Bariatric Endocrinology

Evaluation and Management of Adiposity, Adiposopathy and Related Diseases

J. Michael Gonzalez-Campoy
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To our colleagues, especially our predecessors, whose inquisitive minds, work, and dedication to the advancement of science have led to the publication of this textbook.

To our patients with overweight, obesity, and adiposopathy, for whom we continue this work – they inspire and motivate us.

And to our families, for their unwavering love and support – they allow us to pursue our scientific and medical endeavors, for the common good.

Preface

At its annual meeting in 2017 the United Nations Educational, Scientific and Cultural Organization (UNESCO) inscribed the Caves and Ice Age Art in Swabian Jura, Germany on the World Heritage List. The caves have Aurignacian layers which date from 43,000 to 33,000 years ago. Among the items found in these ancient layers is a 6 cm tall statuette of a woman, carved out of mammoth ivory. This is the oldest known statue depicting a human being, and the woman clearly has obesity. Known as the Venus of Hohle Fels, the statuette helps us understand that for as long as there has been humanity, there have been individuals who can accumulate adipose tissue. Ancient civilizations, including the Egyptians and the Greek, came to regard obesity as a disease, a concept which was forgotten and which up until recently was still the subject of intense debate.

Over the years the condition of having excess adipose tissue has been named obesity, fatness, adiposity, overweight, corpulence, plumpness, chubbiness, stoutness, portliness, heaviness, tubbiness, flabbiness, largeness, chunkiness, heftiness, and bulkiness. Obesity was considered a reflection of success and wealth – those with the means could afford the regular ingestion of excess calories, and perhaps the service of others, leading to the accumulation of fat mass. Historical figures like King Henry VIII of England exemplified obesity as a disease – he was known to be ill from his obesity, and his gout attacks are chronicled for posterity.

With wars and worldwide famine, with infectious diseases that limited longevity, with limitations of the food supply, and with lifestyles that demanded physical activity, the historical prevalence of obesity had been limited. Individuals with obesity were featured attractions in traveling circuses, including Jack "The Happy Fat Man" Eckert and the "Humongous Circus Fat Man 'Tom Ton'", both of whom achieved notoriety at the turn of the nineteenth century.

With the industrialization of the world, humanity changed. Over the second half of the twentieth century, the food supplies of industrialized nations started to provide a steady stream of nutrients. There also developed myriads of disincentives for physical activity. With the advent of public health interventions, including waste disposal and water purification, the burden of infectious diseases significantly abated. And with the implementation of pasteurization, sterile techniques, and

antibiotic treatments, the lifespan of human beings has been significantly prolonged. This all has allowed for the development of chronic diseases, including overweight and obesity, over the extended years of life for modern day humans.

We now understand that overweight and obesity represent a continuum of a complex, multifactorial disease that leads to the loss of health for most individuals who have it. Further, we now also realize that adiposity (the accumulation of fat mass) is but one aspect of the disease. The discovery that adipose tissue is an endocrine organ, and that the adipocyte is an endocrine cell, established that there are changes in anatomy and function that are at the genesis of metabolic diseases. Adiposopathy and "sick fat" are terms that are now engrained in the literature which encompass these pathophysiological changes. For some of our colleagues, these terms are not acceptable (they cannot take ownership of what they did not conceive), and this has led to scientific discordance. We respectfully agree to disagree. Yet, for a new generation of physicians and scientists, familiarity with these terms has opened a new frontier in medicine.

This textbook has been written with an adipocentric perspective. Not only is it a thorough review of obesity medicine, it also helps the reader understand the importance of adipose tissue dysfunction in the genesis of the metabolic complications of overweight and obesity. Bariatric endocrinology is thus born, paving the way for a new generation of physicians to diagnose and treat adiposopathy.

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Abbreviations

11ß-HSD	11-beta-hydroxysteroid dehydrogenase
2-AG	Endocannabinoid 2-arachidonoylglycerol
5-HT	5-hydroxytryptamine, serotonin
A1C	Hemoglobin A1c
AA	Amino acid
AACE	American Association of Clinical Endocrinologists
ACC	American College of Cardiology
ACE	American College of Endocrinology
ACEi	Angiotensin-converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone
AD	Adiposis dolorosa
ADA	American Diabetes Association
ADA	Americans with Disabilities Act
ADHD	Attention deficit hyperactivity disorder
AG	Acylated ghrelin
AGB	Adjustable gastric band
AGPAT	Acylglycerophosphate acyltransferase
AgRP	Agouti-related protein
AHA	American Heart Association
AHI	Apnea-hypopnea index;
AHSD	α-hydroxysteroid dehydrogenase
AICR	American Institute for Cancer Research
ALA	Alpha-linolenic acid
ALLHAT	Antihypertension and Lipid-Lowering treatment to prevent Heart Attack Trial
AMA	American Medical Association
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate-activated protein kinase
AN	Anterior nucleus of the hypothalamus
AP	Area postrema
Apo E	Apolipoprotein E

apo	Apolipoprotein
ARB	Angiotensin receptor blocker
ARC	Arcuate nucleus of the hypothalamus
ART	Assisted reproductive technologies
ASBP	American Society of Bariatric Physicians
ASBS	American Society for Bariatric Surgery
ASMBS	American Society for Metabolic and Bariatric Surgery
ASP	Acylation-stimulating protein
ASSIST	Appetite Suppression Induced by Stimulation Trial
ATP	Adenosine triphosphate
ATP	Adult Treatment Panel
AUD	Alcohol use disorder
BA	Bile acids
BAT	Brown adipose tissue
BBB	Blood-brain barrier
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
BE	Barrett's esophagus
BED	Binge eating disorder
BHSD	β-hydroxysteroid dehydrogenase
BIA	Bioelectrical impedance analysis
BID	Twice daily
BMI	Body mass index
BMOD	Behavior modification
BP	Blood pressure (S = systolic and D = diastolic)
BPD	Biliopancreatic diversion
BPD-DS	Biliopancreatic diversion with duodenal switch
BRFSS	Behavioral Risk Factor Surveillance System
bT	Bioavailable testosterone
BWL	Behavioral weight loss
CABG	Coronary artery bypass grafting
cAMP	Cyclic adenosine monophosphate
CARDIA	Coronary Artery Risk Development in Young Adults study
CART	Cocaine- and amphetamine-related transcript
CB	Cannabinoid receptor
CBT	Cognitive behavioral treatment
CBTgsh	Cognitive behavioral therapy with guided self-help
CCB	Calcium channel blocker
CCK	Cholecystokinin
CDC	Centers for Disease Control and Prevention
CETP	Cholesteryl ester transfer protein
CI	Confidence interval
CKD	Chronic kidney disease
cm	Centimeters
CNPS	Cardiac natriuretic peptide system

CNS	Central nervous system
CO	Cardiac output
COR	Contrave Obesity Research
CPAP	Continuous positive airway pressure therapy
CRC	Colorectal cancer
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CS	Cushing's syndrome
CT	Computerized tomography
CTR	Calcitonin receptor
CV	Cardiovascular
CVA	Cerebrovascular accident;
CVD	Cardiovascular disease
CVO	Circumventricular organs
CY	Cytochrome
DA	Dopamine
DASH	The Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DEXA	Dual-energy X-ray absorptiometry
DGAT	Diacylglycerol acyltransferase
DHA	Docosahexaenoic acid
DHEA	Dehydroepiandrosterone
DJB	Duodenojejunal bypass
dL	Deciliter
DM	Diabetes mellitus
DMN	Dorsomedial nucleus of the hypothalamus
DMPA	Depot medroxyprogesterone acetate
DNA	Deoxyribonucleic acid
DPP	Dipeptidyl peptidase
DPP-4	Dipeptidyl peptidase 4
DPP-4l	Dipeptidyl-peptidase-4 inhibitors
DXA	Dual Energy X-ray absorptiometry
E_2	Estradiol
EAC	Esophageal adenocarcinoma
EASO	European Association for the Study of Obesity
ECG	Electrocardiogram
ED	Erectile dysfunction
EEC	Enteroendocrine cells
eGFR	Estimated glomerular filtration rate
EH	Energy homeostasis
EKG	Electrocardiogram
eNOS	Endothelial nitric oxide synthase
ENS	Enteric nervous system
EPA	Eicosapentaenoic acid
ER	Estrogen receptor

ES	Endoluminal sleeve(s)
EWL	Excess weight loss
FA	Food addiction
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FFA	Free fatty acids
FFM	Fat-free mass
FGF15/FGF19	Fibroblast growth factor 15/19
FH	Familial hypercholesterolemia
FM	Fibromyalgia
FMI	Fat mass index
FML	Familial multiple lipomatosis
fMRI	Functional magnetic resonance imaging
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
FPG	Fasting plasma glucose
FSH	Follitropin or follicle-stimulating hormone
fT	Free testosterone
FTO	Fat mass and obesity associated (gene)
FXR	Farnesoid X receptor
G6P	Glucose-6-phosphate
GABA	Gamma-aminobutyric acid
GBS	Gastric bypass surgery
GC	Glucocorticoid
GCGR	G-protein-coupled glucagon receptor
GERD	Gastroesophageal reflux disease
GES	Gastric electrical stimulation
GH	Growth hormone
GHRL	Growth hormone secretagogue receptor ligand
GHSR	Ghrelin/growth hormone secretagogue receptor
GIP	Glucose-dependent insulinotropic peptide
GK	Glucokinase
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GLUT	Glucose transporter
GLUT4	Glucose transporter 4
GM	Gut microbiota
Gn	Gonadotropin
GnRH	Gonadotropin-releasing hormone
GOAT	Ghrelin O-acyltransferase
GPAT	Glycerol-3-phosphate acyltransferase
GPCR	G-protein-coupled receptor
GRPP	Glicentin-related pancreatic peptide
GWAS	Genome-wide association studies
H&E	History and examination
H&P	History and physical examination

HbA_{1c}	Hemoglobin A1C
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCFA	Healthcare Financing Administration
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HFD	High-fat diet
HIF1	Hypoxia-inducible factor 1
HMG-CoA	3-Hydroxy-3-methyl-glutaryl-coenzyme A
HMGCR	3 Hydroxy-3-methyl-glutaryl-coenzyme A reductase
HOMA	Homeostasis model assessment
HOMA-IR	Homeostasis model assessment of insulin resistance
HP	Highly palatable
HPA	Hypothalamic-pituitary-adrenal
HPAA	Hypothalamic-pituitary-adrenal axis
HR	Hazard ratio
HRT	Hormone replacement therapy
HS-CRP	Highly sensitive C-reactive protein
HSL	Hormone-sensitive lipase
HTN	Hypertension
IAP	Intra-abdominal pressure
ICD	International Classification of Diseases
IFG	Impaired fasting glucose
IGB	Intragastric balloons
IGF	Insulin-like growth factor
IGF-1R	Insulin-like growth factor-1 receptor
IGS	Implantable gastric stimulator
IGT	Impaired glucose tolerance
IIEF-5	International Index of Erectile Function 5
IL	Interleukin
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
INS	Insulin
IPT	Individual psychotherapy
IR	Insulin receptor
ISH	Isolated systolic hypertension
ITT	Intention to treat
IU	International units
IWB	Internalized weight bias
JIB	Jejunoileal bypass
JNC	Joint National Committee
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
Kcal	Kilocalories

kg	Kilogram
kg/m^2	$kilograms/meter^2$
LAR	Leptin-to-adiponectin ratio
lbs	Pounds
LCFA	Long-chain fatty acids
LDJB-SG	Loop duodenojejunal bypass with sleeve gastrectomy
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LEARN	Lifestyle, Exercise, Attitude, Relationships and Nutrition
LEP	Leptin
LEPR	Leptin receptor
LGA	Left gastric artery
LGAE	Left gastric artery embolization
LH	Lutropin or luteinizing hormone
LHA	Lateral hypothalamic area
LOCF	Last observation carried forward
LOFI	Lean-on-the-outside-fat-on-the-inside
LP(a)	Lipoprotein (a)
LPL	Lipoprotein lipase
LRYGB	Laparoscopic Roux-en-Y gastric bypass
LUTS	Lower urinary tract symptoms
LVSG	Laparoscopic vertical sleeve gastrectomy
m	Meter
MAOI	Monoamine oxidase inhibitor
MAP kinase	Mitogen-activated protein kinase
MC	Melanocortin
MC4R	Melanocortin 4 receptor
MCFA	Medium-chain fatty acid
MCH	Melanin-concentrating hormone
MCP	Monocyte chemoattractive protein
MCR4	Melanocortin receptor 4
MDD	Major depressive disorder
METs	Metabolic equivalents
mg	Milligram
MGB	mini gastric bypass
MI	Myocardial infarction
mITT	Modified intention-to-treat
mmHg	Millimeters of mercury
MN	Mammillary nucleus of the hypothalamus
MNT	Medical nutrition therapy
MRFIT	Multiple Risk Factor Intervention Trial
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSH	Melanocyte-stimulating hormone
mTOR	Mammalian target of rapamycin

MTTP	Microsomal triglyceride transfer protein
MUFA	Monounsaturated fatty acids
Myf5	Myogenic factor 5
NA	Nucleus accumbens
NAASO	North American Association for the Study of Obesity
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NB	Naltrexone-bupropion
NCEP ATP	National Cholesterol Education Program Adult Treatment Panel
NCEP	National Cholesterol Education Program
NCHS	National Center for Health Statistics
NEFA	Non-esterified fatty acid
NES	Night-eating syndrome
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
non-SHBG-bound T	Non-sex hormone-binding globulin-bound testosterone
NPC1L1	Niemann-Pick C1-Like 1
NPY	Neuropeptide Y
NTS	Nucleus tractus solitarius
OA	Osteoarthritis
OAGB	One anastomosis gastric bypass
OGTT	Oral glucose tolerance test
OMA	Obesity Medical Association
OR	Odds ratio
OSA	Obstructive sleep apnea
OVRD	Oral volume restricting device
OX	Orexin receptor
OXM	Oxyntomodulin
P_4	Progesterone
PAI-1	Plasminogen activator inhibitor-1
PAP	Phosphatidic acid phosphorylase
PCI	Percutaneous coronary intervention
PCOS	Polycystic ovary syndrome
PCS	Pain Catastrophizing Scale
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Pulmonary embolus;
PFC	Prefrontal cortex
PG	Percutaneous gastrostomy
PGC-1α	PPAR gamma coactivator 1-alpha
PHEN/TPM	Phentermine-topiramate
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
PN	Posterior nucleus of the hypothalamus

POMC	Pro-opiomelanocortin
PON	Preoptic nucleus of the hypothalamus
PP	Pancreatic polypeptide
PPAR	Peroxisome proliferator-activated receptor
PPG	Postprandial glucose
PPNAD	Primary pigmented nodular adrenocortical disease
PR	Peripheral resistance
PRL	Prolactin
PSA	Prostate-specific antigen
PSCK1	Prohormone convertase 1
PTCA	Percutaneous transluminal coronary angioplasty
PTSD	Post-traumatic stress disorder
PUFA	Polyunsaturated fatty acid
PVN	Paraventricular nucleus of the hypothalamus
PYY	Peptide YY
QD	Daily
QOL	Quality of Life
RA	Retinoic acid
RAAS	Renin-angiotensin-aldosterone system
RAMPs	Receptor activity-modifying proteins
RBP	Retinol-binding protein
REE	Resting energy expenditure
REMS	Risk evaluation and mitigation strategies
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
ROS	Review of systems
RR	Relative risk
RR	Risk ratio
RXR	Retinoid X receptors
RYGB	Roux-en-Y gastric bypass
SADI	Single anastomosis duodenoileostomy
SAGI	Single anastomosis gastroileostomy
SASI	Single anastomosis sleeve ileostomy
SBP	Systolic blood pressure
SCALE	Satiety and Clinical Adiposity-Liraglutide Evidence
SCFA	Short-chain fatty acid
SCN	Suprachiasmatic nucleus of the hypothalamus
Sct	Secretin
SctR	Secretin receptor
SD	Standard deviation
SGLT-1	Sodium-dependent glucose transporter 1
SGLT-2	Sodium-dependent glucose transporter-2
SH2B1	Src homology 2B adaptor protein 1
SHAPE	Screened Health Assessment and Pacer Evaluation trial
SHBG	Sex hormone-binding globulin

SIPS	Stomach intestinal pylorus sparing surgery
SL	Symmetrical lipomatosis
SMC	Smooth muscle cell
SNP	Single nucleotide polymorphism
SNRI	Serotonin norepinephrine reuptake inhibitor
SON	Supraoptic nucleus of the hypothalamus
SSRI	Selective serotonin reuptake inhibitor
SVR	Systemic vascular resistance
T	Testosterone
T2DM	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Tetraiodothyronine or thyroxine
TC	Total cholesterol
TEE	Total energy expenditure
TES	The Endocrine Society
TFA	Trans-fatty acids
TG	Triacylglycerol
TG	Triglycerides
TGR5	The G-protein coupled receptor 5
TID	Three times daily
TKA	Total knee arthroplasty;
TNF	Tumor necrosis factor
TOGA	Transoral gastroplasty
TOS	The Obesity Society
TRH	Thyrotropin-releasing hormone
TRT	Testosterone replacement therapy
TRUS	Transrectal ultrasound
TSH	Thyroid-stimulating hormone
TT	Total testosterone
TWIST	Twist-related protein
TZDs	Thiazolidinediones
UAG	Unacylated ghrelin
UCP	Uncoupling protein
UDCA	Ursodeoxycholic acid;
UK	United Kingdom
US	United States
USA	United States of America
USDA	United States Department of Agriculture
UTI	Urinary tract infection;
VAN	Vagal afferent neurons
VBG	Vertical banded gastroplasty
VEGF	Vascular endothelial growth factor
VLC	Very low-calorie
VLCMP	Very low-calorie meal plan
VLDL	Very low-density lipoprotein

VLDL-C	Very low-density lipoprotein cholesterol
VMN	Ventromedial nucleus of the hypothalamus
VSG	Vertical sleeve gastrectomy
VTA	Ventral tegmental area
WAT	White adipose tissue
WC	Waist circumference
WCRF	World Cancer Research Fund
WHI	Women's Health Initiative
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
YFAS	Yale Food Addiction Scale

Chapter 1
Bariatric Endocrinology

J. Michael Gonzalez-Campoy

Pearls of Wisdom

- Bariatric endocrinology developed from the knowledge that adipose tissue is an endocrine organ that actively participates in the regulation of metabolism and that it may become diseased (adiposopathy), thus contributing to the development of metabolic diseases.
- Adipose tissue may develop both anatomical and pathophysiological changes which lead to derangements of structure and function, collectively termed adiposopathy.
- Adipocytes both produce hormones with varied end-organ targets, and have receptors for many circulating hormones, establishing an active cross talk that maintains metabolic homeostasis. Adiposopathy leads to dysregulation of metabolic homeostasis, forcing other tissues to compensate, and leading to metabolic diseases when compensation is inadequate.
- Overweight, obesity, and adiposopathy are caused by both a genetic predisposition and environmental factors, and must be treated like any other chronic disease.
- The goals of bariatric endocrinology are to help individual patients decrease the burden of increased fat mass (treatment of adiposity) and to return adipose tissue function to normal (treatment of adiposopathy).

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1.1 Introduction

Bariatric endocrinology first became a subject at the 2014 meeting of the American Association of Clinical Endocrinologists (AACE) in Las Vegas, Nevada. The co-editors of this textbook held a scientific session that defined obesity as an endocrine disease, adipose tissue as an endocrine organ, and the adipocyte as an endocrine cell. As such, obesity became not just a disease of excessive fat mass but rather a treatment target for clinical endocrinologists, a major goal of treatment becoming the correction of underlying adipose tissue dysfunction. This emerging position has been difficult to understand and accept by the vast majority of physicians who still think of success in the treatment of obesity as merely a reduction in poundage. This textbook of bariatric endocrinology was conceived after the 2014 AACE meeting to set the stage for future generations of clinicians who will have learned that adipose tissue dysfunction is a viable target of medical interventions, in addition to the traditional goal of decreasing fat mass. A brief history of how we got here is important.

In 1903, Dr. Perry published a paper entitled "The Nature and Treatment of Obesity" in the *California State Journal of Medicine*. He described obesity as "20 per cent to 40 per cent excess of weight over the normal of 2.05 pounds per inch of height, or 300 grammes per centimeter." In his paper, he explained that corpulence must be due to excessive muscular development, excessive fatty tissue, excessive water, myxedema, or pseudo-muscular hypertrophy. Prior to his publication, there are no indexed papers with obesity in the title in the National Library of Medicine. For the next half century, the view of adipose tissue became one of a storage organ. Yet the concept that obesity is a risk to health dates back to the writings of Hippocrates. And over this half century, progress was made identifying obesity as a disease.

In 1963, the emerging field of lipidology defined the role that adipose tissue had to play in lipid metabolism. Dr. Martha Vaughan and colleagues at the National Institutes of Health (NIH) documented that there is a hormone-sensitive triglyceride-splitting enzyme activity in adipose tissue. Hormone-sensitive lipase was shown to respond to epinephrine, leading to increased lipolysis and defining adipose tissue as a target of circulating hormones. Insulin was subsequently shown to inhibit this same enzyme, being strongly antilipolytic. In 1976, Dr. Lewis Williams and colleagues identified beta-adrenergic receptors in adipocytes, confirming that the adipocyte was indeed under hormonal control.

The first hints of a circulating factor that could affect fat mass came earlier. In 1959, parabiosis experiments done by Dr. Hervey at the University of Cambridge, in which paired rats were made to exchange blood and plasma by being surgically conjoined at the hip, provided an important clue to the presence of a circulating factor that could regulate energy stores. Damage to the ventromedial hypothalamus leads to obesity caused by overeating in rats. The damage prevents the ventromedial

hypothalamus from responding to physiological signals that suppress appetite. When a rat with a ventromedial hypothalamus lesion is conjoined to a normal rat, the rat with the lesion overeats and gains weight. The normal rat without a lesion, on the other hand, significantly decreases its caloric intake, losing weight and declining food even when made available. When both paired rats have damage to the ventromedial hypothalamus, both overfeed and gain weight. This was strong evidence of a circulating factor that decreases caloric intake by stimulating a hypothalamic target, thus decreasing fat mass. And it was also evidence that there is central regulation of energy balance.

In the late 1980s, adipose tissue was found to produce estrogen. Aromatase, the enzyme responsible for the synthesis of estrogen from testosterone, was identified in adipose tissue. This established the adipocyte as an endocrine cell capable of synthesizing estrogen. The degree of adiposity was subsequently related to the amount of estrogen in the circulation of patients with obesity and reproductive tract cancer. But aromatase and estrogen were not exclusive to adipose tissue.

In 1949, mice homozygous for the ob mutation (ob/ob mice) were first identified at the Jackson Laboratory. These mice exhibit uncontrolled feeding and develop obesity. In 1990, the ob gene was mapped. Subsequently, the gene product of the ob gene was identified as a hormone. When the gene product was given to ob/ob mice, it suppressed excessive feeding and promoted weight loss. Accordingly, this protein was named leptin, a derivative of the Greek root for "thin," *lepto*. Leptin was the first adipocyte-derived hormone (adipokine) to be discovered. A search of the Medi-Span database as of 2016 includes over 13,000 references with the word leptin in the title.

When leptin was characterized as a hormone made exclusively in adipose tissue, the search for other adipocyte products intensified. Adipocytes were also shown to produce adiponectin (which improves insulin sensitivity), adipsin (which is deficient in obesity), resistin (which causes insulin resistance), and visfatin (which has plasma glucose-lowering effects). Additionally, adipose tissue was shown to produce inflammatory cytokines including interleukin-6, tumor necrosis factor-alpha, and macrophage and monocyte chemoattractant protein-1, documenting its potential for macrophage infiltration and the development of inflammation.

By the late 1990s, the view of adipose tissue as a mere storage organ had been replaced by the contemporary perspective that it actively participates in the signaling that regulates the body's energy needs. The concept that adipose tissue may become diseased, or that adiposopathy may develop, was introduced into the medical literature by Dr. Harold Bays in 2004. Adiposopathy is now a treatment target in clinical endocrinology.

With a recognized worldwide obesity epidemic, there were over 64,000 publications on the subject by the end of 2015 (Fig. 1.1). This chapter reviews the epidemiology of obesity, its economic impact, its differential effect in different ethnic groups, the public health efforts to address it, and the principles of bariatric endocrinology that will help treat this disease.

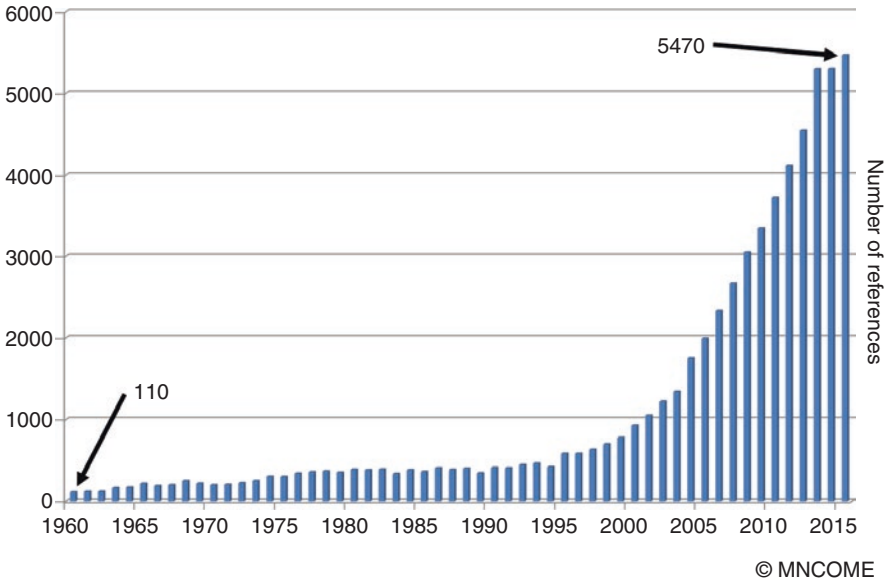

Fig. 1.1 Number of publications with "obesity" in the title by year (1960–2015); Copyright MNCOME

1.2 The Obesity Epidemic in the United States of America (USA)

1.2.1 Adult USA Population

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. It is funded by the Centers for Disease Control (CDC), through the National Center for Health Statistics (NCHS). The survey is unique in that it combines interviews and physical examinations. All counties in the United States are divided into 15 groups based on their characteristics. One county is selected from each large group, and together, they form the 15 counties in the NHANES surveys for each year. Within each of these 15 counties, smaller groups, with a large number of households in each group, are formed. Between 20 and 24 of these small groups are then selected. In each small group, all the houses and apartments are identified, and a sample of about 30 households is selected for interviewers to visit. A computer algorithm randomly selects some, all, or none of the household members.

NHANES data for USA adults ages 20 or higher from 1962 documented that 30.5% of the population had a body mass index (BMI) in the range of 25–29.9 kg/m^2, and 12.8% had a BMI of 30 kg/m^2 or more. By 2012, these numbers had risen to 33.9% and 35.1%, respectively. For this period, there was a 1.7-fold increase in the prevalence of people with a BMI of 30 kg/m^2 or more.

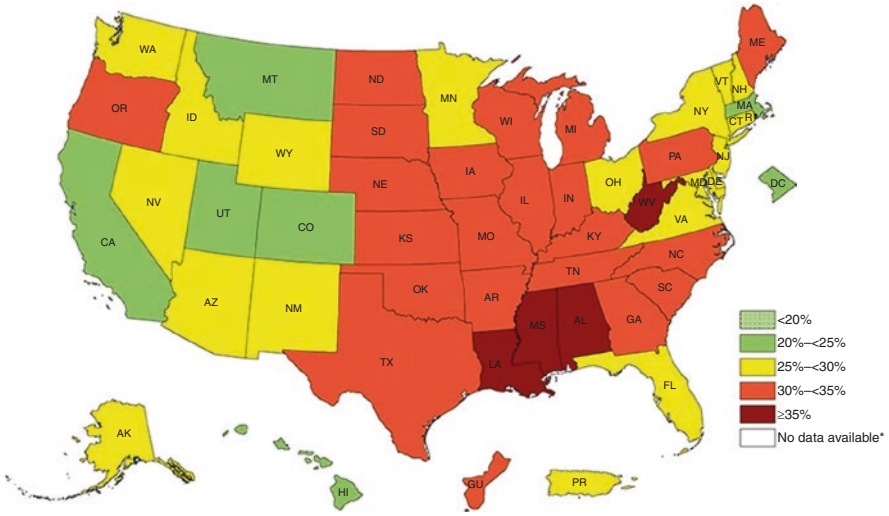

Fig. 1.2 Prevalence of self-reported obesity among USA adults by state and territory, BRFSS, 2015. (From Centers for Disease Control. https://www.cdc.gov/obesity/data/prevalence-maps.html (accessed 9/5/2016))

The Behavioral Risk Factor Surveillance System (BRFSS) is a system of health-related telephone surveys that collect state data about USA residents regarding their health-related risk behaviors, chronic health conditions, and the use of preventive services. It also is funded by the CDC. BRFSS was established in 1984 with 15 states and has expanded to collect data in all 50 states, the District of Columbia, and three USA territories. BRFSS completes more than 400,000 adult interviews each year, making it the largest continuously conducted health survey system in the world.

Figure 1.2 shows the 2015 BRFSS data on the prevalence of self-reported obesity among adults in the USA by state and territory. BRFSS USA data show that in 2015:

- No state had a prevalence of obesity less than 20%.
- In six states (California, Colorado, Hawaii, Massachusetts, Montana, and Utah) and the District of Columbia, obesity ranged from 20% to less than 25%.
- Nineteen states and Puerto Rico had a prevalence of obesity between 25% and less than 30%.
- Obesity prevalence in 21 states and Guam was from 30% to less than 35%.
- Four states (Alabama, Louisiana, Mississippi, and West Virginia) had an obesity prevalence of 35% or greater.
- The south had the highest prevalence of obesity (31.2%), followed by the Midwest (30.7%), the northeast (26.4%), and the west (25.2%).

Using the NHANES 2011–2012 database, the prevalence of obesity is higher among middle-age adults age 40–59 years (40.2%) and older adults age 60 and over (37.0%) than among younger adults age 20–39 (32.3%).

1.2.2 Children and Adolescent USA Population

The prevalence of obesity in 2011–2014 was 17.0%, and extreme obesity (defined as a BMI at or above 120% of the sex-specific 95th percentile on the CDC BMI-for-age growth charts) was 5.8%. Childhood obesity has also been documented to become more prevalent since the first reports by the NCHS using the 1988–1994 NHANES database. This textbook focuses on adult bariatric endocrinology, but these data are included because youth with obesity will swell the ranks of adults having the disease at a much younger age than previous generations.

1.3 Obesity in USA Racial and Ethnic Groups

Using data from 9120 participants in the 2011–2012 nationally representative NHANES database, in the USA non-Hispanic blacks have the highest age-adjusted rates of obesity (48.1%), followed by Hispanics (42.5%), non-Hispanic whites (34.5%), and non-Hispanic Asians (11.7%). Among non-Hispanic black and Mexican-American men, those with higher incomes are more likely to have obesity than those with low incomes. To the contrary, higher-income women are less likely to have obesity than low-income women.

1.4 Obesity in Geographical Regions of the World

In 1988, Gurney and Gorstein published initial data compiled by the World Health Organization (WHO) on the prevalence of obesity in many countries. The publication validated that, for adults, the body mass index is reasonably easy to obtain and correlates well with mortality and morbidity risk. For children, "overweight" is indicated by a weight-for-height ratio above the median NCHS value plus two standard deviations. By 1999, the prevalence of obesity around the world was estimated to exceed 250 million people. The first formal WHO Consultation on obesity concluded that the global obesity epidemic was a consequence of modernization, economic development, urbanization, and other societal changes. These led to widespread reductions in spontaneous and work-related physical activity and to excessive consumption of energy dense foods. The International Obesity Task Force launched a global initiative for coherent action to tackle the epidemic of obesity. Despite increased awareness and attempts to intervene at the public health level, the prevalence of obesity around the world has continued to rise.

Reports on the prevalence of obesity in both adults and children from countries around the world continue to highlight both potential causes and opportunities for intervention. In 2008, the prevalence of obesity (using estimated mean BMI in a regression model to predict overweight and obesity prevalence by age, country, year, and sex) in women ranged from 1.4% (0.7–2.2%) in Bangladesh and 1.5%

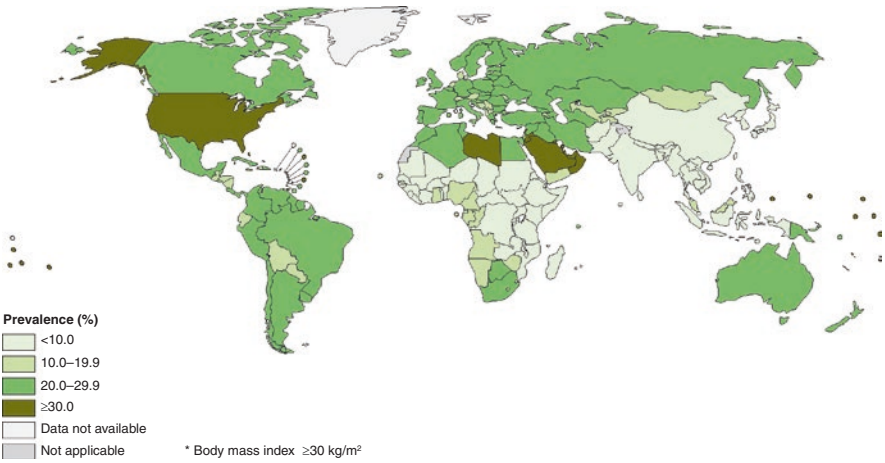

Fig. 1.3 Worldwide prevalence of obesity by BMI*, ages 18+, both sexes, 2014. (From World Health Organization. http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Obesity_2014_BothSexes.png (27/Mar/2015 post; accessed 9/5/2016))

(0.9–2.4%) in Madagascar to 70.4% (61.9–78.9%) in Tonga and 74.8% (66.7–82.1%) in Nauru. Obesity in men was below 1% in Bangladesh, Democratic Republic of the Congo, and Ethiopia and was the highest in Cook Islands (60.1%, 52.6–67.6%) and Nauru (67.9%, 60.5–75.0%). Figure 1.3 shows the latest data on the prevalence of obesity compiled by WHO, as of 2015.

The WHO data have also clearly established the rising rates of diabetes worldwide, parallel to the development of obesity. Some populations around the world seem particularly susceptible to the twin epidemics of obesity and diabetes. In India, for example, defining obesity as a BMI of 25 kg/m^2 or higher, the incidence of obesity rose from 2% to 17.1% of the population between 1989 and 2003. This represented a 750% increase in the incidence of obesity. Over the same period, the incidence of diabetes rose from 2.2% to 6.4% of the population, a 191% increase. At the CDC, Ali Mokdad and colleagues documented the same parallel rise in the incidence of obesity and diabetes in the USA. Between 1998 and 2012, there was a 96% increase in the incidence of obesity, defined as a BMI of 30 kg/m^2 or higher, with a 43% concomitant increase in the incidence of diabetes. It has also been established that the incidence of hypertension, dyslipidemia, and diabetes rises with BMI thresholds from normal to overweight to obesity.

1.5 The Economic Impact of Obesity

Awareness of the increasing prevalence of obesity from data generated by the CDC in the 1980s and 1990s led to significant concern about the financial impact of this disease. Early projections based on the prevalence of obesity of 34 million adults in

the USA in 1980 led to the estimate of 1986 expenditures of $11.3 billion for diabetes, $22.2 billion for cardiovascular disease, $2.4 billion for gallbladder disease, $1.5 billion for hypertension, and $1.9 billion for breast and colon cancers—$39.3 billion or around 5.5% of the costs of illnesses in 1986.

In 2011, a simulation model, to project the probable health and economic consequences in the next two decades from a continued rise in obesity in the USA and the United Kingdom (UK), estimated 65 million and 11 million more adults with obesity in the USA and the UK, respectively, by 2030. The projections were for an additional 6–8.5 million cases of diabetes, 5.7–7.3 million cases of heart disease and stroke, 492,000–669,000 additional cases of cancer, and 26–55 million quality-adjusted life years forgone for the USA and the UK combined. The combined medical costs associated with the treatment of these preventable complications of obesity were estimated to increase by $48–66 billion/year in the USA and by £1.9–2 billion/year in the UK by 2030.

By the end of 2014, the National Center for Weight and Wellness at George Washington University placed the cost of obesity at more than $300 billion annually in direct medical and nonmedical services, decreased worker productivity, disability, and premature death.

There are now projections that weight loss reduces lifetime health-care costs. Using claims data for 2.1 million beneficiaries in the federal government in 2008, there were 857,200 patients with overweight and 521,800 patients with obesity, all aged 18–64 years. Among federal beneficiaries who have overweight or obesity, lifetime expenditures decline by $440 (3% discount rate) for each permanent 1% reduction in body weight. This includes $590 in savings from improved health, offset by $150 in additional expenditures from prolonged life. Estimates range from a $660 reduction for adults aged <45 years with obesity to a $40 gain for adults aged 55–64 years with obesity, where expenditures from increased longevity exceed savings from improved health. If weight loss is temporary and regained after 24 months, lifetime expenditures decline by $40 per 1% reduction in body weight. The long-term benefits from weight loss are substantially greater than the short-term benefits.

There are additional economic correlates to the epidemic of obesity. Obesity results in increased medical expenditures and absenteeism among full-time employees. Approximately 30% of the total costs to employers result from increased absenteeism. Employees with stage 3 obesity represent about 3% of the employed population but account for 21% of the costs of obesity. These costs do not include the additional loss of income to employers from disability and presenteeism (loss of productivity during the time present at work). Physical disabilities magnify the costs of obesity. The combination of physical disabilities and obesity costs employers around $23.9 billion/year or roughly 50% of the total costs attributable to obesity in the USA. Using data on medical expenditures and body weight from the National Health and Interview Survey and the Medical Expenditure Panel Survey, it is estimated that, in a health plan with a coinsurance rate of 17.5%, obesity imposes a welfare cost of about $150 per capita on health insurance costs. The welfare loss to health insurance companies can be reduced by technological change that lowers

pecuniary and nonpecuniary costs of losing weight and also by increasing the coinsurance rate for people with obesity. The workplace has become a venue of active obesity prevention and treatment as a means to decrease health-care costs to employers and to increase productivity. Regardless, the rates of personal bankruptcy have risen along with the incidence of obesity. Using the National Longitudinal Survey of Youth 1979, a duration model was used to investigate the relative importance of obesity on the timing of bankruptcy. Even after accounting for possible endogeneity of BMI and controlling for a wide variety of individual and aggregate-level confounding factors, having obesity puts a person at a greater risk of filing for bankruptcy. Thus, obesity has an impact on the individual employee and also on the employers.

Older adults with obesity are twice as likely to be admitted to a nursing home. Many have comorbidities such as type 2 diabetes mellitus. Older adult patients with obesity and diabetes incurred one in every four nursing home days. Besides the costs of early entrance into nursing facilities, caring for residents with obesity is different than caring for residents who do not have obesity. Residents with obesity need additional equipment, supplies, and staff costs. Unlike emergency rooms and hospitals, nursing homes do not have federal requirements to serve all patients. Some nursing homes are not prepared to deal with patients with stage 2 or higher obesity, having to decline their care. The epidemic of obesity makes this gap in nursing home care a public health concern.

In addition to all the financial considerations mentioned above, an estimated 15 million adults in the USA took prescription medications concurrently with herbal remedies and/or high-dose vitamins in 1997. Alternative medicine professional services in 1997 were estimated at $21.2 billion, with at least $12.2 billion paid out-of-pocket. The total 1997 out-of-pocket expenditures on alternative therapies, estimated at $27 billion, matched the 1997 out-of-pocket expenditures for all USA physician services. Alternative therapies for weight management incurred the American public a $30 billion expenditure in 2003 without documentable long-term benefit.

Medical tourism is a relatively new phenomenon. Facing increasing health-care costs and the dilemma that obesity care is frequently excluded from coverage, many find it cheaper to have medical interventions abroad. This is certainly true for both bariatric surgery procedures and cosmetic surgeries following weight loss. The debate about safety, efficacy, and overall cost of care continues, but there is an increasing call for the globalization of medicine. With cheaper medical consultation, pharmacotherapy, and surgical costs abroad, many patients cross borders to secure medical care at a lower cost.

1.6 Obesity and Mortality

Actuarial tables from insurance companies provided the first data that overweight and obesity conveyed a higher risk of death. In 1972, Ancel Keys and colleagues coined the term BMI and published the formula for calculating it. For most people,