بسم الله الرحمن الرحيم

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Serum 25-Hydroxy Vitamin D Levels Among Adults Patients with Acne Vulgaris in khartoum state

مستويات 25هايدروكسي فايتمين د في مصل المرضى السودانين البالغين المصابين بحب الشباب في ولاية الخرطوم

A dissertation submitted for partial fulfillment for the requirement of M.Sc degree in Medical Laborotary Sciense-Clinical Chemistery

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قال تعالى:

وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ

صدق الله العظيم

سورة الشعراء الآية 80

Dedication

This thesis is dedicated to

My great parents who are behind any success in my life.

My great teacher though our learning journey

My beloved brothers and sisters

My friends who encourage and suppot me

The sudan university, my second magnificent home

All people in my life who touch my heart

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Abstract

Background: Acne vulgaris is a common chronic inflammatory disease of the skin. Vitamin D plays an important role in the immune system, and its deficiency has been implicated in various skin diseases, including atopic dermatitis and psoriasis.

Objectives: The aim of this study wasto evaluate the serum 25 hydoxy vitamin D levels among patients with acne vulgaris .

Methods: This study was a cross sectional case control hospital base study performed in Khartoum state at military Hospital department of Dermatology and venerology, 60 samples were collected from patients suffering from acne vulgaris. Acne severity was classified according to Global Acne Grading System (GAGS). In addition 60 samples were collected from healthy individuals sex and age matched as control group .The levels of serum 25 hydoxyvitamin D was measured in each group by immunoassay analyzer cobas-e-411-2ed generation platform of Electrochemiluminescence binding assay (ECLIA).

Results: The study showed significant decrease in the 25 hydoxy vitamin D concentrations in acne vulgaris patients when compared with the control group (13.7 ± 5.07 ng/mL vs 24.8 ± 11.0 ng/mL) ($p = 0.00$) .The study observed significant decreased in serum 25 hydoxy vitamin D levels with increaseacne grading, mild 11 patients (18.3%) (16.8 ± 3.42 ng/mL), moderate 37 (61.7%) (13.9 ± 4.33 ng/mL) and severe 12 (20%) (10.4 ± 1.64 ng/mL) ($p = 0.01$).The present study showed no correlation between vitamin D levels (ng/ml) and age (years), BMI (kg/m^2) in study group. On the other hand significant correlation was noted between serum vitamin D level (ng/ml) and expoture to sunlight in acne vulgaris patients ($r = 0.36$, $p = 0.04$).

Conclusion: This study revealed that serum vitamin D levels are significantly decreased in patients with acne vulgaris .

المستخلص

المقدمة

حب الشباب الشائع هو مرض التهابي مزمن شائع في الجلد يظهر عادة في المراهقين . يلعب فيتامين (د) دورًا مهمًا في الجهازالمناعي وقد ظهر نقصه في الأمراض الجلدية المختلفة ، بما في ذلك التهاب الجلد التأتبي، الصدفية و حب الشباب.

الأهداف

لتقييم مستوى فيتامين (د) في المصل بين المرضى الذين يعانون من حب الشباب ، وربط العمر ، مؤشر كتلة الجسم ، ضوء الشمس ، درجة ومدة حب الشباب الشائع مع مستوى فيتامين (د) في المصل.

الطريقه

كانت هذه الدراسة عبارة عن مقطع عرضي ، تم إجراؤه في ولاية الخرطوم في قسم المستشفي العسكري للأمراض الجلدية والتناسليه ، وقد تم جمع 60 عينة من المرضى الذين يعانون من حب الشباب الشائع، تم تصنيف شدة حب الشباب وفقا لنظام التصنيف العالمي لعلاج حب الشباب، بالاضافه الى 60 عينه اخرى تم جمعها من الافراد الاصحاء مطابقه لجنس و العمر، تم قياس مستويات فايتمين د في المصل لكل مجموعة من قبل منصة التحليل المناعي كوباس .

النتائج

أظهرت الدراسة انخفاضاً ملحوظاً في تراكيز فيتامين (د) في مرضى حب الشباب الشائع بالمقارنة مع المجموعة المرجعية (13.6 ±5.07) (24.8 ±11.0) القيمه المعنويه = 0.00 ، وقد لاحظت الدراسة نقصان فيتامين (د) مع تطور حب الشباب، 11 مريض بسيط (18.3%) (16.7 ±3.42 نانوجرام//مل) معتدل37 (61.7%) (13.9 ± 4.33 نانوجرام/مل) وحاد 12 (20%) (10.4 ±1.64 نانوجرام/مل) (القيمه المعنويه = 0.01)، وأظهرت الدراسه عدم وجود إرتباط بين العمر، كتلة الجسم و معدل فايتمين (د)، كما أظهرت الدراسه وجود إرتباط ضعيف بين مستوى فايتمين (د) و التعرض لأشعة الشمس في مرضى حب الشباب (معامل بيرسون للإرتباط = 0.36) (القيمه المعنويه = 0.04)

الإستنتاج

خلصت الدراسه بأن إنخفاض فايتمين (د) أحدأسباب حب الشباب ووصف فايتمين (د) كعلاج يساعد في زيادة معدل نجاح علاج حب الشباب .

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Chapter One

Introduction, Rationale and Objectives

1. Introduction, Rationale and Objectives

1.1 Introduction

Acne Vulgaris (AV) is defined as a chronic inflammatory dermatitis of the pilosebaceous unit consisting of open and/or closed comedones and inflammatory lesions, papules, pustules, or nodules (Strauss et al., 2007).

However, new studies have shown that acnes can continue well into adult life, with a 1% (male) and 5% (female) incidence in those over 40 and a 8% (male) and 18% (female) incidence in those over 25 (Goodman., 2006). It is considered a disease of the pilosebaceous gland, and typically occurs during endogenous hormonal stimulation or alteration of prior gland function, resulting in bacterial overgrowth and inflammation this causes the corporal distribution of the disease to most prominently affect areas of high pilosebaceous gland density, the face, neck, chest and back (Knutsen et al., 2012).

There are four main factors that contribute to the pathogenesis of acne: sebaceous gland hyperplasia causing increased sebum production, altered epithelial differentiation of the pilosebaceous unit, bacteria Propionibacterium acnes (p.acne), and inflammation. Sebum is a secretion from sebaceous glands that provides a lipid-rich growth medium for P.acnes. AV is a distressing condition related to the pilosebaceous follicle and which is considered as an adolescent disorder rising as a result of androgenic changes in serum sexual hormones .It is characterized by spontaneous resolution in the late teens or early twenties in the majority of cases (Dreno and Poli., 2003).

However, after reaching adulthood, age20 or up, it has been found that 73.3% of the population has experienced acne at some point with females being affected more. Studies shows that increased stress levels are associated with increased acne severity. The National Institutes of Health (USA) shows that stress can cause acne flare. In Singapore, study of adolescents observed positive correlation between stress levels and acne severity (Suva et al., 2016).

Symptoms of acne are divided into three categories: mild (clogged pores in the skin), moderate (appearance of pimples), and severe (higher counts of pimples and appearance of reddish and painful nodules). the pathogenesis of adult acne, due to a

disease of the pilosebaceous follicle are the most common chronic skin disorders, is attributed to multiple factors such as increased sebum production, alteration of the quality of sebum lipids, inflammatory presses, dysregulation of the hormone microenvironment, interaction with neuropeptides follicular hyperkeratinisation and the proliferation of p.acne within the follicle (Makrantonaki et al., 2011).

Vitamin D as an antioxidant agent, regulate concentrations of calcium, phosphorous, and magnesium in the blood stream and contribute to bone growth. Over the past decade, vitamin D has recognized to function as a hormone and has been linked to a variety of additional body functions, such as immune system regulation and associated conditions, including autoimmune disorders, cardiovascular disease, and cancer (Mansoor et al., 2012). It seems that vitamin D makes superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) which were found at lower levels in papulo-pustular cases of acne vulgaris .Recently, sebocytes were identified as bioactive vitamin D responsive target cells, indicating that vitamin D analogs may be effective in the treatment of acne (Lee et al., 2013). Vitamin D deficiency is very common. It's estimated that about 1 billion people worldwide have low levels of the vitamin D in their blood , 41.6% of adults in the US are deficient. This number goes up to 69.2% in Hispanics and 82.1% in African-Americans (Yildizgoren., 2015).

1.2 Rationale

Acne vulgaris is the most common skin disorder occurring during the second and third decades of life. It is an inflammatory skin condition brought on by overactive sebaceous glands (oil glands). It usually involves the face (99%), frequently the chest (15%) and back (60%). At puberty the oil glands in the skin begin producing an oily material called sebum, ranging from mild comedonalacne with or without sparse inflammatory lesions (IL), to acne conglobate or aggressive fulminate disease with deep-seated inflammation nodules and in some cases associated systemic symptoms.

According to some reports in the literature lower vitamin D levels increase the susceptibility to acne vulgaris. Vitamin D is fundamental for human health, It is fat soluble vitamin which absorbed well with fat and is stored in the liver and fatty tissues. The main role of vitamin D in the body is to manage blood levels of calcium and phosphorus, these minerals are important for healthy bones. The prevalence of acne vulgaris in adolescents ranges from 35%-90% with some racial variation, being more in white than in black Americans.The peak in prevalence and severity is in the age range 14 -17 years for females and 16 - 19 years for males (Burton et al., 1971).

The good natural sources and supplementation with vitamin D will decrease the presence and severity of acne vulgaris in adolescents and young adults. Hence this study is designed to highlight the relationship between serum 25-hydoxy vitamin D level and acne vulgaris in Sudanese people.

1.3 Objectives

1.3.1 General objective

To determine the serum of 25-hydroxy vitamin D levels in Sudanese patients with acne vulgaris at Khartoum state.

1.3.2 Specific objectives

- To compare between means serum 25-hydroxy vitamin D levels in patients with acne vulgaris and control group.
- To compare between means serum 25-hydroxy vitamin D levels in patients regarding sex, family history, smoking, and uses of sun block.
- To compare between means serum 25-hydroxy vitamin D levels according to acne grading in patients with acne vulgaris.
- To correlate between serum 25-hydroxy vitamin D levels with age (years), BMI ($kg/m_{2)}$ and duration (months) in the study group.

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Chapter Two

Literature Review

2. Literature Review

2.1 skin physiology

Skin is the largest organ and visible tissue in human body. By its average size of 1.5–2.0 m^2 and amount of approximately 5% of adult's body mass it is also the biggest individual organ. The thickness of skin depends on the area where it is located, but without the under most layer, subcutis, the average thickness differs between 1- 4 mm.

Skin has multiple functions. It is in a key role working as a protective layer against harmful and lethal factors, such as impacts, UV-light, mechanical , bacteria and viruses. On the other hand, it works as a storage for blood and fat. Skin also has a major role in body's thermoregulation via blood flow and sweating and it is in skin where body produces most of the vital vitamin D. Through the neural endings skin also offers brain the ability to sense, for example pressure and heat (Hiltunen et al., 2010).

The skin is made up of cells like fibroblasts, macrophages and adipocytes embedded in an extra cellular matrix (ECM) consisting of ground substance and fibers formed by collagen and elastin along with glycosaminoglycans (GAG), proteoglycans and glycoproteins. And although skin has the ability to repair itself, bruises, wounds and scratches have a tendency to leave a mark, even after a full recovery (Kanitakis., 2002).

2.1.1 Layers of the skin

Skin has a layered structure. Light's ability to penetrate the layers of skin varies a lot, which is caused by the structure, density and thickness of the layers (Kanitakis., 2002). The topmost layer of skin, stratum corneum, is composed of dead cells from the epidermis below. The layer is very thin but thickens if continuous stress is applied (Hiltunen et al., 2010).Stratum corneum is also very transparent and therefore it doesn't absorb light well , the incoming light gets through easily (Donner et al., 2006). The layer below, epidermis, it is stratified squamous epithelium constantly discarding dead cellular content to stratum corneum by renewing itself. Epidermis doesn't contain blood vessels and its thickness varies from 0,05 mm to 0,20 mm.

Also epidermis is often held the actual topmost layer of skin, because of the fact that stratum corneum is composed solely of the dead cells from epidermis and it is contains most of the skin's melanin (Hiltunen et al., 2010) .

Therefore epidermis is responsible for toning the skin either light or dark and causing the effect of tanning when skin is exposed to the sunlight. Dermis is a layer with a dense network of blood vessels. It's thickness varies between 0.5-1.5 mm and it is mostly made of connective tissue, which has a great importance on enhancing the skin's mechanical endurance (Chu.,2008) . Because of the high number of blood vessels, dermis appears red and tints the skin slightly reddish. The under most layer of the skin, subcutis, has the greatest volumetric variation of all the layers. It is formed of loose connective tissue and adipose tissue and it can be found in many different thicknesses. Even though in many parts it tends to be thin, the thickness of subcutis can normally differ from 2 mm up to 100 mm. The thicker the subcutis gets the more rare it is, but especially overweight people can have subcutis as thick as 10 cm on their abdominal and pelvis regions (Hiltunen et al., 2010).

2.1.2 Skin diseases

the skin is an active immunological organ, possibly associated with certain systemic diseases. The skin may also show secondary signs of other conditions, such as endocrinological or malignant diseases. Skin health affects the individual's self-esteem. Skin diseases are common in all age groups (Seri et al., 2005). For example, it is known that up to 20% of children suffer from atopic eczema and nearly everyone has some form of acne during their adolescence (Williams et al., 2012).

The overall prevalence of skin disorders and their associative factors is incomplete, skin diseases are common and are the fourth leading cause of nonfatal disease burden worldwide (Hay et al., 2014). Approximately one in every three general practice patients have a dermatological problem and in more than half of these, the skin problem is the primary reason for medical consultation (Seri et al., 2005). Skin diseases are rarely fatal but often chronic in nature causing disability and decreasing daily quality of life (Hay et al., 2014). The most frequently seen skin diseases are eczemas, with a prevalence of 9.1%–31.6%, the prevalence of sebaceous gland diseases increases towards adolescence and acne vulgaris is most common in people between 12 and 17 years of age (Tamer et al., 2008).

2.1.3 Acne vulgaris

Acne vulgaris (AV) is a well known chronic involvement of sebaceous follicles which commonly targets individuals face, chest and back. The disease is usually triggered in adolescents among whom sebum production is rising as a result of androgenic changes in serum sexual hormones. Otherwise, children would be also affected. Furthermore, this has not been very rare that some cases with acne vulgaris suffered from the disease for the rest of their lives (Toossi et al., 2015).

An extreme proliferation of Propionibacter acnes founds to be the main predisposing factor in acne vulgaris, This gram positive anaerobic bacterium settles in skin follicles which are usually bulged and ruptured due to bacterial proliferation to distribute local inflammation followed by papules and pustules creation, AV is not indeed terminated at the above condition and there are several consequences such as erythema, post-inflammatory hyperpigmentation (PIH) and scars, Serious aftermaths would be named as fulminant acne, acne conglobuta, septic hydradenitis, acne excoriee and acne mecanica (Toossi et al., 2015).

Acne is considered a chronic disease owing to its prolonged course, pattern of recurrence and relapse, and manifestations such as acute outbreaks or slow onset. Moreover, acne causes profound negative psychological and social effects on the quality of life of patients (Gollnick et al., 2008).

2.1.3.1 Epidemiology of Acne vulgaris

Acne affects approximately 9.4% of the world wide population; it is more common in females 9.8% compared to males 9.0%. It affects about 90% of people during teenage years and sometimes in adulthood. Acne affects 40 to 50 million people which is about 16% in the United States and approximately 3 to 5 million people which is about 23% in Australia, in the United States it is more severe in Caucasians than African descent people, in over 40 years old subjects about 1% of males and 5% of females have problems (suva et al., 2016). About 20% people have moderate and severe cases, acne rates are low in rural areas, it affects all ethnic groups' people and it is not clear if race affects rates of disease (Bhate and Williams., 2013).

2.1.3.2 Pathophythiology of Acne vulgaris

Acne develops in the pilosebaceous unit and involves many processes. Some of the key features underlying acne development include disturbed sebaceous gland activity associated with hyperseborrhoea (excessive sebum) and alterations in sebum fatty acid composition, dysregulation of the hormone microenvironment, interaction with neuropeptides, follicular hyperkeratinization, induction of inflammation and

dysfunction of the innate and adaptive immunity. These processes impair functioning of the pilosebaceous unit, which leads to the transition of a normal pore to microcomedones, and further to cloced comedones (whiteheads), inflammatory lesions, non-inflammatory acne is characterized by the formation of open comedones, Open comedones also known as (blackheads) shows dark colored hyperkeratotic plugs within the follicular opening which is related to the melanin oxidation but not dirt, as it is a common disbelief (Zouboulis et al., 2014).

Propionibacterium acnes a normal component of the cutaneous flora, invade the pilosebaceous unit using lipid rich sebum as a nutrient source and grow in the presence of increased sebum production leading to inflammation via complement activation and the release of metabolic byproducts, proteases and neutrophil-attracting chemotactic factors (Tan and Tan., 2005). Androgens are causative factors for acne which induces sebum production leading to the comedones development. Changes in the skin's natural flora are linked with androgen related sebum production. Diseases like congenital adrenal hyperplasia, polycystic ovarian syndrome and endocrine tumors result in a high level of androgens in body and associated with the development of acne vulgar (Herane and Ando., 2003).

When comedones ruptures , the contents of the pilosebaceous unit spread into the adjacent dermis and it leads to development of inflammatory acne vulgaris lesions such as cysts, nodules, papules and pustules. Sometime cysts may adhere to form channels or draining sinuses. In lesion initiation, abnormal proliferation and differentiation leads to the occurrence of microcomedone in the initial lesion., this is followed by the accumulation of sebum in the follicle lumen, causing a plug, either open or closed, inflammatory components leaking from a follicle to the dermis (suva et al., 2016).

2.1.3.3 Signs and Symptoms of Acne vulgaris

The clinical features of acne include seborrhea, non-inflammatory lesions, and inflammatory lesions. Seborrhea is defined as excess oil production from the pilosebaceous gland. Non-inflammatory lesions consist of both open and closed comedones, colloquially black heads and whiteheads respectively, open comedones are flat or slightly raised 1-5mm lesions with an opening, while closed comedones areoccluded follicles that appear as firm and pale elevated lesions that are 1-2 mm indiameter (Shamban and Narurkar., 2009).

It includes papules, nodules (large papules), pustules and scarring (Thappa et al., 2009). The appearance of acne varies with skin color and it is also associated with psychological and social problems, Acne scars shows inflammation within the dermis and it is created by the wound healing resulting in collagen deposition at one spot (Dawson and Dellavalle., 2013).

2.1.3.4 Causes and Risk Factors of Acne vulgaris

As this illustrates, acne is not a simple disease with a singular cause. There are multiple risk factors contribute to the formation and severity of acne, it's develops due to blockage of follicles, hyperkeratinization and keratin plug formation and sebum microcomedo. Comedones occur as a result of clogging of sebaceous glands with sebum, naturally occurring oil and dead skin cells (Benner and Sammons., 2013).

Hormones one of the risk factor plays an important role in the production of acnes, menstrual cycles and puberty may also causes acne, During puberty increase in androgens level causes the enlargement of follicular glands and sebum production is also increased (Benner and Sammons., 2013). Several hormones are linked with acne like the androgens testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate and insulin like growth factor 1 (IGF-I) (Suva et al., 2016).

Also there is relationship between acne and diet remains unclear although high glycemic diet is associated with worsening of acne (Davidovici and Wolf. 2010). Chocolate contains large amount of sugar that can lead to high glycemic load. It might be possible that acne is linked with obesity and insulin metabolism (Cordain., 2005).

The genetics of acne susceptibility is polygenic as the disease does not follow classic Mendelian inheritance pattern. There are multiple candidates for genes related to acne which includes polymorphisms in Tumor necrosis factor-alpha, Interleukin-1 alpha, CYP1A1 (Taylor et al., 2011).
Also found an association between smoking and acne, while smoking didn't cause the acne, it certainly had an effect on the severity and prevalence of acne. They found that it is a dose dependent relationship: the more frequently someone smokes, the higher the chances that the person develops severe acne (Schafer et al., 2001).
Also Infectious with P. Acne can cause AV, P. Acne are anaerobic bacterium species that mainly causes acne. Staphylococcus aurous has been discovered to play an important role since normal pores colonized only by Propionibacterium acnes, Specific clonal sub strains of P. acnes are also associated with normal skin health and long term acne problems, these strains have the capability of changing, perpetuating or adapting to the abnormal cycle of inflammation, oil production and inadequate sloughing activities of acne pores (Suva et al., 2016).
The environmental factors are those that a person will come into contact with daily, the most obvious of such factors are the weather, found that hot and humid environments adversely affect those with acne, hey believe that chemicals with and rogenagnostic like properties can activate androgen receptors which would lead to increased sebum production (Mazioti et al., 2015).

2.1.3.5 Classification of Acne

The clinical picture embraces a spectrum of signs, ranging from mild comedonalacne, with or without sparse inflammatory lesions (IL), to acne conglobate oraggressive fulminate disease with deep-seated inflammation, nodules and in some cases associated systemic symptoms (Layton et al., 2010).

Acne fulminans, Systemic disorder characterized by presence of fever and arthralgias with an acute eruption of large inflammatory nodules. **Acne conglobata,** sever form of nodular acne that is most commonly seen in young males. Lesions are most prominent on the back, chest and buttocks. **Gram-negative folliculitis,** develop in patients with pre-existing acne vulgaris who have been treated with long-term systemic antibiotics. SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis) PAPA syndrome (sterile pyogenic arthritis, pyoderma gangrenosum and acne). **Neonatal acne,** appears within the first few weeks of life. **Infantile acne,** median age of onset was 9 months. Acne excoriée des jeunes filles: primarily seen in young women, in whom relatively small pimples are chronically self-excoriated, leading to erosions and scarring. **Acne mechanica,** covers a mixed group of disorders in which acne occurs at the site of physical trauma example headbands and tight bra straps. **Endocrine acne**, an endocrine evaluation is indicated for adult females with, sudden onset of severe acne and resistant acne. POCS is the commonest cause of endocrine acne, characterized by irregular menses, hirsutism, obesity and acne. Such patients have increased plasma concentrations of insulin, IGF-1 and androgens (Lord et al., 2003).

2.1.3.6 Acne grading

Acne grading systems may be useful in patient care. Such systems can assist in more specific classification of disease, help determine appropriate treatment options, and monitor improvement during the treatment course. Systematic assessment of the severity of acne AV which is crucial for the management continues to challenge the clinician, An ideal grading system should be accurate, reproducible and simple to use by the clinician over serial office visits. Systems for grading severity of acne include: Acne lesion-counting technique, the most frequently used outcome measures to assess acne, Lesion counts are essential for clinical trials as they offer a reliability not evident in global assessment (Witkowski et al., 1980).

The Plewig and Kligman system divides acne into comedonal, papulopustular, and conglobate. **The Cunliffe score** (Leeds technique) is a photonumeric grading scale, involves comparing the patient's severity of acne to a standard photographic manual and assigning a score from 1 (mild) to 10 (very severe) (Witkowski et al., 1980). **Cook's photographic method** which based on photographic standards,It utilizes

images to grade severity ranging from 0 (least severe) to 8 (most severe) (Cook et al., 1979). The American Academy of Dermatology classification, describes acne as mild, moderate, or severe (Pochi et al.,1991). **The Global Acne** Grading System (GAGS) (Doshi et al.,1997).

2.1.3.7 Diagnosis of Acne

Acne is diagnosed by the identification of lesions. The spectrum of acne lesions ranges from noninflammatory open or closed comedones (blackheads and whiteheads) to inflammatory lesions, which may be papules, pustules, or nodules. Lesions are most likely to occur on the face, neck, chest, and back, where there is a higher concentration of sebaceous glands. Other conditions can mimic acne, and even include the term acne in their nomenclature, but they lack the presence of comedones , such as Acne rosacea, Folliculitis and boils,Pityrosporum folliculitis and Perioral dermatitis (Wolff et al., 2009).

2.1.3.8 Acne Management

The following self-care steps may aid in decreasing the severity of acne, washing the skin with a mild non-drying soap twice a day, avoiding excessive washing, avoiding comedogenic cosmetics such as those containing the agent isopropyl myristate and avoiding squeezing, scrubbing or picking the pimples, healthful diet rich in natural whole foods is the first recommendation, diet with low sugar content, an overall low glycemic load, more dietary fiber, more fish and seafood is helpful in acne (Logan., 2007).

2.1.3.9 Treatment of Acne

Many treatment options exist for acne today. Since there are so many different causes for acne, each treatment is able to target a specific causative factor. No one treatment is significantly better than another treatment. Some treatments, such as antibiotics and topical retinoids, are commonly used together. treatment depend on the severity of the disease and other biological factorsin in patient. This section will attempt to elucidate the main treatment options, how they work, and their drawbacks for acne. **Oral Antibiotics** are commonly prescribed as a first line of defense against acne. It specifically targets P. acnes, it can suppress acne by either directly reducing the bacteria’s proliferation or by anti-inflammatory mechanics. However, over use of antibiotics has led to the rise of antibiotic resistance (Amin et al., 2007).

Topical Therapies includes Topical retinoids witch are versatile agents in the treatment of mild to moderate inflammatory or mixed acne, They prevent the formation and reduce the number of comedones, making them useful against

noninflammatory lesions. Topical retinoids also possess anti-inflammatory properties, making them somewhat useful in the treatment of inflammatory lesions. Topical retinoids are indicated as monotherapy for noninflammatory acne and as combination therapy with antibiotics to treat inflammatory acne (Thiboutot et al., 2009). Overall, adapalene (Differin) is the best tolerated topical retinoid. Limited evidence suggests that tazarotene (Tazorac) is more effective than adapalene and tretinoin (Retin-A) (Thielitz et al., 2008). Tetracycline, erythromycin and clindamycin which have antibacterial action, anti-inflammatory action as they suppress neutrophil chemotaxis. Combinations of topical antibiotics with zinc (solution) and benzoyl peroxide (gel) are currently marketed, the advantage of using a combination of topical erythromycin and benzoyl peroxide is prevention of the development of antibiotic resistance (Michaelsson., 1999). **Anti-androgen Treatment** In females acne can be treated with the use of combined oral contraceptives. Third or fourth generation progestins such as norgestimate, desogestrel or drospirenone combination product may be more beneficial. Oestrogenic oral contraceptive is an effective for acne. Due to androgenic properties of oral contraceptive norethisterone is contradicted in acne. Anti-androgen cyproterone combined with 50 µg of ethinylestradiol is available as Dianette which is most effective hormonal intervention (suva et al., 2016).

Laser and Light Therapies Light and laser therapies can be used for the treatment of acne. Examples include visible light, pulsed-dye laser, and photodynamic therapies. There is insufficient evidence to recommend the routine use of these therapies for the treatment of acne (Thiboutot et al., 2009).

2.2 Vitamin D

Vitamin D (calciferol) comprises a group of fat soluble seco-sterols. The two major physiologically relevant forms of vitamin D are D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is photosynthesized in the skin of vertebrates by the action of solar ultraviolet (UV) B radiation on 7-dehydrocholesterol, Vitamin D2 is produced by UV irradiation of ergosterol, which occurs in molds, yeast, and higher-order plants. However, the effects of vitamin D are not limited to mineral homeostasis and skeletal health maintenance. The presence of vitamin D receptors (VDR) in other tissue and organs suggest that vitamin D physiology extends well above and beyond bone homeostasis (Deluca., 2004).

However, recent studies have shown that vitamin D is important in numerous physiological processes, including the modulation of cell proliferation, differentiation, and apoptosis, and in neuromuscular, hormonal, and immune functions. On the other hand, vitamin D may also play a role in multiple chronic diseases such as cancer, autoimmune diseases, and infections (Polat and Uzun., 2014).

2.2.1 Dietary Sources of vitamin D

Very few naturally occurring foods contain vitamin D. The flesh of fatty fish and fish liver oils are among the best sources. most of the dietary intake of vitamin D comes from fortified milk products and other fortified foods such as breakfast cereals and orange juice, Small amounts of vitamin D are found in beef liver, dairy products, and egg yolk. Vitamin D in these foods occurs primarily as vitamin D3 and its metabolite 25OHD3. Some mushrooms provide vitamin D2 in variable amounts. In some groups, e.g., infants, elderly persons not sufficiently exposed to sunlight, and patients suffering from fat malabsorption, consumption of vitamin D supplements or vitamin D fortified foods are required to meet the daily need,i.e., approximately 2000 IU/day to maintain serum 25(OH)D levels greater than 30 ng/mL (Borel., 2015) .

2.2.2 Vitamin D Production

Vitamin D is unique among hormones because it can be made in the skin from exposure to sunlight. Vitamin Dcomes in two forms, Vitamin D2 is obtained from the UV irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms. Vitamin D3 is synthesized in the skin and is present in oil-rich fish such as salmon, mackerel, and herring; commercially available vitamin D3 is synthesized from the cholesterol precursor 7-dehydrocholesterol naturally present in the skin or obtained from lanolin . Both vitamin D2 and vitamin D3 are used for food fortification and in vitamin D supplements. Vitamin D (D represents D2, or D3, or both) that is ingested is incorporated into chylomicrons, which are absorbed into the lymphatic system and enter the venous blood (Holick., 2007).

2.2.3 Vitamin D Metabolism

Vitamin D that comes from the skin or diet is biologically inert and requires its first hydroxylation in the liver by the vitamin D-25-hydroxylase (25-OHase) to 25(OH)D. However, 25(OH)D requires a further hydroxylation in the kidneys by the 25(OH)D-1_-Ohase (CYP27B1) to form the biologically active form of vitamin D 1,25(OH)2D. 1,25(OH)2D interacts with its vitamin D nuclear receptor, which is present in the small intestine, kidneys, and other tissues. 1,25(OH)2D stimulates intestinal calcium absorption (Christakos et al 2003). Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus are absorbed. Vitamin D sufficiency enhances calcium and phosphorus absorption by 30–40%and 80%, respectively. 1,25(OH)2Dinteracts with its vitamin D receptor in the osteoblast to stimulate the expression of receptor activator of nuclear factor _B ligand; this, in turn, interacts with receptor activator of nuclear factor _B to induce immature monocytes to become mature osteoclasts, which dissolve the matrix and mobilize calcium and other minerals

from the skeleton. In the kidney, 1,25(OH)2D stimulates calcium reabsorption from the glomerular filtrate (Dusso et al., 2005).

2.2.4 Vitamin D Mechanism of Action

The vitamin D receptor is present in most tissues and cells in the body . 1,25(OH)2D has a wide range of biological actions, including inhibiting cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, inhibiting renin production, and stimulating macrophage cathelicidin production. In addition, 1,25(OH)2Dstimulates its own destruction by enhancing the expression of the 25-hydroxyvitamin D-24-OHase(CYP24R)to metabolize 25(OH)D and 1,25(OH)2D into water-soluble inactive forms. There are several tissues and cells that possess 1-OHase activity. The local production of 1,25(OH)2D may be responsible for regulating up to 200 genes that may facilitate many of the pleiotropic health benefits that have been reported for vitamin D (Holick., 2007).

2.2.5 Distributions of vitamin D

The major action of the vitamin D had been thought to be mainly the promotion of intestinal absorption of calcium and phosphorus, important for the prevention of rickets and/or osteomalacia, and once it became clear that rickets was easily and effectively prevented by daily doses as low as 200 IU, Cholecalciferol is one of the fat soluble vitamins and has been thought to be stored in body fat depots. And fat is almost certainly the reservoir of the vitamin in patients with vitamin D intoxication (Heaney et al., 2009).

2.2.6 Clinical Applications of vitamin D

Active vitamin D functions as a hormone, and its main biologic function in people is to maintain serum calcium and phosphorus concentrations within the normal range by enhancing the efficiency of the small intestine to absorb these minerals from the diet (DeLuca., 1988). Thus, maintaining adequate levels of vitamin D prevent rickets , osteomalacia and fractures , reduce the risk for Para thyroid gland hyperplasia and elevated Para thyroid hormone secretion with its potential deleterious effects on bone, inhibit the proliferation, stimulate the differentiation and suppress the immune activity associated with psoriasis disease, improving or preventing the development of frank diabetes ,prevention/treatment of CVD, promote the innate and adaptive immune response, (Bikle, 2013).

When dietary calcium intake is inadequate to satisfy the body’s calcium requirement 1,25(OH)2D, analong with PTH, mobilizes calcium stores from the bone. In the kidney, 1,25(OH)2D increases calcium reabsorption by the distal renal tubules. Apart from these traditional calcium-related actions, 1,25(OH)2D and its synthetic analogs

are increasingly recognized for their potent antiproliferative, prodifferentiative, and immunomodulatory activities (Nagpal et al., 2005).

2.2.7 Daily requirements reference intakes of vitamin D

the optimal intake of vitamin D remains a matter of some disagreement. Current recommendations from the Institute of Medicine call for 200 international units (IU) [5.0 micrograms (μg)] of vitamin D daily from birth through age 50, 400 IU (10 μg) for those aged 51–70 years, and 600 IU (15 μg) for those older than 70 years. Some experts say that optimal amounts for all adults are closer to 800–1000 IU (20–25 μg) daily (Vieth., 2007). The tolerable upper intake level for vitamin D is 2000 IU (50 μg) per day in North America and in Europe; however, some scientists are calling for an upward revision (Hathcock., 2007).

2.2.8 Vitamin D deficiency

characterized by inadequate mineralization or by demineralization of the skeleton. Among children, vitamin D deficiency is a common cause of bone deformities known as rickets. Vitamin D deficiency in adults leads to a mineralization defect in the skeleton, causing osteomalacia, and induces secondary hyperparathyroidism with consequent bone loss and osteoporosis. Potential roles for vitamin D beyond bone health, such as effects on muscle strength, the risk for cancer and for type 2 diabetes, are currently being studied. The Agency for Health care Research and Quality recently reviewed the effectiveness and safety of vitamin D on outcomes related to bone health (Cranney., 2007). The report suggests that vitamin D supplementation has positive effects on bone health in postmenopausal women and older men.

2.2.9 Vitamin D Toxicity

Vitamin D as a fat-soluble vitamin raised concerns about toxicity from excessive supplementation. Hypercalcemia is responsible for producing most of the symptoms of vitamin D toxicity. Early symptoms of vitamin D toxicity include gastrointestinal disorders like anorexia, diarrhea, constipation, nausea, and vomiting. Bone pain, drowsiness, continuous headaches, irregular heartbeat, loss of appetite, muscle and joint pain are other symptoms that are likely to appear within a few days or weeks; frequent urination, especially at night, excessive thirst, weakness, nervousness and itching; kidney stones (Holick., 2007).

2.2.10 Vitamin D in Acne Vulgaris

The demonstration of a role for vitamin D in various diseases, including dermatological diseases, osteoporosis, cancer, and autoimmune diseases, suggests clinical applications for vitamin D and its analogs, As mentioned above, several

studies have shown that vitamin D has dose-dependent antiproliferative effects. Moreover, vitamin D can reduce the risk of skin infections. Further, vitamin D deficiency is related to dermatological diseases such as psoriasis, atopic dermatitis (AD), vitiligo, acne, rosacea, and skin cancer. Recently, sebocytes were identified as bioactive vitamin D responsive target cells, indicating that vitamin D analogs may be effective in the treatment of acne 31(Lee et al., 2013). Vitamin D treatment decreased the expression of IL-6, IL-8, IL-17, and matrix metalloprotein-9 in cultured sebocytes. They proposed that vitamin D could be a therapeutic alternative for the treatment of acne and other Th17-mediated skin diseases.(Polat and Uzun., 2014).

2.2.11 Assessment of vitamin D Status

Some clinical laboratories use conventional units for 25(OH)D (nanogram per milliliter [ng/mL]) whereas other laboratories use international system (SI) units (nanomole per liter [nmol/L]). The conversion factor to SI units is: 1 ng/mL = 2.496 nmol/L. No common definition exists for adequate vitamin D status measured as 25(OH)D serum concentrations (Dawson et al., 2005).

The Institute of Medicine defined vitamin D deficiency as serum 25(OH)D concentrations of less than 11 ng/mL (27.5 nmol/L) for neonates, infants, and young children. Because the lower limit of the normal range can be as low as 8 ng/mL (20 nmol/L) and as high as 15 ng/mL (37.5 nmol/L), depending on the geographic location, vitamin D deficiency has been defined as a concentration of less than 12 ng/mL (mid-range between 8 and 15 ng/ mL) for adults, more recently, some scientists have suggested that the criteria used to define adequate status should be revised upwards; serum 25(OH)D concentrations between 20 ng/mL (50 nmol/L) and 32 ng/mL (80 nmol/L) have been defined as sufficient (Norman et al., 2007). A common definition for high serum vitamin D concentrations is also lacking.

Chapter Three

Materials and methods

3. Materials and methods

3.1 Study design

This was quantitative case control study.

3.2 Study area and duration

This study was conducted in Khartoum state at military Hospital department of Dermatology and venerology, during March to August 2018.

3.3study population

The study includes 60 patients diagnosed with acne vulgaris attended to military Hospital department of Dermatology & Venerology Hospital and 60 healthy control matched by sex and age volunteer.

3.4 Inclusion criteria

Known Sudanese patients newly diagnosed with acne vulgaris disease, male and female.

3.5 Exclusion criteria

Known Sudanese patients treated with vitamin D, Presence of known systemic diseases or other dermatological diseases, Patients with other variants of acne (drug induces acne, acne fulminans and Acne conglobata).

3.6 Ethical consideration

Approval for this study was taken from the department of clinical chemistry and verbal consent was taken from both test and control subjects.

3.7 Data collection and clinical examination

Each site used a standardized questionnaire which collected the demographic and symptom information assessed in this study. Clinical examinations done by clinicians in above mentioned hospital. Case group with acne was randomly selected from patients. Control subjects for this group were randomly selected from college students taking into consideration matching in age and sex.

3.8 Study variable

Dependent: Level of serum 25-hydroxy vitamin D.

Independent: Gender (male-female), Duration (months), Age (years), BMI,

Grade (Mild-Moderate-Severe)**,** smoking, sunlight (minutes), family history and generation (first-second).

3.9 Sample collection

Three ml of venous blood was collected in plain container, the blood samples were allowed to clot and after centrifugation at 2000 RPM for minute, the serum was separated and stored at 8°C prior to analysis.

3.10 Estimation of vitamin D

First, the sample was incubated with a pretreatment reagent for 9 minutes. Thereby, the natural Vitamin D binding protein (VDBP) in the sample was denatured to release the bound vitamin D (25-OH). Second, the sample was further incubated with a recombinant ruthenium-labeled VDBP to form a complex of vitamin D (25-OH) and the ruthenylated-VDBP. Third, with the addition of a biotinylated vitamin D (25-OH) a complex consisting of the rutheniumlabeled VDBP and the biotinylated vitamin D (25-OH) was formed. The entire complex becomes bound to the solid phase (by the interaction of biotin and streptavidin-coated microparticles which were captured on the surface of the elecrode). Unbound substances were removed. Applying voltage to the electrode induces chemiluminescent emission which was measured by a photomultiplier. (holick., 2007).

3.11 Quality control

Sample representing the normal and pathological level of serum vitamin D was used for assessment of the quality control. Result mean±2SD of the target values of the control sera were accepted.

3.12 Statistical analysis

Data was analyzed by using Statistical Program for Social Sciences SPSS (version 16) software program . Data were expressed as (mean ± standard deviation) . Student's t test and ANOVA test used for the comparison of vitamin D levels between the study group. The mean and standard deviation of vitamin D level was obtained, and the mean difference is significant at $p \leq 0.05$. Correlation (r) between vitamin D levels with age, BMI and duration of acne and expoture to sunlight is considered to be statistically significant at $P \leq 0.05$.

Chapter four

Results

4. Results

This study included 60 patients with acne vulgaris (5 males and 55 females) and 60 healthy subjects as a control group, age-sex matched (6 males and 54 females).

This study showed that there was no significant difference ware found in patients means of vitamin D ng/mL levels regarding , age (21.9 ± 3.05) and BMI (22.8 ± 2.49) (P > .05). (Table 4.1)

Also showed there was significant diffrance in means of vitamin D ng/mL levels in study group patients and controls (13.6 ± 5.07 vs 24.8 ± 11.7) respectively, serum levels of vitamin D significantyl lower in patients with acne vulgaris than contols group (P =0.00). (table 4.2)

No significant diffrance were seen in patients means of vitamin D levels regarding to sex, smoking and uses of sunblock (P > .05).(table 4.3)

No significant diffrance was seen between family history in patients with acne vulgaris and healthy controls (P > .05).(table 4.4)

Also showed that the Serum vitamin D ng/mL levels decreased with advanced grade of acne patients, mild 11 (18.3%), moderate 37 (61.7%), and severe 12 (20%) (16.8 ± 3.42 ng/ml, 13.9 ± 4.33 ng/ml , 10.4 ± 1.64 ng/ml) respectively, In comparison with vitamin D levels in the control group was 24.81 ± 11.07 ng/mL (p = 0.01). (table 4.5).

As illustrated in figure (4.1). There was no correlation between serum vitamin D ng/mL levels and duration (months) of acne vulgaris in the study group patients (r = 0.13, p = 0.31).

As presented in figure (4.2), There was a positive correlation between serum vitamin D ng/mL levels and the expoture to sun light (minutes) in the study group patients (r = 0.36) , (p = 0.04).

As illustrated in figure (4.3) There was a Positive corelation seen between meas duration (months) of acne vulgaris and age (years) in the study group patients (r = 0.49 , p = 0.01).

Table (4.1): Compression between means of age(years) and BMI (kg/m^2) in study group .

	Patients = 60	Controls = 60	p.value
Age	21.9 ± 3.05	23.5 ± 3.86	0.39
BMI	22.8 ± 2.49	21.5 ± 2.07	0.23

- Results was expres as mean±SD
- T test was used to compare between means
- P.value considerd significant at level < 0.05

Table (4.2): Compression between means of vitamin D (ng/mL) levels in patients with acne vulgaris and healthy control subjects .

Sampel	No	Vitamin D mean±SD(ng/ml)	p.value
Cases	60	13.6 ± 5.07	**0.00***
Control	60	24.8 ± 11.0	

- Results was expres as mean±SD
- T test was used to compare between means
- P.value considerd significant at level < 0.05

Table (4.3): Compression between means of vitamin D (ng/mL) levels in patients regarding sex, smoking and uses of sunblock.

Parameter	No	Vitamin D mean±SD(ng/ml)	p.value
Sex			
Male	5	16.5 ± 4.92	0.99
Female	55	13.4 ± 5.05	
Smoking			
Yes	2	15.7 ± 4.73	0.77
No	58	13.6 ± 5.12	
Sunblock			
Yes	15	12.9 ± 4.42	0.70
No	45	13.9 ± 4.18	

- Results was expres as mean±SD
- T test was used to compare between means
- P.value considerd significant at level <0.05

Table (4.4): Compression between family history in patients with acne vulgaris and healthy controls.

Family history	Cases=60	Controls=60	p.value
Yes	13.3% (n= 8)	3.3% (n=2)	0.30
No	86.7% (n=52)	96.7% (n=58)	0.45

- Results was expres as mean±SD
- T test was used to compare between means
- P.value considerd significant at level <0.05

Table (4.5): compression between means of vitamin D (ng/mL) levels and acne grading in patients .

Vitamin D(ng/ml) ANOVA					
Severity	No	Mean ± SD(ng/ml)	Min	Max	p.value
Mild	11	16.7 ± 3.42	14	27	0.00*
Moderate	37	13.9 ± 4.33	6.2	24	
Sever	12	10.4 ± 1.64	6.4	17.4	

- Results was expres as mean±SD
- One ANOVA test was used to compare between means
- P.value considerd significant at level <0.05

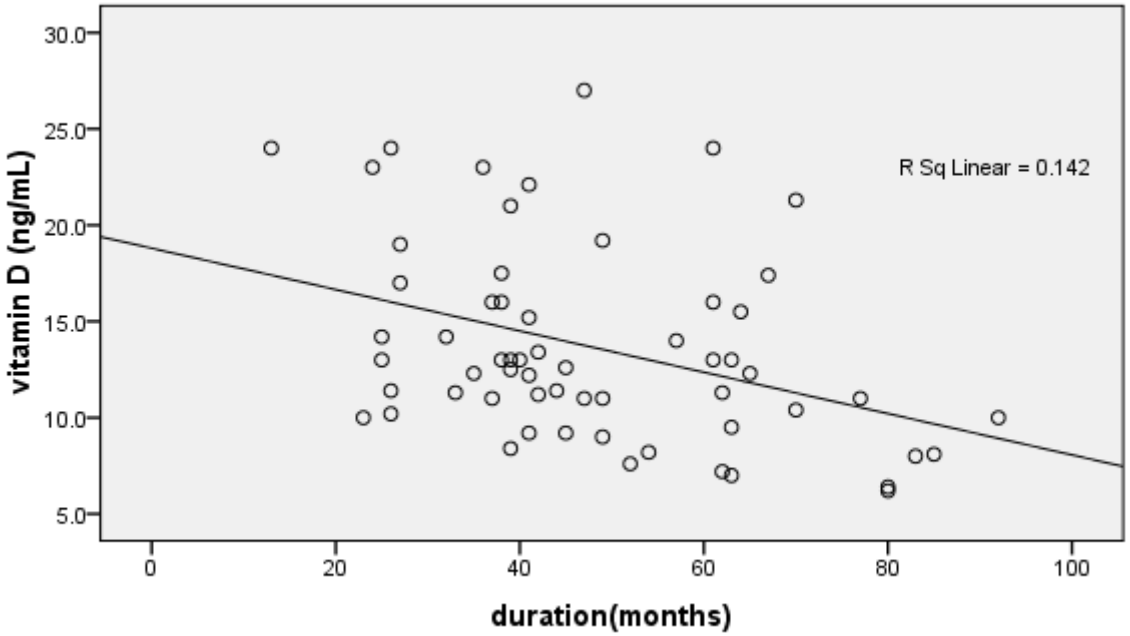

Figure (4.1): Scatter plot shows correlation between serum vitamin D levels and Duration (months) of acne in patients.

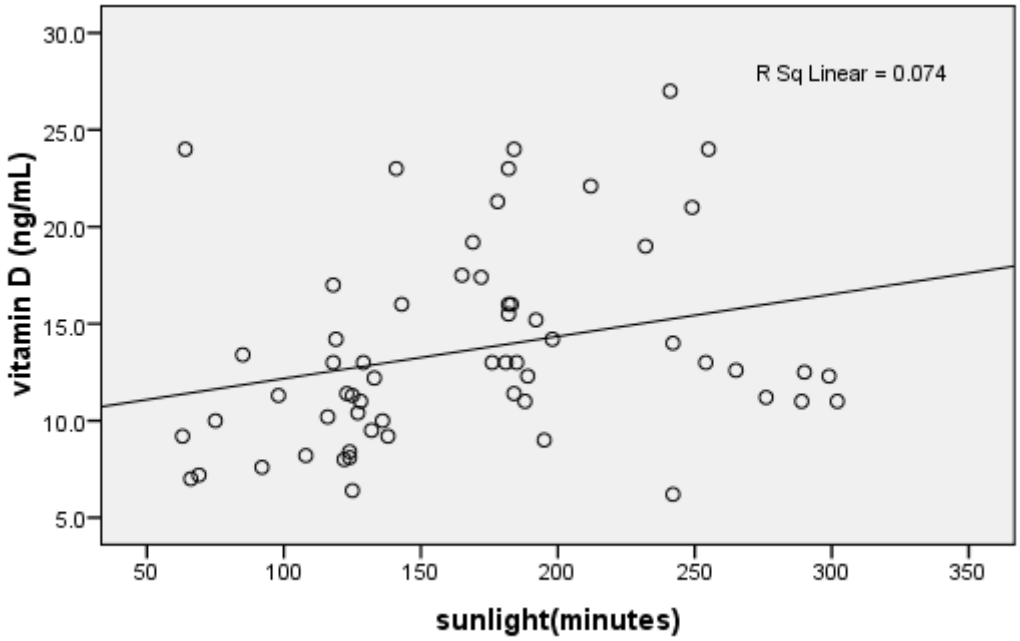

Figure (4.2): Scatter plot shows correlation between means vitamin D (ng/ml) levels and expotur to sunight (minutes) in patients with acne .

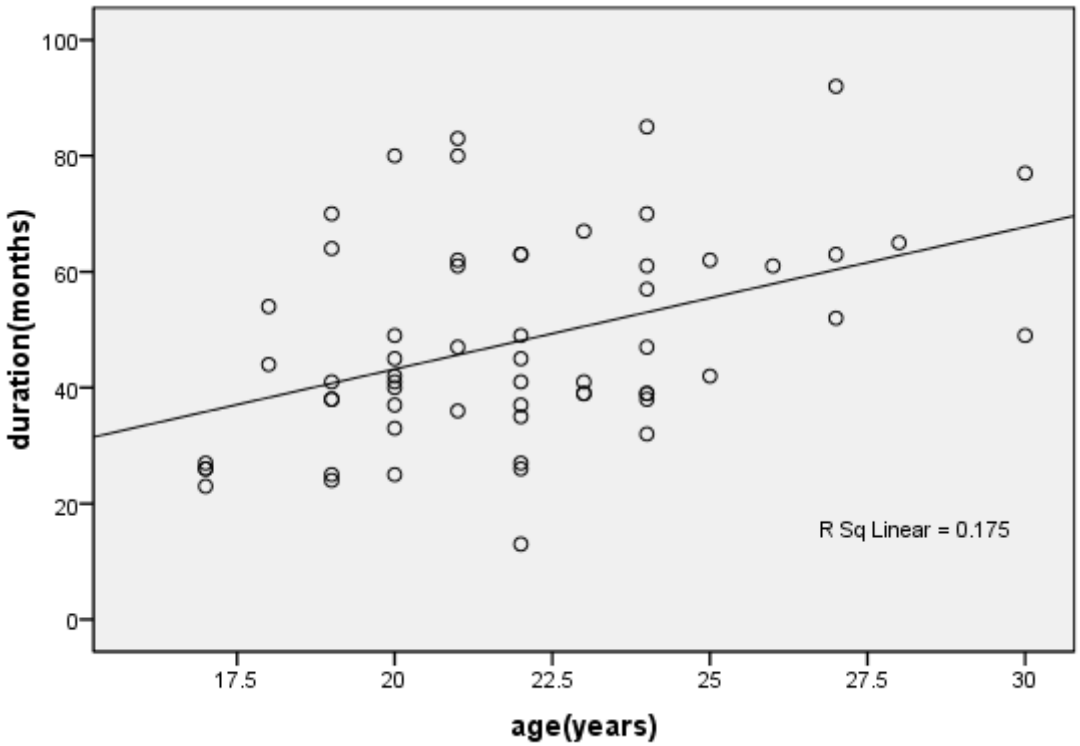

Figure (4.3): Scatter plot shows correlation between dutation of acne (months) and age (years) in patients .

Chapter Five

Discussion , Conclusions& Recommendations

5. Discussion , Conclusions& Recommendations

5.1 Discussion:

Acne vulgaris (AV) is a multifactorial chronic inflammatory disorder of the pilosebaceous follicles of human skin. AV can persist throughout life and may cause permanent scarring on the face. Four pathogenesis steps are thought to play critical roles in the formation of acne lesions including alteration of keratinization processes, leading to comedo formation, follicular colonization by P.acnes, increased sebum production, and inflammatory mediators around pilosebaceous units. Isotretinoin acts on all mentioned processes in acne pathogenesis (Lee., et al 2013).

In this study, there was significant low serum levels of 25 hydroxy vitamin D in acne vulgaris patients compared with control group, This is in agreement with a previous study performed by El hamd et al (2018),wich found there wae a significant lower vitanmin D levels in patients than contol group. The mechanism of vitamin D functions in some medical conditions has been focused by several researches Youssef et al (2011), as well as other investigators explained the effect of vitamin D and its derivatives which help infection prevention too. Vitamin D is also known by some authorities as a preventive factor against cancers and skin inflammatory diseases like psoriasis and ictiosis, in addition to mediating the beneficial dermatologic effects of light (Ekiz et., al 2014).

According to our data demonstrated that there was no corelation between serum 25-hydroxy vitamin D levels and age, BMI in patients with acne vulgaris and healthy controls . this result agree with the result observed by Elhamd et al (2018), whom deduced that there was no corelation between the patients age,BMI and serum vitamin D level in study group .

The present data demonstrated that there was no significant diffrance in serum 25 hydoxy vitamin D levels in patients with acne vulgaris and sex, smoking, uses of sunblock, this result agreement with the result observed by Lim et al, (2016) whom deduced that there was no diffrace in levels of vitamin D in acne vulgaris patients regarding to sex, smoking, and uses of sunblock.

The curent syudy observed that there was no significan diffrance between family history in patients with acne vulgaris and healthy controls .this results in agreement with Tossi et al (2015), which found there were no diffrance on levels of vitamin D in acne vulgaris patients regarding to family history and generation.

In this study,the Serum levels of 25 hydroxy vitamin D was found to be inversely corelated with acne severity suggesting that there was a connection between low

vitamin D level and acne, this is in agreement with a previous study performed by EL hamd et al (2018), which found a decrease in the levels of 25 hydroxy vitamin D in patients with sever acne than those with mild and modrate acne, On the other hand Toossi et al (2015) found no significant correlation with severity of acne.

Propionibacter acnes is known as the main microorganism in acne vulgaris and studies have shown that the bacterium stimulated genes which were linked to expression of some immunologic factors and cytokines, especially in human T lymphocytes in order to block vitamin A and vitamin D. This is the main provider of suitable environment for more microbial proliferation on the skin level in acne vulgaris (Thiboutot., 2014).

In this study there was no correlation between duration of acne and serum vitamin D levels in patients diseased with acne vulgaris. this result in agreement with Lim et al (2016), wich hound there was no diffrance in vitamin D levels and duration of acne.

Also there was significant positive correlation between serum vitamin D levels and expoture to sunlight in patients with acne vulgaris, vitamin D levels were high in patients with long expoture to sunlight. this finging is similar in the finging of Tossi et al (2015), wich found there was incease in vitamin D levels in patiens who expotued to sun light more than two hours per day. These results may indicate that vitamin D may play a potential role in acne vulgaris or acne vulgaris negatively affects vitamin D synthesis.

Also in this study shows, there was a positive corelation between durationof acne and age in study group patients.

5.2 Conclusions:

This study concluded that, Acne patients showed significantly low level of serum 25 hydroxy vitamin D when compared with a control group of comparative sex and age matched. Relationbetween vitamin D levels and acne severity ware inversely. Serum vitamin D levels are affected by expoture to sunlight and duration of acne in certine age period.

5.3 Recommendations:

- Measuring serum vitamin D levels may be necessary for acne patients and especially for young (teenage) patients with severe acne and low response to anti-acne treatment.
- Health education, good and healthy diets are important factors to achieve good vitamin D level.
- Prescribing vitamin D supplement for patients with low serum vitamin D levels may help increase the success rate of acne treatment.
- Further researches with large sample size and controlled clinical trial on the safety and efficacy of oral vitamin D in acne treatment is needed to establish the role of vitamin D as a therapeutic tool in acne vulgaris.

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Appendices

AL Sudan University

Faculty of Medical Laboratory Sciences

College of post graduate studies

Questionnaire

Serum 25-hydroxy vitamin D Levels among Sudanese Patients with Acne Vulgaris

- **general information**

1. Name: ……

2. Age.....

3. Gender

male: ..... Female: .....

- **clinical data**

3. Duration of acne vulgaris …….....years

4. Grade of acne vulgaris

Mild..... Moderate..... Severe.....

4.Do you have history of taken any treatment containing vitamin D ?

Yes..... No.....

6. uses of sunblok?

yes..... no.....

7. expoture to sunlight/day? yes..... no.....

if yes, how mutch.....

- **family history**

8.have any family history? yes..... on.....

If yes, first generation…… second generation.....

- **body mass index**

wight/kg..... hight/meters.....

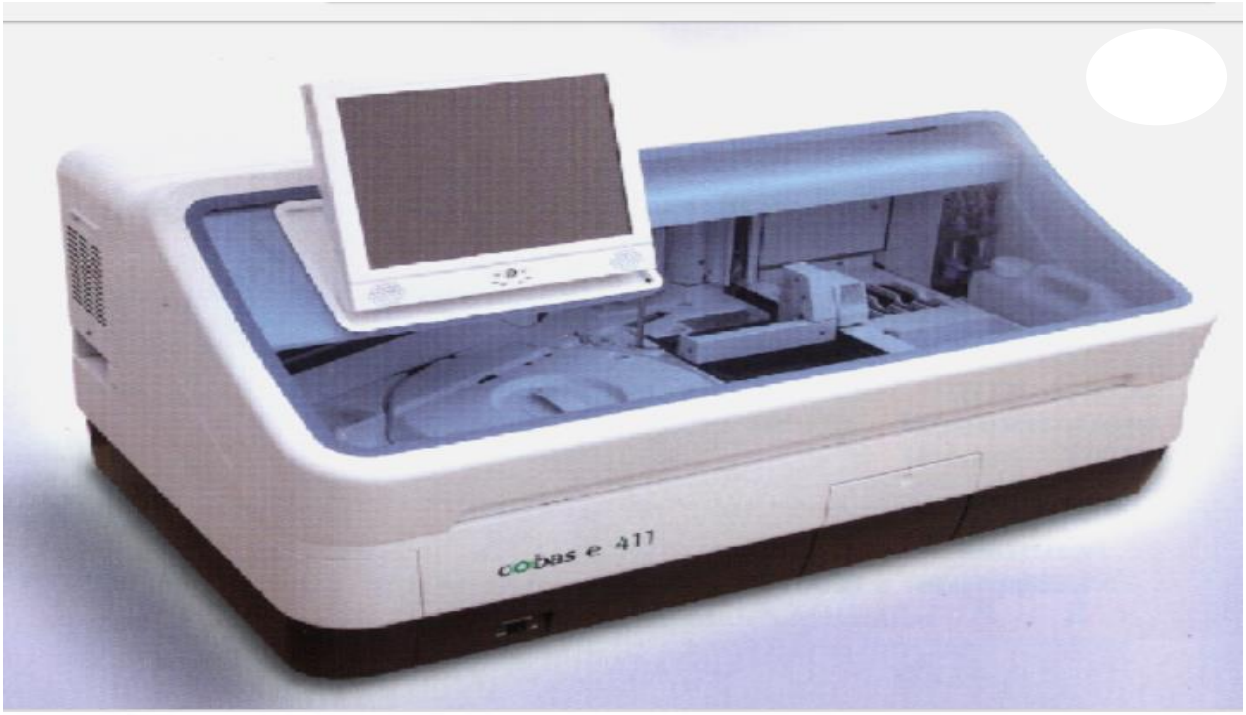
BMI = ...

10.Do you agree to join to this study?

Yes..... No.....

- **lab investigation**

Result for vitamin D level = ……ng/ml.



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