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RESEACH ARTICLE

PECULIARITIES OF THE EFFECTS OF CALCIUM LACTATE AND FINOPTINE ORAL ADMINISTRATION ON URINARY HYDROXYPROLINE EXCRETION IN PSORIATIC PATIENTS

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Abstract

Background of the Study: Pathogenesis of psoriasis involves disorders in Connective Tissue Metabolism (CTM) - that of collagen, elastin and glycosaminoglycan structural macromolecules. The disorder influences the production, concentration, and urinary excretion of hydroxyproline byproduct. Changes occurring in CTM are also associated with calcium ion imbalance and homeostasis in the human body. However, Finoptine is believed to have the potential for reversing the trend. **Aim of this Study**: To investigate the peculiarities of the effect of administration of finoptine on calcium ion constituent and urinary hydroxyproline concentrations excretion. **Materials and Methods:** A total of 15 subjects of between 25-40 years, comprising 8 male psoriatic patients as the experimental group and 7 apparently normal male individuals as control group were investigated. Using Stegnman-Staeder's quantitative method as modified by Utevskaya and Persky, urinary hydroxyproline was measured and documented. **Results:** It was found that calcium lactate enhanced the production of hydroxyproline in both psoriatic patients and apparently normal subjects. However, Finoptine is shown to have considerably inhibited the activity of calcium lactate, particularly in psoriatic patients as compared to the normal subjects in the control group, leading to remarkable reduction in hydroxyproline produced by the former. **Conclusion:** The effect of interaction, which appeared to have occurred between Finoptine and calcium ions, resulting in marked decrease in the stimulation and production of hydroxyproline, may serve as a useful mechanism for chemotherapy and management of psoriasis.

Key words: Psoriasis, collagen, connective tissue, finoptine

Introduction

Psoriasis is essentially a multifactorial, genetically-determined chronic immune mediated inflammatory skin disease that is characterized by hyper-proliferation of epidermal cells and inflammation [11]. Out of the five main types of psoriasis: *plaque, guttae, inverse, pustular,* and *erythrodermic*, the first (also known as *Psoriasis vulgaris*) makes up about 90% of cases of the desease and it can produce serious complications (Schett., *et al* 2022; QAP, 2013; IHME, 2021). The disease clinically presents with periodic flare-ups of well-defined red patches commonly covered by silvery flake scales, often located on the extensor surfaces and scalp, and may extend to other areas of the body (Fig. 1) (Annie. and Rachel, 2024).

The prevalence of psoriasis appears slightly higher among women. While some studies indicated the average age of onset to be 33 years of age, and that about 75% cases of the desease occurred before the age of 46 (Nevitt. and Hutchinson, 1996), others suggested that the onset was bimodal with two (2) peaks of the disease: the first between 16 and 22, and the second between 57 and 60 years of age (Theodorakopoulou., *et al* 2016). While a study indicated that psoriasis is prevalent regardless of ethnic origin in all countries

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(Alessandra-Madalina., *et al* 2023), another reported that the disease is prevalent worldwide but it frequency varies widely with ethnicity and geographical distribution (Mohd., 2018; Sergi, 2017). The prevalence of psoriasis in the world varies within 1.2-5% in the general populations; this makes an average of about 3% (or 3,000 patients per 100,000 of the human population) (Parisi, R., Iskandar, I.Y.K., Kontopantelis, E., Augustin., *et al* 2020; Sergi, 2017). The disease is rare in Africans and North American Indians (Alessandra-Madalina., *et al* 2023; Monica. and Alexa, 2013). In Nigeria, a prevalence rate of <0.1-0.5% has been reported (Olusola. and Ayesha, 2016). However, recent studies have shown increasing frequency of psoriasis (from 0.6-1.5%) among individuals attending to dermatology outpatients in different parts of the country (Henshaw., *et al* 2014). The prevalence of the disease was shown to be higher in the East than in the West of the African continent. The disorder in West Africa is similar to that found among the African-Americans; as was thought, because of the similarity in genetic ancestry (Rosa., *et al* 2020; Edward, 2016). It has been reported that Africans either lack the psoriasis susceptibility gene or have genetic factors that promote resistance to the disease (Rosa., *et al* 2020). Dietary factors have, at the same time, been thought to partly contribute to the low prevalence (Paras., *et al* 2021). The African staple diet, especially the corn, which is rich in linolenic acid, a precursor of prostaglandin E2 (PGE2) and low in polyunsaturated fatty acids encourage overproduction of PGE2, thereby suppressing cellular immunity underlying psoriasis and directly block T-cell signaling. According to Diallo (2012), the high content of polyunsaturated fats in the diet and low plasma levels of arachidonic acid contribute to the reduced prevalence of inflammatory diseases such as psoriasis.

Although other precipitating factors have been implicated in the initiation of the disease's plague, which include infectious agents such as pyogenic bacteria (e.g. staphylococcal and streptococcal species) and immunodeficiency virus (HIV) infections as well as nutrition, trauma, obesity and alcohol consumption, environmental influences (weather, cultural habits, socio-economic factors, stress events, drugs), and the epidemiology of the disease have not been adequately elucidated due to paucity of data and research (Karen., *et al* 2009). Apart from the aforementioned triggering factors, the disease has been reported to be associated with Human Leukocyte Antigens (HLA) B13, B17 and B37, all of which are linked to CW6, as well as Human Leukocyte Antigen Receptor-7 (HLADR7) (Honma. and Nozaki, 2021). Gene linkages have been found to be related to chromosomes 6p, 17q, 4q, 1q, 3q, 19q and 1q (Van de Kerkhof., 2003; Honma. and Nozaki, 2021).

Currently, psoriasis is thought to result from genetically determined immune dysregulation (innate and acquired), leading to the production of large amounts of cytokines, such as tumor necrosis factor-α, interferon-α, interleukin-12 [IL-12 (IL-2)] and recently implicated are IL-17 and IL-23, as well as interferon-gamma (Alessandra-Madalina., *et al* 2023; Psoriasis, 2019). Subsequently, as a result of the over-activeness of T-helper lymphocytes. These chemicals trigger inflammation in the skin and other organs. In the skin, the inflammation pathophysiologically produces three characteristic processes: epidermal proliferation with loss of differentiation due to abnormally rapid multiplication of keratinocytes; dilatation and proliferation of dermal blood vessels; accumulation of inflammatory cells, such as neutrophils and T-lymphocytes (Alessandra-Madalina., *et al* 2023; Armstrong and Read, 2020). In healthy skin, keratinocytes take about a month to divide, mature, migrate to skin surface, and slough off to make way for younger cells. This process in psoriasis is speeded up to as little as three to five days (Namazi, 2004). The result is thickened red skin that sheds silvery scales of keratinocytes that have matured before their time (Fig. 1) (Psoriasis, 2019; Michalek., *et al* 2017). According to these authors, the immune dysregulation is thought to be stimulated by an undetermined antigen, provoked by environmental factors such as trauma, infections, stress, drugs, sunlight, and metabolic derangement. Several genes have been associated with psoriasis. However, only PSORS1 is well-characterized and confirmed in 30-50% of patients (Honma. and Nozaki, 2021).

The different types of connective tissue are among the most advanced structural composite materials known to consist of macromolecular building blocks (Wu., *et al* 2024). In animal tissues, various highly differentiated cells, including fibroblasts, osteoblasts, odontoblasts, chondroblasts, parenchymal organs, and muscular tissues synthesize the main collagen content (Wu., *et al* 2024). Hydroxyproline is a major component of

collagen, which accounts for 13-14% of collagen's total amino acid content (He., *et al* 2023; Park, 2022; Bishnu, 2014). Various abnormalities in OHPr metabolism have been shown to play important roles in the pathophysiology and pathogenesis of many diseases [25]. Due to its highly restricted distribution in collagen, the measurement of OHPr levels can be used as an indicator of both the presence and metabolism of collagen (He., *et al* 2023; Man., *et al* 2023; Amit., *et al* 2016; Bishnu, 2014). It has been reaffirmed that the morphological changes that occur in CTM are closely related to the intensity of collagen degradation, which typically becomes higher than normal in psoriatic patients (Yan, 2017; Hergen. and Erdodan, 1995). According to these authors, such changes are also associated with disorders in calcium content, functions of calcium transporting systems in cells, and calcium homeostasis in general.

Calcium ions are universal regulators whose abnormal increase in body fluids may precipitate increase in their cytoplasmic concentration and may result in disturbances of their regulatory functions. It has been suggested that such disturbances may be normalized either through the activation of Ca-ATpase or through suppression of calcium flow, by employing blockers of calcium canal such as finoptine (Yan, 2017; Hergen. and Erdodan, 1995). This ultimately leads to the removal of excess calcium, normalize calcium ion imbalance and, thus, enhances prognosis in the management of psoriasis.

Finoptine drug (or Verapamil hydrochloride) is a synthetic derivative of papaverine, and when taken orally is well absorbed (90%) (Yan, 2017). Finoptine refers to calcium antagonists and actively inhibits its entry into the cardiac muscle cells, decreases myocardial contractility, slows down atrio-ventricular conduction.

The aim of the study is to investigate the peculiarities of the effect of administration of finoptine on calcium ion constituent and urinary hydroxyproline concentrations excretion. The following tasks were set as the objectives of the study – To determine hourly excretion of hydroxyproline in urine before and after calcium lactate intake in the control group; hourly concentrations of hydroxyproline in urine after oral intake of calcium lactate in the psoriatic patients and the control group; and hourly concentration of hydroxyproline in urine of the psoriatic patients and the control group after oral intake of calcium lactate and finoptine.

MATERIALS AND METHODS

Design of the Study

The study was partly carried out in the Kharkov Dermatology and Venerology Research Center, Ukraine, and partly in Physiology Research Laboratory of the Faculty of Basic Medical Sciences, Bayero University, Kano-Nigeria. A total of 15 subjects comprising 8 male psoriatic patients (Group A) and 7 apparently normal persons (Group B: control), of between 25 and 40 years were investigated. The two groups were further subdivided into A1, A2 and B1, B2, respectively for prospective monitoring of time-based urinary hydroxyproline content in relation to oral administration of calcium lactate and finoptine.

Group A1 consisted of 5 psoriatic patients who were fed orally with calcium lactate in order to determine the hourly trend of hydroxyproline excretion.

Group A2 consisted of 3 psoriatic patients who, after 30 minutes of oral calcium lactate administration, were, in addition, fed with finoptine.

Group B1 was a control group consisting of 2 (two) subjects. Urinary hydroxyproline in them was determined before and after the oral calcium lactate intake.

Group B2 consisted of 5 subjects (also control) with all having oral calcium lactate intake but 3 out of them were, in addition, fed with finoptine 30 minutes afterwards. The amounts of calcium lactate and finoptine given in all the cases were 0.25mg and 0.8mg per 1kg of body weight respectively (Maulik, 2019; Yan, 2017). Ethical clearance [(№ 057/23 (685/23)] was obtained from the Ethical Committee of the Faculty of Biology of the V. N Karazin Kharkov National University, Ukraine.

Analytical Determination of Hydroxyproline

The *de novo* synthesized OHPr content was estimated using oxidation and condensation methods earlier

proposed by modified Utevskaya and Persky (1982). The method was based on condensation reaction of products obtained from the interaction of hydroxyproline oxidation (pyrole) with para-di-methyl-amine-benzo-aldehyde (DABA).

Urine Hydrolysis

Briefly after receiving a consent, fresh urine ($10cm^3$) collected from each of the psoriatic patients and the control group was filtered to remove mechanical admixtures including epithelial cells, followed by hydrolysis. Two ($2cm^3$) of 12M HCl solutions were added to $2.0cm^3$ of filtered urine in a glass ampoule. The ampoule was sealed up using Bunsen flame and final hydrolysis was carried out in an air thermostat at 120ºC (± 1.5ºC) for 4 hours.

Neutralization of Hydrolyzate

The hydrolyzate obtained was neutralized using 10N, 1N and 0.01N solutions of NaOH, while the pH in each case was determined using litmus indicator paper. The neutralized solution was filtered and utilized to determine the concentration of hydroxyproline as previously described by Hergen and Erdodan (1995).

The data was expressed as Mean±SEM. Chi-square method and student's test were used to determine the differences in hydroxyproline concentration between the normal and the psoriatic patients. All the analyses were carried out using IBM-SPSS version 20.0 statistical software. $P < 0.05$ was set as the level of significance.

Colour Reaction

Reagents

№ 1 - Stock hydroxyproline standard: 1mmol (13.113mg) of L-hydroxyproline (Reanal: Hungary) was dissolved in $100cm^3$ of water and stored at 4°C. Working standards ranging from 0.05 to 2.0mmol were prepared immediately before use.

№ 2 – Stock (Initial) Buffer Solution for chloramine B: Into one-liter volumetric flask - 50g of citric acid and 120g of sodium acetate, 34 grams of NaOH were weighed and diluted to the $100cm^3$ mark with distilled water.

№ 3 - Working Buffer Solution: This was freshly prepared by mixing $500cm^3$ of the stock buffer solution, $150cm^3$ of n-propanol, 84cm3 of 96% ethanol, and $100cm^3$ of distilled water.

№ 4 – Solution of Chloramine B: Chloramine B was prepared immediately before colour reaction procedure: 1.41g was dissolved in a mixture of $10cm^3$ of n-propanol, $84cm^3$ of working buffer solution and 10cm3 of distilled water.

№ 5 – Para-dimethyl-amino-benzo-aldehyde (DABA): This was prepared by weighing and dissolving 15mg of DABA in $26cm^3$ of 60% perchloric acid and n-propanol, all adjusted to $100cm^3$ with n-propanol. This solution was immediately prepared prior to carrying out the colour reaction.

Procedure

$1cm^3$ of chloramine B solution was added to $2cm^3$ of the sample solution containing neutralized hydrolyzate, mixed well and allowed to stand for 20 minutes at room temperature. During this time, $0.5cm^3$ of n-propanol was added to the resulting mixture and agitated thoroughly. After 20 minutes, $1cm^3$ each of DABA and hydrogen perchlorate solutions were added, and the resulting solution was thoroughly mixed and heated in a water bath (ultra-thermostat U-5) for 20 minutes at 60°C. The obtained coloured solutions were cooled to room temperature and optical densities was measured on a colorimetric apparatus KFK-2MP by recording the absorption difference at $\lambda = 540nm$ between the sample and the reference, in cuvettes of 0.5cm thick. Concentration of hydroxyproline in urine samples was determined by calibration graph in which L-hydroxyproline was used.

RESULTS

The results of the investigation are presented in tables 1-3. Table 1 shows the baseline determination of hydroxyproline in urine before and after the calcium lactate intake in the control group. No significant change ($P=0.05$) in the concentration of hydroxyproline was recorded. Table 2 indicates the time-based concentration of hydroxyproline in the urine of the psoriatic patients and the control group after oral administration of calcium lactate. Significant changes ($P<0.05$) in hydroxyproline excreted in urine were

recorded at 10.00am (1.47mg versus 0.96mg) and 12.00am (0.75mg versus 0.54mg) in the psoriatic patients and the control after the oral intake of calcium lactate and finoptine. The largest concentration (20.28mg) of hydroxyproline was found in the preformed portion of night urine of the psoriatic patients. During the next hour, concentration of hydroxyproline began to decrease drastically and remained in that trend till the end of the termination time of the investigation. A significant reduction ($P<0.05$) in hydroxyproline concentration was, nonetheless, found only two hours (9.00am) in the control group (Table 3) after calcium lactate and finoptine were administered.

Table 1: Hourly Excretion of Hydroxyproline in Urine Before and After Calcium Lactate Intake in the Control Group

	Hydroxyproline (mg)	
Time	**Control Group (B), n=7**	**Psoriatic Patients (A), n=8**
8.00am	6.83±1.19	6.99±2.07
9.00am	2.20±0.75	2.37±0.35
10.00am	0.75±0.16	1.47±0.29*
11.00am	0.80±0.05	1.03±0.14
12.00 Noon	0.54±0.17	0.96±0.17*

*Significant compared to control.

Table 2: Hourly Concentrations of Hydroxyproline in Urine After the Oral Intake of Calcium Lactate in the Psoriatic Patients and the Control Group

	Hydroxyproline (mg)	
Time	**Control Group (B), n=7**	**Psoriatic Patients (A), n=8**
8.00am	6.83±1.19	6.99±2.07
9.00am	2.20±0.75	2.37±0.35
10.00am	0.75±0.16	1.47±0.29*
11.00am	0.80±0.05	1.03±0.14
12.00Noon	0.54±0.17	0.96±0.17*

*Significant compared to control

Table 3: Hourly Concentration of Hydroxyproline in Urine of the Psoriatic Patients and the Control Group After the Oral Intake of Calcium Lactate and Finoptine.

	Hydroxyproline (mg)	
Time	**Control Group (B), n=7**	**Psoriatic Patients (A), n=8**
8.00am	5.41±2.45	20.28±8.69*
9.00am	1.65±0.55	3.72±0.82
10.00am	1.69±0.69	2.27±0.82*
11.00am	1.47±1.10	1.52±0.59
12.00 noon	1.30±0.12	1.30±0.36

*Significant compared to control.

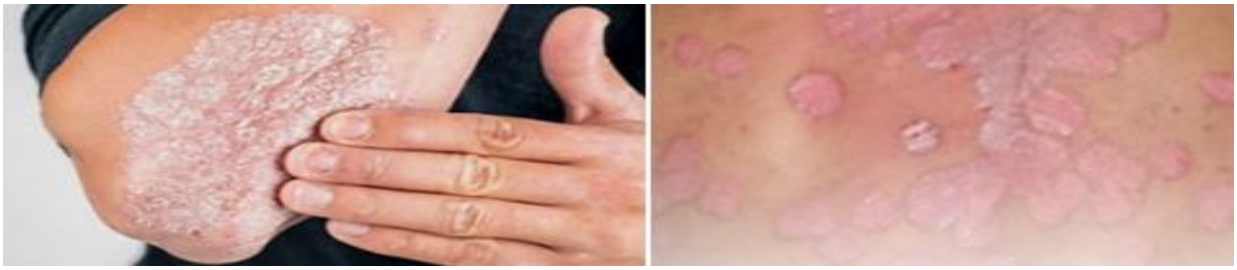

Figure 1: Psoriasis. From: free to use images of psoriasis - Search (bing.com)

DISCUSSION

Analysis of the obtained results showed that calcium lactate enhanced production of hydroxyproline in both psoriatic patients and apparently normal subjects (control group). However, finoptine considerably inhibited the activity of calcium lactate particularly in the psoriatic patients as compared to the control group, leading to remarkable reduction in hydroxyproline produced by the former (Table 3). The outcome of the study underscored the reports conducted by Schett., *et al* (2022), which reiterated that the calcium metabolic disorder that occurs during psoriasis is often manifested in the profound level of hydroxyproline produced by the victim of the disorder. The researcher further emphasized that the amount of hydroxyproline produced and excreted is directly related to the rate and intensity of *in vivo* collagen degradation effectively manifesting as skin eruption (El-ta'alu, Kot. and Persky, 2010).

The progressive but significant ($p<0.05$) decrease in the concentration of hydroxyproline excreted at 8.00am – 9.00am (range: 20.28mg - 3.72mg) in psoriatic patients (Table 3) following the oral intake of finoptine may be due to active and steady suppression of calcium flow by finoptine through appropriate substitute as earlier suggested by Maulik (2019). However, such a significant decrease in the concentration of preformed hydroxyproline in urine was not recorded in the control group (range: 1.30mg - 5.41mg) under a similar condition in the present study. This could be due to active binding of calcium ions by finoptine in psoriatic patients (due to high rate of collagen degradation), thus, inhibiting the stimulation of excessive hydroxyproline production in these patients.

CONCLUSION

There was no significant change ($P=0.05$) in the baseline concentration of hydroxyproline in urine before and after the calcium lactate intake in the control group; there were significant changes ($P<0.05$) in hydroxyproline excreted in urine at 10.00am (1.47mg versus 0.96mg) and 12.00am (0.75mg versus 0.54mg) in psoriatic patients and the control after the oral intake of calcium lactate and finoptine. The highest concentration (20.28mg) of hydroxyproline was excreted in the preformed portion of night urine of the psoriatic patients. A significant reduction ($P<0.05$) in hydroxyproline concentration was, nonetheless, found only two hours afterward (9.00am) in the control group after calcium lactate and finoptine were administered.

RECOMMENDATION

Considering the findings, challenges, and significance of this study, we recommend that production of finoptine-containing drugs may prove useful in the management of psoriasis and in the normalization, as well as the reversal of skin turnover.

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Authors' Contributions:

ABE carried out all the experiments in the methodology, while SA helped in the statistical analyses involved**.**

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