https://doi.org/10.31351/vol33iss3pp195-208

Cutaneous and Systemic Adverse Effect of Topical Corticosteroid Misuse on Iraqi Women

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Received 20/7/2023, Accepted 11/10/2023, Published 15/9/2024

Abstract

Topical corticosteroids (TCS) are the most widely prescribed and abused topical medications worldwide. TCs have melanogenic, anti-pruritic, atrophogenic, immune suppressive effects on the epidermis and sex-hormone-like, in addition to anti-inflammatory activity. Several of these, if used without judgment, may have serious local and systemic negative repercussions. The current study was a cross sectional observational study designed to evaluate the possible local and systemic effects of topical corticosteroid misuse among women in Basrah City and Amara City, Iraq. Totally 125 participants were categorized into three major groups: control individuals, patients who utilize TCs for 1–3 months, and patients with long-term TC use for more than 3 months. A questionnaire was filled out, and a full skin examination was performed by a special dermatologist. Blood was drawn for hematological (Hb, RBCs, PT and INR), hormonal (ACTH, cortisol, insulin, IL-6, testosterone and VIT-D3), and biochemical analysis (RBS). TCS abuse was linked to the development of skin conditions with various percentages and frequencies, such as erythema, photosensitivity, dryness, acne, atrophy, infections, pigmentation, hirsutism, and rosacea. TCs also have systemic adverse effects in addition to their cutaneous ones, especially with prolonged use. TCS prolongs bleeding time compared to the control group. Long-term TCS suppresses ACTH and decreases cortisol concentrations significantly (p-value less than 0.5) while having no effect on insulin or testosterone levels. Interestingly, TCS significantly (p-value less than 0.5) reduced serum vitamin D and serum interleukin 6 compared to the normal control group. TCS misuse is a big disaster in Iraq, associated with huge skin impacts and systemic deterioration, including hormonal and hematological consequences that require medical intervention and educational and legal approaches for successful treatment.
Keywords :Glucocorticoid , Misuse, Skin, Side effects, Topical corticosteroids.

التأثيرات الضارة الجلدية والجهازية لسوء استخدام الكورتيكوستيرويدات الموضعية على النساء العراقيات

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الخلاصة

الكورتيكوستيرويدات الموضعية هي أكثر الأدوية الموضعية التي يتم وصفها وإساءة استخدامها في جميع أنحاء العالم. لها تأثيرات ميلانينية ، ومضادة للحكة ، وضامرة ، ومثبطة للمناعة على البشرة وشبيهة بالهرمونات الجنسية ، بالإضافة إلى نشاطها المضاد للالتهابات الموضعية والجهازية المحتملة لإساءة استخدام الكورتيكوستيرويد الموضعي بين النساء في مدينة البصرة ومدينه العمارة، العراق. تم تصنيف إجمالي ١٢٥ مشاركًا إلى ثلاث مجموعات رئيسية: الأفراد الاصحاء، والمرضى الذين يستخدمون الكورتيكوستيرويدات الموضعية لمدة ١-٣ أشهر ، والمرضى الذين يستخدمون الكورتيكوستيرويدات الموضعية على المدى الطويل لأكثر من ٣ أشهر.

تم ملء استمارة استبيان وإجراء فحص كامل للجلد من قبل طبيب الأمراض جلدية. تم سحب الدم للتحليل الدموي والهرموني والكيميائي الحيوي. ارتبطت الكورتيكوستيرويدات الموضعية بتطور الأمراض الجلدية بنسب و ترددات مختلفة ، مثل الحمامي ، والحساسية الضوئية ، والجفاف ، وحب الشباب ، والضمور ، والالتهابات ، وصبغات الجلد ، والشعرانية ، والوردية. تحتوي الكورتيكوستيرويدات الموضعية أيضًا على آثار ضارة جهازية بالإضافة إلى آثارها الجلدية ، خاصة مع الاستخدام المطول. الكورتيكوستيرويدات الموضعية تطيل أيضًا وقت النزف مقارنةً بمجموعه الاصحاء. يقوم الكورتيكوستيرويدات الموضعية على المدى الطويل بقمع الهرمون الموجه لقشر الكضريه ويقلل من تركيزات الكورتيزول بشكل كبير بينما لا يكون له أي تأثير على مستويات الأنسولين أو هرمون التستوستيرون. ومن المثير للاهتمام ، أن الكورتيكوستيرويدات الموضعية خفضت بشكل ملحوظ فيتامين د في الدم وانترلوكين-٦ في الدم مقارنة بمجموعة الاشخاص الاصحاء الطبيعية. يعتبر سوء استخدام الكورتيكوستيرويدات الموضعية كارثة كبيرة في العراق ، ترتبط بآثار جلدية ضخمة وتدهور جهازي، بما في ذلك التأثيرات الهرمونية والدموية التي تتطلب التدخل الطبي والأساليب التعليمية والقانونية للعلاج الناجح.

الكلمات المفتاحية: جلوكوكورتيكويد ، سوء الاستخدام ، الجلد ، الآثار الجانبية ، الكورتيكوستيرويدات الموضعية.

Introduction

The most commonly used and misused topical drugs globally are topical corticosteroids (TCs)[1]. TCs are used to treat the symptoms of a variety of inflammatory dermatoses, including psoriasis, eczema, lichen planus, atopic dermatitis, lichen simplex chronicus, vitiligo, and lupus erythematosus[2]. Regrettably, because of the widespread availability of TCs as over-the-counter preparations and their bleaching and aesthetic benefits, they have been widely misused for lightening, acne, infections, pruritus, and rash[3]. Mechanistically, TCS act primarily through their genetic mechanism, the nuclear glucocorticoid receptor, which changes protein transcription. Non-genomic processes may generate certain immediate effects that the traditional glucocorticoid-receptor mechanism cannot. Most body cells have glucocorticoid receptors, which cause systemic effects. Keratinocytes and fibroblasts in the epidermis and dermis contain glucocorticoid receptors[4].

TCs have melanogenic, anti-pruritic, atrophogenic, immune suppressive effects on the epidermis and sex-hormone-like, in addition to anti-inflammatory activity. Several of these, if used without judgment, may have serious local negative repercussions[5]. Evidently, patients misuse TCs for personal reasons or because pharmacists dispense them without a prescription, and non-specialist doctors may also do so. When taken for an extended period of time, precise dermatological prescriptions, patient monitoring, and follow-up are essential to avoid the development of disastrous outcomes or adverse reactions. The diagnosis, steroid potency, delivery vehicle, frequency of dosage, course of therapy, and side effects must all be considered while prescribing TCs. Topical steroids' anti-inflammatory properties directly contribute to their effectiveness and side effects, and no one medication has been shown to have the optimal benefit-to-risk ratio[6]. The British National Formulary classifies TCs into four categories, starting with the most potent Class I and ending with the least potent Class IV. Physicians should know about one or two drugs in each potency category. High-potency formulations should only be used for a short time and are needed for places like soles and palms. Low- to medium-potency formulations can be used for a longer time for acute inflammatory lesions on the face and intertriginous areas[7].The most common TCS adverse effects are shrinkage of the skin, perioral dermatitis, striae, telangiectasia, rosacea, and hypertrichosis. Systemic impacts exist, such as glaucoma, hypothalamic-pituitary-adrenal suppression, and hyperglycemia[8].

Dependency or addiction is a key issue with long-term TC misuse, and it is thought to be the primary cause of illness flare-ups and the rebound phenomenon. The syndrome is caused by long-term inappropriate use of TC, which leads to both psychological and physical reliance on the substance. Every effort to discontinue the offending medicine results in a recurrence of symptoms, which is both physically and psychologically upsetting to the patient[9].TCs withdrawal and addiction may cause a variety of symptoms, such as searing pain, intense itching, shedding skin or desquamation, edema, serous exudate or ooze, skin sensitivity, and psychological issues that lead to long-term overuse[10].

In Iraq and other poor countries, people buy TCs without a prescription at some local pharmacies to treat a wide range of medical problems. This is against the law. It might be due to several issues, including poor education, insufficient regulatory enforcement, and low patient income. Patients' compliance and lack of knowledge of the detrimental effects of TCs are due to poor patient counseling and education or a lack of experience on the part of healthcare providers [11]. However, many cosmetics are sold without labeling, with fictitious names for herbal and natural substances or concealed identities. Clobetasol, betamethasone, and dexamethasone are often included in these products. Indeed, cheap prices and widely available fake TCs at pharmacies, stores, and marketplaces in Iraq enable facial TC usage. Lack of knowledge, an absence of limits, vendors making rapid gains, and inexpensive pricing are the primary reasons these compounds are abused in Basra city. Our city uses fake cosmetics and topical corticosteroids[12].

Aim of the study: The present study was designed to evaluate both local and systemic side effects of long-term topical corticosteroid use and abuse in corticosteroid-dependent women.

Material and Methods

Participants

The enrolled participants are females with 12-60 years old. Patients with continuous application of TCs to any part of the body for at least 30 days were recruited. We selected females with cutaneous adverse effects from TCs. This usage should have continued until the day of presentation to the center, or if discontinued, no more than two weeks before. Researchers were instructed to determine if the use of TC was suitable and warranted in each situation. Unjustifiable or inappropriate usage was defined by the following criteria: incorrect indication (e.g., acne), undiagnosed dermatitis (in the investigator's judgment), unsuitable potency, or more than 1 month of use after the previous consultation. We excluded participants who were on oral steroids for any reason, patients with any medical history of chronic diseases, patients with cardiovascular, endocrine, or respiratory problems, pregnant women, and breastfeeding mothers.

Totally 155 women using TCS were seen, but we exclude 75 patients according to our excluding criteria, 125 participants were involved in the study: 80 patients with clear one or more cutaneous adverse effects of TC abuse, while the remaining 45 individuals were considered a control group. Patients are divided into two groups depending on the duration of application of TCs: the first group of individuals utilizes TCs for 1–3 months, while the second group includes patients with long-term TC use (LTTC-use) for more than 3 months as shown in Figure 1.

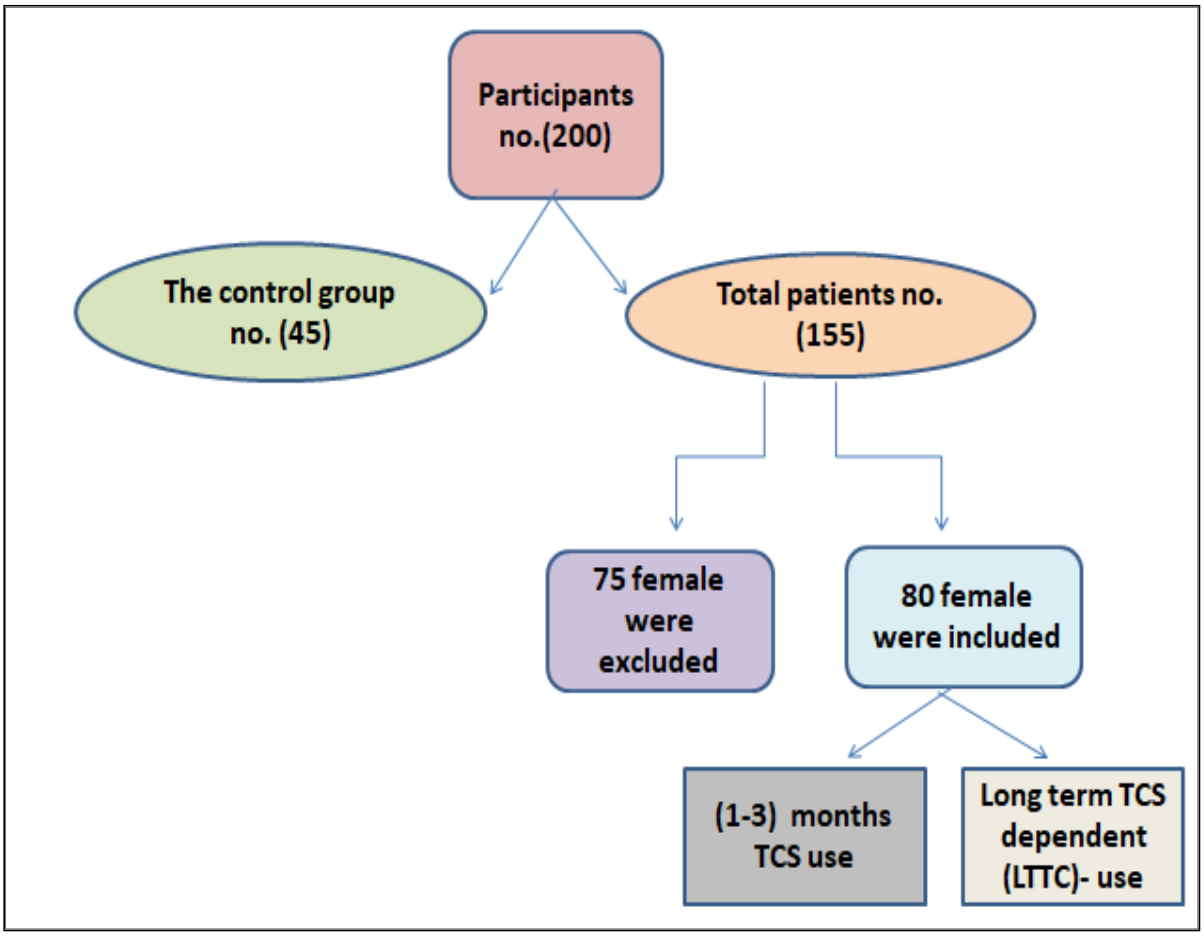

Figure 1. Flow chart shows number of participants and patients allocation.

A questionnaire

The pre-designed survey questionnaire covered exact data about age, body mass index (BMI)[13], medical, surgical, and drug histories, level of education, and material state. Key details include information about the duration of TC use, associated topical and systemic side effects, causes behind use or abuse, type of medication, dose, and dosage form. Further information about the purpose of TC use, frequency of daily application and duration, source of a drug offer, and site of application A clinical examination was performed by a special dermatologist to diagnose and determine the size,

extent, and degree of skin involvement and its adverse effects. The percentage of areas exposed was measured using the Palmer method(the simplest method, often described as representing 1% of the patient's total body surface area)[14]. Questionnaire details shown in Table 1.A digital camera was also used to capture medical situations via photography.

Measurements of the parameters

Blood investigation

The blood samples were draw between 8 and 10 a.m., one ml of whole blood in an EDTA ,then centrifuged to plasma to check ACTH by (Roche cobas e 411); 2 ml in a sodium citrate tube, plasma take to check PT and INR by (STAGO STart MAX, France); 3 ml in a gel tube, take serum, and then stored in a cold setting to prevent any effects of the environment on the samples; they were then checked for other biochemical parameters as; VitD3, IL6, cortisol, insulin, testosterone by Roche cobas e 411 and random blood sugar by cobas c111). For all patients and control groups, hormonal and biochemical test was estimated by ELISA technology.

Statistical analysis

This work was statistically evaluated using the Chi-square method for analysis. Fisher exact tests with the Koopman asymptotic score and the method of Katz to evaluate the relative risk and correlations. One-way analysis of variance with Bartlett's post hoc analysis for multiple comparisons was utilized by GraphPad Prism for Windows (version 8.0).

Table 1.A questionnaire including information's and clinical characteristics of patients.

Number of patient						
Gender						
Age						
Marital status						
Level of education						
Weight						
Length						
Disease history						
Skin diseases						
Drugs history						
Type of corticosteroids	Dermodin	Betnosam	Elica			
	H.C	Mixed				
Purpose of use	Lightening		Allergy			
	Infection					
Site of application	Face		Other			
Reason behind use or abuse	Dermatologist	GP	Pharmacist			
	Personal use	Friends				
Duration of application	30-40 days		41-60 days			
	60-90 days		More			
Frequency of daily use	One time		More			
Skin adverse effect	Acne	Erythema	atrophy	pigments		
	Hirsutism	Telengactasia	dryness	Stria		
		Photosensitivity	Rosacea	Thin skin		
Systemic side effects	Cushing					

Results

Overall, 125 females participated in the present study; of them, 80 patients were admitted to an outpatient dermatology clinic with a specified dermatological condition owing to TCS-dependent abuse or misuse. while the remaining 45 individuals represent the control group. The mean age was 26.8 years for the control group and 29.86 years for the TCSD group. TCS-dependent women had considerably higher BMI values than the control group, as shown in Table (2). No significant differences were detected between groups in terms of age, marital status, and place of residence.

Table 2. Demographic information compared control group and topical corticosteroids dependent women (TCSDW).

General characteristic	Control(n=45)	TCSDW(n=80)	P-Value
Age(Mean±SD)	26.80± 7.692	29.86±12.38	0.1354
BMI(Mean±SD)	25.91± 5.090	28.96±7.692	0.0187
Marital Status			
Married(n)	[22]	49	0.1935
Single(n)	23	31	
Residence			
Urban(n)	27	39	0.2650
Rural(n)	18	41	

The results are given as Mean ±SER, (P>0.05) no significant difference between groups , (P<0.05) significant change between groups. BMI (body mass index).

In the present work, clobetasol propionate was the most frequently used TCS on the skin, followed by betamethasone, mometasone, and hydrocortisone. On the other hand, around 42.5% of women applied mixed cream to their faces, as represented in Figure (2A). Most patients abused TCS on the face (42.4%), followed by the hands and trunk (Figure 2B), with a frequency of twice or more daily applications (51.5%) for more than 3 months (73.75%), as shown in Figures (2C and 2D).

Most patients (37.5%) used TCS for personal use, seeking cosmetic purposes. Other patients (23.75%) used topical formulations of CS according to dermatologist prescriptions for the treatment of various diseases; this percent represents the authorized medical use of TCS and requires more monitoring. Moreover, general practitioners and pharmacists prescribe and dispense TCS without evidence base and participate largely in this problem. Friends and colleagues are also engaged and contribute to TCS abuse, as shown in Figure (2E).

In this study, levels of education are considered a significant factor in TCS abuse. Most participants around two-thirds of the patients on TCS abuse looked to be uneducated or could just read and write, as documented in Figure (2F).

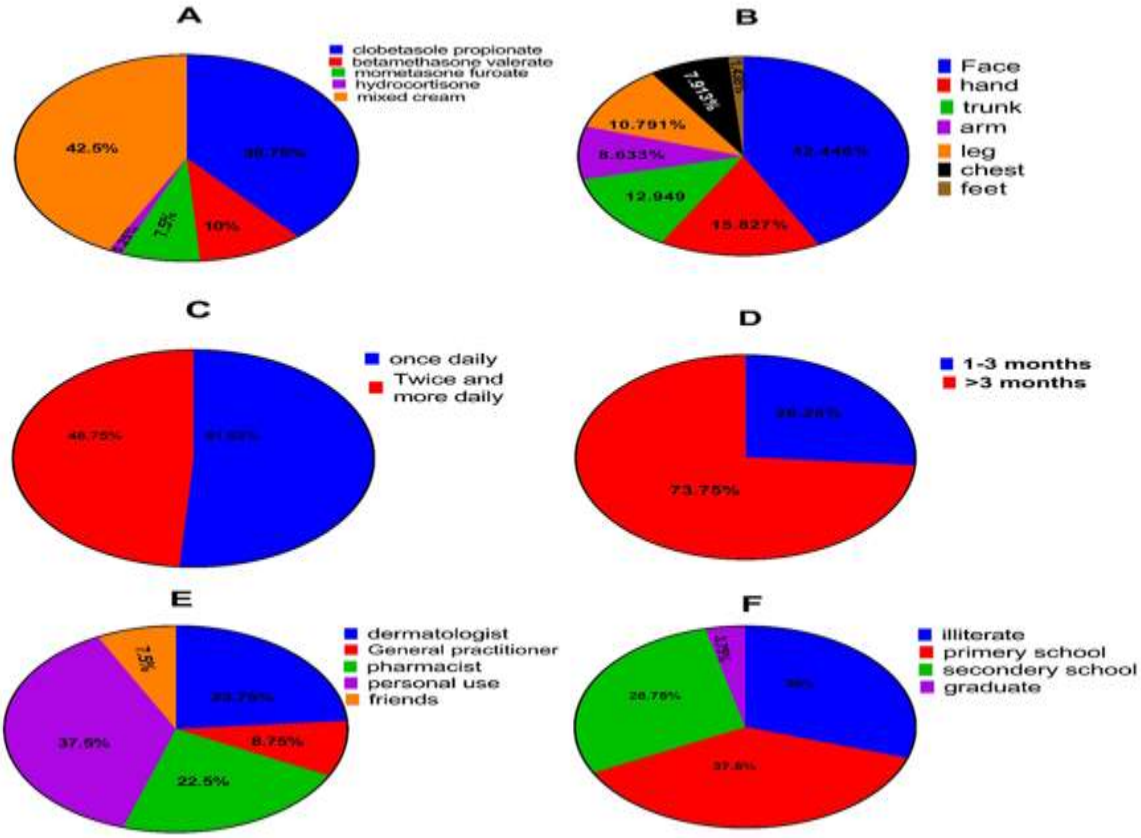

Figure 2. (A) Types of topical corticosteroid use on the skin (no. patients 80) , (B) Site of skin application of topical corticosteroid.(C) Frequency of daily use.(D) Represent duration of use (E) Source of information about use on the skin (F) Educational level of females participate in the study.

Most patients abuse TCS for cosmetic purposes on the skin for lightening, redness, and brightness, or for acne and infection. On the other hand, 25% of patients use and abuse TCs for dermatological diseases with or without prescriptions for allergies, eczema, psoriasis, and other disorders, as shown in Figure (3). The duration and time of application of TCs were known to have distinct patterns of skin adverse effects, as illustrated in Table (3).

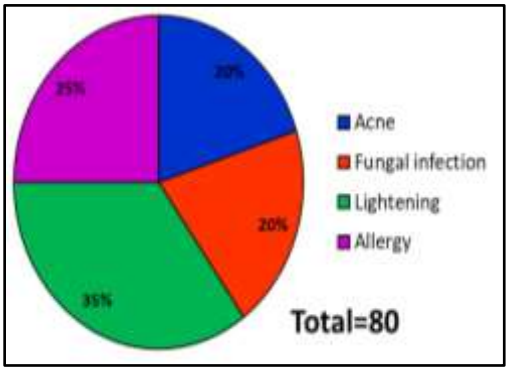

Figure 3. The purpose behind use and abuse of topical corticosteroids on the skin.

Skin side effects	1-3 months use (n=25)	Long term use (n=55)	P-Value	Relative risk
Acne	8	19	0.999	1.083
Erythema	12	37	0.1380	1.712
Atrophy	6	20	0.3140	1.525
Pigmentation	7	31	0.0325*	2.221
Hirsutism	0	5	0.0291*	5.538
Telengactasia	2	7	0.7125	1.458
Dryness	12	22	0.2113	0.6159
Stria	0	3	0.6599	1.948
Photosensitive	11	28	0.6338	1.211
Infection	4	14	0.7712	1.286
Rosacea	0	5	0.0295*	5.677
Milia	2	1	0.2288	0.4481
Thin skin	1	2	0.999	0.9351

Table 3. Observation of side effects of topical corticosteroids among study groups.
*** represent a significant difference . pigmentation, hirsutism and rosacea were significant differences in p-value less than 0.05, and other side effects had no significant change (p>0.05) between groups.**

Participants who used CS for an extended period of time (Group 3) had significant differences from Group 2 in terms of an elevated relative risk for the onset of pigmentation, hirsutism, and rosacea. In this research, TCS abuse was linked to the development of skin conditions with various percentages among TCSDW as erythema, photosensitivity, dryness, acne, atrophy, and infections as seen in Figures 4 and 5.

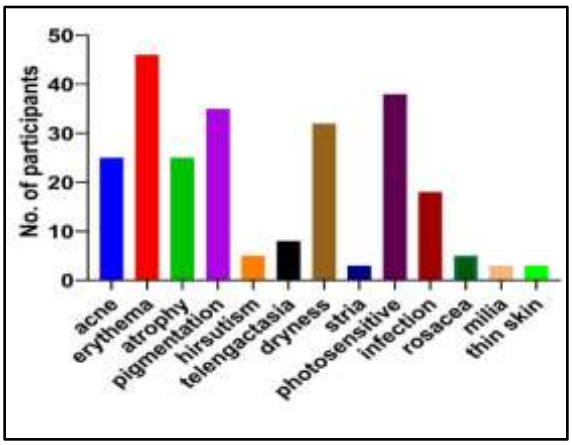

Figure 4. Cutaneous adverse effects of long-term topical corticosteroid misuse among Iraqi women (n=80).

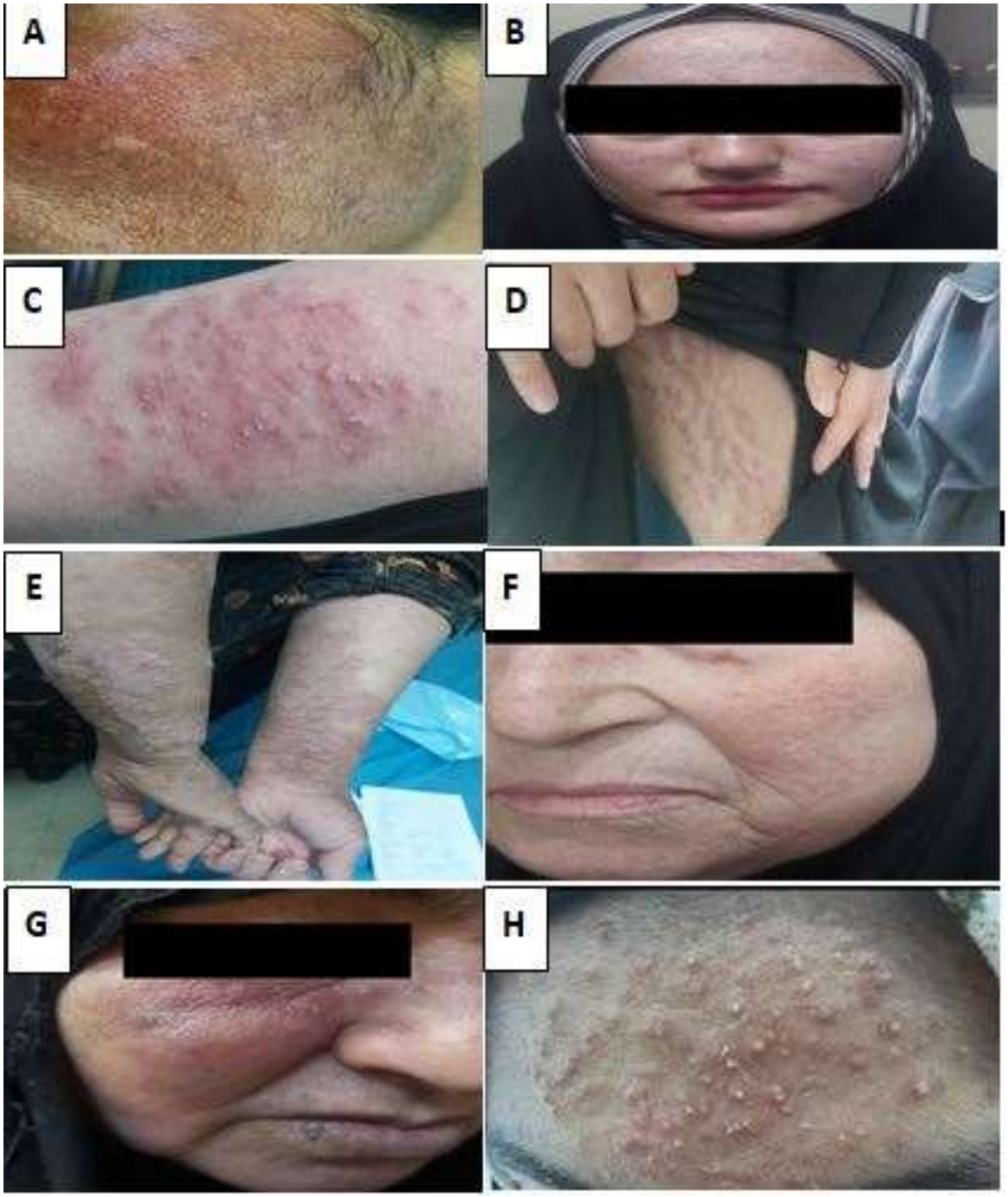

Figure 5. Pictures of patients with cutaneous adverse effects A-Erythema, telangiectasia and hirsutism on the face. (B) Erythema, Pustules, and many open and closed comedones on the forehead and acne. (C) Tinea incognito of the forearm. (D) Striae on the left thigh in a thin,16-year old female. (E) Atrophy, pigmentation in a psoriatic patient. (F) Closer view of the left cheek showing milia and thin skin along with telangiectasia (G) chronic abuse of steroids as emollient induce rosacea. (H) steroid abuse induce acne .

On the other hand, there was a highly significant elevation in PT (15.56± 0.19 Sec.) in TCS-dependent women in Group 3 compared to the control group. A significant elevation in PT in Group 2 (14.44± 0.22 sec) was observed in comparison with a control group (14.04± 0.17 sec), while INR no significant change between study groups as shown (Figure 6).

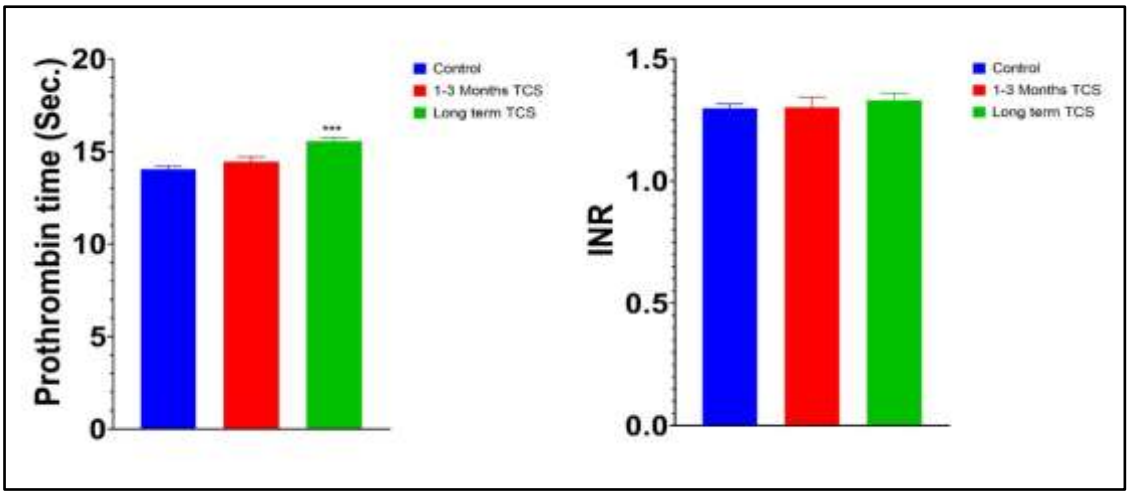

Figure 6. Effect of TCS on prothrombin time and INR among the study groups. * represent a highly significant difference P< 0.0001. INR (international normalized ratio) of the participants in the study (n=125), no significant changes were observed among groups.**

As compared to the control group and patients in Group 2 with TCs used for 1-3 months, serum cortisol levels in women on TCS for lengthy periods of time (Group 3) were considerably low as shown in Figure 7 . On the other hand, it was clearly shown that group 3 had a very significant decrease in ACTH levels compared to the other groups (p<0.0001). Figure 7 shows that the level of ACTH was substantially lower in patients with TCs abuse compared to the control group.

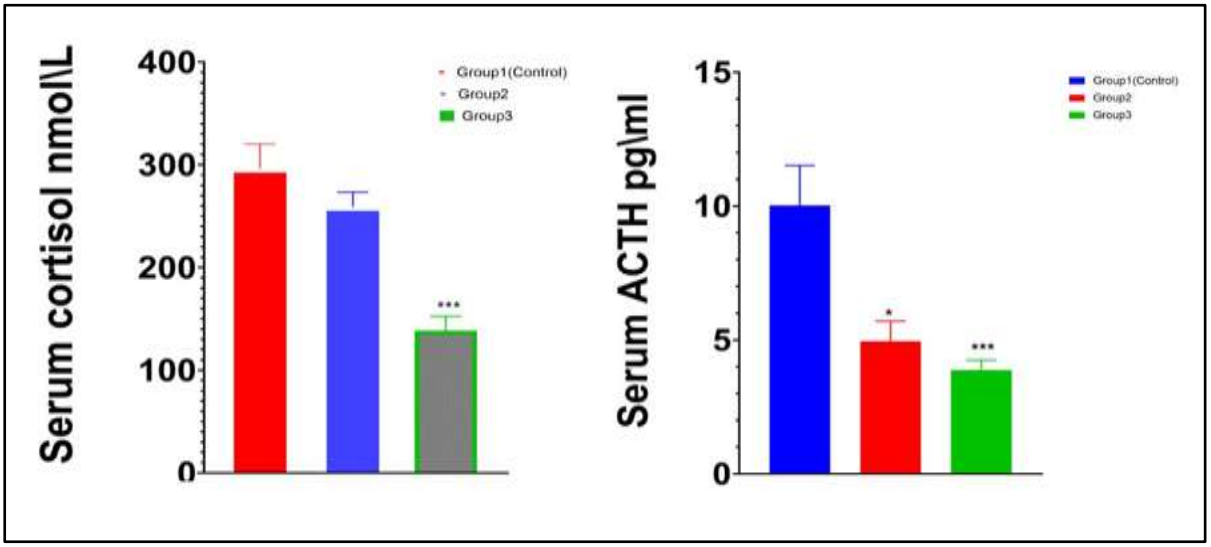

Figure 7. Effect of TCS on serum cortisol and serum ACTH of study groups. * represents a highly significant differences among groups P< 0.001. Serum ACTH (Adrenocorticotropic Hormone) levels of the subjects in the study (n=125). *** Represents a highly significant difference between groups P<0.0001. * represent significant difference among group P< 0.05.**

In the current study, serum insulin and random serum sugar (RSS) levels were evaluated and compared to the control group as shown in Figure 8. The Figure gives an overview of the considerable increase in RSS (135.42± 11.16 mg/dl) in patients who used TCs for a long duration in Group 3. On the other hand, there were no discernible variations in serum insulin levels among the studied groups.

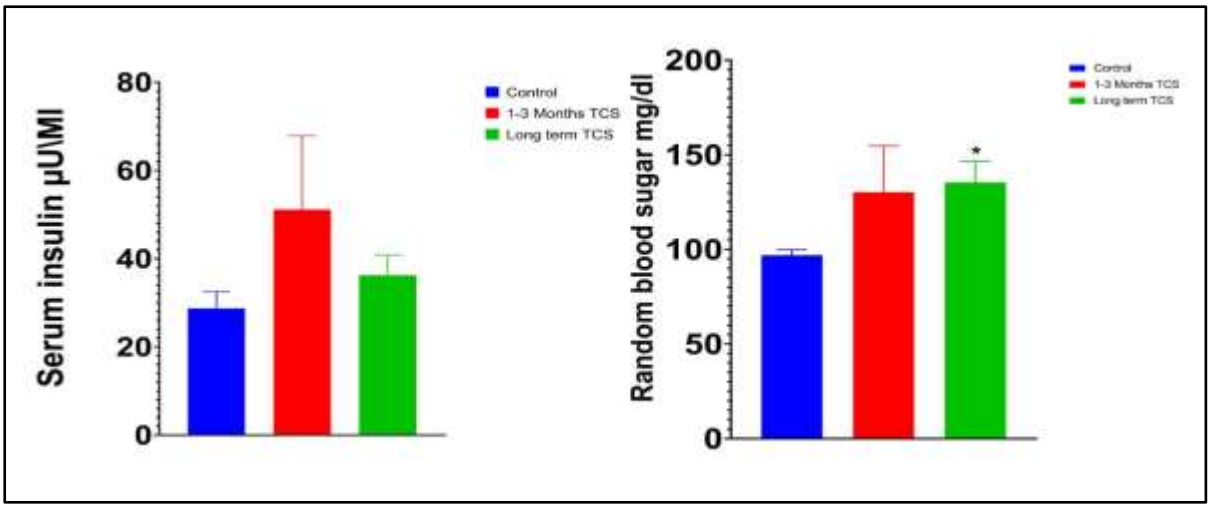

Figure 8. Impact of TCS on serum insulin and random blood sugar of study groups.No significant change between groups. RBS (Random blood sugar) of the subjects in the study (n=125).). * represents a significant difference among group P<0.05.

The most striking result to emerge from the data is that long-term TCS abuse decreases serum concentrations of IL-6 (2.19±0.24 pg\ml) significantly compared to those observed in the control group. This value refers to the systemic anti-inflammatory effect of TCS in prolonged use, as shown in Figure (9).

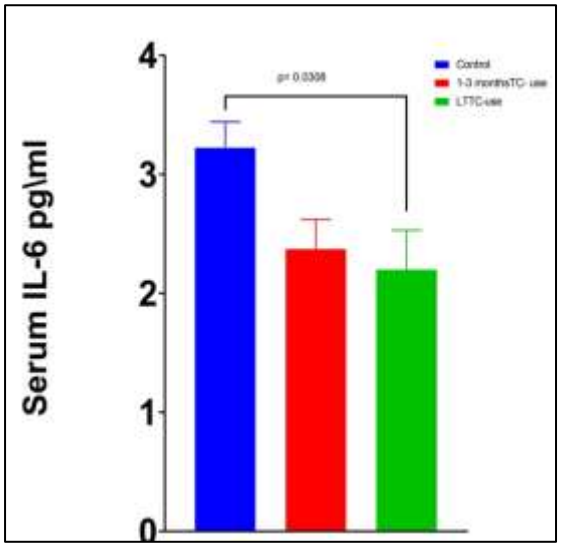

Figure 9. Influence of TCS on serum interleukine-6 of study groups. P<0.05 is considered significantly different (n=125).

The most surprising aspect of our data was the serum concentration of vitamin D (Figure 10). It has been found that there is a highly significant reduction (P<0.0001) of serum levels of vitamin D in patients with long-term TCS abuse (6.55± 0.59 ng/ml) compared to Group 2 patients and control Group 1 (24.64± 1.87 ng/ml). In addition, post hoc analysis revealed a significant difference in vitamin D levels in patients on TCS for 1-3 months (P= 0.0121) compared to the remaining groups.

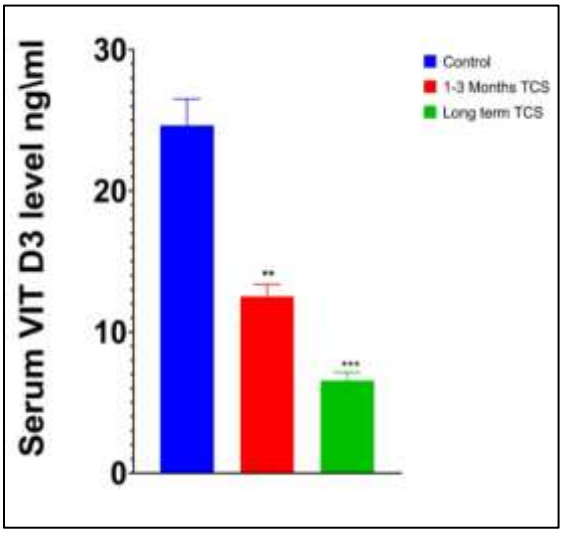

Figure 10. Impact of TCS on serum vitamin D3 of study groups. ** represents high significant difference P<0.01 , * represents very highly significant difference P<0.0001.**

In order to get complete information about the cause and side effects of TCS abuse, serum testosterone concentrations were measured in TCS-dependent women and control groups. There were no significant differences among groups (P>0.05), as documented in Figure 11.

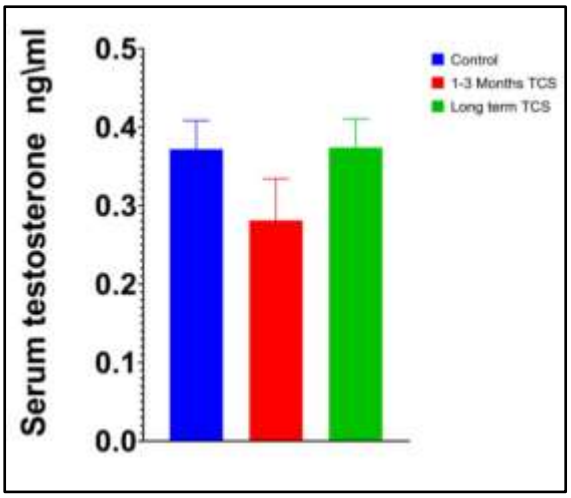

Figure 11. Effect of TCS on testosterone level of study groups. There were no significant differences among groups (P>0.05).

Discussion

Abuse and steroid dependence appear to be common problems in our country. The high percentage of patients who attend the Department of Dermatology with TCS adverse effects. This is because patients apply anything to their skin without visiting a dermatologist, which reflects a lack of knowledge and inadequate education. On the other hand, there are no strict laws or regulations limiting the sale of OTC drugs. This is the first study in Iraq that deals with the topical and systemic side effects of TCS. Actually, routine TCS abuse was prevalent and considered a big problem worldwide[8, 15-17]. Regionally, too many cases have been reported of women dependent on TCS in different governments[11, 15, 18].The recruited patients in this work, with their mean ages, seem to be consistent with the purpose behind the abuse. TCS was used by women for cosmetic and fairness reasons. Surprisingly, these products enhance the lightening of the skin[12]. In reviewing the literature, skin lightening appeared to be the most common reason for using TCS[19, 20], followed by fungal infection and acne[21]). Many potent corticosteroids, such as clobetasol and betamethasone, were illegally buried in some fake cosmetic products and sold without labeling of their constituents[22]. In tune with Jaccob et al. (2021), different women in the present study used such fake cosmetic products as mixed creams under different trade names[12]. While others prefer individual TCS like clobetasol, betamethasone, mometasone, and hydrocortisone.

An interesting finding was that the commonest site of application of TCS was on the face for cosmetic and fairness purposes. Our findings appear to be consistent with different research[5, 21]. Long-term, frequent application of more potent TCS is associated with diverse skin side effects, most often erythema, pigmentation, photosensitivity, dryness, atrophy, rosacea, and red face syndrome[6, 23]. Our results demonstrated that twice or more daily applications of TCS for more than 3 months were associated with more prominent side effects. They abuse TCS without prescriptions for personal purposes; the same findings were documented in many countries. Some of these items can be obtained locally or on the Internet. [22, 24]. Dispensing or offering TCS varied in different regions, Sonali R *et al*. found that dermatologist's prescriptions are the most common source of TCS [25], while Hon *et al*. (2006) In China, general practitioners are the most common source of TCS prescriptions, followed by newspapers[26]. On the other hand, pharmacists were the main source of TCS offerings in Asha Nyati[24]. The levels of education of patients in our study appear to be critical factors in drug abuse. In agreement with our results, Al Dhalimi M. *et al*. recorded that most of the patients with CS abuse were illiterate[20]. On the contrary, Alotaibi SH concluded that highly educated individuals are more prone to drug abuse, mainly for fake cosmetic products[8].

Our study showed erythema as the most common side effect of TCS, may occur as a result of cytokine release, nitric oxide deposits, and vasodilation[27]. Meena S. *et al*. (2017) also found that erythema was present in all patients[21]. In contrast, Asha N. concluded that the most common adverse effect was acne[28].

Prolonged use of TCs was known to have distinct patterns of skin adverse effects, as illustrated in Table 3. Participants who used CS for an extended period of time (Group 3) had significant differences from Group 2 in terms of an elevated relative risk for the onset of pigmentation, hirsutism, and rosacea.

TCS application may also cause hypopigmentation. This is more noticeable in darker skin tones, although it may occur in all skin types. After discontinuing TCS usage, re-pigmentation is common[6]. Small melanocytes' production of melanin can be inhibited by steroids, resulting in patchy patches of hypopigmentation. Steroids stimulate vellus hair growth via an unknown mechanism. Rarely are there reports of local and disseminated hirsutism caused by TCS. Various degrees of hirsutism are still the most prevalent side effect of systemic corticosteroid use. Even months after stopping the steroid medication, the darker hair may persist[26]. Within six months, TCS use results in an acne rosacea-like condition due to an increase in Propionibacterium acnes and Demodex folliculorum. This condition is also known as "iatrosacea" "topical steroid-dependent face" (TSDF), and topical steroid-induced rosacea-like dermatitis" (TCIRD)[29].

The most important clinically relevant finding was the systemic side effect of TCS. These adverse effects are comparable to those of parenteral or oral glucocorticoids but less severe. However, many factors influence the severity of systemic

adverse effects, such as the period of systemic contact with the drug, the quantity of drug applied or absorbed into the system, the drug absorption vehicle, the total surface area exposed, the site of application, the chemical properties of the TC formulation or its molecule, and skin condition[30].

In our findings, there was a highly significant prolongation in PT with long-term TCS use compared to control but no significant difference in INR. Similar results were also noted by Czarnetzki C *et al*., who showed that dexamethasone was associated with an increased risk of bleeding[34]. Similarly, inhaled corticosteroids use in COPD patients increased the risk of ecchymosis (bruising) and bleeding from thin skin[35]. Bellis J. *et al*. found that long-term glucocorticoid use can result in coagulopathy, GI tract bleeding, and venous thromboembolism[36, 37]. Recent evidence indicates that short-term use of steroids increases the risk of coagulopathy[38]. In contrast to our results, Majoor C. *et al*. found that high-dose oral glucocorticoids are associated with decreased PT[39].

Our results revealed that serum cortisol and ACTH levels were significantly low. Short-term administration of TCS was associated with a non-significant reduction of cortisol but not ACTH compared to the control group. Mechanistically, exogenous TC molecules can inhibit the release of CRH and ACTH, resulting in reduced adrenal gland stimulation and low levels of naturally produced cortisol[30].

A significant amount of TCS can be absorbed through the skin into circulation, which can lead to high blood sugar and the unmasking of latent diabetes mellitus. This occurs via multiple mechanisms, such as stimulating the activity of rate-limiting enzymes, enhancing the transport of alanine, an essential substrate for gluconeogenesis in the liver, and making the body less sensitive to insulin[26].

In the current study, serum insulin and random serum sugar (RSS) levels were evaluated and compared to those in the control group. Also, B. Sitte *et al*., observed increased levels of glucose in TCS-treated skin from responders[40]. Unfortunately, few studies have been carried out on TCS use causing hyperglycemia[41-43].

In our results, there were no significant variations in serum insulin levels among the studied groups. However, another study by Hwang JL *et al*., (2014) that showed significant differences in insulin levels and steroid-induced insulin resistance will provide insight into future diabetes prevention efforts and targeted therapies[44]. Long-term glucocorticoid exposure induces a diabetic-like condition owing to a rise in blood sugar, while low glucocorticoid amounts cause hypoglycemia, reduced glycogen storage, and insulin hypersensitivity[45]. It synergistically inhibits insulin release from pancreatic beta cells and induces insulin resistance, resulting in reduced glucose absorption and consumption in target organs (adipose tissue and muscles)[44].

The most amazing finding we can get from our results is that chronic TCS misuse significantly decreases IL-6 blood levels compared to the control group. This was consistent with the findings of Gras MP *et al*., who noted that TCS-induced down-regulation of pro-inflammatory cytokines[46] ; also, the study of Uva L *et al.*, found that the activity and expression of several cytokines associated with inflammatory diseases may be inhibited by treatment with GC[47]. TCS have anti-inflammatory effects. The glucocorticoids' most significant therapeutic properties are their strong anti-inflammatory and immunosuppressive abilities. Glucocorticoids' therapeutic effects are the consequence of many activities. Furthermore, these medicines inhibit leukocyte and macrophage responses to antigens and mitogens. CG also reduces pro-inflammatory cytokine synthesis and release. They interfere with the release of arachidonic acid (the precursor of leukotriene's and prostaglandins) from membrane-bound phospholipids by inhibiting phospholipase A2. Prostaglandin and leukotriene synthesis are thought to be key to anti-inflammatory effects. Finally, these drugs have an effect on the inflammatory response by stabilizing basophil membranes and mast cells, which results in reduced histamine release[48].

The most interesting aspect of our data was the highly significant reduction of serum levels of vitamin D in patients with long-term TCS abuse. Sanchez-Armendariz K. (2018) observed that TCS is associated with a decrease in serum Vit D3 levels to less than 20 mg/mL[49]. Vitamin D is a well-known seco-steroid with the ability to modulate calcium absorption during osteogenesis. In addition, vitamin D influences several biological processes, such as cell proliferation and differentiation, apoptosis, and inflammation[50] . TCS increases urine calcium excretion and decreases intestinal calcium absorption, resulting in a negative calcium balance through an anti-vitamin D action[47, 49].

The present findings revealed that serum testosterone concentrations were measured in TCS-dependent women and control groups. There were no significant differences among the groups. These findings match those of Borges C *et al.*, who found that the use of betamethasone did not change testosterone levels in male rats[51]. In contrast, Alison Stout *et al*., (2019) examined testosterone blood levels following intra-articular glucocorticoids, which have several systemic effects and were found to lower testosterone serum levels[52]. Growth hormone (GH), testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and synthesis are all reduced by GC[53].

Conclusion

TCS misuse is a big disaster in Iraq associated with huge skin impacts, such as erythema, photosensitivity, dryness, acne, atrophy, infections, pigmentation, hirsutism, rosacea, and systemic deterioration, including hormonal (ACTH, Cortisol, Vit D, IL-6) and hematological (Hb, RBCs, PT) consequences that require medical intervention, educational and legal approaches for successful treatment.

Acknowledgment

Authors thank the college for continuous support. Thanks to staff of Abu AL-Khasib Hospital and AL -Sadr Teaching Hospital.

Funding

We were not funded by anyone.

Conflicts of Interest

No think declared

Ethics Statements

This was a cross-sectional observational multicenter study carried out from October 2022 to March 2023. Patients were admitted to outpatients dermatology clinics at Abu-al Khasib Hospital in Basra City and Al-Sadr Teaching Hospital in Al-Amara City, Iraq. Informed consent was obtained according to the Helsinki Declaration, and the study was authorized by the ethical committee at the Basra University College of Pharmacy (EC 10 in 2022).

Author Contributions

The authors confirm contribution to the paper as follows: Teeba .H .Sagban, Abdullah. Ayob Yaqoub,Ausama Ayob Jaccob and Huda.A. Khadim declare that they have no conflict of interest Author; data collection:Teeba.H.Sagban, Abdullah. Ayob Yaqoub., Huda. A. Khadim; analysis and interpretation of results:Teeba.H.Sagban and Ausama Ayob Jaccob; draft manuscript preparation: Teeba.H.Sagban, and Ausama Ayob Jaccob. All authors reviewed the results and approved the final version of the manuscript.

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