THE JOURNAL OF INFECTIOUS DISEASES • VOL. 128, No. 2 • AUGUST 1973

Hypovitaminosis A in Patients with Mucocutaneous Candidiasis

Leopoldo F. Montes, Carlos Krumdieck, and Phillip E. Cornwell

From the Departments of Dermatology and Microbiology and Division of Nutrition, University of Alabama in Birmingham, Medical Center, Birmingham, Alabama

Levels of vitamin A and β-carotene in serum were studied in twelve patients with mucocutaneous candidiasis. Subnormal levels of vitamin A were found in seven patients. The remaining five patients had normal concentrations (20–70 μg/100 ml), but they were all in the lower half of the range. All 12 patients had normal levels of β-carotene. One explanation for these findings is that the enzymatic ability to cleave β-carotene (deficiency of carotenoid 15,15′-dioxygenase) may be impaired in some of these patients. The possible relationship between hypovitaminosis A and abnormal keratinization, which would make these patients' epithelia susceptible to fungal invasion, is discussed.

Two broad classifications of mucocutaneous candidiasis are recognized, the severe generalized candidiasis, also called chronic mucocutaneous candidiasis, and the usually localized common candidiasis.

As a result of studies by several groups, it has been possible in recent years to reach a better understanding of chronic mucocutaneous candidiasis. Patients with this condition have infection of the superficial layers of the skin, oral mucosa, upper respiratory tract, gastrointestinal tract, and urinary and vaginal epithelium [1]. Interestingly, despite the massive character of the infection, fungemia is not observed. In most patients there is deficient cellular immunity and apparently normal humoral immunity [2]. Endocrine abnormalities or thymic disorders [3] are sometimes present. Electron microscopic studies have clearly shown invasion of superficial epithelial cells by *Candida albicans.* The fungus perforates the plasma membrane of the epithelial cells, penetrates them, and becomes an intracellular parasite [4].

Such a mechanism of invasion occurs also in the more frequent forms of localized candidiasis like common oral thrush, candidal intertrigo, nail infection, or vaginal infection [5].

The observation of abnormally low levels of vitamin A in serum of one patient with chronic mucocutaneous candidiasis led us to undertake a survey of levels of vitamin A and β-carotene in serum in a group of patients affected by various forms of superficial candidiasis.

Materials and Methods

Twelve patients with different forms of mucocutaneous candidiasis were included in this study. Six milliliters of blood was drawn from each patient, and the concentrations of vitamin A and β-carotene in plasma were determined by a modification of the method of Neeld and Pearson [6]. The accuracy of the assay was increased approximately fourfold by doubling the amount of petroleum ether used in the initial extraction of plasma, and by doubling the intensity of the final color by cutting in half the volume in the spectrophotometer cuvette. The uncertainties resulting from the transient nature of the colored complex formed with trifluoroacetic acid are minimized by use of a Spectronic 505 split-beam recording spectrophotometer. A plot of the optical density at 620 nm against time is obtained, and the highest ab-

Received for publication October 4, 1972, and in revised form March 12, 1973.

This work was supported by career development award no. 5-K3-AI-31, 201-05, by USPHS grant no. AI 09815, by grant RR-32 from the Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health, and by an equipment grant from the Kresge Foundation.

We thank Drs. Harvey Blank, Hady Lopez, Gedeon Matoltsy, and Juan Navia who provided valuable suggestions in this study.

Please address requests for reprints to Dr. Leopoldo F. Montes, Department of Dermatology, 239 Zeigler Building, University of Alabama in Birmingham, Medical Center, Birmingham, Alabama 35294.

sorbancy reading is used to calculate the vitamin A content of the sample. It has been our experience that samples low in vitamin A reach a maximal absorption in less than the 25 sec after addition of the trifluoroacetic acid which, according to the original procedure, must elapse before the sample is read. Obviously, if this time limit is adhered to, concentrations of vitamin A lower than the true amount present will be obtained whenever a dilute sample is assayed.

Results

When matched by age with results that we obtained in over one thousand normal subjects of different ages, levels of vitamin A in serum were below normal in seven of the 12 patients; the remaining five patients had normal levels (20–70 μg/100 ml), but they were all in the lower half of the range. The range of normal values with our modification of the original method is the same as described by Neeld and Pearson [6]. All 12 patients had normal levels of β-carotene in their sera (table 1).

Discussion

While vitamin A has an antikeratinizing effect, vitamin A deficiency has a keratinizing effect [7]. Because of this relationship between vitamin A and keratinization, it seems logical to propose that an abnormality in keratinization of the superficial epithelial cells, secondary to hypovitaminosis A, may account for their susceptibility to invasion by *C. albicans.* Abnormalities of keratinization are not apparent in uninvolved epithelium of patients with mucocutaneous candidiasis, but they are evident in the infected epithelium where hyperkeratosis and parakeratosis are striking (figure 1).

The thick plasma membrane of horny cells in keratinizing epithelia possesses greater resistance to chemical injury than does their keratin content. Thus its primary function seems to be protection of the content of the horny cells [8]. In mucocutaneous candidiasis the continuity of the plasma membrane is disrupted to allow penetration of the fungus [1, 4]. Whether or not vitamin A influences the stability of the plasma membrane of horny cells is still unknown. Vitamin A effects the membrane of other cells and of subcellular organelles [9], and recent evidence has shown that vitamin A may be a normal constituent of plasma membranes [10]. Lopez demonstrated that rats deficient in vitamin A are significantly more susceptible to experimental systemic candidiasis than are normal rats [11]. Anderson and Campbell observed resolution of dermatophytosis in Guernsey cattle after administration of vitamin A [12]. Guernsey cattle are known to convert carotene to vitamin A less efficiently than the other major dairy breeds and to have less resistance to infections with *Tricophyton verrucosum.* Whether or not administration of vitamin A is also beneficial in patients with candidiasis is still unknown.

Table 1. Concentrations of β-carotene and vitamin A in sera of patients with candidiasis.

Patient	Age/sex	Type of candidiasis	β-carotene (μg/ml)	Vitamin A (μg/ml)
1*	2 F	Chronic mucocutaneous	126	10.5
2*	3 F	Chronic mucocutaneous	165	13.2
3	6 F	Chronic mucocutaneous	120	15.0
4	7 M	Chronic mucocutaneous	75	10.5
5*	9 M	Chronic mucocutaneous (hypoparathyroidism)	165	10.8
6	11 F	Chronic mucocutaneous (hypoparathyroidism)	128	21.0
7	32 F	Onychomycosis	120	18.3
8	42 F	Onychomycosis	75	15.0
9	43 F	Chronic mucocutaneous	105	42.3
10*	57 F	Chronic mucocutaneous	105	24.0
11	60 F	Oral candidiasis	120	20.4
12	65 F	Onychomycosis	210	36.0

NOTE. Normal values: β-carotene, 40–230 μg/ml; vitamin A, 20–70 μg/ml.

* Patients 1, 2, 5, and 10 were the subject of separate papers [1, 3, 15] that described their clinical and immunologic status.

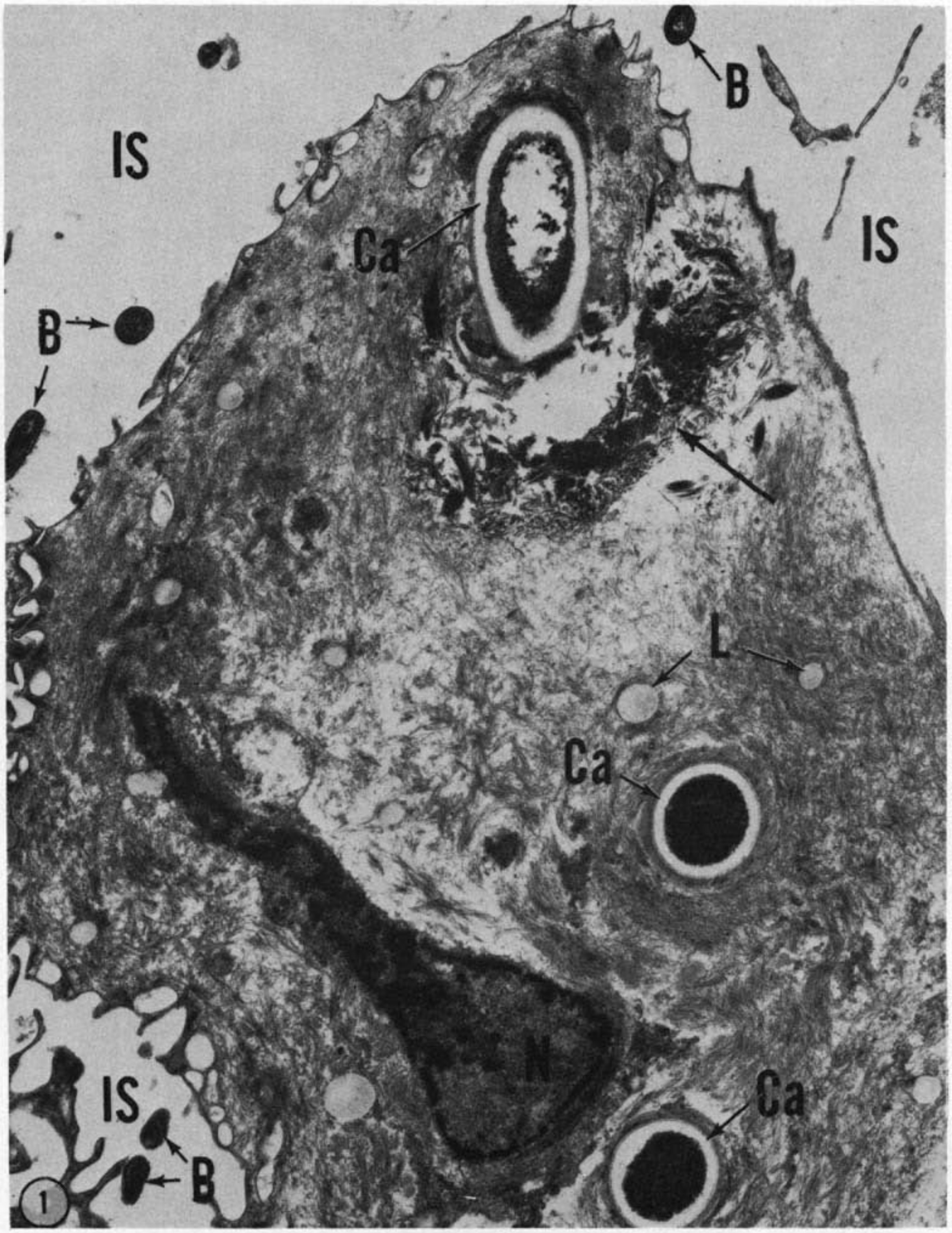

Figure 1. Superficial epithelial cell in oral candidiasis invaded by *Candida albicans* (Ca). As shown by the presence of a prominent nucleus (N), the epithelium is parakeratotic. While *C. albicans* are intracellularly located within the epithelium, bacteria (B) remain extracellular, in the intercellular spaces (IS). Arrow shows remnants of cell organelles that were not eliminated during the keratinization process (×11,000).

A mechanism that would logically explain the observation reported here is impaired enzymatic ability to cleave β-carotene (carotenoid 15, 15′-dioxygenase) [13] in some of these patients. Such a deficiency was described by McLaren and Zekian who pointed out that failure of conversion of β-carotene may also be secondary to hypothyroidism [14]. This may have been the case in patient no. 5 who was affected by severe hypothyroidism [15]. If our hypothesis is correct, the ingestion of β-carotene should not cause an increase in levels of vitamin A in serum. This, as well as an attempt to measure levels of carotenoid 15, 15-dioxygenase in serum, will be the aim of further studies in candidiasis.

References

1. Montes, L. F., Cooper, M. D., Bradford, L. G., Lauderdale, R. O., Taylor, C. D. Prolonged oral treatment of chronic mucocutaneous candidiasis with amphotericin B. Arch. Dermatol. 104:45–56, 1971.
2. Kirkpatrick, C. H., Rich, R. R., Bennett, J. E. Chronic mucocutaneous candidiasis: model building in cellular immunity. Ann. Intern. Med. 74: 955–978, 1971.
3. Montes, L. F., Ceballos, R., Cooper, M. D., Bradley, M., Bockman, D. Chronic mucocutaneous candidiasis, myositis and thymomo. A new triad. J.A.M.A. 222:1619–1623, 1972.
4. Montes, L. F., Wilborn, W. H. Ultrastructural features of host-parasite relationship in oral candidiasis. J. Bacteriol. 96:1349–1356, 1968.
5. Montes, L. F. Oral amphotericin B in superficial candidiasis. Clin. Med. 78:14–17, 1971.
6. Neeld, J. B., Jr., Pearson, W. N. Macro and micromethods for the determination of serum vitamin A using trifluoroacetic acid. J. Nutr. 79:454–462, 1963.
7. Rothman, S. Physiology and biochemistry of the skin. University of Chicago Press, Chicago, 1954, p. 382.
8. Matoltsy, A. G., Parakkal, P. Membrane-coating granules of keratinizing epithelia. J. Cell Biol. 24:297–307, 1965.
9. Roels, O. A. Biochemical systems. *In* W. H. Sebrell and R. S. Harris [ed.] The vitamins. Vol. 1. Academic Press, New York, 1967, p. 209.
10. Logan, W. S. Vitamin A and keratinization. Arch. Dermatol. 105:748–753, 1972.
11. Lopez, H. Estudio experimental de la accion patogena comparada de la *Candida albicans* en animales sanos y en animales sometidos a dieta de carencia de vitamina A. Boletin del Instituto Universitario Habana, Cuba 2:22–54, 1946.
12. Anderson, P. C., Campbell, J. R. Vitamin A therapy for "winter ringworm" in Guernsey cattle. J. Invest. Dermatol. 42:173–174, 1964.
13. Olson, J. A., Lakshmanan, M. R. Enzymatic transformation of vitamin A, with particular emphasis on carotenoid cleavage. *In* H. F. DeLuca and J. W. Suttie [ed.] The fat soluble vitamins. University of Wisconsin Press, Madison, 1969, p. 213–226.
14. McLaren, D. S., Zekian, B. Failure of enzymic cleavage of β-carotene. The cause of Vitamin A deficiency in a child. Am. J. Dis. Child. 121:278–280, 1971.
15. Montes, L. F., Pittman, C. S., Moore, W. J., Taylor, C. D., Cooper, M. D. Chronic mucocutaneous candidiasis. Influence of thyroid status. J.A.M.A. 221:156–159, 1972.