REVIEW

Obesity-related complications: few biochemical phenomena with reference to tumorigenesis

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Abstract

Overweight or obesity is currently a common health problem in westernized societies globally. Obesity is linked with a sizeable number of disease aetiologies, notably type-2 diabetes, cardiovascular disorders and certain cancers, perhaps through some common mechanisms that favor persistent low-grade inflammation. Both epidemiological and laboratory studies have demonstrated that the pathogenesis of certain cancers and the related prognosis are influenced by obesity. Clinically, a complex situation is present in obesity, which usually shows higher blood levels of various bio-molecules, e.g., lipids like triglycerides, hormones like insulin, and fat cell-secreted adipokines like leptin. On the contrary, obesity is associated with lower concentrations of substances like sex hormone-binding globulin and adiponectin. Many of these biochemical compounds are used routinely for clinical diagnosis and assessment during the follow-up period. Nonetheless, approximately one-fifth of the total cancer burden is associated with obesity. Excess adipose tissue and different hormonal substances possibly play a significant role in this complex obesity-related carcinogenesis. A precise understanding of the pertinent pathological processes is definitely useful in early diagnosis, clinical management, and designing of novel pharmaceutical agents.

Keywords: Obesity, cancer, insulin resistance, cholesterol, oestrogen, adipokines, clinical biochemistry

INTRODUCTION

For more than 3 decades, overweight/obesity has been emerging as a major health problem worldwide. The World Health Organization (WHO) estimates more than 1.4 billion adults globally were overweight in 2008; of these, over 200 million men and nearly 300 million women were obese. Recent reports from different parts of the world, including developing countries, have shown an excessive weight gain within populations. In the United States, nearly 70% of the adult population is either overweight or obese. Our preliminary study also indicates a similar trend in Anguilla, probably due to a prevalent westernized lifestyle (unpublished data). This health disorder has been induced by inappropriate diets and widespread physical inactivity, common characteristics that are currently observed in westernized societies. Nonetheless, the rapid increase in obesity in the Caribbean region is associated with non-communicable diseases, which are the main public health problem and, thus, become a significant economic burden on the health systems in this area.

Excess body weight increases the risk of several clinical conditions, e.g., cardiovascular diseases including hypertension and cerebrovascular disorders, type-2 diabetes, liver disease, and certain cancers, all of which are considered major health problems in westernized societies. Perhaps the aetiological link between obesity and diseases is a chronic, low-grade inflammatory state that leads to complex pathological situations such as insulin resistance, metabolic syndrome, and oxidative stress. It is believed that overfeeding activates the responsible pathway in all metabolically active cells that leads to increased cytokine production and ultimately recruits
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1. INFLUENCE OF OBESITY ON TUMOUR DEVELOPMENT: EVIDENCE FROM *IN VIVO* STUDIES

To comprehend the association between obesity and cancer, several *in vivo* studies have been conducted. Apart from proper understanding of disease processes, *in vivo* studies are useful for intervention strategies and could be conducted in a realistic time frame. Although there are several rodent and non-rodent experimental models to study obesity-related cancers, the majority of animal studies have been conducted on mice. Nevertheless, obesity possibly increases susceptibility to tumour development at various sites in different animal species (Table 1).

Breast cancer is a leading cancer worldwide; and overweight or obesity has been associated with increased risk of breast cancer in postmenopausal women. Furthermore, tumour formation in mammary tissue is common among laboratory rodents, especially rats and mice, and generally has a positive correlation with the body weight of these animals. The mammary tumour-promoting effects of obesity may be due to complex interactions involving energy intake and energy retention (body mass) mediated through paracrine and endocrine mechanisms. In a report by Hakkak *et al* it was documented that obesity increased the susceptibility of ovariectomized Zucker rats to 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumours, suggesting sufficient tumour promoting effects of adipose tissue-derived factors in this obese animal model. Similarly, studies using the mouse model showed obesity accelerated tumour growth in ovariectomized (or oestrogen depleted state) but not in non-ovariectomized animals. Obesity is an independent prognostic factor in patients with breast cancer. In female Zucker rats (fa/fa), DMBA-induced mammary tumours showed a significantly shorter latency period in the obese group compared to the lean group. In addition to a significantly higher mammary tumour incidence, tumours from obese rats exhibited higher invasive characters. The results of a study on F(2) mice demonstrated that animals fed a high-fat diet were not only more likely to experience decreased mammary cancer latency but also increased tumour growth and pulmonary metastases occurrence. Similarly, among transgenic MMTV-TGF-alpha mice, consumption of a high fat diet increased adiposity and shortened mammary tumour latency in relation to body weight. The transgenic

immune cells in the extracellular environment inducing an overall systemic inflammation. Finally, this inflammatory response plays a critical role in the development of obesity-related diseases.

Obesity has been reported to change leukocyte counts and cell-mediated immune responses. Characteristics of different lymphocyte classes, including peripheral CD4+ helper and CD8+ cytotoxic T-cells, were shown to be modified in obesity. In addition, many of these modifications in the relative proportions of the lymphocyte sub-populations depended on the degree of obesity. Interestingly, a study on experimental animals observed infiltration of obese adipose tissue by a large number CD8+ cells that promoted accumulation of macrophages. This study also noticed that the number of CD4+ and regulatory T cells was diminished. On the other hand, another study on obese persons found a reduction of different subsets of T cell populations and their functions as well as an enhanced production of tumour necrosis factor-alpha (TNF). It is noteworthy that pro-inflammatory cytokines like interleukin-6 (IL-6) and TNF, which are produced by the infiltrating macrophages in the adipose tissue, may perpetuate obesity-related pathologies including cancer.

Recent investigations have documented an important role of the extracellular matrix (ECM) in tumour development and progression. It is hypothesized that the malignant features of cancer cells cannot be manifested without the necessary interplay between cancer cells and their local environment. On the other hand, obesity has been shown to influence several components of the ECM as well as its structural changes. In obesity, unusual alterations of ECM components and their tissue remodeling processes can influence immune cell recruitment and activation, which actively contribute to inflammation. In this connection, a number of reports have revealed abnormal characteristics of several ECM components in the development of insulin resistance and metabolic syndrome. However, apart from the metabolic complications, obesity-related tissue remodeling may also lead to a permissive pro-tumorigenic environment. In this review, an attempt has been made to focus mainly on the neoplastic role of selected obesity-related compounds that we could measure in clinical biochemistry laboratories.
TABLE 1: Salient findings of some recent in vivo studies that documented a positive association between obesity and tumor development in different sites

<table>
<thead>
<tr>
<th>Authors/Species/Site</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al.23 Male A/J mice were placed on either a high-fat diet (HFD) or a normal diet; and azoxymethane (AOM) was administered, followed by dextran sodium sulfate. The HFD group had two-fold higher numbers of colonic tumours, as compared with the normal diet group.</td>
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<tr>
<td>Gravaghi et al.24 Mice/G.I. tract The investigators generated C57BLKS-mLepr(db/db); Apc(1638N+/+) mice combining both leptin receptor (db) and adenomatous polyposis coli (Apc) mutations. The db mutation results in obesity and type-2 diabetes, the Apc mutation is a key initiating event of intestinal neoplasia. The combination of Apc(1638N+) and db mutations enhanced gastric, small intestinal and colonic tumours.</td>
<td></td>
</tr>
<tr>
<td>Iatropoulos et al.25 C57BL/6 (B6) male mice were given a high-fat diet (diet-induced obesity - DIO) and low fat diet (lean control), and subsequently hepatocarcinogen 2-acetylaminofluorene. The DIO group had an increased incidence of hepatocellular proliferation and steatosis, conditions which can be associated with hepatic neoplasia.</td>
<td></td>
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<tr>
<td>Soga et al.26 FLS-Lep(ob)/Lep(ob) mouse was generated from the Fatty Liver Shionogi (FLS) mouse, which develops hereditary fatty liver and spontaneous liver tumours, and leptin-deficient C57BL/6JWakShi (B6)-Lep(ob)/Lep(ob) mouse. The FLS-Lep(ob)/Lep(ob) mice had severe hyperlipidemia and hyperinsulinemia. Furthermore, FLS-Lep(ob)/Lep(ob) mice developed multiple hepatic tumours including hepatocellular adenomas and carcinomas following steatohepatitis.</td>
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<tr>
<td>Zyromski et al.27 Lean (C57BL/6J) and obese [leptin receptor- and leptin-deficient: Lepr(db/db) and Lep(ob/ob)] mice were inoculated with murine pancreatic cancer cells (PAN02). Obese mice developed larger tumours, and a significantly greater number of mice developed metastases; mortality was also greater in obese mice.</td>
<td></td>
</tr>
<tr>
<td>White et al.28 Accelerated tumour growth from PAN02 murine pancreatic cancer cells in overweight C57BL/6J mice maintained on high-fat diets.</td>
<td></td>
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<tr>
<td>Schneider et al.29 All hamsters were treated with the pancreatic carcinogen N-nitrosobis-(2-oxopropyl)amine. In the high-fat diet group, 50% of the animals developed malignant lesions; however, none was found in the metformin group.</td>
<td></td>
</tr>
<tr>
<td>Zhang et al.30 Enhancement of oestrogen-induced endometrial pro-proliferative gene expression and suppression of anti-proliferative gene expression was seen in the endometrium of Zucker fa/fa obese rats vs. lean controls.</td>
<td></td>
</tr>
<tr>
<td>Yu et al.31 High-fat diet increased focal glandular hyperplasia with atypia and malignant lesions from 58% in the control diet–fed Pten−/− mice to 78% in obese mice. PTEN is a known tumour suppressor that is frequently mutated or deleted in many cancers.</td>
<td></td>
</tr>
<tr>
<td>Yakar et al.32 Tumour growth rate was increased in obese mice vs. control mice, when C57BL/6 mice were injected sc with Lewis lung carcinoma cells.</td>
<td></td>
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<tr>
<td>Mori et al.33 By intravenous injection of Lewis lung carcinoma cells, the number of lung cancer colonies was markedly promoted in Lepr(db/db) and Lep(ob/ob) obese mice compared to C57BL/6 mice.</td>
<td></td>
</tr>
<tr>
<td>Katiyar and Meeran 34 Chronic exposure to ultraviolet (UVB) radiation resulted in greater oxidative stress in the skin of Lep(ob/ob) obese mice, e.g., elevated levels of NO production, greater depletion of antioxidant defense enzymes, activation of NF-κB and higher levels of pro-inflammatory cytokines, which might increase the risk for cancer.</td>
<td></td>
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</tbody>
</table>
MMTV-TGF-alpha mice develop mammary tumours in the latter part of their life and the tumours are oestrogen receptor (ER)-positive. Therefore, these mice are considered to mimic the ER-positive breast cancer development in postmenopausal women. Here it may be worth noting that postmenopausal obesity has been shown to be more consistently associated with an increased risk of ER-positive than ER-negative breast cancer.43 Alternatively, in a study on MMTV-neu mice that develop ER-negative but HER2/neu-positive mammary tumours, the time of onset of a first tumour and tumour growth rates were not altered. However, mice on high-fat diets had an earlier onset of a second tumour and a two-fold greater incidence and a greater absolute number of multiple tumours.44

Among men, prostate cancer is one of the most common types of cancer. Although breast and prostate cancers bear many similarities, the role of body weight in the development of prostate cancer is a controversial subject. Perhaps obesity leads to a more aggressive prostate cancer, but not low-grade disease.45 Nevertheless, in a study conducted on Hi-Myc mice, the diet-induced obesity (DIO) regimen significantly increased the incidence of prostatic adenocarcinoma with aggressive stromal invasion as compared with the control group.46 In addition, DIO increased several growth-associated and inflammatory factors, e.g., Akt, nuclear factor kappa B (NF-κB), TNFα, IL-6, etc. In another study, investigators observed that consumption of a Western-type diet, which is enriched in both fat and cholesterol, accelerated prostate tumour incidence and tumour burden in the TRAMP mouse model compared to chow-fed control group.47 Furthermore, they found that this diet was associated with higher histological grade, extent of tumour, and metastases. Therefore, dietary fat and cholesterol might play an important role in the development of prostate cancer.

2. ROLE OF CHOLESTEROL IN CANCER

Several studies have documented increased concentrations of circulating cholesterol in obese persons.48-50 Adipose tissue is the body’s largest pool of free cholesterol, and multiple signaling pathways may be responsible for the regulation of cholesterol homeostasis in adipocytes. Altering cholesterol balance profoundly modifies adipocyte metabolism, and cholesterol imbalance is associated with enlarged adipocytes seen in obese individuals.51 The influence of cholesterol on cancer risk has been an area of investigation for a long-time since different molecules linked with cholesterol biosynthesis, including sex hormones, may favor tumorigenesis.52-54

2.1 Cholesterol and cancer

Several large studies have indicated that elevated plasma cholesterol levels increase the risk of developing prostate cancer of increased invasiveness. In a cohort study on 5,586 subjects, it was determined that men with low cholesterol had a lower risk of high-grade prostate cancer.45 Likewise, many studies demonstrated that cholesterol influenced the risk of developing high-grade prostate cancer.56-58 There are several proposed mechanisms for this pathological phenomenon such as hypercholesterolemia that may cause increased tumour angiogenesis, reduced tumour apoptosis and increased tumour cell proliferation. One of the proposed mechanisms involves cholesterol’s vital role in cell membranes, which could affect various signaling pathways and relevant proteins like the cell survival kinase Akt. Furthermore, cholesterol-rich microdomains or ‘lipid rafts’ have been implicated in tumour growth and aggressiveness (Figure 1).59,60 Lipid rafts, enriched in cholesterol and sphingolipids, are present within cell membranes and are essential in signaling processes.

Although the association between blood cholesterol level and breast cancer risk is controversial, many studies have reported elevated serum levels of total cholesterol among women with breast cancer.61-64 Moreover, a higher tissue concentration of cholesterol was observed in breast cancer cases compared to benign breast diseases.65 Analogous findings have been demonstrated in a recent in vitro study.53 Interestingly, in a prospective cohort study, a trend towards risk of recurrence was seen with higher total cholesterol in multivariate analysis.66 Similarly, a study on Norwegian breast cancer patients showed that women in the highest tertile of total cholesterol had a 29% increase in mortality compared to women in the lowest tertile.67

Evidence linking cholesterol and colon cancer is also conflicting. In the Framingham Study, colon cancer risk in men was inversely correlated to serum cholesterol levels.68 On the other hand, in a study on colorectal adenomas, levels of low-
FIG. 1: Examples of various raft associated signaling pathways.

Lipid rafts aid in the colocalization of enzymes and receptors which have been implicated in the anti-apoptotic and growth promoting behaviors in various cancers, including breast and prostate. The black squares represent cholesterol which is highly concentrated in raft domains.

density lipoprotein-cholesterol (LDL-C) were positively associated with adenoma frequency.\textsuperscript{69} Of note, LDL-C contains high concentrations of cholesterol compared to other lipoprotein classes (Table 2). Fascinatingly, Houghton \textit{et al} found a direct relationship between cholesterol levels and a greater likelihood of adenomas with villous histology.\textsuperscript{70} Amongst colonic adenomatous polyps, the villous type is associated with an elevated risk for developing into cancer in comparison with other types like tubular and tubulovillous adenomas. Nonetheless, like the Framingham Study, an Italian study on newly diagnosed cancer cases observed significantly lower total cholesterol and LDL-C in colon cancer patients vs. non-cancer subjects, as well as in patients with metastasis vs. patients without metastasis.\textsuperscript{71} Conversely, in another Italian study, colorectal cancer patients with distant metastasis showed significantly higher levels of total cholesterol and LDL-C than patients without metastasis.\textsuperscript{72} Furthermore, a large prospective study reported that high total cholesterol was positively associated with colon cancer risk among Korean men.\textsuperscript{73}

### 2.2 Cholesterol transport protein in cancer

The 18 kDa translocator protein (TSPO) or peripheral benzodiazepine receptor (PBR) is situated at the mitochondrial membrane and is involved in various biological functions, including cholesterol binding and transport from the outer to the inner mitochondrial membrane for steroid hormone biosynthesis. TSPO has been shown to be over-expressed in cancer tissues and correlated with aggressive malignant behavior. A study that analyzed concentration and distribution of TSPO in normal tissue and tumours from different sites, observed that there was a progressive increase in TSPO levels parallel to the invasive and metastatic ability of breast cancer. In colorectal and prostate cancers, TSPO levels were also higher in cancer tissue than in the corresponding non-cancerous tissues and benign lesions.\textsuperscript{74} However, significantly higher expression of TSPO in breast cancer was revealed by Galiègue \textit{et al} who also noticed a negative correlation between TSPO expression and ER status as well as a positive correlation between TSPO and cellular proliferation marker Ki-67. In addition, high TSPO expression level was significantly correlated with a shorter disease-free survival in lymph node-negative patients.\textsuperscript{75} On the other hand, Königsrainer \textit{et al} demonstrated over-expression of TSPO in 67\% of colorectal tumours, and expression levels were significantly higher in tumours of the colon in comparison with tumours of the rectum.\textsuperscript{76}

The nature of participation of cholesterol in carcinogenesis is a subject of much debate. However, in the era of statin medications, this issue has gained a new dimension. Statins are cholesterol-lowering drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, leading to decreased cholesterol biosynthesis. Several studies have observed anti-neoplastic effects of statins, though the drugs can act through both cholesterol-dependent and -independent mechanisms.\textsuperscript{77-79} Nevertheless, by influencing different cellular pathways, pleiotropic characteristics of cholesterol could create an environment that might favor the pathological processes of cancer.

### TABLE 2: Cholesterol and triglyceride contents of different lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein class</th>
<th>Percent weight</th>
<th>Origin of the lipoprotein</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Free cholesterol</td>
<td>Cholesteryl ester</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>Chylomicron</td>
<td>1.6</td>
<td>1.4</td>
<td>88</td>
</tr>
<tr>
<td>Very-low-density lipoprotein (VLDL)</td>
<td>7</td>
<td>10</td>
<td>56</td>
</tr>
<tr>
<td>Intermediate-density lipoprotein (IDL)</td>
<td>8</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Low-density lipoprotein (LDL)</td>
<td>6-10</td>
<td>35-45</td>
<td>6-12</td>
</tr>
<tr>
<td>High-density lipoprotein 2 (HDL$_{2}$)</td>
<td>4-6</td>
<td>15-20</td>
<td>3-6</td>
</tr>
<tr>
<td>High-density lipoprotein 3 (HDL$_{3}$)</td>
<td>1-3</td>
<td>8-15</td>
<td>3-6</td>
</tr>
</tbody>
</table>
3. TRIGLYCERIDES IN CANCER

Higher blood levels of triglycerides are commonly seen in obese subjects. Many studies have reported an increased incidence of prostate cancer with elevated triglyceride levels. In the Swedish AMORIS study, high glucose levels showed a positive association between hypertriglyceridemia and prostate cancer risk. Interestingly, there is evidence that links increased triglyceride levels to high-grade prostate cancer. Similarly, the risk of breast cancer was shown to be correlated with elevated serum triglyceride levels, and higher triglyceride levels were found to be present in breast cancer tissue compared to benign breast diseases. As with prostate and breast cancers, hypertriglyceridemia has been demonstrated to be associated with an increased risk of colon cancer and colorectal adenoma, a precursor lesion for cancer.

Elevated serum triglyceride levels are often correlated with obesity; however, the association is exceedingly dependent on the location of adipose stores, individual genetic variability and other co-morbidities, including insulin resistance. Of note, higher triglyceride concentrations are an important component of metabolic syndrome that creates a low-grade inflammatory state and may favor pathogenesis of several diseases including cancer. Therefore, more epidemiological and laboratory studies are required to understand the precise role of hypertriglyceridemia in this complex pathology.

4. HORMONAL LINKS IN OBESITY-RELATED CANCERS

Possibly, a sizable number of cancers are associated with obesity, e.g., cancers of the colon, endometrium, breast (postmenopausal cases), kidney, oesophagus (adenocarcinoma type), ovary, pancreas, gall-bladder, liver, prostate (aggressive diseases), melanoma, uterine cervix (adenocarcinoma), urinary bladder, and hematopoietic tissues like non-Hodgkin’s lymphoma (NHL), multiple myeloma, and leukemia. Alternatively, a substantial number of cancers perhaps are linked to hormonal aetiology, particularly with sex hormones, such as cancers of the breast, endometrium, ovary, and prostate. Furthermore, several investigators have suggested oestrogenic connections in malignancies of different sites including the thyroid, lung, kidney, uterine cervix, and colon. It has been estimated that obesity is currently responsible for approximately 20% of all cancer cases, whereas hormone-related cancers constitute about 35% of the total cancer morbidity. Nevertheless, many of the above-mentioned cancers fall into both categories and, thus, reveal a correlation between obesity and hormonal pathology. A good example of such relationship may be the pathological process of breast cancer in postmenopausal women.

It is known that obesity in postmenopausal women is a risk factor for the development of breast cancer. Obesity may affect the disease process in several ways. Aromatase enzyme present in adipose tissue converts androgens to oestrogens; so more aromatase activity and oestrogens are expected in persons with excessive adipose tissue. In postmenopausal women, androgens mainly come from the adrenal glands under the influence of adrenocorticotropic hormone (ACTH), a peptide derived from pro-opiomelanocortin (POMC) of the anterior pituitary. Perhaps, intratumoural oestrogen production also plays an important role in cancer progression in conjunction with local aromatase and other enzymes associated with steroid biosynthesis (Figure 2). In general, studies have observed elevated circulating levels of oestrogens and androgens as well as decreased levels of sex hormone-binding globulins (SHBG) in postmenopausal women with higher body weights and breast cancer. It is thought that lower SHBG concentrations increase bioavailable oestrogens and cancer risk. Also, oxidative metabolites of oestrogen may increase the risk.

4.1 Insulin resistance and cancer

Obesity and associated insulin resistance eventually lead to a state of hyperinsulinaemia that enhances the synthesis of insulin-like growth factor-I (IGF-I) and its bioavailability by decreasing the binding proteins (IGFBPs) (Table 3). This situation is believed to favor tumour growth by stimulating cell proliferation, inhibiting apoptosis, and generating a condition of inflammation and oxidative stress. Furthermore, obesity related hyperinsulinaemia inhibits hepatic secretion of SHBG, and, thus, increases bioavailability of sex-steroid hormones. Of note, there is substantial evidence to demonstrate that cancers of the colon, liver, pancreas, and endometrium are associated with insulin resistance. Moreover, evidence suggests that hyperinsulinaemia is involved in the neoplastic growth of both the breast and prostate.
4.2 Adipokines in cancer

Adipose tissue acts as an endocrine organ and releases several hormone-like adipokines, e.g., leptin, TNFα, IL-6, monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), resistin, adipin, adiponectin, proteins of the renin-angiotensin system, etc. The majority of these adipokines participate in the pro-inflammatory processes in obesity and perpetuate the state of insulin resistance (Table 3). Moreover, the pathologic characters of many of these adipokines, for instance, leptin, TNFα and IL-6, in different cancers are now fairly comprehensible.\textsuperscript{112-114} On the contrary, adiponectin is an anti-inflammatory adipokine, and a growing body of evidence suggests its anti-cancer effects.\textsuperscript{114,115} Adiponectin levels are low in obesity and lipodystrophy; both conditions are linked with insulin resistance and increased susceptibility to tumour development. Adiponectin belongs to complement protein C1q; however, it has a close structural homology with TNFα, which also inhibits the expression and secretion of adiponectin in adipocytes.\textsuperscript{116} Furthermore, TNFα modifies the expression of IL-6, and IL-6 decreases adiponectin secretion.\textsuperscript{117} In obesity, these mechanisms probably work to lower the adiponectin levels.

4.3 Role of endocrine disruptors

Lipophilic environmental organic pollutants or xenobiotic chemicals like organochlorine compounds and polycyclic aromatic hydrocarbons (PAH) can accumulate in adipose tissue. Local release of such chemicals from the adipocytes adjacent to tumour tissue may influence the biological behavior of malignancy. The harmful effects of xenobiotic chemicals are probably mediated through different mechanisms including production of reactive free radicals and oxidative stress, endocrine disruption, and alteration of immune function. Endocrine disrupting agents that could manipulate the actions of steroid hormones might play a significant role.
### TABLE 3: An overview of few important adipocyte-derived hormone-like cytokines or adipokines that facilitate pro-inflammatory conditions and insulin resistance in obesity

<table>
<thead>
<tr>
<th>Adipokines or related cytokines</th>
<th>Sources</th>
<th>Biochemical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour necrosis factor-alpha (TNFα)</td>
<td>Mainly produced by macrophages and other cells of the monocytic lineage, also by adipose tissue to a lesser extent.</td>
<td>On human chromosome 6, the gene for TNFα is present as a single copy gene. TNFα is released as a transmembrane protein (27 kDa/233 amino acids) that undergoes proteolytic cleavage by the TNF alpha converting enzyme (TACE) to form the soluble form (17 kDa/157 amino acids). The metalloprotease TACE is a glycoprotein; however, TNFα is not the sole substrate of TACE. TNFα functions via two transmembrane receptors: TNFR1 and TNFR2. In obesity-related inflammation, both receptors can signal through NF-κB or mitogen-activated protein kinase (MAPK).</td>
</tr>
<tr>
<td>Interleukin-6 (IL-6)</td>
<td>Macrophages, T-cells, muscle cells, adipose tissue, etc.</td>
<td>The human IL-6 gene is located on chromosome 7: it is a single-chain glycoprotein with a molecular weight of about 21 kDa – 28 kDa (184 amino acids). IL-6 first binds to its receptor (IL-6R): the complex then associates with the signal transducing membrane protein gp130, thereby inducing its dimerization and initiation of intracellular signaling mainly through the janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. In addition, activation of the Ras-Raf-MAPK signaling pathway may occur. A soluble form of IL-6R, present in the circulation and inflammation sites, can bind IL-6.</td>
</tr>
<tr>
<td>Leptin</td>
<td>Synthesized primarily from adipose tissue; other important sites are gastric mucosa, lymphoid tissues, mammary epithelium, etc.</td>
<td>The gene for human leptin is present on chromosome 7; it is a 16 kDa protein (167 amino acids), which physiologically plays a vital role in the regulation of food intake and energy homeostasis. At least 6 alternatively spliced isoforms of leptin receptor (Ob-R) are present; the long transmembrane isoform Ob-Rb perhaps is important for leptin’s pro-inflammatory effects. Signaling through Ob-R particularly engages the JAK2/STAT3 pathway. Leptin is also associated with other signaling pathways such as the insulin receptor substrate phosphatidylinositol 3-kinase (PI3K) and MAPK. In the pro-inflammatory obese state, leptin is thought to be an important mediator to promote tumour growth, angiogenesis, and other adverse neoplastic pathologies.</td>
</tr>
<tr>
<td>Insulin-like growth factor-I (IGF-I)</td>
<td>Mainly produced by the liver; to a lesser extent, synthesis can also occur in extra-hepatic tissues including adipose tissue</td>
<td>The IGF system consists of IGF-I and IGF-II, their receptors, binding proteins (IGFBPs), and IGFBP proteases. In human, the IGF-I gene is located on chromosome 12; it is a polypeptide with 70 amino acids and a molecular weight of 7.6 kDa. IGF-I shares high structural homology with pro-insulin. In general, IGF-I acts via its receptor: IGF-IR or hybrid insulin receptor/IGF-IRs. IGFBP-3 is the most abundant IGF carrier in blood and is critical in determining the bio-available IGF-I. Elevated circulating levels of IGF-I in obesity perhaps are supportive for cell proliferation and anti-apoptotic effects through the activation of PI3K/Akt and MAPK pathways.</td>
</tr>
<tr>
<td>Resistin</td>
<td>In humans, mainly derived from macrophages; small amounts from adipose tissue (main site for rodents)</td>
<td>The human resistin gene is situated on chromosome 19; it is a 12.5 kDa cysteine-rich polypeptide which contains 108 amino acids (prepeptide). There are distinct interspecies variations in resistin’s biosynthetic source and chemical structure. Although the mechanisms of action are incompletely understood, it seems likely that resistin functions as a pro-inflammatory molecule by involving signaling pathways like NF-κB and MAPK.</td>
</tr>
</tbody>
</table>
TABLE 4: Selected dietary compounds that probably have anti-cancer effects as well as biological properties by which they may reduce obesity or obesity-related complications

<table>
<thead>
<tr>
<th>Groups</th>
<th>Subdivisions</th>
<th>Descriptions in brief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotenoids</td>
<td></td>
<td>Characteristics: Pigments which are present usually in plants (isoprenoid compounds). Some carotenoids can be converted to vitamin A.</td>
</tr>
<tr>
<td>Provitamin A carotenoids</td>
<td></td>
<td>Carotenoids with vitamin A activities such as α-carotene, β-carotene and β-cryptoxanthin. Among this group, β-carotene is the most important. Vitamin A is not synthesized in the body and should be received from carotenoids.</td>
</tr>
<tr>
<td>Non-provitamin A carotenoids</td>
<td></td>
<td>Compounds do not have pro-vitamin A properties such as lycopene, lutein and crocetin.</td>
</tr>
<tr>
<td>Retinoids</td>
<td></td>
<td>Characteristics: The retinoids are natural and synthetic derivatives of vitamin A, which act through interaction with two basic types of nuclear receptors: retinoic acid receptors (RAR) and retinoid X receptors (RXR).</td>
</tr>
<tr>
<td>Vitamin A</td>
<td></td>
<td>The term vitamin A is used to denote all vitamin A derivatives with retinol-like activities. Retinol is the principal compound for vitamin A.</td>
</tr>
<tr>
<td>Rexinoids</td>
<td></td>
<td>Agents that activate the RXR such as 9-cis-retinoic acid, allitretinoin and bexarotene.</td>
</tr>
<tr>
<td>Terpenoids</td>
<td></td>
<td>Characteristics: Terpenoids are a large group of natural products, which have five-carbon unit isoprene structure that is the basis of their nomenclature.</td>
</tr>
<tr>
<td>Monoterpenes</td>
<td></td>
<td>Contain two isoprene units, e.g., limonene, perillyl alcohol, carvone and menthol.</td>
</tr>
<tr>
<td>Diterpenes</td>
<td></td>
<td>Contain four isoprene units, e.g., vitamin A and crocetin.</td>
</tr>
<tr>
<td>Tetraterpenes</td>
<td></td>
<td>Contain eight isoprene units and include various carotenoids, e.g., α- and β-carotene, lycopene, lutein and zeaxanthin.</td>
</tr>
<tr>
<td>Fat-soluble vitamins</td>
<td></td>
<td>Characteristics: Vitamins A, D, E and K are stored in the liver and excess intake may cause toxicity.</td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
<td>Vitamin D, or cholecalciferol, synthesized in the skin during exposure to the sun light.</td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td>Tocopherol, a powerful anti-oxidant, found in vegetable oils and green leafy vegetables like spinach, etc.</td>
</tr>
<tr>
<td>Flavonoids</td>
<td></td>
<td>Characteristics: Flavonoids are a large group of plant secondary metabolites consisting of two aromatic rings linked through an oxygenated heterocyclic structure that is fused to one of these aromatic rings.</td>
</tr>
<tr>
<td>Flavone</td>
<td></td>
<td>Active compounds like apigenin and luteolin found in celery, sweet red pepper, rosemary, etc.</td>
</tr>
<tr>
<td>Flavonol</td>
<td></td>
<td>Examples: Quercetin, kaempferol and myricetin found in onions, tomatoes, tea, etc.</td>
</tr>
<tr>
<td>Catechin</td>
<td></td>
<td>Examples: Epigallocatechin-3-gallate (EGCG) found in tea, apples, plums, etc.</td>
</tr>
<tr>
<td>Isoflavone</td>
<td></td>
<td>Examples: Genistein, daidzein and glycitein found in soya beans, chickpeas, legumes, etc.</td>
</tr>
<tr>
<td>Plant defense molecules</td>
<td></td>
<td>Characteristics: A large number of chemicals with diverse chemical structures serve in the defense of the plants against different predators and phytopathogenic organisms.</td>
</tr>
<tr>
<td>Stilbenoids</td>
<td></td>
<td>The most important compound in this group is resveratrol which is found in grapes, berries and several other fruits.</td>
</tr>
<tr>
<td>Thaumatin-like (PR-5) proteins</td>
<td></td>
<td>Osmotin, present in fruits and vegetables such as grapes, tomatoes and carrots.</td>
</tr>
<tr>
<td>Vanilloids</td>
<td></td>
<td>This group includes compounds like curcumin (from turmeric), gingerol (from rhizome of ginger) as well as capsaicin, the pungent constituent of hot peppers, which may repel fungi and herbivores.</td>
</tr>
<tr>
<td>Organosulfur compounds</td>
<td></td>
<td>Active compounds like allicin, ajoene and diallyl sulfide present in Allium vegetables such as garlic and onion.</td>
</tr>
</tbody>
</table>
OBESITY AND TUMOUR DEVELOPMENT

in the pathogenesis of sex hormone-related cancers by influencing vulnerable cells.\textsuperscript{118-120} Interestingly, Baillie-Hamilton hypothesized that several synthetic organic and inorganic chemicals, in lower concentrations, can cause weight-promoting effects and may play a significant role in the development of obesity.\textsuperscript{121} Subsequently, a number of studies concluded an obesity-promoting role of various environmental chemicals such as organochlorine pesticide residues, organotin compounds and bisphenol A.\textsuperscript{122-124} Furthermore, in the body these chemical residues have been shown to increase the risk for insulin resistance and diabetes.\textsuperscript{125,126}

In harmony with the current obesity trend, obesity-related malignancies continue to be the leading neoplastic diseases according to the various international and regional reports. In general, obesity and related insulin resistance or metabolic syndrome is apparently connected with several pathologies such as dyslipidemia, activation of different growth factors, and dysregulation of sex-steroid hormones. The results of their multifaceted interactions possibly support a persistent low-grade inflammation, which may generate a carcinogenic environment for vulnerable cells.

5. PREVENTIVE ASPECTS OF OBESITY-RELATED DISEASES

A number of dietary constituents have been suggested, which possibly have both anti-obesity and anti-cancer properties (Table 4). Regular consumption of these compounds may be helpful to lower the risk of developing health disorders like insulin resistance/metabolic syndrome and cancer.\textsuperscript{127} Interestingly, increased levels of adiponectin have been demonstrated by several dietary components like soy isoflavone\textsuperscript{128} and curcumin,\textsuperscript{129} and extracts of fruits like bitter melon\textsuperscript{130} and lychee.\textsuperscript{131} Also, a dietary compound osmotin has been demonstrated to have functional similarity with adiponectin.\textsuperscript{132} These food derived components may be an important consideration for investigation into obesity-related cancer prevention. Additionally, dietary energy restriction or caloric restriction has been suggested to provide longevity and inhibit carcinogenesis.\textsuperscript{133} In experimental animals, a number of studies have observed that caloric restriction (without malnutrition) delays or protects against the development of tumours. Several mechanisms have been proposed for the beneficial effects of caloric restriction, e.g., consistent reduction in circulating levels of growth factors, anabolic hormones, inflammatory cytokines and oxidative stress markers linked to various malignancies, and a connection with molecules such as adiponectin, adenosine monophosphate-activated kinase (AMPK) and sirtuins.\textsuperscript{134,135} However, in human subjects, combining caloric restriction and physical activity perhaps is a suitable approach with a favorable impact on health-related quality of life.\textsuperscript{136,137}

CONCLUSION

Obesity is a perplexing health disorder created by different inflammatory, angiogenic and growth-promoting factors. Interaction between these factors propels a pro-tumorigenic inflammatory microenvironment. In general, obesity is a preventable health disorder, and thus a substantial reduction in the incidence of obesity-related cancers could be achievable through preventive measures at different levels, particularly primary prevention as well as early detection and management. However, active efforts are underway to evaluate the role of different pathological components in a precise manner. Obviously, the development of appropriate diagnostic tools, prevention strategies, and pharmaceutical agents depends on the proper understanding of the underlying patho-mechanisms.

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