85]

6) **Bullous disease of hemodialysis** - It is a well known entity with an incidence of 2-18% in patients undergoing hemodialysis. It is also known as pseudoporphyria of hemodialysis.Korting first reported it in 1975 as a bullous dermatosis resembling porphyria cutanea tarda undergoing maintainance hemodialysis. All these patients had normal porphyrin levels. In chronic kidney disease the normal porphyrin excretion is retarded so it may be sometimes confusing to distinguish between Porphyria cutanea tarda and pseudoporphyria. However in pseudoporphyria the porphyrin levels are only moderately elevated so accurate assays of porphyrin levels are of prime importance.[86] Pseudoporphyria may also develop in association with medications like furosemide, nalidixic acid, tetracycline naproxen, pyroxidine or amiodarone.

The clinical presentation of pseudoporphyria is similar to sporadic porphyria cutanea tarda. Clinically there are tense vesicles and bullae distributed on the dorsal hands, face and occasionally the feet. Secondary changes include erosions and crusts. The bullae heal with scarring and milia formation. The skin is fragile and easily traumatized. Hyperpigmentation of sun-exposed skin is seen. Hypertrichosis is also observed.

Laboratory findings. All types of porphyria cutanea tarda have increased serum iron, ferritin and hepatocellular iron. Those patients who are not anuric excrete increased uroporphyrin I greater than uroporphyrin III, 7-carboxyl porphyrins in the urine. Anuric patients demonstrate markedly elevated plasma levels of uroporphyrin.[87]

Histopathology. Porphyria cutanea tarda in characterized by subepidermal vesiculation with little or no inflammation. The base of bulla is corrugated and lined by well preserved dermal papillae (festooning). There is mild thickening of basement membrane zone and vessel walls, which can be highlighted with periodic acid-Schiff stain. The findings in pseudoporphyria are similar although periodic acid-Schiff stain reveals less vessel wall thickening.

Management. In both the scenarios sun protection is vital.Broad-spectrum physical blockers such as zinc oxide or titanium dioxide are preferred. Unfortunately, standard hemodialysis does not effectively remove uroporphyrin. High flow rate dialysis with a high-flux polysulfate dialyzer can reduce plasma porphyrin levels by upto 37%[88], however this is insufficient to induce clinical remission. N-acetyl cysteine, which is an antioxidant, may help in reducing the blistering.[89] Treatment of true Porphyria cutanea tarda in the patients is limited as antimalarials work by forming complexes with porphyrins and getting excreted in urine. In chronic kidney disease patients the urine production is reduced. Further the porphyrin antimalarial complexes cannot pass through the dialysis membrane. For patients without renal problem phlebotomy is the treatment of choice. In this procedure 500 ml of blood is removed every fortnightly. However this procedure is limited in these patients as these patients already have low hemoglobin due to reduced erythropoietin formation. Small volume phlebotomies (50-100 ml) every week over 1 year have been reported to induce remission. These patients are treated with erythropoietin along with small volume phlebotomies. This has been shown to mobilize hepatic iron stores. Complete resolution may require several months of therapy. Desferoxamine may also lower porphyrin levels in some patients but it has side effects and so can be used only for limited time. Renal transplantation provides complete resolution of symptoms.[90]

7) **Calciphylaxis** - It is characterized by progressive cutaneous necrosis associated with small and medium vessel calcification. It occurs in the setting of end stage renal disease, diabetes and hyperparathyroidism. Many of these patients are also on hemodialysis. The exact cause is not

known. Generally vascular calcifications are common in patients with chronic kidney disease and most of the times they are asymptomatic. In calciphylaxis there is sudden thrombosis in the calcified vessels. It is a type of induced systemic hypersensitivity in which tissues respond inappropriately to certain challenging substances with calcium deposition. The challenging agents include glucocorticoids, albumin infusions, intramuscular tobramycin, iron dextran complex, calcium heparinate, immunosuppresive agents and vitamin D. It occurs closely following initiation of hemo- or peritoneal dialysis.

It is a very painful condition. Initially there is a preinfarctic stage. In this stage there is mottling of skin or it may have a livedoreticularis like pattern or skin may appear dusky red or violaceous. Later bullae may start forming over the ischaemic area. These bullae eventually become necrotic. The central infarcted site becomes black or yellowish. This infarcted area keeps becoming larger. When this is debrided deep ulcers are seen which may even reach up till the fascia. This ulcer can become secondarily infected and may take a sinister course like cellulitis or septicemia. The calciphylactic skin changes are mostly seen on distal extremities, especially over the lateral and posterior calves, abdomen, buttocks, fingers and glans penis. On investigation uremia is present. The calcium x phosphate product is elevated. Parathyroid hormone levels are elevated. For

Histopathology deep incisional biopsy should be taken. There is calcification of small to medium sized blood vessels in the dermis and subcutaneous tissue. Intraluminal fibrin thrombi are present. If the ischaemia is severe lobular or septal fat necrosis may take place along with lymphohistiocytic infiltrate. Radiographs of affected extremities show calcium deposition outlining small and medium sized vessels.

The differential diagnosis includes panniculitis, necrobiosis lipoidica with ulceration, dystrophic calcification, disseminated intravascular coagulation, pyoderma gangrenosum and warfarin necrosis.

Overall the prognosis is bad and mortality rate is very high. Treatment of renal failure helps in improving the condition. Aggressive debridement of wound helps in preventing secondary infection and in wound healing. Subtotal or total parathyroidectomy may help as this condition is related to hyperparathyroidism. Phosphate binding agents may also help.

In addition to vascular calcification and calciphylaxis, nodular calcification may occur in the skin and fat of patients with chronic kidney disease. These deposits are identical to calcinosis cutis of CREST syndrome. The involved skin may ulcerate here also but this is without the severe pain and livedo reticularis like lesions.

DISCUSSION

64 patients were examined in the study. No controls were taken in the study. In an Egyptian study by Attia et al, a total of 206 uremics were taken.[7] They were then compared with controls which were age and gender matched. This is a limitation of the present study which is a cross sectional study. A case control study would have helped to eliminate the confounding errors.

Table 24: Sample size of various studies

Study	**Sample size**
Present study	64
Eyptian study by Attia et al	206
Indian study by Udayakumar et al[3]	100
Indian study by Tawade et al[39]	35

Larger the sample size, greater is the power of the study. However due to time restriction only 64 patients were examined.

The criteria for choosing the patients in the present study was that the patient should be having chronic kidney disease stage 5. It is defined as the end stage renal disease with Glomerular filtration rate < 15 mL/min per 1.73 m^2 In the study by Attia et al, predialysis lab parameters were taken to include patients into the study. They were

Serum creatinine - >4 mg/dl

Blood urea >100 mg/dl

Serum potassium > 6.5 meq/l

Serum bicarbonate <15 meq/l.

In the study by Makhlough et al all the patients who were undergoing hemodialysis were taken into study.[21] All the patients having skin pathologies were excluded.

In the present study, out of 64 patients 50 were men and 14 were women. Thus men constituted 78.12% of cases. This value is much higher than those seen in other studies. In an Israel study conducted by Dyachenko et al, men constituted 60% of the cases.[92] In a similar study by Attia et al, men constituted 53% of cases.[7] The kidney disorders are not known to affect the different sexes differentially. The male preponderance in our study was probably due to the fact that increased number of men seek treatment for their disorders due to socioeconomic factors prevailing in the country.

Table 25: Comparison of the number of males and females taking part in various studies

Study	Men	Women
Present study	50 (78.12%)	14 (21.87%)
Tawade et al	30 (85.71%)	5 (14.28%)
Udayakumar et al	70 (70%)	30 (30%)
Attia et al	110 (53.39%)	96 (46.60%)
Makhlough et al	80 (52.3%)	73 (47.7%)

Cause of renal failure

In the present study hypertension was the most common cause of renal failure, followed by diabetes and chronic tubulointerstitial disease. This differed from the study by Attia et al, where diabetes was the most common cause followed by hypertension.

Table 26: Comparison of etiology of chronic kidney disease in various studies

Cause of renal failure	**Present study (in %)**	**Attia et al (in %)**[7]
Diabetes Mellitus	32.8	11.6
Hypertension	70.3	9.8
Renal stones	1.5	9
Chronic pyelonephritis	1.5	3
SLE	1.5	2.4
Chronic tubulointerstitial disease	18.75	-
Others	20.31	60

Duration of dialysis

Patients of chronic kidney disease stage 5 were taken into the study irrespective of the duration of dialysis. The range varied from less than 3 months to more than 5 years. The duration of dialysis was categorically divided and correlated

with PTH levels. In all these categories the least abnormal values were found between 6 to 36 months. There was a statistically significant correlation with normal parathyroid hormone levels during this period. This means that on an average it takes 6 months of hemodialysis for the parathyroid hormone levels to become normal. It remains normal till 36 months and after that it starts to rise abnormally even after continuing hemodialysis.

Pruritus

In the present study 28.1% patients complained of itching prior to dialysis where as 40.6% patients complained of itching post dialysis. Thus there was an increase in the incidence of itching post dialysis. No objective criteria was used to measure the intensity of pruritus. Patients were asked only two questions regarding pruritus. They were

1) Was there pruritus prior to dialysis?

2) Has the itching increased after dialysis?

In the study by Maklough et al, the prevalence of pruritus was 61.4%. In the study by Dyachenko et al, prevalence of pruritus was 74.3% at the time of dialysis

Table 27: Comparison of prevalence of pruritus in various studies

Study done	**Prevalence of pruritus**
Present study	40.6%
Makhlough et al[21]	61.4%
Dyachenko et al[92]	74.3%

Thus the prevalence of purritus was lower in comparison to other studies.

In the study by Makhlough et al, an elaborate scoring system proprosed by Duo et al was used to quantify pruritus and then the intensity of itch was compared with various parameters.[22] The total scoring of pruritus is calculated as follows:

(Severity of pruritus x distribution of pruritus) + sleep disorder. (See **Table 2,3,4**)

The drawback of this scoring system is that pruritus is a subjective symptom and the perception of itch may vary from person to person even if the same level of pruritus exists in two individuals. Thus the resultant score is prone for errors. The advantage of this method is that pruritus is quantified and so correlational studies can be easily carried out.

Dyachenko et al studied hemodialysis related pruritus and associated cutaneous manifestations.[92] In their study the patients were considered to have pruritus if they had either of the two conditions

1) At least 3 episodes of itching during a period of 2 weeks or less, with the symptom appearing several times during the day, lasting for at least a few minutes, and troubling the patient
2) The appearance of itch in a regular pattern during a period of 6 months.

To be defined 'uremic' the pruritus had to appear shortly before the onset of dialysis, or at any time thereafter, without evidence of any other active disease, which could explain it

In the present study pruritus was considered only as either present or absent. This was probably an oversimplification and the scoring system by Duo et al, could have given more statistically relevant results.

The etiology of pruritus is still unknown. The hypothesis of the present study was to see if there was a correlation between pruritus and parathyroid hormone levels. In the present study there was no correlation between pruritus and parathyroid hormone. In the study by Makhlough et al there was a statistically positive correlation between pruritus and parathyroid hormone.

Table 28: Comparison between parathyroid hormone and pruritus in different studies

Subgroup		**Hyperparathyro-idism present**	**Hyperparathyroidism absent**	**P value**
Present study				
	Pruritus present	17 (43.58%)	9(36%)	P = 0.546
	Pruritus absent	22 (56.42%)	16(44%)	
Makhlough et al (males)	Pruritus present	37 (64.3%)	19 (61.3%)	P = 0.001
	Pruritus absent	15 (35.7%)	12 (38.7%)	
Makhlough et al (females)	Pruritus present	27 (64.3%)	19 (61.3%)	P = 0.18
	Pruritus absent	15 (35.7%)	12 (38.7%)	

Makhlough et al had divided the patients into males and females. As can be seen from **Table 28** that the statistically significant correlation between pruritus and parathyroid hormone levels was obtained only for males and not for females. Neither pruritus nor parathyroid hormones are known to affect the sexes differentially. In the present study the patients were not divided on the basis of sex. Thus there is still no clear consensus whether hyperparathyroidism is the cause for uremic pruritus. According to the present study pruritus seen in hemodialysis patients has no relation to parathyroid hormone.

Also in the present study the prevalence of itching prior to dialysis was 28.1% whereas after starting dialysis the prevalence of itching was 40.6%. So there was 12.5% increase in the prevalence of pruritus. This increase in pruritus can be attributed to the dialysis procedure. It might either be that the pruritogens are not filtered through the dialysis membrane or the constituents of the diasylate fluid may be causing increase in pruritus.

In the present study the sample was collected before starting the dialysis procedure as during the dialysis procedure many patients are administered heparin which can alter the laboratory results. This was similar to the study by Makhlough et al in which blood was withdrawn prior to starting the dialysis procedure.

Analysis was done in various studies between pruritus and duration of dialysis. In the study by Makhlough et al there was no relation between pruritus and duration of dialysis. Similar results were found in a study by Dyachenko et al and in our study.

Pallor

In the present study prevalence of pallor was 65.62%. This was slightly less than that seen in the study by Dyachenko et al (75.7%). In an Egyptian study by Attia et al, the patients were divided into adults and children. Among adults the prevalence of pallor was 48.5%. In children the prevalence of pallor was only 18%. They hypothesized that in Egypt there is free supply of erythropoietin in their health programs which accounted for the low prevalence of pallor. Udayakumar et al studied 100 patients undergoing hemodialysis in India. The prevalence of pallor in their study was 60%. They hypothesized that the prevalence of pallor was low in their study due to darker complexion of the patients. Thus, the figures in the present study correlate with the Indian study by Udayakumar et al. Pallor did not have a statistically significant correlation with parathyroid hormone.

Table 29: Comparison of pallor between various studies

Study	**Prevalence of pallor**
Present study	65.62%
Attia et al	48.5%
Udayakumar et al	60%
Dyachenko et al	75.7%

Skin colour changes post dialysis

In the present study 21.87% patients complained of darkening of skin post dialysis. This differed from other studies. In the study by Udayakumar et al 40% of patients experienced darkening post dialysis. In the study by Dyachenko et al the 75.7% patients complained of hyperpigmentation after starting hemodialysis. In the study by Attia et al hyperpigmentation was seen in 17.8% of their cases but only in 3% of controls.[7] In contrast to all the other studies which showed pigmentation more in a photodistributed area, the present study showed patients complaining of generalized diffuse pigmentation. The earlier studies had suggested that the increased pigmentation was due to the inability of kidneys to excrete beta-melanocyte stimulating hormone but that does not explain the presence of pigmentation of sun exposed area. The present study does not have that discrepancy as the pigmentation was seen in a diffuse pattern. There was no statistically positive correlation between hyperpigmentation and parathyroid hormone.

Table no 30: Comparison between skin darkening post dialysis in various studies

Study	**Prevalence of skin darkening**
Present study	21.87 %
Udayakumar et al	40 %
Attia et al (cases)	17.8%
Attia et al (controls)	3 %
Dyachenko et al	78.7%

Half and half nail

Half and half nail is a specific feature of patients with chronic kidney disease stage 5. Even among these patients it is seen more commonly in patients undergoing hemodialysis.[91] In the present study it was seen in 15.62% of cases. It was similar to the prevalence seen in study by Dyachenko et al (18.6%). In an Indian study by Tawade et al the prevalence was 17%. Thus the prevalence of half and half nail was more or less similar in various studies. In the present study, no correlation was found between this nail change and parathyroid hormone. No similar studies were found which compared the two variables.

Table 31: Comparison of half and half nail in various studies

Study	Prevalence of half and half nail
Present study	15.62%
Dyachenko et al	18.6%
Tawade et al	17%
Udayakumar et al	21%

Terry's nail

In the present study Terry's nail was found in 23.44% of patients. This is unusual because none of the literature pertaining to nail changes in hemodialysis patients mentions this finding. Terry's nails are usually seen in cirrhosis of liver, heart failure and in diabetes mellitus. In the present study the patients with Terry's nails

were not suffering from these disorders. Thus Terry's nails can also be considered as one of the cutaneous manifestations of patients undergoing hemodialysis. In the present study there was no statistically relevant correlation between Terry's nail and parathyroid hormone levels.

Muehrcke's lines

In the present study the prevalence of Muehrcke's lines was 7.8%. This was similar to study by Udayakumar et al who reported prevalence of 5% in their study.[3] In the present study there was no correlation between Muehrcke's lines and parathyroid hormone.

Hair changes

In the present study 39.1% patients reported that they had lost hair post dialysis. In the study by Udayakumar et al, 30% of patients had sparse body hair whereas 11% had diffuse alopecia at the time of inspection. They did not mention whether these changes were present before the hemodialysis or they appeared after starting it. In the Egyptian study by Attia et al, among adults the prevalence of hair loss was 33.7% cases whereas in children the prevalence of hair loss post dialysis was 34.9%.[7] Thus our study has similar findings. The hair loss in dialysis patients may be due to stress of the disease per se or the dialysis procedure due to which the hair enter into telogen effluvium. Another cause can be anemia in these patients, which may cause hair loss.

Table 32: Comparison of hair loss after dialysis in various studies

Study	Prevalence of hair loss
Present study	39.1%
Udayakumar et al	41%
Attia et al (adults)	33.7%
Attia et al (children)	34.9%

Xerosis

In the present study prevalence of xerosis was 95.31%. Xerosis has been known to be the most common manifestation of patients undergoing hemodialysis. Our study also found similar result. It was the most common manifestation seen in our study. However it did not have a statistically positive correlation with parathyroid hormone.

Acquired perforating dermatosis

In our study acquired perforating dermatosis was seen in 3(4.7%) cases. Out of these 3 cases 2 were diabetic. Out of the 3, one patient consented for skin biopsy. The skin biopsy did not reveal any evidence of altered elastin material, nor was there any evidence of folliculitis. Thus it was neither elastosis perforans serpinginosa nor perforating folliculitis. In the study by Dyachenko et al, no case of perforating disorder was found. Tawade et al reported a prevalence of 17% in their study of 35 patients on hemodialysis. Udayakumar et al reported a prevalence of 21% in their study of 100 patients on haemodialysis. Attia et al reported a prevalence of 2.5%

among their patients. Thus there is a wide variability in the prevalence of acquired perforating disease in various studies.

Table 33: Comparison of prevalence of acquired perforating dermatosis among various studies

Study	Prevalence of APD
Present study	4.7%
Dyachenko et al	0%
Tawade et al	17%
Udayakumar et al	21%
Attia et al	2.5%

Bullous disease of hemodialysis

This was not seen in the present study. This was because it is a rare disorder and the sample size of the present study was small. Attia et al reported a single case (0.6%) of bullous dermatosis in their study of 206 patients. Udayakumar et al did not report any case of bullous dermopathy in their study. Dyachenko et al also did not report any case of bullous dermopathy in their study.

Nephrogenic systemic fibrosis

No case of nephrogenic systemic fibrosis was found in the present study. This was probably because of it being a rare disorder and the sample size being small.

Calciphylaxis

In the present study no case was found to have calciphylaxis. This was so because it is also a rare disorder and the sample size being small. It was not reported by Attia et al, Dyachenko et al and Udayakumar et al.

Thus parathyroid hormone was not statistically significant to any of the cutaneous changes seen in patients undergoing hemodialysis.

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CONCLUSION

This study showed that almost as many as 95% of patients with chronic kidney disease stage 5 undergoing hemodialysis have at least one cutaneous manifestation. The prevalence of cutaneous manifestations seen in this study was similar to those found in other studies. Xerosis was the most common manifestation seen in 95% of patients. Pruritus was seen in 41% cases. The severity of pruritus was found to increase after dialysis. This could have been due to the bicarbonate diasylate which was used in this study. 22% of patients were found to have increased pigmentation post dialysis. 39% of patients lost their hair post dialysis, thus it was a common occurrence among our patients. Among nail disorders Terry's nail had an unusual higher prevalence in comparison to other studies. Thus we propose that it also be considered as one of the manifestations seen in patients of chronic kidney disease stage 5 undergoing hemodialysis. Parathyroid hormone was tested in all the patients but it did not reveal statistically significant correlation with any of the cutaneous manifestation seen in patients undergoing hemodialysis. We conclude that parathyroid hormone is not the cause for pruritus in patients of chronic kidney disease stage 5 or any other cutaneous manifestation seen in these patients.

Further, among the various cutaneous manifestations which are specific for patients of chronic kidney disease stage 5 only acquired perforating dermatosis was seen. There were no cases of bullous disease of hemodialysis, nephrogenic systemic fibrosis, calciphylaxis. Possible reasons for this may be that the sample size of the present study was small. Another explanation may be that these conditions are not relevant to the Indian population as most of the cases described are from western literature. The kind of dialysis done may also play a role. All our patients used the bicarbonate media for dialysis. Perhaps it has a protective role in prevention of the above mentioned disorders.

SUMMARY

This was a cross sectional study done on 64 patients from 1st January, 2012 to 31st December 2012. The source of data were patients undergoing hemodialysis in the department of Nephrology in KLES Dr. Prabhakar Kore Hospital and MRC, Belgaum. The inclusion criterion was patients diagnosed with chronic kidney disease stage 5 who were undergoing hemodialysis. Exclusion criteria included all the patients who were having other skin conditions not related to those seen in hemodialysis patients and those patients who did not give their consent for taking part in the study.

The objective was to study various cutaneous manifestations seen in patients of chronic kidney disease stage 5 undergoing hemodialysis and their correlation to parathyroid hormone.

The sample size was 64 patients. All the patients were examined thoroughly for all the skin manifestations. In addition systemic examination was also done. It was noted down in a pretested pro-forma. All the existing laboratory investigations present in the patients' case records were noted down. Before starting the hemodialysis procedure, 2-3 ml of blood was taken from each patient and tested for serum parathyroid hormone levels.

All the results were tabulated. Percentages were used as categorical outcomes. The prevalence of abnormal parathyroid hormone level values between the groups was compared by chi square test.

Almost all the patients had atleast one cutaneous manifestation. Xerosis was the most common manifestation (95%). 41% of patients developed pruritus after dialysis whereas 28% of patients had pruritus before starting dialysis. 22% patients developed diffuse darkening post dialysis. 39% patients complained of hair loss post dialysis. There was unusually high incidence of Terry's nails. None of the skin manifestation had a positive correlation with parathyroid hormone levels.

Out of all the specific disorders associated with patients of chronic kidney disease stage 5 undergoing hemodialysis, only acquired perforating dermatosis was seen. It was seen in 3 cases (4.7%). Other specific manifestations like nephrogenic systemic fibrosis, calciphylaxis, bullous disese of hemodialysis were not seen in our study. This was probably due to the small sample size or due to the fact that they are rare disorders. Another possible explanation is that the prevalence of these disorders may be higher in the western population. The type of dialysis done may also have a role. All the patients of the study were treated with bicarbonate diasylate fluid which may have a protective role against development of these disorders.

Skin conditions are very common in patients with chronic kidney disease. It is estimated that 80% of patients with chronic kidney disease have at least one skin manifestation. The term chronic renal failure is no longer used. It is referred to as chronic kidney disease. It has 5 stages. Stage 5 is the end stage renal disease defined by GFR < 15 mL/min per 1.73 m^2.[1]Stage 5 is the end stage requiring intervention of some kind for survival. It may be dialysis or renal transplantation. Dialysis is of 2 types, hemodialysis and peritoneal dialysis. In hemodialysis movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate.[2] Peritoneal dialysis is another type of dialysis in which dextrose containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time. The peritoneal membrane is used as the filtering membrane across which the substances are filtered. In our hospital hemodialysis is done on a routine basis. Peritoneal dialysis is not done and renal transplantation is done infrequently.

Since most of the patients of chronic kidney disease stage V are invariably on some form of renal replacement therapy there is an overlap between the skin manifestations due to chronic kidney disease and skin manifestations seen in hemodialysis patients. No study has been done on the skin manifestations in hemodialysis patients in our hospital so that was the basis of starting this study. On a look through literature there were numerous studies describing skin manifestations in dialysis patients[3] so a need was felt to explore things further. There are some studies which have correlated some skin manifestations to Parathyroid hormone. Massry et al postulated that itch associated with chronic kidney disease was due to secondary hyperparathyroidism and that it could even respond to parathyroidectomy.[4] There also seems to be correlation between dry skin and hyperparathyroidism[5]. Also there is an obvious correlation with the calcemic manifestations seen in chronic kidney disease patients and Parathyroid hormone levels.[6] However this is not true in all cases and in other studies no such correlation has been found between Parathyroid hormone levels and these conditions. In addition Pubmed search at the time of starting this study did not show any result for cutaneous changes in hemodialysis and their correlation to Parathyroid hormone. With this backdrop this study was initiated and to our knowledge no such study has been done in India so far.

Parathyroid hormone is produced from parathyroid glands. It is an 84-amino-acid single chain peptide. It causes calcium resorption from bones, and calcium resorption from the kidneys. This hormone maintains extracellular fluid calcium concentrations within a narrow normal range. Increased level of parathyroid hormone is known as hyperparathyroidism. This can be primary or secondary. Primary hyperparathyroidism is due to excess secretion from either an adenoma or hyperplasia of the parathyroid glands. Secondary hyperparathyroidism occurs due to an adaptive response to an underlying pathology causing increase in the parathyroid hormone levels. Patients with secondary hyperparathyroidism may develop bone pain, ectopic calcification and pruritus. The bone disease in patients with secondary hyperparathyroidism and renal failure is termed renal osteodystrophy. In patients on long-term dialysis especially who have excess aluminium in their dialysis regimen, aluminum intoxication may occur. Aluminum starts to deposit in the bones and causes severe osteomalacia, acute dementia and unresponsiveness. Prevention is by avoiding aluminum excess in the dialysis regimen.

Various studies done on cutaneous changes in hemodialysis patients have shown that at least 80% of patients have at least one cutaneous manifestation[7].

The cutaneous manifestations of patients undergoing dialysis can be arbitrarily divided into 2 types, non-specific and specific skin lesions.

Table 1: Cutaneous manifestations of patients undergoing hemodialysis

Non- specific changes	**Specific changes**
Pruritus	Uremic fetor
Xerosis	Tongue sign of uremia
Pallor	Uremic frost
Pigmentary changes	Dialysis related amyloidosis
Hair abnormalities	Uremic neuropathy
Nail changes e.g. Koilonychias, subungualhyperkeratosis, Mees' lines	Nail changes e.g. Half and half nail
Purpura	Acquired perforating dermatosis
Lesions at site of cannula insertion	Nephrogenic systemic fibrosis
Oral mucosal changes – xerostomia	Bullous disease of hemodialysis
	Calciphylaxis

Non-specific findings

1) **Pruritus** - The prevalence of pruritus in hemodialysis patients in various studies varies from 50-90 %.[8]The largest study done so far analyzed data from 18,801 patients undergoing hemodialysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS) from 1996-2004) and indicated that 42% of hemodialysis patients experienced moderate to severe pruritus.[9]It is the most characteristic and annoying symptom of chronic kidney disease.[10] It is also referred to as 'uremic pruritus' which literally means pruritus secondary to uremia which is untrue. The pruritus does not have relation with gender, age or duration of dialysis. The pruritus seems to be less in patients on ambulatory peritoneal dialysis than on hemodialysis patients. Pruritus also depends on the type of dialysis machine e.g. depending on the permeability of the dialysis membranes the ones with high permeability have been thought to have decreased pruritus. [11] In those patients on regular dialysis the pruritus seems to be maximum on 2 days after the last dialysis session, least on the day following dialysis. Also itching is relatively high during the dialysis procedure.[6]

Clinical characteristics of itch

The intensity of itch associated with chronic kidney disease ranges from sporadic discomfort to complete restlessness during the day and night. It could be intermittent or persistent.[12] It can be generalized in 25-50% of patients, and it predominantly affects the back (70%), abdomen (46%), head (46%), and arms (43%).

Uremic pruritus is absent in acute renal failure.[13] Exact cause for itching in chronic renal failure is not known. It is multifactorial in origin. The common causes are uremicxerosis, secondary hyperparathyroidism, hypervitaminosis A, uremic neuropathy, elevated serum histamine levels and iron deficiency anemia. Of these uremic xerosis is perhaps the most important cause as it is the most common cutaneous manifestation in chronic kidney disease patients. It is present in 90-100 % patients having pruritus.[14] The level of uremic pruritus is directly proportional to the

xerosis. Xerosis is due to dehydration of skin resulting from atrophy of eccrine glands and loss of lipids on skin due to atrophy of sebaceous glands however Yosipovitch et al did not find any evidence between the severity of pruritus and objective parameters of xerosis.

Endogenous opioids are important players in the pathogenesis of itch. An increased ratio of serum beta-endorphin to dynorphin A was reported in hemodialysis patients compared with healthy controls and the ratio increased with increased intensity of itch.[15]

Some studies have reported significant association between serum parathyroid hormone and itching whereas others have not found any association. Kidney failure, hyperphosphatemia, hypocalcemia and decreased levels of calcitriol (vitamin D) are factors which increase parathyroid hormone levels.[16] Thus the raised parathyroid hormone level in kidney failure is actually a type of secondary hyperparathyroidism.[17] It has been reported that pruritus in some patients can completely disappear after parathyroidectomy.[18] Hyperparathyroidism can stimulate mast cells to release histamine. This can promote micro precipitation of calcium and magnesium salts in the skin. On the other hand all patients with severe hyperparathyroidism do not have pruritus. Also there is no difference in the number of mast cells in patients with hyperparathyroidism in patients having and not having pruritus.[19] In experimental intradermal injections of parathyroid hormone failed to produce pruritus. Also in the same study immunohistochemistry was negative for parathyroid hormone in skin biopsies in patients undergoing hemodialysis.[20] In a recent Iranian study there was a significant correlation was found between itching score and serum intact parathyroid hormone in hemodialysis patients.[21]

Impact on the quality of life

It was found in Dialysis Outcomes and Practice Patterns Study that patients undergoing hemodialysis with pruritus were more likely to feel drained and have poor sleep quality, depression and lower mental and physical composite scores of quality of life than patients with no or mild pruritus. Moreover pruritus in hemodialysis patients is associated with 17% higher mortality rate than the patients on hemodialysis who are not having pruritus. (insert end note AA)

The difficulty which an investigator faces with pruritus is the subjectivity of the symptom. It is a purely subjective symptom and each patient may have a different threshold for what he or she finds bothersome. There are a few ways of objectively measuring pruritus. One way is to ask the patient to rate his or her pruritus on a scale of one to ten, one being 'no itching' and ten being the 'most severe' itching which the patient just can't tolerate. Another scale is the modified scoring system proposed by Duo.[22] The total scoring of pruritus is calculated as follows:

(Severity of pruritus x distribution of pruritus) + sleep disorder.

Table 2: The severity of pruritus is assessed as:

1 point	Slight itching
2 points	Itching with scratching
4 points	Itching and scratching with excoriations
5 points	Itching causing total restlessness

Table 3: The distribution of pruritus is scored as

1 point	Pruritus maximum in 2 areas of the body
2 points	Pruritus maximum in more than 2 areas of the body
3 points	Generalized pruritus

Table 4: The sleep disorder is monitored as

2 points (maximum of 10 points)	Every waking up due to itching
1 point (maximum of 5 points)	Each scratching

There may be some sort of pruritogen which is not adequately filtered through the dialysis membrane thus accumulating in the body under the skin and cause itching. The type of dialysate may also have a role in pruritus. Lower levels of Magnesium in the dialysate have been correlated with lower levels of pruritus.[23]

Treatment of pruritus

There are various treatment modalities which have variable efficacy for treatment of pruritus.

Wang et al have proposed a therapeutic ladder for management of pruritus in end stage renal disease.[24]

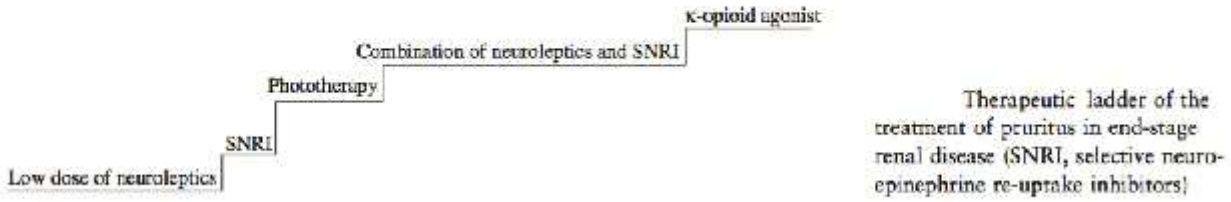

Figure 1 – Therapeutic ladder of the treatment of pruritus in end stage renal disease (SNRI, selective neuroepinephrine re-uptake inhibitors)

The first line of management is with neuroleptics. Gabapentin and pregabalin are structural analogs of the neurotransmitter GABA. The exact mechanism of their mechanism is not clear. They probably inhibit the central itch pathways just like in neuropathic pain.[25] In a placebo controlled double blinded study by Gunal et al in 25

patients with end stage renal disease associated pruritus found that 300 mg of oral gabapentin given after each hemodialysis session was safe and effective regimen.[26] Gabapentin is a neurotoxic drug. In another study it was suggested that starting 100 mg initially with a slow upward titration can reduce this side effect.[27]

The second line of management is SNRI (Selective neuroepinephrine re-uptake inhibitors). They relieve the itching probably by reducing central sensitization to itch. Mirtazapine has been found to be effective in treatment of nocturnal pruritus.[28]It has also been found to be effective in renal pruritus.[29]

The third line of management is phototherapy.UVB therapy is effective in severe intractable pruritus.[30] It is considered the treatment of choice in many centers. UVA therapy without psoralens is also said almost just as effective.[31] The exact mechanism of action is not known. Probably it works via chemical modification of pruritogens in the skin or an alteration of skin sensitivity to pruritogens. It may also work by reducing post inflammatory cytokines. It is important to inform the patient that the in the first 2 weeks the itch may worsen and the reduction in pruritus may take 1-2 months.

If itching is not controlled by the above measures the fourth line management is using a combination of neuroleptics like Gabapentin and selective neuroepinephrine re-uptake inhibitors like Mirtazapine.

If itching is still not controlled then the fifth line of management is κ–Opioid agonists. A recent kappa receptor agonist, nalfurafine(TRK-820) has shown antipruritic effect in the treatment of ESRD associated pruritus. However it is not available commercially.[32]

Other alternatives are activated charcoal, cholestyramine, erythropoietin, ondansetron and naltrexone.[33] Sedating antihistaminic like hydroxyzine have some role in control of pruritus. Other antihistaminics do not help much because histamine does not play a significant role in uraemic pruritus.[34]Various topical therapies can also be used. Emollients help to a certain extent as xerosis is one of the most common causes of pruritus. In a double blinded placebo controlled study 0.025% capsaicin was found to significantly reduce pruritus in comparison to placebo.(insert reference AB)Pramoxine 1% lotion was found to be efficient in treatment of uremic pruritus in a recent study.[35]

Renal transplantation is curative for uremic pruritus.

2) **Xerosis** - Uremic patients tend to have a very dry skin. It is the most common cutaneous manifestation seen in patients undergoing hemodialysis.[36] It is seen in up to 90% of patients. This is thought to be due to reduction in the eccrine sweat glands which reduces water content of the skin and also reduction in size of pilosebaceous units due to which there are decreased lipids on skin surface.[37] High dose diuretics may lead to iatrogenic dehydration leading to dryness of skin.[38]Xerosis is also a manifestation of Diabetes Mellitus and since Diabetes mellitus is the most common cause of chronic kidney disease in most centers, xerosis may be attributed to it. Also uraemia has been known to cause peripheral neuropathy which could also affect peripheral autonomic nerves thus leading to decreased sweating secondary to autonomic nervous dysfunction. This could in turn cause xerosis.

Treatment **–** Emollients can help only to a certain extent.

3) **Pallor** - Kidneys are the sites for erythropoietin production, which is essential for normal erythropoiesis. Thus in chronic kidney disease there is reduced erythropoietin

production which causes decreased RBC production leading to anemia. Udayakumar et al. reported pallor in 60% of uremic patients.[39] Pallor may be difficult to appreciate in some patients as they start developing diffuse pigmentation all over body.

Treatment **–** Erythropoietin injections can help in RBC synthesis to a certain extent.

4) **Pigmentary changes** - Two different types of pigmentation patterns may be seen. First one is diffuse hyperpigmentation present all over the body but more so in sun exposed areas. The prevalence for this has been estimated as around 20-25%.[40] The diffuse hyperpigmentation has been attributed to increased melanin in the basal layer of epidermis and upper region of dermis due to failure kidneys to excrete beta-melanocyte stimulating hormone (β-MSH).[41] Hyperpigmented macules over palms and soles have also been reported.

The second type of pigmentation pattern seen is yellowish discoloration of skin. This has been reported in as many as 40% of patients. This has been attributed to accumulation of carotenoids and nitrogenous pigments like urochromes in the dermis.[42]

There might be a third kind of skin colour change which may be described that is the pale skin due to severe pallor. This is described more so in western literature and difficult to ascertain in Indian skin.

5) **Hair abnormalities** - Sparse body hair and diffuse alopecia have been described.[43] The exact cause is not known. One of the causes can be severe anaemia which is very common in these patients. The second hypothesis is that these patients are under lot of stress which can precipitate telogen effluvium. The hair in these patients is dull and lusterless. This is so because of decreased sebum secretion.[44]

6) **Nail changes–** Nail changes may be specific or non-specific.

Specific nail changes

Half and Half Nails- The classical nail change described is Lindsay's nails (half and half nails). These nails are red or pink in the distal half and white in the proximal half.A distinct line appears to separate the two zones. The red colour in the distal half does not fade with pressure.[45] Studies have shown prevalence from 16-50%.[46]The pathogenesis is not known. Stimulation of nail bed melanocytes by increased levels of plasma melanotrophic hormones and vascular changes have been suggested as possible causes.[47] They have also been reported after cancer chemotherapy; in a breast cancer patient after androgen use; after exposure to paraquat.[48] Erythematous crescent is a reddish discoloration of the distal nail involving less than 40% of distal nail bed. It is also seen in chronic renal failure.[49] They may also be present in normal healthy adults. Once present these changes may remain permanently even after hemodialysis.

Non-specific nail changes

A) **Koilonychia** – There is loss of convex curvature of the nails. The nails either become flat or truly concave or'spoon like nails'. It affects fingernails more than toenails. It can be acquired or heredity. The acquired form is much more common and associated with iron deficiency anemia. They may even be

present in normal individuals and may be a racial characteristic in Ladhakhi and Tibetan populations.[50] It has also been described in post renal transplant patients and after hemodialysis.

B) **Subungual hyperkeratosis** - It refers to hyper proliferation of keratinous debris under the nails)

C) **Onycholysis–**It is breakage in the distal end of nail plate.

D) **Mees' lines –** These are white transverse bands seen on nail plate. Generally there is a single band but multiple bands may occur. They result from focal parakeratosis of the nail matrix. They have a contour similar to the distal edge of lunula. They are seen in a variety of systemic disorders. Some of them are

a. Arsenic, thallium or heavy metal poisoning
b. Carbon monoxide poisoning
c. Drug induced **–** due to chemotherapeutic agents like cyclophosphamide, vincristine
d. Psoriasis
e. Renal allograft rejection
f. Chronic renal failure

E) **Muehrcke's lines –**These are also narrow white transverse bands parallel to the lunula. Like Mees' lines they are span the entire width of the nail. They occur in pairs and they represent abnormality in the nail bed. They frequently occur on the second, third and fourth finger nails. Unlike in Mees's lines squeezing the distal digit will make the lines temporarily disappear. Hypoalbuminemia is an important cause of these lines. They have been reported in various conditions. Some of them are

a) Chemotherapy
b) Hypoalbuminemia (nephrotic syndrome, glomerulonephritis, liver disease, malnutrition)
c) Malnutrition
d) Heart transplant recipients[51]

F) **Terry's nails –** There is leukonychia affecting the entire nail plate except the distal 20% or 2 mm distal margin. The distal margin corresponds to the onychodermal band, which is characteristic.[52]Terry's nails are a result of changes in nail bed vascularity, a decrease in the proximal portion and an increase at the distal edge. All nails are affected uniformly. They are generally seen in cirrhosis of liver, heart diseases or diabetes mellitus.

G) **Splinter hemorrhages –** They have also been described which are seen more commonly than in normal population.[53] They present as longitudinal red colored

streaks beneath the nail plate due to extravasation of red blood cells from the damaged capillaries.

7) **Purpura** - Purpurae are reddish non-blanchable lesions due to extravasation red blood cells into the skin or mucosa. Dialysis patients are often on heparin which may increase the incidences of bleeding. Also in hemodialysis patients arteriovenous shunt is formed which may lead to extravasation of blood due to trauma during the dialysis process.[54]

8) **Lesions at site of cannula insertion** - The cannula is inserted into the arteriovenous fistula during dialysis procedure. There might be extravasation of blood, phlebitis due to repeated manipulation of cannula during multiple sittings per week. Eczema may develop at the site of shunt formation either due to cleaning of the area with betadine or secondary to extravasation of blood. There may also be infections which may be local or rarely cause dangerous septicemia.[55]

9) **Oral mucosal changes** - Oral changes are very common in patients undergoing hemodialysis. [56]They may be specific or non-specific.
Specific signs - Teeth marking is seen along with macroglossia which is known as the '**tongue sign of uremia**'. This finding was first described by Mathew in Chronic kidney disease patients.[57]When urea levels are more than 200 mg/100 ml, a condition known as '**uraemic fetor**' is described. This is an ammoniacal odor produced secondary to high urea concentration in the saliva which breaks down to release ammonia which has a pungent odor. These patients have fewer fungiform taste buds which may cause impairment of taste.[58]

Non-specific signs - Xerostomia (dry mouth) has been reported which may be due to dehydration. Ulcerative stomatitis has been described classically in patients with high urea levels (>150 mg/100 ml) but fortunately this condition is now rarely seen.

10) **Acantholytic dermatosis–**A case of persistant acantholytic disease (Grover's disease) has been described since 6 months in a patient who was on hemodialysis since 9 years.[59]Grover first described this disorder.[60] It is also known as Grover's disease. It is characterized by pruritic, edematous papules or papulovesicles with excoriations. The lesions occur mainly on the upper trunk and histologically show epidermal acantholysis that resemble Darier's disease. The lesions may be transient in which case the condition is called transient acantholyticdermatosis. There is a variant of this disease in which the lesions are persistent. It this case it is called persistant acantholytic dermatosis.The cause is unknown but actinic damage has been implicated as an initiating factor.

Treatment **–** There are reports of good response to systemic retinoids. For persistent small lesions surgical excision can deliver excellent results.[61]

Specific findings

1) **Uremic frost**- This is seen in in those people whose urea levels are very high (>200 mg/100 ml). The frost consists of white/yellow coating of urea crystals on the beard or on the trunk. It occurs due to urea secretion through the sweat glands which deposits as beads on surface as it cannot evaporate.[62] It is more commonly seen in acute renal failure.

In erythema papulatumuremicum, large papules and nodules on an erythematous base are seen over palms, soles and face. In a few weeks they desquamate and form fissures. This change is also not seen in the present era.

2) **Dialysis related amyloidosis** - It is a type of secondary systemic amyloidosis in which there is deposition of beta 2-microglobulin. It is frequently associated with musculoskeletal and joint complaints. Deposits in the wrist area leads to carpal tunnel syndrome, deposits in bones lead to bone cysts.[63] Heart is the most common extra-articular organ involved followed by the gastrointestinal tract. This visceral form β_2M amyloidosis is a major complication of chronic renal failure and occurs mainly in patients who have been on dialysis for more than 10 years. Lingual deposits of amyloid on the tongue have described presenting as multiple white-yellow and red coloured non-tender, firm nodules of different size.[64]It is closely related to use of low flux, bioincompatible cellulose membranes, which can cause tissue deposition of beta 2 microglobulin as amyloid fibrils.[65] Other visceral deposits of β2M amyloid include large amyloid protein masses in subcutaneous tissues, especially in the gluteal region, which is also a rare manifestation of dialysis related amyloidosis.[66] The treatment of dialysis related amyloidosis is limited to the management of symptoms and surgical removal of amyloid deposits. New high-flux, biocompatible dialysis membranes are available which are more permeable to beta 2-microglobulin which might delay the onset of dialysis related amyloidosis.[67]

3) **Uremic neuropathy** affects about 60% of patients with chronic kidney disease or patients on long term hemodialysis. This appears to be a predominantly sensorimotor neuropathy.[68] This is a manifestation of uaemia.

4) **Acquired perforating dermatosis–**There is lot of ambiguity regarding this terminology. Perforating disorders are a group of disorders, which are characterized by transepidermal elimination of amorphous material. Currently there are 4 disorders, which are recognized as primary perforating disorders. They are elastosis perforans serpiginosa, Kyrle's disease, perforating folliculitis and reactive perforating collagenosis. These perforating dermatoses can occur in diabetes mellitus and in patients with chronic renal failure, many of who are undergoing hemodialysis.[69] The distinction between these four dermatoses is not clear-cut especially in the case of hemodialysis patients; the conditions may overlap. Thus the name 'acquired perforating disorder' has been proposed for the perforating dermatoses occurring in the setting of chronic kidney disease/ hemodialysis. Gracia Bravo et al have used the term 'uremic follicular hyperkeratosis' for it.[70] When these conditions occur outside the setting of diabetes mellitus or chronic kidney disease they occur as separate entities. This dermatosis occurs in up to 10% of patients undergoing hemodialysis.[71] Clinically the patients present with hyperkeratotic papules with a central crust filled

crater on the trunk and on extensor surfaces often in a linear distribution.[72] The extensor surface of limbs are more commonly involved.

The histologic features may resemble any of the four primary perforating dermtosis.

Chang et al, where they studied 9 Guatemalan patients with acquired perforating disease associated with chronic kidney disease.[73] Out of these 6 were on hemodialysis. Out of these 6 in 5 patients the lesions started after starting hemodialysis. In lesions resembling Kyrle's disease there is a keratotic plug showing parakeratosis and basophilic cellular debris filling an epidermal invagination. There is acanthosis in the surrounding area.[74]In perforating folliculitis, a widely dilated follicle is seen which is filled with a keratotic plug containing parakeratosis, suppurative inflammation and basophilic necrotic debris. In reactive perforating collagenosis there is broad cup-shaped epidermal invagination containing parakeratotic debris, inflammatory cells, vertically oriented degenerated basophilic collagen.[75]

The exact etiology for the disorder is not known. Possible explanations are diabetic microangiopathy, dysregulation of vitamin A or D metabolism, inflammation and connective tissue degradation caused by dermal deposition of substances like uric acid or calcium salts which are accumulated in excess during renal failure.[76] It is also thought that that this is a reaction pattern to constant itching and scratching in chronic kidney disease.

Treatment options consist of topical and intralesional corticosteroids, topical and systemic retinoids, cryotherapy and ultraviolet therapy. Oral vitamin A (1,00,000 U/day) has also been tried.

5) **Nephrogenic fibrosing dermopathy –** Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis (NFD/NSF) is a recently recognized fibrosing disorder of the skin that occurs in patients with renal insufficiency. NFD was originally described in 1997 in 15 patients receiving hemodialysis, who developed lesions on their extremities and trunk, characterized by thickening and hardening of the skin, papules and nodules with hyperpigmentation, and flexion contractures.[77]On examination the lesions are well defined and may have finger like projections. The plaques may be erythematous, yellow or skin coloured. Patients describe pain, paresthesias and pruritus but are most bothered by the limitations in the mobility resulting from flexion contractures. On examination of eyes most patients have scleral plaques. Clinically the lesions resemble scleroderma or morphea but they have distinct biopsy findings correlating with scleromyxoedema. Scleromyxoedema is a condition characterized my mucin deposition in the viscera and immunoglobulin G (IgG) lambda paraproteinemia. However these 2 conditions were lacking from the described patients. Scleroderma tends to involve the head and neck area. These areas are spared in nephrogenic systemic fibrosis.

There seems to be no correlation between ethnic background, sex or the cause of chronic kidney disease. This condition occurs in patients on end stage renal disease most of whom are on hemodialysis.[78]. The histopathology of Nephrogenic fibrosing dermopathy is similar to scleromyxoedema. There is proliferation of fibroblasts in the dermis and subcutaneous septae, along with deposition of collagen and mucin.

It has been recently discovered that this condition occurs in people who have had a gadolinium scan magnetic resonance procedures. Gadolinium is a radiocontrast

media. Such contrast media are not recommended if the glomerular filtration rate is less than 30 ml/min. It is hypothesized that the retention of Gadolinium in patients with kidney disease is profibrotic. In some studies it has been shown by skin biopsies that Gadolinium has been retained in the skin of patients with chronic kidney disease even more than 2 years after the intake of Gadolinium.[79]These patients have also been shown to have abnormal scintigraphy with increased uptake of ^{99mTc}-hydroxymethylene diphosphonatein the skeletal muscle underlying the involved skin, demonstrating an abnormal process extending deeper than the dermis.[80,81]The disease process can involve the underlying organs also so a new terminology "Nephrogenic systemic fibrosis" has been proposed. Involvement of the diaphragm can even lead to death. 10% of the patients with nephrogenic systemic fibrosis have a fatal course.

Recently a classification scheme was proposed for the clinical subtypes seen based on data from published reports and the NFD registry organized through Yale University, United States of America.[82]

Table 5: Clinical subtypes of nephrogenic fibrosing dermopathy (NFD): a proposed classification scheme[83]

Subtypes	**Description**	**% Of previously reported patients (n = 100)**	**5 of patients from case series (n = 9)**	**NFD progression**
1	New onset acute renal failure or acute decompensation from chronic renal failure	25	22	May be transient
2	Pneumonia like disorder followed by renal failure	6	0	Usually transient
3	Surgical procedure or acute blood loss followed by acute renal failure	18	22	May be transient
4	Kidney transplant	34	55	May be transient
5	Chronic renal failure, unknown	3	11	Usually chronic

	trigger			
6	Thrombotic event, renal failure may predate or follow the event	12	11	May be transient

Treatment – Since there are very few cases described in literature no definitive therapy exists. The most dramatic improvement was seen in 3 patients who were treated with plasmapheresis.[84] Other therapies tried with variable success are UV-A1 phototherapy, prednisone, extracorporeal photopheresis, methotrexate.[85]

6) **Bullous disease of hemodialysis** - It is a well known entity with an incidence of 2-18% in patients undergoing hemodialysis. It is also known as pseudoporphyria of hemodialysis.Korting first reported it in 1975 as a bullous dermatosis resembling porphyria cutanea tarda undergoing maintainance hemodialysis. All these patients had normal porphyrin levels. In chronic kidney disease the normal porphyrin excretion is retarded so it may be sometimes confusing to distinguish between Porphyria cutanea tarda and pseudoporphyria. However in pseudoporphyria the porphyrin levels are only moderately elevated so accurate assays of porphyrin levels are of prime importance.[86] Pseudoporphyria may also develop in association with medications like furosemide, nalidixic acid, tetracycline naproxen, pyroxidine or amiodarone.

The clinical presentation of pseudoporphyria is similar to sporadic porphyria cutanea tarda. Clinically there are tense vesicles and bullae distributed on the dorsal hands, face and occasionally the feet. Secondary changes include erosions and crusts. The bullae heal with scarring and milia formation. The skin is fragile and easily traumatized. Hyperpigmentation of sun-exposed skin is seen. Hypertrichosis is also observed.

Laboratory findings. All types of porphyria cutanea tarda have increased serum iron, ferritin and hepatocellular iron. Those patients who are not anuric excrete increased uroporphyrin I greater than uroporphyrin III, 7-carboxyl porphyrins in the urine. Anuric patients demonstrate markedly elevated plasma levels of uroporphyrin.[87]

Histopathology. Porphyria cutanea tarda in characterized by subepidermal vesiculation with little or no inflammation. The base of bulla is corrugated and lined by well preserved dermal papillae (festooning). There is mild thickening of basement membrane zone and vessel walls, which can be highlighted with periodic acid-Schiff stain. The findings in pseudoporphyria are similar although periodic acid-Schiff stain reveals less vessel wall thickening.

Management. In both the scenarios sun protection is vital.Broad-spectrum physical blockers such as zinc oxide or titanium dioxide are preferred. Unfortunately, standard hemodialysis does not effectively remove uroporphyrin. High flow rate dialysis with a high-flux polysulfate dialyzer can reduce plasma porphyrin levels by upto 37%[88], however this is insufficient to induce clinical remission. N-acetyl cysteine, which is an antioxidant, may help in reducing the blistering.[89] Treatment of true Porphyria cutanea tarda in the patients is limited as antimalarials work by

forming complexes with porphyrins and getting excreted in urine. In chronic kidney disease patients the urine production is reduced. Further the porphyrin antimalarial complexes cannot pass through the dialysis membrane. For patients without renal problem phlebotomy is the treatment of choice. In this procedure 500 ml of blood is removed every fortnightly. However this procedure is limited in these patients as these patients already have low hemoglobin due to reduced erythropoietin formation. Small volume phlebotomies (50-100 ml) every week over 1 year have been reported to induce remission. These patients are treated with erythropoietin along with small volume phlebotomies. This has been shown to mobilize hepatic iron stores. Complete resolution may require several months of therapy. Desferoxamine may also lower porphyrin levels in some patients but it has side effects and so can be used only for limited time. Renal transplantation provides complete resolution of symptoms.[90]

7) **Calciphylaxis -** It is characterized by progressive cutaneous necrosis associated with small and medium vessel calcification. It occurs in the setting of end stage renal disease, diabetes and hyperparathyroidism. Many of these patients are also on hemodialysis. The exact cause is not known. Generally vascular calcifications are common in patients with chronic kidney disease and most of the times they are asymptomatic. In calciphylaxis there is sudden thrombosis in the calcified vessels. It is a type of induced systemic hypersensitivity in which tissues respond inappropriately to certain challenging substances with calcium deposition. The challenging agents include glucocorticoids, albumin infusions, intramuscular tobramycin, iron dextran complex, calcium heparinate, immunosuppresive agents and vitamin D. It occurs closely following initiation of hemo- or peritoneal dialysis.

It is a very painful condition. Initially there is a preinfarctic stage. In this stage there is mottling of skin or it may have a livedoreticularis like pattern or skin may appear dusky red or violaceous. Later bullae may start forming over the ischaemic area. These bullae eventually become necrotic. The central infarcted site becomes black or yellowish. This infarcted area keeps becoming larger. When this is debrided deep ulcers are seen which may even reach up till the fascia. This ulcer can become secondarily infected and may take a sinister course like cellulitis or septicemia. The calciphylactic skin changes are mostly seen on distal extremities, especially over the lateral and posterior calves, abdomen, buttocks, fingers and glans penis. On investigation uremia is present. The calcium x phosphate product is elevated. Parathyroid hormone levels are elevated. For

Histopathology deep incisional biopsy should be taken. There is calcification of small to medium sized blood vessels in the dermis and subcutaneous tissue. Intraluminal fibrin thrombi are present. If the ischaemia is severe lobular or septal fat necrosis may take place along with lymphohistiocytic infiltrate. Radiographs of affected extremities show calcium deposition outlining small and medium sized vessels.

The differential diagnosis includes panniculitis, necrobiosis lipoidica with ulceration, dystrophic calcification, disseminated intravascular coagulation, pyoderma gangrenosum and warfarin necrosis.

Overall the prognosis is bad and mortality rate is very high. Treatment of renal failure helps in improving the condition. Aggressive debridement of wound helps in preventing secondary infection and in wound healing. Subtotal or total parathyroidectomy may help as this condition is related to hyperparathyroidism. Phosphate binding agents may also help.

In addition to vascular calcification and calciphylaxis, nodular calcification may occur in the skin and fat of patients with chronic kidney disease. These deposits are identical to calcinosis cutis of CREST syndrome. The involved skin may ulcerate here also but this is without the severe pain and livedo reticularis like lesions.

Methodology

Source of Data: The source of data includes cases of chronic kidney disease stage 5 undergoing hemodialysis at KLES Dr. Prabhakar Kore Hospital and MRC, Belgaum.

Inclusion criteria: Cases of chronic kidney disease stage 5 on hemodialysis and who were willing to be a part of the study

Exclusion criteria: Cases of acute renal failure or those who were having milder grades of chronic kidney disease other than grade 5. Patients of chronic kidney disease stage 5 who were not willing to be a part of the study were excluded from the study.

The formula used for sample estimation was $4PQ/D^2$. In this formula 'P' is the prevalence. 'Q' is 100-P. D is disallowable error which can vary from 5-20% of 'P'. Based on previous studies the the prevalence of skin manifestations in patients of chronic kidney disease stage V, it was seen that at least 80% of the patients had one cutaneous manifestation. So 'P' became 80, 'Q' became 20 and 'D' was taken as 10% of 'P' that is 8. The resultant sample size was 64.

The study was a one year cross sectional descriptive study from January 2012 to December 2012. A predesigned and pretested pro-forma was used. An informed and signed consent was taken first which was also signed by the principal investigator and a witness who wasn't related to either the patient or the principal investigator. The pro forma contained patient's basic demographic data like name, age and sex. Various relevant laboratory parameters like hemoglobin, creatinine, blood urea, serum potassium, serum calcium and serum phosphate levels were noted down from patient's records. Serum parathyroid hormone levels were measured in all patients. In apart from this any other relevant investigation was carried out like skin biopsy for acquired perforating disorder, or 10% potassium hydroxide mount for superficial fungal infections. Cause of chronic kidney disease, duration of dialysis was noted. Then general physical examination was done. Skin colour changes, pruritus, skin turgor changes, nail changes, hair changes and any evidence of specific disorders for hemodialysis were looked for. Later enquiry was made about any other illness related to cardiovascular, respiratory and nervous system. In the end the pro forma was signed by the principal investigator, the guide and the co-guide.

PROCEDURE

Parathyroid hormone levels analysis was done using IMMULITE®/ IMMULITE® 1000 Intact PTH Analysers. The kit is intended for in vitro diagnostic use for quantitative measurement of intact parathyroid hormone in EDTA plasma or serum. In this study serum sample was used in all the patients. This kit is a solid phase two site chemiluminescent enzyme labelled immunoassay.[91]

BD vacutainer™ with gel was used to collect the sample. The specimen was allowed to clot at room temperature. Serum was separated from the cells using centrifuge machine. Anticoagulant therapy may delay the clotting process. The patients undergoing hemodialysis are administered heparin therapy to prevent

blockage of the arteriovenous shunt so the sample was collected in all cases before the dialysis process started. When the analysis was delayed the samples were stored at 2-8 ℃ for not more than 8 hours as per the instructions on the kit. According to the manufactures of the kit the reference range for intact PTH samples was 11-67 pg/ml. The median value was 31 pg/ml.

Limitations of the kit - Heterophile antibodies present in the human serum can react with the immunoglobulins present in the assay components causing false reading of the test.

Specificity - the IMMULITE Intact PTH assay is highly specific for intact PTH with particularly low cross reactivity to most PTH fragments, as well to other naturally occurring compounds which may be present in the patient samples.

Skin biopsy was performed in one case that consented for biopsy to be taken. Prior history of allergy to lignocaine was asked which was negative. The area was cleaned with 70% alcohol. 1 ml of plain lignocaine 2% injection was given intralesionally and a disposable punch of 4 mm was used to do punch biopsy following which the wound was sealed with antibiotic ointment and dressing. The biopsy specimen was sent to pathology lab in 10% formalin for histopathologic examination. No other special tests were done in the study.

Statistical analysis - Percentages were used for categorical outcomes. The prevalence of abnormal parathyroid hormone level values between groups were compared by chi square test.

Discussion

64 patients were examined in the study. No controls were taken in the study. In an Egyptian study by Attia et al total of 206 uremics were taken. They were then compared with controls which were age and gender matched. This is a limitation of the present study which is a cross sectional study. A case control study would have helped to eliminate the confounding errors.

Table 24: Sample size of various studies

Study	Sample size
Present study	64
Eyptian study by Attia et al	206
Indian study by Udayakumar et al	100
Indian study by Tawade et al	35

Larger the sample size greater is the power of the study. However due to time restriction only 64 patients were examined. Increasing the sample size would have increased the power of the study.

The criteria for choosing the patients in the present study was that the patient should be having chronic kidney disease stage 5. It is defined as the end stage renal disease with Glomerular filtration rate < 15 mL/min per 1.73 m^2 In the study by Attia et al predialysis lab parameters were taken to include patients into the study. They were

Serum creatinine - >4 mg/dl
Blood urea >100 mg/dl
Serum potassium > 6.5 meq/l
Serum bicarbonate <15 meq/l.

In the study by Makhlough et al all the patients who were undergoing hemodialysis were taken into study. All the patients having skin pathologies were excluded.

In the present study out of 64 patients 50 were men and 14 were women. Thus men constituted 78.12% of cases. This value is much higher than those seen in other studies. In an Israel study conducted by Dyachenko et al men constituted 60% of the cases.[92] In an Egyptian study by Attia et al men constituted 53% of cases. (add end note). The kidney disorders are not known to affect the different sexes differentially. The result in our study is probably due to the fact that increased numbers of men seek treatment for their disorders probably due to socioeconomic reasons.

Table 25: Comparison of the number of males and females taking part in various studies

Study	**Men**	**Women**
Present study	50 (78.12%)	14 (21.87%)
Tawade et al	30 (85.71%)	5 (14.28%)
Udayakumar et al	70 (70%)	30 (30%)
Attia et al	110 (53.39%)	96 (46.60%)

Makhlough et al	80 (52.3%)	73 (47.7%)

Cause of renal failure– In the present study hypertension was the most common cause of renal failure, followed by diabetes and chronic tubulointerstitial disease. This differed from the study by Attia et al where diabetes was the most common cause followed by hypertension.

Table 26: Comparison of etiology of chronic kidney disease in various studies

Cause of renal failure	Present study (in %)	Attia et al (in %)
Diabetes Mellitus	32.8	11.6
Hypertension	70.3	9.8
Renal stones	1.5	9
Chronic pyelonephritis	1.5	3
SLE	1.5	2.4
Chronic tubulointerstitial disease	18.75	-
Others	20.31	60

Duration of dialysis– Patients of chronic kidney disease stage V were taken into the study irrespective of the duration of dialysis. The range varied from less than 3 months to more than 5 years. The duration of dialysis were categorically divided and correlated with PTH levels. In all these categories the least abnormal values were found between 6 months to 36 months. There was a statistically positive correlation with normal parathyroid hormone levels during this period. This means that on an average it takes 6 months of hemodialysis for the parathyroid hormone levels to become normal. They remain normal till 36 months and after that they start to rise abnormally even after continuing hemodialysis.

Pruritus:

In the present study 28.1% patients complained of itching prior to dialysis where as 40.6% patients complained of itching post dialysis.. Thus there was an increase in the incidence of itching post dialysis. No objective criteria were used to measure the intensity of pruritus. Patients were asked only two questions regarding pruritus. They were

1) Was there pruritus prior to dialysis?
2) Has the itching increased after dialysis?

In the study by Maklough et al the prevalence of pruritus was 61.4%. In the study by Dyachenko et al prevalence of pruritus was 74.3% at the time of dialysis

Table 27: Comparison of prevalence of pruritus in various studies

Study done	Prevalence of pruritus
Present study	28.1%
Makhlough et al	61.4%

Dyachenko et al	74.3%

In the study by Makhlough et al an elaborate scoring system proprosed by Duo et al (insert reference AD)was used to quantify pruritus and then the intensity of itch was compared with various parameters. (insert reference AC) The total scoring of pruritus is calculated as follows:

(Severity of pruritus x distribution of pruritus) + sleep disorder.

The severity of pruritus is assessed as:

1 point	Slight itching
2 points	Itching with scratching
4 points	Itching and scratching with excoriations
5 points	Itching causing total restlessness

The distribution of pruritus is scored as

1 point	Pruritus maximum in 2 areas of the body
2 points	Pruritus maximum in more than 2 areas of the body
3 points	Generalized pruritus

The sleep disorder is monitored as

2 points (maximum of 10 points)	Every waking up due to itching
1 point (maximum of 5 points)	Each scratching

The drawback of this scoring system is that pruritus is a subjective symptom and the perception of itch may vary from person to person even if the same level of pruritus exists in two individuals. Thus the resultant score is prone for errors. The advantage of this method is that pruritus is quantified and so correlational studies can be easily carried out.

Dyachenko et al studied hemodialysis related pruritus and associated cutaneous manifestations.(insert reference AE) In their study the patients were considered to have pruritus if they had either of the two conditions

1) At least 3 episodes of itching during a period of 2 weeks or less, with the symptom appearing several times during the day, lasting for at least a few minutes, and troubling the patient
2) The appearance of itch on a regular pattern in a regular pattern during a period of 6 months.

To be defined ‘uremic’ the pruritus had to appear shortly before the onset of dialysis, or at any time thereafter, without evidence of any other active disease, which could explain it.

In the present study pruritus was considered only as either present or absent. This was probably an oversimplification and the scoring system by Duo et al could have given more statistically relevant results.

The etiology of pruritus is still unknown. The hypothesis of the present study was to see if there was a correlation between pruritus and parathyroid hormone levels. In the present study there was no correlation between pruritus and parathyroid hormone. In the study by Makhlough et al there was a statistically positive correlation between pruritus and parathyroid hormone.

Table 28: Comparison between parathyroid hormone and pruritus in different studies

Subgroup		Hyperparathyroidism present	Hyperparathyroidism absent	P value
Present study				P = 0.546
	Pruritus present	17 (43.58%)	14 (56%)	
	Pruritus absent	22 (56.42%)	11 (44%)	
Makhlough et al (males)				P = 0.001
	Pruritus present	37 (64.3%)	19 (61.3%)	
	Pruritus absent	15 (35.7%)	12 (38.7%)	
Makhlough et al (females)				P = 0.18
	Pruritus present	27 (64.3%)	19 (61.3%)	
	Pruritus absent	15 (35.7%)	12 (38.7%)	

Makhlough et al had divided the patients into males and females. As can be seen from table 27 that the statistically significant correlation between pruritus and parathyroid hormone levels was obtained only for males and not for females. Neither pruritus nor parathyroid hormones are known to affect the different sexes differentially so there seems to be some fallacy in the above results in the above study. In the present study the patients were not divided on the basis of sex. Thus there is still not clear consensus whether hyperparathyroidism is the cause for uremic pruritus. According to the present study pruritus seen in hemodialysis has no relation to parathyroid hormone.

Also in the present study the prevalence of itching prior to dialysis was 28.1% whereas after starting dialysis the prevalence of itching was 40.6%. So there was 12.5% increase in the prevalence of pruritus. Thus this increase in pruritus can be attributed to the dialysis procedure. It might either be that the pruritogens are not filtered through the dialysis membrane. The constituents of the diasylate fluid may be causing increase in pruritus.

In the present study the sample was collected before starting the dialysis procedure as during the dialysis procedure many patients are administered heparin. This could possibly alter the laboratory results. This was similar to the study by Makhlough et al in which blood was withdrawn prior to starting the dialysis procedure.

Analysis was done in various studies between pruritus and duration of dialysis. In the study by Makhlough et al there was no relation between pruritus and duration of dialysis. In the study by Dyachenko et al also there was no relation between the two. Our study also had a similar finding.

Pallor

In the present study prevalence of pallor was 65.62%. This was slightly less than that seen in the study by Dyachenko et al (75.7%). In an Egyptian study by Attia et al, the patients were divided into adults and children among adults the prevalence of pallor was 48.5%. In children the prevalence of pallor was only 18%. They hypothesized that in Egypt there is free supply for erythropoietin in their health programs which accounted for the low prevalence of pallor. Udayakumar et al studied 100 patients undergoing hemodialysis in India. The prevalence of pruritus in their study was 60%. They hypothesized that the prevalence of pallor was low in their study due to darker complexion of the patients. Thus the figures in the present study correlate with the Indian study by Udayakumar et al. Pallor did not have a statistically positive correlation with parathyroid hormone.

Table 29: Comparison of pallor between various studies

Study	Prevalence of pallor
Present study	65.62%
Attia et al	48.5%
Udayakumar et al	60%
Dyachenko et al	75.7%

Skin colour changes post dialysis

In the present study 21.87% patients complained of darkening post dialysis. This differed from other studies. In the study by Udayakumar et al 40% of patients experienced darkening post dialysis. In the study by Dyachenko et al the 75.7% patients complained of hyperpigmentation post dialysis. In the study by Attia et al hyperpigmentation was seen in 17.8% of their cases but only in 3% of controls. In contrast to all the other studies which showed pigmentation more in a photodistributed area, in the present study patients complained of generalized diffuse pigmentation. The earlier studies had suggested that the increased pigmentation was due to the inability of kidneys to excrete beta-melanocyte stimulating hormone but that does not explain why the pigmentation would occur more in a sun distributed area. The present study does not have that discrepancy as the pigmentation was seen in a diffuse pattern. There was no statistically positive correlation between hyperpigmentation and parathyroid hormone.

Table no 30: Comparison between skin darkening post dialysis in various studies

Study	Prevalence of skin darkening
Present study	21.87 %
Udayakumar et al	40 %
Attia et al (cases)	17.8%
Attia et al (controls)	3 %

Dyachenko et al	78.7%

Half and half nail

Half and half nail is a specific feature of patients with chronic kidney disease stage 5. Even among these patients it is seen more commonly in patients undergoing hemodialysis.[93] In the present study it was seen in 15.62% of cases. It was similar to the prevalence seen in study by Dyachenko et al (18.6%). In an Indian study by Tawade et al the prevalence was 17%. Thus the prevalence of half and half nail was more or less similar in various studies. In the present study there was no correlation was found between this nail change and parathyroid hormone. No similar studies were found which compared the two variables.

Table 31: Comparison of half and half nail in various studies

Study	**Prevalence of half and half nail**
Present study	15.62%
Dyachenko et al	18.6%
Tawade et al	17%
Udayakumar et al	21%

Terry's nail

In the present study Terry's nail was found in 23.44% of patients. This is unusual because none of the literature pertaining to nail changes in hemodialysis patients mentions this finding. Terry's nails are usually seen in cirrhosis of liver, heart failure and in diabetes mellitus. In the present study the patients with Terry's nails were not suffering from this disorder. Thus Terry's nails can be also be considered as one of the cutaneous manifestations of patients undergoing hemodialysis. In the present study there was no statistically relevant correlation between Terry's nail and parathyroid hormone levels.

Muehrcke's lines

In the present study the prevalence of Muehrcke's lines was 7.8%. This was similar to study by Udayakumar et al who reported prevalence of 5% in their study. In the present study there was no correlation between Muehrcke's lines and parathyroid hormone. In our knowledge no other study has compared these 2 variables.

Hair changes

In the present study 39.1% patients reported that they had lost hair post dialysis.in the study by Udayakumar et al 30% of patients had sparse body hair whereas 11% had sparse body hair at the time of inspection. They did not mention whether these changes were present before the hemodialysis or they appeared after starting it. In the Egyptian study by Attia et al, among adults the prevalence of pruritus was 33.7% cases whereas in children the prevalence of hair loss post dialysis was 34.9%. Thus our study has similar findings. The hair loss in dialysis patients may be due to stress

of the disease per se or the dialysis procedure due to which the hair enter into telogen effluvium. Another cause can be anaemia in these patients, which may cause hair loss.

Table 32: Comparison of hair loss after dialysis in various studies

Study	Prevalence of hair loss
Present study	39.1
Udayakumar et al	41%
Attia et al (adults)	33.7%
Attia et al (children)	34.9%

Xerosis

In the present study prevalence of xerosis was 95.31%. Xerosis has been known to be the most common manifestation of patients undergoing hemodialysis. Our study also found similar result. It was the most common manifestation seen in our study. However it did not have a statistically positive correlation with parathyroid hormone.

Acquired perforating disorder

In our study it acquired perforating disorder was seen in 3(4.7%) of cases. Out of these 3 cases 2 were diabetic. Out of the 3 one patient consented for skin biopsy. The skin biopsy did not reveal any evidence of altered elastin material, nor was there any evidence of folliculitis. Thus it was neither elastosis perforans serpinginosa nor perforating folliculitis. In the study by Dyachenko et al they did not find any case of perforating disorder in their study. Tawade et al reported a prevalence of 17% in their study on 35 patients on hemodialysis. Udayakumar et al reported a prevalence of 21% in their study of 100 patients on haemodialysis. Attia et al reported a prevalence of 2.5% among their patients.

Table 33: Comparison of prevalence of acquired perforating dermatosis among various studies

Study	**Prevalence of APD**
Present study	4.7%
Dyachenko et al	0%
Tawade et al	17%
Udayakumar et al	21%
Attia et al	2.5%

Bullous disease of hemodialysis

This was not seen in the present study. This was because it is a rare disorder and the sample size of the present study was small. Attia et al reported a single case (0.6%) of bullous dermatosis. Udayakumar et al did not report any case of bullous dermopathy in their study. Dyachenko et al also did not report any case of bullous dermopathy in their study.

Nephrogenic systemic fibrosis

No case of nophrogenic systemic fibrosis was found in the present study. This was probably because is a very rare disorder and the sample size was small.

Calciphylaxis

In the present study no case was found to have calciphylaxis. This was so because it is also a rare disorder and the sample size was small. It was not reported by Attia et al, Dyachenko et al, Udayakumar et al.

Thus parathyroid hormone was not statistically significant to any of the cutaneous changes seen in patients undergoing hemodialysis.

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CONSENT FORM

I.D. No. | | | | | |

Name of the participant (in block letters)	
Address	
Email	
Contact number	

A study of cutaneous manifestations in patients of chronic kidney disease stage 5 undergoing hemodialysis and their correlation to parathyroid hormone levels at a tertiary care hospital in Belgaum, a cross sectional study.

The study is conducted by Post graduate student in M.D Dermatology under the guidance of Professor of Dermatology, and under the co-guidance of Professor, Department of Nephrology, J N Medical College, Belgaum.

Respected Sir/Madam, we invite you to participate in our study as, you are eligible for the same. During the study you will be asked some questions in detail regarding your present complaints.

Purpose of the study:

The purpose of this study is to know the various skin manifestations and their relation to parathyroid hormones in patients of chronic kidney disease stage 5 undergoing hemodialysis. You are being asked to participate in this research because you have been diagnosed to have chronic kidney disease stage 5 and urgent dialysis is required.

So an attempt will be made to study the skin manifestations and co-relate them with the parathyroid hormone levels.

Procedure and treatment:

Should you choose to participate, you will be asked to give a detailed history of your disease, undergo a physical examination, and consent to a few routine blood (one of which will be to measure parathyroid hormone levels) and urine investigations. In addition to this, you will agree to undertake other relevant investigations if required.

Risks and benefits:

You may undergo some amount of discomfort during the process of investigations, which may include slight pain and bleeding. However all necessary steps and precautions will be taken to ensure your safety. The result of you taking part in this research would help health care providers towards a better understanding of this disease, and thus we will be able to provide improved patient care

Alternatives:

If you decide not to participate in this study, you will still be receiving the usual standard care for your disease.

Privacy and confidentiality:

Your privacy will be respected and all information collected about you during the course of this study will be kept confidential. Your identity will remain undisclosed.

Relations with the Institutional policy:

The J. N. Medical College will provide, within the limitations of the laws of the State of Karnataka, facilities and medical attention to patients who suffer injuries as a result of participating in this project. In this process if you suffer any physical injury as the result of your participation in this study, you may contact Department of Dermatology, KLE'S Dr. Prabhakar Kore Hospital and MRC, Belgaum.

Financial incentives:

You shall not be receiving any payment or any financial incentives for participating in this study.

Authorization to publish results:

The results of this study may be published for scientific purpose or presented to a scientific group. Your identity however will be maintained confidential at all times.

Voluntary participation:

Your participation in this study is voluntary. Your decision whether or not to participate will neither affect the care for your current disease, nor your future relations with the doctor or the hospital. In case you need further information regarding your rights as a study participant, you may please contact Dr. V.D. Patil , principal and chairman of the ethical committee, J N Medical College, Belgaum on telephone No. 08312473777

STATEMENT OF CONSENT

I Mr/Ms/Mrs

_____

Volunteer and consent to participate in this study. I have read the consent document or it has been read to me in my vernacular language. I accept to participate in the study. All the information regarding this study has been provided to me and I have understood the same. I have been given the opportunity to ask questions and obtain appropriate answers.

Signature or left thumb print of participant:

Date:

Witness name:

Signature of witness:

Date:

Signature of the investigator:

Date:

If the participants are Minors (under 18), the parents sign the form, rather than the participants.

PRO-FORMA

Name of the patient -_____

Hospital ID no. - _____

Age-_____

Sex-_____

Address- _____

Lab parameters	
Haemoglobin	
Serum creatinine	
Blood urea	
Serum potassium	
Serum bicarbonate	
PTH levels	
Serum calcium	
Serum phosphate	
GFR (Glomerular Filtration Rate)	

CAUSE OF CHRONIC KIDNEY DISEASE

1) Diabetes Mellitus
2) Hypertension
3) Renal stones
4) Chronic Pyelonephritis
5) Systemic Lupus Erythematosus
6) Other co-morbidities

Type of diasylate used

Duration of dialysis

1) <3 months
2) 3-6 months
3) 6-12 months
4) 1-3 years
5) 3-5 years
6) >5 years

General Physical examination

Vital	Present	Absent
Pallor		
Icterus		
Cyanosis		
Clubbing		
Lymphadenopathy		
Edema		

Essentials:

Blood pressure _____

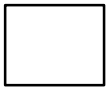
Pulse rate _____

Temperature

Respiratory rate _____

Skin colour changes

1) Pallor
2) Muddy brown
3) Hemochromatosis (bronze)
4) Yellow



Pruritus	**Was it present before the initiation of dialysis**	**Whether increased or decreased after dialysis**

Skin turgor	**Normal**	**Abnormal**

Nail changes	Present	Absent
Absent lunula		
Half and Half nail syndrome		
Koilonychia		
Subungal hyperkeratosis		
Onycholysis		
Mees' lines		
Muercheke's lines		
No changes		

Hair changes

1) Sparse body hair ☐
2) Diffuse alopecia
3) No changes

	Present	**Absent**
Xerosis		
Coated tongue		
Tongue sign		
Gynaecomastia		
Xerostomia		
Uremic fetor		
Uremic neuropathy		
Infection		
Phlebitis		
Hematoma		
Allergic and contact eczema		
Digital ischaemia and aneurysm		
Venous hypertension		
Pseudo-kaposi sarcoma		

Any other cutaneous finding _____

Acquired perforating dermatosis

Underlying association

1) Diabetes Mellitus
2) Truama
3) Liver disease
4) Internal malignancy
5) None

Bullous disease of hemodialysis

1) Present
2) Absent

If present associated drug use?

Nephrogenic systemic fibrosis	**Present**	**Absent**
Face involvement		
Sharp pain		
Joint contractures		
MR angiography with Gadolinium done in past?		
Temporal relationship		

Calcification	**Present**	**Absent**
1) Calcinosis cutis		
1) Calciphylaxis		
1) Calcemic uremic arteriopathy		

Systemic Examination

Cardiovascular system

Respiratory system

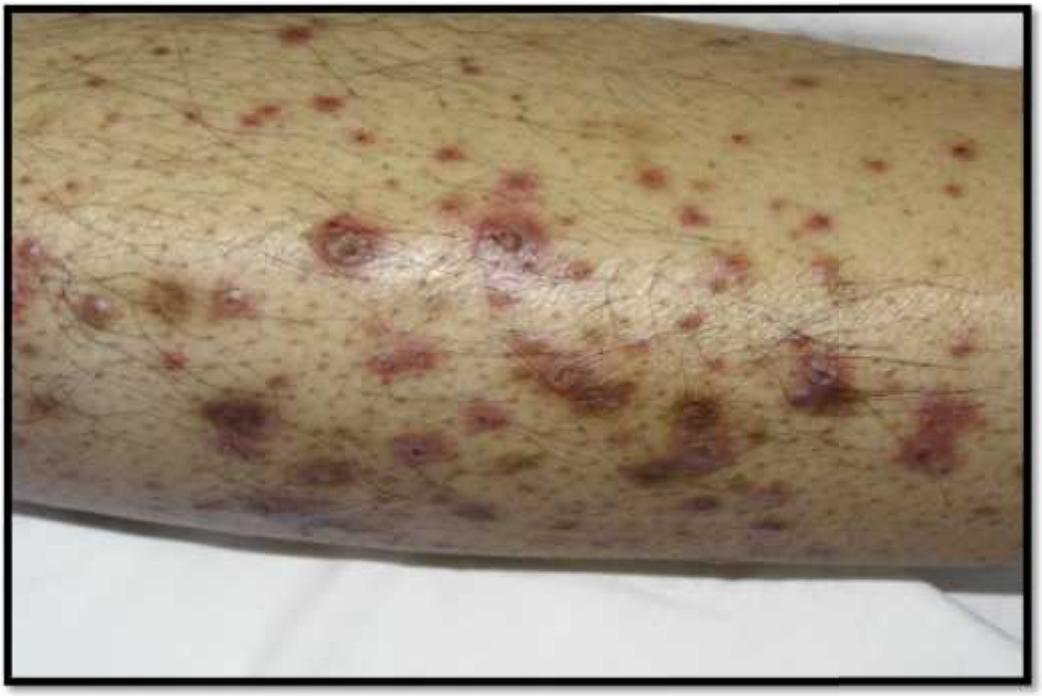
Nervous system

Investigator signature _____

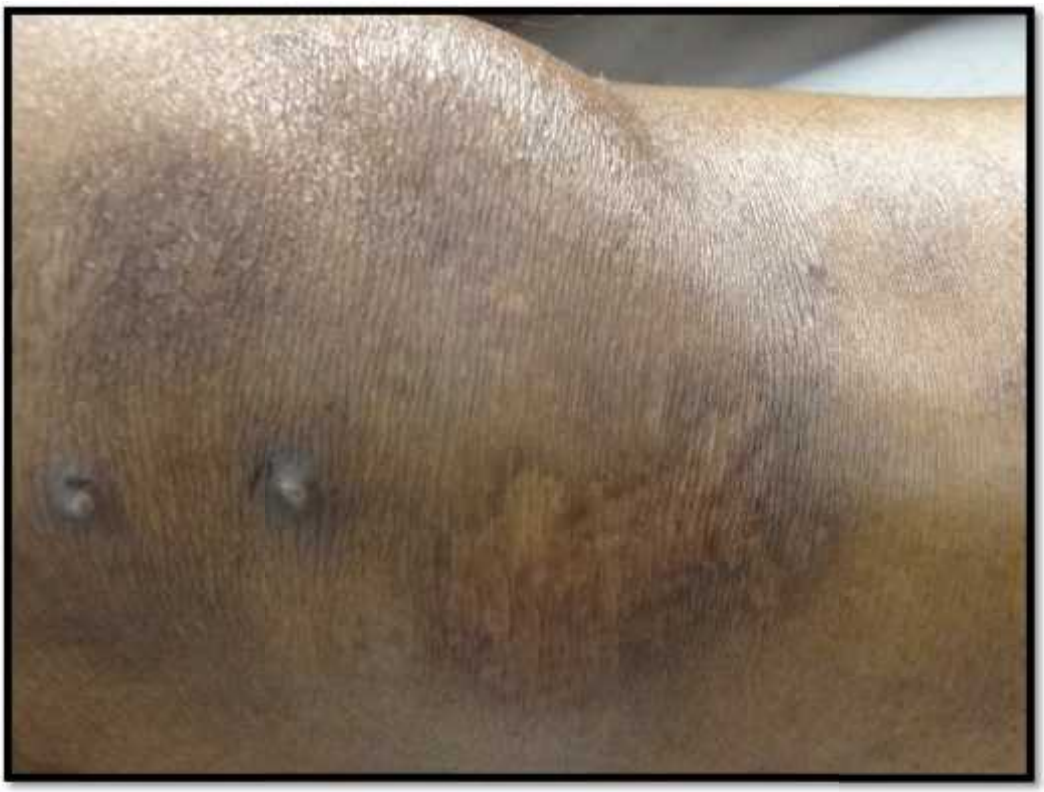
Guide signature _____

Co-guide signature _____

PHOTOGRAPHS

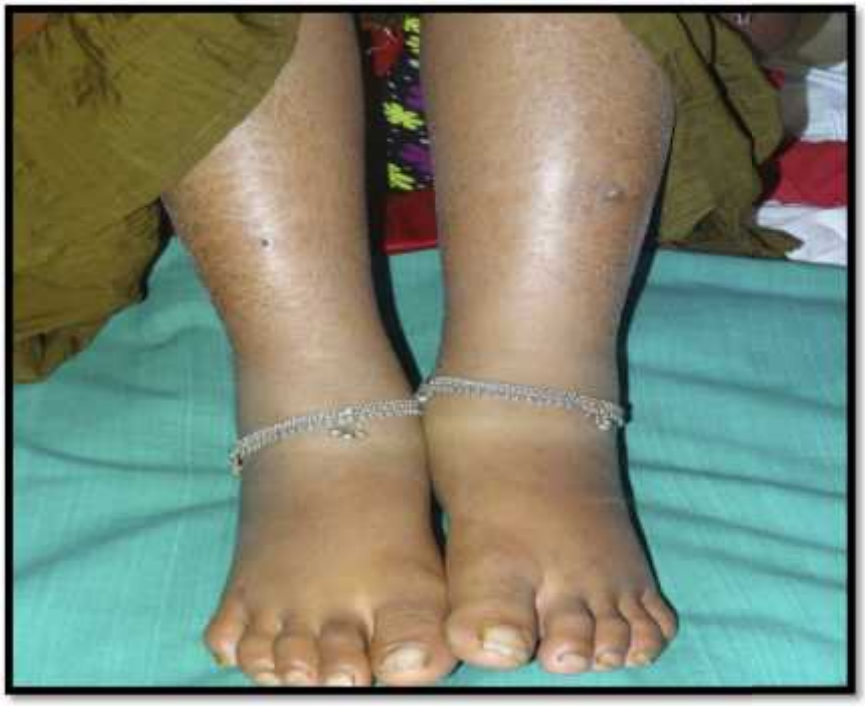


Photograph 2: Acquired perforating dermatosis

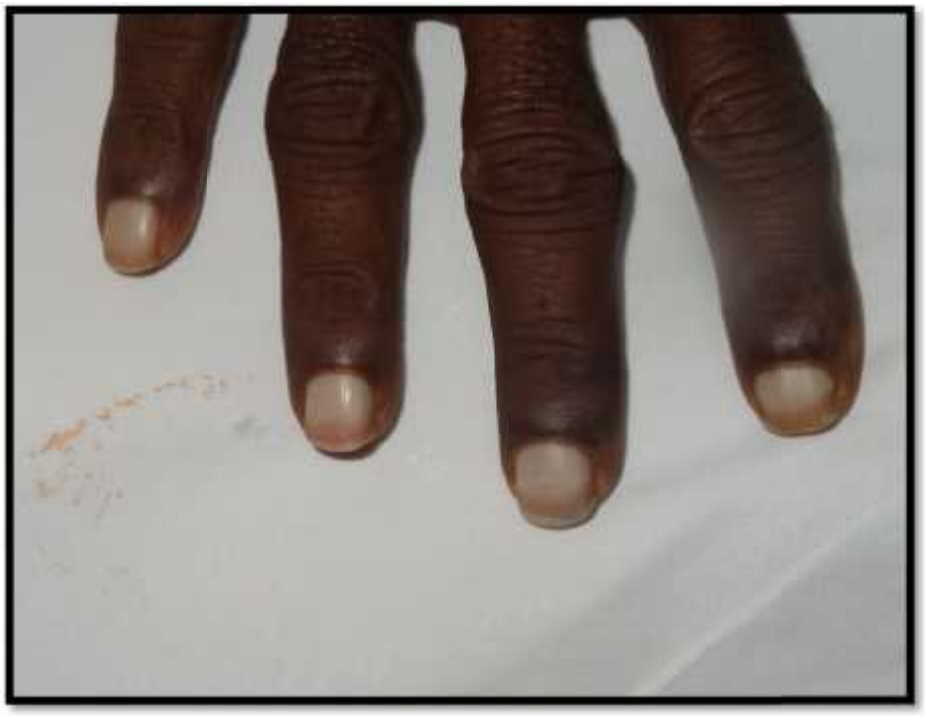


Photograph 3: Acquired perforating dermatosis

Photograph 4: Diffuse darkening post dialysis

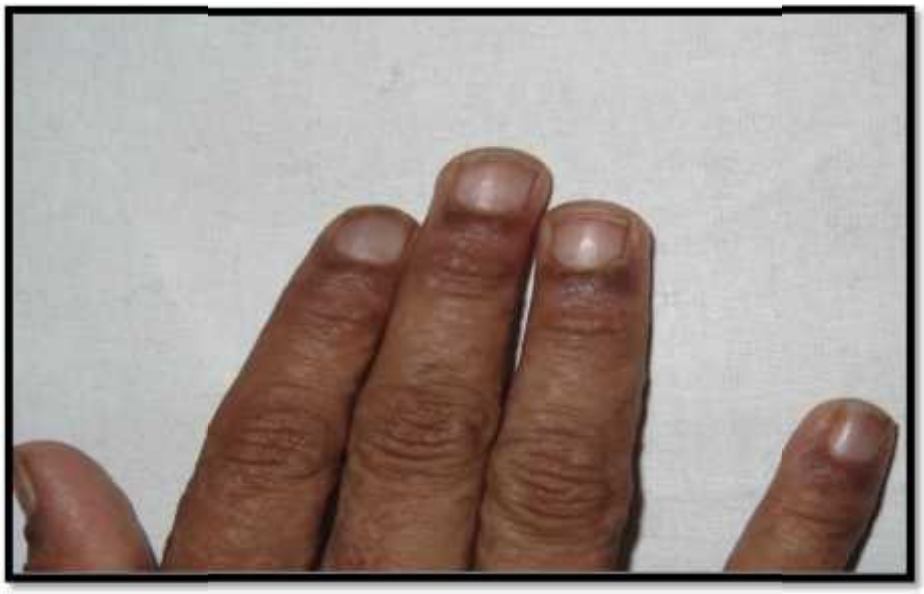


Photograph 5: Pedal edema

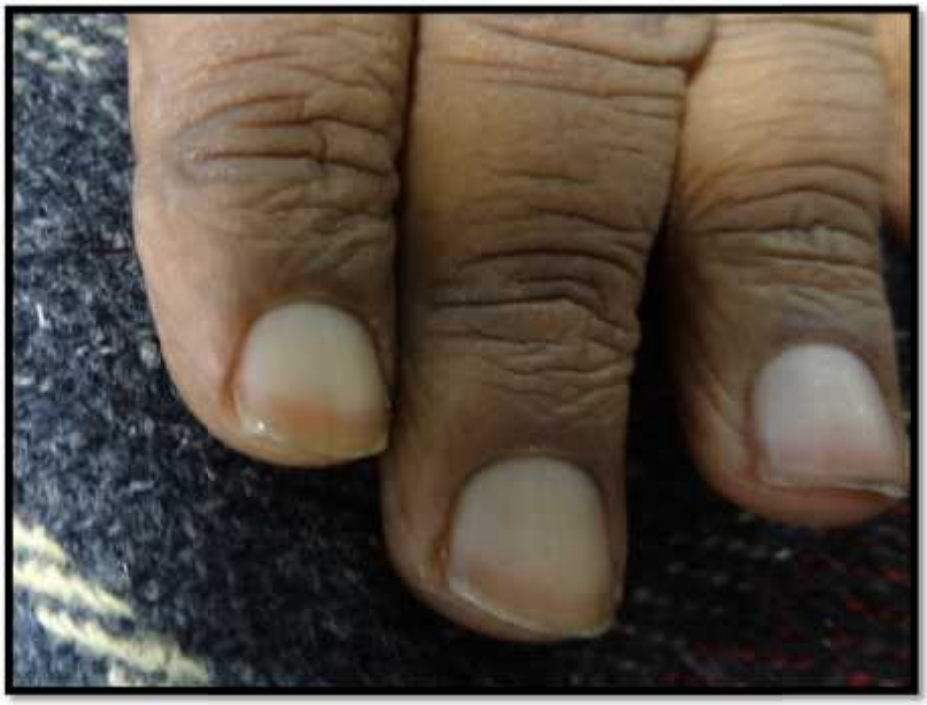


Photograph 6: Half and half nail over index finger

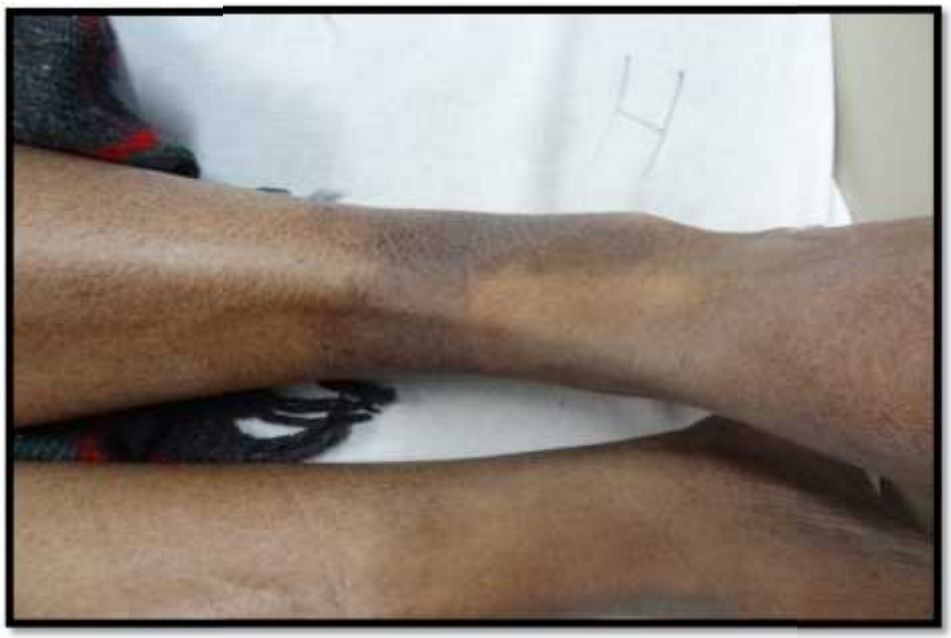
Photograph 7: Muehrcke's lines



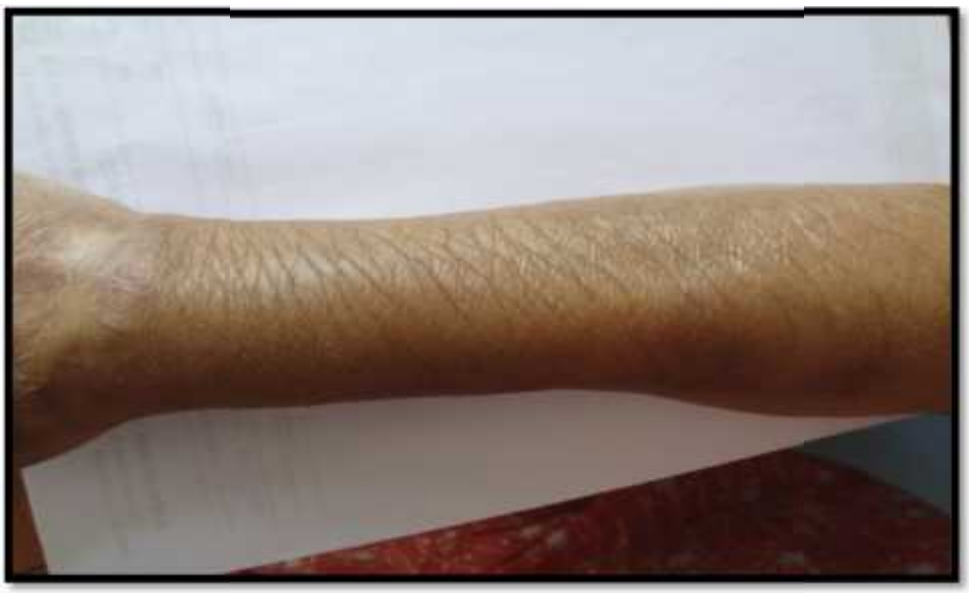
Photograph 8: Terry's nails



Photograph 9: Terry's nails



Photograph 10: Xerosis



Photograph 11: Loss of skin turgor post dialysis

KEY TO MASTER CHART

Age – age in years

Hb- haemoglobin in gm/dL

Creatinine – serum creatinine in mg/dL

Urea – serum urea in mg/dL

Potassium – serum potassium in meq/L

Bicarbonate – serum bicarbonate in meq/L

PTH – serum parathyroid hormone in pg/ml

Ca- serum calcium in meq/L

PO_4 - serum phosphate in meq/L

HBV – Hepatitis B virus

- \- Hepatitis B absent
- \+ Hepatitis B present

HCV – Hepatitis C virus

- \- Hepatitis C absent
- \+ Hepatitis C present

HIV – Human immunodeficiency virus

- \- HIV absent
- \+ HIV present

Cause of CKD – cause for chronic kidney disease stage 5

1- Diabetes mellitus
2- Hypertension
3- Renal stones
4- Chronic pyelonephritis
5- Systemic lupus erythematosus
6- Chronic glomerulonephritis
7- Other causes
8- Chronic tubulointerstitial disease

Duration of dialysis

1. <3 months
2. 3-6 months
3. 6-12 months
4. 12-36 months
5. 36-60 months
6. >60 months

Pallor

0 – absent
1 - present

Icterus

0– absent

1 - present

Cyanosis

0– absent

1- present

Clubbing

0 – absent

1 - present

Lymphadenopathy

0 – absent

1 - present

Edema

0 – absent

1 - present

Skin colour changes

1. Pallor
2. Muddy brown colour
3. Hemochromatosis
4. Yellowish discoloration
5. Diffuse darkening

Pruritus at present

0 – absent

1 - present

Pruritus before dialysis

0 – absent

1 – present

Pruritus after dialysis

1 – increased

2 – reduced

Skin turgor

0 – normal

1 – abnormal

Absent lunula

0 – absent

1 - present

½ and ½ nail – half and half nail

0 – absent

1 - present

Koilonychias

0 – absent

1 - present

Subungual hyperkeratosis

0 – absent

1 - present

Onycholysis

0 – absent

1 - present

Mees' lines

0 – absent

1 - present

Terry nail

0 – absent

1 - present

Muehrcke's lines

0 – absent

1 - present

Hair changes

1 – sparse body hair post dialysis

2 – diffuse alopecia post dialysis

3 – no hair loss post dialysis

Xerosis

0 – absent

1 – present

Coated tongue

0 – absent

1 – present

Xerostomia

0 – absent

1 – present

Uremic fetor

0 – absent

1 – present

Tongue sign

0 – absent

1 – present

Allergic contact dermatitis

0 – absent

1 – present

Uremic neuropathy

0 – absent

1 – present

Phlebitis

0 – absent

1 – present

Hematoma

0 – absent

1 – present

Acquired perforating dermatosis

0 – absent

1 – present

Nephrogenic systemic fibrosis

0 – absent

1 – present

Calcification

0 – absent

1 – present

MASTER CHART