Vitamins and mineral as skin nutrients

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Synopsis

The deficiency of many vitamins due to decreased intake or reduced bio-availability can determine skin lesions of different types and seriousness. In some cases, e.g. niacin deprivation where the early clinical symptom is dermatitis, vitamin deficiency can be recognised mainly by skin alterations (stomatitis, glossitis and seborrhoeic dermatitis). The ascertaining of a possible vitamin deficiency is important to correctly evaluate the pathogenetic mechanisms causing dermatitis; in fact, the clinical symptoms of a vitamin deficiency are sometimes very similar to those of EFA deficiency. As important as the effects of vitamin deprivation are the consequences of a deficiency of minerals and ultratrace elements. Particularly relevant from this point of view are manganese, zinc, copper, silicon, selenium, for the physiological role they play in skin formation and maintenance. Last but not least the following consideration: the entire skin is accessible to the clinician. It is never overemphasized that the whole surface area of any patient should be inspected whenever it is possible. Such an inspection, which should be part of any thorough physical examination is often overlooked not taking into due account that it could provide important information on the general nutritional condition of the patients with special regard to their vitamin and mineral intake.

Riassunto

La carenza di molte vitamine dovuta ad una diminuzione nell'assunzione o nella biodisponibilità possono provocare lesioni della pelle di vario genere e entità. In alcuni casi, ad esempio in mancanza di niacina, la dermatite è il primo sintomo clinico. La carenza di vitamine può essere riconosciuta soprattutto dalle alterazioni della pelle (stomatiti, glossiti e eczemi seborroici) anche prima di una possibile identificazione delle funzioni delle vitamine.

L'accertamento di una possibile carenza di vitamine è importante al fine di poter valutare correttamente i meccanismi patogeneticci che provocano le dermatiti, infatti i sintomi clinici della carenza di vitamine sono talvolta molto simili a quelli della carenza di EFA. Le conseguenze derivanti da carenza di minerali e di elementi ultratrace sono gravì quanto quelle della carenza di vitamine. Da questo punto di vista, risultano particolarmente importanti: il manganese, lo zinco, il ferro, il potassio, il rame, il cobalto, il silicio, il selenio, il cromo e il molibdено per il ruolo fisiologico nella formazione della pelle e nel suo mantenimento. Ultime, ma non per questo meno importanti, le seguenti considerazioni: l'intera superficie della pelle è "accessibili-
le" al clinico ma il fatto che tale area dovrebbe essere esaminata ogni qualvolta che si presenta l'occasione non viene mai messo abbastanza in evidenza. Un simile esame, che dovrebbe far parte di ogni visita accurata è spesso lasciato da parte e non debitamente considerato, dato che invece potrebbe fornire delle informazioni importanti sulle condizioni nutrizionali generali dei pazienti soprattutto per ciò che riguarda vitamine e minerali.

Résumé
Le manque de beaucoup de vitamines du à une diminution d'immission ou de la biodisponibilité peut provoquer plusieurs lésions plus ou moins graves. Quelques fois, la dermatite est le premier symptôme clinique du manque de vitamines, c'est le cas par exemple de la niacine. L'avitaminose peut être reconnue surtout grâce aux altérations de la peau (stomatites, glossites et eczémas séborrhéiques) même avant qu'il soit possible vérifier les fonctions des vitamines. La vérification d'une éventuelle carence de vitamines est très importante pour pouvoir évaluer d'une façon correcte les mécanismes pathogéniques qui provoquent les dermatites; en effet, quelques fois, les symptômes cliniques du manque de vitamines ressemblent aux effets d'une carence de EFA. Le niveau de gravité du manque de substances minérales d'éléments «ultratrace» ou de vitamines est toujours le même. A ce propos le zinc, le fer, le manganèse, le potassium, le cuivre, le cobalt, le silicium, le sélénium, le chrome et le molybdène sont particulièrement importants pour le rôle physiologique qu'ils jouent dans la formation de la peau et pour la maintenir en bon état. Dernièrement, il faut rappeler que l'entière surface de la peau peut être examinée par le clinicien mais on devrait le faire chaque fois que l'occasion se présente, à chaque visite des patients mais, au contraire, on ne tient pas compte de cette pratique. Elle pourrait nous donner des informations très importantes sur les conditions nutritionnelles des sujets (surtout pour les vitamines et les substances minérales).

Resumen
La falta de muchas vitaminas debida a un reducido aporte o a una menor disponibilidad puede determinar lesiones de la piel de diferente tipo y gravedad. En algunos casos, por ejemplo la falta de niacin, cuyo primer sintoma clinico es la dermatitis, la carencia de vitaminas se puede reconocer sobre todo por alteraciones de la piel (stomatitis, glossitis y dermatitis seborréicas) aun antes de identificar las funciones de las vitaminas. La comprobación de una posible falta vitamínica es importante para evaluar correctamente los mecanismos patogénicos que causan la dermatitis; en efecto, los síntomas clínicos de una carencia vitamínica son a veces muy semejantes a los de una carencia EFA. Igualmente importantes son las consecuencias de una falta de minerales y de elementos «ultratrace». Muy notables, desde este punto de vista, son manganeso, cinc, hierro, potasio, cobre, cobalto, silicio, selenio, cromo y molibdeno por su papel fisiológico en la formación y la conservación de la piel. En fin, pero no último, el hecho que la entera piel es accesible a los clínicos. Nunca se subraya demasiado que toda la área superficial de cada paciente tiene que ser examinada toda vez que es posible. Este examen, que tendría que formar parte de otro fisico más profundo, a menudo se considera de escasa utilidad, mientras que podría proveer importantes informaciones sobre la condición nutricional general del paciente, con particular respecto a la asunción de vitaminas y minerales.
Synopse
Der Mangel an vielen Vitaminen, der auf eine verringerte Einnahme oder eine gerinne biologische Verfügbarkeit zurückzuführen ist, kann Hautschäden verschiedener Art und Ernsthaftigkeit verursachen. In einigen Fällen wie z. Bsp. bei Niacin-Entzug, dessen frühes klinisches Symptom die Dermatitis ist, kann Vitaminmangel hauptsächlich durch Hautveränderungen erkannt werden (Stomatitis, Glossitis und seborrhöische Dermatitis), und das sogar bevor die Funktionen der Vitamine erkannt werden können. Die Feststellung eines möglichen Vitaminmangels ist für die korrekte Berücksichtiung der pathogenetischen Mechanismen, die Dermatitis verursachen von Wichtigkeit, tatsächlich sind die klinischen Symptome eines Vitaminmangels manchmal denen eines EFA-Mangels sehr ähnlich. Die Konsequenzen eines Mangels an Mineralien und Spurenelementen sind jedoch genauso ausschlaggebend wie die eines Vitaminmangels.


Introduction
It is well documented that malnutrition results in skin changes and lesions of different types and seriousness. In case of protein-caloric deficiency chronic wasting is accompanied by loss of subcutaneous fat and produces fine wrinkling of the skin, especially in old subjects where the skin itself has lost its elasticity. In protein-deficiency conditions the skin is shiny and often friable over areas of dependent edema, due to reduced plasma oncotic pressure which in turn is caused by low plasma albumin concentration. A tendency to excessive bruising may occur, even in the absence of any other signs of deficiency of vitamins C and K, presumably as evidence of increased fragility of the capillary walls or loss of strenght of the supporting connective tissue.

As a matter of fact, protein or caloric malnutrition or both are accompanied by deficiencies of specific nutrients, especially vitamins, essential fatty acids and minerals giving rise to dry and scaly skin (EFA deficiency), persisting mounds of keratin around the hair follicles (folicular hyperkeratosis, due to vitamin A deprivation), perifollicular hemorrhages and cutaneous petechiae, which are seen together almost exclusively in scurvy because of a deficiency of ascorbic acid. As a rule the lack of many vitamins, due to decreased intake or reduced bio-availability, can be early recognized mainly by skin alterations (stomatitis, glossitis and seborrhoeic dermatitis); in some cases, e.g. niacin deprivation where the early clinical symptom is dermatitis, the clinical description of the skin pathology was reported even before the functions of the vitamins itself could be identified.
The functions and the effects of deprivation of minerals and vitamins can be better focused and understood when the main compartments of the skin are considered separately. In this presentation we will deal with the influence of such nutritional factors on the biochemistry and functions of derma macromolecules.

Macromolecules of the intercellular matrix

The macromolecules synthesized by fibroblasts are the main and bulky components of the dermis and can be grouped into four categories: 1 - collagen; 2 - elastin; 3 - proteoglycans; 4 - structural glycoproteins which constitute together with glycosaminoglycans the so called «ground substance». These macromolecules are build up according to a «coded» program which reflects the characteristics of morphogenesis, maturation and aging of the skin. The exact timing of the biosynthesis process is due to the need of a strict coordination between the synthesis of macromolecules and the morphogenesis of the derma fibrous network. The auto rearrangement of these molecules is an unencoded process and it happens because of the mutual affinity of the molecules. Should this biosynthesis program be modified the dermis architecture would be distorted. Even if the occurred changes are due not only to modifications in the rate of synthesis but result also from the excretion of lytic enzymes such as collagenase, elastase and from other lysosomal digestive processes, there are also some external factors which can influence skin structure: one is represented by the nutritional aspects.

Minerals, ultratrace elements and vitamins: how nutrients can selectively influence dermis components

a) Biosynthesis of collagen

The chemistry of the primary component of collagen is remarkably constant for all the different tissues; therefore the differentiation depends upon the changes it undergoes after its initial production in the fibroblast, i.e. we assume that we are dealing with a post-translational process (for details on collagen biosynthesis in skin see ref. 1,2). Thus the degree of hydroxylation of proline and lysine will determine the number of these molecules available for subsequent oxidative deamination to form stable collagen fibres. The hexoses (glucose and galactose) contained in a covalent linkage in tropocollagen molecules make the hydroxylysine residues they are attached to be more easily deaminated (3). The more hydroxylsine is formed, the more material will be available for the production of firm cross-linkages. Also the association of hydroxylsine with complexes of galactose and glucose residues of the glycosaminoglycans hinders the extent of cross-linking and thus exerts a modifying effect on the physical state of collagen.

In this respect factors in the environment of the developing connective tissue have a critical determining influence on the nature and physical characteristics of the tissue finally produced. These factors include trace elements and vitamins such as:

1 - manganese, a cofactor of the glycosyltransferase acting on the lysine residue «selected» to be hydroxylated (4);

2 - vitamin C, folate and ferrous iron involved in the hydroxylation of proline and lysine acting as an electron donor in the oxidative system (5). Moreover, some authors have reported that one of the roles
of vitamin C in the enhancement of collagen synthesis is related to the formation of large synthesizing polysome (6);

3 - in order to build up the collagen it is necessary to join together molecules of tropocollagen with intermolecular bindings; this is achieved by converting the lysine residue into its aldehyde derivative, allylisine; this step is enzymatic and it is brought about by a copper-dependent amine oxidase; therefore copper-deficient diets prevent the formation of the intermolecular bonds (7, 8).

4 - Two additional elements are needed for assembling the final collagen structure, zinc and silicon. The action of the former was recognized in the '70s, mainly in wound healing which indicates its involvement in collagen synthesis (9, 10). A dependence on silicon for maximal prolyl hydroxilase activity has been demonstrated (11); moreover, as it will be discussed later, this element plays an important structural role in the final framework of the dermis.

b) The second macromolecular system of the dermis: glycosaminoglycans, glycosaminoglycuronoglycans and glycoproteins

The non-cellular portion of the dermis consists broadly of two parts: 1 - the protein moiety (collagen and elastin) and 2 - a number of complex mucopolysaccharides, which according to the modern terminology are nowadays referred to as glycosaminoglycans (GAG), glycosaminoglycuronoglycans (formerly acidic mucopolysaccharides) and proteoglycans. The chemistry and biosynthesis of these compounds are beyond the scope of this presentation (details can be found in ref. 12). Broadly fig. 1 outlines the general steps involved in proteoglycan synthesis (14). The initial translation product referred to as the precursor protein is released in-

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**Fig. 1:** Proteoglycan biosynthesis.
to the rough endoplasmic reticulum having attached N-linked oligosaccharide built up only by many residues of mannose (high-mannose portion). When it is processed in the Golgi complex several post translational modifications occur which include the following: 1- addition of the glycosaminoglycan chains to the appropriate serine and threonine residues; 2- addition of O-linked oligosaccharides; 3- conversion of the high-mannose N-linked oligosaccharides to complex forms which include other saccharide residues (galactose, N-acetylhexosamines, fucose, sialic acid); 4- possible processing of the protein by removal of portions of the polypeptide. In their natural state glycosaminoglycans exist in firm association with tropocollagen molecules thus controlling the degree of polymerization; moreover, they might have an "organizing" role in that they determine the architectural design of the connective tissue by controlling the orientation of the fibrous elements of the dermis and its physical state: as to whether it is a highly fibrous structure or a gel containing a great content of water. In fact, GAG, which can be regarded as polyanions and are located between collagen fibrils, can retain water to an extent which is related to their chemical structure (1). In this respect hyaluronic acid plays a very important role; because of its great capability to retain water and of its natural elasticity, hyaluronic acid is one of the most important dermal components responsible for its gel-like properties. Moreover, the network of hyaluronic acid molecules has a high electrical charge and acts as an anionic charged membrane (13); therefore by acting as a molecular sieve, it allows smaller molecules to pass whilst it prevents the passage of macromolecules (1). The degree of viscosity of the hyaluronic acid gel can be modified by depolymerization either enzymatically or by agents such as cysteine, riboflavin, hydroquinol

Fig. 2: Schematic representation of proteoglycan aggregate (modified from Lennarz WJ: The Biochemistry of Glycoproteins and Proteoglycans. Plenum Press, 1980).
ne and ascorbic acid. Free radicals produced by irradiation can also have a depolymerizing effect.

Hyaluronic acid and proteoglycans can form large aggregates which are schematically outlined in Fig. 2.

Structural glycoproteins which include specialized molecules such as fibronectins and laminine are synthesized in situ from the mesenchymatous cells of the connective tissue and can be found in basal membranes and in the intercellular space, free or associated with the other proteins or proteoglycans of the matrix. Fibronectins are large proteins that are secreted by fibroblasts and are also normally found in serum. Fibronectin forms immobilized fibrillar arrays across the surface of many cells, especially fibroblasts, and interconnects cells together. It is made up of two not identical polypeptides which are linked near the C-terminus by disulfide bonds. Native fibronectin contains specific domains with specific high-affinity binding sites for the cell surface, collagen, fibrin, proteoglycans, sulfated GAG and extracellular proteins and polysaccharides (Fig. 3) (15).

Laminin, a 400,000 m.w. fibrous glycoprotein, is a linking factor for epithelial cells and promotes, by an unknown mechanism, their differentiation. Whereas fibronectin binds to all types of collagen, lamin binds preferentially to type IV collagen.

Vitamins and trace elements involved in the biosynthesis and organization of this macromolecular system of the dermis are:

1. vitamin A. Retinoic acid and retinol, two forms of vitamin A, are polyisoprenoid compounds widely distributed in animal tissues, capable of stimulating glycoproteins and GAG synthesis (16) (see Fig. 4);

2. the elongation process generating the complex type oligosaccharides of glycoproteins and GAG requires a series of spe-

Fig. 3: Model of the structural domains of fibronectin.
cific glycosyltransferase enzymes («one linkage, one glycosyltransferase» theory) (see Fig. 5) requiring manganese.

3 - as previously pointed out, silicon plays an important metabolic role in connective tissue; a structural role for this mineral has also been proposed mainly supported by the finding that it is a component of animal glycosaminoglycans and their protein complexes. In the connective tissue silicon contributes to the structural framework by forming links or

![Diagram of the biosynthesis of N-glycosidically linked oligosaccharide chains.](image-url)

Fig. 4: Possible role of retinol in the biosynthesis of N-glycosidically linked oligosaccharide chains. Synthesis of the dolichol-oligosaccharide intermediate begins with synthesis of the primer N-acetylgalactosaminyl-pyrophosphoryldolichol (reaction 1) and proceeds, possibly by direct donation from GDP-Man, to the Man₃ intermediate (reaction 2). The chain is then built up to the Man₅Glc₃ intermediate by the addition of dolichol-linked mannose (reaction 3) and glycosyl residues (reaction 4), whereupon the lipid-oligosaccharide is transferred to an asparagine residue of the acceptor protein (reaction 5). Processing to the final «complex» or polymannose glycoprotein then occurs (reaction 6). (Adapted from Montgomery et al. Biochemistry, 1983). The phosphorylation of retinol to RetP and the formation of a mannosyl adduct (MRP) analogous to MDP have been demonstrated (reaction 7). It has been postulated that MRP can participate in donation of mannol residues to protein, either in a manner analogous to MDP by donating residues to the growing oligosaccharide precursor (reaction 3) or in a mechanism involving direct donation to glycoprotein (reaction 6). Abbreviations used in this figure are: DolP, dolichyl phosphate; RetP, retinyl phosphate; UDP, uridine diphosphate; GDP, guanosine diphosphate; MDP, mannosyl dolichyl phosphate; MRP, mannosyl retinyl phosphate; Man, mannose; GlcNAC, N-acetylglucosamine; Asn, asparagine.
bridges within and between individual polysaccharide chains and perhaps by linking polysaccharide chains to proteins (Fig. 6). In this way, silicon may aid in the development of the architecture of the fibrous elements of the connective tissue and may contribute to its structural integrity by providing strength and resilience (17); 4 - to prevent and/or control hyaluronic acid depolymerization, vitamin A and E and selenium might have a role as scavengers of free radicals.

c) The elastic tissue of the dermis: elastin

The elastic fibres are an integral part of the dermis but their constitution is so different from collagen that it seems better to consider this tissue as a separate entity. It has a different amino acid composition and in the skin it is apparently in a different physical state. Because of these chemical and physical differences, it is possible that elastic fibres may be produced by a different group of cells than those producing tropocollagen. Thus, the-

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Fig. 5: Proposed sequence for the processing of peptide-bound N-linked oligosaccharide chains: ■, N-acetylglucosamine residues; ○, mannose residues; ▼, glucose residues; ●, galactose residues; □, sialic acid residues; and ▲ fucose residues. The wavy line represents the polypeptide chain; the broken line is the mRNA. (Modified from Lennarz W.J: The Biochemistry of Glycoproteins and Proteoglycans. Plenum Press, 1980).
There is the hypothetical possibility that clones of special fibroblasts (elastoblasts) may be present in the dermis together with collagen-producing cells. It is also possible that the same cells may «switch» from producing tropocollagen to the formation of elastin (18). The composition of elastin is unusual in that it contains large amounts of proline, glycine, alanine and a greater quantity of valine than any other known protein. Moreover, there are cross-links not present in collagen which are characteristic of the elastic tissue, due to the condensation of three oxidized lysine residues present in the precursor molecule, tropoelastin, with an intrachain residue of lysine according to the scheme of Fig. 7, giving rise to desmosine and isodesmosine (19). The biosynthesis of elastin requires also the secretion of structural glycoproteins by fibroblasts (20).

For these reasons a complete maturation of proelastin to tropoelastin and elastin requires some of the nutritional factors needed for collagen maturation and matrix formation, i.e. mainly copper, manganese and vitamin A.

Conclusive remarks

The functional integrity of the dermis depends on the availability of proteins and energy as well as of vitamins and minerals.

Also the «physiological» aging process of the skin is impaired and speeded up by protein-caloric malnutrition and by a deficiency of selected nutrients. Since the entire skin is accessible to the clinician it should be inspected whenever it is possible because this examination could provide important information on the general nutritional condition of the patient with special regard to his vitamin and mineral intake.
Fig. 6: Model of the arrangement of fibronectin, collagen and proteoglycans in the extracellular matrix. Role of silicon.

Fig. 7: Assembling mechanism of desmosine.
REFERENCES


