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Nutrition and skin. Collagen integrity: a dominant role for amino acids

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Abstract The skin is an important organ, and the need for attention to its metabolic requirements is often underestimated by professionals involved with its integrity and beauty. Amino acids are the indispensable nutritional basis for the maintenance of its integrity. The skin has very peculiar amino acid needs, which should be acknowledged and supplied if necessary.

The skin makes up for about 8% of an adult's body weight, and its gross protein content is around 22%, accounting for one eighth of the body's total proteins. Collagen makes up for 70% of the total nitrogen content of skin proteins.

Because of its tensile strength, this extracellular protein bears structural stresses either as the connective tissues of any parenchymal organ (such as liver, kidneys, intestines, lungs, and heart) or as the protein matrix of the skeleton and its related structures (bone, teeth, cartilage, tendons, and ligaments), or it forms the fibrous matrix of the skin and blood vessels. Collagen is therefore the most abundant protein in human body. Its tensile strength and flexibility are the result of a complex molecular structure, itself the consequence of a well-described peculiarly regular amino acidic content.

Although there are almost 20 different types of collagen, their composition is fairly similar: from any given 3 amino acids, one is glycine, the smallest of all amino acids. The rather monotonous composition of collagen peptides is not only limited to the absolutely regular recurrence of the glycine residue, but this is also accompanied, in the following 2 positions, called *positions X and Y*, by a very frequent Y position occupied by hydroxyproline, in up to 50% of cases, and hydroxylysine, in most of the remaining sequences. These amino acids are typical of collagen structures and are very rarely found in other proteins. One of the most interesting characteristic of collagen synthesis is in that either hydroxyproline or hydroxylysine is the metabolic dead end of proline and lysine, which means it is possible that they have to be discarded once collagen structure becomes old and needs to be renewed. This is due to the fact that to obtain maximum physicochemical performance, "fresh" proline and lysine should be inserted in the newly formed propeptide. Only after the synthesis of the full precursor chain a specific vitamin C–dependent hydroxylase, acting stereologically (ie, it is activated by particular parts of the molecule) on the Y position, is activated to attach them to an $-OH$ moiety. This is fundamental for a cascade of events, which allows a Maillard reaction to form tight inter- and intramolecular bonds, entangling 3 peptides into fibrils and tightening them solidly into the complex collagen units.

Scurvy clinical presentation, that is, bones, tendons, skin, and vessel fragility, and poor wound healing, is related to the impaired activity of this enzymatic activity.

Glycine positioned among any 3 amino acids allows regular bending of the peptide strand and the formation of a left-handed helical structure, intertwined with 2 other peptides in a right-handed superhelical structure, very similar

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to the structure of a rope. The small differences in amino acids driven by the regularity of sequences in any peptide allow to distinguish about 33 genetic variations of them (subunits), and the different types of collagen, identified by a Roman numeral, differ in the type of subunits. As a general example, the most abundant collagen type, called *type I* (ie, one), which is present in skin, bones, tendon, blood vessels, and cornea, has a triple chain composition formed by 2 α_1 and 1 α_2 chains. Elastin also has an extremely regular composition of amino acids but a far greater abundance of a particular amino acid, leucine.

Amino acids are the "letters" indispensable to the DNA-dependent "writing" of proteins. But only carbohydrates (ie, glucose) or lipids (with a noteworthy exception of few polyunsaturated fatty acids) can be synthesized by the liver by using amino acids. Conversely, amino acids cannot be originated from carbohydrates or lipids unless certain amino acid donors such as $-NH_3$ (ammonia) are present. These peculiar 10 amino acids can only be synthesized in extremely small amounts, and then only locally. These have therefore been defined "essential" amino acids and should be continuously introduced with foodstuff in amounts capable of meeting turnover needs. Neither glycine nor proline is an indispensable amino acid, and they can be synthesized from other amino acids, whereas lysine also is an essential one. Another fundamental peculiarity of protein synthesis, common to collagen and to any other protein, is that all amino acids to be found in the final protein should also be present inside the cells, at their synthesizing sites, and in the correct number of molecules.

The need of simultaneous availability of all amino acids (think of them as letters of the alphabet) to "write" a protein (the "word" you need) is a limiting factor for the synthesis. The availability of amino acids for protein synthesis is threatened by their eventual duty in the maintenance of energy needs, which can consume an unpredictable amount of different amino acids. Not all amino acids have an equal degree of participation in this fate.[1,2] This mechanism may become dramatically relevant in all energy-demanding pathological conditions that increase burden on metabolism.[3,4]

Indeed, the specific dominant role of amino acids as rulers of metabolism requirements springs from the fact that, from among the peculiar atoms that make up the mammal body, carbon, oxygen, hydrogen, and nitrogen, only the first 3 can be introduced with either carbohydrates, lipids, or proteins, whereas nitrogen needs can only be replenished by amino acids.

It is therefore important to stress the notion that, without amino acids, no protein synthesis can take place, and when no synthesis is possible, the first metabolic reaction is to reduce catabolism to maintain the integrity of the complex protein machinery of cells and tissues. Although this inhibitory process is activated for survival purposes, it causes a general aging of proteins, which become older and older and eventually lose their efficiency, whether they are contractile, structural (ie, collagens), enzymatic, or defensive (ie, antibodies) proteins.

The role of the stoichiometric ratios of special formulation of amino acids in the control of anabolic/catabolic ratios, and in the drive entry of carbohydrates or lipid-derived metabolic intermediates, has been recently detailed[5] and proved to be effective in reversing insulin resistance and malnutrition in patients with type 2 diabetes affected by chronic heart failure and in protecting against ischemia reperfusion injury.[6,7]

We should not be surprised, at this point, at the results reported by a recent randomized, prospective, controlled, multicentric study, which observed a twice-increased rate of pressure ulcer healing in the group treated with collagen protein hydrolysate supplement, when compared with the group that received the same standard wound care plus placebo.[8] On the contrary, in a previous study, topical collagen and hydrocolloid dressings did not show significant differences in healing outcome.[9] There is no contradiction in those studies: the oral route allows a more elevated amino acid supplementation to the dermis and, consequently, a more abundant supply of appropriately not hydroxylated proline and lysine to dermis fibroblasts. It seems likely that an excessive presence of amino acids at the dead end of their metabolic flows (we are speaking of hydroxyproline and hydroxylysine) impairs, and not promotes, any synthetic improvement topically. On the contrary, flooding plasma with a concentrated and fortified supplement should provide a far better amount of hydroxylated lysine and proline, effectively promoting immediate synthesis improvement of procollagen assembly and hydroxylation before secretion.

On these bases, one would be tempted to hypothesize an abundant choice of articles dealing with correct nitrogen intake for the maintenance of skin youth, and deeply discussing amino acids in terms of skin nutrition, or dealing with the antiaging properties of selected amino acid formulations suitable to promote skin integrity and beauty. This is wrong.

A PubMed search (http://www.ncbi.nlm.nih.gov) on "nutrition influence on dermis" results in just 2 articles, dated 1994 and 2005, one of them dealing with the relationships between serum cholesterol and skin cholesterol synthesis in humans,[10] the other studying the relationship between diet and skin in the aging rat.[11] This latter is interesting because it shows that aging and malnutrition reduce the thickness and depth of epidermis and dermis, with a cumulative effect if aging and malnutrition were present in the examined population.

A "nutrition and skin" search gives back 4530 articles, with 142 references published in 2005. Twenty-eight articles dealt with skin-fold measurement or hair or body composition and nutritional habits or malnutrition; 25 articles examined the possible pathogenic role of vitamins (12 articles, most about vitamin D) and/or micronutrient deficiency or introduction.[12] In 12 articles, skin lesions and wound care were related to peculiar pathological conditions.[13,14] Food and experimental or veterinarian reports

were studied by 26 articles, food and allergies were studied by 14 reports, 25 articles studied obstetric or neonatal pathological conditions or nutritional deficiencies,[15,16] and 6 dealt with clinical dermatologic conditions.[17] One article was a letter about the definition and possible future of nutrigenomics, using as an example the knowledge about genetic control of the enzyme critical for folate regeneration methyltetrahydrofolate reductase,[18] and one was about self-perception of technical skills by nurses.

In this group, we were able to identify only four articles that generically assessed the malnutrition/skin relationship, two dealing with selective nutritional deficiencies and skin in internal medicine patients (pellagra and vitamin B_{12} deficiencies in two malnourished patients,[19] essential fatty acids and vitamins[20]), another with the identification of serum amyloid A production by white adipocyte and its diet regulation,[21] and a fourth observed the negative incidence of protein-energy malnutrition effects on infection rate, healing, and mortality in elderly burn patients.[22] The search engine of the *American Journal of Clinical Nutrition* showed 26 entries when asked for "skin," 11 of which studied subcutaneous fat thickness evaluation and significance in different pathological conditions,[23-33] 2 dealt mostly with essential fatty acids metabolism and skin,[34,35] 9 were about vitamins (mostly vitamins D and E),[36-42] and 6 specifically studied protein nutrition and dermis.

Two were published in 1970 by the same author and reported alterations of proteins and amino acidic content in plasma and skin of kwashiorkor patients,[43] and the effects of experimental protein deficiency on skin weight.[2]

One was published in 1975 and studied the ratio between urinary and sweat nitrogen losses.[44]

In 2001, 2 articles were published about wrinkling and aging skin, focusing on the role of dietary fatty acids and micronutrients.[34,35] One of the same authors published a further study[45] in 2003, reporting noninvasive biophysical methods to assess skin variables such as hydration, surface pH, and sebum content in a population studied for its food intake.

Two different semiquantitative and qualitative food-frequency questionnaires recorded 3 months of introduction of macronutrients and fibers, and of micronutrients and fluid, in an attempt to find possible associations with skin conditions noninvasively evaluated.

Conversely, a very satisfactory series of articles is obtained by searching for "malnutrition and wound healing," which I believe is the right choice. Fifty detailed nutrition requirement articles were found in October 2006, starting the search from December 2003, among a total of 433 articles. In 2006, several excellent articles were published, which may be worthy of dermatologists' attention, even those not particularly interested in developing advanced knowledge in wound care.

Reviews were 19, none with a free full text option, and many did not even have abstracts. Eight articles have been published on the same newspaper (*Advanced Skin and Wound Care*), whereas the others have been published on 36 different magazines. Two articles are in other languages than English (French and Spanish). If you wish to invest in just one article, I suggest the excellent "Practical aspects of nutritional support for wound-healing patients," published on the *American Journal of Surgery*,[46] because it gives a wide and wise overview of the many aspects of wound healing related to nutritional problems and of the possible solutions, with a very professional but practical and easy-to-understand approach to the most advanced management techniques. I also recommend either "Nutritional considerations in wound care"[47] or "Do malnutrition and nutritional supplementation have an effect on the wound healing process?,"[48] which would be appreciated by either the scientifically advanced or the most empirical reader. An intriguing article should attract physicians mostly involved in prevention, "Nutritional status and food intake in nine patients with chronic low-limb ulcers and pressure ulcers: importance of oral supplements," which reported high frequency of micronutrient deficits and protein-calories malnutrition in a small group (nine patients) of people aged 71 ± 10 years before and after surgery.[49] This article reminds us that most dermatological problems could be prevented not with topical therapies, but with a more careful approach to general metabolism requirements. In case of doubts about a peculiar patient, the advice of a specialist in internal medicine and clinical nutrition is priceless.

A must do as the very first easy-to-read and most synthetic (sometimes excessively so) document, therefore unsatisfactory for most professionals, could be found at the "National Pressure Ulcer Advisory Panel. Frequently asked questions" Internet address. Available at http://www.npuap.org.

There is still a long way to go before nutritional skills and skin are linked and promoted correctly.

Therapeutic box

A major claim of most cosmetic treatments is the efficiency in skin nutrition. To date, basing on marketing attractive claims, many different molecules or mixtures of vitamins, salts, and vegetable extracts have been put on the market, although with unpredictable efficiency.

Amino acids are unique molecules because they are the only substrate really necessary for promoting the synthesis of any protein. The adequacy of type and number of amino acids required for protein synthesis can be predicted on the basis of the quality and quantity of amino acids present in each protein. But collagen synthesis is different because some of its amino acids should be provided in the precursor form to activate the synthetic drive by fibroblasts. Collagen synthesis is, therefore, efficiently maintained only when those specific amino acids are continuously available and are present in a specific ratio.

A functional cluster of amino acids that is suitable for collagen synthesis promotion is protected by patents (eg, US patent no. 5 198 465) and is widely available in Europe in the form of a topical cosmetic, as well as a medical device, for the treatment of localized skin damages (bed sores, diabetic foot, etc). It is also available for intradermal injections (commercial name, Jalu-Pro). Indeed, the local injection of this formulation may be a potent tool in skilled hands because it is known that chemotaxis is the strongest force in nature that drives life: living beings are attracted by food. When we fill the dermis injecting the proper amino acid formulation, we send a very strong biologic message to fibroblasts. The choice of the injection site allows the physician to drive fibroblasts to the target site where the promotion of the synthesis of integral dermis is desired, such as in fibrotic tissue nodules, wrinkles, or stretches. Feeding fibroblasts with the right food (ie, the right amino acids formulation) means also promoting growth factors production, thus, activating all those complex balances of the catabolic-anabolic pathways that restore a normal structure of dermal architecture. Synthetically, the zonation of the chemotactic stimulus, aiming at functionally driving the collagen synthesis induced by the right cluster of amino acids, elicits maximal trophism and physiologic rejuvenation of collagen structure at the injection site. By now, there is no chance to find this formulation in the United States, either as topical treatment or as medical device for injections.

References

1. Millward DJ. Macronutrients intakes as determinants of dietary protein and amino acid adequacy. J Nutr 2004;134:1588S-96S.
2. Vasanhta L, Srikantia SG, Gopalan G. Biochemical changes in the skin in kwashiorkor. Am J Clin Nutr 1970;23:78-82.
3. Baracos VE. Cancer-associated cachexia and underlying mechanisms. Annu Rev Nutr 2006;26:13.1-13.27.
4. Millward DJ, Bowtell JL, Pacy P, et al. Physical activity, protein metabolism and protein requirements. Proc Nutr Soc 1994;53: 223-40.
5. Dioguardi FS. Wasting and the substrate-to-energy controlled pathway: a role for insulin resistance and amino acids. Am J Cardiol 2004;93 (supplement):6A-12A.
6. Scognamiglio R, Negut C, Piccolotto R, et al. Effects of oral amino acid supplementation on myocardial function in patients with type 2 diabetes mellitus. Am Heart J 2004;147:1106-12.
7. Scarabelli TM, Pasini E, Stephanou A, et al. Nutritional supplementation with mixed essential amino acids enhances myocyte survival, preserving mitochondrial functional capacity during ischemia-reperfusion injury. Am J Cardiol 2004;93:35A-40A.
8. Lee SK, Posthauer ME, Dorner B, Redovian V, Maloney MJ. Pressure ulcer healing with a concentrated, fortified, collagen protein hydrolysate supplement: a randomized controlled trial. Adv Skin Wound Care 2006; 19:92-6.
9. Graumich JF, Blough LS, McLaughlin RG, et al. Healing pressure ulcers with collagen or hydrocolloid: a randomized, controlled trial. Am Geriatr Soc 2003;51:147-54.
10. Thomas JR. Effects of age and diet on rat skin histology. Laryngoscope 2005;115:405-11.
11. Wu-Pong S, Elias PM, Feingold KR. Influence of altered serum cholesterol levels and fasting on cutaneous cholesterol synthesis. J Invest Dermatol 1994;102:799-802.
12. McNaughton SA, Marks GC, Green AC. Role of dietary factors in the development of basal cell cancer and squamous cell cancer of the skin. Cancer Epidemiol Biomarkers Prev 2005;14:1596-607.
13. Firth J. Risk assessment of skin in rheumatic disease. Nurs Times 2005; 101:54-5.
14. Wolfwolff H, Hansson C. Rearing larvae of *Lucilia sericata* for chronic ulcer treatment—an improved method. Acta Derm Venereol 2005;85: 129-40.
15. Morrill JF, Heinig MJ, Pappagianis D, et al. Risk factors for mammary candidosis among lactating women. J Obstet Gynecol Neonatal Nurs 2005;34:37-45.
16. Sipetic S, Vlajinac H, Kocev N, et al. Early infant diet and risk of type I diabetes mellitus in Belgrade children. Nutrition 2005;21:474-9.
17. Rothe MJ, Bernstein ML, Grant-Kels JM. Life-threatening erythroderma: diagnosing and treating the "redman". Clin Dermatol 2005;23: 206-17.
18. Treloar V. Nutrigenomics. Arch Dermatol 2005;141:1469-70.
19. McDonald A, Forsyth A. Nutritional deficiencies and the skin. Clin Exp Dermatol 2005;30:388-90.
20. Wahlqvist ML. Dietary fat and the prevention of chronic disease. Asia Pac J Clin Nutr 2005;14:19-26.
21. Poitu C, Viguerie N, Cancello R, et al. Serum amyloid A: production by human white adipocyte and regulation by obesity and nutrition. Diabetologia 2005;48:519-28.
22. Demling RH. The incidence and impact of pre-existing protein energy malnutrition on outcome in the elderly burn patient population. J Burn Care Rehabil 2005;26:93.
23. Shephard RJ, Jones G, Ishii K, et al. Factors affecting body density and thickness of subcutaneous fat: data on 518 Canadian city dwellers. Am J Clin Nutr 1969;22:1175-89.
24. Crawford PB, Keller CA, et al. An obesity index for six-month-old children. Am J Clin Nutr 1974;27:706-11.
25. Albrink MJ, Meigs JW. Serum lipids, skin-fold thickness, body bulk, and body weight of native Cape Verdeans, New England Cape Verdeans, and United States factory workers. Am J Clin Nutr 1971; 24:344-52.
26. Seltzer CC, Greater MJ. Reliability of the triceps skin fold over the subscapular skin fold as an index of obesity. Am J Clin Nutr 1967;20: 950-3.
27. Jenícek M, Demirjian A. Triceps and subscapular skin-fold thickness in French-Canadian school-age children in Montreal. Am J Clin Nutr 1972;25:576-81.
28. Merrow S, Triceps B. Skin-fold thickness of Vermont adolescents. Am J Clin Nutr 1967;20:978-85.
29. Malina RM. Skin fold-body weight correlations in Negro and white children of elementary school age. Am J Clin Nutr 1972;25: 861-3.
30. Frisancho AR. Triceps skin fold and upper arm muscle size norms for assessment of nutritional status. Am J Clin Nutr 1974;27:1052-8.
31. Corbin CB. Standards of subcutaneous fat applied to percentile norms for elementary school children. Am J Clin Nutr 1969;22:836-41.
32. Stine OC, Saratsiotis JB, Furno OF. Appraising the health of culturally deprived children. Am J Clin Nutr 1967;20:1084-95.
33. Baertl JM, Morales E, Verastegui G, et al. Diet supplementation for entire communities: growth and mortality of infants and children. Am J Clin Nutr 1970;23:707-15.
34. Purba M, Kouris-Blazos A, Wattanapepaiboon N, et al. Skin wrinkling: can food make a difference? J Am Coll Nutr 2001;20:71-80.
35. Boelsma E, Hendricks HFJ, Roza L. Nutritional skin care: health effects of micronutrients and fatty acids. Am J Clin Nutr 2001;73: 853-64.
36. Stahl W, Heinrich U, Jungmann H, et al. Carotenoids and carotenoids plus vitamin E protect against ultraviolet light–induced erythema in humans. Am J Clin Nutr 2000;71:795-8.

37. McArdle F, Rhodes LE, Parslew RAG, et al. Effects of oral vitamin E and β-carotene supplementation on ultraviolet radiation–induced oxidative stress in human skin. Am J Clin Nutr 2004;80:1270-5.
38. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80:1678S-88S.
39. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 2004;79:362-71.
40. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690-3.
41. Aboul-Dahab VW, Zaki K. Studies on rickets and malnutrition in the undernourished child. Am J Clin Nutr 1963;13:98-105.
42. Bereston ES. Vitamins in dermatology. Am J Clin Nutr 1954;2:133-9.
43. Vasantha L. Biochemical changes in skin in experimental protein and calorie deficiency. Am J Clin Nutr 1970;23:99-104.
44. Huang PC, Lo CC, Ho WT. Protein requirements of men in a hot climate: decreased urinary nitrogen losses concomitant with increased sweat nitrogen losses during exposure to high environmental temperature. Am J Clin Nutr 1975;28:494-501.
45. Boelsma E, van de Vijver LPL, Goldbohm RA, et al. Human skin condition and its association wit nutrient concentrations in serum and diet. Am J Clin Nutr 2003;77:348-55.
46. Mechanick JI. Practical aspects of nutritional support for wound-healing patients. Am J Surg 2004;188(Suppl to July):52S-6S.
47. Langemo D, Anderson J, Hanson D, et al: Nutritional considerations in wound care. Adv Skin Wound Care. 2006, Jul-Aug; 19:297-8, 300, 303.
48. Mandal A. Do malnutrition and nutritional supplementation have an effect on the wound healing process? J Wound Care 2006;15: 254-7.
49. Raffoul W, Shahin Far M, Cayeux MC, et al. Nutritional status and food intake in nine patients with chronic low-limb ulcers and pressure ulcers: importance of oral supplements. Nutrition 2006;22: 82-8.