Apostolos Pappas *Editor*

Nutrition and Skin

Lessons for Anti-Aging, Beauty and Healthy Skin

Springer

Nutrition and Skin

Apostolos Pappas
Editor

Nutrition and Skin

Lessons for Anti-Aging, Beauty and Healthy Skin

Springer

Editor
Apostolos Pappas
The Johnson & Johnson Skin Research Center
CPPW, A Division of Johnson & Johnson
Consumer Companies, Inc.
Skillman, NJ 08558, USA
apostolos_pappas@yahoo.com

ISBN 978-1-4419-7966-7 e-ISBN 978-1-4419-7967-4
DOI 10.1007/978-1-4419-7967-4
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011935453

© Springer Science+Business Media, LLC 2011
All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, LLC, 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.
The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.
While the advice and information in this book are believed to be true and accurate at the date of going to press, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

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

Preface

Good health has been always associated with nutrition and skin quality. It is apparent that we all desire to live longer healthy lives while maintaining a youthful appearance. A vast amount of epidemiological and clinical studies link various nutrients to health benefits in tissues and organs. Recent interest in these relations is triggering progressive reexploration by the dermatological community, particularly where connections between diet and skin have previously been dismissed. A promising volume of publications and findings now support ideas and validate theories that key nutrients are imperative for healthy skin.

Today's global economy urges food scientists and professionals to identify novel ways that can help producers reach consumers. Undoubtedly, in the world of food science the dining table is the predominant route from the food producer to the consumer. However, from any farmer who harvests flaxseeds or soybeans to every ingredient manufacturer who markets tocopherols, polyphenols, or plant extracts, it is apparent that there are many other routes to reach the consumer. The wide variety of non-food consumer products offers numerous examples.

The abundant use of vitamins and antioxidants by the cosmetic industry and their effects on skin care and dermal health has been greatly underestimated, or perhaps unseen, in the food science community, which is wholly focused on dietary use of these nutrients. Thus, not only might topical application of these products further establish the efficacy of these functional ingredients for use on skin, but their ingestion might be even more efficacious.

Current consumer trends have brought anti-aging and consumer products—from nutritional supplements to skin care—into billion dollar ranges that only drugs used to reach. All of these products are tightly connected with the health, wellness, and needs of the modern-day consumer. The main pillars of the marketing power behind these products are the pharmacological activity of "nutraceuticals."

This book serves to educate and decode the role of vitamins, essential fatty acids, and other nutraceuticals on skin health and their tremendous impact on skin health. In addition, a discussion of the potential role of functional foods is provided. Focus on skin conditions such as acne, dermatitis, dry scaly skin, or alopecia can provide

comprehensive knowledge regarding the relation of nutrition and skin, as can a review of current nutritional clinical studies in dermatological research.

The contributing authors are leaders in their field who concentrate on facts and actual scientific studies. They outline the need for more studies in this new field that is so close to the heart of the consumers in our society. Indeed, the effort here is to concentrate not only on what we know but what we do not (but need to) know to meet consumers' needs. We seek to elucidate not only the potential health benefits that certain diets or nutrients bring to various tissues and organs but also the contributing effects on our skin health and visible condition. It is up to all of us—scientists, doctors, the industry, the sponsoring agencies, the government, and all the people—to find this extra time, effort, and help to address, although not life-threatening, an issue closely associated with the quality of life, health, and well-being.

Skillman, NJ Apostolos Pappas

Contents

Contributors

Michael Anthonavage Presperse, LLC, Somerset, NJ, USA

Robert J. Boyle Department of Paediatrics, Imperial College London, London, UK

Karen E. Burke Department of Dermatology, Mount Sinai Medical Center, New York, NY, USA

Maxim E. Darvin Center of Experimental and Applied Cutaneous Physiology (CCP), Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Germany

Rana Mohsen Elewa Departments of Dermatology, Venereology, Allergology, and Immunology, Dessau Medical Center, Dessau, Germany

Ulrike Heinrich Institut für Experimentelle Dermatologie, Universität Witten-Herdecke, Witten-Annen, Germany

Nikiforos Kollias Johnson & Johnson Consumer Companies Inc, Skillman, NJ, USA

Juergen Lademann Center of Experimental and Applied Cutaneous Physiology (CCP), Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Germany

Sampo J. Lahtinen Danisco Health & Nutrition, Kantvik, Finland

Aikaterini I. Liakou Departments of Dermatology, Venereology, Allergology, and Immunology, Dessau Medical Center, Dessau, Germany

Neil Mann School of Applied Sciences, RMIT University, Melbourne, VIC, Australia

Angus M. Moodycliffe Nestlé Research Center, Lausanne, Switzerland

Apostolos Pappas The Johnson & Johnson Skin Research Center, CPPW, A Division of Johnson & Johnson Consumer Companies, Inc., Skillman, NJ, USA

Anthony Vincent Rawlings AVR Consulting Ltd, Northwich/Cheshire, UK

Jörg Reichrath Department of Dermatology, The Saarland University Hospital, Homburg/Saar, Germany

Myriam Richelle Nestlé Research Center, Lausanne, Switzerland

Robyn Smith Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Georgios N. Stamatas Johnson & Johnson Consumer France, Issy-les-Moulineaux, France

Mimi L.K. Tang Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, VIC, Australia

Murdoch Children's Research Institute, Melbourne, VIC, Australia

Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia

Sagar K. Thakkar Nestlé Research Center, Lausanne, Switzerland

Michael J. Theodorakis University of Athens Medical School, Athens, Greece

Léa Trémezaygues Department of Dermatology, The Saarland University Hospital, Homburg/Saar, Germany

Petra Winkler J&J, Medical Affairs, EMEA, Neuss, Germany

Christos C. Zouboulis Departments of Dermatology, Venereology, Allergology, and Immunology, Dessau Medical Center, Dessau, Germany

Chapter 1
Introduction and Overview

Apostolos Pappas

Throughout history, our traditions, anecdotal evidence, epidemiological studies, and most recently clinical studies have reflected the idea that nutrition is associated with health, beauty, and graceful aging. Multiple pathways and cofactors are implicated in skin biology, and certain common skin conditions have been shown to be critically affected by nutritional patterns and habits.

Linking food and good nutrition to overall health and appearance is important to the modern consumer. It seems that everyone, from the youngest to the oldest consumer, is very much aware of his or her appearance. It is instinctual that food and wellness are closely associated, and skin is the only organ that is tightly associated with the desirable appearance. Skin is the largest organ of the human body and plays a role in thermoregulation, protection, metabolism, and sensation. Various nutrients are fundamental for normal skin functions, and their presence and function still intrigue many scientists.

The early part this book explores the relations of the most important and essential nutrients with skin. Why are they the most important and essential (together)? These two terms have harmoniously coinhabited books of nutritional research. The term essential has been used mainly to denote nutrients that the human body cannot synthesize and relies on dietary sources to provide; they include, for example, vitamins, essential fatty acids, and amino acids as well as many bioactive agents with beneficial pharmacological activity that belong to the wide category of nutraceuticals.

Zouboulis and Elewa recap the essentiality of vitamin A for normal differentiation and maintenance of epithelial tissues in skin and mucous membranes. They comprehensively review the multiple activities of retinoids (metabolites of vitamin A)

A. Pappas (✉)
The Johnson & Johnson Skin Research Center, CPPW, A Division of Johnson & Johnson Consumer Companies, Inc., Grandview Road 199, Skillman, NJ 08558, USA
e-mail: apostolos_pappas@yahoo.com

A. Pappas (ed.), *Nutrition and Skin: Lessons for Anti-Aging, Beauty and Healthy Skin*,
DOI 10.1007/978-1-4419-7967-4_1, © Springer Science+Business Media, LLC 2011

that are used as therapeutic agents for various skin diseases. They discuss the essential aspects, including the profound management of these potent agents.

Reichrath and Trémezaygues undertook the enormous task of discussing the multifaceted roles of vitamin D and its biologically important metabolites. The studies are numerous, but the authors have carefully reviewed them for this chapter, summarizing the positive effects of vitamin D and its analogues in a variety of skin diseases.

Burke eloquently reviews the photoprotection that vitamins C and E offer against induced photodamage. Their activities are conversed in full spectrum, covering both topical and oral use. Their synergies with other antioxidants are discussed in detail.

Richelle's team powerfully compiled information on the most studied antioxidants in skin research to date, the carotenoids. They have accurately and carefully elaborated on important issues such as their bioavailability and their protective role against solar ultraviolet damage; a role that may significantly complement the use of sunscreens and overall contribute extensively to skin health.

Lademann's team complements successfully the rest of the vast range of antioxidant activities and their observed benefits to skin, revealing in addition ways to assess their important activities. The nature of free radical scavengers is discussed in detail, especially in regard to how they reflect both the lifestyle and the physical condition of people.

Petra Winkler excels in her difficult task to review and focus on the knowledge currently available on several minerals and their impact on the skin. The focus on the deficiencies of certain minerals is discussed together with their association with many skin diseases.

Finally, Boyle and colleagues offer a powerful message on the beneficial and perplexing relation of probiotics and skin with a complete review of the published clinical research. Many manuscripts loosely associate our microbiota to health. Boyle's team focus on the facts—using direct evidence of their beneficial effects on skin. Also, a special focus on eczema prevention and an additional call for further studies is outlined.

The latter part the book focuses on the clinical crossover between nutrition and dermatology. There is a strong need to expand this knowledge and an urgent wish to see it enriched and more powerful in the near future.

The first topic discussed in this portion of the book is how nutrition may play a role in acne. Many nutritional factors are discussed especially essential nutrients and dairy products. Also addressed is the need for more proper clinical studies that would help elucidate the relation between diet and acne. So far, only studies that examined the high glycemic index and load have been able to establish a valid relation between diet and acne. Thus, in the next chapter Larsen (Smith) discusses her pioneering studies on the relation of the glycemic load and acne symptoms through improvements in insulin metabolism.

Consequently, Rawlings distills years of experience into a chapter that addresses atopic dermatitis as it relates to nutrition, with a focus on essential fatty acid metabolism. Stratum corneum health, especially its skin barrier function, is discussed

in relation to its deficiencies due to essential fatty acids. These results and intervention studies with these fatty acids are summarized.

Anthonavage identifies, with detail and depth, research areas unchartered by nutritionists and food scientists with respect to hair biology. As the fundamental element of beauty and noticed appearance, hair encapsulates a range of factors and information that relates to nutritional status and metabolic activities.

Stamatas and Kollias, in a comprehensive summary, capture the enormous potential that are available to scientists and health professionals in the form of imaging and spectroscopic techniques. These innovations can be employed to assess the presence and amount of certain nutrients directly in the skin.

The circle closes with another chapter by Zouboulis's team, who undertook the extensive task of summarizing the nutritional clinical studies in dermatology. Nutritional supplementation, caloric content and composition, nutritional imbalances, hyperinsulinemia, and important nutrients are summarized in relation to characteristic skin pathologies, skin metabolism, skin physiology, and skin properties.

My hope is that this publication bridges a gap in scientific knowledge and encourages food science and nutritional professionals to view dermatological research with a new perspective. It is also hoped that it will inspire new research and product development to help with more efficient decisions by today's highly anticipating consumer.

May this book be an asset not only for the food scientist, nutritionist, and dermatologist but also any scientist who has a pathos for food, nutrients, and metabolic research. I hope it will be the cornerstone for more books to come on this subject and, more importantly, more studies to be done in this new field. Furthermore, it is my hope that it will bridge the gap between the two disciplines.

Part I
Nutrients and Skin

Chapter 2
Vitamin A and the Skin

Rana Mohsen Elewa and Christos C. Zouboulis

Core Messages

- Vitamin A (vit. A) is essential for normal differentiation and maintenance of epithelial tissues in skin and mucous membranes, vision (retinaldehyde), reproduction (retinol), and embryonic morphogenesis.
- Retinoids (compounds with biological activities similar to those of vit. A) are used as therapeutic agents for hyperkeratotic and parakeratotic skin diseases, acne and acne-related disorders, and hand eczema. They are also used as prophylaxis for epithelial skin tumors in immune-suppressed patients and as therapy for non-melanoma skin cancers and cutaneous T-cell lymphoma.
- Regular monitoring is essential for the avoidance and management of a wide range of adverse effects.

2.1 Introduction

Retinoids refer to compounds that have biological activities similar to those of naturally occurring vitamin A (vit. A) but not necessarily the same chemical structure (Zouboulis and Orfanos 2000). The definition of retinoids does not include a structural homology to vit. A. Retinoids are used as therapy and prophylaxis systemically or as local applications for various skin diseases and tumors. They are also used in the cosmetic field for acne, seborrhea, psoriasis, epithelial tumors, and hand eczema. Retinoids perform their actions through binding to

C.C. Zouboulis (✉)
Departments of Dermatology, Venereology, Allergology, and Immunology,
Dessau Medical Center, Auenweg 38, 06847 Dessau, Germany
e-mail: christos.zouboulis@klinikum-dessau.de

A. Pappas (ed.), *Nutrition and Skin: Lessons for Anti-Aging, Beauty and Healthy Skin*,
DOI 10.1007/978-1-4419-7967-4_2, © Springer Science+Business Media, LLC 2011

retinoid receptors (RAR and RXR), members of the hormone nuclear receptor subfamily. In addition to its toxicity, a deficiency of vit. A causes skin manifestations. Owing to the wide range of adverse effects of retinoids, precautions and regular monitoring are essential for long-term therapy.

2.2 Naturally Occurring Retinoids

Natural retinoids include vit. A (retinol) and its metabolic derivatives retinaldehyde and retinoic acid (Zouboulis and Orfanos 2000). The normal concentration of vit. A in plasma is 0.35–0.75 μg/mL. Retinoic acid is produced by in vivo oxidation of retinol. Its two isoforms are all-trans retinoic acid and 13-*cis* retinoic acid, with normal plasma concentrations of 0.55–1.20 and 0.80–2.40 ng/mL, respectively. Retinoic acid can fully substitute for retinol, except for maintaining reproduction. Daily requirement of vit. A is 0.8–1.0 mg (2,400–3,000 IU), which can be found in ten medium-sized eggs or 100 g of butter. Hypervitaminosis occurs with intake of more than 18,000–60,000 IU vit. A per day for children and 50,000–1,00,000 IU for adults. Higher uptakes usually do not result in elevated retinol levels, however the stored retinol esters level are increased wherever retinol esters are stored.

2.3 Synthetic Retinoids

The synthetic retinoids (Table 2.1) are either chemical modifications of naturally occurring vit. A or chemically different compounds with the capacity to bind or antagonize retinoid nuclear receptor proteins (Zouboulis and Orfanos 2000). Nonaromatic, monoaromatic, and polyaromatic compounds have been developed through chemical modification. Modification of the polyene chain diminishes bioactivity; modification or esterification of the carboxylic end diminishes the toxicity while maintaining the activity; and ring substitution diminishes the toxicity and markedly increases the activity.

2.4 Absorption, Distribution, and Metabolism

The oral bioavailability of retinoids can be increased, especially by fatty acids, which prevent the binding of retinoids with albumin and hence improve the clinical effect (Avis et al. 1995). The metabolism of retinoids generally occurs in the liver. It involves oxidation and chain shortening to produce biologically inactive metabolites. Retinoids are excreted through feces and urine.

Isotretinoin is detectable after 30 min in blood, and maximum concentrations are reached 2–4 h after oral intake (Ganceviciene and Zouboulis 2007). The half-life elimination rate of isotretinoin ranges from 7 to 37 h, and that of its known

Table 2.1 Synthetic retinoids in current use

Chemical structure	Generic name	Initial trade name	Approved medical use
First generation			
All-trans retinoic acid	Tretinoin	Retin-A	Topical treatment of acne vulgaris, photodamage
		Vesanoid	Systemic treatment of acute promyelocytic leukemia
9-*cis* retinoic acid	Alitretinoin	Toctino	Systemic treatment of therapy-resistant hand eczema
		Panretin	Topical treatment of AIDS-associated Kaposi sarcoma
13-*cis* retinoic acid	Isotretinoin	Accutane	Systemic treatment of severe recalcitrant acne and acne-related dermatoses
		Isotrex	Topical treatment of acne
Second generation			
Monoaromatic compound	Etretinate	Tigason	Systemic treatment of psoriasis
Etretinate derivative	Motretinide	Tasmaderm	Topical treatment of acne vulgaris
Free acid metabolite of etretinate	Acitretin	Neotigason	Systemic treatment of psoriasis and severe disorders of keratinization
Third generation			
Polyaromatic retinoids (retinoids)	Adapalene	Differin	Topical treatment of acne
	Tazarotene	Tazorac	Topical treatment of plaque-type psoriasis, acne vulgaris, and photodamage
	Bexarotene	Targretin	Systemic treatment of cutaneous T-cell lymphoma, breast cancer, and Kaposi sarcoma
			Topical treatment of cutaneous T-cell lymphoma

metabolites is 11–50 h (Benifla et al. 1995). The major metabolites of isotretinoin in blood are 4-oxo- and 4-hydroxy-isotretinoin; several glucuronide conjugates are detectable in bile (Vane et al. 1990). Because there is interconversion between the two isomers, isotretinoin and tretinoin, in vivo, about 10–30% of the drug is metabolized via tretinoin. Isotretinoin is excreted in feces after conjugation or in urine after metabolization. In contrast to vit. A, there is neither liver nor adipose tissue storage. More than 99% of isotretinoin in plasma is bound to plasma proteins, mainly albumin (Rollman and Vahlquist 1986). Serum albumin has a critical function as a retinoid-binding protein in reducing the concentration of active retinoids and restricting the biological effects on sebaceous gland cells (Tsukada et al. 2002). After discontinuation of therapy, isotretinoin disappears from serum and skin within 2–4 weeks. It seems likely that isotretinoin therapy interferes with the endogenous metabolism of vit. A in the skin because vit. A levels increased by about 50% and dehydrovitamin A levels decreased by around 80% in some patients (Orfanos and Zouboulis 1998).

Acitretin is eliminated more rapidly than etretinate. Etretinate is highly lipophilic, binds strongly to albumin, is stored in adipose tissue, and is released slowly (half-life of 120 days), whereas the half-life of acitretin is only 2 days. Reesterification of acitretin to etretinate occurs only in cases of alcohol consumption (Wiegand and Chou 1998).

Bexarotene in plasma is 99% bound to plasma proteins. It is excreted via the hepatoiliary system, and its terminal half-life is 7–9 h (Ethan Quan and Wolverton 2003).

2.5 Mechanism of Action

2.5.1 Retinoid Receptors and Gene Regulation

Retinoids enter the cell by non-receptor-mediated endocytosis, interact with cytosolic proteins, and finally bind to nuclear receptors. The retinoid nuclear receptors are members of the steroid thyroid hormone receptor superfamily. Retinoid A receptors (RAR) bind all-trans retinoic acid and 9-*cis* retinoic acid with high affinity, whereas they barely bind to 13-*cis* retinoic acid. Retinoid X receptors (RXR) also bind 9-*cis* retinoic acid and are selective for bexarotene, which is a specific RXR ligand (rexinoid). 14-Hydroxy-retro-retinol does not bind or activate retinoid receptors, whereas acitretin does not bind but does activate RAR.

The RAR and RXR families each include three members: α, β, γ. Each receptor is mapped on a different chromosome. High expression of RAR-γ and RXR-α was detected in healthy and psoriatic epidermis, as well as in sebaceous gland cells.

Retinoid receptors target and regulate the genes that have retinoid-responsive elements (RARE and RXRE) in their promoter regions. The retinoid receptor–gene interaction occurs because RAR genes have retinoid-responsive elements, which

allow a positive feedback mechanism. On the other hand, the retinoid-binding proteins may antagonize the retinoid interaction with their nuclear receptors. Specific retinoid effects can occur via interaction of retinoid receptors with other signal transduction mechanisms.

2.5.2 Effect on Epidermal Growth and Differentiation

Retinoids promote cell proliferation in normal epithelia, whereas they normalize it in hyperproliferative conditions. Retinoids induce and modulate the expression of growth factors and their receptors. Keratinocyte proliferation by retinoids is mediated through induction of cyclic adenosine monophosphate (cAMP), epidermal growth factor (EGF) receptor binding, protein kinase C (PKC), and transforming growth factor-α (TGFα). Retinoids down-regulate cell growth which is mediated by a TGFβ2-regulated inhibition of the EGF binding to its receptor. Retinoids have also a keratolytic effect through shifting the terminal keratinocyte differentiation toward a nonkeratinizing mucosa such as epithelium. As for differentiation, retinoic acids down-regulate most of the markers of terminal differentiation in vitro (loricrin, transglutaminase, involucrin, filaggrin, keratins 1 and 10), whereas keratins 19 and 13, the markers of nonstratified and wet epithelia, are up-regulated. Adapalene and retinoic acid restore the architecture of epidermis and antagonize hyperkeratosis. RAR-α receptor agonists promote differentiation in T47D breast carcinoma cells in vitro.

2.5.3 Effects on Sebaceous Gland Activity

See the section Seborrhea, Acne, and Acneiform Disorders later in the chapter.

2.5.4 Immunomodulatory and Antiinflammatory Properties

Isotretinoin, etretinate, and acitretin were proved to inhibit angiogenesis both in vitro and in vivo (in mice with T47D cell-induced tumors) most probably through RAR-α. Retinoids can stimulate humoral and cellular immunity through enhancing antibody production, increasing blood T-helper cells, and preventing Langerhans cells depletion from epidermis by ultraviolet (UV) light and in vitro increasing cell surface antigens of T and natural killer cells. Antiinflammatory activity of retinoids has also been shown. Inhibition of neutrophil migration in psoriatic skin, inhibiting LTB4-induced migration of neutrophils (topical isotretinoin more than tretinoin or retinoids), and inhibition of nitric oxide and tumor necrosis factor-α (TNFα) production have been reported.

2.6 Therapeutic Uses

2.6.1 Psoriasis and Related Disorders

The orally administered aromatic retinoids (etretinate and acitretin) are used to treat psoriasis, both initially and for maintenance. Retinoids have a synergistic effect with other psoriasis treatment modalities. They are considered the drug of choice in cases of pustular psoriasis and palmoplantar psoriasis. Retinoids were found effective in the juvenile types of pityriasis rubra pilaris. Retinoids act on both the epidermal and dermal levels to exhibit their antipsoriatic action. They reduce proliferation, enhance differentiation, regulate the desquamation of the corneocytes, modulate lymphocyte function, and inhibit neutrophil migration.

The daily dose of acitretin is 0.5 mg/kg body weight divided into two administrations to avoid serum peaks and complications (Table 2.2). Taking acitretin with meals that include some fat increases the blood absorption two- to fivefold. Retinoids being metabolized in the liver interact with ketoconazole and phenytoin but not with oral contraceptives.

2.6.2 Disorders of Keratinization

Etretinate and acetretin are superior to isotretinoin because of the latter's sebum-drying property. The severity of Darier's disease, ichthyosis vulgaris, congenital ichthyosis, and palmoplantar keratodermas can be successfully controlled with retinoids. Usually the treatment is prescribed with a low dose (0.2–0.5 mg/kg/day); a lifelong maintenance dose is required with long-term contraception and control of

Table 2.2 Doses of acitretin and therapeutic effect

Disease	Dose	Duration of therapy
Pustular psoriasis	High initial dose (0.5–1.0 mg/kg) reduced to 0.20–0.25 mg/kg over 3–6 months	Maintenance 6–12 months
Erythrodermic psoriasis	Low initial dose (0.20–0.25 mg/kg) increased to 0.5–0.6 mg/kg over 3 months	Maintenance 6 months
Plaque-type psoriasis		
Monotherapy or combined with anthraline or topical steroids	0.3–1.0 mg/kg/day	4–12 weeks
With UVB	0.2–0.5 mg/kg/day	6 weeks
With PUVA	0.2–0.5 mg/kg/day	4–6 weeks

UVB ultraviolet B radiation; *PUVA* psoralen + ultraviolet A radiation

bone density to avoid bone toxicity. Interestingly, other keratinization disorders such as pachyonychia congenita, inflammatory linear verrucous epidermal (ILVEN) nevus, Netherton's syndrome, and monilethrix do not respond to retinoids,

2.6.3 Seborrhea, Acne, and Acneiform Disorders

Isotretinoin proved to be the most effective sebostatic retinoid both in vivo and in cell cultures; and it is the best retinoid for treating severe acne (Zouboulis and Orfanos 2000). Although it shows low binding affinity for intracellular retinoid-binding proteins and for RAR and RXR, isotretinoin has strong sebostatic activity. It undergoes a specific and selective intracellular isomerization process into tretinoin, which in turn binds to RARs. The superior sebostatic effect of isotretinoin over tretinoin (its metabolite) is attributed to the delayed initiation of inactivation of isotretinoin; incubation of sebocytes with tretinoin leads to rapid enhancement of cellular retinoic acid-binding protein levels, which promotes the metabolism by cytochrome P 450 enzymes (Tsukada et al. 2000). It was also found that isotretinoin inhibits 3α-hydroxysteroid oxidation, leading to decreased levels of dihydrotestosterone and androstanedione, which may contribute to the sebosuppressive effect (Guy et al. 1996; Karlsson et al. 2003). Lipogenesis is also reduced by TGFβ2 and TGFβ3, which are rapidly and transiently expressed as a response to retinoid administration (Downie et al. 2002). Isotretinoin decreases sebum production, decreases the number of proliferating sebocytes and the size of the sebaceous gland, inhibits sebocyte differentiation in vivo and in vitro (Orfanos et al. 1997; Zouboulis et al. 2000; Ganceviciene and Zouboulis 2007), and directly suppresses abnormal desquamation of sebaceous follicles. Isotretinoin thus alters the follicular microenvironment via its sebostatic effect and hence markedly reduces the *Propionibacterium acnes* count (King et al. 1982). It also has immunosuppressive and antifibrosis effects when tested on renal allografts (Adams et al. 2005). Through RAR-independent mechanisms, it was associated with cell cycle arrest, induction of apoptosis, decreased proliferation, decreased lipogenesis rate, and decreased DNA synthesis (Zouboulis et al. 1993; Nelson et al. 2006; Zouboulis 2006a). Isotretinoin acts in a receptor-independent manner by influencing cellular signaling pathways through direct protein interactions or by enzyme inhibition (Imam et al. 2001).

Isotretinoin reduces monocyte and neutrophil chemotaxis and their migration to the epidermis, minimizing the excessive inflammation that causes scarring (Zouboulis 2006a). The matrix metalloproteinases (MMPs) were found to be elevated in acne lesions, raising a possibility of involvement in acne pathophysiology through mediation of inflammation and collagen degradation. Isotretinoin induced reduction of Pro-MMP-9 and MMP-13 (Papakonstantinou et al. 2005). Isotretinoin has a strong influence on sebaceous lipid composition, as it decreases wax esters, triglyceride fractions, and squalene; it relatively increases the cholesterol level and the levels of free sterols and total ceramides (Orfanos and Zouboulis 1998).

2.6.3.1 Dosing, Therapeutic Effect, and Monitoring

The required dose is 0.5 mg/kg/day, an initially high dose for 3 months; maintenance requires a lower dose. A cumulative dose of more than 150 mg/kg administered over 6–12 months has been considered necessary to ensure a long-lasting remission (Zouboulis and Piquero-Martin 2003). Owing to relevant recurrence rates, current treatment concepts individualize dosage and duration (Zouboulis 2006b). Longer treatment duration might be needed in patients with extrafacial lesions, low-dose therapy, or severe acne. Contraception is essential during treatment with isotretinoin, and using an antiandrogen-containing contraception is of a great value (Zouboulis and Rabe 2010).

The European directive recommendations for the use of isotretinoin for treatment of acne note that treatment should start at 0.5 mg/kg, and that it should be used only for severe acne (nodular or conglobata) that is not responding to antibiotics or topical therapy; it should not be used as a first-line treatment. It is not recommended in children under 12 years of age. The liver enzymes and serum lipids should be checked before therapy, 1 month after its initiation, and every 3 months after that. All forms of peeling and wax depilation should be avoided during therapy and 6 months afterward. The pregnancy-preventing program for female patients during their childbearing period includes a medically supervised pregnancy test before, during, and 5 weeks after therapy begins. The test should be repeated monthly, and double contraception should be used. Only 30 days of oral isotretinoin can be supplied to female patients at a time (Layton et al. 2006).

2.6.3.2 Retinoid Local Therapy in Acne

Tretinoin, isotretinoin, motretinide, adapalene, and tazarotene are used for the local therapy of acne. Retinaldhyde, retinol, and retinyl esters, however, are used in cosmetic preparations. Early use of retinoids is recommended (Gollnick et al. 2003). Topical retinoids were found to perform their therapeutic action by increasing follicular epithelium turnover, reversing abnormal desquamation of the sebaceous duct. Hence the mature comedones are expelled and formation of microcomedones is inhibited; moreover, the aerobic follicular environment no longer favors the growth of *Propionibacterium acnes* (Lavker et al. 1992; Thielitz et al. 2007). Retinoids also show immunomodulatory activities (Bikowski 2005; Jones 2005).

Tretinoin and isotretinoin can be used alone or in combination with topical erythromycin, clindamycin, or benzoyl peroxide in different concentrations (Mills and Kligman 1978;Korting and Braun-Falco 1989; Marazzi et al. 2002).

Adapalene 0.1% was proved to have the same efficacy as tretinoin 0.025% but with more rapid onset of action (Cunliffe et al. 1998). Adapalene was also used in combination with clindamycin 1%, benzoylperoxide, or both (Zhang et al. 2004; Thiboutot et al. 2007; Del Rosso 2007). Addition of adapalene local therapy to the systemic doxycycline 100 mg/day significantly raised its efficacy (Thiboutot et al. 2005).

Tazarotene, which has been approved for topical acne treatment only in the United States, showed a stronger reduction in disease severity than adapalene but with