INTRODUCTION
The principal role of vitamin D is to regulate calcium and phosphate metabolism and to preserve bone tissue mineralization. Nonetheless, its extra-skeletal functions are also appreciated, including those regarding its immunomodulatory, antiproliferative and anti-infective effects. Vitamin D is of further interest in dermatology, as it is synthesized in the skin following exposure to UV rays, and its deficiency has been repeatedly demonstrated in certain diseases, such as psoriasis, atopic dermatitis and vitiligo. In addition, some derivatives of vitamin D synthesis, such as calcipotriol and tacalcitol, are commonly used as medications for the topical treatment of psoriasis and other immune-mediated skin diseases, given their anti-inflammatory properties. This article will deal with the role of vitamin D in psoriasis.

SKIN AS A VITAMIN D SYNTHESIZING ORGAN
Vitamin D and parathormone regulate the homeostasis of calcium and phosphate, acting in the intestine, bone tissue and kidneys. Following exposure to sunlight, 7-dehydrocholesterol (7-DHC or provitamin D) is converted into previtamin D3 in the skin; in turn, previtamin D3 undergoes isomerization into vitamin D3 (cholecalciferol) within several hours [1]. The cutaneous synthesis of vitamin D3 is influenced by various factors, such as skin phenotype, age, the use of sunscreens, season, latitude, the time of exposure to the sun, and the surface area exposed to it [Table I] [2]. Vitamin D3 synthesized in the skin and consumed with food is metabolized in the liver by the 25-hydroxylase enzyme into 25(OH)D3, or calcifediol, which represents the main circulating metabolite of vitamin D; it is the best gauge of general vitamin D status. Levels of 25(OH)D3 between 30 and 100 ng/mL indicate an adequate general vitamin D status, while levels below 20 ng/mL signal vitamin D deficiency, which can be associated with muscular weakness, bone pain and an increased risk of bone fracture. Levels between 20 and 30 ng/mL indicate insufficiency [3]. In turn, 25(OH)D3 is converted in the kidneys, thanks to the 25(OH)D-1α-hydroxylase enzyme, into its metabolically active form, 1,25(OH)2D3. Renal production of 1,25(OH)2D3 is mainly regulated by parathormone. Once activated into 1,25(OH)2D3, vitamin D carries out its biological activity by activating its high-affinity nuclear receptor. Vitamin D receptors are ubiquitous in the body, present also in keratinocytes: this explains why vitamin D can carry out antiproliferative functions. At our latitude, 80% of vitamin D requirements is supplied by exposure to sunlight, while only 20% derives from food consumption. Vitamin D is not present in most foods: the major food source is animal fat, and especially fatty fish, such as salmon and herring [4].

IMMUNE FUNCTIONS OF VITAMIN D
Vitamin D plays an important role in the regulation of the innate and acquired immune systems. Vitamin D can act on the cells of the immune system, including lymphocytes, macrophages, dendritic cells and keratinocytes, in an endocrine, autocrine and paracrine manner. Regarding its effects on the innate immune system, vitamin D stimulates macrophages and epithelial cells to produce antimicrobial peptides such as defensins and cathelicidins.
Antimicrobial peptides perform their microbicidal action by forming destructive pores on the bacterial membrane and by inhibiting enzymatic and mitochondrial activity as well as the synthesis of nucleic acids and bacterial proteins. In addition, the link between vitamin D and its receptor stimulates the mechanism of autophagy by means of the production of IL-37, which mediates the fusion of the phagolysosome with the lysosome. Autophagy removes damaged proteins or organelles and carries out the microbicidal action against intracellular pathogens [6].

Vitamin D modulates some important functions of the acquired immune system [7]. In particular, vitamin D inhibits the expression of cytokines Th1 (IL-2, TNF-α, INF-γ) and promotes that of cytokines Th2 (IL-3, IL-4, IL-5, IL-10).

VITAMIN D AND PSORIASIS

Psoriasis is a chronic inflammatory disease of the skin that affects ca. 3% of the population of Italy; it manifests itself through erythematous scaly plaques located on such areas of the body as the elbows, knees and scalp. In some patients, psoriasis is more diffused and can involve much of the cutaneous surface (Fig. 1). In 30% of cases, psoriasis can be associated with a form of spondyloarthropathy known as psoriatic arthritis, which can result in a clinical progression with many symptoms for the patient and cause serious bone alteration (Fig. 2). Frequently finger- and toenails are also affected, which can become an important source of embarrassment for patients (Fig. 3). Psoriasis is triggered in genetically predisposed individuals as a result of altered reactivity of the immune system.

Psoriasis is mediated by T cells, in particular by the subpopulations Th1 and Th17. In addition, psoriatic skin is infiltrated by myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs), which are attracted to psoriatic skin by chemerin produced above all by fibroblasts. Fibroblasts release pro-chemerin converted into chemerin, thanks to elastase released by the neutrophil granulocytes [10]. mDCs and pDCs express the receptors TLR-7 and -9, which recognize the substances released by the damaged keratinocytes, such as ssDNA, dsDNA and the antimicrobial peptide cathelicidin/LL-37. The LL37 and DNA complexes are powerful activators of the pDCs that release IFN-α and TNF-α, activators of adaptive immune response. LL-37 plays a fundamental role in the pathogenesis of psoriasis, as it also represents an important autoantigen [11]. Most patients with psoriasis express T lymphocytes, including Th17, which are reactive toward LL-37 [11]. Activated mDCs migrate to the draining lymph nodes causing the differentiation of naïve T cells in Th1 and Th17 effector cells. Sensitized Th1 and Th17 CD4+ lymphocyte populations and activated effector CDB+T cells penetrate and accumulate according to a chemotaxis gradient in the skin. The keratinocytes activated by the cytokines that are produced by the Th17 and Th1 lymphocytes (INF-γ, IL-22, IL-17, TNF-α) release chemokines such as CCL20, CCL2, CCL5 and IL-8, which in turn recruit leucocytes, thus expanding the inflammatory process. The accumulation of T lymphocytes in the skin results in the secretion of proinflammatory cytokines of growth factors that stimulate the proliferation of keratinocytes, causing the appearance of psoriatic lesions.

Vitamin D can have significant effects in the pathogenetic mechanism of psoriasis. The gene that controls the expression of the vitamin D receptor (VDR), located on the 12q13.11 chromosome, contains more than 200 single-nucleotide polymorphisms (SNPs). In particular, the four most-studied SNPs (FokI, BsmI, Apal, TaqI) have been associated with various immune-mediated diseases, including psoriasis, atopic dermatitis and asthma [12]. Vitamin D inhibits

[Figures 1, 2, 3]
NF-κB by increasing IκBα levels; it reduces the capacity of NF-κB to bind with DNA; it suppresses the transcription of NF-κB; and it represses the expression of IL-1, IL-6, IL-8 and TNF-α, proinflammatory cytokines that play an important role in the pathogenesis of psoriasis. In addition, vitamin D stimulates the expression of CT1A-4 and Foxp3, which in the presence of IL-2 induce the formation of Tregulatory lymphocytes (Treg). VDR signaling also acts in the JNK/c-Jun pathway, inhibiting cellular proliferation [13]. In vitro studies and trials on animal models indicate the existence of an immunomodulating effect of vitamin D, which is shown by the switch from Th1/Th17 to Th2/Treg. Vitamin D is an important positive regulator in the expression of cathelicidin on the part of keratinocytes. By contrast, vitamin D and its analogs reduce the expression of other antimicrobial peptides, such as psoriasin (S100A7) and koebnerisin (S100A15), on the part of keratinocytes activated by IL17A, IL-22 and TNF-α. Psoriasin and koebnerisin act as powerful chemotactic and alarmin agents, which spread psoriatic inflammation.

Vitamin D deficiency has been reported in patients with psoriasis in various observational studies. In particular, in a study conducted in Florence, Ricceri et al. found that 97% of patients with psoriasis showed vitamin D levels below 30 ng/ml [14]. In another study carried out in Verona on 145 patients affected by chronic plaque psoriasis, 112 by rheumatoid arthritis and 141 healthy controls, we observed that vitamin D deficiency (25(OH)D levels < 20 ng/ml) was significantly greater in patients affected by psoriasis than in those suffering from rheumatoid arthritis and in the controls [15]. This deficiency in the population with psoriasis was particularly frequent during winter as compared to summer (81% vs. 37%). Another study conducted in Spain showed that vitamin D deficiency affected patients with psoriasis and metabolic syndrome more frequently than the control group; there was an inverse correlation between 25(OH)D3 serum levels and glycermia and lipids [16]. Various open clinical trials have been conducted to study the effectiveness of vitamin D3 supplementation in psoriasis and psoriatic arthritis. In the only randomized, placebo controlled trial, 9 of 20 patients (45%) treated with 1 gram of 1-hydroxyvitamin D3 showed a slight improvement with respect to 8 of 21 subjects (38%) given the placebo. This difference was not statistically significant [17]. It has been reported that biological treatment with anti TNF-α biological drugs reduces vitamin D serum levels, unlike other systematic treatments, including those using cyclosporine and acitretin, by means of a mechanism that is currently unknown [18].

CONCLUSIONS

Vitamin D is produced by keratinocytes following exposure to sunlight; it regulates multiple immunological functions, in addition to skeletal ones. Beyond the skeletal system, vitamin D has immunomodulating, anti-inflammatory, anti-inflammatory and anti-inflammatory stress effects; it further controls cellular proliferation. Vitamin D deficiency has been described in several immune-mediated diseases, including psoriasis, which is a common skin disease that can also involve the musculoskeletal system. The clinical significance of hypovitaminosis D in psoriasis as well as the role and mode of its administration is topics currently under study. It is not known whether maintaining adequate levels of vitamin D can prevent the onset of autoimmune diseases or have a favorable effect on the natural course of the diseases, including psoriasis, even if there are some biological presuppositions that warrant such a hypothesis.

References