Nutrition and Health
Series Editor: Adrianne Bendich

Giamila Fantuzzi
Carol Braunschweig *Editors*

Adipose Tissue and Adipokines in Health and Disease

Second Edition

Humana Press

Nutrition and Health

Adrianne Bendich, Ph.D., FACN, FASN, Series Editor

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Preface

In the last 10 years, adipose tissue and adipokines—messenger proteins produced by adipocytes—have become the focus of extensive investigation as a result of the recognition of the health problems associated with the ever-expanding worldwide obesity problem that affects both children and adults. Numerous advances have been made since publication of the first edition of *Adipose Tissue and Adipokines in Health and Disease*, in terms of basic adipocyte biology, understanding of the determinants of obesity, distribution of body fat and weight loss, as well as the mechanisms linking excess adiposity to various comorbidities. The second edition of *Adipose Tissue and Adipokines in Health and Disease* appears 5 years after the initial volume of the Nutrition and Health series on the same topic. The aim of the current edition remains to provide comprehensive information regarding adipose tissue, its physiological functions and its role in disease, collecting in one place updated information spanning the range of adipose tissue studies, from basic adipocyte biology to epidemiology and clinical aspects.

The volume is divided in four parts: the first two deal with basic adipose tissue and adipokine biology, while the last two address the problem of obesity and alterations in adipose tissue function from an epidemiological and clinical standpoint.

The chapters that compose Part 1, *Adipose Tissue*: *Structure and Function*, provide an overview of the evolution and biology of adipose tissue and adipokines as well as a state-of-the-art discussion about different types and function of adipose tissue and its distribution in the body. Part 2, *Adipose Tissue Inflammation and Adipocyte Dysfunction in Obesity*, tackles the topic of mechanisms linking expansion of adipose mass to disease pathogenesis by way of inflammation, dysfunctional cellular responses as well as alterations in micronutrient metabolism. Part 3, *Obesity*, addresses epidemiological, genetic and epigenetic aspects of obesity as well as both positive and negative outcomes of rapid weight loss. Finally, the chapters collected under Part 4, *Adipose Tissue and Disease*, explain mechanisms by which obesity and adipose tissue dysfunction increase risk of various pathologies, from diabetes to cancer.

This volume is expected to serve as a useful resource not only for physicians interested in adipose tissue biology but also for basic scientists who want to know more about applied aspects of the field. The book specifically targets endocrinologists, residents and fellows, internists, nutritionists and general practitioners who are exposed to an ever-expanding obese population and need access to relevant, updated research results collected in one place.

Chicago, IL, USA

Giamila Fantuzzi, Ph.D.
Carol Braunschweig, Ph.D.

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, interchapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patients' as well as health professionals' questions which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Adipose Tissue and Adipokines in Health and Disease, *Second Edition*, edited by Giamila Fantuzzi, Ph.D. and Carol Braunschweig, Ph.D. clearly exemplifies the goals of the Nutrition and Health Series. The major driver of this unique and timely Second Edition is to provide the reader with the most recent objective, data-driven summaries of the current scientific understanding of the biochemical, physiological, and pathological relationships between the bioactive molecules synthesized by adipose tissue and their effects on other cells and tissues in the body. Within the past 5 years, since the first edition was published, there has been intensive interest in the obesity epidemic and numerous laboratory experiments and clinical studies published in scientific publications have linked the increased risk of obesity to the actions of the adipokines. Thus, it is of great value to the scientific community, health practitioners, graduate, and medical students to now have a volume that examines the totality of the evidence and also suggests avenues where future clinical studies can provide more definitive answers to questions concerning the role of adipose tissue and adipokines in human health and disease.

Adipose Tissue and Adipokines in Health and Disease, *Second Edition* represents the most comprehensive compilation of recent data on the critical drivers of caloric intakes in children and adults and the potential consequences of biochemical signals that result in overconsumption. The volume chapters examine the adverse effects to the heart, kidneys, brain, and overall metabolism as well as the potential risk of cancer associated with increased bodyweight. The expertise of the volume's editors

Giamila Fantuzzi and Carol Braunschweig helps the reader to understand the relevance of the endocrine functions of adipose tissue and the complex biochemical interactions associated with maintaining the "ideal" body weight.

Dr. Giamila Fantuzzi is a Professor in the Department of Kinesiology and Nutrition at the University of Illinois at Chicago. From 2000 to 2004 she was an Assistant Professor in the Department of Medicine at the University of Colorado Health Sciences Center. Dr. Fantuzzi is a graduate of the University of Milano, Italy, where she obtained a Ph.D. in Experimental Endocrinology. She completed her postdoctoral fellowships in the laboratory of Neuroimmunology at the Mario Negri Institute for Pharmacological Research in Milano, Italy and in the Division of Geographic Medicine and Infectious Diseases at the New England Medical Center of Tufts University in Boston, MA. Dr. Fantuzzi has published extensively on the role of cytokines, adipokines, and adipose tissue in the regulation of inflammation. Her current research focuses on the role of adipose tissue in regulating inflammation in the pancreas and the gastrointestinal tract. Her research is currently funded by the National Institutes of Health and she received past funding from the Cystic Fibrosis Foundation, the Crohn's and Colitis Foundation of America, the Broad Medical Research Program, and the National Pancreas Foundation. Dr. Fantuzzi is an active member of several scientific societies and serves as an appointed member of the Tumor Microenvironment Study Section of the US Center for Scientific Review.

Dr. Carol Braunschweig is a Professor and Associate Head in the Department of Kinesiology and Nutrition at the University of Illinois at Chicago. Dr. Braunschweig received her BS and MS in Nutrition at Michigan State University and her Ph.D. in Epidemiology at the University of Michigan. Prior to her work in academia she was a nutrition support specialist in the Department of Pharmacy at the University of Michigan. Dr. Braunschweig's current research focuses on the role of nutritional intake and body composition on disease risks and outcomes in diverse populations including minority, the disabled, children, and hospitalized patients. Her research is currently funded by the National Institutes of Health and she received past funding from the American Cancer Society, Center for Disease Control, and the Department of Health and Human Services. She is an active member of several scientific societies and is also the Director of Clinical Nutrition at the University of Illinois Center for Clinical and Translational Sciences in Chicago, IL.

This 22 chapter volume is organized into four parts including six chapters within the first part on the basics of adipose tissue structure and function; four chapters in the second part on adipose tissue inflammation and adipocyte dysfunction in obesity; four chapters in the third part on obesity; and a final part that includes eight chapters that review the role of adipose tissue in chronic diseases.

The overview section on the structure and function of adipose tissue begins with a chapter that examines the relevance of the development of adipose tissue in evolution. This is especially important as the chapter helps us to understand the recent global trend towards obesity in humans. We learn that our closest primate relatives also have the potential to store fat in adipose depots for later utilization, and there is strong evidence that captive primates become fat when too much food and not enough exercise are provided. The importance of fat for the development of the human brain, reproduction, and immune system function is reviewed. The second chapter describes the development of white adipose tissue, its formation in adulthood, the process of differentiation of the adipocyte stem cells, and the new data that suggests that there are physiological as well as genetic differences in the adipose tissue that is deposited in regional fat depots throughout the body. The role of adipose tissue in the development of obesity is also reviewed in this chapter that includes more than 150 relevant references. The next chapter describes the metabolic events within white adipose tissue including the formation and breakdown of triglycerides and cholesterol, lipid droplet metabolic activities, microvesicles, and the other factors that stimulate white adipose tissue metabolism. There is an in-depth review of the lipases and other enzymes and bioactive molecules involved in fat metabolism in adipose tissue. The chapter includes over 200 recent references. The fourth chapter in this section examines the

concept of metabolically healthy obesity and reviews the relevant animal models used to describe the distribution of fat and its metabolic consequences that are associated with reduced risk of inflammatory responses associated with obesity. The authors describe the epidemiology of this population of apparently metabolically healthy obese individuals and their significantly lower incidence of cardiovascular disease and diabetes. Chapter 5 examines the important changes in white adipose tissue with aging and its consequences to fat metabolism and overall health in the elderly. The chapter includes a detailed description of the age-associated decrease in subcutaneous white adipose tissue and the consequent alteration in the balance between it and the inflammation-provoking visceral adipose tissue. The final chapter in this section describes the two best characterized adipokines, leptin and adiponectin, their synthesis in adipocytes, the stimuli for their synthesis, their actions, and the consequences of imbalance in the face of obesity. The chapter emphasizes the role of these two key adipokines in regulating inflammatory and immune responses that act as critical mechanisms to link nutritional status and adiposity to several pathologies including infectious and autoimmune diseases, diabetes, cardiovascular disease, and cancer.

The second part contains four chapters that explore adipocyte dysfunction and adipose tissue inflammation in the obese individual. Chapter 7 examines the sources of inflammatory molecules and cells associated with the inflammation that include adipose tissue and other tissues that are activated in response to obesity. A number of intracellular organelles participate in the synthesis of adipokines and other cell regulators. The endoplasmic reticulum is one of the critically important organelles involved in lipid synthesis, glucose metabolism, and protein processing. The next two chapters describe the role of the endoplasmic reticulum and effects of endoplasmic reticulum stress that may cause an aberrant unfolded protein response in adipose tissue. Recent data point to a link between adipocyte maturation and control of fat deposition. The next chapter describes the process known as autophagy which can be initiated when there is an increase in endoplasmic stress. Autophagy is a mechanism for intracellular degradation of cytoplasmic components including macromolecules and organelles. The chapter includes a detailed description of the core processes and genetic factors involved in adipocyte autophagy. There is a review of the recent data that suggest that normal adipose cell formation and adipocyte homeostasis are dependent upon autophagy. The last Chapter 10 describes the consequences of micronutrient deficiencies on adipose tissue and includes over 250 references. Micronutrient deficiencies in obese individuals may be due to an increased requirement related to the increased body size; there may be decreased absorption; metabolism may be altered as a result of the ongoing inflammatory process; and there may be increased deposition and sequestration of especially fat-soluble essential nutrients in the larger than normal mass of adipose tissue. The chapter reviews the resultant physiological changes that have the potential to promote increased fat deposition and increased risk of chronic diseases including cardiovascular disease, type 2 diabetes, and cancer. Specific micronutrients that are reviewed include vitamins A, C, and D, iron, selenium, and zinc.

The third part contains four chapters that examine the broad field of obesity with emphasis on its epidemiology in children, the genetics of obesity, and a separate chapter on the epigenetics and a final chapter on the physiological consequences of rapid weight loss. Chapter 11 describes the different reference standards used by nations to classify children as obese. Childhood obesity is considered a global public health crisis, and the prevalence is increasing in many parts of the world. Globally, the prevalence of overweight and obesity has increased in preschool age children, from approximately 4 % in 1990 to 7 % in 2010. The authors provide a strong rationale for the need for national policies and programs to combat the obesity epidemic. The genetics of obesity is complex and continues to include a host of genetic factors such as discrete genetic defects or chromosomal abnormalities that are both autosomal and X-linked disorders, multiple gene involvement, and alterations to small and large segments of the genome. The chapter includes a detailed description of polygenic obesity studies that include three main approaches: candidate gene studies, genome-wide linkage, and genome-wide association studies. The authors indicate that about 20 loci are consistently associated with

obesity-related traits in obese adults. In children, the most important locus discovered was in the "fat mass and obesity-associated" gene. In addition to the complexities associated with genetic effects on the risk of obesity, there are environmental factors that can affect genetic functions. The next chapter examines several nutritional factors that are known to influence epigenetic phenomena including DNA methylation, histone modifications, noncoding RNA expression, and chromatin remodeling mechanisms. These epigenetic factors include transcriptional regulatory pathways and phenotypic plasticity. The evidence concerning the role of epigenetic phenomena in obesity development and early life exposure to environmental/nutritional factors is reviewed. Chapter 14, the final chapter in this section on obesity discusses the overall effects of weight loss for the obese patient. The chapter reviews both nonsurgical and surgical strategies for slow and rapid weight loss, respectively. The chapter emphasizes the beneficial effects of bariatric surgery including rapid and significant weight loss and improvements in metabolic diseases including diabetes in a relatively short time period. Detailed descriptions of the many other potential benefits of bariatric surgery are included, and an equally detailed discussion of potential adverse effects of the surgery itself as well as the gastrointestinal changes that can affect nutritional status is also reviewed.

The fourth and last part in the volume examines the importance of adipose tissue and its effects in disease states. There are eight chapters that include an examination of the effects of human lipodystrophy, adipose tissue's role in type 2 diabetes, adipokines, and nonalcoholic fatty liver disease, and other chapters on cardiovascular disease, kidney disease, joint disease, and finally, cancer. Lipodystrophy is a disease characterized by the lack of adipose tissue. The cause is usually due to genetic defects; however recently HIV-infected patients who have been treated with protease inhibitors have also shown symptoms of this disease. Chapter 15 includes a detailed description of the genetic lipodystrophies that are inherited as autosomal dominant or recessive traits. The genetic loci that affect differentiation of adipose tissue or lipid storage are reviewed and illustrated in relevant figures. The clinical effects of the lack of adipose tissue include insulin resistance, hypertriglyceridemia, fatty liver, and diabetes. The author explains that this disease has provided evidence of a role for adipose tissue at the center of energy homeostasis and has helped to identify a number of new genetic loci which affect adipogenesis and/or lipid storage. The next chapter examines the effects of obesity and how these may worsen the adverse effects and/or hasten the development of type 2 diabetes. The risk of type 2 diabetes is increased exponentially when body mass index is above the overweight category. However, not every patient with type 2 diabetes is obese or vice versa. The authors indicate that obesity is associated with insulin resistance as is type 2 diabetes. Obesity results in increased production of adipokines/cytokines, excess nutrient consumption, ectopic fat deposition, mitochondrial dysfunction, and impairment of certain brain functions involved in the regulation of energy homeostasis. Obesity can also adversely affect insulin sensitivity in the liver and result in chronic inflammation. In type 2 diabetes, there is a destruction of beta cell function. Another serious disease that is associated with obesity and worsened by obesity's proinflammatory adipokines is nonalcoholic fatty liver disease. The authors of Chap. 17 indicate that nonalcoholic fatty liver disease represents a spectrum of pathological conditions characterized by significant lipid deposition in the liver of patients who do not consume excessive amounts of alcohol. The disease includes steatosis and the most severe forms: nonalcoholic steatohepatitis and related cirrhosis, and hepatocellular cancer. The link between nonalcoholic fatty liver disease and obesity is described in detail and extensively referenced in over 250 citations. Major factors include the decreased production of adiponectin and increased and/or ineffective production of leptin, other adipokines, and inflammatory cytokines from adipose tissue such as TNF-α that are seen in obesity. The next chapter on the association between obesity and cardiovascular disease reminds us that obesity is a leading modifiable risk factor of cardiovascular disease. The authors indicate that obesity is associated with premature atherosclerosis, increased myocardial infarction, hypertension and heart failure risk, and cardiovascular deaths. A number of factors that contribute to cardiovascular disease in obesity including insulin resistance, hypertension, lipid

abnormalities, and premature coronary artery disease are reviewed. The proinflammatory state seen in obesity is considered to have a pathological role in cardiovascular disease progression. New weight-loss drugs, their mode of action, and effects on cardiovascular function are described. The next chapter examines the effects of obesity on the respiratory system and its consequences. Obesity is a major risk factor for the development of asthma; is associated with increased health care utilization in chronic obstructive pulmonary disease; is associated with decreased response to influenza vaccine; and is a significant risk factor for mortality from H1N1 influenza. Obesity is associated with pulmonary hypertension which may be linked to breathing at low lung volumes which increases airway resistance and predisposes to airway closure and expiratory flow limitation. Sleep apnea is also reviewed as there is increased risk with obesity.

Chapter 20 reviews the effects of obesity on kidney function as well as the effects of kidney function loss on the obese patient. As reviewed in detail in other chapters in this section, obesity directly affects the development and progression of type 2 diabetes, hypertension, and dyslipidemia; diabetes and hypertension are the two most common causes of renal impairment. Diabetes is considered a major causative factor in almost half of all cases of end-stage renal disease and need for kidney dialysis treatment. There is an in-depth review of the mechanisms involved in obesity's adverse effects on kidney function. Another major adverse effect of obesity is joint pain and osteoarthritis that are both examined in the next chapter. Obesity results in joint loading and obesity-related inflammatory processes, and obesity plays a major role in the pathogenesis of osteoarthritis in both weight-bearing and nonweight bearing joints. The knee, hand, and hip joints are particularly affected in obese women and are discussed in detail. Data are presented that link adipokines to osteoporosis development and progression. There is also a discussion of the benefits of weight loss. The last chapter in the volume reviews the data associating obesity with significant cancer risk. Obesity is a major risk factor for colon, esophageal, pancreatic, endometrial, kidney, and postmenopausal breast cancer. In addition, obesity significantly increases the cancer mortality rates of both men and women. The chapter describes the epidemiologic studies associating obesity with colon and breast cancer risk and the mechanisms by which adipose tissue and adipokines increase these risks. The link between the location of adipose tissues, waist circumference, waist-to-hip ratio, and specific adipose depots on cancer risk in the colon and breast are described and over 150 relevant references are included in the chapter.

The logical sequence of the sections enhances the understanding of the latest clinical and laboratory studies of adipocytes and their bioactive secretions as well as related cytokines and their functional effects on human metabolism. This unique volume serves as a critical resource for practice-oriented physicians, integrative health care practitioners, researchers involved in the genetics of adipose tissue, molecular and cellular biologists, physiologists and other academicians involved in the education of graduate students and postdoctoral fellows, medical students, interns and residents, allied health professionals, and nutritionists who are actively involved in providing data-driven recommendations on the role of adipose tissue in the health of their students, patients, and clients. The volume is of great importance as it contains balanced objective evaluations of the pathology of obesity and the newest data on the effects of the major adipokines including leptin and adiponectin as well as the more recently discovered adipokines and related cytokines that can affect the ability to lose weight either from dieting or bariatric surgery.

Adipose Tissue and Adipokines in Health and Disease, *Second Edition*, contains over 50 detailed tables and figures that assist the reader in comprehending the complexities of the interactions between the involuntary synthesis of adipokines and the consequences of the proinflammatory effects of the majority of these molecules. There are chapters that review in detail the chronic effects of obesity in children, teens, and adults who are at great risk for developing diabetes, nonalcoholic liver disease, bone and joint inflammation and deterioration, kidney disease as well as cardiovascular diseases, and certain cancers. There are in-depth discussions of the genetic aspects of fat metabolism and laboratory

animal models that help to elucidate the epigenetic factors that influence the risk of obesity-related adverse effects. Health professionals involved in the care of obese and overweight patients are provided balanced documentation and awareness of the newest research on the critical importance of maintaining optimal body weight throughout life. Hallmarks of the 22 chapters include keywords and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined, and consistent use of terms between chapters. There are over 2,300 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text, with chapters written by well-recognized, practice and research oriented investigators, provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics of fat metabolism, adipokine biochemistry, and the consequences of acute and chronic dietary overconsumption in young children through adolescence and adulthood. The overarching goal of the editors is to provide fully referenced information to practicing health professionals and educators so they may have a balanced perspective on the value of assuring the best nutritional quality for their patients and clients.

In conclusion, *Adipose Tissue and Adipokines in Health and Disease*, *Second Edition*, provides health professionals in many areas of research and practice with the most data-driven, up-to-date, well-referenced and comprehensive volume on the current state of the science and medical practice with regard to the nutritional care of patients and clients who want to understand the rationale behind the increased health risks associated with being overweight or obese. The volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N.
Series Editor

About the Series Editor

Dr. Adrianne Bendich, Ph.D., FASN, FACN has served as the "Nutrition and Health" Series Editor for over 15 years and has provided leadership and guidance to more than 100 editors that have developed the 60+ well respected and highly recommended volumes in the Series.

In addition to "Adipose Tissue and Adipokines in Health and Disease," edited by Giamila Fantuzzi and Carol A. Braunschweig, major new editions in 2013–2014 include:

1. *Integrative Weight Management* edited by Dr. Gerald E. Mullin, Dr. Lawrence J. Cheskin, and Dr. Laura E. Matarese, 2014
2. *Nutrition in Kidney Disease, Second Edition* edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2014
3. *Handbook of Food Fortification and Health, volume I* edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
4. *Handbook of Food Fortification and Health, volume II* edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
5. *Diet Quality*: *An Evidence-Based Approach, volume I* edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
6. *Diet Quality*: *An Evidence-Based Approach, volume II* edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013

7. *The Handbook of Clinical Nutrition and Stroke*, edited by Mandy L. Corrigan, MPH, RD; Arlene A. Escuro, MS, RD; and Donald F. Kirby, MD, FACP, FACN, FACG, 2013
8. *Nutrition in Infancy, volume I* edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
9. *Nutrition in Infancy, volume II* edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
10. *Carotenoids and Human Health*, edited by Dr. Sherry A. Tanumihardjo, 2013
11. *Bioactive Dietary Factors and Plant Extracts in Dermatology*, edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
12. *Omega 6/3 Fatty Acids*, edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson, and Dr. Sherma Zibadi, 2013
13. *Nutrition in Pediatric Pulmonary Disease*, edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013
14. *Magnesium and Health*, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012
15. *Alcohol, Nutrition and Health Consequences*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
16. *Nutritional Health, Strategies for Disease Prevention, Third Edition*, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
17. *Chocolate in Health and Nutrition*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
18. *Iron Physiology and Pathophysiology in Humans*, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

Earlier books included "*Vitamin D, Second Edition*" edited by Dr. Michael Holick; "Dietary Components and Immune Function" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; "Bioactive Compounds and Cancer" edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; "Modern Dietary Fat Intakes in Disease Promotion" edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "Iron Deficiency and Overload" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "Nutrition Guide for Physicians" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; "Nutrition and Metabolism" edited by Dr. Christos Mantzoros; and "Fluid and Electrolytes in Pediatrics" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include "Handbook of Drug-Nutrient Interactions" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "Probiotics in Pediatric Medicine" edited by Dr. Sonia Michail and Dr. Philip Sherman; "Handbook of Nutrition and Pregnancy" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; "Nutrition and Rheumatic Disease" edited by Dr. Laura Coleman; "Nutrition and Kidney Disease" edited by Dr. Laura Byham-Gray, Dr. Jerrilynn Burrowes and Dr. Glenn Chertow; "Nutrition and Health in Developing Countries" edited by Dr. Richard Semba and Dr. Martin Bloem; "Calcium in Human Health" edited by Dr. Robert Heaney and Dr. Connie Weaver; and "Nutrition and Bone Health" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich is President of Consultants in Consumer Healthcare LLC, and is the editor of ten books including "Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fourth Edition" coedited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the *Journal of Nutrition in Gerontology and Geriatrics and Antioxidants*, and has served as Associate Editor for *Nutrition* the international journal; served on the Editorial Board of the *Journal of Women's Health and Gender-Based Medicine*, and served on the Board of Directors of the American College of Nutrition.

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI)

intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. She is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* Awardee, and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences. Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN. Dr. Bendich is Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.

About the Volume Editors

Dr. Giamila Fantuzzi, Ph.D., is a Professor in the Department of Kinesiology and Nutrition at the University of Illinois at Chicago. From 2000 to 2004 she was an Assistant Professor in the Department of Medicine at the University of Colorado Health Sciences Center.

Dr. Fantuzzi is a graduate of the University of Milano, Italy, where she obtained a Ph.D. in Experimental Endocrinology. She completed her postdoctoral fellowships in the laboratory of Neuroimmunology at the Mario Negri Institute for Pharmacological Research in Milano, Italy and in the Division of Geographic Medicine and Infectious Diseases at the New England Medical Center of Tufts University in Boston, MA.

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Dr. Carol Braunschweig, Ph.D. is a Professor and Associate Head in the Department of Kinesiology and Nutrition at the University of Illinois at Chicago. Dr. Braunschweig received her BS and MS in Nutrition at Michigan State University and her Ph.D. in Epidemiology at the University of Michigan. Prior to her work in academia she was a nutrition support specialist in the Department of Pharmacy at the University of Michigan. Dr. Braunschweig's current research focuses on the role of nutritional intake and body composition on disease risks and outcomes in diverse populations including minority, disabled, children, and hospitalized patients. Her research is currently funded by the National Institutes of Health and she received past funding from the American Cancer Society, Center for Disease Control, and the Department of Health and Human Services. She is an active member of several scientific societies and is also the Director of Clinical Nutrition, UIC Center for Clinical and Translational Sciences.

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We would also like to thank Series Editor Dr. Adrianne Bendich for her light, but firm, touch that has been instrumental in keeping us on track.

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Part I
Adipose Tissue: Structure and Function

Chapter 1
Adipose Tissue in Evolution

Karin Isler

Keywords Primates • Adaptation • Evolution • Adipose depots • Body fat content

Key Points

- To understand the recent global trend toward obesity in humans, we need an evolutionary perspective on the costs and benefits of storing fat in adipose depots. In general, wild-living monkeys and apes appear to be relatively lean compared to humans, but in captivity, some species tend to accumulate fat depots from lack of exercise and too much food. In short, there are two strategies to survive lean periods: cognitive flexibility (and thus a large brain) or physiological flexibility through storing fat. Humans combine these two usually exclusive strategies, which may have evolved together with our unique form of locomotion, a striding bipedal gait.

Introduction

For storage and later utilization of ingested energy, fat is the most efficient form, because 1 g of fat contains nine calories, whereas 1 g of protein or carbohydrates contains only four calories. Ever since Neel's [60] concept of a "thrifty genotype," the human ability to store fat in adipose depots has been related to our species' potential to withstand periodic famines. This ability, while being adaptive for subsistence cultures in a rough and highly variable Pleistocene environment, has become a maladaptation in modern societies due to the continuous availability of the preferred sweet and fatty foods. To understand the recent global trend toward obesity in humans, we need an evolutionary perspective on the costs and benefits of adipose depots (cf. [10, 68, 84]), which can be gained by looking at other mammals and, in particular, primates. Many animals living in natural habitats manage to meet the challenge of alternating periods of food scarcity and abundance by storing fat. Others rely more on skillful retrieval and extraction of hidden high-quality foods, and thus follow a strategy of cognitive instead of physiological flexibility. In this chapter, I will present comparative evidence for an almost unique human strategy to combine physiological and cognitive buffering of lean periods.

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Adipose Depots in Primates and Humans

In contemporary humans, the amount of body fat accounts for about 14 % of the total body weight in a healthy man and 24 % in a woman [61]. This high amount of stored fat is not entirely due to modern, industrial lifestyle, as even in hunter-gatherer populations, or subsistence cultures inhabiting harsh environments, body fatness in women is around 20 % [47]. The published information on body fat content of wild mammals is limited (Fig. 1.1), but it is evident that humans lie in the upper range of the distribution. In general, large animals store more fat relative to their energy throughput, as metabolic rates exhibit a negatively allometric relationship with body mass [44]. Large animals can not only thrive on foods of low energy density (e.g., herbivore ungulates, elephants) but also tolerate fluctuations of energy input better than small animals (cf. [23]).

We humans belong to the order of Primates, and we are most closely related to monkeys, and in particular to apes such as chimpanzees, bonobos, gorillas, and orangutans. Pond [64] demonstrated that nonhuman primates and humans share a unique distribution of fat deposits, in that they accumulate a "paunch," which consists of subcutaneous and intra-abdominal deposits of fat in the anterior abdominal region. Both deposits increase disproportionately with adiposity through adipocyte proliferation [66]. The relative amount of body fat is known for some monkeys and lemurs [59, 63, 66], but only very few ape specimens [88–90], as complete cadavers of apes are very difficult to obtain. Postmortem examinations, although crucial for the welfare of these valuable animals in captivity, usually destroy the most information on abdominal fat deposits [90]. Therefore, we cannot infer whether the last common ancestor of African apes and humans already possessed an increased ability to store fat [64]. Nevertheless, although the amount of adipose tissue in captive apes may be a gross overestimation of even the fattest individuals in wild settings (cf. [90]), the potential to store fat in adipose depots for later utilization is clearly present in our relatives. There is ample evidence of captive primates becoming fat with too much or the wrong sort of food and not enough exercise [21, 65, 89, 90]. To assess whether or not it is feasible to use this potential in the wild, indirect measures of fatness such as variation in body mass or the excretion of ketone bodies in the urine are more readily available than direct data obtained from dissections.

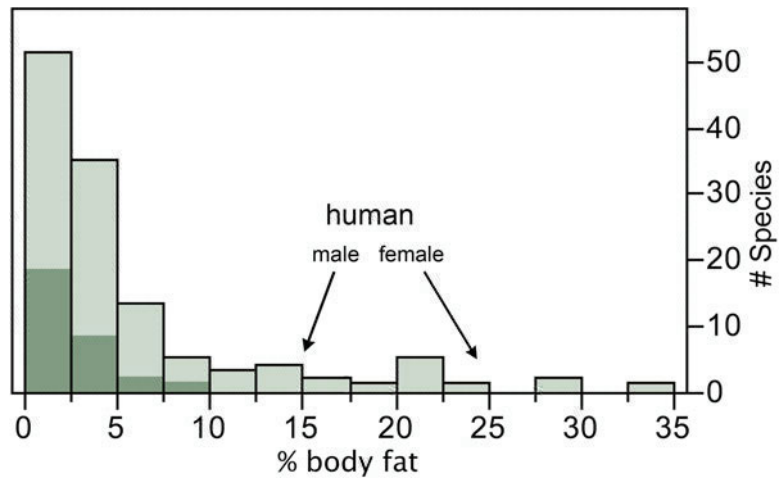

Fig. 1.1 Adipose depots mass as percentage of total body mass in a sample of 123 species of mammals (data from [59], complemented with data from [65] for large mammals). Nonhuman primates are *dark shaded*. Human males and females are indicated with an *arrow*