Biomedicine & Pharmacotherapy 126 (2020) 110103

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Angiogenesis in obesity

Priya Nijhawans[a], Tapan Behl[a,*], Shaveta Bhardwaj[b]

[a] Chitkara College of Pharmacy, Chitkara University, Punjab, India
[b] GHG Khalsa College of Pharmacy, Punjab, India

ARTICLE INFO

Keywords:
Obesity
Angiogenesis
Adipose tissue
Endothelial cells

ABSTRACT

Purpose: Angiogenesis is considered as a major progenitor in the progression of obesity. The current manuscript enumerates the extrinsic role of angiogenesis in obesity.
Result: High caloric diet and lack of physical exercise are the most common causes of obesity and related metabolic conditions. A grossly elevated levels of fat in adipose tissue escalate certain complications which further worsen the state of obesity. Enlargement of white adipose tissue (WAT), deposition of fat mass, proliferation of endothelial cells, production of inflammatory cytokines induces the formation of denovo capillaries from parent microvasculature. Also, several intracellular signaling pathways precipitate obesity. Though, angiostatic molecules (endostatin, angiostatin and TNP-470) have been designed to combat obesity and associated complications.
Conclusion: Adipose tissue trigger growth of blood capillaries, and in turn adipose tissue endothelial cells promote pre-adipocyte proliferation. Modulation of angiogenesis and treatment with angiostatic substances may have the potential to impair the progression of obesity.

1. Introduction

Obesity is a systemic inflammatory condition that threatens the public health domain globally. The most common causes of obesity are high fat diet, lack of sleep, western lifestyle, a neurological and endocrine disorder. In 2016 approximately 650 million were obese. In United States nearly 70 % of the population is obese. [1]. Obesity promotes the development of coronary heart disease, liver cirrhosis, hypertension, stroke, dyslipidemia, metabolic syndrome, arthritis, insulin resistance and cancer like gastrointestinal cancer, liver cancer that are responsible for vascular dysfunctioning.

Adipose tissue is an endocrine organ surrounded by a dense network of blood capillaries, regulates the production of hormones, angiogenic factors and cytokines [2,3]. It encompasses a mixture of varying adipocytes with a stromal vascular cell covering, housing mesenchymal stem cells, endothelial cells, fibroblasts. The adipokines transmit signals from adipose tissue to the brain and other parts of the body by upregulating the level of some adipokines [4,5]. A functional link between endothelial cells and adipocytes is regulated by paracrine signaling pathway Expansion of adipose tissues is accelerated by hypoxia, hyperplasia, inflammation, structural remodeling of blood capillaries, infiltration of macrophage, through angiogenesis [6–8]. Formation of de novo vasculature from the parent one and activation and relocation of endothelial cells induces angiogenesis [9–11]. Angiogenesis is a multistep process, participates in the healing process, organ restoration, growth of the female reproductive system and fetal development during pregnancy. The event of angiogenesis is counterbalance by proangiogenic molecules including, monocyte, tumor necrosis factor alpha (TNF-α), interleukin-6, endothelial and anti- angiogenic molecules such as endostatin, [12], Kallistatin [13]. However, if the proangiogenic molecules are overexpressed, it promotes angiogenesis by dysregulating endothelial function [14,15], if antiangiogenic molecules predominate over the angiogenic regulators, angiogenesis is repressed. Angiogenesis sustained inflammation by supplying nutrients and oxygen to inflammatory cells and induces Crohn disease and ocular disorders. In a study conducted on animal model such as rabbit and chick chorioallantic membrane (CAM), [16–18] it has been observed that adipose tissue regulates angiogenesis by secreting various angiogenic modulators [19]. However, the process of angiogenesis is balanced by targeting its angiogenic factors.

2. Pathogenesis of obesity

There are several pathological mechanisms that contributes to the progression and management of obesity. Obesity occurs due to lack of physical exercise, genetic predisposition, high caloric intake, and mental disorders [20,21]. Apart from this, the monogenic form of obesity occurs due to deficiency of leptin and mutation of melanocortin

* Corresponding author.
E-mail address: tapan.behl@chitkara.edu.in (T. Behl).

https://doi.org/10.1016/j.biopha.2020.110103
Received 12 November 2019; Received in revised form 3 March 2020; Accepted 11 March 2020

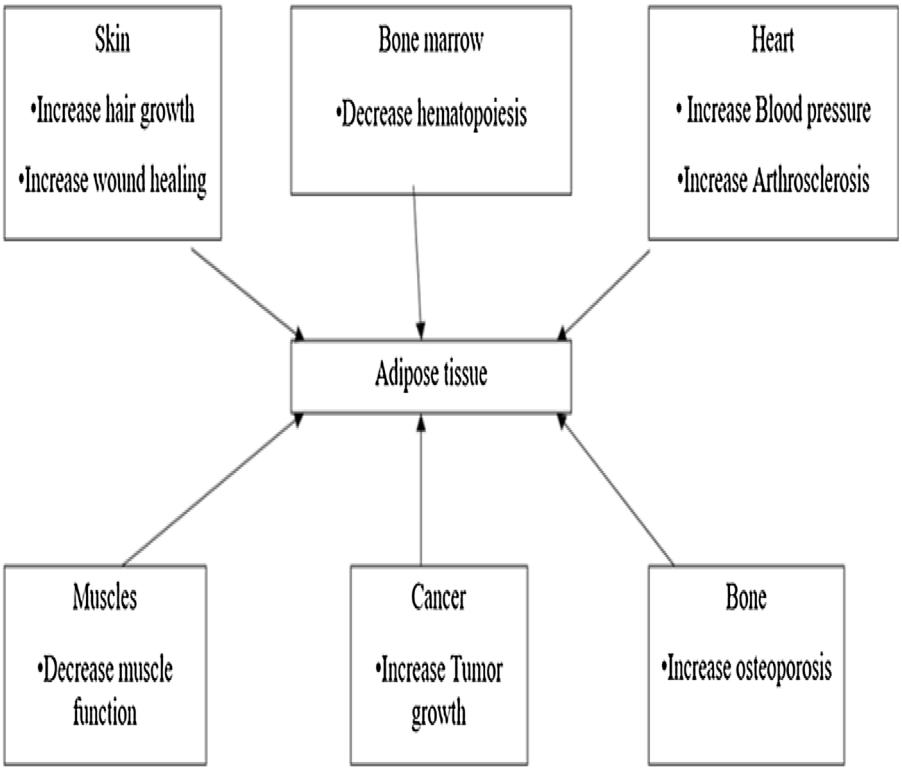

Fig. 1. Several effects regulated by Adipose Tissue.

4 receptors that are secreted in the hypothalamus and regulates energy homeostasis [22]. Obesity is a major reason for certain inherited syndrome such as Prader will syndrome, corex syndrome and MOMO syndrome. There are various endogenous substances, act on numerous intracellular signaling pathway, and promotes appetite, metabolism, energy storage, and expenditure.

2.1. Leptin

Leptin is a substance produced in the peripheral region. Leptin helps in controlling appetite and satiety in the hypothalamus region of CNS. Adipocytes secretes type 1 cytokine leptin in response to the amount of energy present in the body. Appetite and satiety are regulated by signals present in the hypothalamus [23]. The signals begin from the hypothalamus (arcuate nucleus) that has an output to the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH). The arcuate nucleus comprises of two neurons [24].The first neuron is neuropeptide y (NPY) and agouti related protein that provide input to LH and dysregulate the function of VMH. The other is pro-opiomelanocorticotropin and cocaine (POM/CART) which stimulates input to VMH and inhibit input to LH. Thus, NPY stimulate feeding whereas POM regulate satiety. Though, inhibition of NPY neuron and activation of POM result in a deficiency of leptin and development of obesity [25].

2.2. Ghrelin

Ghrelin is a peptide hormone, generated by ghrelinergic cells present in the stomach, lung, gonads, pancreatic cell and jejunum. It acts as a neuropeptide in CNS and induces energy distribution and expenditure. It increases hunger by acting on a hypothalamic brain and enhance gastric acid secretion and gastrointestinal motility when food is administered. Ghrelin level is increased before a meal and reduced after. Data conducted over the years revealed that ghrelin act as a messenger between homeostasis in body and brain though adiposity cascades [26–28].

2.3. Nesfatin-1

Nesfatin -1 is a polypeptide encoded in the N terminal region of protein precursor, Nucliobindin2 (NUCB2) [29]. Nesfatin is produced in the hypothalamus region as well as in pancreatic cells and it takes part in the stimulation of appetite and storage of lipids. Nesfatin-1 is present in the paraventricular nucleus, arcuate nucleus, and nucleus of tractus solitaries. Increased level of Nesfatin-1 in the hypothalamus, prevent appetite and weight gain. Nesfatin-1 diminishes hunger by inactivating NPY and stimulating POM in the hypothalamic center in CNS. It also regulates insulin secretion from pancreatic cells It has been reported that intraerebroventricular injection of nesfatin-1 in patients stimulates insulin secretion and gastric emptying [30].

3. Adipose tissue

Adipose tissue consists of adipocytes, macrophages, and fibroblasts. As such, it induces sustained inflammation, regulates homeostasis and secrete free fatty acids during caloric restriction. During obesity, fat stores in adipose tissue of liver, kidney heart, lungs. In addition, excess visceral accumulation contribute to the progression of various complications including hypertension, dyslipidemia which attributed to a stronger predictor of morbidity and mortality [31]. The two types of adipose tissues is brown adipose tissue (BAT) and white adipose tissue (WAT). BAT transform nutrient into energy. Brown fat cells exhibit homeostasis and mitochondrial genetic program which dissipate energy by stimulating biogenesis of mitochondria [32].

White adipose tissue (WAT) stores triglycerides. WAT is also functioned as an endocrine organ, express a unique paracrine and autocrine activity by regulating the production of molecules [33]. Adipocytes stimulate the secretion of molecules, regulate body weight and induce chronic inflammation (IL-6) (Fig. 1).

It exhibit a unique property to remold or expand in any dimension. This effect is mediated by elevating the number of adipocyte cells (hypertrophy) or by employing new adipose cells (hyperplasia). In

obese state, enlargement of adipose tissue is regulated by various factors such as sustain inflammation, the release of inflammatory cytokines, over production of extracellular matrix, infiltration of immune cells and neovascularization. Although, infiltration of macrophages (immune cells) expedite chronic inflammation and insulin resistance. However, deposition of macrophages inhibits the release of inflammatory cells, resulting in weight loss [34].

Macrophages are categorized into two types namely M1 and M2 macrophages. Lumeng et al. studied a model in which he proposed that conversion of M2 anti-inflammatory macrophages into inflammatory M1 macrophages promotes the progression of obesity and its related complications [35]. Macrophages are activated by T cytotoxic cells present in adipocytes, which elevate insulin sensitivity and inflammation. Macrophages induce the progression of obesity and its associated metabolic syndrome by eliminating apoptotic cells and inhibit the release of toxic substances. Therefore, obese subjects are classified as the fully dysregulated metabolic system and moderate dysregulated metabolic system [36].

3.1. Mechanisms of angiogenesis

The denovo development of microvasculature during the progression of neonatal occurs through the event of vasculogenesis, in which angioblasts form into primary blood vessel. And further vessels growth occurs during organ and tissues development through the event of angiogenesis, in which new blood capillaries develop from parent vessel. From the evidence, it has been clear that angiogenesis [37–40] regulates the development of organs and tissue and perform varied functions. Insights into the mechanism of angiogenesis are taken from experimental models i.e developing zebrafish embryo and the mouse retina. Angiogenesis regulates the proliferation of endothelial cells, relocation to extra cellular matrix, the formation of a lumen and maintains the circulation of the body. The proliferation of endothelial cells is regulated by the VEGF family of growth factors. These growth factors and their receptors are known as master regulators of endothelial cell formation. VEGF-A, act via VEGFR2 function as a mitogenic and chemoattractant signal for endothelial cells. In response to VEGF-A endothelial cells multiply, and acquire a phenotype accompanied by the development of branches. The action of VEGFs and their receptors are regulated by the Notch signaling pathway, which manifests the responsiveness of endothelial cells to VEGF. The activation of Notch signaling by Delta-like 4 (Dll4) in the tip cell dysregulates the action of VEGF signaling in the adjacent cell, resulting in the acquisition of a stalk-cell phenotype. The continuous interaction between VEGF, Notch and, Dll4 leads to the event of angiogenesis.

4. Angiogenesis in adipose tissue

Angiogenesis regulates various pathological processes and participate in wound healing, cancer and inflammatory conditions.

The event of angiogenesis is regulated by

(i) Activation and proliferation of endothelial cells by angiogenic stimuli.
(ii) The incursion of endothelial cells into the stroma of adipose tissue by cleavage of basement membrane components.
(iii) Formation of the lumen by endothelial cells.
(iv) Finally, blood capillaries are arranged in adipocytes through the formation of endothelial cells and basement membrane [41–43].

The dense network of blood capillaries is necessary to inhibit the prevalence of hypoxia. Hypoxia is a chronic condition and is defined as the amount of blood flow to WAT and supply of oxygen to fat cells when hypertrophied adipocyte is larger.

Although, tissue hypoxia is manifested by various cellular and molecular mechanism namely (i) infiltration of macrophages by phagocytic stimuli, (ii) deficit in oxygen supply [44,45]. Hypoxia is triggered by Hypoxia inducible factor-1 (HIF-1) and it is comprised of HIF-1 α and HIF1-β. [46] Hypoxia promotes angiogenesis by regulating the production of VEGF, platelet derived growth factors (PDGF) and various inflammatory mediators (IL-6, TNF-α) in endothelial cells (ECs) [47]. Hypoxia inhibits angiogenic response and induces EC death. Endothelial cells hasten its response when oxygen deficiency occurs. Acute hypoxia releases inflammatory cytokines by adhering to leukocytes on endothelium cell lining resulting in inflammation. Also, sustainable hypoxia regulates the expression of certain cytokines such as Nuclear factor Kappa B by activating HIF-1, by promoting endothelial cell death and apoptosis. Accumulating pieces of evidence hypothesis that during hypoxia, deposition of extracellular matrix in WAT results in fibrosis and mild inflammation [48]. Angiogenesis is a physiological process, regulates several body functions. The physiological event of angiogenesis is stimulated by the enlargement of adipose tissue under the effect of VEGF [49]. However, in pathological conditions, the EC continues to proliferate and significantly result in tumor progression. The capillaries are surrounded by endothelial cell layer and comprised of pericytic cells and basement membrane components. The process of angiogenesis is regulated as angiogenic factors (VEGF, TNF- α and β) released from tumor cells to the EC receptors. When EC activates and migrates the cell releases various digestive enzymes viz. protease and heparanese and degrade extracellular matrix (ECM). Degradation of ECM stimulates the growth of new vasculature. The new microvessels are likely to be mature by reconstructing basement membrane components and endothelial lining.

5. VEGF intracellular signaling

The vascular endothelial derived growth factor is an angiogenic agent that plays an intrinsic role in the angiogenic events [50]. VEGF is divided into six members (VEGF-A – VEGF-F) [51]. Few hormones such as estrogen and thyroid stimulating hormone (TSH), also stimulates signaling of VEGF in other cells [52] (Fig. 2).

VEGF promotes the activity of ECs by binding to transmembrane receptor tyrosine kinase (RTKS, located in endothelial cell lining. During the event of angiogenesis VEGF-R1 and VEGF-R2 sited on EC are activated while VEGF-R promotes intracellular signaling. However, VEGF-R1 acts as a negative regulator of angiogenesis. Therefore, VEGF-A binds to VEGF-R2 site to activate numerous angiogenic signaling

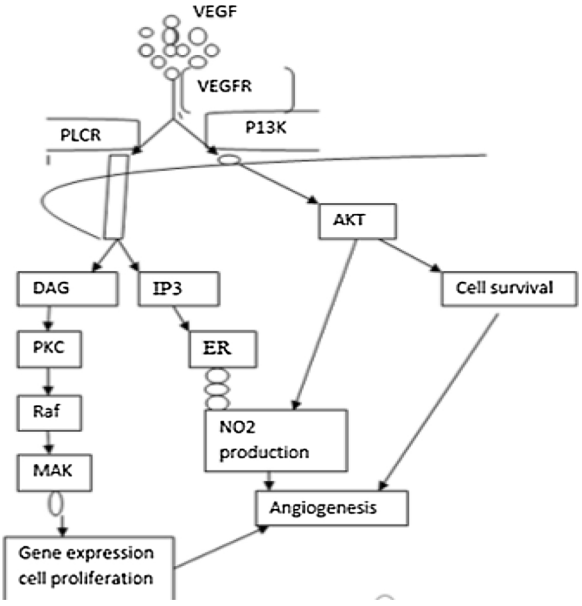

Fig. 2. VEGF Intracelluar Signalling Pathway.

pathway, which leads to cellular proliferation, mitogenesis and overproduction of growth factors. VEGF-C bind to VEGF-R3, promotes mitogenesis in lymphatic cells.

6. Notch signaling pathways

Notch is a heterodimeric compound, consist of notch extracellular domain (NECD) and notch intracellular domain (NICD [53]. The notch cell signaling elicit tumor angiogenesis and generates inactive tumors. Notch delta like 4 (DLL4) stimulates cell signaling pathway through endocytosis in stromal cells to increase vascular functions [54]. Although inhibition of DLL4 may induces proliferation in ECs, elicit angiogenic events [55]. Beside this, tumor cells diffuse poorly, decreases oxygen concentration in cell and tumor progression is inhibited. It has been stated that DLLL4 present in ECs activates Notch 3 receptor, by transforming tumor progression from inactive to active state [56]. Consequently such an outcome reflects Notch signaling pathway as a therapeutic molecule for the designing of denovo angiostatic compound.

6.1. Role of hypoxia in adipose tissue angiogenesis

Adipose tissue in experimental animals becomes hypoxic when fed with high fat diet (HFD). Hypoxia has been identified by using chemical indicators of hypoxia and direct monitoring of tissue oxygen tension by microelectrodes [57–59]. The expression and secretion of pro-angiogenic factors by cultured adipocytes are regulated under low oxygen [60,61]. Also, it has been evidenced that enlargement of adipose tissue after administration of HFD is not accompanied by elevated blood flow [62]. Overexpression of active form of HIF-1α in adipose tissue failed to promote pro-angiogenic responses as it levels increased in local inflammation [63]. Inhibition of HIF-1α and HIF-1β in adipose tissue decrease lipid accumulation, and prevent HFD-induced obesity and insulin resistance [64,65]. Nevertheless, HIF-1α promotes growth and maintenance of brown adipose tissue, as the expression of HIF-1α impairs thermogenesis and energy expenditure [66]

6.2. Functional link between adipocytes and endothelial cells

Endothelial cells regulate homeostasis and provide a barrier between the capillaries wall and blood lumen. Also, endothelium induces the release of certain cytokines in response to metabolic stress, hypoxia and oxidative stress and maintain vascular tone coagulation, and fibrinolysis [67]. The interaction between the endothelial cell and release of inflammatory cytokines in adipose tissue results in development of cardiovascular disease in obese subjects [68]. Dysfunctioning of endothelial cells is a multifactorial process in obesity. Obesity is characterized by the production of reactive oxygen species (ROS) due to the dysregulation of mitochondria function. When the amount is low it functions as an intracellular secondary messenger and if the amount is high it results in cellular toxicity. The major enzymes responsible for ROS generation are cyclooxygenase (COX), lipoxygenase (LOX), NADPH oxidase and leptin, resulting in decrease nitric oxide (NO) production. The NO generation is diminished due to peroxynitrite formation (ONOO) [69]. Accumulation of ROS and production of inflammatory adipokines NFκB signaling induces apoptosis and inflammation by stimulating the countenance of growth factors and adhesion molecule. Inflammatory mediators are activated by NFκB signaling and regulates the expansion of ECs by increasing the expression of intracellular cell adhesion molecule-1 (ICAM-1). Thus resulting in the relocation of leukocytes, induces the progression of arthrosclerosis.

6.3. Dysfunctional adipose tissue in obesity and tumor development

Obesity is defined as the accumulation of fat in different organs of the body which results in the expansion of adipose tissue and metabolic dysfunctioning. Alteration in adipose tissue and the progression of cancer occurs due to altered cytokine and lipid secretion profiles. Energy equilibrium and fuel homeostasis is required to maintain a strict balance between energy intake and energy expenditure stimulated by CNS. There are two distinct types of adipose tissue, white and brown, with varied locations and functions [70]. The function of white adipose tissue (WAT) is to maintain energy homeostasis by storing triglycerides and secreting fatty acids. Also, WAT plays a significant role in immune and inflammatory regulation, glucose and lipid thermogenesis, by producing several adipokines [71,72].WAT is a heterogeneous tissue, comprises a peripheral subcutaneous component (SAT) and visceral adipose tissue (VAT) [73]. Obesity in abdominal is related to subcutaneous fat with an elevation VAT that is concerned with the development of metabolic disorders and tumor progression [74–76]. Brown adipose tissue (BAT) is present in the axillary region, thymus and in the dorsal midline region of the thorax and abdomen [77]. BAT plays a vital role in thermogenesis, through uncoupling protein- (UCP-1) [78,79]. Cancer is characterized by cachexia, a complex syndrome that involved profound metabolic imbalances [80]. The colorectal tumor-induced cachexia on BAT in an animal model has been studied [81]. Researchers had demonstrated the presence of another type of adipose tissue known as brown-like adipose tissue [82].

BAT is a thermogenic adipose tissue characterizes by bycold-induced signals via the sympathetic nervous system. The restriction in adipose tissue enlargement results in fat accumulation in other parts of the body [83]. Expanded fat depots in obesity are less efficient in storing dietary fatty acids so that obese subjects exhibit an elevation in plasma free fatty acids (FFA). An analysis of cancer-induced modifications in the lipid provide clues correlating obesity and cancer. Alteration in lipid metabolism induces cancer progression by an FFA increase, due to its function as an oncogenic cascade. It has been reported that increased fatty acid synthase (FASN) activity has been shown in breast cancer cell lines or cancer precursor lesions in distinct locations. The inhibition of the FASN activity decreases the cancer cells' proliferative activity. Additionally, research demonstrated a correlation between mutations in the FASN enzyme and cancer incidence [84]. Moreover, FASN act as an important biomarker of over nutrition induced insulin resistance.

6.4. Clinical relevance of increased adiposity on the cardio metabolic and overall comorbities risk

Surplus adiposity errands the assembling of cardiometabolic variation viz. type 2diabetes (T2D), hypertension, and dyslipidemia, resulting in morbidity [85,86] and decrease life expectancy. The menace of developing obesity-related disorders is related to the grade of adiposity [87] and storage of fat in the visceral section [86]. Obese subjects might not be at elevated risk for the progression of metabolic syndrome, and hence their clinical condition is known as metabolically healthy obesity (MHO) [88]. In comparison, obese individuals suffering from insulin resistance, high blood pressure, and dyslipidemia are measured as having metabolically abnormal obesity (MAO) [89]. The privation of consent measures to define MHO does not allow the precise measurement of the prevalence of the MHO and MAO phenotypes, making the comparison between distinct investigation tough [90]. Therefore, the reported occurrence of MHO varies, ranging from 3 % to 57 % of obese subjects, relying on the techniques used to define this condition [91–93]. Numerous mechanisms have been studied to define the fewer harmful metabolic profile of MHO patients. Among them, an inferior inflammatory outline, complex lipolytic action [94], elevated physical activity, and decreased liver fat evidenced by lowering liver enzyme concentrations [95] have been studied. All the above-listed parameters might distinguish metabolically unhealthy from a metabolically healthy obese person [96–99].

Table 1
The case studies for PHB-targeted nanotherapy in obesity are discussed under:

Case study	NP description	Therapeutic effect	Action of NP biconjugate	References
1. KLA-encapsulated liposomes for PHB targeted delivery	Liposomes were formulated from phosphatidylcholine and cholesterol (Chol). A therapeutic peptide (KLA) was compressed with the liposomes, and the targeting peptide (AHP) was bind to the liposomal surface.	KLA promotes apoptosis by acting on ECs and thus prevent weight gain in obese mice and rats	In vitro, AHP-targeted nanocarriers was occupied by ECs extracted from WAT. In vivo, AHP-targeted liposomes gathered in the WAT vasculature. Also, NPs without a targeting peptide were present in the WAT vasculature as NPs are also occupied by EPR. PHB-mediated uptake of the NPs by ECs lead to reduction of body weight of obese animal model. Body weight decrease in mice treated with NP-conjugate was associated with decrease levels of leptin, adipocyte size, macrophage content and elevated levels of adiponectin.	[121]
AHP-targeted delivery of AuNPs to PHB in obese rats	AuNPs were developed by Turkevich method, polyethylene glycol (PEG) was used to passivate the NPs. AHP was bind to the surface of the NPs for targeted delivery to PHB	AHP-AuNPs were synthesized for targeted delivery in the WAT vasculature of obese rats, and the biodistribution of PHB-targeted AuNP was analyzed 24 h post treatment	AHP increase the uptake and accumulation of the AuNPs by the WATs in obese Wistar rats after 24 h. Targeted AuNPs showed decreased non-specific uptake by reticuloendothelial system organs in comparison to non-targeted AuNPs. Non-targeted NPs stored in the liver and pancreas, while AHP-targeted NPs accumulated in the WAT depots.	[122–124]

7. Role of angiogenesis in obesity

Angiogenesis is an essential element involved in the enlargement of WAT. Adipose tissue growth occurs through hypertrophy and hyperplasia and relied on the plasticity of microvessel in the tissue. The relocation of adipocytes elevates during obesity. It allows an adequate supply of nutrients and oxygen to new blood vessels [100,101]. Obesity-related vascular disorders take place when lipid storage exceeds a normal level due to the accumulation of fat in various organs of the body.

The event of angiogenesis is more susceptible during the expansion of ECs and is supplemented by the activation of receptors. The formation of new vessels in adipocytes is regulated by an equilibrium between the pro-angiogenic and anti-angiogenic agents. The pathogenesis of neovascularization occurs due overexpression of pro-angiogenic molecules in WAT. The adipocytes produce certain angiogenic substances including VEGF, angiopoietin, leptin [102]. The process of adipogenesis is accompanied by angiogenesis. Angiogenesis is prevented by triggering pro-angiogenic factors result in the regulation of WAT mass in obesity [103,104]. It has been stated that various angiogenic inhibitors angiostatin and endostatin have an anti-angiogenic. All angiogenic inhibitors perform different modes of action. TNP 470 decreases appetite, fat mass, and expansion of adipose tissue by inhibiting methionine aminopeptidase-2 in ECs [105]. Angiostatin and endostatin dysregulates the function of ECs by reducing the fat mass [106].

Antibodies restrained the formation of blood capillaries by reducing the expansion of WAT mass in the obesity-induced model [107]. Kolomin et al. proposed that the progression of obesity is inhibited by inducing PHB into WAT of dietary-induced obese mice. Therefore, angiogenesis is turn out to be the potential target for the management of obesity.

7.1. Current therapeutic approach in the management of obesity

Treatment of obesity along with caloric restriction includes lifestyle changes and adequate physical exercises. Also, surgical operations might provide an alternative operation in the management of obesity [108,109]. Constraining of angiogenesis process helps in reducing the progression of obesity. Administration of anti-angiogenic compounds such as endostatin, angiostatin, TNP-470 and VEGF inhibitors in obese mouse, results in weight loss. Barnhart et al. proposed that when obese monkeys are treated with adipotide induce apoptosis of WAT, it leads to loss of fat mass, a proliferation of ECs and increased EC cell death. A peptide is designed to inhibit the progression of angiogenesis by causing apoptosis in WAT, thus improving glucose tolerance [110]. Recently two anti-obesity drugs have been used in the management of obesity viz. orlistat (lipase inhibitors) and Lorcaserin (serotonin 2 receptor) [111]. Various efforts have been made to mitigate the progression of obesity by increasing lipid mobilization and oxidation. Fewer antidiabetic drugs have been approved for the management of weight loss and for lowering the risk of cardiovascular diseases [112,113], inhibition of DPP4 enzyme activity by antidiabetic medications stimulates insulin secretion that lowers blood glucose level [114].

In recent years, vascular targeted nanotherapy has been used in the management and treatment of high fat diet induced obesity in experimental animals [115–117]. Targeted nanotherapy is done by binding to targeted peptide nano polymers (NPs) which act as drug carriers. Nanotherapy targeting at ECs in the WAT for the management of obesity in animal models has been studied. PHB-targeting ligand (AHP) attached to a KLA peptide (AHP-KLA), and promotes cell death in the WAT vasculature in experimental animals [118]. Inhibition of WAT vasculature results in body weight loss. The scientist had discovered that AHP (PHB ligand) and KLA when binds to NPs, the action of drugs increases while AHP-KLA interaction decreases its action. The same effect was seen in animal models by using distinct nanocarriers. Various PHB

ligands were developed viz. oncomirs (miR-361) and FLs (FL3 and 37) [119,120] which showed similar effects as AHP. PHB has been proved to be a novel approach to combat obesity and related secondary metabolic disorder (Table 1).

The use of nanocarriers in association with active targets is arising as a therapeutic approach for the treatment of diseases. The nanosystems increase the drug availability to target organ by enhancing the drug EPR action [122–124].

8. Conclusion

High caloric intake and inadequate physical activity result in the storage of fat. Obesity is involved in the development of diabetes mellitus, stroke, cancer. Enlargement of adipocytes occurs due to weight gain. During obesity, adipose tissue stimulates the enlargement of endothelial cells which in turn enhances the formation of denovo blood capillaries. The event of angiogenesis is inhibited by elevating the level of serum leptin that counteracts the accumulation of lipids in adipocytes. In recent years, various antiangiogenic compounds have been designed i.e. endostatin, angiostatin, and TNP-470 which acts by modulating the pathogenesis of angiogenesis. Additionally, anti-angiogenic agents also offer opportunity in the management of obesity and metabolic disorders. New antiangiogenic molecules are become available, which can be useful in obesity management. Moreover, this means of management is an interesting method, enlightening the antiangiogenic molecules interfering with angiogenesis.

Funding source

This present review did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgement

The present study received no funding from any source or any governing body.

References

[1] C.L. Ogden, et al., Prevalence of childhood and adult obesity in the United States, JAMA 311 (2014) 806–814, https://doi.org/10.1001/jama.2014.732.
[2] N. Halberg, et al., The adipocyte as an endocrine cell, Endocrinol. Metab. Clin. North Am. 37 (2008) 753–768, https://doi.org/10.1016/j.ecl.2008.07.002.
[3] D.L. Crandall, et al., A review of the microcirculation of adipose tissue: anatomic, metabolic, and angiogenic perspectives, Microcirculation 4 (1997) 211–232.
[4] R. Cao, et al., Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) (2001) 6390–6395, https://doi.org/10.1073/pnas.101564798.
[5] M.R. Sierra-Honigmann, et al., Biological action of leptin as an angiogenic factor, Science 281 (1998) 1683–1686, https://doi.org/10.1126/science.281.5383.1683.
[6] N. Ouchi, et al., Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells, J. Biol. Chem. 279 (2004) 1304–1309, https://doi.org/10.1074/jbc.M310389200.
[7] S. Nishimura, et al., Adipogenesis in obesity requires close interplay between differentiating adipocytes, stromal cells, and blood vessels, Diabetes 56 (2007) 1517–1526, https://doi.org/10.2337/db06-1749.
[8] A. Bouloumie, et al., Angiogenesis in adipose tissue, Ann. Endocrinol. 63 (2 Pt 1) (2002) 1–5.
[9] M. Khazaei, Z. Tahergorabi, Systemic ghrelin administration alters serum biomarkers of angiogenesis in diet-induced obese mice, Int. J. Pept. (2013), https://doi.org/10.1155/2013/249565.
[10] J. Folkman, Angiogenesis, Annu. Rev. Med. 57 (2006) 1–18, https://doi.org/10.1146/annurev.med.57.121304.131306.
[11] P. Carmeliet, Angiogenesis in health and disease, Nat. Med. 9 (2003) 653–660, https://doi.org/10.1038/nm0603-653.
[12] W. Risau, I. Flamme, Vasculogenesis, Annu. Rev. Cell Dev. Biol. 11 (1995) 73–79, https://doi.org/10.1146/annurev.cb.11.110195.000445.
[13] R.Q. SMiao, Kalistatin is a new inhibitor of angiogenesis and tumor growth, Blood 100 (2002) 3245–3252, https://doi.org/10.1182/blood-2002-01-0185.
[14] J. Lawler, Thrombospondin-1 as an endogenous inhibitor of angiogenesis and tumor growth, J. Cell. Mol. Med. 6 (2002) 1–12, https://doi.org/10.1111/j.1582-4934.2002.tb00307.
[15] N. Ferrara, Role of vascular endothelial growth factor in regulation of physiological angiogenesis, Am. J. Physiol., Cell Physiol. 280 (2001) C1358–C1366, https://doi.org/10.1152/ajpcell.2001.280.6.C1358.
[16] J. Folkman, Role of angiogenesis in tumor growth and metastasis, Semin. Oncol. 29 (2002) 15–18, https://doi.org/10.1053/sonc.2002.37263.
[17] J.J. Castellot Jr., Differentiation-dependent stimulation of neovascularization and endothelial cell chemotaxis by 3T3 adipocytes, Proc. Natl. Acad. Sci. U. S. A. 79 (1982), https://doi.org/10.1073/pnas.79.18.5597 5597–5560.
[18] K.J. Silverman, Angiogenic activity of adipose tissue, Biochem. Biophys. Res. Commun. 153 (1998) 347–352, https://doi.org/10.1016/S0006-291X(88)81229-4.
[19] Y. Cao, Angiogenesis modulates adipogenesis and obesity, J. Clin. Invest. 117 (2007) 2362–2368.
[20] J. Silha, et al., Angiogenic factors are elevated in overweight and obese individuals, Int. J. Obes. 29 (2005) 1308–1314, https://doi.org/10.1038/sj.ijo.0802987.
[21] R.L. Leibel, R.J. Seeley, T. Darsow, E.G. Berg, Biologic responses to weight loss and weight regain: report from an American Diabetes Association Research Symposium, Diabetes 64 (2015) 2299–2309, https://doi.org/10.2337/db15-0004.
[22] C.N. Ochner, et al., Treating obesity seriously: When recommendations for lifestyle change confront biological adaptations, Lancet Diabetes Endocrinol. 3 (2015) 232–234, https://doi.org/10.1016/S2213-8587(15)00009-1.
[23] W.H. Le Riche, G. Van Belle, Study of phendimetrazine bitartrate as an appetite suppressant in relation to dosage, weight loss and side effects, Can. Med. Assoc. J. 87 (1962) 29–31.
[24] R. Khera, et al., Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis, JAMA 315 (2015) 2424–2434, https://doi.org/10.1001/jama.2016.7602.
[25] Muruzaabal, et al., Immunocytochemical detection of leptin innonmammalian vertebrate stomach, Gen. Comp. Endocrinol. 128 (2002) 149–152.
[26] K.M. Gadde, et al., Effects of low-dose, controlled-release, Phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial, Lancet 377 (2011) 1341–1352, https://doi.org/10.1016/S0140-6736(11)60205-5.
[27] B.M. Popkin, C. Hawkes, Sweetening of the global diet, particularly beverages: patterns, trends, and policy responses, Lancet Diabetes Endocrinol. 4 (2006) 174–186, https://doi.org/10.1016/S2213-8587(15)00419-2.
[28] C.M. Apovian, et al., Pharmacological management of obesity: an endocrine society clinical practice guideline, J. Clin. Endocrinol. Metab. 100 (2015) 342–362, https://doi.org/10.1210/jc.2014-3415.
[29] S. Oh-I, et al., Identification of nesfatin-1 as a satiety molecule in the hypothalamus, Nature 443 (2006) 709–712.
[30] W.T. Garvey, et al., American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity, Endocr. Pract. 22 (Suppl. 3) (2016) 201–203, https://doi.org/10.4158/EP161365.GL.
[31] S.B. Heymsfield, et al., Emerging technologies and their applications in lipid compartment measurement, Trends Endocrinol. Metab. 26 (2015) 688–698, https://doi.org/10.1016/j.tem.2015.10.003.
[32] N. Alexopoulos, Visceral adipose tissue as a source of inflammation and promoter of atherosclerosis, Atherosclerosis 233 (2014) 104–111, https://doi.org/10.1016/j.atherosclerosis.2013.12.023.
[33] S. Kajimura, et al., Transcriptional control of brown fat development, Cell Metab. 11 (2010) 257–262, https://doi.org/10.1016/j.cmet.2010.03.005.
[34] G. Frühbeck, et al., The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation, Am. J. Physiol.—Endocrinol. Metab. 2280 (6) (2001) E827–E847, https://doi.org/10.1152/ajpendo.2001.280.6.E827.
[35] K. Sun, et al., Adipose tissue remodeling and obesity, J. Clin. Invest. 121 (2011) 2094–2101.
[36] C.N. Lumeng, et al., Obesity induces a phenotypic switch in adipose tissue macrophage polarization, J. Clin. Invest. 117 (2007) 175–184, https://doi.org/10.1172/JCI29881.
[37] H.M. Eilken, R.H. Adams, Dynamics of endothelial cell behavior in sprouting angiogenesis, Curr. Opin. Cell Biol. 22 (2010) 617–625.
[38] P. Carmeliet, R.K. Jain, Molecular mechanisms and clinical applications of angiogenesis, Nature 473 (2011) 298–307.
[39] A.S. Chung, N. Ferrara, Developmental and pathological angiogenesis, Annu. Rev.Cell Dev. Biol. 27 (2011) 563–584.
[40] M. Potente, H. Gerhardt, P. Carmeliet, Basic and therapeutic aspects ofangiogenesis, Cell 146 (2011) 873–887.
[41] C.M. Apovian, et al., Adipose macrophage infiltration is associated with insulin resistance Endothelial Dysfunction and vascular endothelial dysfunction in obese subjects, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1654–1659, https://doi.org/10.1161/ATVBAHA.108.170316.
[42] P. Carmeliet, R.K. Jain, Angiogenesis in cancer and other diseases, Nature 407 (6801) (2000) 249–257, https://doi.org/10.1038/35025220.
[43] S.D. Hursting, Mini review. The year in obesity and cancer, Mol. Endocrinol. 26 (2012) 1961–1966, https://doi.org/10.1210/me.2012-1283.
[44] J. Incio, R. Soares, Obesity, diabetes and metabolic syndrome impact on tumor angiogenesis, in: R. Ruben, B.R.R. Gonzalez-Perez (Eds.), Tumor Angiogenesis Regulators, CRC Press, New York, USA, 2013.

[45] S. Corvera, O. Gealekman, Adipose tissue angiogenesis: impact on obesity and type-2diabetes, Biochim. Biophys. Acta 1842 (2014) 463–472, https://doi.org/10.1016/j.bbadis.2013.06.003.
[46] A.Y. Lemoine, et al., Adipose tissue angiogenesis in obesity, Thromb. Haemost. 110 (2014) 661–668, https://doi.org/10.1160/TH13-01-0073.
[47] K. Lolmede, Effect of hypoxia on the expression of proangiogenic factors in differentiated 3T3-F442A adipocytes, Int. J. Obes. Relat. Metab. Disord. 27 (2003) 1187–1195.
[48] J.A. Forsythe, et al., Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factosr 1, Mol. Cell. Biol. 16 (1996) 4604–4613, https://doi.org/10.1128/mcb.16.9.4604.
[49] I.J. Fidler, L.M. Ellis, The implications of angiogenesis for biology and therapy for cancer metastasis, Cell. 79 (1994) 185–188, https://doi.org/10.1016/0092-8674(94)90187-2.
[50] T.A. Fregene, et al., Tumor associated angiogenesis in prostate cancer, Anticancer Res. 13 (1993) 2377–2381.
[51] M. Ohta, The significance of circulating vascular endothelial growth factor (VEGF) protein in gastric cancer, Caner let. 19 (2003) 215–225.
[52] Y. Yokoyama, et al., Expression of VEGF-D and its receptor, as a prognostic factor in endometrial carcinoma, Clin. Cancer Res. 9 (2003) 1361–1369.
[53] A. Adini, et al., Placental growth factor is a survival factor in tumor progression and macrophages, Cancer Res. 62 (2000) 2749–2752.
[54] J.L. Li, et al., Delta like 4 notch ligands regulate tumor angiogenesis improve tumor vascular function and tumor growth in vivo, Cancer Res. 67 (2007) 11244–11253, https://doi.org/10.1158/0008-5472.CAN-07-0969.
[55] J. Ridguay, Inhibition of DLL4 signaling inhibit tumor growth by deregulating angiogenesis, Nature 444 (2006) 1083–1087, https://doi.org/10.1186/s12885-015-1605-2.
[56] D.B. Cines, et al., Endothelial cells in physiology and in the pathophysiology of vascular disorders, Blood 91 (1998) 3527–3561.
[57] M.E. Rausch, et al., Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration, Int. J. Obes. 32 (2008) 451–463.
[58] J. Ye, et al., Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice, Am. J. Physiol. Endocrinol. Metab. 29 (2007) E1118–E1128.
[59] N. Hosogai, A. Fukuhara, K. Oshima, Y. Miyata, S. Tanaka, K. Segawa, S. Furukawa, Y. Tochino, R. Komuro, M. Matsuda, I. Shimomura, Adiposetissuehypoxiainobesity and its impact on adipocytokines dysregulation, Diabetes 56 (2007) 901–911.
[60] K. Lolmede, et al., Effects of hypoxia on the expression of proangiogenic factors in differentiated3T3-F442A adipocytes, Int. J. Obes. Relat. Metab. Disord. 27 (2003) 1187–1195.
[61] G.H. Goossens, et al., Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation, Circulation 124 (2011) 67–76.
[62] P. Trayhurn, Hypoxia and adipose tissue function and dysfunction in obesity, Physiol. Rev. 93 (2013) 1–21.
[63] N. Halberg, et al., Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue, Mol. Cell. Biol. 29 (2009) 4467–4483.
[64] C. Jiang, et al., Disruption of hypoxia-inducible factor 1 in adipocytes improves insulin sensitivity and decreases adiposity in high-fat diet-fed mice, Diabetes 60 (2011) 2484–2495.
[65] K.Y. Lee, et al., The differential role ofHif1beta and the hypoxic response in adipose function, fibrosis, and in-Flammarion, Cell Metab. 14 (2011) 491–503.
[66] X. Zhang, et al., Adipose tissue-specific inhibition of hypoxia-inducible factor 1{alpha} induces obesity and glucose intolerance by impeding energy expenditure in mice, J. Biol. Chem. 285 (2010) 32869–32877.
[67] M. Higgins, Hazards of obesity—the Framingham experience, Acta Med. Scand. Suppl. 723 (1998) 23–36.
[68] A. Avogaro, S.V. De Kreutzenberg, Mechanisms of endothelial dysfunction in obesity, Clin. Chim. Acta 360 (2005) 9–26, https://doi.org/10.1016/j.cccn.2005.04.020.
[69] H. Matsushita, et al., Hypoxia-induced endothelial apoptosis through nuclear factor-kappaB (NF-kappaB)-mediated bcl-2 suppression: in vivo evidence of the importance of NF-kappaB in endothelial cell regulation, Circ. Res. 86 (2000) 974–981, https://doi.org/10.1161/01.res.86.9.974.
[70] G. Frühbeck, et al., BAT: a new target for human obesity? Trends Pharmacol. Sci. 30 (2009) 387–396, https://doi.org/10.1016/j.tips.2009.05.003.
[71] V. Catalán, et al., Adipokines in the treatment of diabetes mellitus and obesity, Expert Opin. Pharmacother. 10 (2009) 239–254, https://doi.org/10.1517/14656560802618811.
[72] I. Falcao-Pires, et al., Physiological, pathological and potential therapeutic roles of adipokines, Drug Discov. Today 17 (2012) 880–889, https://doi.org/10.1016/j.drudis.2012.04.007.
[73] A. Rodríguez, et al., Visceral and sub-cutaneous adiposity: are both potential therapeutic targets for tacklingthe metabolic syndrome? Curr. Pharm. Des. 13 (2007) 2169–2175, https://doi.org/10.2174/138161207781039599.
[74] C.S. Fox, et al., Abdominal visceral and subcutaneous adipose tissue compartments: associa-tion with metabolic risk factors in the Framingham Heart Study, Circulation 116 (2007) 39–48, https://doi.org/10.1161/CIRCULATIONAHA.106.675355.
[75] A. Koster, et al., Body fat distribution and inflammation among obese older adults with and without metabolic syndrome, Obesity 18 (2010) 2354–2361, https://doi.org/10.1038/oby.2010.86.
[76] (a) P. Bjorntorp, The associations between obesity, adipose tissue distribution and disease, Acta Med. Scand. Suppl. 723 (1988) 121–134 89; (b) S. Gesta, Y.H. Tseng, C.R. Kahn, Developmental origin of fat: tracking obesity toits source, Cell 131 (2007) 242–256, https://doi.org/10.1016/j.cell.2007.10.00490.
[77] B. Feng, T. Zhang, H. Xu, Human adipose dynamics and metabolic health, Ann. N. Y. Acad. Sci. 1281 (2013) 160–177, https://doi.org/10.1111/nyas.12009.
[78] B. Cannon, J. Nedergaard, Brown adipose tissue: function and physiological significance, Physiol. Rev. 84 (2004) 277–359, https://doi.org/10.1152/physrev.00015.2003.
[79] E. Bruera, ABC of palliative care. Anorexia, cachexia, and nutrition, BMJ 315 (1997) 1219–1222, https://doi.org/10.1136/bmj.315.7117.1219.
[80] M. Tsoli, et al., Activation of thermogenesis in brown adipose tissue and dysregulated lipid metabolism associated with cancer cachexia in mice, Cancer Res. 72 (2012) 4372–4382, https://doi.org/10.1158/0008-5472.CAN-11-3536.
[81] J. Wu, P. Cohen, B.M. Spiegelman, Adaptive thermogenesis in adipocytes: is beige the new brown? Genes Dev. 27 (2013) 234–250, https://doi.org/10.1101/gad.211649.112.
[82] S. Virtue, A. Vidal-Puig, Adipose tissue expandability, lipotoxicity and the metabolic syndrome – an allostatic perspective, Biochem. Biophys. 1801 (2010) 338–349, https://doi.org/10.1016/j.bbalip.2009.12.006.
[83] P.L. Nguyen, et al., Fatty acid synthase polymorphisms, tumor expression, body mass index, prostate cancer risk, and survival, J. Clin. Oncol. 28 (2010) 3958–3964, https://doi.org/10.1200/JCO.2009.27.0793.
[84] J.M. Fernandez-Real, et al., Extracellular fatty acid synthase: a possible surrogate biomarker of insulin resistance, Diabetes 59 (2010) 1506–1511, https://doi.org/10.2337/db09-1756.
[85] J. Gómez Ambrosi, et al., Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity, Int. J. Obes. 36 (2012) 286–294.
[86] A. Tchernof, J.P. Despr´es, Pathophysiology of human visceral obesity: an update, Physiol. Rev. 93 (2013) 359–404.
[87] N. Stefan, et al., Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications, Lancet Diabetes Endocrinol. 1 (2013) 152–162.
[88] V. Primeau, et al., Characterizing the profile of obese patients who are metabolically healthy, Int. J. Obes. (2011) 35971–35981.
[89] R.P. Wildman, et al., The obese without cardiometabolic risk factor clustering and the normal weight with cardio-metabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004), Arch. Intern. Med. 168 (2008) 1617–1624.
[90] J. Naukkarinen, et al., Characterizing metabolically healthy obesity in weight-discordant monozygotic twins, Diabetologia 57 (2014) 167–176.
[91] P. Marques-Vidal, et al., The association between inflammatory biomarkers and metabolically healthy obesity depends of the definition used, Eur. J. Clin. Nutr. 66 (2012) 426–435.
[92] G. Plourde, A.D. Karelis, Current issues in the identification and treatment of metabolically healthy but obese individuals, Nutr. Metab. Cardiovasc. Dis. 24 (2014) 455–459.
[93] S. Velho, et al., Metabolically healthy obesity: different prevalence's using different criteria, Eur. J. Clin. Nutr. 64 (2010) 1043–1051.
[94] G. Frühbeck, J. Gómez-Ambrosi, J. Salvador, sLeptin-induced lipolysis opposes the tonic inhibition of endogenous adenosine in white adipocytes, FASEB J. 15 (2001) 333–340.
[95] H. Mangge, S. Zelzer, P. Puerstner, et al., Uric acid best predicts metabolically unhealthy obesity with increased cardiovascular risk in youth and adults, Obesity (Silver Spring) 21 (2013) E71–E77.
[96] V. Messier, et al., Metabolically healthy but obese individuals: relationship with hepatic enzymes, Metabolism 59 (2010) 20–24.
[97] J.E. Shaw, et al., Impact of new diagnostic criteria for diabetes on different populations, Diabetes Care 22 (1999) 762–766.
[98] J. Fan, et al., Combined effect of obesity and cardio-metabolic ab-normality on the risk of cardiovascular disease: a meta-analysis of prospective cohort studies, Int. J. Cardiol. 168 (2013) 4761–4768.
[99] G.M. Hinnouho, et al., Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? Diabetes Care 36 (2013) 2294–2300.
[100] C.K. Kramer, B. Zinman, R. Retnakaran, Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis, Ann. Intern. Med. 159 (2013) 758–776.
[101] W. Bakker, et al., Endothelial dysfunction and diabetes: roles of hyperglycemia, impaired insulin signaling and obesity, Cell Tissue Res. 335 (2009) 165–189, https://doi.org/10.1007/s00441-008-0685-6.
[102] Y. Cao, Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic disorders, Nat Rev Drug Discv. 9 (2) (2010) 107–115, https://doi.org/10.1038/nrd3055.
[103] V. Christiaens, H.R. Lijnes, Angiogenesis and development of tissue, Mol. Cell. Endocrionol. 318 (1–2) (2010) 2–9, https://doi.org/10.1016/j.mce.2009.08.006.
[104] M.M. Guerro, Adipose tissue and adipokines: for better or worse, Diabetes Metab. 30 (1) (2014) 13–19.
[105] E. Brakheliem, et al., Angiogenesis inhibitor TNP470 prevent diet induce obesity and genetic obesity in mice, Circ. Res. 94 (12) (2004) 1579–1588, https://doi.org/10.1161/01.RES.0000132745.76882.70.
[106] Y.M. Kim, et al., Assessment of the anti-obesity effects of the TNP-470 analog, CKD-732, J. Mol. Endocrinol. 38 (4) (2007) 455–465, https://doi.org/10.1677/jme.1.02165.
[107] M.A. Rupnick, et al., Adipose tissue mass can be regulated through the vasculature, Proc. Natl. Acad. Sci. U. S. A. 99 (16) (2002) 10730–10735, https://doi.org/10.1073/pnas.162349799.
[108] J. Tam, et al., Blockade of VEGFR2 and not VEGFR1 can limit diet induced fat

tissue expansion: role of local versus bone marrow derived endothelial cells, PLoS One 4 (3) (2009), https://doi.org/10.1371/journal.pone.0004974 e4974.
[109] F.M. Sacks, et al., Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates, N. Engl. J. Med. 360 (2009) 859–873, https://doi.org/10.1056/NEJMoa0804748.
[110] L. Sjostrom, et al., Effects of bariatric surgery on mortality in Swedish obese subjects, N. Engl. J. Med. 57 (2007) 741–752, https://doi.org/10.1056/NEJMoa066254.
[111] D.H. Kim, et al., Rapid and weight-independent improvement of glucose tolerance induced by a peptide designed to elicit apoptosis in adipose tissue endothelium, Diabetes 61 (2012) 2299–2310, https://doi.org/10.2337/db11-1579.
[112] P.M. O'Neil, et al., Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study, Obesity 20 (7) (2012) 1426–1436, https://doi.org/10.1038/oby.2012.66.
[113] K.H. Saunders, Pharmacologic approaches to weight management: recent gains and shortfalls in combating obesity, Curr. Atheroscler. Rep. 18 (7) (2017), https://doi.org/10.1007/s11883-016-0589-y.
[114] A. Cahn, I. Raz, Emerging gliptins for type 2 diabetes, Expert Opin. Emerg. Drugs 18 (2) (2013) 245–258, https://doi.org/10.1517/14728214.2013.807796.
[115] M.N. Hossen, K. Kajimoto, H. Akita, M. Hyodo, H. Harashima, A comparative study between nanoparticle-targeted therapeutics and biconjugate as obesity medication, J. Control. Release 171 (2) (2013) 104–112.
[116] M.N. Hossen, et al., Vascular-targeted nanotherapy for obesity: unexpected passive targeting mechanism to obese fat for the enhancement of active drug delivery, J. Control. Release 163 (2) (2012) 101–110.
[117] Y. Xue, et al., Preventing diet-induced obesity in mice by adipose tissue transformation and angiogenesis using targeted nanoparticles, Proc. Natl. Acad. Sci. U. S. A. 113 (20) (2016) 5552–5557.
[118] M.G. Kolonin, et al., Reversal of obesity by targeted ablation of adipose tissue, Nat. Med. 10 (6) (2004) 625–632.
[119] J. Han, et al., Flavaglines ameliorate experimental colitis and protect against intestinal epithelial cell apoptosis and mitochondrial dysfunction, Inflamm. Bowel Dis. 22 (1) (2016) 55–67.
[120] C. Basmadjian, et al., Flavaglines: potent anticancer drugs that target prohibitins and the helicase eIF4A, Future Med. Chem. 5 (18) (2013) 2185–2197.
[121] N. Thovhogi, et al., Targeted delivery using peptide-functionalized gold nanoparticles to white adipose tissues of obese rats, J. Nanopart. Res. 17 (2) (2015) 11.
[122] D. Bobo, et al., Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date, Pharm. Res. 33 (10) (2016) 2373–2387.
[123] A.C. Anselmo, S. Mitragotri, Nanoparticles in the clinic, Bioeng. Transl. Med. 1 (1) (2016) 10–29.
[124] G. Pillai, Nanomedicines for cancer therapy: an update of FDA approved and those under various stages of development, SOJ Pharm Sci. 1 (2) (2014) 13.