

**Skin and serum levels of calcium, phosphorus and vitamin D3 in uremic pruritus patients before and after broad band ultraviolet B (UVB) phototherapy**

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**Abstract**

**Background:**

Pruritus is one of the commonest frustrating manifestations in chronic renal failure. The exact cause of uremic pruritus is unknown and several factors are reported to be involved in its pathogenesis, the most important of which are abnormalities in calcium and phosphorus metabolism. Broad band UVB phototherapy plays an important role in treatment of uremic pruritus through different mechanisms.

**Aim of work:**

The aim of this work was to evaluate skin and serum levels of calcium and phosphorus and their regulating hormone, vitamin D

in uremic patients before and after broad band UVB phototherapy to verify their role in the pathogenesis of uremic pruritus.

### **Patients and Methods:**

The study included 18 patients of uremic pruritus and 9 controls. A 4 mm punch biopsy and 5cm blood sample were taken from all patients before and after UVB phototherapy (when patients reported clinical disappearance of itching). Similar samples were taken from controls before the start of the study.

### **Results:**

The serum and skin calcium in uremic patients before UVB phototherapy were lower than the controls, and they increased significantly after phototherapy. The serum levels of calcium were normalized after phototherapy. On the other hand, though the skin content of calcium was increased significantly after phototherapy, it was still significantly less than controls.

The serum phosphorus in uremic patients before UVB phototherapy was higher than the controls, and it decreased significantly after UVB phototherapy, though it remained significantly higher than controls. On the other hand, skin content of phosphorus in uremic patients before UVB phototherapy was less than in controls, and it decreased significantly after UVB phototherapy.

Serum and skin contents of vitamin D in uremic patients increased significantly after UVB phototherapy.

### **Conclusion:**

It appears from this study that hyper- or hyperphosphatemia may represent a circulating pruritogenic substance that stimulates itching pathways in uremic patients. In addition, we postulate that hypocalcaemia and low skin calcium content, together with the previously reported disrupted calcium ion gradient, may have a direct relation to the stimulation of itching pathways. The main role of UVB in improving pruritus may be related to its systemic normalizing effect on both calcium and phosphorus (increasing calcium and lowering phosphorus).

## **Introduction**

Uremic pruritus is one of the common manifestations of chronic renal failure (CRF) that appears to be almost equally frustrating to

both patients and physicians [1].

The pathophysiologic mechanisms underlying uremic pruritus are not exactly known and it appears that multiple combined factors integrate in the pathogenesis of this condition, such as increased amount of substance P [2], accumulation of histamine releasing mast cells in uremic skin [3] and the presence of circulating pruritogenic substances [4].

Moreover, low serum albumin and transferrin levels, together with high serum ferritin level in uremic patients coincide with the possible role of inflammation in the development and severity of uremic pruritus [5].

Abnormalities in calcium and phosphorus metabolism in CRF has been also claimed to provide an explanation for uremic pruritus. Hyperparathyroidism with secondary hypercalcemia and skin calcification may stimulate mast cell degranulation with consequent release of histamine [6].

Blachley and colleagues [7] suggested that microprecipitation of divalent ions such as calcium, phosphorus and magnesium in the skin might be one of the causative factors in uremic pruritus. However, Memose and colleagues [8] pointed to the presence of abnormal calcium ion distribution in the skin with higher amounts in the lower epidermis and suggested that the disrupted calcium ion gradient is the factor responsible for the development and /or maintenance of uremic pruritus.

Ultraviolet B (UVB) phototherapy was found to be effective in the treatment of uremic pruritus through suppressing histamine release from mast cells [3], and causing degeneration of cutaneous nerve endings [9]. Moreover, narrow band UVB relieves uremic pruritus suggested to be through inactivating a circulating pruritogenic substance or through producing a photoproduct which relieves pruritus [10].

Vitamin D is synthesized in the skin after exposure of 7-dehydrocholesterol to sun light, in the UVB range (290-315nm). The active form is synthesized via successive hydroxylation in the liver and kidney [11], however, keratinocytes can make their own active form of vitamin D3 (1, 25 (OH) 2 D3) in response to sun exposure [12]. The serum vitamin D binding protein has a preference for vitamin D3; it selectively promotes the translocation of it from the skin at the dermoepidermal interface into the circulation [13]. The major physiologic function of vitamin D, either in the serum or the skin is calcium homeostasis [14].

Accordingly, the aim of this work was to evaluate skin and serum levels of calcium and phosphorus and their regulating hormone,

vitamin D, in uremic patients before and after broad band UVB phototherapy in order to add more to the understanding of the possible role of these two elements in the pathogenesis of uremic pruritus.

## **Patients and methods**

### **Patients**

This study was carried out on 18 patients with uremic pruritus referred by the nephrologists to the Dermatology Clinic, Kasr EL Aini hospital, Cairo University and 9 healthy volunteers who served as controls. The patients' group consisted of 10 males and 8 females and their ages ranged from 20 to 67 years. The patients' skin type was between type III and IV.

All patients were subjected to full history taking including the severity and duration of itching, a detailed history of the treatments of uremia that were received by the patient and history of other associated diseases. Careful skin examination was carried out to exclude local causes of itching, and different laboratory investigations were carried out to exclude associated systemic causes of pruritus. A written consent was signed both by the patients and the controls after explaining the aim of the work.

A 4mm punch skin biopsy and a 5cm blood sample were taken from the patients before UVB and after UVB when the patients reported clinical disappearance of itching (average after 6-13 sessions). The tissue and blood samples were used for detection of the skin and serum levels of calcium, phosphorus and vitamin D. Similar samples were taken from controls before the start of the study. All samples were stored at -20°C until processing.

## **Methods**

### **Total body UVB phototherapy:**

All patients were subjected to a total body UVB phototherapy, (UV 1000 Waldman lighting which is equipped with UVB lamps with a radiation spectrum of 285 to 350 nm with a maximum at 310 to 315 nm), treatment was given as 3 times/week. The starting dose depended on the patient's skin type, according to the schedule supplied by the manufacturer, so the starting dose was 50mJ/cm<sup>2</sup>. Every session the dose was increased by 0.05 J/cm<sup>2</sup> until disappearance of itching was reported by the patients. After disappearance of itching the sessions were withdrawn to 2

times/week for 1 month followed by once weekly for another month.

#### **Quantitation of calcium:**

The calcium level was measured calorimetrically at 546nm according to O-cresolphthalein direct method (Quimica Clinica Aplicada S.A).

#### **Quantitation of inorganic phosphorus:**

The level of inorganic phosphorus was measured photometrically at 650nm by Fiske-Subbarow, direct method (Quimica Clinica Aplicada S.A).

#### **Quantitation of 1, 25(OH) 2 vitamin (vit.) D:**

1, 25(OH)<sub>2</sub> vit. D was measured by radioimmunoassay Kit provided from Biosource Europe S.A. Prior to measurement, samples were extracted with a mix of solvents and applied on cartridges to separate 1,25(OH)<sub>2</sub> vit. D from other vit. D metabolites. A fixed amount of I<sup>125</sup> labeled 1, 25(OH)<sub>2</sub> vit. D competes with 1, 25(OH)<sub>2</sub> vit. D from extracted samples for a fixed amount of specific antibody coated on the inner surface of incubation tubes. After an overnight incubation, an aspiration followed by washing, stop the competition reaction, then tubes were counted using gamma counter.

#### **Statistical methods:**

The data was coded and entered in an IBM compatible computer using the statistical package SPSS (version 10). The data was summarized using the mean and standard deviation for continuous variables, and percent for discrete variables. Statistical differences between two independent means were tested using the student t-test. Non parametric ANOVA (Kruskal Wallis) compared more than two independent means. Correlation analysis was used to assess association between two continuous variables and the correlation coefficient was expressed as r value. P value was significant at a value less than 0.05[15].

## **Results**

#### **Subjects' Data**

The study was carried out on 18 uremic patients having uremic pruritus and 9 healthy volunteers who served as controls. The patients' group consisted of 10 males (55.6 %) and 8 females

(44.4%) and their ages ranged from 20 to 67 years (mean of  $47 \pm 14$  years). The control group consisted of 5 males (55%) and 4 females (44%) and their ages ranged from 27 to 61 years (mean of  $43.4 \pm 10.9$  years).

The duration of the CRF varied from 1 month to 180 months (mean  $37.22 \pm 46.13$  months), while the duration of pruritus varied from 10 days to 3 years with a mean of  $10.01 \pm 11.83$  months.

Ten of the patients (55.6%) were under regular hemodialysis 3 times/week, two patients (11.1%) were under regular hemodialysis 2 times/week, one patient (5.6%) was under peritoneal dialysis and five patients (27.8%) were under conservative treatment.

### **Results Of UVB Phototherapy**

Disappearance of itching occurred in all patients following UVB phototherapy. The disappearance of itching occurred after 6-13 sessions (mean of  $8.56 \pm 2.18$ ) and the total joules received until clinical disappearance of itching varied from 1.15 to 4.6 J/cm<sup>2</sup> (mean of  $2.16 \pm 0.87$ ).

### **Results Of Serum And Skin Content Of Calcium, Phosphorus And Vit.amin D Before And After Uvb Phototherapy (Tables [1](#), [2](#), [3](#))**

#### *Serum and skin content of calcium:*

Serum and skin contents of calcium in uremic patients before UVB phototherapy were found to be statistically lower than the controls ( $P < 0.001$ ), and they both increased significantly after UVB phototherapy ( $P < 0.001$ ). The serum levels of calcium were normalized after UVB phototherapy, i.e. no statistically significant difference was found between serum calcium level in controls and serum calcium in uremic patients after UVB therapy ( $P = 0.870$ ). On the other hand, though the skin content of calcium has increased significantly after UVB phototherapy, still it was significantly less than controls ( $P < 0.001$ ).

#### *Serum and skin content of phosphorus:*

Serum content of phosphorus in uremic patients before UVB phototherapy was found to be statistically higher than the controls ( $P < 0.001$ ), and it decreased significantly after UVB phototherapy ( $P = 0.001$ ), however, it remained significantly higher than controls ( $P < 0.001$ ). On the other hand, skin content of phosphorus in uremic patients before UVB phototherapy was statistically less than the controls ( $P < 0.0010$ ), and it decreased significantly after UVB phototherapy ( $P = 0.0016$ ).

### Serum and skin content of vitamin D:

Serum and skin contents of vitamin D in uremic patients increased significantly after UVB phototherapy ( $P < 0.001$ ).

## **Discussion**

The pathophysiology of uremic pruritus is still unknown. A number of different mechanisms have been proposed to explain the origin of uremic pruritus, but none of them is completely convincing. Abnormalities in calcium and phosphorus metabolism in CRF are one of the main theories that explain uremic pruritus [6,7] .

UVB Phototherapy was found to improve uremic pruritus mostly acting through a systemic mechanism in addition to its local effects, by inactivating a circulating substance or substances which are responsible for the pruritus. This mechanism is supported by the observation that exposure of one half of the body to UVB in patients suffering from uremic pruritus leads to bilateral improvement [16]. Accordingly, it was reasonable to evaluate the effect of UVB on the expected pruritogenic substances such as  $Ca^{++}$  and phosphorus, in our study, both locally in the skin and systemically in the serum.

Holick [17] found that the concentration of  $1,25 (OH)_2 D_3$  in the serum rises by about 20% within 2 days of broad band UV radiation, the rise was within the accepted normal range of 16-65pg/ ml. These data are similar to those obtained in our study; as efficient UVB exposure resulted in rise of both the skin and serum levels of  $1,25 (OH)_2 D_3$  and the mean serum level of  $1,25 (OH)_2 D_3$  after UVB therapy was still within the normal range.

Before UVB our patients had statistically significant serum hypocalcaemia. Hypocalcaemia and hyperphosphataemia are the main metabolic abnormalities in CRF, due to defective renal tubular excretion of phosphate, leading to phosphate retention and defective intestinal absorption of calcium [18] . These abnormalities usually represent a triggering factor that increases the secretion of parathyroid hormone (PTH), which increases the synthesis of  $1,25 (OH)_2 D_3$  in the renal proximal tubules, in an attempt to enhance the effect of PTH in lowering circulating or tissue phosphorus and maintaining serum calcium concentrations within the normal range [11]. Moreover, our patients had statistically significant low skin calcium and phosphorus contents than normal controls. Serum hypocalcaemia can explain skin low calcium content in our patients before UVB therapy. For calcium/phosphorus solubility product to



be constant, serum hyperphosphataemia must develop [18].

The rise in the skin content of vitamin D3 and subsequently serum content after UVB phototherapy in our study gives an explanation of changes in both the skin and serum contents of calcium and phosphorus as vitamin D3 stimulates calcium absorption from the GIT and causes rise in serum and subsequently skin calcium content. On the other hand it lowers serum and tissue contents of phosphorus. UVB phototherapy can also cause direct photoinactivation of phosphorus ions [19].

Blachley and colleagues [7] performed a study that was almost similar to this study, where they measured serum levels of calcium, phosphorus, magnesium and parathormone; in addition to tissue levels of calcium, phosphorus and magnesium pre and post UVB phototherapy in both uremic and non-uremic pruritic patients, together with normal healthy volunteers. They found a statistically insignificant rise in serum calcium and fall in serum phosphorus levels after UVB phototherapy, these results are similar to ours, but our results were statistically significant. This may be attributed to higher efficacy of newer UVB devices that give the patients the best chance of treatment.

Blachley and colleagues [7] also found that the skin content of calcium and phosphorus was significantly elevated in uremic pruritus patients than the control group, but no significant difference between the controls and the uremic non pruritic patients. Besides in our patients, tissue levels of both ions were statistically significantly lower in uremic pruritic patients than controls. This difference in the skin content of calcium and phosphorus before treatment may be related to the long term dialysis that most of our patients had already received. After UVB phototherapy, the skin phosphorus content showed significant reduction, while no significant changes occurred in tissue calcium content in the uremic pruritic patients in their study, but in our study there was a significant rise in tissue calcium content and further lowering of tissue phosphorus content which was statistically significant. Our results could be explained by changes that occurred in vitamin D both in the skin and serum.

So it appears from this study that serum hyperphosphatemia may represent a circulating pruritogenic substance that stimulate itching pathways, as all patients had hyperphosphatemia before UVB therapy and a drop in both the serum and skin levels of phosphorus was associated with improvement of pruritus.

On the other hand, our study contradicts the belief of hypercalcemia, skin calcification and microprecipitation of calcium in the skin as causes of uremic pruritus [8], because our patients with pruritus had low serum and skin calcium content before UVB



phototherapy and the clinical improvement of itching following UVB phototherapy was associated with an increase in the serum and skin calcium content. Our data may support the role of disrupted calcium ion gradient in the skin rather than calcium content in the development and/ or maintenance of pruritus and may prove that UVB restores such an abnormal gradient (7). However, our patients before UVB therapy showed significantly lower serum and skin levels of calcium than normal controls, a finding that can not be overlooked.

So we finally postulate that hyperphosphatemia, hypocalcaemia and low skin calcium content have direct relation to stimulation of itching pathways. This could act together with the previously described disrupted calcium ion gradient; however this remains to be verified by immunohistochemical studies.

Moreover, the main role of UVB in improving pruritus may be related to its systemic normalizing effect on both calcium and phosphorus (increasing calcium and lowering phosphorus). However, the persistence of statistically significant high phosphorus levels after UVB phototherapy in relation to controls and in spite of significant lowering of its level by UVB may explain the recurrence of itching after stoppage of UVB phototherapy. Further studies are needed to clarify this effect on non treated uremic pruritic patients, uremic non-pruritic patients and treated uremic pruritic patients.

## References

1. Goicoechea M; de Sequera P; Ochando A; Andrea C; Caramelo C. Uremic pruritus: an unresolved problem in hemodialysis patients. *Nephron*. 1999;82(1): 73-74
2. Tarng DC; Cho YL; Li U; Huang TP. Haemodialysis related pruritus: a double blind, placebo-controlled, crossover study of capsaicin 0.025% cream. *Nephron*. 1996; 72 (4): 617-22.
3. Imazu LE; Tachibana T; Dannok K; Tanaka M; Imamura S. Histamine releasing factor(s) in sera of uremic pruritus patients is a possible mechanism of UVB therapy. *Arch. Dermatol. Res*. 1993; 285 (7): 423-7.
4. Schwartz IF and Iaina A. Uremic pruritus. *Nephrol. Dial. Transplant*. 1999; 14: 834-39.
5. Virga G; Visentin I; La Milia V; Bonadonna A. Inflammation and pruritus in haemodialysis patients. *Nephrol. Dial. Transplant*. 2002; 17 (12): 2164-9.

6. McHenry CR; Wilhelm SR; Ricanali E. Refractory renal hyperparathyroidism: clinical features and outcome of surgical therapy. *Am Surg.* 2001; 67 (4): 310-6; discussion, 316-7.
7. Blachley JD; Blankenship DM; Menter A; Parker TF3rd; Knochel JP. Uremic pruritus: skin divalent ion content and response to ultraviolet phototherapy. *Am J Kidney Dis.* 1985; 5 (5): 237-41.
8. Memose A; Kudo S; Sato M; Saito H; Nagai K; Katabira Y; Funyu T. Calcium ions are abnormally distributed in the skin of haemodialysis patients with uremic pruritus. *Nephrol Dial. Transplant.* 2004; 19 (8): 2061-6.
9. Fjellner B and Hgermark O. Influence of ultraviolet light on itch and flare reactions in human skin induced by histamine and histamine liberator compound 48-80. *Acta Derm. Venereol (Stock.)* 1982; 62: 137-40.
10. Fjellner B. Experimental and clinical pruritus. *Acta Derm Venereol (Stock)* 1981; 97: 1-34.
11. Hollick MF, Krane SM and Potts JT. Calcium, Phosphorus and Bone metabolism: Calcium Regulating hormones. In *Harrison's Principles of Internal Medicine*. Editors; Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL and Longo DL. 14th edition, 1998; ch 353: 2214-2227. Mc Graw Hill Companies, Inc., New York.
12. Bikle DD; Nemaric MK; Whitney JO. Neonatal human foreskin keratinocytes produce 1,25 dihydroxy vit.amin D3. *Biochemistry*, 1986; 25 : 1545-8.
13. Mac Laughlin JA and Holick MF. Photobiology of vit.amin D3 in the skin. *Textbook of biochemistry and physiology of the skin*, edited by Gold Smith LA, 1983; vol 2 , Oxford university press.
14. Bikle DD. A calcitropic hormone regulating calcium induced keratinocyte differentiation. *J AM Acad Dermatol.* 1997; 37: 542-52.
15. Baumgartner TA and Strong CH *Conducting and reading research in health and human performance*. 2nd edition, 1998; McGrawHill, Inc., New York.
16. Gilchrist BA; Rowe JW; Brown RS; Steinman TI; Arndt KA. Ultraviolet phototherapy of uremic pruritus: Long term results and possible mechanism of action. *Annals of Internal Medicine*, 1979; 91: 17-21.

17. Holick MF; Krane SM; John JP. Calcium, phosphorus and bone metabolism: Calcium regulating hormones. Harrison's principles of internal medicine, 12th edition. Editors; Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL and Longo DL.1991; 339:1888. .Mc Graw Hill Companies, Inc., New York

18. Kanis JA. Renal bone disease. In Concise Oxford Textbook of Medicine.2000. Editors; Ledingham JG and Warrell DA. 4thedition; ch. 12.30: 1223-1228. Oxford university Press, Inc., New York.

19. Jiraskova M; Jirasek L; Stork J. Therapy of pruritus using ultraviolet irradiation in patients on hemodialysis. Cas Lek Cesk,2001;140(6):173-177 (abs.).