

Medication Related Cutaneous Disorders in End Stage Renal Disease Patients in Lagos.

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Bolaji Otike-Odibi, Olaitan Christiana Okunoye

Department of Internal Medicine, University of Port-Harcourt Teaching Hospital, Port Harcourt, Nigeria.

ABSTRACT

BACKGROUND

In End Stage Renal Disease (ESRD) patients, a wide range of cutaneous manifestations are present which may be due to the medications prescribed. Most patients' with ESRD are on numerous medications for their primary ailment, with transplant patients needing long term steroids and cytotoxics for allograft survival. The purpose of the study is to identify the medication related cutaneous disorders in End Stage Renal Disease patients and the causative drugs.

METHODS

A simple random sampling technique was used to select 138 ESRD patients (GFR < 15mls/min) from the Lagos University Teaching Hospital, Life Support and St Nicholas Hospital, Lagos, Nigeria as well as Renal transplant patients. Also 138 non-renal, non-hypertensive, non-diabetic patients from the medical wards of L.U.T.H, with Chronic Kidney disease stage 0, GFR > 90mls/min were used as controls. They were all examined for medication related disorders and list of drugs used collated.

RESULTS

The ESRD patients consisted of seventy six (55%) on dialysis, fifty-two (38%) on conservative management and ten (7%) post-transplant. Medication related disorders included hypertrichosis due to cyclosporine and minoxidil, gingival hyperplasia due to cyclosporine and steroid

acne from prednisolone. These skin disorders were significantly present in 14(10.1%) of the study population, while controls had no medication disorders ($X^2 = 12.7$; $P = 0.0001$). The distribution of skin disorders in this fourteen patients, showed that 7 (50%) had hypertrichosis, 5 (36%) had steroid acne and 2 (14%) had gingival hyperplasia. Five patients on dialysis had medication related disorders, with four (5.3%) having hypertrichosis and one (1.3%) having steroid acne. Four (40%) of the ten transplant patients had medication related disorders with two having gingival hyperplasia and the others steroid acne. Five patients ((9%) who were conservatively managed had medication related disorders with three having hypertrichosis and two with steroid acne. Comparison of the three groups showed significant differences with $X^2 = 10.85$; P value = 0.04.

CONCLUSION

Medication related skin disorders are more common in patients with ESRD. The leading disorders are hypertrichosis, steroid acne and gingival hyperplasia. It is important for physicians to be aware of these complications so that alternative drugs that would improve the quality of life of patients with ESRD can be used.

Keywords: *Cutaneous disorders; Medication use; ESRD/CKD.*

Correspondence: *Dr B. Otike-Odibi*
Email: *otike_odibi@yahoo.co.uk*

INTRODUCTION

Cutaneous examination of patients with ESRD has shown that 50- 100% of patients with ESRD have at least one dermatologic condition [1]. Studies have also shown that 50-100% of renal transplant recipients have a transplant related cutaneous complaint. Dermatologic disorders associated with renal transplantation are a function of the immunosuppressive medication prescribed, as well as the immunosuppressive conditions produced [2].

The best therapeutic intervention for many patients with cutaneous manifestations of ESRD is renal allograft transplantation. Unfortunately, renal transplantation has its own set of complications, predominantly resulting from the immunosuppressive medications that are essential for allograft survival. Medication related cutaneous disorders are expected because of the various medications ESRD patients use, first for treatment of their primary ailments and secondly for treatment of the end stage renal disease in addition to the maintenance of the renal allograft which requires cytotoxics and steroids.

Medication related cutaneous disorders could be viral, bacterial, fungal and parasitic infections which can all be due to drugs that cause immunosuppression. Other cutaneous manifestations include malignancies like squamous cell carcinoma, basal cell carcinoma, keratoacanthoma, Kaposi sarcoma and melanoma [1]. Other conditions like hypertrichosis, gingival hyperplasia and steroid acne can also occur.

ESRD is a major problem in the developing world due to its impact on people in their prime [3] with adverse effect on the quality of life of most patients on renal replacement therapy. This situation therefore leads to withdrawal from work and a reduction of man hours which affects the economy. Although many lives are saved and subsequently maintained on dialysis intervention, most individuals endure a great deal of morbidity as a result of the inadequacy of renal replacement therapy.

Due to the enormous morbidity and adverse impact on the quality of life which patients with ESRD experience from the disease, the addition of medication related disorders increase the burden of suffering and reduces the quality of life of these patients [3]. A good knowledge of the spectrum of medicated related skin disorders in this setting will be essential in the planning for the optimal care of these patients. It is on this background that the purpose of the study is to identify the medication related cutaneous disorders in End Stage Renal Disease patients and the causative drugs among ESRD patients in Lagos, Nigeria.

MATERIALS AND METHODS

From August 2006 to June 2007, one hundred and thirty eight (138) adult patients aged 15years and above, who fulfilled the inclusion criteria were selected by a simple random sampling technique. A minimum sample size was calculated using the formula [4].

$$n = Z^2/pq/d^2$$

where n = minimum sample size, z = standardized normal deviation(which corresponds with the specified confidence level of 1.96)

P = Best estimation of the population prevalence

$$Q = 1-p$$

d = tolerable margin of error =0.05

An estimated prevalence rate of 1/1000³ with a 5% margin of tolerable error was used to calculate the minimum sample size using the above formula. The value of 138 was obtained.

This multicenter study was conducted at 3 nephrology centers in metropolitan Lagos. They were the Lagos University Teaching Hospital (LUTH) Nephrology Outpatient clinic and Dialysis Centre and two private hospitals with significant interest in Nephrology i.e Life Support Dialysis Centre and St Nicholas Hospital, Lagos. Lagos is a cosmopolitan, multi-religious city with residents from all over the country. The centers were chosen because of their high turnover of patient's with ESRD due to their interest in nephrology.

The Medical outpatient nephrology clinic provided conservatively managed ESRD patients. Patients on dialysis came from LUTH and Life Support Dialysis centers respectively while the transplant patients were recruited from St Nicholas hospital. Controls who were non-renal, non-hypertensive and non-diabetic patients, with Chronic Kidney Disease Stage 0, and GFR > 90mls/min were recruited from the medical wards of LUTH.

A standard questionnaire was administered to each study participant. The questionnaire appraised their demographics, general examination and comprehensive dermatologic examination for lesions documented.

Ethical clearance for this study was obtained from the ethical committee of Lagos University Teaching Hospital, the management of Life Support and St Nicholas Hospitals respectively.

RESULTS

Demographics of study population:

The study subjects were made up of 55 females and 83 males. They were aged between 15 and 83 years, with a mean age \pm SD of 45.4 ± 14.9 years. The controls were made up of 56 females and 82 males; with age range of 17 to 84 years and a mean \pm SD of 45.6 ± 13.3 years. $X^2 = 0.00$; $df = 1$, P value = 1.00 (Not Significant for age).

ESRD patients were composed of 55 females with a mean age of 42 ± 14.7 years and a range of 16 - 83 years. There were 83 male ESRD patients, with a mean age of 47.6 ± 14.5 years. The age range was from 15- 78 years. The females were significantly younger. (P value = 0.02).

Table 1: showing Comparison of demographic data of cases and controls

Characteristic	Cases N = 138	Controls N = 138	Statistics
Gender			
Male	83	82	$X^2 = 0.00$; $df = 1$; $P = 1.00$
Female	55	56	
Age range (years)	15 - 83	17 - 84	
Mean age \pm SD (years)	45.4 ± 14.9	45.6 ± 13.3	$T = 0.11$; $P = 0.91$
Educational level			
Primary	17	18	$X^2 = 6.49$; $df = 3$; $P = 0.09$
Secondary	40	59	
Tertiary	77	58	
Post - tertiary	4	3	
Marital status			
Single	20	12	$X^2 = 1.73$; $df = 1$; $P = 0.19$
Married	118	126	

The treatment categories included dialysis, conservative management and post-transplant. Seventy-six (55%) were on dialysis, 52 (38%) on conservative management and 10 (7%) were post-transplant patients.

Spectrum of skin disorders:

Cutaneous manifestations were seen in 134 ESRD patients (97.1%) and 91 controls (65.9%). The difference was statistically significant. ($X^2 = 42.4$; $P < 0.0000001$) see Figure 1.

These skin disorders included general skin changes such as xerosis, pruritus, uremic frost, sallow yellow cast, hyperpigmentation, acquired ichthyosis, half and half nails and pallor. Microbial disorders observed were pityriasis versicolor, and a viral infection. Medication related cutaneous disorders consisted of steroid acne, gingival hyperplasia and hypertrichosis.

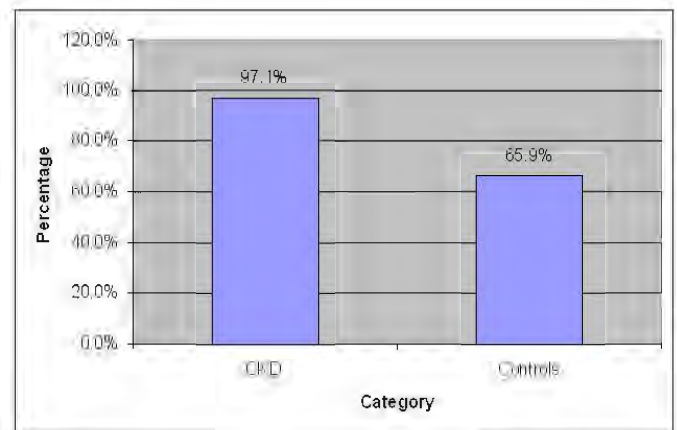


Figure 1 showing frequency of cutaneous manifestations of ESRD in Cases compared to Controls.

Impact of mode of ESRD care on prevalence and pattern of skin disorders:

Medication related disorders included hypertrichosis due to, cyclosporine and minoxidil, gingival hyperplasia due to cyclosporine and steroid acne due to prednisolone (Figure 2 and Table 2). They were significantly present in 14 (10.1%) of the study population, while controls had no medication disorder. ($X^2 = 12.7$; $P = 0.0004$).

Five (6.6%) of the seventy-six patients on

dialysis had medication related disorders, with four (5.3%) having hypertrichosis and one (1.3%) having steroid acne. Four (40%) of the 10 transplant patients had medication related disorders, with two having gingival hyperplasia and the remaining two steroid acne. Five patients (9%) who were conservatively managed had medication related disorders with three having hypertrichosis and two with steroid acne. With significant differences on comparison of the three groups: $X^2=10.85$; P value = 0.04.

Table 2: showing frequency of medication related disorders in ESRD cases

Type of medication-related disorder	Frequency N = 138	%
Hypertrichosis	7	5.1
Gingival hyperplasia	2	1.4
Steroid acne	5	3.6

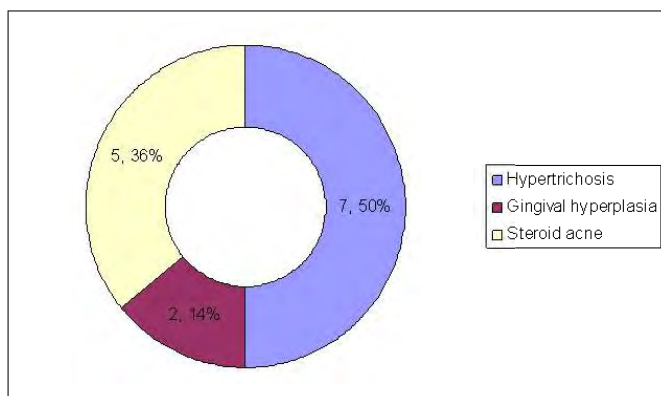


Figure 2: showing subtypes of medication related disorders amongst ESRD cases.

Role of other drugs in causing the disorders:
Other drugs used by ESRD patients in this study included anti-hypertensive such as alpha adrenergic blockers, calcium channel blockers, ACEI, beta – blockers, diuretics and vasodilators as shown in Table 3.

Table 3: showing medications utilized by ESRD cases

Drug category	Frequency	Percentage %
Antihypertensives*	77	55.1
Oral hypoglycaemics	8	5.8
Insulin	2	1.4
Cytotoxic drugs	10	7
Antibiotics (including antituberculous drugs)	5	3.5
Supplements (including calcium, iron, etc)	68	49.3
Antiretroviral drugs	5	3.5
Lipid lowering drugs (statins)	4	2.8
Antihistamines	1	0.7
Steroids	9	6.5
Diuretics	44	31.9

DISCUSSION

This study was a multicenter prospective study aimed at providing useful information on the medication related cutaneous disorders in Lagos. The mean age for subjects in this study was 45.4 ± 14.9 , which alludes to the fact that the young and active people are the one largely affected by ESRD[3]. This is consistent with studies by Pico [5] and Alebiosu [6] whose studies on Chronic Kidney disease patients had mean ages of forty five respectively.

The prevalence of cutaneous manifestations in the study population of 97.1% is high and comparable to that Pico[5] Nanette[7] and Udayakumar [8] who found cutaneous manifestations in 100% of patients studied. Nunley[1] also reported a similar prevalence of cutaneous manifestations as seen in our study. Though this prevalence reported in our study is far higher than the 50% reported by Velasco[9] in ESRD/CKD patients. Our findings are consistent with the high prevalence of cutaneous manifestations from other studies from the western world, which indicates that ESRD is a global disease with similar presentation, treatment and morbidity.

A small number of the study population had medication related disorders in contrast to the controls who were all negative. Five patients (3.6%) had steroid acne; seven patients (5.1%) had hypertrichosis and two patients (1.4%) gingival hyperplasia. This is comparable to the findings of Pico et al[5] who reported thirteen (13%) of patients with medication related cutaneous disorders. Lugo-Janer et al[10] reported more than half of subjects in his study to have medication related cutaneous disorders. The study was on transplant patients only, and they are expected to have more of these disorders because of the cytotoxic drug regimen used to maintain their transplant. Our study also showed that the transplant population had a higher prevalence of medication related skin disorders.

A greater number of transplant cases had medication disorders compared to the dialysis

category findings contrasted with about two-thirds of the dialysis population having medication disorders.

This contrast is probably due to the fact that the dialysis population in this study were on fewer medications that have been implicated with cutaneous side effects.

Gingival hyperplasia which is due to cyclosporine use was the most reported oral cutaneous manifestation.. This same pattern has been established in several studies [11-14] with a prevalence of 22% to 58%. Also, other drugs like calcium channel blockers such as nifedipine, amlodipine, diltiazem and verapamil were implicated[11-14]. This study did not show any patient with benign or malignant tumours probably because of the small number of transplant patients and also the short duration of the transplantation. This is contrasted by some studies which showed 16-39% having benign tumours (15.3%) having precancerous and neoplastic lesions[15-17]. Longer exposure to immunosuppressive drugs (> 60 months) were associated with pre malignancy and malignant lesions[15].

A single Italian center observational study showed majority of medication related cutaneous side effects, twenty six out of thirty were noted in patients who were receiving corticosteroids and especially males[13]. This is most likely due to the fact that it was also associated with outdoor jobs and unused sunscreens which is more common in males[13].

This study showed that 5(36%) had steroid induced cutaneous side effects, this was probably due to the fewer number of subjects in this study.

CONCLUSION

This study has shown that medication related skin disorders are more common in patients with ESRD. The leading disorders are hypertrichosis, steroid acne and gingival hyperplasia and the common causative drugs

are prednisolone, cyclosporine and minoxidil. It is important for physicians to be aware of these complications so that alternative drugs that would improve the quality of life of patients with ESRD can be used.

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