Biswanath Dinda *Editor*

Natural Products in Obesity and Diabetes

Therapeutic Potential and Role in Prevention and Treatment

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ISBN 978-3-030-92195-8 ISBN 978-3-030-92196-5 (eBook)
https://doi.org/10.1007/978-3-030-92196-5

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

• This book is dedicated to the people suffering from obesity and diabetes and the medical professionals who look after them.
• The editor also dedicates this book to Late Mrs. Chitralekha Dinda, wife of Biswanath Dinda, who lost her life in this corona pandemic, and whose constant sacrifice and encouragement helped the editor to finish the book.

Preface

The field of natural products science is immense, fascinating, and interesting because of structural diversity, versatile biological activities, and occurrence of natural molecules from various sources, as well as the specific metabolic origin, fate, and cellular biotransformation of these phytogenic compounds. These natural metabolites have defensive roles against harmful pathogens and environmental stress to protect parent organisms under various environments. Various herbal extracts have been used in the treatment of different diseases and ailments since the stone-age period. In many countries, these natural products have been used in their traditional folk medicine based on ethnobotanical knowledge. Various polyherbal formulations have been found to have potential efficacy in the treatment of obesity and diabetes. Most of these polyherbal formulations have poor scientific data on the composition and contents of bioactive phytochemicals and the mode of action in the treatment of diseases. As a result, the practitioners have no idea of the effective doses and treatment period of these phytomedicines. Most of currently prescribed synthetic oral drugs for the treatment of obesity and diabetes and their associated complications on their long-term use by the patients caused many adverse side effects. For this reason, most of leading pharmaceutical industries and research institutes have paid attention to the discovery of natural drugs as an alternative to currently used synthetic drugs. Recently, only a few natural and semi-natural molecules are in the global market for the treatment of these diseases. The major shortcomings of natural drugs in clinical trials in humans and in treatment are the lack of scientific data on the effective doses and the composition and contents of active phytochemicals and their active metabolites in disease-specific organs in humans, in addition to the requisite dose for a patient to cure the disease. Recently introduced "omics" technologies have been applied to evaluate the effective doses as "personalized medicine" for the treatment of the present global pandemic of obesity and diabetes.

The contributors of this monograph have highlighted the various aspects of natural products, particularly the impact of multi-omics biotechnology, gut microbiota dysbiosis, and cultivation and harvesting factors of plants and dietary vegetables and fruits on the composition and concentrations of anti-obese and antidiabetic phytochemicals present in them. Moreover, the contributors have elaborately discussed the different aspects of many natural molecules having potential

anti-obesity and antidiabetic activities, such as their major therapeutic targets, pharmacokinetics, metabolism, nanoformulations benefits and clinical progress. It will help for extensive studies of these natural molecules on toxicity and efficacy in future in human mimic animal models and humans and for large-scale application in global market as safe and low-cost drugs. In spite of sincere efforts for the publication of this monograph in correct form, any printing and other errors in this edition due to overlooking are regretted.

I hope this monograph will be useful for the practitioners in the field of traditional folk medicine, growers of fruits, vegetables, and crops, and students and researchers in the field of natural science and pharmaceutical chemistry.

I will appreciate valuable suggestions and comments from the readers of this book for its improvement in the next edition.

I am grateful to the publishers for their kind support and interest in the publication of this monograph. I am also grateful to Prof. A Basak, University of Ottawa, Canada, and Prof. G. H. Maity, Jadavpur University, India, for their kind help in providing some articles in the preparation of the manuscript of this monograph.

I wish to express my heartfelt thanks to all the contributors of this book including editorial and technical management staff for their sincere efforts in this endeavor.

Agartala, Tripura, India Biswanath Dinda
October, 2021

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Abbreviations

ABCG5	ATP-binding cassette subfamily G member 5 protein
ACADM	Acyl-Coenzyme A dehydrogenase medium chain (C-4 to C-12)
ACADS	Acyl-CoA dehydrogenase short-chain
ACAT1	Acetoacetyl-CoA thiolase 1
ACC1	Acetyl-CoA carboxylase 1
ACE	Angiotensin-converting enzyme
Acly	ATP-citrate lyase
ACO	Acyl CoA oxidase
ACS	Acyl-CoA synthetase
ACSL3	Acyl-CoA synthetase long-chain family member 3
AgRP	Agouti-related protein
Akt	Protein kinase B
ALT	Alanine transaminase
AMPK	5′-Adenosine monophosphate (AMP)-activated protein kinase
Ang II	Angiotensin II
ANP	Atrial natriuretic peptide
AP-1	Activator protein-1
aP2	Adipocyte protein 2
ApoE	Apolipoprotein E
AS-160	Akt substrate of 160 kDa protein
AST	Aspartate transaminase
ATF4	Activating transcription factor 4
ATGL	Adipose triglyceride lipase
ATP5α	ATP synthase subunit alpha
BAECs	Bovine aortic endothelial cells
β-3-AR	Beta-3-adrenergic receptor
BAT	Brown adipose tissue
BBS-4	Bardet-Biedl syndrome 4
BCFAs	Branched-chain fatty acids
BDDE	Bis-(2,3-dibromo-4,5-dihydroxybenzyl)-ether
BDNF	Brain-derived neurotrophic factor
BGL	Blood glucose level
BK	Bradykinin

BMPR	Bone morphogenetic protein receptor
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
BPN	3,4-Dibromo-5-(2-bromo-6-(ethoxymethyl)-3,4-dihydroxybenzyl)-benzene-1,2-diol
BSEP	Bile salt export pump
Bw	Body weight
CA	Cholic acid
CAD	Coronary artery disease
CaMKK	Calcium/calmodulin-dependent protein kinase kinase
CAT	Catalase
CB2R	Cannabinoid type 2 receptor
CCG	Cholecystokinin
CD2AP	CD2-associated protein
C/EBPα	CCAAT/enhancer-binding protein alpha
CD36	Cluster of differentiation 36
CD38	Cluster of differentiation 38
CDK4	Cyclin-dependent kinase 4
ChREBPα	Carbohydrate response element binding protein alpha
CHOP10	C/EBP homologous protein 10
Cidea	Cell death-inducing DFFA (DNA fragmentation factor-α)-like effector A
CITED1	Cbp/p300-interacting transactivator with Glu/Asp rich carboxy-terminal domain 1
CK-MB	Creatinine kinase - myocardial form present in heart and muscle
CNS	Central nervous system
Cox-2	Cyclooxygenase-2
CpG	Cytosine preceding guanosine
CPK	Creatinine phosphokinase
CPT-1	carnitine palmitoyltransferase 1
CREB	cAMP-response element binding protein
CREG1	Cellular repressor of adenovirus early region 1A-stimulated gene 1
CRP	C-reactive protein
CTGF	Connective tissue growth factor
CVD	Cardiovascular disease
CYP7A1	Cholesterol 7alpha-hydroxylase
CYP2E1	Cytochrome P4502E1
DCM	Diabetic cardiomyopathy
Defb2	Defensin beta 2
DGAT1	Diacylglycerol acyltransferase-1
DIO2	Deiodinase type II
DKK2	Dickkopf WNT signaling pathway inhibitor 2
DKO	Double knockout
DM	Diabetes mellitus
DMAPP	Dimethylallyl pyrophosphate

DN	Diabetic nephropathy
DPN	Diabetic peripheral neuropathy
DPP4	Dipeptidyl peptidase 4
DR	Diabetic retinopathy
DRP-1	Dynamin-related protein-1
dw	Dry weight
EAT	Epididymal adipose tissue
EGCG	(−)-Epigallocatechin-3-*O*-gallate
EGFR	Epidermal growth factor receptor
Elovl3	Elongation of very long chain fatty acids protein 3
EMT	Epithelial mesenchymal transition
eNOS	Endothelial nitric oxide synthase
ERDJ4	Endoplasmic reticulum (ER) localized-Dna J homolog 4
ERK	Extracellular signal-regulated kinase
ERRα	Estrogen-related receptor alpha
ET-1	Endothelin-1
EWAS	Epigenome-wide association study
FABP4	Fatty acid-binding protein 4
FADS1	Fatty acid desaturase-1
FAS	Fatty acid synthase
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
FBPase	Fructose-1,6-bisphosphatase
FG	Fasting glucose
FGF21	Fibroblast growth factor 21
FoxO1	Forkhead box-containing protein O1
FTO	Fat mass and obesity-associated protein
FXR	Farnesoid X receptor
fw	Fresh weight
GABA	Gamma aminobutyric acid
GAD65	Glutamic acid decarboxylase 65
GADA	Glutamate decarboxylase alpha
GATA2	Zinc finger transcription factor-binding protein 2
GCK	Glucokinase
GDM	Gestational diabetes mellitus
GFAT	Glutamine:fructose 6-phosphate aminotransferase
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GK rats	Goto-Kakizaki rats
GLIS3	GLIS family zinc finger 3
GLP-1	Glucagon-like peptide-1
GLUT4	Glucose transporter type 4 protein

GlyK	Glycerol kinase
GOAT	Ghrelin-*O*-acyltransferase
GOT	Glutamic-oxaloacetic transaminase
G6Pase	Glucose-6-phosphatase
GP	Glycogen phosphorylase
GP_X	Glutathione peroxidase
G6PC	Glucose-6-phosphatase
G6PD	Glucose-6-phosphate dehydrogenase
GPDH	Glyceraldehyde 3-phosphate dehydrogenase
GPP	Geranyl pyrophosphate, also known as geranyl diphosphate
GPT	Glutamic pyruvic transaminase
GR	Glutathione reductase
GRP-43	G-protein-coupled receptor 43
GS	Glycogen synthase
GSH	Glutathione
GSK-3β	Glycogen synthase kinase 3 beta
GSR	Glutathione-disulfide reductase
GWAS	Genome-wide association study
HbA1c	Hemoglobin A1c, commonly known as glycosylated hemoglobin
HDACs	Histone deacetylases
HDL	High-density lipoproteins
HGMCs	Human glomerular mesangial cells
HIP	Hybrid insulin peptide
HK-2	Hexokinase-2
HLA	Human leukocyte antigen
HMGCS-1	3-Hydroxy-3-methylglutaryl-CoA synthase 1
HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase
HMTs	Histone methyltransferases
4-HNE	4-Hydroxynonenal
HNF4α	Hepatocyte nuclear factor 4 alpha
HO-1	Heme oxygenase-1
HOMA-IR	Homeostasis model assessment-estimated insulin resistance
hs-CRP	High-sensitive C-reactive protein
11β-HSD1	11beta-Hydroxysteroid dehydrogenase type 1
HSF1	Heat shock factor 1
HSL	Hormone-sensitive lipase
HSP72	Heat shock protein 72
IAPP	Islet amyloid polypeptide
ICAM-1	Intercellular adhesion molecule-1
IDDM	Insulin-dependent diabetes mellitus
IL-6	Interleukin-6
IPP	Isopentenyl pyrophosphate
JNK	c-Jun N-terminal kinase
KCNJ11	Potassium inwardly rectifying channel subfamily J, member 11

KCNQ1	Potassium voltage-gated channel subfamily Q member 1
Keap 1	Kelch-like ECH-associated protein 1
KLF4	Kruppel-like factor 4
KM mice	Kunming mice
L-NAME	N^G-nitro-L-arginine methyl ester
LBP	LPS-binding protein
LCAD	Very long-chain acyl CoA dehydrogenase
LCAT	Lecithin cholesterol acyltransferase
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LKB1	Liver kinase B 1
LPL	Lipoprotein lipase
LPO	Lipid peroxidase
LPS	Lipopolysaccharides
LSS	Lanosterol synthase
MAPK	Mitogen-activated protein kinase
MARCKS	Myristoylated alanine-rich C kinase substrate
MCAD	Medium-chain acyl CoA dehydrogenase
MC-4R	Melanocortin-4-receptor
MCP-1	Monocyte chemotactic protein-1
MDA	Malondialdehyde
MDA5	Melanoma differentiation-associated protein 5
MEST	Mesoderm-specific transcript
MGL	Monoacylglycerol lipase
MHC	Major histocompatibility complex
MMP-9	Matrix metalloproteinase-9
MODY	Maturity-onset diabetes of the young
MOGAT	Monoacylglycerol O-acyltransferase
MOR	(μ)-Opioid receptor
MPO	Myeloperoxidase
α-MSH	Alpha-melanocyte-stimulating hormone
MSI2	Musashi RNA binding protein 2
MTNR1B	Melatonin receptor type 1B
m-TOR	Mammalian target of rapamycin
MTP	Microsomal triglyceride transfer protein
Muc 2	Mucin 2
MUFA	Monounsaturated fatty acid
MyD88	Myeloid differentiation factor 88
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NDUFS8	NADH: ubiquinone oxidoreductase core subunit 8
NEFAs	Non-esterified fatty acids
NEGR1	Neuronal growth regulator 1
NFAT	Nuclear factor of activated T-cells

NGAL	Neutrophil gelatinase-associated lipocalin
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
NF-κB	Nuclear factor-kappa B
NIDDM	Non-insulin-dependent diabetes mellitus
NLRP3	Nucleotide-binding domain and leucine-rich repeat-containing-pyrin domain 3 inflammasome
NOD mice	Non-obese diabetic mice
NOX2	NADPH oxidase 2
NPPA	Natriuretic peptide A
NQO1	NAD(P)H quinone dehydrogenase 1
NRF-1	Nuclear respiratory factor-1
OGTT	Oral glucose tolerance test
ORAC	Oxygen radical absorbance capacity
PAI-1	Plasminogen activator inhibitor-1
PAP	Phosphatidate phosphatase
PARK2	Parkin 2
PARP	Poly(ADP-ribose) polymerase
PDE1	Pyruvate carboxylase E1
PDGF	Platelet-derived growth factor
PDI	Polymer density index
PDK1	Phosphoinositide-dependent kinase 1
PDK4	Pyruvate dehydrogenase kinase 4
PDX1	Pancreatic duodenal homeobox 1
PEPCK	Phosphoenolpyruvate carboxykinase
PERK	RNA-activated protein kinase -like ER kinase
PFK	Phosphofructo kinase
PGC1α	Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha
PID1	Phosphotyrosine interaction domain containing 1
PK	Pyruvate kinase
PKCδ	Protein kinase C delta
PLs	Phospholipids
PLPP2	Phospholipid phosphatase 2
P-CO	Protein carbonyl
POMC	Pro-opiomelanocortin
PON	Paraoxonase
PPARD	Peroxisome proliferator activated receptor delta
PPARγ	Peroxisome proliferator-activated receptor gamma
PPBG	Postprandial blood glucose
PRDM-16	PR-domain containing zinc finger protein16
PS	Particle size
PTEN	Phosphatase and tensin homolog
PTP1B	Protein-tyrosine phosphatase 1B
PTPN2	Protein tyrosine phosphatase non-receptor type 2

PUFA	Polyunsaturated fatty acid
RAGE	Receptor for advanced glycation end product
RAS	Renin-angiotensin system
RBP-4	Retinol binding protein-4
ROS	Reactive oxygen species
RXR	Retinoid X receptor
s.c.	Subcutaneous injection
SCD1	Stearoyl-CoA desaturase 1
SCFAs	Short-chain fatty acids
scWAT	Subcutaneous white adipose tissue
SDHB	Succinate dehydrogenase complex iron sulfur subunit B
SFRP5	Secreted frizzled-related protein 5
SGLT2	Sodium-glucose co-transporter-2
SH2B1	Src homology 2B adapter protein 1
SHP	Small heterodimer partner
SHRs	Spontaneously hypertensive rats
SIRT1	Silent mating type information regulation 2 homolog-type 1
Smad7	Mothers against decapentaplegic homolog 7
SOCS3	Suppressor of cytokine signaling 3
S1P	Sphingosine 1-phosphate
SREBP-1c	Sterol regulatory element binding protein-1c
STAT	Signal transducer and activator of transcription
STZ	Streptozotocin
TAC	Total antioxidant capacity
TBARS	Thiobarbituric acid reactive substance
TBC1D1	TBC1 domain family member 1
TBC1D4	TBC1 domain family member 4, also known as AS160
TBX-1	T-box transcription factor-1
TC	Total cholesterol
TCF7L2	Transcription factor 7-like 2
T1DM	Type 1 diabetes mellitus
TFAM	Transcription factor A, mitochondrial
TG	Triglycerides
TGFβ1	Transforming growth factor beta1
TGR5	Transmembrane G-protein-coupled receptor 5
TLR4	Toll-like receptor 4
TMEM18	Transmembrane protein 18
TNF-α	Tumor necrosis factor-alpha
TRIF	Toll/interleukin-1 receptor (TIR)-domain containing adaptor protein inducing interferon beta
TrKB	Tropomyosin-receptor kinase B
TRPA1	Transient receptor potential ankyrin 1
TRPV1	Transient receptor potential vanilloid type 1
TXNIP	Thioredoxin interacting protein

TYK2	Tyrosine kinase 2
UCP-1	Uncoupling protein-1
USP18	Ubiquitin specific peptidase 18
UUO	Unilateral ureteral obstruction
VAT	Visceral adipose tissue
VEGF-A	Vascular endothelial growth factor-A
VLDL	Very low density lipoproteins
ZnT8	Zinc transporter 8 protein
ZP	Zeta potential

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Obesity and Diabetes

1

Biswanath Dinda and Shekhar Saha

1.1 Introduction

An increasing pandemic of obesity and diabetes (diabetes mellitus, DM) has become a serious health concern worldwide because these diseases contribute to the development of many chronic diseases including cardiovascular diseases, stroke, kidney diseases, ocular diseases, hypertension, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, osteoarthritis, and some types of cancer, among others. Obesity is a complex metabolic disease commonly accompanied by insulin resistance, increased oxidative stress, and low-grade inflammation and is characterized by accumulation of an excess fat mass in the body. Diabetes is a metabolic disorder characterized by destruction of pancreatic beta-cells or impaired insulin secretion and insulin action. The rise of obesity has been attributed to different potential factors including genetic predisposition, Western-type fast food diet, lack of physical activity, and social status. According to the report of the International Obesity Task Force, more than 600 million people are obese, and the number of obese-born children in developing countries is increasing at an alarming rate. One of three children born in this century is expected to develop obesity-related diabetes. Currently prescribed synthetic drugs for obesity and diabetes have several side effects on long-term use. A variety of natural products including antioxidant phytochemicals has emerged as promising potent herbal drugs for the treatment of obesity, diabetes, and their associated complications. Recent "omics" technologies (genomics, proteomics, transcriptomics, metabolomics, and microbiomics) have potentially improved our knowledge to identify the mechanism of action of these traditional natural

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B. Dinda (ed.), *Natural Products in Obesity and Diabetes*,
https://doi.org/10.1007/978-3-030-92196-5_1

medicines and the process of biosynthesis in nature and their efficient identification. Recent understanding on the diagnosis, clinical pathogenesis, epidemiology, risk factors, clinical treatments, and consequences of obesity and diabetes are summarized in this chapter.

1.2 Obesity and Its Diagnosis and Associated Complications

Obesity is the most common chronic metabolic disease worldwide, and its incidence is increasing at a high rate, generating enormous social cost. It is now reaching in pandemic shape worldwide, doubling its prevalence in more than that in 1980 in 70 countries, and over 600 million adults were found obese in 2015 (Afshin et al. 2017). The prevalence of overweight and obese people is extremely high in different parts of Europe, the USA, and Mexico. As it is a global phenomenon, it has been coined as "globesity" by WHO. If we search the history of the beginning of the epidemic obesity, we find that India had a leading role in the spread of obesity. In about 400 BC, Indian great physician Sushruta discovered sugarcane in the Ganges River Valley and reported that intake of sugary liquids could increase body weight. Subsequently, sugarcane was brought to China, Persia, and Egypt for cultivation and production of refined sugar (sucrose). At one time, sugar was so expensive that only kings and loyal families could afford it. Many kings in European countries became severely obese and were accused of being pregnant for this obesity. In 1907, Sir Richard Havelock Charles, a British physician stationed in India, observed that the reported type 2 diabetes cases were increased rapidly among the wealthy Bengali Indians living in Calcutta, whereas it was still rare among the poor Punjabi, and he linked this with an increasing intake of sugar. Later on, other world experts including Nobel laureate Sir Frederick Grant Banting, who received Nobel Prize for the discovery of insulin, pointed out that refined sugar might be a major cause of adult onset of obesity and diabetes. Later on, Prof Elliott Joslin coined the word "overnutrition" or high-calorie intake which was the cause of both obesity and diabetes (Bhishagranta 1911; Banting 1929; Joslin et al. 1934). Obesity is a complex metabolic disease characterized as an increased fat mass in the body, particularly from an increased mass of adipose tissue from sustained positive energy balance (energy intake > energy expenditure). In the body of obese individual, the increased fat mass, mainly as triglycerides, not only stored in the white adipose tissue but also stored in the liver and other tissues including skeletal muscle for utilization in the nutritionally deprived states such as in starvation. It is commonly accompanied by insulin resistance and enhanced inflammation.

Obesity is conventionally diagnosed by body mass index (BMI), which is the accurate approximation of obesity in obese individuals. Pre-obesity and obesity classes I, II, and III (extreme obesity) are defined as a BMI of 25–29.99 kg/m^2, 30–34.99 kg/m^2, 35–39.99 kg/m^2, and 40 kg/m^2 or greater, respectively. Pre-obese adult individuals are known as "overweight" individuals. For obese and overweight adult patients having a BMI > 25 mg/m^2 but <35 kg/m^2, clinicians also access their waist circumference (WC) to explore the risk factors of the patients. As per guide

line of the US Centre for Disease Control and Prevention, in USA, a WC >102 cm (40 inches) for men and > 88 cm (35 inches) for women indicate abdominal adiposity and have an increased risk of cardiometabolic diseases, whereas, in Southeast Asian and East Asian populations, a WC >80 cm (31 inches) for women and a WC > 85 cm (33 inches) for men indicate a higher risk factor on cardiometabolic diseases (Centre Dis Control Prevn, 2017).

The abnormal adiposity in obesity due to an increase mass of adipose tissue from increased adipocyte size (hypertrophy) and adipocyte number (hyperplasia or adipogenesis) leads to an excessive strain and a low-grade inflammation. In order to get relief from the strain, adipocytes release inflammatory adipokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, as well as free fatty acids (FFAs) by enhanced lipolysis from their fat depots to the systemic circulation for storage in other diverse sites. Lipotoxicity from excessive FFAs and inflammatory adipokines results in the injury of pancreatic β-cells and leads to pancreatic β-cell dysfunction, which, in turn, decreases insulin synthesis and secretion. Moreover, FFAs also decrease the utilization of insulin-stimulated muscle glucose, contributing a hyperglycemic state. Furthermore, excessive FFAs in serum inhibit lipolysis of serum triacylglycerol levels and contribute to hypertriglyceridemia and consequently lead to insulin receptor dysfunction and insulin-resistant state. Lipotoxicity-induced insulin receptor dysfunction and hyperglycemia in adipose tissues are pathophysiologic basis of obesity which contribute to the conditions of insulin resistance and development of type 2 diabetes and other vascular complications (McKeigue et al. 1991; Unger 1995). Obesity-induced manifestations of inflammation in many tissues and organs lead to some forms of cancer, including breast, uterus, and ovarian cancer in women and prostate, kidney, colorectal, esophageal, pancreas, and liver cancer in men (Carroll 1998; Calle et al. 2003). Possibly, chronic adipokine-associated inflammation promotes cancers through the stimulation of cellular proliferation by modulation of the activities of insulin-like growth factor-1, several growth hormones and sex hormones, leptin, and others in different tissues/organs. Available evidence indicates that obesity accounts for 20–30% of the risk for breast, esophageal, and kidney cancers. Obesity-induced complications, also enhance degenerative joint diseases such as gut and osteoarthritis and result from increased weight-bearing load on joints from increased adiposity and injurious effects of inflammatory adipokines on joint synovial fluid and muscles (Schaffler et al. 2003). Obesity causes obstructive sleep apnea from the accumulation of extra adipose tissue on the upper respiratory tract and hypopharynx, which adversely affects ventilation and results in secondary hypoxia and hypercapnia. Excessive bronchial and peribronchial adipose cells secrete inflammatory adipokines that enhance bronchial mucosal inflammation, causing asthma in obese women (Bergeron et al. 2005). In overweight women of child-bearing age, obesity-associated cholesterol gallstone disease is occurred from enhanced mobilization of cholesterol from fat depots into the biliary ducts during fasting. This enhanced cholesterol level stimulates increased biliary cholesterol secretion and supersaturation of bile in the gallbladder, promoting gallstone formation (Bonfrate et al. 2014). Obesity-associated dyslipidemia, hypertension, and atherosclerosis are the risk

factors of many diseases, such as coronary artery disease, myocardial infarction, and stroke. All these diseases are originated from endothelial dysfunction by the secretion of diverse inflammatory adipokines, particularly from white adipose tissues (WAT) of visceral fat depots. Accumulating evidence demonstrates that perivascular fat tissues enhance endothelial vasomotor tone function by secreting rennin, angiotensinogen, and angiotensin II, to induce vasomotor dysfunction and cause hypertension and endothelial injury. These RAS proteins increase the expression of inflammatory vasoconstrictor, endothelin-1 (ET-1), in the aortic endothelium, which, in turn, mediates thromboxane A_2-dependent contraction in arteries for the induction of arterial hypertension (Engeli et al. 2003; Barton et al. 2012). Endothelial injury on the walls of arteries enhances the uptake of oxidized low-density lipoproteins, FFAs, and other lipid metabolites to form foam cells. These foam cells subsequently stimulate the macrophage and smooth muscle cell infiltration and secretion of inflammatory cytokines, MCP-1, macrophage migration inhibitory factor (MIF), and ET-1 to enhance the formation and stability of atherosclerotic plaques within the vascular walls. Other adipokines, such as plasminogen activator inhibitor 1 (PAI-1), IL-6, TNF-α, TNF-β, resistin, visfatin, and matrix metalloproteinases, MMP-9 and MMP-3, play an active role for thinning of atheroma cap, subsequently rupture of plaque, and release of the tissue factor and its coagulation and remodeling of plaque to cause thrombosis. Moreover, these MMPs along with troponin (C-reactive protein) participate in remodeling of cardiovascular tissue resulting in reduction of heart size, myocardial infarction, and heart failure (Rajala and Scherer 2005; Liu et al. 2006). Obesity is also a feature of polycystic ovarian syndrome, in which adipocyte secretagogues enhance metabolic abnormalities of hyperandrogenemia in obese women from insulin resistance and hyperinsulinemia and lead to a high risk of infertility, menstrual dysfunction, and pregnancy complications. Possibly, the secretion of sex hormone binding globulin, growth hormone, and insulin-like growth factor binding proteins is decreased significantly resulting in impaired ovulatory function (Dag and Dilbaz 2015). Obesity is a risk factor for pregnancy-specific disorder, preeclampsia, affecting 2–8% of all pregnancies and resulting in maternal or neonatal mortality. Adipocytes secrete several adipokines including RAS, prostaglandins, and others to induce hypertension and fluid retention in this syndrome. Endarteritis obliterans within the placenta induces toxicity by increasing the levels of inflammatory adipokines (Jeyabalan 2013). Obesity is associated with urinary incontinence (involuntary loss of urine) due to bladder to urethra stress in women. The common morbidities of obesity are depicted in Fig. 1.1 (Balaji et al. 2016).

1.3 Diabetes and Its Diagnosis and Classification

Diabetes mellitus (DM), commonly known as diabetes, is a chronic metabolic disorder, characterized by persistent hyperglycemia (high blood glucose levels) from impaired insulin secretion from pancreatic beta-cells or increased insulin resistance to insulin-responsive cells in peripheral tissues or both. The term, insulin

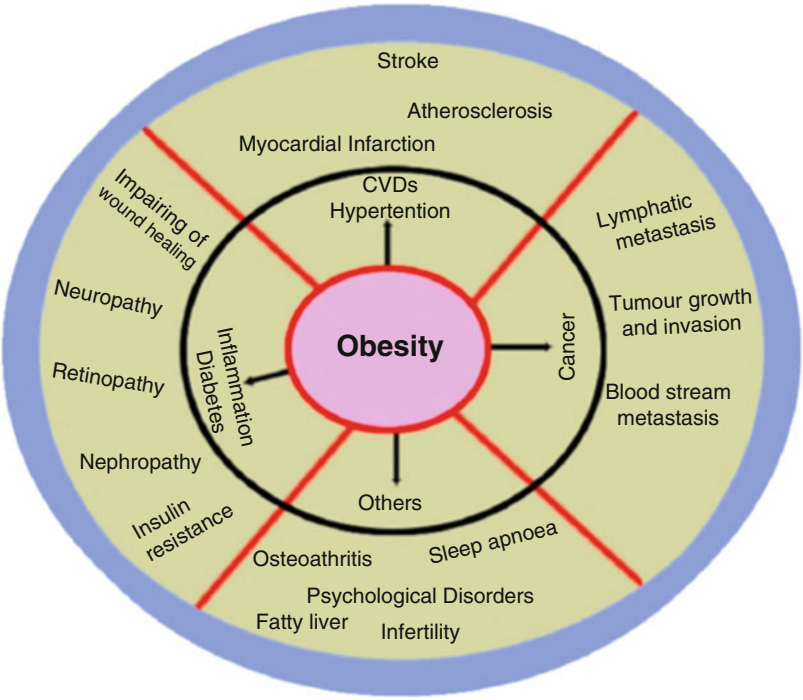

Fig. 1.1 Obesity and its associated morbidities. Adapted from Balaji et al. 2016 with permission of Elsevier. Copyright (2015) Elsevier

resistance, usually denotes resistance to action of insulin on glucose uptake from plasma and metabolism or storage of glucose as glycogen in the skeletal muscle and liver. Chronic hyperglycemia is associated with dyslipidemia, hypertension, and dysfunction or failure of different organs' functions, such as the heart, kidneys, eyes, nerves, and blood vessels, causing diabetic cardiovascular diseases, diabetic nephropathy, diabetic retinopathy, and diabetic peripheral neuropathy, which are responsible for morbidity, disability, and premature deaths of young adults. The global prevalence of diabetes among adults has increased from 4.7% on 1980 to about 8.5% in 2014. According to the report of WHO, about 422 million of adult are living with diabetes in 2014. More than half of these people are unaware of their disease status and even do not receive any treatment. The Asia-Pacific region is generally considered as the epicenter of diabetes (Chan 2016). As per the IDF Diabetes Atlas, the highest prevalence of diabetes was in North American and Caribbean region (11.5%) (International Diabetes Federation 2017). Over half of diabetic people are living in Southeast Asia and Western Pacific region (Ogurtsova et al. 2017).

Diagnosis

Currently, diabetes is usually diagnosed by blood or plasma glucose levels. A fasting plasma glucose level > or = 126 mg/dl or postprandial (2 h after an oral glucose

challenge of 75 g of glucose or a full meal) plasma glucose level, > or = 200 mg/dl, in an individual adult is sufficient evidence to diagnose DM. In addition to plasma glucose levels, glycosylated hemoglobin (HbA1c) levels are also considered to diagnose diabetes in individuals with risk factors. As per guidelines on diabetes by the American Diabetes Association, adult individuals with an HbA1c levels in the range of 5.7–6.4% are considered to have an increased risk of diabetes (pre-diabetes) and cardiovascular disease, and those with HbA1c > or = 6.5% are diagnosed as having diabetes. The most common symptoms of diabetes include thirst, polyuria (frequent urination), weight loss, and blurring of vision (American Diabetes Association 2014).

Classification

Diabetes mellitus (DM) is classified into four subtypes: type 1, type 2, MODY, and gestational diabetes. Type 1 diabetes (T1DM, previously known as insulin-dependent diabetes or IDDM) is an autoimmune disease that leads to destruction of pancreatic β-cells and depends on insulin supply. Type 2 diabetes (T2DM, previously known as non-insulin-dependent diabetes or NIDDM) is a progressive insulin resistance-related metabolic disease, leading to dysfunction of insulin secretion. The T1DM accounts for only 5–10% of the reported cases of diabetes, while T2DM accounts for 90–95% of reported cases of diabetes. In most of the type 1 diabetic patients, the insulin deficiency is found from destruction of pancreatic β-cells from autoimmune T-cell process. As per the estimate of the International Diabetes Federation (IDF), more than one million subjects of <20 years of age were affected by T1DM in 2017 worldwide. Major diagnostic criterion is the development of diabetic ketoacidosis (DKA), characterized by acidosis, ketonemia, ketonuria, and high HbA1c levels >6.5% (Durazzo et al. 2019). The third type is monogenic DM (because inherited from mutation of a single gene), known as maturity-onset diabetes of the young, MODY, characterized by defective pancreatic β-cell function and impaired insulin secretion. MODY is more like type 1 diabetes than type 2. Early symptoms of MODY include blurry vision, recurrent skin infections, fatigue, frequent urination, and high blood sugar levels. Up to 5% of all reported diabetes cases are diagnosed as MODY. Mutations of three genes, namely, hepatocyte nuclear factor 1 homeobox A (HNF1A) (MODY3), hepatocyte nuclear factor 4 homeobox A (HNF4A) (MODY1), and enzyme glucokinase (GCK) (MODY2), are the most common causes of MODY representing about 52%, 10%, and 32% of MODY cases, respectively, in the UK (Shields et al. 2010). The mutation of HNF1A has been reported as a common cause of MODY in other European countries, such as Sweden, Italy, Spain, and Germany. Mutations of other genes (with locus name), such as pancreas/duodenum homeobox 1 (PDX 1) (MODY 4), HNF-1B (MODY5), neurogenic differentiation 1 (NEUROD1) (MODY6), Krüppel-like factor 11 (KLF 11) (MODY 7), cholesteryl ester lipase (CEL) (MODY 8), paired homeobox 4 (PAX4) (MODY 9), INS (insulin) (MODY10), B-lymphoid tyrosine kinase (BLK) (MODY 11), ATP-binding cassette CB (ABCCB) (MODY12), inward rectifying potassium channel J11 (KCNJ11) (MODY13), adaptor protein, phosphotyrosine interaction, PH domain, and leucine zipper-containing-1 (APPL1)

(MODY 14), have been reported in a few cases. Serum low high-sensitive C-reactive protein (CRP) levels are considered as a biomarker in detection of HNF1A MODY cases (Gardner and Tai 2012; Naylor et al. 2018; Peixoto-Barbosa et al. 2020).

The fourth subtype of diabetes is gestational diabetes mellitus (GDM), developed among pregnant women from increased insulin resistance mainly in the skeletal muscle due to the increased level of insulin antagonist serum hormone and impairment of pancreatic β-cell function. GDM is associated with increased risk of T2DM in women later in their life (about 7.4-fold risk of T2DM, compared to with normoglycemic pregnant women). Exposure of the offspring to hyperglycemia in pregnancy period in untreated GDM-affected mothers has been found to have a high risk of childhood overweight and obesity from increased insulin resistance (Melmed et al. 2015).

1.4 Epidemiology of Obesity and Diabetes

According to the report of WHO, in 2016, more than 1.9 billion adults, 18 years and older, were overweight. Among them, over 650 million were obese. Moreover, it was estimated that about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. The prevalence of overweight and obesity among children and adolescents (5–19 years) has increased dramatically at an alarming rate from 4% in 1975 to over 18% in 2016. Furthermore, in 2019, 38.2 million children under the age of 5 were identified as overweight or obese (WHO fact sheets on obesity 2020). Another survey on the prevalence rate of overweight and obesity in different regions of the world between the period 1980 and 2015 reported that in low-income countries, obesity was generally higher from wealthy and urban families, whereas in high-income countries, it affected mostly in disadvantaged groups. In 2015, the prevalence of obesity in ten countries was much higher and in alarming rate, Egypt (35.3%), the USA (33.6%), Iraq (31.9%), South Africa (30.8%), Mexico (28.6%), Turkey (28.5%), the UK (24.3%), Russia (24%), Argentina (23.2%), and Brazil (22.6%), while in 1980, only two countries had the prevalence of obesity above 20%: Iraq (28.8%) and South Africa (22.6%). This increase in global obesity rate is mainly due to rapid changes in socioeconomic status, adoption of high-calorie fat-rich food, and sedentary lifestyle (Chooi et al. 2019).

According to the report of WHO, the number of people with diabetes had increased from 108 million in 1980 to 422 million in 2014, and diabetes was the seventh leading cause of death in 2016. The prevalence of diabetes rate in 2016 was in the following order: the USA and Caribbean (11.5%), the Middle East and North Africa (10.7%), South and Central America (9.6%), Southeast Asia (9.1%), Western Pacific (8.8%), Europe (7.3%), and Africa (3.8%). China, India, and the USA were the top three countries with the largest number of people with diabetes (WHO fact sheets on diabetes, 2020). Another survey reported that in 2017, 425 million individuals were affected in diabetes, and this number is expected to rise to 629 million by 2045. Among the reported cases of diabetes, more than 85% were T2DM.

Many of these diabetic patients had vascular complications including ischemic heart disease, stroke, nephropathy, retinopathy, and peripheral neuropathy (Forouhi and Wareham 2019). As per the IDF report on global diabetes, ninth edn, in 2019, the global diabetes prevalence was 9.3%, and about 463 million people were affected in diabetes worldwide (International Diabetes Federation 2019). Among them, 88 million people had diabetes from Southeast Asia region. Out of 88 million people, 77 million belonged to India. China had the highest number of people affected in diabetes in the world (116.4 million). The prevalence was higher in urban (10.8%) than in rural (7.2%) areas and in higher-income countries (10.4%). The IDF also estimated that 2.58 billion of children and adolescents (under the age of 19 years) were affected globally in type 1 diabetes and European countries were badly affected. India had the highest number of children and adolescents with type 1 diabetes (95.6 thousand), followed by the USA (94.2 thousand), Brazil (51.5 thousand), and China (28.7 thousand) (IDF diabetes atlas, International Diabetes Federation 2019). As per the US National Diabetes Statistics Report of 2020, in 2018, in the USA, about 34.2 million people of different ages (10.5% of US population) had diabetes (CDCP, US 2020).

1.5 Pathogenesis of Obesity and Diabetes

1.5.1 Pathogenesis of Obesity

The pathogenesis of obesity is a multifactorial process involving interactions among several genes, proteins, hormones, and inflammatory factors with environments. In an obese individual, the high levels of serum FFAs; glycerol; hormones such as ghrelin, neuropeptide NPY, melanocortin-4 receptor (MC4R), and beta-3-adrenergic receptor (β-3-AR); and pro-inflammatory adipokines such as leptin, TNF-α, IL-6, and PPAR-γ are found, which are possibly involved in the development of fat accumulation in the adipose tissue and liver and insulin resistance to skeletal muscle and other tissues in the development of obesity. Hence, these are considered as marker genes in the pathogenesis of obesity (Clement et al. 1995). Ghrelin, a gastric secreted peptide from the stomach, acts as an orexigenic (appetite-stimulating) hormone and stimulates feeding by its action on the growth hormone secretagogue receptor (GHSR), located in CNS of the brain. In a double-blind cross-over study, treatment of ghrelin into healthy volunteers leads to 30% increase of food intake. Ghrelin increases hypothalamic AMPK activity to increase both food intake and body weight. Moreover, it reduces glucose-stimulated insulin secretion and increases the mRNA levels of several fat storage-related (lipogenetic) proteins, SREBP1, ACC, FAS, and LPL, in the liver and adipose tissues. Plasma ghrelin levels inversely correlate with BMI (Wren et al. 2001; Zigman et al. 2006; Scerif et al. 2011).

Inflammatory adipokines, TNF-α and IL-6, on increased secretion from visceral fat of an obese individual, enhance insulin resistance through liberation of free fatty acids (FFAs) and reduce the levels of anti-inflammatory genes, adiponectin and IL-10, and impair insulin signaling in adipocytes. Both FFAs and TNF-α induce

JNK activation, which in turn increases serine phosphorylation of IRS-1 at ser307 and impairs insulin signaling and reduces GLUT4 protein expression to the cell membrane surface for glucose uptake in the cells of insulin-sensitive metabolic tissues such as the skeletal muscle, adipose tissue, and liver. Therefore, these FFAs and TNF-α are the key players of insulin resistance and potential biomarkers in the pathogenesis of obesity (Hotamisligil 1999; Hirosumi et al. 2002).

Another adipokine leptin is found in high concentrations in the serum of obese patients, and it correlates positively with fat mass of adipocytes. High serum leptin levels positively correlate with increased serum T_4, T_3, and TSH levels and leptin deficiency in the brain. Brain leptin-deficient mice have been shown to be hyperphagic and obese. High leptin level in the brain promotes the sensation of satiety and increases energy expenditure by stimulating anorexigenic (appetite-suppressing) pro-opiomelanocortin (POMC) neurons and inhibiting the activity of orexigenic (appetite-stimulating) NPY and GABA neurons. In vivo, hyperleptinemia (high leptin level in the brain), induced in normal rats, decreased TG content in the liver, skeletal muscle, and pancreas without increasing FFAs or ketones through increased intracellular fatty acid oxidation. Leptin in the brain stimulates the neurons in the arcuate nucleus of the hypothalamus to activate leptin signaling through binding of the leptin receptor LEPR to SH2B1. Activation of leptin receptor increases the phosphorylation of STAT3 and its translocation to the nucleus, where it activates POMC to stimulate the expression of melanocortin (MC) peptides. An elevated expression of MC peptides, it on binding to their receptor MC4R reduce food intake and increase energy expenditure, while antagonists of MC, agouti-related protein (AgRP) and neuropeptide Y (NPY) on upregulation, suppress the expression of POMC and activity of MC4R and lead to increased food intake and reduced energy expenditure to enhance fat mass and linear growth. Disruption of POMC expression in the brain from leptin deficiency results in hyperphagia (excessive eating) and early onset of obesity in humans. Central administration of NPY to rodents induces hyperphagia, decreases energy expenditure, activates lipogenic genes in the liver and adipose tissue, and contributes to the development of obesity. Moreover, Y1 receptor of NYP stimulates the proliferation of rat pre-adipocytes and 3T3-L1 pre-adipocytes in vitro (Shimabukuro et al. 1997; Cowley et al. 2001; Mizuno et al. 2003; Yulyaningsih et al. 2011; Farooqi and O'Rahilly 2014).

High levels of beta-3-adrenergic receptor (β-3-AR) in plasma are associated with increased plasma leptin and insulin levels and reduced insulin action in metabolic tissues in obese women. Therefore, β-3-AR is also a genetic marker of visceral obesity and insulin resistance for obese women (Sakane et al. 1997).

Expression levels of adipokine, adiponectin, are decreased in the adipose tissue of obese and diabetic patients. Adiponectin increases insulin-stimulated glucose uptake in the adipose tissue and liver through AMPK activation. Hence, low level of plasma adiponectin is a genetic marker in the pathogenesis of both obesity and diabetes (Oh et al. 2007).

Three serum microRNAs, miR-138, miR-376a, and miR-15b, have been identified as potential predictive biomarkers in obese patients. The serum levels of miR-138 and miR-376a were significantly lowered, and the serum levels of miR-15b