Nutrition for Healthy Skin

Jean Krutmann • Philippe Humbert
(Editors)

Nutrition for Healthy Skin

Strategies for Clinical and Cosmetic Practice

Springer

Jean Krutmann, MD
Professor of Dermatology and
Environmental Medicine Director
IUF-Leibniz Research Center for
Environmental Medicine
Auf'm Hennekamp 50
D-40225 Düsseldorf
Germany
krutmann@uni-duesseldorf.de

Philippe Humbert, MD, PhD
Saint-Jacques University Hospital
Department of Dermatology
University Hospital
University of Franche-Comte
INSERM U 645, IFR 133
25030 Besançon
France
philippe.humbert@univ-fcomte.fr

ISBN 978-3-642-12263-7 e-ISBN 978-3-642-12264-4
DOI 10.1007/978-3-642-12264-4
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2010933086

Cover design: eStudioCalamar, Figueres/Berlin

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

The intimate relationship between dermal demand of nutrients and adequate supply from the blood circulation seems to have been understudied. In fact, the title of this book can be read in two ways; balanced nutrition is necessary for maintaining healthy skin, and there are nutritive aspects to restore healthy conditions after a disease state has developed. Skin care has an important metabolic and nutritive component. Maintenance and restoration are integral processes in skin health.

It is satisfying to see that the two editors, Professors Jean Krutmann from Düsseldorf, Germany, and Phillippe Humbert from Besancon, France, have been able to compile the pertinent aspects by attracting contributions from the world leaders in this subject area. Three major sections make up the treatise: Nutrition and Skin, and its scientific basis; Functional Food, addressing botanicals and other micronutrients as well as probiotics and; thirdly, Aspects of Clinical Dermatology, culminating in the topic of beauty from inside.

The need for scientifically sound information on this subject area is particularly urgent, since the general public is being supplied with suggestions from the news media and, increasingly, from the Internet with material which is not always based on sufficient scientific evidence. The present treatise will also be good for delineating the problems and limitations in current knowledge. The authors, the editors, and the publisher can be congratulated to a timely opus!

Duesseldorf, Germany — Helmut Sies

Preface

The relationship between nutrition and skin has become a “hot” topic that is exciting researchers and clinicians worldwide. New insights into the effects of orally applied, biologically active molecules on skin functions have stimulated a continuously growing interest in the development of nutritional supplements and, most importantly, functional food products to benefit human skin. This monograph attempts to provide an up-to-date overview regarding all aspects of nutrition and skin. It includes in-depth, critical discussions of the molecular basis as well as current concepts propagated for nutrition-based cosmetic, preventive, and therapeutic dermatological strategies. The explosion of knowledge in this field over even the last few years is remarkable with consequences for practicing dermatologists, patients, cosmetic and nutritional industry, and consumers in general. To capture the depth and breadth of this learning, we have recruited leading experts from multiple subdisciplines. All authors are internationally recognized, and we are very grateful for their excellent contributions. We hope that this book will serve you as a state-of-the-art reference and will further stimulate your interest in this fascinating area.

Duesseldorf, Germany — Jean Krutmann
Besançon, France — Philippe Humbert
March 2010

Contents

Part I

Nutrition and Skin: The Scientific Basis

Cutaneous Changes in Nutritional Diseases

1

Matthias Schmuth and Peter O. Fritsch

Core Messages

- Abnormal nutrition causes cutaneous changes that are either due to insufficient food supply; i.e., inadequate intake of nutrients, vitamins, and minerals, or to excess calory intake.
- In countries with inadequate food supply, protein-energy malnutrition (*marasmus*, *kwashiorkor*) is common and children ≤ 5 years are at highest risk. In 2001, approximately 50% of childhood deaths were indirectly or directly attributable to inadequate nutrition.
- In countries with adequate food supply, the most common nutritional abnormalities are obesity due to excess food consumption, and malnutrition due to psychological (anorexia nervosa, bulimia) or medical conditions (metabolic disease, chronic illness, hospitalization), affecting both children and adults.
- Skin changes provide important clues for lack or overabundance of individual nutritional components and can help clinicians to correctly detect, diagnose, and consequently treat nutritional disease, which can be confirmed by laboratory testing.
- While the importance of individual components for normal function of the skin is undisputed, there are many compensatory mechanisms in place. Nutritional disease is rarely the result of the deficiency of a single nutrient.
- While substitution of deficient nutritional components usually results in rapid resolution of symptoms, toxic effects of overload have become more common with the increasing popularity of dietary supplementation. This is particularly common with lipophilic vitamins (A, D, E, and K) because they accumulate in the tissue.

1.1 Nutritional Deficiencies

1.1.1 *Marasmus and Kwashiorkor*

Nutritional deficiencies can be exogenous or endogenous. The primary exogenous reason is insufficient intake of nutrients. Endogenous etiologies include intestinal or metabolic disease that interferes with the absorption and delivery of nutrients to the cellular machinery (e.g., intestinal malabsorption, gastrointestinal and metabolic disease, infections, cancer) (Table 1.1). With prolonged nutritional deficiencies, energy storage is exhausted and energy supply lags behind. Because of their increased nutritional needs during the growth phase, children ≤ 5-years old are particularly susceptible to the developmental and physiologic consequences of poor nutrition.

M. Schmuth (✉) and P.O. Fritsch
Universitätsklinik für Dermatologie und Venerologie,
Anichstrasse 35, 6020, Innsbruck, Austria
e-mail: matthias.schmuth@i-med.ac.at
e-mail: peter.fritsch@i-med.ac.at

J. Krutmann and P. Humbert (eds.), *Nutrition for Healthy Skin*,
DOI: 10.1007/978-3-642-12264-4_1, © Springer-Verlag Berlin Heidelberg 2011

Table 1.1 Causes of nutritional deficiency

Exogenous (inadequate food intake)	Endogenous (inadequate food absorption/metabolization)
Poverty	Intestinal malabsorption
Old age	Gastrointestinal disease
Alcoholism	Metabolic disease
Psychiatric disorders	Chronic systemic disease
Diets (e.g., "fad diets," "allergy diets")	Cancer
Child neglect	Recurrent infections
	AIDS (inadequate intake, e.g., due to candida esophagitis)

Table 1.2 Differential diagnosis of hyperkeratotic papules on the extremities due to nutritional deficiency

Vitamin A deficiency (phrynoderma)
Vitamin C deficiency
Essential fatty acid deficiency

Marasmus is due to insufficient (although balanced) nutritional quantities. Marasmus is not only due to decreased overall caloric supply, but also results from a deficit in essential nutritional components (e.g., vitamins, essential amino acids, minerals). Therefore, the cutaneous changes of marasmus are multifold. Aside from a decrease in the subcutaneous fat, the dermal and epidermal layers are thinned which gives the skin an aged appearance. In addition, there is dryness of the skin, sometimes to the degree of ichthyosis-like scaling. Vitamin A and C deficiency result in follicular hyperkeratosis (see below, Table 1.2). Because of anemia and vasoconstriction, the skin color is pale, while in sun-exposed areas there is spotty hyperpigmentation. The hair is dry, loses color ("premature graying"), and hair loss (telogen effluvium) is common. The growth of the nails is delayed, and the nail plates may show longitudinal ridging. Marasmus is corrected by carefully restoring protein-calorie intake and by supplementation of vitamins, essential fatty acids, and zinc according to their respective blood levels.

Kwashiorkor occurs if normal carbohydrate consumption is coupled with insufficient protein intake; i.e., chronic malabsorption such as in cystic fibrosis. It is most common in infants in third world countries as soon as their mothers discontinue breast feeding. Kwashiorkor can also occur in children receiving a calorie-rich diet that is poor in proteins of animal origin [4]. These children show the cutaneous changes of marasmus (see above), and in addition develop diffuse edema due to hypoalbuminea, and increased vulnerability of the skin (e.g., to mechanical trauma), which results in erosions and blisters in areas of friction. A further characteristic of kwashiorkor is a reddish-brown scaly dermatitis ("flaky paint"), and dusky erythematous plaques with a waxy appearance in pressure-exposed areas (diaper area, over bony prominences) with a thickened, pigmented stratum corneum on histology. Depigmentation of the skin can be observed (predominantly in the perioral area and on the lower legs). Moreover, depigmentation of the hair to a reddish color is often observed. Correction of kwashiorkor must be undertaken carefully; electrolyte imbalances need to be taken into account, combined with supplementation of vitamins, essential fatty acids, and zinc as above.

In both marasmus and kwashiorkor, individual hair shafts show pigmented areas alternating with depigmented areas ("signe de la bandera" or "flag sign"), reflecting intermittent periods of food availability. In fact, because of overlapping features, a clear distinction between marasmus and kwashiorkor can not always be made with certainty. In these cases, the term *protein-calorie malnutrition* is used instead. Generally, chronic nutritional deficiencies increase the susceptibility to opportunistic infections by causing a secondary immune deficiency. Particularly problematic are mixed infections of the skin with fusiform bacteria and spirochetae (e.g., bacterium fusiforme, spirochäta refringens) causing necrotizing ulcerative gingivitis, noma, or cancrum oris which can be life-threatening. In adults, similar treatment-recalcitrant ulcerations occur on the lower legs following insect bites.

Most commonly, malnutrition is due to inadequate food availability, but it is also seen in individuals with medical conditions, particularly in hospitalized patients, which often can simply be ascribed to poor logistics (negligence of nutritional needs in patients waiting for a complex diagnostic workup). Other reasons are individuals voluntarily subjecting themselves to unusual diets and individuals with excessive alcohol consumption [3]. *Anorexia nervosa* and *bulimia* are psychiatric disturbances that lead to physical disturbances. Cutaneous changes associated with these disorders are manifold including dry skin, pruritus, patchy hyperpigmentation, freckles, lanugo hair, brittle terminal hair and nails, and paronychia. Russell's sign refers

to callus formation on the hand used to elicit vomiting, which is another diagnostic clue. Early recognition is desirable, because the mortality is much lower with early intervention.

1.1.2 Essential Fatty Acid Deficiency

Malnutrition is a common cause of essential fatty acid (e.g., linoleic, linolenic, and arachidonic acid) deficiency. Patients present with diffuse eczematous skin changes that can be pruritic and preferentially affect the periorificial areas. With long-standing essential fatty acid deficiency, there can also be depigmentation and alopecia (telogen effluvium). In children, there is growth failure. Essential fatty acid deficiency is associated with impaired wound healing, capillary fragility, abnormal liver, and kidney function, and neurologic damage. The differential diagnosis includes zinc deficiency (see below), and necrolytic migratory erythema. Plasma levels of linoleic, linolenic, and arachidonic acids are decreased. In contrast, palmitoleic and oleic acids are increased, and there is abnormal presence of 5,8,11-icosatrienoic acid in plasma. Therapeutic fatty acid supplementation is effective.

1.1.3 Vitamin Deficiencies

Vitamins are cofactors in metabolism; nutritional vitamin deficiency results in metabolic disturbances. In Western societies, this is mostly due to impaired intestinal absorption (e.g., in inflammatory bowel disease, inherited metabolic disease, parenteral nutrition, following surgery), or due to alcoholism. Because the deficiency usually involves multiple vitamins, it is often difficult to determine the relative role of individual vitamins [1].

Vitamin A deficiency causes ichthyosis-like skin changes with generalized fine scaling and a thickening of the outermost skin layer, the stratum corneum ("phryonoderm"), which is particularly pronounced in the follicular openings, causing follicular hyperkeratosis [2]. This is often associated with effluvium and fragility of the hair. One of the earliest signs of vitamin A deficiency, however, is impaired night vision and the inability to see in bright light. Metaplasia of the conjunctival epithelium in vitamin A deficiency has been called keratoconjunctivitis sicca (Bitot macules), which can progress to keratomalacia, permanent scarring and blindness. Finally, vitamin A deficiency is associated with an increased incidence of epidermal neoplasias (anticarcinogenic activity of vitamin A). The differential diagnosis of vitamin A deficiency includes lichen pilaris, ichthyosis vulgaris, Darier disease, and other vitamin deficiencies (see biotin, vitamin C deficiency below). Extracutaneous manifestations include growth failure and mental retardation. For diagnosis plasma retinol levels are measured. Vitamin A supplementation resolves ophthalmologic symptoms within days and cutaneous changes within weeks.

Vitamin B1 (thiamin) is involved in carbohydrate metabolism, and B1 deficiency is known as *beriberi*. It is seen with gastrointestinal disease, a diet restricted to polished rice, alcoholism, pregnancy, lactation, and diabetes mellitus. Mucocutaneous changes include edema and glossitis with glossodynia. Predominant are neurologic symptoms including peripheral neuropathy, confabulation (Korsakoff's syndrome), and encephalopathy (Wernicke). Low urinary aneurin excretion is used as a diagnostic test. Supplementation is effective.

Vitamin B2 (riboflavin) can be due to a poor diet, but can also be caused by medications that impair its absorption (galactoflavin, phenothiazines, tricyclic antidepressants). Cutaneous changes that indicate vitamin B2 deficiency include seborrheic dermatitis-like scaling on the face (nasolabial folds), head, and genitocrural region. In addition, these patients present with cheilitis, perleche, pallor, and atrophy of the tongue

Table 1.3 Differential diagnosis of cheilitis due to nutritional deficiency

Zinc deficiency – genetic – acquired
Biotin deficiency
Vitamin B2 deficiency*
Vitamin B6 deficiency
Vitamin B12 deficiency*
Folic Acid deficiency
Zinc deficiency*
Iron deficiency*

* in association with angular involvement (perleche)

(Table 1.3). Ophthalmologic involvement includes blepharitis, conjunctivitis, and corneal vascularization. Vitamin B2 is a cofactor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are involved in many redox reactions. On blood testing patients show a normochromic anemia. Decreased erythrocyte glutathione reductase activity confirms the diagnosis. The differential diagnosis includes seborrheic dermatitis and zinc deficiency. In mild cases, the recommended treatment is riboflavin 3–10mg daily per mouth, in refractory cases 2 mg daily via the intravenous route.

Vitamin B3 (niacin) deficiency causes pellagra. Pellagra is characterized by a triad consisting of changes in skin, nervous system, and the gastrointestinal tract ("3D's": dermatitis, dementia, diarrhea). An early symptom is diarrhea. At later stages, patients report increased UV sensitivity (face, sun-exposed distal upper extremities) and sun-burn-like pruritic or burning erythematous macules, and occasionally blisters (Table 1.4). The facial rash at times resembles the butter fly rush of lupus erythematodes, but is always associated with other components of the triad. Quite characteristic is the sparing of the forehead as well as eczema of the neck and upper chest that can resemble a necklace (Casal's necklace) (Fig. 1.1). Here the skin is erythematous to brown (or black), scaly. Sometimes there is an eczema craquele-like appearance with fissures and occasionally there are crusts. These lesions are common on the dorsal hands (Fig. 1.2), and can also be found on the feet and in the genitocrural region. Glossitis and stomatitis can also be present. Neurologic symptoms include peripheral polyneuropathy, encephalopathy, and depression. The differential diagnosis includes contact eczema, photo-induced dermatitis, and porphyria cutanea tarda. Pellagra is a clinical diagnosis, there are no laboratory markers. Niacin is a component of nicotinamide-adenine-dinucleotide (NAD) catalyzing redox reactions. A frequent setting for niacin deficiency is a niacin-deficient diet, which has occurred with the introduction of corn as a major food that only contains bound niacin that cannot be used by the human body. This is exemplified by endemic pellagra in geographic areas with predominant corn consumption, e.g., in South America. Aggravating factors include alcoholism, long-standing antibiotic therapy, isoniazid, 5-fluoruracil, inflammatory bowel disease, abnormalities of tryptophan metabolism (carcinoid), and Hartnup disease (see below). As with the other vitamin deficiencies, vitamin B3 supplementation will resolve the symptoms, but exogenous niacin can release histamine causing urticaria and worsening of preexistent asthma. Niacinamide is the preferred choice for supplementation, because it avoids these adverse effects.

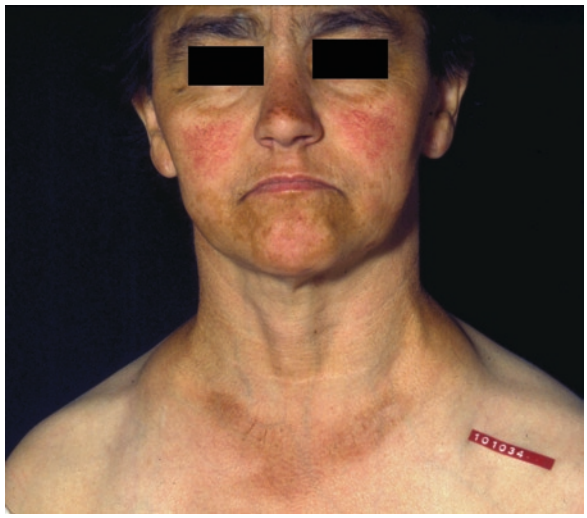

Fig. 1.1 Pellagra: butter fly rash and Casal's necklace

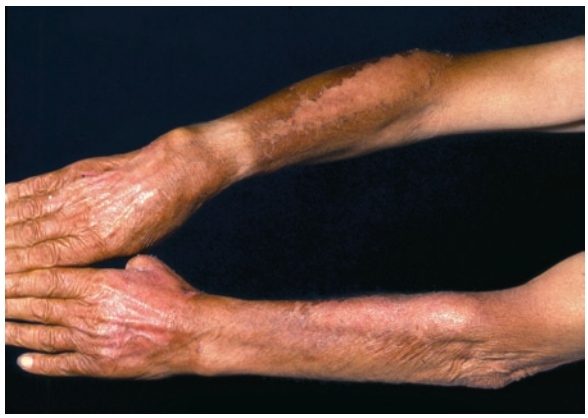

Fig. 1.2 Pellagra: scaly, erthematous to brown plaques on the dorsal hands

Table 1.4 Differential diagnosis of photosensitive eruptions due to nutritional deficiency

Vitamin B3 deficiency (pellagra)
Hartnup disease

Vitamin B6 (pyridoxine) deficiency is usually accompanied by other deficiencies and is associated with seborrhoic dermatitis-like skin changes in perioricial distribution (eyes, nose, mouth) as well as cheilitis and glossitis. Pyridoxine is a cofactor of enzymes involved in amino acid metabolism (e.g., transaminases, synthetases, hydroxylases) and the metabolization of linoleic acid into arachidonic acid. Associations have been described with drugs such as isoniazid, penicillamine, hydralazine hydrochloride, oral contraceptives, phenelzine sulfate, cycloserine, and with uremia and liver cirrhosis. Diagnosis is made by measuring pyridoxine serum levels. Supplementation is effective.

Lack of *vitamin B12* (cyanocobalamin), because of decreased intrinsic factor, is known for causing pernicious anemia, but can rarely also be due to strict vegetarian diet. Aside from its hematologic consequences (megaloblastic anemia), occasionally vitamin B12 deficiency also is associated with atrophic glossitis, angular cheilitis, mucositis, and symmetric acral (dorsal fingers and toes) and flexural hyperpigmentation. Poliosis, vitiligo, and alopecia areata occur with increased frequency. The differential diagnosis for the hyperpigmentation includes Addison's disease. Intramuscular supplementation is effective (1 mg per month), resolving symptoms within 2–12 weeks.

Folic acid deficiency has similar mucocutaneous changes to vitamin B12 deficiency including hyperpigmentation and glossitis, but cheilitis and mucosal erosions have also been described. Decreased serum folate is diagnostic; oral supplementation is effective.

Vitamin C deficiency is the cause of scurvy. In the past, this was common among sailors and other people without access to fresh fruits and vegetables for extended periods of time. Although vitamin C deficiency has become much less common today, it is still encountered in the setting of urban poverty where it preferentially affects the very young and the aged (exacerbated by general malnutrition, mental incapacity, alcoholism). It is also seen with fad diets. Cutaneous changes of vitamin C deficiency include follicular hyperkeratosis on the extensor surfaces of the extremities, which characteristically show perifollicular hemorrhage (Fig. 1.3). The propensity for hemorrhage is due to fragile blood vessels, which is particularly pronounced in newborns and infants that present with petechia (over mechanical pressure points) and intestinal as well as urinary tract bleeding. In children, subperiosteal hemorrhage with radiographic alterations and pseudoparalysis has been described. Adults with long-standing vitamin C deficiency report impaired wound healing, bleeding gums, gingivitis, gingival hypertrophy, and loss of teeth. General symptoms of scurvy include fatigue, muscle weakness, myalgia, arthralgia, diarrhea, and anemia. The onset is approximately 1–3 months after onset of insufficient vitamin C intake. Long-standing, severe vitamin C depletion can result in diffuse edema, oligura, anemia, dyspnea, and neuropathy. Supplementation with vitamin C is usually successful, if the deficiency is recognized early enough. Left untreated, the condition can lead to death. Low vitamin C serum levels are diagnostic. The recommended dose for vitamin C supplementation in individuals with deficiency varies between 100–1,000 mg of ascorbic acid per day. Infants should be treated with 50 mg of ascorbic acid up to four times per day.

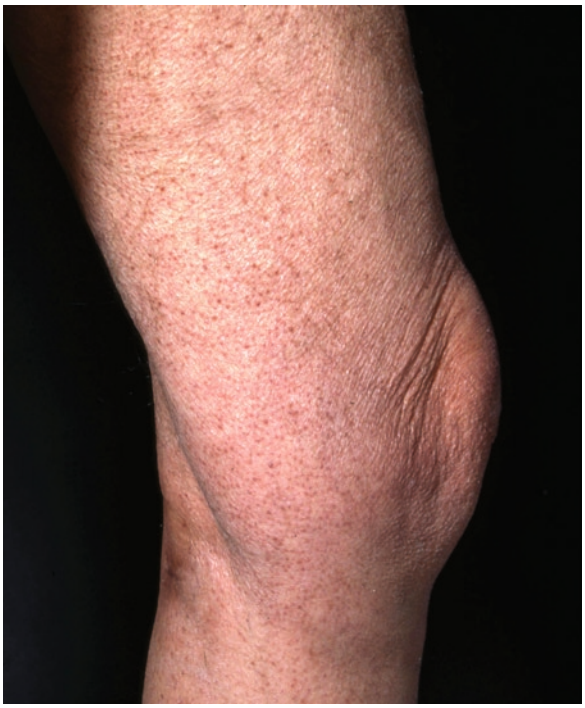

Fig. 1.3 Scurvy: follicular hyperkeratoses with perifollicular hemorrhage

Vitamin D deficiency is not associated with cutaneous changes (it primarily causes bone disease; i.e., rachitis in children and osteomalacia in adults). Vitamin D deficiency has also been associated with higher susceptibility to infections; i.e., tuberculosis.

Vitamin E deficiency is not associated with cutaneous changes (it primarily causes neurologic abnormalities).

Biotin (vitamin H) deficiency causes an exfoliative dermatitis on acral skin, cheilitis, and/or periorificial dermatitis. If occurring in newborns, the disease may present with erythroderma and alopecia. The most common extracutaneous feature is enteritis. Other extracutaneous findings include metabolic acidosis, developmental delay, hearing loss, paraesthesias, seizures, and conjunctivitis. Biotin deficiency is associated with impaired cellular immunity, there is a predisposition for infections; i.e., candida dermatitis. Biotin is a cofactor of carboxylases (biotinidase, holocarboxylase). Decreased serum biotin levels can be acquired or genetic. The differential diagnosis includes essential fatty acid deficiency. Hyperamonemia and organic aciduria are used for screening; the definitive diagnosis is established by assaying carboxylase synthetase activity in fibroblasts. Supplementation is effective.

Vitamin K deficiency, in severe cases, can lead to hemorrhage of the skin and mucous membranes. Clinical hemorrhage together with a prolonged prothrombin time leads to the diagnosis. This is seen in newborns or in later life in individuals with malabsorption, cystic fibrosis, liver disease, and drugs (warfarin, salicylates, cephalosporins). Treatment consists of parenteral vitamin K (1 mg newborns, 2 mg children, 5–10 mg adults).

1.1.4 Trace Element Deficiencies

Zinc deficiency is known for the classic triad of dermatitis, alopecia, and diarrhea. However, only 20% of patients present with all three components of the triad at a given time. Zinc deficiency can be hereditary or acquired. H*ereditary zinc deficiency (acrodermatitis enteropathica)* is an autosomal recessive intestinal abnormality of zinc absorption due to a mutation in a zinc transport protein. Human milk contains a zinc transport protein that is much less abundant in cow's milk. Therefore, infants typically develop cutaneous changes days to weeks after being switched to bottle feeding (cow milk). Following intestinal absorption, zinc is bound to albumin. Whereas 99% of body zinc is intracellular, zinc storage is poor (total body zinc 2–3 g) and depletion occurs rapidly; i.e., within a month (zinc deficiency = <70mg/dl). Patients initially present with a perioral erosive dermatitis and perleche that progresses to involve the entire face, scalp, acral sites, and the diaper area. This can be accompanied by ulcerations of the oral mucous membranes and glossitis. The periorificial distribution is helpful in making the diagnosis. Palmar erythema, sometimes with anular or collarette-like scaling, may be present. If the dermatitis is accompanied by alopecia (telegon effluvium) and/or photophobia, zinc deficiency needs to be considered. Conversely, telogen effluvium alone without accompanying skin changes cannot be ascribed to zinc deficiency. Other differential diagnoses of zinc deficiency include seborrheic dermatitis or other eczematous eruptions. At times, patients present with persistent cutaneous infections, e.g., candida dermatitis, paronychia, as well as with onychodystrophy, blepharitis, and conjunctivitis. There is an immunodeficiency, preferentially due to functional impairment of T cells. Before the advent of zinc supplementation, affected individuals, primarily newborns and infants, would die from infections. The predominant extracutaneous symptom is diarrhea with electrolyte imbalance of variable degree. Long-standing zinc deficiency also leads to delayed wound healing, growth retardation, anorexia, anemia, hypogonadism, and altered mental status. Individuals with zinc deficiency are frequently infertile. If they conceive, infants may show malformations.

The cutaneous changes of *acquired zinc deficiency* are similar, but usually milder than those of hereditary deficiency. Because of its relatively mild symptoms, acquired zinc deficiency may be underdiagnosed. It can develop relatively quickly with an unbalanced diet (exclusive high fiber content interferes with absorption), parenteral nutrition lacking sufficient zinc supplementation, malabsorption (including cystic fibrosis), or abnormal intestinal loss of zinc. Chronic diarrhea is a common cause and can lead to a vicious cycle where diarrhea compromises zinc absorption and zinc deficiency in turn causes diarrhea. Other disease associations include chronic renal failure, malignancy, drugs, alcoholism, HIV infection, and pregnancy (Table 1.5). Zinc is a critical component of many enzymes. An important consequence of zinc deficiency is poor incorporation of essential fatty acids into eicosanoids. Skin histology shows a "pallor" of the upper epidermis. In more pronounced cases, there may be vacuolar degeneration of the upper epidermis,

Table 1.5 Causes of acquired zinc deficiency

Poor Intestinal Zinc Absorption	Malabsorption
	Chronic liver and pancreatic disease
	Other gastrointestinal disease
	Alcoholism
	Unbalanced diet (e.g., exclusive high fiber)
	Parenteral nutrition lacking zinc supplementation
Increased Zinc Excretion	Liver cirrhosis
	Renal disease
	Diabetes mellitus
	Dialysis
Increased Catabolism	Cancer
	Chronic recurrent infections, AIDS
	Trauma, burns
Decreased Serum Albumin	Nephrotic syndrome
	Liver cirrhosis

Table 1.6 Differential diagnosis of periorificial dermatitis due to nutritional deficiency

Zinc deficiency – genetic – acquired
Essential fatty acid deficiency
Biotin deficiency
Vitamin B2 deficiency
Vitamin B6 deficiency
Glucagonoma syndrome
Pseudoglucagonoma syndrome

epidermal hyperplasia, and hyperkeratosis. In later stages, there is epidermal atrophy with flattening of the rete ridges and dermal fibrosis. The differential diagnosis of zinc deficiency (see Table 1.6) includes abnormal amino acid absorption, biotin deficiency, essential fatty acid deficiency, and the glucagonoma syndrome ("necrolytic migratory erythema"), all of which may show similar histologic changes. Serum zinc levels are measured for diagnosis. Because alkaline phosphatase is zinc-dependent, it can serve as an additional surrogate marker. Supplementation of zinc can be achieved by the oral or intravenous routes (1–2 mg/kg/day in the acquired, 3 mg/kg/day in the hereditary form).

Iron deficiency is associated with pallor of the skin, dry/scaly skin, perleche, glossitis, dull, shaggy hair, in the case of long-standing deficiency with telogen effluvium and coilonychia [5]. Blood smears typically show microcytic, hypochromic anemia. Serum iron is decreased, being tightly regulated between intestinal absorption, protein-bound transport (transferrin), and intracellular storage (ferritin). Supplementation is effective.

Copper deficiency (*Menkes Syndrome, Kinky hair Syndrome, Steely hair disease*) is due to X-chromosomal recessive mutations in the Cu(2+)-transporting ATPase (ATP7A). Patients present with saggy and hypopigmented skin, there are follicular hyperkeratoses, and the hair is sparse, hypopigmented, and brittle (pili torti, monilethrix, occasionally trichorrhexis nodosa). In addition patients lack eyebrows and lashes. Extracutaneous changes include neurodegenerative changes. At birth and for the first few months, infants appear normal, but subsequently develop hypotonia, seizures, and failure to thrive resulting in death by 2–3 years of age. Another feature is tortuous, elongated arteries due to immature elastin fibers. Copper is a component of enzymes important for elastin, collagen, and melanin synthesis, e.g., lysyl hydroxylase, tyrosinase, etc. Total body copper content is 80 mg, 90% of which is associated with ceruloplasmin, the remainder with other plasma proteins, mainly albumin. Due to fluctuations, serum copper and ceruloplasmin are unreliable predictors in the neonatal period. However, because the lack of copper impairs the function of enzymes of catecholamine synthesis and metabolism, there is a distinctive increase in the dihydroxyphenylacetic acid to dihydroxyphenolglycol ratio that is of diagnostic value. Despite the defective transport protein, intramuscular copper injections can be effective if commenced within days after birth, particularly in individuals with residual ATP7A activity.

Selenium deficiency presents with a whitish discoloration of the nails and effluvium. It has been reported in patients receiving parenteral nutrition. Extracutaneous features include cardiomyopathy, muscle pain, and weakness. Because selenium is essential for glutathione peroxidase, low activity of this enzyme and low plasma selenium are diagnostic. Supplementation is effective (2 mg/kg/day).

1.2 Excess Nutrition

1.2.1 Obesity

In Western societies excess nutrition has become a significant problem (Table 1.7). Overweight (body mass index 25–29.9) and obese (body mass index ≥ 30) individuals have an increased general morbidity, predominantly from metabolic and cardiovascular disease. There are several characteristic skin changes that are more common in overweight individuals, and can be used as markers for individuals at risk for internal disease. In overweight and obese individuals, pseudoacanthosis nigricans is an indicator for insulin resistance and metabolic syndrome. The skin folds of obese individuals are subject to increased friction, they are commonly hyperpigmented (inner thighs, submammary region) and carry skin tags (achrocordon). The enlarged surface between the folds creates a niche for microbial growth, which is further exacerbated by sweating. Over time, this commonly leads to intertiginous eczema, secondary overgrowth of bacteria, erythrasma, dermatophyte, and yeast infections. Other skin findings associated with obesity include hyperhidrosis, striae distensae, stasis dermatitis, venous hypertension, and leg ulcers.

1.2.2 Hypervitaminoses

With the increased popularity of vitamin supplementation, excess vitamin intake has become more common (often triggered by aggressive advertisements promoting the vitamin's beneficial effects). Because lipophilic vitamins (A, D, E, K) can accumulate in tissue, these are more prone to having toxic effects. Syndromes due to excess hydrophilic vitamins are not as well described.

Table 1.7 Causes of excess nutrition

Exogenous (excess food intake)	Endogenous (abnormal metabolism)
Social	
Depression	Genetic
Anxiety	
Iatrogenic	

Several meta-analyses have failed to demonstrate sustained beneficial effects of vitamins A, B6, B12, C, E, and beta-carotene on carcinogenesis and cardiovascular disease.

Hypervitaminosis A develops with excess supply of vitamin A. Today, this is seen with long-term vitamin (over)supplementation. The skin findings of hypervitaminosis A include pruritus, generalized scaling, dry mucous membranes, alopecia (telogen effluvium), cephalea, nausea, increased serum transaminases, and lipids. Hyperostoses similar to those seen with retinoid medication have been described. Hypervitaminosis A is also characterized by an orange-yellowish skin tint. In contrast to generalized jaundice from hyperbilirubnemia, there is sparing of the sclera, eyelids, ears, and axillary folds. The same pattern of skin discoloration is seen with excessive beta-carotene consumption (the natural provitamin of vitamin A contained in carrots, red palm oil, etc.) which is used for self-tanning. The skin color is particularly evident in the palms and soles (depends on the thickness of the epithelium; i.e., mucous membranes are less affected). This is quite common in children and vegetarians, it is sometimes also seen with renal disease, diabetes mellitus, and thyroid disease (myxedema) due to a decreased ability to convert beta-carotene into vitamin A in these diseases. Serum carotenoid levels are increased. Patients should be educated about the limitations of photoprotection by beta-carotenes (cf. Chap. 6).

Historically, hypervitaminosis A was seen in inuit populations who consumed polar bear liver that contains excessive amounts of vitamin A causing hypervitaminosis A. Therefore, inuits have learned to be very careful about eating polar bear liver while hunting.

Hypervitaminosis C develops after long-standing dietary intake of vitamin C which then interferes with vitamin B12 metabolism and bears the symptoms of its deficiency (see above). The combination of vitamin C with estrogen medication can lead to kidney (oxalat) stones.

Hypervitaminosis D, e.g., in patients with renal disease supplemented with vitamin D, can result in anorexia, cephalea, vomiting, diarrhea, hypercalcemia, and calcium deposition in the skin (*calcinosis cutis*).

Hypervitaminosis E is rare and only manifests after very high vitamin E consumption, causing gastrointestinal upset, cephalea, and icterus in premature neonates.

1.2.3 Trace Element Deposition

Dietary *zinc* supplementation can be toxic if overdosed causing nausea, vomiting, upper intestinal hemorrhage, vertigo, and neutropenia. In these cases, serum zinc levels are markedly increased. Therefore, monitoring of serum zinc levels and blood counts are warranted with long-standing zinc supplementation.

Because normally 95% of nutritional iron is not absorbed (mucosa block), *iron overload* is usually due to an inherited abnormality in iron absorption (primary hemochromatosis) or to parenteral iron overload (secondary hemochromatosis). Iron is deposited in many tissues including liver, heart, and skin. Diffuse bronze-color hyperpigmentation of the skin with a predilection of sun-exposed areas can facilitate the early diagnosis of hemochromatosis. The hyperpigmentation not only derives from cutaneous iron deposits, but also from an induction of melanogenesis. Other cutaneous changes include ichthyosis-like scaling, alopecia, and coilonychia. Organ involvement consists of the classic triad of diabetes mellitus, cardiomyopathy, and liver cirrhosis (which in turn has the characteristic cutaneous findings of palmar erythema, teleangiectasia, etc.). Therapy consists of deferroxamine and bloodletting.

High content of either *lead* or *mercury* in food is associated with a bluish-gray discoloration of the gums.

Aluminum intoxication can cause porphyria-like bullous skin changes.

Arsenic is well known as a skin carcinogen that increases the incidence of Bowen disease and basal cell carcinoma. The nails show whitish lines (Mees lines). Extracutaneous consequences of arsenic ingestion are lung cancer, vomiting, diarrhea, hepatic/renal damage, as well as peripheral neuropathy.

Argyrosis is the term for cutaneous deposition of silver metal. In cases of chronic silver consumption, the skin has a diffuse grayish color with a predilection of sun-exposed areas, but also involving the sclerae, mucous membranes, and finger nails (typically toe nails are not affected). Silver deposits can be visualized by dark field or electron microscopy. No therapy is available. Argyrosis has become rare since many of the silver-containing medications (e.g., for the treatment of rheumatoid arthritis) have been discontinued.

Chrysiasis, the deposition of gold in the skin, is similar to argyrosis. Only the color of gold deposits is somewhat different; i.e., diffuse bluish-gray. In contrast to argyrosis, the mucous membranes are typically not affected in chrysiasis. Other cutaneous changes associated with gold intake are maculopapular, vesiculobullous, and urticarial eruptions, occasionally also an erythema multiforma-like rash. Gold-containing medications (e.g., for the treatment of rheumatoid arthritis) have become rare.

1.3 Abnormalities of Amino Acid Metabolism

Hartnup disease is an autosomal recessive disorder of intestinal and renal amino acid transport presenting with amino aciduria. Patients show a sun-burn-like photosensitive eruption reminiscent of pellagra, sometimes blistering, onset is at <13 years. Post-inflammatory hypopigmentation is a common residual. The differential diagnosis of the skin changes includes pellagra and lupus erythematodes. The primary extracutaneous feature is intermittent ataxia, sometimes also nystagmus and tremor. A high-protein diet or oral nicotinamide supplementation have been reported to be beneficial (nicotinamide is photoprotective, cf. Chap. 11.).

Phenylketonuria is an autosomal recessive abnormality of phenylalanine metabolism; i.e., lack of downstream metabolic product tyrosine and accumulation of phenylalanine. Paucity of tyrosine results in diffuse hypopigmention of the skin and hair of affected individuals (“blond and blue eyed”). Other cutaneous changes include eczematous (early onset atopic dermatitis, but also unspecific dermatitis) and scleroderma-like skin lesions. Phenylalanine accumulation is toxic for the brain and causes mental retardation, developmental delay, microcephaly, seizures, and behavioral and psychiatric problems. Urinary screening for phenylalanine accumulation has been widely established for approximately 40 years. Strictly speaking this is not a nutritional disease, but it is the prototype of an inherited condition that can be cured by dietary restriction of phenylalanine together with supplementation of tyrosine and other amino acids. Incompliant adults experience recurrences of the dermatologic manifestations. Individuals resuming the diet may show darkening of their hair.

Tyrosinemia is a rare autosomal recessive disorder of tyrosine metabolism with accumulation of tyrosine

metabolites in the liver, kidneys, and central nervous system. Tyrosinemia type II (Richner-Hanhart syndrome, oculocutaneous tyrosinemia) is characterized by photophobia, corneal ulcerations with onset during the first year of life (the latter can be misinterpreted as herpes keratitis). A painful focal palmoplantar keratoderma occurs during early childhood or may be delayed until adolescence. Although again not a nutritional disease in the strict sense, a diet restricted in tyrosine and phenylalanine will clear the keratitis, keratoderma, and will ameliorate or prevent cognitive impairment.

Arginine-Succininc Acid disease is due to mutations in the gene encoding for arginine succinase and manifests with fragile hair (trichorhexis nodosa) and neurologic symptoms.

Alkaptonuria is an autosomal recessive defect of the enzyme homogentisic acid (or alkapton) oxidase. Cutaneous changes include a grayish-blue discoloration of the ears and the axillae (ochronosis). There can also be arthritis and darkening of the urine (due to oxydation).

Eosinophilia-Myalgia-Syndrome stands for a scleroderma-like disorder with woody induration of the distal extremities that historically was observed in individuals who consumed large quantities of contaminated L-tryptophan.

1.4 Nutrition, Skin Physiology, and Skin Pathology

In this chapter, the characteristic skin findings that are reproducibly associated with either lack or abundance of individual nutrients, vitamins, or trace elements are described. These observations allow us to deduce the importance of individual nutritional components for skin physiology. The substitution of deficient components rapidly reversesas associated skin changes. In contrest the prophylactic supplementation of nutrients to enhance skin physiology has yielded disappointing results. The available studies not only fail to consistently prove beneficial effects of vitamin supplementation on skin physiology, but meta-analyses even indicate an increased risk for cardiovascular disease with high doses of vitamins B6, B12, C, and E. Thus, to date it is still controversial if prophylactic vitamin supplementation can have sustained beneficial effects. One possible explanation is that the metabolism of cutaneous tissues, in particular the epidermis, is remarkably autonomous; i.e., many metabolic reactions in the epidermis occur independent from the rest of the body. Furthermore, while several of the vitamins mentioned above are potential oxygen radical scavengers, systemic delivery is unlikely to achieve a sufficient concentration in the epidermis to effectively prevent free radical formation.

Similarly complex is the evidence for nutritional supplementation effects on skin pathology. For example, there is a decade-long discussion about the dietary factors that may elicit or exacerbate acne vulgaris, but suggestive data has not been replicated. Approximately 10% of children with severe atopic dermatitis experience flares upon food allergen exposure. However, diagnostic testing and recommendations for avoidance of individual food ingredients should regularly be reevaluated (retested), because of the risk of developing nutritional deficiency due to unnecessary food restriction. Thus, the goal of testing is to identify food that is tolerated in order to reduce the risk for nutritional deficiency. Current evidence does not support a major role for maternal dietary restrictions during pregnancy or lactation for infants with atopic disease. However, there is moderate evidence from meta-analyses that prophylactic (but not therapeutic) use of dietary probiotics may be beneficial for atopic dermatitis; these findings warrant replication. For treating psoriasis, the supplementation of omega-3-fatty acids has been proposed to have beneficial effects by modulating eicosanoid metabolism, but again the replication of the data is not sufficient. Finally, not only psoriasis, but also leg ulcers have been shown to be associated with nutritional deficiencies. Yet, it remains to be established if poor nutrition is a direct cause or merely an associated bystander of these skin pathologies.

References

1. Barthelemy, H., Chouvet, B., Cambazard, F.: Skin and mucosal manifestations in vitamin deficiency. J. Am. Acad. Dermatol. **15**, 1263–1274 (1986)
2. Bleasel, N.R., Stapleton, K.M., Lee, M.S., Sullivan, J.: Vitamin A deficiency phrynoderma: Due to malabsorption and inadequate diet. J. Am. Acad. Dermatol. **41**, 322–324 (1999)

3. Kuhl, J., Davis, M.D.P., Kalaaji, A.N., Kamath, P.S., Hand, J.L., Peine, C.J.: Skin signs as the presenting manifestation of severe nutritional deficiency. Arch. Dermatol. **140**, 521–524
4. Liu, T., Howard, R.M., Mancini, A.J., Weston, W.L., Paller, A.S., Drolet, B.A., Esterly, N.B., Levy, M.L., Schachner, L., Frieden, I.J.: Kwashiorkor in the United States. Fad diets, perceived and true milk allergy, and nutritional ignorance. Arch. Dermatol. **137**, 630–636 (2001)
5. Trost, L.B., Bergfeld, W.F., Calogeras, E.: The diagnosis and treatment of iron deficiency and its potential relationship to hair loss. J. Am. Acad. Dermatol. **54**, 824–844 (2006)

Skin Aging

Jean Krutmann

2

Core Messages

- Skin aging is caused by
  (i) UV radiation,
  (ii) Infrared radiation,
  (iii) tobacco smoke and
  (iv) traffic related particulate matter
- Damage to macromolecules such as mtDNA and proteins in dermal fibroblasts drives chronic skin aging

2.1 Introduction

For decades it has been appreciated that aging is the consequence of both genetic and environmental influences. Genetic factors are evident, e.g., in the >100-fold variation among species in the rate of aging; and recent studies of fruit flies, worms, and even mice have identified specific longevity genes whose modification can greatly alter lifespan [22]. Conversely, a role for environmental factors can be deduced both from epidemiologic and laboratory-based experimental data. Such influences include ionizing radiation, severe physical and psychological stress, overeating versus caloric restriction, and in the case of skin ultraviolet irradiation.

In this regard, skin is no exception as skin aging results from intrinsic (genetic, endocrinologic) and extrinsic (environmental) factors. In this chapter I will focus on extrinsic skin aging for the following reasons: (a) The overall topic of this chapter is functional food for skin or, in other words, manipulation of skin aging by nutrition-based strategies; (b) It has already been shown for topical approaches (sunscreens, cosmeceuticals, etc.) that extrinsic skin aging can be effectively manipulated. (iii) And thus, nutrition-based anti-skin-aging strategies will be most effective if they are directed against extrinsic skin aging.

Extrinsic and intrinsic skin aging can be clearly distinguished at a clinical, histological, and molecular level. The two most prominent clinical signs of extrinsic skin aging are the formation of coarse wrinkles and an increase in the number of pigment spots (Fig. 2.1). Interestingly, ethnic differences exist, because, e.g., Caucasian women develop earlier and more severe skin wrinkling whereas Japanese women show more lentigines at a younger age. Among all environmental factors, solar ultraviolet (UV) radiation is most important for extrinsic skin aging, a process accordingly also termed photoaging.

Within recent years substantial progress has been made in elucidating the underlying molecular mechanisms. From these studies it is now clear that both UVB (290–320 nm) and UVA (320–400 nm) radiation contribute to photoaging. UV-induced alterations at the level of the dermis are best studied and appear to

J. Krutmann
IUF-Leibniz Research Center for Environmental Medicine,
Auf'm Hennekamp 50, D-40225 Düsseldorf, Germany
e-mail: krutmann@uni-duesseldorf.de

J. Krutmann and P. Humbert (eds.), *Nutrition for Healthy Skin*,
DOI: 10.1007/978-3-642-12264-4_2,

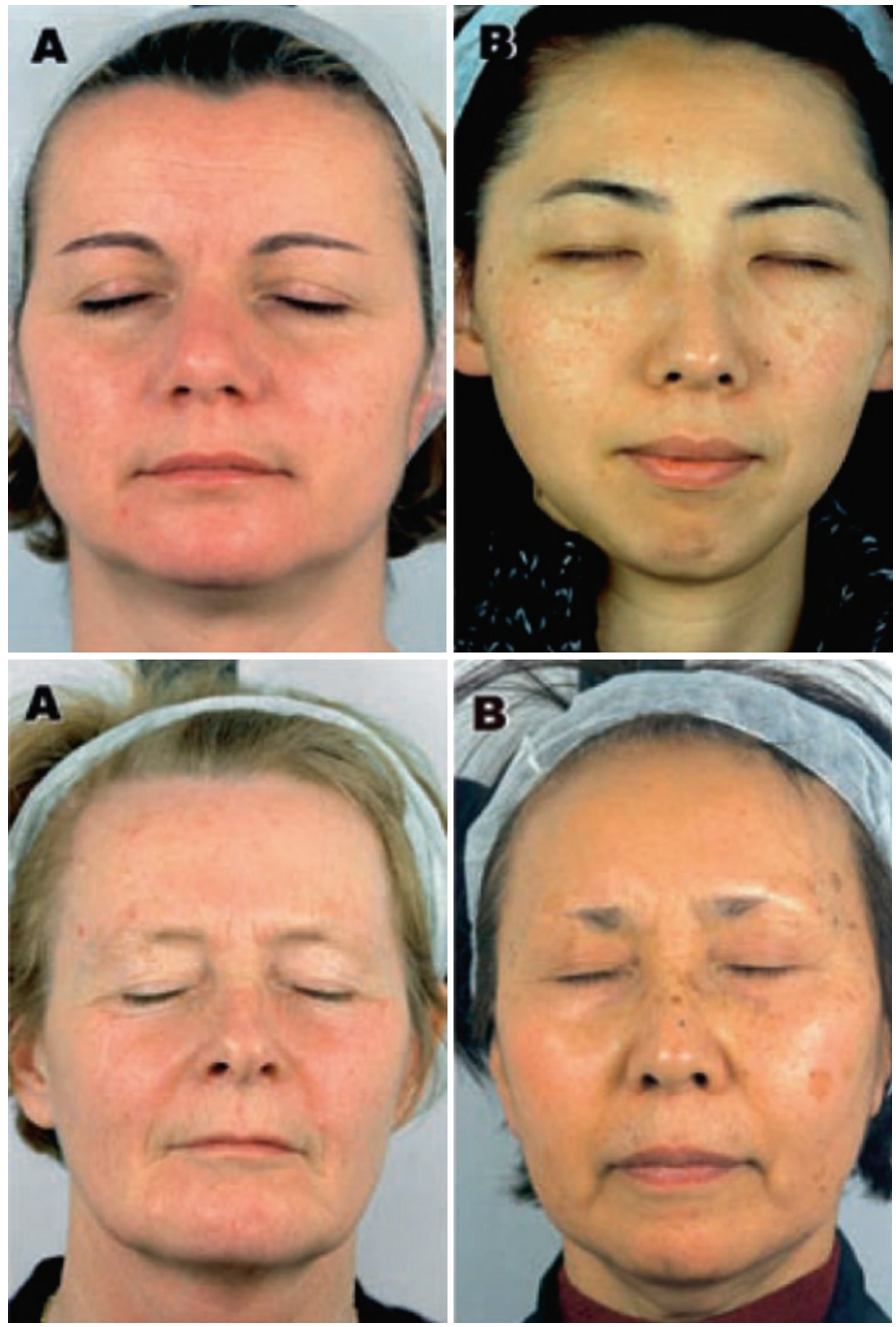

Fig. 2.1 Coarse wrinkle (**a**) and pigment spot (**b**) formation in extrinsic skin aging

be largely responsible for the phenotype of photoaged skin. It is also generally agreed that UVB acts preferentially on the epidermis where it not only damages DNA in keratinocytes and melanocytes but also causes the production of soluble factors including proteolytic enzymes which then in a second step affect the dermis; in contrast UVA radiation penetrates far more deeply on average and hence exerts direct effects on both the epidermal and the dermal compartments (Fig. 2.1). UVA is also 10–100 times more abundant in sunlight than UVB, depending on the season and time of day. It has therefore been proposed that, although UVA photons are individually far less biologically active than UVB photons, UVA radiation