Vitamin D deficiency in patients with chronic venous ulcers

Prevalência de deficiência de vitamina D em pacientes com úlceras de perna de etiologia venosa

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A B S T R A C T

Objective: To study if the prevalence of vitamin D deficiency in patients with venous leg ulcer is higher than in the control population. **Methods**: Serum levels of 25 hidroxi (OH)-vitamin D3 was studied by chemiluminescence in 27 patients with chronic venous ulcer and 58 controls at the Evangelical Hospital of Curitiba. **Results**: The levels of 25 OH-vitamin D3 were below 8 ng/dl in 11.1% of ulcer patients and 3.4% of controls; between 8 and 20 ng/dl in 46.1% of ulcer patients and 25.8% of controls; between 21 and 30 ng/dl in 22.2% of ulcer patients and 27.5% of controls and above 30 ng/dl in 43.1% of controls and 18.5% of ulcer patients (p=0.04). **Conclusion**: There is an increased prevalence of vitamin D deficiency in patients with chronic venous leg ulcers.

Key words: Vitamin D. Vitamin D deficiency. Varicose ulcer. Leg ulcer. Wound healing.

INTRODUCTION

Vitamin D is recognized as an active element since 1919 when their properties on calcium homeostasis and the prevention of rickets were discovered[1]. Since then multiple attributes have been related to this substance and its deficiency has been implicated in metabolic syndrome, diabetes mellitus, cardiovascular disease, hypertension, muscle weakness, pain, immune dysfunction and the appearance of certain forms of cancer[2-4].

There are also some evidences that vitamin D can act on tissue healing[5-8]. Thus, individuals with deficiency of vitamin D and open chronic skin lesions – as in venous ulcers of the lower limbs – may have healing difficulties.

Vitamin D existent in the human body comes primarily from two sources: food and epidermal synthesis from sun exposure. Foods that are rich in vitamin D include oily fish, egg yolk and milk[9]. However its major source is the epidermic synthesis that results from dehydrocholesterol exposure to ultraviolet rays[10].The ingested or skin synthesized vitamin D is biologically inactive. It is necessary an initial hydroxylation in the liver and a second one in the kidney to become the active form: the dihydroxy-vitamin D3 or calcitriol. So, individuals with inadequate exposure to sunlight, liver or kidney dysfunction have deficiencies in the active form of this vitamin. There are also some medications that interfere with the action of cytochrome P-450 – as anticonvulsants that accelerate vitamin D catabolism and decrease its serum level[11].

Interestingly, even in countries where sun exposure is considered high, as is the case of Brazil, there is a high prevalence of vitamin D deficiency [12,13]. This deficiency may be even higher in certain population groups such as children and elderly or in those with low intake and that work in the dark[12,14].

Venous ulcers are common entities that interfere in the quality of life of affected individuals[15,16]. They tend to be chronic and recurrent.It is estimated that 50% of cases persist for seven to nine months and can last up to five years in 34% of cases[17,18]. It is necessary to recognize the details of the pathophysiological mechanisms involved in leg ulcers healing to propose new therapeutic interventions.

Individuals who suffer an injury in the skin, with loss of mechanical barrier which is the first defense mechanism of immunity, show an increased of local expression of TLR (toll like receptor)-2 and transforming growth factor β. These, in turn, increase expression of 1α-

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hydroxylase in keratinocytes, leading to increased synthesis of calcitriol. The calcitriol produced induces the formation of cathelicidin and â defensins. In turn, these substances modulate the levels of cytokines (interleukin IL-6, IL-8, IL-10, IL-18) as well as the level of the receptor factor of epidermal growth. The latter stimulates proliferation and migration of keratinocytes[7,8,19]; the first play a key role in local inflammatory process.

Heilborn et al.[5] studied the process of healing of chronic ulcers of the lower limbs comparing them with the healing of normal tissues and showed that individuals with chronic venous ulcers have lower production of cathelecidin the edges of the wound, which could interfere in the healing process.

Given the possibility that vitamin D favors the healing of chronic venous ulcers and the great difficulty in closing them, it should be studied if the patients with these lesions cannot have deficiency of this nutrient. This deficiency would act as an aggravating factor in the healing process.

Thus, this study aims to verify if the vitamin D deficiency in these patients is greater than it is in the normal population.

METHODS

This study was approved by the Ethics Committee of the local entity and all participants signed an informed consent.

The sample comprised 85 individuals (27 of ulcer group and 58 controls) with a mean age of 59.35 years ± 9:55, 14 males and 71 females. Individuals with ulcers were recruited from the outpatient clinic of Vascular Surgery of the Evangelical Hospital of Curitiba at random from the order of arrival for consultation and agreement with the willingness to participate. The control subjects were obtained from the rheumatology clinic of the same hospital and where individuals who sought the treatment of soft tissue involvement. Pregnant women, individuals under 18 years, with a history of autoimmune disease, in the use of anticonvulsants, those with liver and kidney diseases were excluded in both groups. The ulcer group included only individuals with venous ulcers.

All subjects underwent measurement of 25 OH-vitamin D3 and creatinine. Serum creatinine was measured in automated manner using Vitros equipment (fusion model kit 5.1 and Johnson & Johnson) and assuming normal value of 0.6 to 1.1 mg/dl. To enter the study, all patients should have creatinine equal to or below 1.2 mg/dl. The dosage of vitamin D was made by chemiluminescence after collection of material in the dark, using Liaison ® equipment, kit from DiaSorin and assuming normal value of 30 ng/ml. For purposes of data analysis dosage of vitamin D were divided into the following ranges: <8 ng/dl; 8-20 ng/dl; 21-30 ng/dl and >30 ng/dl. This division follows the one proposed by Holick[9] defining 30 mg/dl of 25-OH vitamin D as normal; value between 21-30 ng/dl as deficiency; below 20 ng/dl as insufficiency and below 8 ng / dl as severe insufficiency.

Data were analyzed using frequency tables and the chi-square analysis of the groups formed according to the levels of vitamin D. The significance was 5% and the calculations were made using the software Graph Pad Prism version 5.0.

RESULTS

In the ulcer group, patients had a mean age of 57.41 ± 2.11 years and the control group, 60.26±11.22 years (p=0.21). The ulcer group mean creatinine was 0.95 ± 0.22 mg/dl and the control group 0.83 ± 0.15 mg/dl.

The values for vitamin D groups are shown in figure 1. It can be seen that 46.1% of patients with ulcers have values of 25 OH-vitamin D between 8 and 20 ng/dl and 43% of control patients have values above 30 ng/dl (p=0.04).

DISCUSSION

Data from this study suggest that the population of patients with venous leg ulcers have decreased levels of vitamin D in relation to the population without these ulcers. However, these data cannot provide reasons for this occurrence. The authors speculate that this can be due to the fact that patients with venous ulcers were told to stay at home as part of treatment. They also use more clothes in order to avoid the unpleasant odor and bad aesthetic appearance of the wounds, factors that can promote deficiency by decreasing the synthesis of epidermal action of ultra violet rays. However, regardless of cause, it is

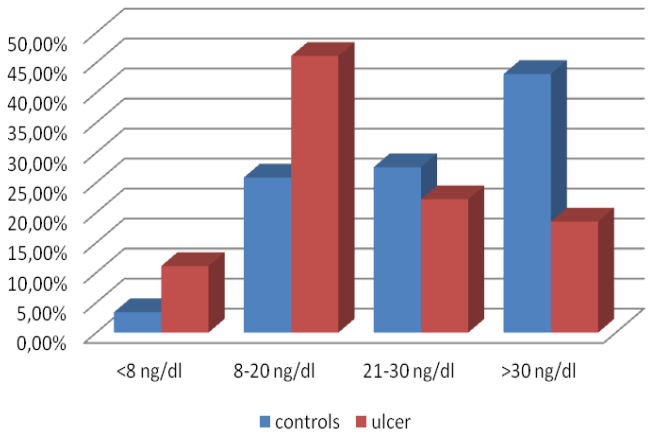

Figure 1 - *Distribution in percentages of serum 25 OH-vitamin D in control subjects (n=58) and with venous ulcers (n=27) with p=0.04.*

possible that these reduced levels contribute to the great difficulties encountered in closure of wounds.

1-25 (OH)2-Vitamin D controls directly or indirectly more than 200 genes, including those responsible for the regulation of cell proliferation, differentiation, apoptosis and angiogenesis[9]. It is known that various extra-skeletal effects of vitamin D – like the local regulation of various tissues and cells in the epidermis – is done through the action of growth factors and cytokines.

According to Shauber *et al.*[7], the active vitamin D acts as a signaling molecule of the innate immune response by increasing the expression of the Toll like receptor -2 potentiating the function of antimicrobial peptides. This action is influenced by histone acetylation and requires the presence of the receptor co-activator steroid 3 (SRC3) – which mediates the activities of histone acetyl transferase (HAT). The HAT activity is important for the performance of cathalecidine and increased expression of CD14 – which increases the antimicrobial function of keratinocytes against microorganisms such as *Staphylococcus aureus*.

Wand *et al.*[20] proved *in vitro* that treatment with vitamin D increases the production of hCAP-18 (a recently discovered protein) in human skin cells by binding to vitamin D responsive element in the human gene. The hCAP-18 is a peptide of the innate defense system and is important in maintaining an environment free of microorganisms. Heilborn *et al.*[5] found a deficiency of this peptide in patients with chronic ulcers of the lower limbs.

These findings raise the possibility that replacement of vitamin D might contribute to the healing process and this is one aspect that deserves further studies. This possibility is particularly attractive when it is observed that the great difficulty in closing these ulcers, with significant loss of quality of life for the patient, high costs to society and early retirement[15-18]. Further studies are needed to clarify not only the cause of the vitamin D deficiency but also to study if the vitamin replacement can affect the healing process.

In conclusion, there is a higher prevalence of vitamin D deficiency in patients with chronic venous leg ulcers than in controls.

R E S U M O

Objetivo: *Estudar se a prevalência da deficiência de vitamina D em indivíduos com úlcera de perna de causa venosa é maior do que em população controle.* ***Métodos:*** *Estudaram-se os níveis séricos de 25-OH-vitamina D por quimioluminescência em 27 portadores de úlcera venosa crônica e 58 controles do Hospital Universitário Evangélico de Curitiba.* ***Resultados:*** *Os níveis de 25-OH-vitamina D3 eram inferiores a 8 ng/dl em 11.1% dos pacientes com úlcera e 3,4% dos controles; entre 8 e 20 ng/dl em 46.1% dos pacientes com úlcera e 25.8% dos controles; entre 21 e 30 ng/dl em 22.2% dos pacientes com úlcera e 27.5% dos controles e acima de 30 ng/dl em 43.1% dos controles e 18.5% dos pacientes com úlcera (p=0.04).* ***Conclusão:*** *Existe aumento de prevalência de deficiência de vitamina D em pacientes com úlceras venosas crônicas de pernas.*

Descritores: *Vitamina D. Deficiência de vitamina D. Úlcera varicosa. Úlcera da perna. Cicatrização.*

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