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Review

How the association between obesity and inflammation may lead to insulin resistance and cancer

Mohammad Nurul Amin [a, b], Md. Saddam Hussain [a], Md. Shahid Sarwar [a], Md. Mizanur Rahman Moghal [c], Abhijit Das [a], Mohammad Zahid Hossain [d], Jakir Ahmed Chowdhury [e], Md. Shalahuddin Millat [a], Mohammad Safiqul Islam [a, *]

[a] Department of Pharmacy, Noakhali Science and Technology University, Sonapur, Noakhali, 3814, Bangladesh
[b] Department of Pharmacy, Atish Dipankar University of Science and Technology, Sonapur, Uttara, Dhaka, Bangladesh
[c] Department of Pharmacy, Mawlana Bhashani Science and Technology University, Santosh, 1902, Tangail, Bangladesh
[d] Department of Pharmacy, State University of Bangladesh, Dhanmondi, Dhaka, 1206, Bangladesh
[e] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka, 1000, Bangladesh

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ABSTRACT

Background and objectives: Obesity is associated with metabolic dysfunction and over nutrition. Increased body mass index and obesity are strongly amalgamated with changes in the physiological function of adipose tissue, leading to altered secretion of adipocytokines, inflammatory mediators release as well as chronic inflammation and insulin resistance. The purposes of this study were to review the evidence of how obesity and inflammation may lead to insulin resistance and cancer.

Summary: Recent findings suggested that increased level of inflammatory mediators in obesity, plays an introductory and cabalistic role in the development of different types of inflammatory disorders including type 2 diabetes mellitus. Link between elevated body mass index and type 2 diabetes mellitus (T2DM). Several of the factors—such as increased levels of leptin, plasminogen activator inhibitor-1, decreased levels of adiponectin, insulin resistance, chronic inflammation etc. consequently result in carcinogenesis and carcinogenic progression too.

Conclusion: This review summarizes how cytokine production in adipose tissue of obese subject creates a chronic inflammatory environment that favors tumor cell motility and invasion to enhance the metastatic potential of tumor cells. High levels of cytokine in the circulation of affected individuals have been associated with a significantly worse outcome. This article also reconnoiters the mechanisms that link obesity to numerous disorders such as inflammation, diabetes, cancers and most specifically combine these processes in a single image. Understanding these mechanisms may assist to understand the consequences of obesity.

1. Introduction

Excess accumulation of adipose tissue is known as obesity [1]. Normally obesity may be defined as a state of positive energy balance leading to increase in adipose tissue mass. Increased adipose tissue mass is closely related to the changes in the size or number of adipocytes and these cells are good sources of energy consisting of 80% lipid and 20% of water and protein [2,3]. Hypertrophy and hyperplasia of the adipocytes are the main two ways that can increase the adipose tissue mass [2]. Adipogenesis may be described as the formation of adipocytes from preadipocytes; which are the fibroblast-like precursor cells. It is an important regulatory process involved in the development of obesity. These newly developed cells can further increase in size by accumulating more lipid droplets or can increase in cell number, when deplete their own storage capacity. Thus, both increase in cell number (hyperplasia) and cell size (hypertrophy) may easily contribute to adipose mass. Thus, adipogenesis is a continuous process which occurs throughout the lifetime in response to normal cell turnover [4].

In mammals, two available types of adipose tissue are white adipose tissue (WAT) and brown adipose tissue (BAT). They are

* Corresponding author.
E-mail address: research_safiq@yahoo.com (M.S. Islam).

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different in functions, localization and cellular composition [5]. BAT consists of an uncoupling protein named thermogenin or uncoupling protein (UCP)-1 which contributes to thermogenesis [6]. WAT reserves energy as triacylglycerols. Majority of adipose tissues are WAT in human body that is present as subcutaneous or visceral fat. Thus human body can store limitless amount of fat [3]. World Health Organization (WHO) has suggested three classifications of obesity utilizing the body mass index (BMI) which is calculated by dividing weight in kilograms by height in meter square [7]. People with a BMI greater than 25 are considered overweight (class I), Individuals with a BMI greater than 30 are obese or of class II, and those with a BMI over 40 are considered morbidly obese, and have an increased risk of death [7].

In recent times, obesity is the most frequently encountered metabolic disease all over the world and its incidence is rising rapidly [8,9]. Unfortunately, obesity is rapidly becoming pandemic in the developed world1 as well as in many developing nations [10]. Overweight and obese individuals are at an increased risk of developing various chronic disorders [11]. Recent study explored that 1 in 4 adults in the United States is considered obese [12]. According to WHO, there will be about 2.3 billion overweight people aged 15 years and above, and over 700 million obese people worldwide in 2015 [13]. It was recently recommended that overweight is a common condition in Western nations [14]. Moreover, it is observed that the frequency of obesity is highest in the USA, Europe and lowest in East Asia and sub-Saharan Africa [15]. Actually obesity is such a condition in which energy intake exceeds energy expenditure [16]. It is a complex disease caused by various factors including genetic, diet, lifestyle and environmental factors [17]. The danger of obesity is very fearful throughout the world because it occurs in people of almost all aged, even in children and adolescents [18,19].

It has been considered as one of the serious global health problems which has close association with various types of diseases including cardiovascular disease [20], type 2 diabetes [21,22], hypertension, dyslipidemia, liver disease and also several types of cancer [21,23,24]. Recent data indicates that some forms of obesity are commonly associated with chronic low-grade inflammation [25]. We present here a broad overview to develop the mechanisms that link obesity to inflammatory disorders, diabetes and cancers.

2. Overview of adipose tissue and adipokines

Adipose tissue is essential for the life of mammals. It represents the main source of free fatty acid (FFA) in the postprandial fasting state for energy use and heat production [26]. Adipose tissue is considered as an endocrine organ which secretes a number of peptides named adipokines. These adipokines involve in many bodily functions including inflammation, thermoregulation, atherosclerosis, angiogenesis, blood pressure regulation and so on [27]. Precisely, they work as a network to regulate various functions of human body locally and systemically [28]. Few adipokines are interleukin (IL)-6, IL-8, IL-1β, vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α) [29]. Excretion of different adipokines and some related hormones, including leptin, adiponectin (ApN) and insulin are altered in obesity [30]. Adipokines play a vital role in many patho-physiological events. For example, TNF-α, IL-6 and leptin can induce insulin resistance, whereas adiponectin stimulates insulin sensitivity. Besides, Galletti et al. [31] has found circulating leptin as an important link between central obesity, hypertension and metabolic syndrome. Some results from an Italian prospective study emphasized that higher circulating plasma leptin levels are an important predictor of the risk of metabolic syndrome and high blood pressure [31]. Normally, adiposity contributes to the inflammatory process in patients with obesity. Abnormal levels of various adipokines and metabolites from adipose tissue trigger monocytes. Thus, inflammation-related adipokines called 'inflammatory cytokines' are increased due to activated monocytes. Adipose tissue contains energized macrophages that produce many inflammatory cytokines together with adipocytes. These inflammatory cytokines are leptin, ApN, TNF-α, IL-1 andIL-6 etc. [32].

Several studies have reported that circulating adipokines increase the risk of different types of cancer, including cancers of the colon, kidney, esophagus and breast [33]. The effect of adipokines on atherosclerosis, inflammation and insulin sensitivity may provide a link between adiposity and development of various types of obesity-related cancers [34].

3. Relationship between obesity and inflammatory disorders focusing on adipokines as casual factor

Obesity-induced inflammation or inflammatory disorder is a major feature of adipose tissue dysfunction [35]. Actually, adipose tissue is not only a depot for storage of excess energy in the form of TAG (triacylglycerols), but also an active endocrine organ secreting different peptides called adipocytokines [36]. Adipocytokines produce several types of peptides, hormones and other molecules that affect cardiovascular system, not only in an endocrine mechanism but also by autocrine and paracrine manner [37]. This might lead to adipocytokine-induced systemic inflammation, atherosclerosis and inflammatory changes in the liver [32]. It is likely that inflammation promoted by obesity or obesity related cytokine, accelerates the atherosclerosis and this atherosclerosis is responsible for many types of cardiovascular disease (CVD) including heart disease and vascular disease etc. [32]. The production and expression of inflammatory adipokines, such as IL-6, TNF-α and monocyte chemoattractant protein 1 (MCP-1) have been shown to be raised in obese and insulin-resistant subjects [38]. Visceral fat appears to secrete several adipocytokines more than subcutaneous one, and an increased abdominal adiposity in obese subject renders this individual more prone to cardiovascular and metabolic problems [39]. Adipose tissue in obese subjects has been shown to be inflamed by inflammatory macrophages compared to lean counterparts [40,41]. Macrophages are considered to be the significant and key contributors of adipocyte inflammation [42]. Inflammatory macrophages accumulate normally within adipose tissue and such accumulation is responsible for local inflammation. This local inflammation is responsible for different metabolic disorders including atherosclerosis and systemic inflammation [32]. Moreover, macrophages are also well known to secrete cytokines. These cytokines directly reach the liver and can create hepatic inflammation [43]. Furthermore, systemic inflammation is closely related to endothelial dysfunction, which may be an essential marker of atherosclerotic process. Thus, endothelial dysfunction may play a critical role in the development of a chronic inflammatory disorder such as atherosclerotic CVD [32]. Obesity, hypercholesterolemia, diabetes, hypertension, and smoking etc. are well known atherogenic risk factors [44].

Over and above, there is an association between higher BMI and subclinical inflammation. Recent study has described that leptin promotes cholesterol uptake by macrophages. Then, it triggers the development of atheromatic lesions. Hypo-adiponectinemia in obese individual may also contribute to endothelial dysfunction and proatherogenic effects [32,45]. Finally, increased secretion of proinflammatory adipocytokines such as IL-6, IL-1, and TNF-α, by adipose tissues, sustains inflammation of vascular wall and stimulates pro-atherogenic gene expression [46].

Besides, C-reactive protein (CRP) is another inflammatory marker, Serum levels of which are raised in individuals with a

higher BMI [47]. Epidemiologic studies have described CRP as an independent predictor of stroke, peripheral arterial disease, sudden cardiac death and myocardial infarction [48,49]. Again, several studies verified that value of hsCRP helps to predicting incident of myocardial infarction (MI) and stroke [50–52]. Most research, but, suggest that high-sensitivity C-reactive protein (hsCRP) is a more powerful marker for Myocardial Infraction than stroke [53]. The courting of hsCRP to vascular results may rely upon the population studied, which include medical, behavioral threat factors, ethnic and age differences [54–57]. Thus, high-sensitivity C-reactive protein (hsCRP) characterizing underlying inflammatory disorders such as., stroke, vascular events, and mortality in a prospective cohort study.

An apolipoprotein which is found in mammalian liver known as serum amyloid A (SAA), also an important marker of inflammation [58]. Levels of SAA are positively linked with BMI. SAA is expressed normally in both the liver and adipose tissue. There is an association between SAA and some metabolic disorders like insulin resistance, diabetes and metabolic syndrome [32]. Moreover, resistin is recently identified as another adipokine, which is a significant marker for atherosclerosis. Obese individuals contain higher levels of resistin than slim subjects. The levels of resistin are changed with changes in the BMI ′ In summary, all the previous studies support the significant role of some major adipocytokines in the development of inflammatory disorders and summary of these studies have been shown in Fig. 1.

4. Relationship between obesity and type 2 diabetes mellitus

Obesity has a complex relationship with diabetes mellitus (DM), especially with type 2 diabetes mellitus (T2DM) [59]. Obesity may be a precursor or risk factor for T2DM, following insulin resistance [60,61]. Nowadays, T2DM in children and adolescents is a public health problem worldwide. The alarming rates of youth T2DM, parallel the escalating rates of obesity, which is a risk factor affecting insulin sensitivity [62]. A few studies have developed a link between insulin resistance and intra-abdominal fat accumulation (visceral obesity) [63]. Visceral adiposity is suggested as a

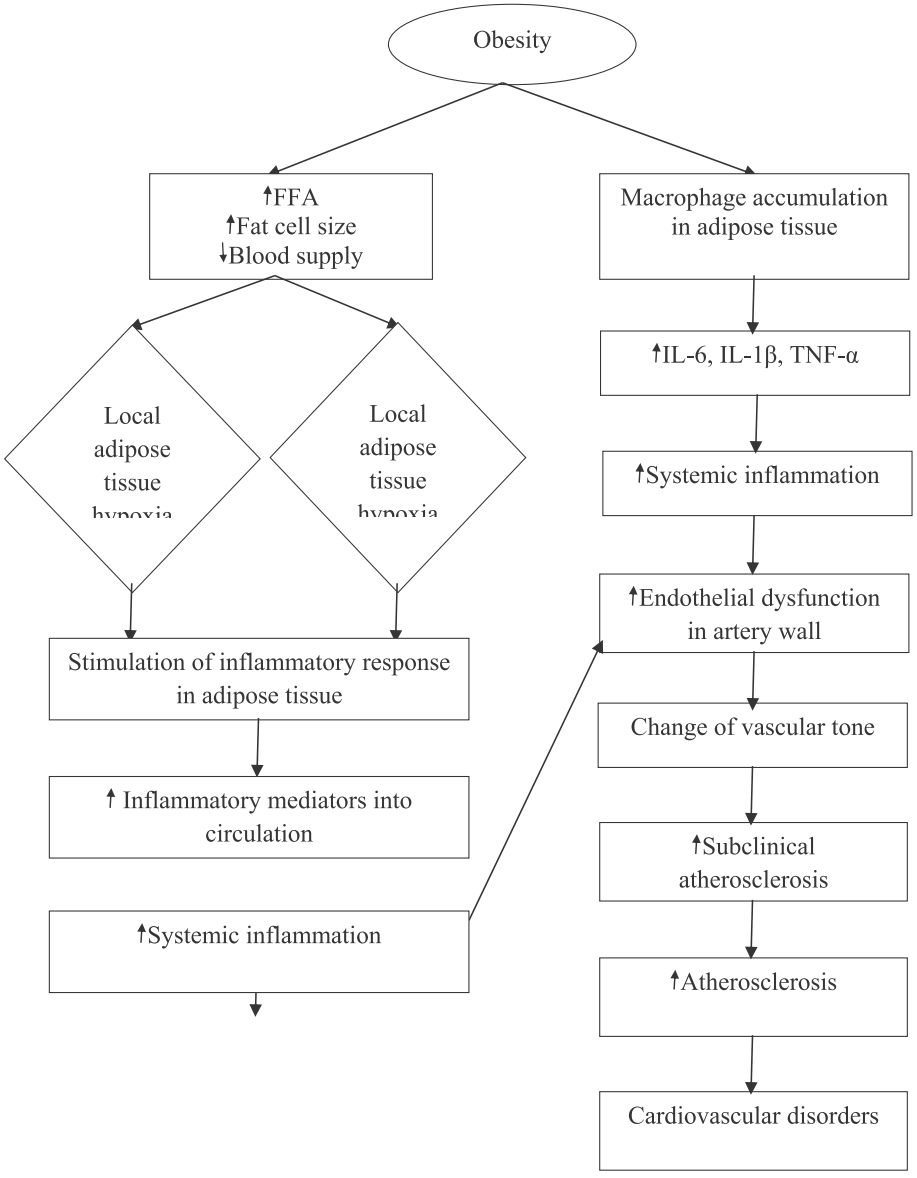

Fig. 1. Mechanisms of inflammation induced by obesity.

risk factor for T2DM in adults too [64]. Adipokines and hormones released by the visceral adipocytes, induce the insulin resistant condition and the chronic inflammatory state that goes frequently along with visceral obesity or visceral adiposity [65]. Visceral adiposity is also a risk factor for insulin resistance in children. Due to insulin resistance, children with adiposity can be affected by metabolic disorders and hypertension [66]. Visceral fat shows promoted lipolytic activity with high release of FFA, which may adversely affect the action of insulin. In most obese individuals, plasma levels of FFA are raised, which has been shown to have a significant and key contributing role in the pathogenesis of insulin resistance [66].

Adipocytes release a number of adipokines such as leptin, adiponectin, resistin and visfatin, as well as cytokines and chemokines including TNF-α, IL-6, and monocyte chemoattractant protein-1; all of which also show essential roles in the pathogenesis of diabetes, inflammation and atherosclerosis [66]. The release of adipokines by adipose tissue leads to a chronic sub inflammatory condition that could play a key role in the development of insulin resistance and T2DM [67]. Subcutaneous fat is mainly responsible for almost 80% of total leptin production. It is expressed and even produced exclusively by WAT. In adipose tissue, TNF-α and IL-6 are expressed [66]. Insulin signaling is inhibited by these cytokines and TNF-α may show a role in the systemic insulin resistance of T2DM [68,69]. TNF-α also decreases the tyrosine kinase phosphorylation of insulin receptor. This negatively affects the insulin signaling, resulting in insulin resistance. Furthermore, elevated levels of CRP in obese subjects are strongly related to insulin resistance [66]. Adiponectin, a protein, highly expressed in adipose tissue, may be the molecular association between obesity and insulin resistance. Visfatin is a newly discovered adipocyte hormone, expressed in visceral fat. This contains a direct relation with T2DM [70]. Finally, all the previous studies support the significant role of some major adipokines, cytokines and chemokines in the development of T2DM and all these findings summarized in Fig. 2.

5. Relationship between obesity and cancer

The prevalence of obesity among children, adolescents and adults has been increasing during the last decades (Fig. 3). The World Health Organization calculates that there are more than 1.6 billion overweight adults in the world and approximately 400 million of these are obese. Thus, obesity has been recognized as one of the major health hazard and this health problem is linked to several types of cancer [71]. Adipose tissue secretes adipokines or inflammatory molecules into the bloodstream. Among them leptin, adiponectin and other pro-inflammatory molecules are major contributors in the development of various cancers [72].

6. Obesity and breast cancer risk

Breast cancer is a common type of cancer throughout the world. Risk of developing breast cancer is increased in obese postmenopausal women [73]. Lorincz et al. [73] have proposed some hypotheses in 2006 to describe the association of postmenopausal breast cancer with obesity. According to one hypothesis, the cause of this association is the elevated estrogens level in circulation in obese postmenopausal women [73]. In postmenopausal women, estrogen biosynthesis occurs normally in adipose tissue of the thighs, breast, and buttocks. Estrogens level in circulation increases with BMI which support the hypothesis that circulating estrogens may be an important factor in breast cancer risk in postmenopausal women [73]. Thus, estrogen plays a significant role in the progression of breast cancer. Moreover, an increased expression of estrogen receptor (ER) in human mammary epithelial cells (HMECs) accelerates the risk of breast cancer [74]. Recent study reports that stimulation of the ER (ER-alpha) is a mitogenic signal in breast epithelial cells. As estradiol is a ligand of the ER receptor, so binding of ER by estradiol produces more pronounced cell proliferation [75].

Insulin resistance is a common pathological condition in individuals with obesity where insulin action is impaired in adipose tissue. During insulin resistance, insulin is markedly increased in circulation to avert hyperglycemia [76,77]. So, insulin is included as a hormone which is frequently increased in conditions of obesity [77]. This hyperinsulinemia is correlated with BMI [78]. Furthermore, insulin increases serum levels of the structurally similar but more potent substance—insulin like growth factor (IGF)-1, thereby

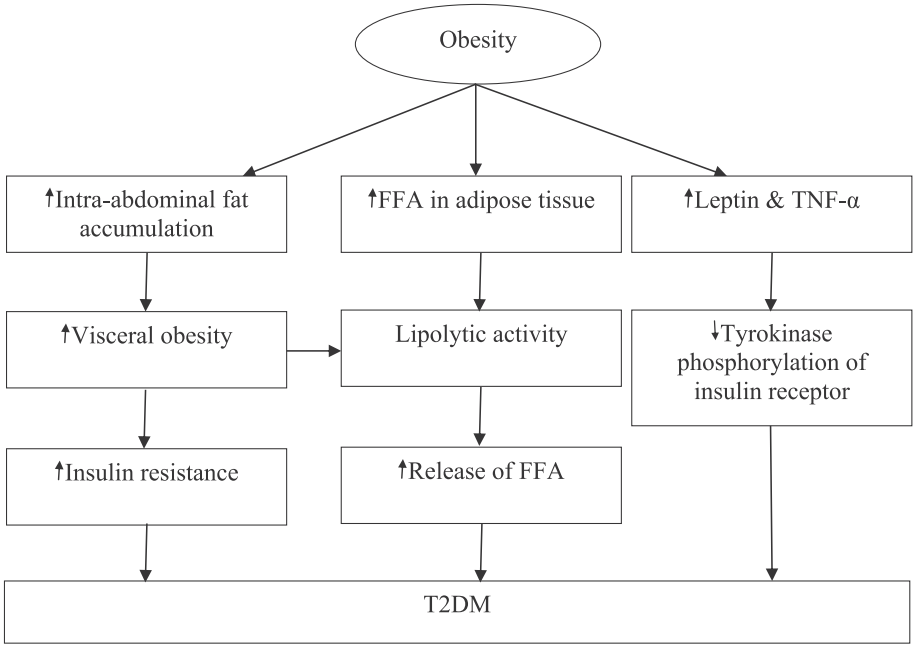

Fig. 2. Relationship between obesity and T2DM.

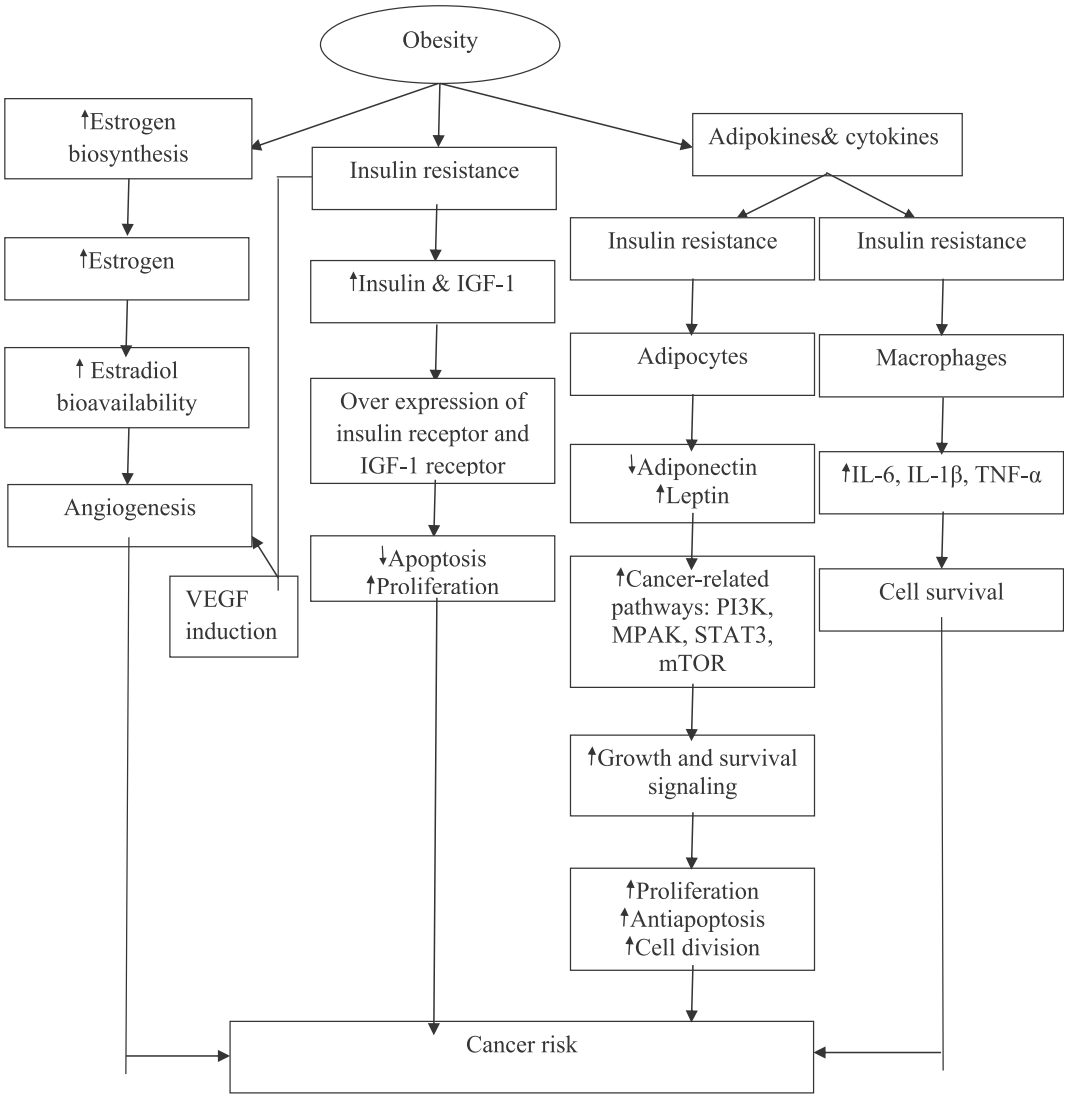

Fig. 3. Relationship between obesity and cancer.

acting indirectly via the IGF/IGFR system which is present on most cells throughout the human body. Current studies suggest that IGF receptor (IGF-1R) is normally over expressed in breast cancer cells and activation of IGF-IR results in a chain of events, leading to cell proliferation and inhibition of apoptosis. Hence, elevated circulating serum levels of both IGF-1 and insulin increase breast cancer risk [75]. These statements also supported by a meta-analysis which suggested that risk of breast cancer in premenopausal women increases with high IGF-I levels [79]. Again, recent meta-analysis data indicates that IGF-1 CA19 repeat polymorphisms are unlikely to be a major determinant of susceptibility to cancer [80].

Lorincz et al. described that adiposity may influence tumor growth. MCF-7 cells (breast cancer cells) proliferation and migration may be stimulated by adipocyte-secreted factors [74]. Cytokines or adipokines secreted by adipocyte include leptin, IL-6, IL-8, IL-1β, TNF-α, VEGF, chemokine (C–C motif) ligand 2 (CCL2), and CCL5. Leptin may contribute to an increased risk of breast cancer in patients with obesity. Leptin expression is more common in human breast cancer lines and mammary tumors. It stimulates the growth of cancer cells from the breast [72,75,81,82]. Elevated leptin levels can stimulate multiple signaling pathways, including phosphoinositide3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT3), and mammalian target of rapamycin (mTOR) [82]. Several current studies demonstrate a strong link between pro-inflammatory cytokines and breast CSCs (cancer stem cells). For example, IL-6, IL-8 and leptin have recently been shown to stimulate breast CSC growth and survival [82]. One study documented that leptin may also play a role in the proliferation of MCF-7 by MAPK signaling pathways activation [73]. Leptin also can collaborate with IGF-1 to increase cell proliferation through activation of ER [73,75].

Besides, adiponectin (ApN) decreases cell proliferation and promotes apoptosis in both estrogen-sensitive and estrogen-insensitive breast cancer cells. This growth-inhibitory action of ApN may be due to adiponectin-induced expression of certain apoptotic genes [75]. Plasma levels of ApN are reduced in obesity [83]. ApN exerts its anti-carcinogenic effects through its two receptors, namely AdipoR1 and AdipoR2 [35,73]. In vitro, ApN decreases the growth of several cell lines of breast cancer and promotes apoptosis. ApN also has been shown to reduce tumor angiogenesis in in vitro experiments. Thus, the reduced levels of ApN may be associated with the risk of breast cancer in obesity [35]. Adiponectin is an insulin-sensitizing hormone produced with

the aid of adipocytes, which had been confirmed to be positively related to breast most cancers risk [84,85] and negative consequences in women with early breast cancer [86]. Collectively, this evidence leads to the hypothesis that adiponectin may act as a molecular mediator linking excess adiposity with carcinogenesis [87]. We lately found that low stages of adiponectin in premenopausal women at excessive chance for breast cancer elevated the risk of breast neoplastic occasions with the aid of 12% [88]. Linking of adiponectin to breast cancers became first pronounced by Miyoshi et al. [89]. Who suggested that low serum adiponectin level had been associated with a multiplied breast cancers chance and probably with a greater aggressive breast cancers phenotype. Over the beyond decade, many authors have investigated the association among adiponectin and breast cancer in case-control [90–105]. Most of the studies replicates the role of circulating adiponectin as a biomarker of breast cancer risk.

Alongside, IL-6, serves as an antiapoptotic factor. It stimulates the progression of breast cancer by directly promoting the biosynthesis of estrogen [73]. TNF-α is another key regulator of estrogen biosynthesis and IL-6 synthesis [73]. PAI-1 (plasminogen activator inhibitor-1) is also an adipokine. It's over expression is found in different types of cancer like colorectal, renal, breast, prostate and endometrial cancer [73,106].

7. Obesity and prostate cancer risk

Prostate cancer (PC) is the most common cancer in elderly male populations of western countries. Its incidence increases quickly in men over 50 years of old [107]. Several recent studies report positive associations between adiposity and prostate cancer risk. Obesity is positively associated with a metabolic condition, characterized by elevated levels of insulin, IGFs and various cytokines. These three elevated factors are thought to raise the risk of developing high-grade prostate cancer [107]. One research indicates that adipocytes may secrete biological compounds that act to promote carcinogenesis in nearby prostate cells. As in breast cancer, the proper development of prostate cancer seems to be closely related with hormones and signaling molecules that are also implicated in obesity. These biological compounds are testosterone and various adipokines such as leptin, IL-6 and adiponectin [107].

Serum levels of testosterone are normally reduced in obese individuals. This observation is due to increased conversion of androgens to estrogen via aromatase activity within the adipocytes. That is how, the presence of excess adipose tissue in obese subjects creates imbalanced levels of circulating androgens [75,108]. Actually, there is a complex biological association between sex hormones and obesity. The processes involved in this association are also unclear [109]. Recent study has explored an association between testosterone and PC [110].

Sidewise, most obese individuals have some degree of insulin resistance and this is closely related with elevated levels of circulating insulin [72]. It is also documented that obesity is associated with increased level of circulating IGF, which act as mitogens. IGF family consists of two polypeptide ligands, IGF-I and IGF-II, two membrane-bound receptors, IGF-IR and IGF-IIR, and six insulin-like-growth factor binding proteins (IGFBPs), as well as IGFBP proteases. Ligands IGF-I and IGF-II may synergize with other factors to create mitogenic affects [73]. The effect of IGF seems to be important in various cancers, as transgenic expression of Igf1 or Igf1r in mice promotes the development of skin cancer [111] and prostate cancer [112]. It is suggested that elevated levels of IGF1 or IGF2 in human may definitely contribute to the risk of cancer, as higher levels of IGFs have been associated to an increased risk of prostate cancer [113].

It has been demonstrated that different adipokines may also play a critical role in the development of prostate cancer. Systemic leptin induces anti-apoptotic activity. Expression of various growth factors such as VEGF are also accelerated by leptin in prostate cancer cells. Thus, the risk of prostate cancer is closely related to high levels of circulating leptin [114,115]. Further investigation asserts that mitogenic effects of systemic leptin may be produced through the phosphoinositide-3 kinase (PI3K) and MAPK pathways [106]. According to in vitro studies, leptin induces the proliferation of PC cell lines [107]. In addition to leptin, numerous in vitro and in vivo models have also demonstrated mitogenic activities of IL-6. IL-6 stimulates cell proliferation in LNCaP and MDA PCa 2b PC cells [67,108]. Thereto, one study found a negative link between plasma adiponectin and PC [107]. As in breast cancer, it is observed that adiponectin may also show a protective role in PC. So, it is not surprising that individuals with PC exhibit decreased plasma levels of adiponectin [109].

8. Obesity and colon cancer risk

Colon cancer is the third most available cancer in the world. Incidence rates of this cancer are approximately 10-fold higher in developed than in developing nations [110]. Excess adipokines secreted from adipose tissue during obesity can directly influence colonic dysplasia because adipokines such as IL-6, leptin, and adiponectin modulate tumorigenesis in several models of colon cancer in a paracrine fashion [111]. A possible relation between excess body weight and colon cancer risk has been examined by experts in many epidemiological and cohort studies which have documented that obesity is closely related with a higher risk of colon cancer [112–114]. A concrete body of evidence illustrates that leptin signaling might be positively involved in the development of colon cancer risk. Data from a study detected an almost 3-fold increased risk of colorectal cancer among people having high leptin levels [115]. A case–control study with Japanese women also reported that serum levels of leptin increased the risk of colon cancer [116]. Numerous in vitro experiments have proposed an important mitogenic activity of leptin in colonic epithelial cells [117,118]. More than that, the receptor of leptin is over expressed in human colon cancer cells [119]. In Caco-2, HT-29 and T-84 colon cancer cell lines, leptin potentiates proliferation and anti-apoptotic activity [120–122]. Leptin can stimulate proliferation through the activation of the NF-κB (nuclear factor κB) dependent pathways [117,118]. Increased levels of the proinflammatory cytokine, IL-6 during obesity may positively regulate cell proliferation and stimulate anti-apoptotic activity of premalignant intestinal epithelial cells. Current study asserts that reduced serum levels of IL-6 are directly associated with the reduction of colorectal cancer in obese rats [123,124]. Furthermore, as in breast and prostate cancer, decreased concentration of adiponectin in obesity may increase cancer risk [67] and plasma adiponectin levels are reduced in obese subjects [35]. Clinical studies demonstrate an inverse link between serum adiponectin levels and the risk of various cancers such as endometrial and colorectal cancer [35]. Hence, it has been suggested that upregulation of adiponectin might be of therapeutic use in the treatment of some cancers [125]. Another adipokine, PAI-1 induces angiogenesis and tumor growth. Its over expression is found in different types of cancer like endometrial and colorectal cancer [35,126,127]. However, PAI-1 has been shown to be a strong regulator of both vascular cellular migration in vitro angiogenesis and in vivo tumor growth. PAI-1 can either promote or inhibit tumor growth and angiogenesis [128]. Low concentrations of PAI-1 can stimulate tumor angiogenesis while treatment of animals with excessive doses of PAI-1 inhibits angiogenesis and tumor growth [129]. Hence, PAI-1 seems to have a multifunctional position in regulating the tumor growth. Therefore, in cancer therapy,

inhibition of the levels of PAI-1 in certain individuals might be a target to treat cancers [130].

9. Obesity and liver cancer risk

Liver cancer is another common cancer in the world. Its incidence is increasing day by day and hepatocellular carcinoma (HCC) has risen to become the third leading cause of cancer death [131,132]. Obesity has been established by numerous clinical studies as a significant risk factor for liver disorders. A prospective mortality study reported that high BMI was related with higher rates of liver cancer-related death. Compared to subjects with normal BMI, the risk of mortality from liver cancer was 1.68 and 4.52 times higher in women and men respectively, with BMI >35 kg/m2.133 Similarly, results obtained from UNOS (United Network of Organ Sharing) database on all liver transplantation from 1991 to 2000 carried out in the United States showed that the incidence of HCC in individuals undergoing liver transplantation was 3.4% with a slightly higher prevalence among obese subjects at 4.0%. Furthermore, in this research obesity was confirmed to be an independent and significant risk factor for HCC in patients with alcoholic cirrhosis and cryptogenic cirrhosis [134].

Insulin resistance in obesity increases risk for cancers [67]. By up-regulating the receptors of growth hormone (GH), insulin increases the production of IGF-1 in liver [135]. IGF-1 enhances cancer development through binding to its receptor named IGF-1 receptor (IGF-1R). IGF-1 also stimulates anti-apoptotic activity through few signaling systems, including the PI3−K-AKT system and the MAPK systems [136]. Interestingly, in some neoplasms or tumors, the IGF-1 receptors are expressed highly. So, definitely these tumors may be stimulated by IGF-1 [137,138]. Over expression of IGF/IGFR has been observed in liver cancer [67]. Jenifer et al. in 2010 found the higher levels of IGF in liver tumors [67].

10. Obesity and other cancer risk

According to recent findings IARC identifies eight additional cancer sites linked to overweight and obesity such as cancers of endometrial, esophageal, thyroid, mammary gland, colon, liver, pancreas, skin, ovaries, and pituitary gland. According to cohort and case-control studies obesity increases the risk of endometrial and esophageal cancer [63]. In fact, the development of endometrial cancer risk is about 2−3-fold higher in obese women than in slim women [139]. As in breast cancer, the potential mechanism for the increase of endometrial cancer risk linked with obesity is the increase in systemic estrogens. High BMI may be closely associated with pancreatic cancer risk in men and women, as reported by Calle et al. in 2004 [140]. Moreover, high BMI is strongly related to gastroesophageal reflux and frequent reflux is directly and positively associated with esophageal adeno-carcinoma. Thus, the developed gastroesophageal reflux itself is considered to be a risk factor for esophageal cancer [141,142].

Actually, various types of adipokines are directly related to almost all types of cancer. Bianchini et al. [33]. Described systemic adipokines to be important contributing factors for increased risk of many types of cancer, including cancers of kidney, esophagus and so on. For example, leptin is an adipokine which positively affects various tumorigenic pathways. It exerts its effects by inducing endothelial cell hyperplasia and suppressing apoptosis. Besides, increased cell proliferation is strongly related with leptin in many types of cancer including prostate, ovary and lung cancer. Increased pathway activation by leptin is also found in cancers such as colorectal, pancreatic, ovarian and lung cancer [67]. Also, there is a close relation between high leptin levels and endometrial cancer [143,144]. Recently, a study has demonstrated that leptin proliferate the cells of endometrial cancer through activation of cyclooxygenase (COX) enzyme named COX-2 [145]. Many authors also suggested a positive link between leptin and esophageal adenocarcinoma. In vitro studies found that leptin promotes the proliferation of human esophageal cancer cells (OE-33, OE-19, KYSE-410) by activating epidermal growth factor receptor system and reducing apoptosis [146].Thus, leptin may have a significant role in the promotion of different tumor growth. High levels of PAI-1, another adipokine, has been observed in many obesity-related cancer, such as endometrial, colorectal, thyroid, renal, prostate cancer and so on [35]. Elevated serum levels of IL-6 were also found in individuals with cancers of the gastrointestinal tract, lymph nodes, skin, lung, pancreas, ovary, prostate and kidney [67]. In summary, all the previous studies support the significant role of few major adipokines in the control of growth and proliferation of several types of cancers. Besides, over expression of IGF/IGFR, hyperinsulinemia and insulin resistance increase risk for cancers too. Over expression of IGF/IGFR was obtained in cancers of the colon, stomach, pancreas, lung, thyroid and ovaries [147].

11. Overview of all synoptic mechanism in one feature

Obesity can be characterized by primary deposition of triglycerides in subcutaneous adipose tissue, the increase of which can result in insulin resistance and limit further subcutaneous lipid accumulation, according to several epidemiological studies (Fig. 4). Subsequently, these triglycerides divert to visceral fat depot [58,148]. Visceral fat increases the release of free fatty acids (FFA), resulting in accelerated lipolytic activity. Insulin action and glucose disposal can be affected in several tissue alternatively. This phase can also leads to stimulation of inflammatory mediators release into circulation, turning into systemic inflammation too [58,149−153]. Diabetes is itself an inflammatory condition where inflammation, the key regulator to the pathogenesis of diabetes mellitus, is deliberated to be associated with adipose tissue enlargement and increased adipose tissue macrophages [135,154−156]. Consequent increase of macrophages are accountable for all adipose tissue tumor necrosis factor-α (TNF-α) expression, altered amount of interleukin-6 (IL-6); along with other proinflammatory cytokines [156−159]. Increased level of cytokines including IL-6, IL-12, TNF- α etc. can cause hepatic production and secretion of acute-phase proteins such as C-reactive protein (CRP), amyloid-A, 1-acid glycoprotein, haptoglobin and plasminogen activator inhibitor-1 (PAI-1). Early stages of diabetes are characterized by these proteins and play role in disease progression as well [160−163]. Thus proinflammatory cytokines play the vital role in elevated risk of diabetes [161,162]. In case of interference, in regular activity of insulin for regulating inflammation as well as proinflammatory transcription factors by insulin resistance, the inflammatory process may be upregulated by activated correlated genes. Hyperinsulinaemia, the hallmark of pathological conditions of insulin resistance, is considered to have role in tumor initiation and progression. Chronic hyperinsulinaemia enhance the bioavailability of insulin-like growth factor 1 (IGF-1) by the retrenchment of hepatic gene expression and IGFBP-1 and IGFBP-2 protein production, in insulin-resistant subjects. Recent epidemiological and clinical evidences point to that, hepatic synthesis of sex-hormone binding globulin (SHBG) is inhibited by insulin and IGF-1. These hormones stimulate the overian synthesis of sex steroids, estradiol and testosterone in circulation. This can promote cellular proliferation and inhibit apoptosis, in breast epithelium and endothelium. Moreover, overproduction of reactive oxygen species (ROS), which can cause the damage of DNA, contributing to mutagenesis and carcinogenesis, also promote the cancer risk in insulin resistant subjects [160,164].

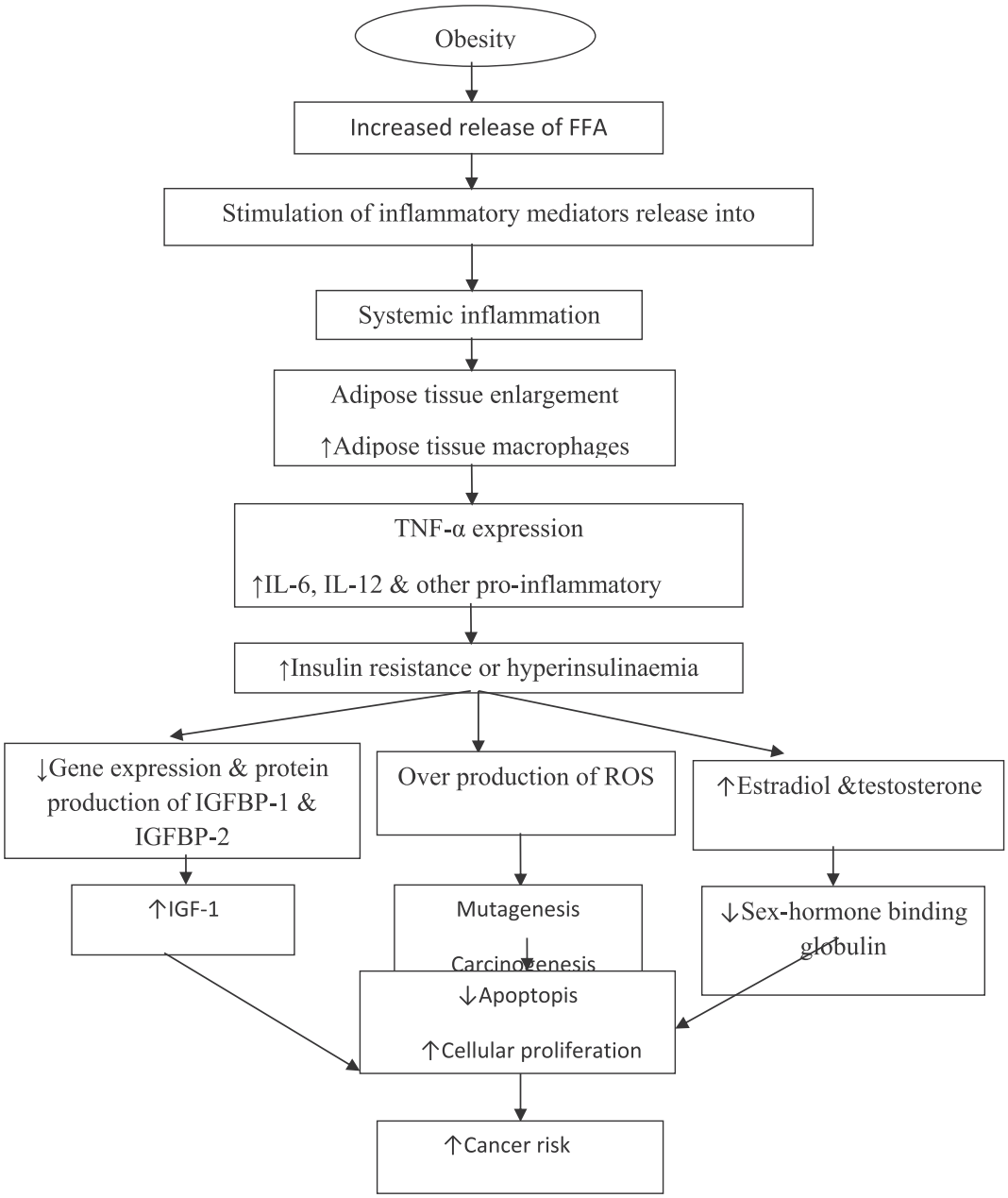

Fig. 4. Physiognomy of adjoining obesity to inflammation, diabetes and cancer.

12. Conclusion

The incidence of obesity has significantly increased worldwide during recent decades. Normally, visceral obesity plays a vital role in the development of T2DM by mobilizing FFAs and stimulating insulin resistance. Besides, obesity and obesity-related disorders constitute a serious threat to the health of all populations on earth. Obesity is responsible for diseases including cancers, atherosclerosis, CVD and diabetes where inflammation plays a significant role in the pathogenesis. Actually, adipose tissue plays a crucial role in carcinogenesis, by secreting inflammatory cytokines. Numerous epidemiological data report that hyperinsulinaemia has a significant contribution in the neoplastic transformation process. Currently, many theories suggest that a combination of factors released by the adipocyte, such as increased leptin, inflammatory cytokines and decreased adiponectin secretion, result in the increased incidence of cancer risk. Attempts to reduce increased insulin sensitivity and adiposity, may have positive effects in decreasing the incidence of cancer risk. Besides, development of various obesity-related diseases can also be reduced by controlling the bioavailability of at least few adipokines, such as IL, adiponectin and leptin in obesity. Administration of exogenous adiponectin may counteract the obesity related consequences [165,166]. Inhibition of certain levels of leptin receptors by mutant leptin or monoclonal antibodies might be an additional alternative strategy. Other possible way might be the reduction of the receptors of inflammatory cytokines through the appropriate use of their agonists. Besides, lifestyle changes and therapeutics that may reduce adiposity could offer the benefit of preventing obesity-related morbidity and mortality.

Conflicts of interest

None of the authors declare a conflict of interest.

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Abbreviations

WAT	White adipose tissue
BAT	Brown adipose tissue
UCP	Uncoupling protein
WHO	World Health Organization
BMI	Body mass index
FFA	free fatty acid
VEGF	Vascular endothelial growth factor
TNF- α	tumor necrosis factor-α;
APN	Adiponectin
TAG	Triacylglycerols
CVD	Cardiovascular disease
MCP-1	Monocyte chemoattractant protein 1
CRP	C-reactive protein
HsCRP	high-sensitivity C-reactive protein
SAA	Serum amyloid A
DM	diabetes mellitus
T2DM	Type 2 diabetes mellitus
ER	Estrogen receptor
HMECs	human mammary epithelial cells
IGF-1R	IGF receptor
CCL2	Chemokine (C–C motif) ligand 2
PI3K/AKT	Phosphoinositide3-kinase/protein kinase B
MAPK	Mitogen-activated protein kinase
STAT3	Signal transducer and activator of transcription 3
CSCs	cancer stem cells
PC	Prostate cancer
IGFBPs	Insulin-like-growth factor binding proteins
P13K	Phosphoinositide-3 kinase
NF-Kb	nuclear factor κB
HCC	Hepatocellular carcinoma
UNOS	United Network of Organ Sharing
GH	growth hormone
COX	Cyclooxygenase

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