OBESITY: CURRENT STATUS

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ABSTRACT

The present paper reviews on pathophysiology, pharmacotherapy and latest treatment used for the obesity. The objective of the review is to update the knowledge with a complementary angle and perspective. Obesity is essentially an excessive accumulation of triacylglycerol in fatty tissue that is the net result of excessive energy intake compared to energy usage. It is a multifactorial, chronic disorder with complex interaction between genetic and environmental factors. It is the major health burden in the western world, in terms of increased risk of diabetes (type 2), cardiovascular morbidity, cancer and also in economic costs to healthcare providers. It also increases the risk of several malignancies in breast, colon, pancreas, and endometrium. The various etiological factors responsible for the development of disease include sedentary lifestyle/physical activity, genetic determinants, excess of calorie intake, environment factors, various health disorders etc. Numerous different types of drug which had been used in the past for the treatment of obesity have currently been withdrawn due to undesirable long-term side effects. Current insights provided by the new biology are leading to the development of novel anti-obesity drugs with central/anorexigenic effects.

KEYWORDS: BMI, haematopoiesis, NAFLD, ARC.

1. INTRODUCTION

Obesity is a condition in which the natural energy reserve stored in the fatty tissue of humans is increased to a point where it is associated with certain health conditions. It is a serious socio-economic and also increasingly clinical problem. Although obesity is an individual clinical condition, it is increasingly viewed as a serious and growing public health problem.
The most widely used formula for relating the height and weight of an individual is Body Mass Index (BMI). BMI is defined as a ratio of weight (kilograms) and height$^2$ (square meters).\[^{2}\] The prevalence of overweight (body mass index (BMI) between 25 and 30 kg/m$^2$) and obesity (BMI of 30 kg/m$^2$ or higher)\[^{3}\] is increasing rapidly worldwide, especially in developing countries. Four major etiological factors for development of obesity are genetic determinants, environmental factors, food intake and exercise. Obesity increases the risk of the development of various pathologic conditions including: insulin-resistant diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, endocrine problems, and certain forms of cancer.\[^{4}\] Obesity is thought to be the second most preventable cause of death behind smoking; a recent study suggests that the health care costs of obesity exceed those of smoking.\[^{5}\] Adipose tissue is a tissue entity that can, through hyperplasia and hypertrophy,\[^{6}\] vary enormously between individuals, more so than any other tissue. Adipose tissue is not purely a storage tissue for triacylglycerol, it acts as an endocrine organ also, releasing numerous chemical messengers (adipokines) that communicate and affect other tissues.\[^{7,8}\]

Obesity is a complex medical problem with to date poor pharmacotherapy-based management. The current drug therapy does not cure obesity but only achieves moderate reduction in weight loss, moreover with authority for use time-limited. Major classes of these drugs are: appetite suppressants, inhibitors of fat absorption, stimulators of thermogenesis and stimulators of fat mobilization. The appetite suppressants are further divided into noradrenergic agents, serotonergic agents and mixed noradrenergic-serotonergic agents. These are either used for short term therapy or have considerable side-effects. This article provides information concerning potential molecular targets of the homeostatic system and new anti-obesity drugs at present in development.

2. ENERGY BALANCE IN BODY

The disturbance of the homeostatic mechanisms controlling energy balance causes obesity. The amount of the adipose tissue is tightly regulated through neural and humoral signals transmitted to the brain. Failure of fat cells to send adequate signals or failure of the brain to respond to appropriate signals causes obesity.\[^{9}\] Android (apple shaped) obesity to refer to adipose tissue accumulated preferentially in the trunk/upper body area associated with diabetes and heart disease. Gynoid (pear shaped) obesity to refer to preferential adipose tissue accumulation in the hips and thighs, typically described as female obesity.\[^{10}\] Body weight is
regulated by a complex system, including both peripheral and central factors. Two of the hormones that seem to play an important role in the regulation of food intake and body weight are leptin and ghrelin. Both originate in the periphery and signal through different pathways to the brain, particularly to the hypothalamus. In the hypothalamus, activation of the leptin or ghrelin receptor initiates different signalling cascades leading to changes in food intake.

2.1 Leptin
Leptin acts through the leptin receptor (LEPR or OBR). One of the splice variants of the OBR gene (OB-Rb) and full signalling capabilities, is widely expressed in the human brain. OBRb is highly expressed in the hypothalamus and cerebellum. In addition, the leptin receptor is expressed in other tissues, such as the human vasculature, stomach and placenta. Importantly, leptin is released into the circulatory system by the adipose tissue as a function of the energy stores. Leptin has been reported to have influence on various biological mechanisms, including reproduction (initiation of human puberty), the immune and inflammatory response, haematopoiesis, angiogenesis, bone formation, and wound healing. Leptin functions as a feedback mechanism that signals to key regulatory centres in the brain to inhibit food intake and to regulate body weight and energy homeostasis. Hypothalamus is the primary centre for regulation of food intake and body weight. After leptin is released by the adipose tissue into the bloodstream, it crosses the BBB and binds to the hypothalamic leptin receptors, giving information about the status of the body energy stores. By binding to its receptors, leptin influences the activity of various hypothalamic neurones and the expression of various orexigenic and anorexigenic neuropeptides. Orexigenic peptides, which levels are influenced by leptin, include neuropeptide Y (NPY), melanin concentrating hormone, agouti-related protein (AgRP), galanin, orexin and galanin-like peptide. Anorexigenic peptides, which expressions seem to be modulated by leptin, include pro-opiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript, neurtensin, corticotropin-releasing hormone (CRH) and brain-derived neurotrophic factor. The orexigenic and anorexigenic neurones, which are located in the various hypothalamic regions (arcuate nucleus [ARC], lateral hypothalamus, perifornical hypothalamus and paraventricular nucleus), interact with each other. More recent data indicate that leptin also seems to play a role in short-term regulation of food intake and body weight. Leptin is produced not only by adipose tissue, but also in small amount by the stomach.
2.2 Ghrelin

Ghrelin peptide was originally isolated from the stomach, but ghrelin protein has also been identified in other peripheral tissues, such as the gastrointestinal tract, pancreas, ovary and adrenal cortex.\textsuperscript{[49,50,51,52,53]} In the brain, ghrelin producing neurones have been identified in the pituitary, in the hypothalamic ARC, and in a group of neurones adjacent to the third ventricle between the dorsal, ventral, paraventricular and arcuate hypothalamic nuclei.\textsuperscript{[47,49,56]} The effects of leptin on energy homeostasis are opposite (although not complementary) to those of ghrelin; leptin induces weight loss by suppression of food intake, whereas ghrelin functions as an appetite-stimulatory signal.

The effects of ghrelin on energy balance are at least in a large part mediated by the hypothalamus. Korbonits \textit{et al} proposed three different pathways for the appetite inducing effects of ghrelin.\textsuperscript{[57]} First, after release into the bloodstream by the stomach, ghrelin may cross the BBB and bind to its receptors in the hypothalamus.\textsuperscript{[53,57,58]} Second, ghrelin may reach the brain through the vagal nerve and nucleus tractus solitarius.\textsuperscript{[60,57]} Third, ghrelin is produced locally in the hypothalamus, where it may directly affect the various hypothalamic nuclei.\textsuperscript{[47,57]} Ghrelin stimulates the activity of neurones expressing NPY, AgRP and orexin.\textsuperscript{[62,63,64]} On the other hand, ghrelin has an inhibitory effect on POMC neurones and CRH-producing neurones.\textsuperscript{[47]}

2.3 Energy expenditure

It is determined by physical activity, metabolic rate and thermogenesis. The metabolic side of energy expenditure includes cardio-respiratory work, the maintenance of ion gradients and various enzymatic activities. Brown fat is specialized in adaptive thermogenesis. Its thermogenic capacity is possible through the expression of the uncoupling protein-1 (UCP-1), which uncouples oxidative phosphorylation from electron transport through mitochondrial respiratory chain.\textsuperscript{[65]} Brown fat cells are rich in mitochondria, and produce more heat and less ATP than white fat cells.

2.4 Systemic oxidative stress

It is part of the numerous biological alterations reported during chronic obesity oxidative stress-associated obesity has also been shown to alter the function of many cell types or tissues (including vascular endothelial cells, myocytes, or pancreatic-$\beta$-cells) leading to consider oxidative stress as a contributor in obesity-related metabolic diseases. Oxidative
stress results from an imbalance between the production of ROS and biological systems’ ability to detoxify the reactive intermediates or to repair the resulting damages, which can impact all components of the cell, including proteins, lipids, and DNA. Examples of ROS include superoxide anions (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and hydroxyl radical (OH-). Furthermore, reactive nitrogen species (RNS) might form by combination of nitric oxide (NO-) with O$_2^-$ to form peroxynitrite (ONOO-) and act together with ROS to damage cells, causing nitrosative stress.

3. ASSOCIATED DISEASES WITH OBESITY

3.1 Insulin Resistance
Normal glucose homeostasis is maintained by a delicate balance between insulin secretion by the pancreatic β-cells and insulin sensitivity of the peripheral tissues (muscle, liver and adipose tissue). Insulin resistance is a key feature of the metabolic syndrome and often progresses to T2DM. Decreased insulin sensitivity and impaired β-cell function are the two key components in T2DM pathogenesis based on long-term experience in adults.\cite{66,67,68,69} The major link between obesity and T2DM is insulin resistance. Insulin resistance in both of these conditions is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output.\cite{70}

3.2 Non-Alcoholic Fatty Liver Disease
Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis in the absence of a history of significant alcohol use or other known liver diseases. Subjects with NAFLD have a 2-fold greater risk of diabetes.\cite{71} Free fatty acids (FFAs) play a pivotal role in the development of simple hepatic steatosis. The development of NAFLD is closely linked to an excess flow of FFAs arising from visceral adipose tissue. Obesity results in marked enlargement of the intra-abdominal visceral fat depots. The development of insulin resistance leads to continuous lipolysis within these depots, releasing fatty acids into the portal circulation, where they are rapidly translocated to the liver and reassembled into triglycerides.

3.3 Atherogenic Dyslipidaemia
The dyslipidaemic state frequently observed in patients with visceral obesity is a key feature of the clustering abnormalities of the metabolic syndrome and has been extensively described in the literature.\cite{72,73,74,75} It includes high levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, relatively normal total and low density lipoprotein (LDL)
cholesterol levels, but more LDL particles (as quantified by high apo-lipoprotein B levels) that are smaller and denser than normal. In abdominal obesity, HDL particles are also small in size because of the presence of hypertriglyceridemia.\textsuperscript{[76]} HDL could be anti-atherogenic in a number of ways.\textsuperscript{[77,78]} HDL particles promote cholesterol efflux from the arterial wall (as they do in all tissues) and favor its transport to the liver. HDLs also prevent chemical modification of LDLs within the artery wall, thereby reducing their uptake by macrophages. In addition, HDLs hinder the processes that recruit macrophage precursors (monocytes) to the arterial wall, reducing the number of lipid-accumulating cells therein.

3.4 Hypertension
Hypertension is a powerful risk factor for an array of cardiovascular complications such as left ventricular hypertrophy, atrial and ventricular arrhythmias, diastolic heart failure, systolic heart failure, and ischemic heart disease with or without congestive heart failure.

3.5 Coronary Artery Disease
BMI increases the risk of CAD, and weight gain from any initial BMI further increases the risk (especially weight gain of 20 kg or more). Dyslipidaemia may be the most important relationship of BMI to CAD.\textsuperscript{[79]} Obesity increases VLDL (triglycerides) through increased production and decreased clearance of triglyceride rich lipoproteins due to lack of stimulation of lipoprotein lipase.\textsuperscript{[80]}

3.6 Polycystic Ovary Syndrome (PCOS)
PCOS has been described as ‘the thief of womanhood’ as it is commonly associated with oligomenorrhoea and hirsutism.\textsuperscript{[81]} Multiple ovarian cysts are actually a common ultrasound finding (up to 20% in 18-25 y/o) however this finding is usually not associated with infertility, although it may be associated with hirsutism.\textsuperscript{[82]} It is generally the association of obesity with multiple ovarian cysts that leads to infertility.\textsuperscript{[83]} Sex hormone binding globulin (SHBG) is usually low in PCOS. The most important hormone that SHBG binds is testosterone. The presence of increased total testosterone in PCOS is uncommon compared to the prevalence of increased free testosterone estimates. Increased LH pulse frequency and amplitude occurs in PCOS. This may be in part due to the effects of elevated free testosterone.\textsuperscript{[84,85]}

4. PHARMACOTHERAPY
The historical progress of drug therapy for obesity has been discouraging, since no drug has achieved a long-term favourable benefit-risk ratio. The search for a drug with the best benefit-risk ratio should include the achievement of at least a 10-20% weight loss, which would imply an intermediate effect between the modest outcomes of lifestyle interventions. Various drugs have been approved by USFDA for obesity in recent times that include Orlistat, Lorcaserin, Phentermine-Topiramate, Naltrexone + Bupropion. Phentermine, benzphetamine, phendimetrazine, and diethylpropion, which are approved only for short-term use in the USA, and orlistat, have failed to combat the obesity epidemic. Combined phentermine and topiramate (Qsymia) and lorcaserin (Belviq) were both approved in 2012 by the FDA for the body weight management of adults.

4.1 Commercially available drugs for the treatment of obesity

In Europe, the only available drug for the treatment of obesity is orlistat. The other ones which have been already approved by the FDA in the USA are still under evaluation by the European Medicines Agency (EMA).

4.1.1 Orlistat

A gastrointestinal lipase inhibitor drug, has been used effectively and safely in the treatment of obesity.[86] Orlistat significantly reduces body weight, and improves glycaemic control and several cardiovascular risk factors in overweight and obese subjects with type 2 diabetes.[87,88] In type 2 diabetic patients, orlistat also attenuates postprandial increases in triglycerides, remnant-like particles, cholesterol, and free fatty acids.[89] The anti-hyperglycemic effect of orlistat has been attributed to a weight loss-associated decrease in insulin resistance[90] and augmentation of the post-prandial increases in plasma levels of glucagon-like peptide 1 (GLP-1).[91]

Orlistat (Xenical) is a potent and selective inhibitor of pancreatic lipase required for hydrolysis of dietary fat in gastrointestinal tract into fatty acids and mono-acylglycerol.[92] It was approved by the U.S. FDA in 1999 as a long-term obesity management in conjunction with reduced-calorie diet.

4.1.2 Bupropion

Bupropion is a dopamine and norepinephrine-reuptake inhibitor that has been marketed as an anti-depressant and for smoking cessation. Bupropion increases dopamine activity and POMC neuronal activation, thereby reducing appetite and increasing energy expenditure.
Bupropion, which inhibits the reuptake of norepinephrine and dopamine, is approved for the treatment of depression and smoking cessation. These neurotransmitters are involved as well in the regulation of food intake. Central side effects include mouth dryness, insomnia, anxiety and palpitations. Bupropion was combined with naltrexone in its sustained release form (Contrave™).

Given the pathophysiology behind the anti-obesity efficacy of the selective serotonin-receptor agonists and the dopamine-reuptake inhibitors, an ideal drug would combine serotonergic and dopaminergic activity. This is exactly the case of zonisamide, a marketed antiepileptic drug that exerts dose-dependent biphasic dopaminergic and serotonergic activity. The combination of bupropion with the antiepileptic agent zonisamide has been evaluated in phase II trials.

4.1.3 Topiramate

Topiramate is another anticonvulsant agent associated with weight loss. It is a sulphamate-substituted fructose that is approved as an antiepileptic/antimigraine agent and has multifactorial effects on the CNS, including action on the orexigenic GABA systems causing appetite suppression. dose-related side effects seen with topiramate treatment including suicidality, metabolic acidosis, acute myopia, and secondary angle closure glaucoma, a lower dose of topiramate was used (in a special controlled release formulation) in a novel anti-obesity drug called in combination with phentermine. In 2012 the FDA approved phentermine and topiramate extended-release as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management. Approval was denied by European regulatory authorities, who cited potential risk to the heart and blood vessels, psychiatric side effects, and cognitive side effects in explaining their decision.

4.2 Drugs under clinical investigation

4.2.1 Cetilistat

Cetilistat treatment was also well-tolerated and the common orlistat-induced GI adverse events, such as flatus with discharge and oily spotting, occurred in only 1.8-2.8% of subjects in the cetilistat-treated group. Cetilistat is equipotent with orlistat regarding fecal fat excretion; it however achieves a much better tolerance profile. Cetilistat acts more like a detergent, whereas orlistat may promote the coalescence of micelles, leading to oil-drops and increased gastrointestinal adverse events. Based on the above findings, this novel lipase inhibitor is currently at the furthest stage in the clinical development of new drugs of this class.
4.2.2 Tesofensine
Tesofensine is another novel pharmacological agent which inhibits the uptake of presynaptic noradrenaline, dopamine, and serotonin. Patients receiving this drug for the treatment of Alzheimer’s and Parkinson’s diseases reported weight loss.[97] Central effects: mouth dryness, constipation, insomnia, anxiety and a significant increase in heart rate (7.4 beats/min), with no associated changes in blood pressure.[98]

4.2.3 Glucagon-Like Peptide-1 (GLP1) Analogues:
Liraglutide and exenatide are glucagon-like peptide-1 receptor analogues (GLP-1R) which were developed and approved for the treatment of type 2 diabetes. GLP-1R agonists had additional beneficial effects on systolic and diastolic blood pressure, plasma concentrations of cholesterol, and glycemic control. GLP-1R agonists were associated with nausea, diarrhea and vomiting, but not with hypoglycemia. GLP-1 analogues that have a slightly different molecular structure but a significantly longer duration of action compared to wild GLP-1 have been used for therapeutic interventions in patients with diabetes, in whom they significantly improved glycemic control, fasting plasma glucose, β-cell function, and probably β-cell regeneration. Currently, the GLP-1 analogues used in clinical practice for diabetes control are exenatide, lixisenatide, and liraglutide.

4.2.4 Metformin
This oral hypoglycemic agent, decreases calorie intake in a dose-dependent manner and leads to a reduction in body weight in subjects with type 2 diabetes and obesity. Exenatide: exenatide is a member of a new class of agents known as incretin mimetics currently in development for the treatment of type 2 diabetes.

4.3 Drugs approved by FDA advisory panels
4.3.1 Lorcaner (Belviq™)
Lorcaserin (1R-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine; Belviq®, Arena Pharmaceuticals, Inc., San Diego, CA, USA) is approved by the U.S. FDA for long-term weight management in June, 2012. Lorcaner is a serotonin type 2C receptor agonist. Serotonin has been shown pharmacologic effects on weight loss. Fenfluramine and dexfenfluramine as serotonin type 2B receptor agonists were also used for weight loss. However, they were removed from market due to damage to heart valves through serotonin 2B receptor. When serotonin-2C receptor is activated in the hypothalamus, food intake is
reduced. The most common adverse events in clinical trials include headache, nausea, dizziness, fatigue, dry mouth, and constipation.

4.3.2 Phentermine/Topiramate

Qsymia® is the combination of phentermine and topiramate as an ER medication (Vivus Inc. Mountain View, CA, USA). As previous described, phentermine, a sympathomimetic drug, has been widely used as short-term appetite suppressant. Topiramate is an anticonvulsant drug. Following anecdotal reports of weight loss occurring in patients with epilepsy, it was evaluated as a potential antiobesity drug in clinical trials. Two clinical studies provided efficacy and safety data for the approval of this medication: EQUIP and CONQUER. The most common side effects reported in the clinical trials include paraesthesia, dizziness, dysgeusia (altered taste), insomnia, constipation, and dry mouth. Topiramate is associated with oral clefts if used during pregnancy.

4.4 Drugs used in the past for obesity

4.4.1 Rimonabant

In obesity-lipids study, it has shown to reduce body weight and improve cardiovascular risk factors in obese patients, such as a reduction in waist circumference, increase in HDL cholesterol and reduction in triglycerides. In addition, rimonabant use at a daily dose of 20 mg also resulted in an increase in plasma adiponectin levels that was partly independent of weight loss alone.

rimonabant is a selective cannabinoid-1 receptor blocker with both central and peripheral actions. A 20 mg/day dose of rimonabant, along with a low calorie diet, resulted in significant weight reduction and improvement in cardiovascular risk factors such as waist circumference, HDL cholesterol, tri-glycerides, insulin resistance and the incidences of metabolic syndrome.

4.4.2 Sibutramine

Sibutramine is an anti-obesity drug that induces satiety and thermogenesis. Sibutramine use has been shown to reduce weight, lower the levels of nonesterified fatty acids, decrease hyperinsulinemia, and reduce insulin resistance. It has been used as an effective adjunct to oral hypoglycemic therapy in obese subjects with type 2 diabetes.

4.5 Alternative and Complimentary Approaches

4.5.1 Bariatric Surgery
Bariatric surgery for severe obesity results in long-term weight loss, which leads to an improved life-style and recovery from diabetes\textsuperscript{107,108}, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, hypertension, and hyperuricemia\textsuperscript{108,109,110}.

4.5.2 Adiponectin

Its administration in rodents has insulin-sensitizing, anti-atherogenic and anti-inflammatory effects and under certain settings also decreases body weight. Therefore, adiponectin replacement in humans may represent a promising approach to prevent and/or treat obesity, insulin resistance and type 2 diabetes.

4.5.3 Antioxidants Diet Supplementation

\(\omega\)-3-Polyunsaturated Fatty Acids. Fish oil, a major source of \(\omega\)-3-polyunsaturated fatty acids (PUFAs), is recommended for the management of hypertriglyceridemia and to prevent from secondary cardiovascular disorders\textsuperscript{111}.

4.5.4 Vitamins

Increased oxidative stress in obesity may be exacerbated by decreased availability of antioxidants\textsuperscript{112,113}.

4.5.5 Apelin

Apelin has been recently identified as a novel peptide hormone abundantly secreted by adipocytes\textsuperscript{114}. By interacting with G-coupled apelin receptors (APJ), apelin is implicated in various physiological functions including regulation of cardiovascular functions, fluid homeostasis, vessel formation, and cell proliferation. Of particular importance, apelin has been shown to mediate antiobesity and antidiabetics properties particularly by promoting glucose utilization and \(\beta\)-oxidation in skeletal muscles\textsuperscript{115} and by suppressing lipolysis and adipogenesis\textsuperscript{116,117}. Interestingly, apelin is shown to prevent cardiomyocytes, vascular smooth muscle cells, and neurons from oxidative stress\textsuperscript{118,119,120}. Antioxidant properties of apelin have been also recently reported in adipocytes\textsuperscript{117} and excess of ROS in fat cells enhances apelin release. Apelin promotes the expression of antioxidant enzymes and suppresses the expression of prooxidant ones especially via AMPK pathway.\textsuperscript{117} Moreover, apelin stimulates the release of adiponectin and enhances mitochondrial biogenesis. These effects contribute to counteracting oxidative-stress induced dysregulation in adipocytes.

4.5.6 Acupuncture
It is among the oldest healing practices in the world and is today becoming one of the most rapidly growing complementary therapies. It was shown that it acts on the satiety centre situated in the hypothalamic ventromedial nucleus and also influences the feeding centre in the lateral hypothalamic area. Acupuncture was shown to increase the expression of the anorexigenic peptides a-MSH, obestatin and CART (200), in the hypothalamic ARC and to downregulate the orexigenic peptide NPY (in ARC) and ghrelin (in the stomach).\footnote{121} Finally, it exerts a regulatory action on serotonin and its metabolism in the raphe nuclei, thus further decreasing hunger.

4.6 Future approaches to treat obesity treatment

As long as the prevalence of obesity is on the rise, the need for better tolerated and more efficacious pharmacotherapies will increase. Recent advances in our knowledge about energy homeostasis regulation at the molecular level are enabling novel anti-obesity drugs to be designed targeting specific molecules crucial for energy balance modulation. In addition, a shift away from pharmacological agents that act on pathways in the CNS could lead to drugs with fewer side effects and more favourable risk/benefit ratios. Therefore, pharmacological intervention for the management of obesity in the future will most likely be a combination of the above.

5. CONCLUSION

The very complicated, multi-pathway regulation of body mass on one side, and the effects of obesity on fertility, (auto)immunity, cardiovascular disease, non-alcoholic fatty liver disease, endocrine problems, cancer development, diabetes and other diseases show the interconnected nature of various body functions. Considerable variation in body fat topography is observed with age, sex, genetics, ethnicity, hormonal factors, diet, level of physical activity/exercise, pharmacological agents, and other factors such as smoking and stress. The safety and efficacy of many anti-obesity drugs beyond two years have not yet been established and long-term effects on morbidity and mortality are also to be determined. Recent advancements in stem cell research at least theoretically open new possibilities for obesity treatment.

6. ABBREVIATIONS

AgRP = Agouti Related Protein
AMPK = Adenosine Monophosphate Activated Protein Kinase
ARC = Arcuate Nucleus
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