

OBESITY INDUCES DNA DAMAGE

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ABSTRACT

A diet rich in saturated lipids, refined carbohydrates associated with a sedentary lifestyle leads to obesity in both adults and children. Obesity is associated with the existence of a chronic inflammatory process, that will further lead to systemic oxidative stress and DNA oxidative damage.

There is currently a positive correlation between obesity and cancer due to nuclear but also mitochondrial DNA injury. Obesity is a risk factor for the development of several types of cancer such as breast, prostate or colorectal.

The purpose of this review is to present the effects of obesity on human body, by describing the chronic inflammatory process, oxidative stress, and the molecular mechanisms involved in cancer progression.

Keywords: obesity, DNA damage, cancer

INTRODUCTION

Obesity is a serious health problem of the young but also of the adult population around the world. This complex chronic condition is characterized by significant increase in fat mass, disorders of lipid and glucose metabolism, chronic inflammation, oxidative stress (OS) and DNA damage. DNA damage has been reported in overweight or obese people, which will further lead to the development of cancer (1,2).

USA has the highest rate of obesity, with more than 60% of the adult population being overweight or obese, followed by Europe. In USA after smoking, poor diet and lack of physical activity represent the second leading cause of mortality, causing 400,000 cases per year (3). A positive correlation has been reported between obesity and cancer incidence. In men, obesity is associated with an increased incidence of the esophagus, prostate, stomach, liver, pancreas, kidneys cancers. In women, a positive correlation was observed for breast, cervix, uterus and ovarian cancers (4).

Studies performed suggest that over 90,000 deaths annually recorded could be avoided if the adult population would have a normal weight and body mass index of less than 25 (4). In Romania, in 2018, according to the World Health Organization (WHO) lung, colorectal, breast, prostate and bladder the most common neoplasms for both sexes. For women from Romania, breast cancer has the highest incidence, and prostate cancer is the most common in men (5).

OBESITY INDUCED INFLAMMATION AND OXIDATIVE STRESS

In inflammation, neutrophils and macrophages are recruited and activated and will generate reactive oxygen (ROS) and nitrogen (RNS) species. Mitochondrial oxidative metabolism, apoptosis, enzymatic reactions of nicotinamide adenine dinucleotide phosphate (NAPPH) oxidases, superoxide dismutase, myeloperoxidase and nitric oxide synthase contribute to ROS production in cells (6).

Adipose tissue secretes a large amount of pro-inflammatory cytokines such as IL-6 and TNF- α , IL-6, IL-10, MCP-1 (monocyte chemoattractant protein-1) which will lead to ROS (reactive oxygen production) production. IL-6 and TNF- α activate C-reactive protein and again ROS production (7).

Obesity is associated with the installation of OS, due to the high and constant production of ROS and decreased levels of antioxidants. Increased levels of ROS lead to endogenous DNA damage. Lipids can undergo oxidation processes, stimulate the production of free radicals and the accumulation of these reactive species in the adipose tissue. Lipid peroxidation is induced by ROS and lead to the formation of DNA reactive lesions (7-9).

ROS are superoxide anion ($O_2^{\cdot-}$) ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and hydroxyl radical (HO \cdot) the most dangerous, being HO \cdot , formed as a result of the Fenton and Weber-Weiss reactions. During aerobic respiration, $O_2^{\cdot-}$ and H_2O_2 are generated. Neutrophils and macrophages activated in the inflammatory process generate numerous oxidizing agents such as peroxynitrite (ONOO \cdot), nitrosoperoxycarbonate (ONOOCO $_2^{\cdot-}$), hypochlorous acids (HOCl) and diazotrioxide (N_2O_3) (10).

REACTIVE OXYGEN SPECIES AND DNA DAMAGE

ROS participates in the process of lipid peroxidation with the formation of products such as malondialdehyde (MDA), which will interact with DNA forming DNA adducts (11).

ROS can also attack the nitrogenous bases from DNA structure, taking place processes of oxidation, methylation, nitration, deamination, double and single stranded DNA cleavage or cross-links in DNA structure. 8-hydroxy guanine (8-HOdG), 7,8 dihydroxy 8-oxoguanine, thymine glycol, 4,6-diamino 5-formamidopyrimidine (Fapy Ade) and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (Fapy Gua) are the most common DNA mutations due to ROS attack. These DNA lesions can induce DNA mutations during replication. 8-HOdG being able to induce GC transversion to TA leading to activation of the mutagenesis process and cancer initiation (12,13).

Adipose tissue *via* adipokines secrete proinflammatory cytokines such as TNF- α and IL-6 that amplify the ROS formation process, which will contribute to DNA damage (14). Setayesh T et al. tested DNA damage in overweight mice and reported and increased level of injury versus the control

group. Mice that received a diet poor in calories and protein, present about 30% decrease in DNA damage versus hypercaloric diet (15).

ROS may induce also lesions of mitochondrial DNA. Mitochondrial DNA is highly susceptible to oxidative damage because there are no nucleotide excision repair mechanisms (16).

Despite the fact that mitochondrial DNA encodes 1% of mitochondrial proteins, mitochondrial disorders are associated with an increased number of DNA lesions. Mitochondrial DNA damage is associated with diabetes, cancer and neurodegenerative disorders (16-18).

Obesity leads to beta oxidation process disorders and glucose homeostasis (19,20). Mitochondrial DNA oxidation can induce the synthesis of pro-inflammatory cytokines such as IL-6, TNF- α , pro-IL-1 β , through toll-like receptor activation (21).

OBESITY AND CANCER

Cancer is the leading cause of mortality in developing countries and the second leading cause in developing countries. 12.7 million cases and 7.6 million deaths were reported in USA in 2008 (22). In a report published in 2018, the mortality rate from cancer is very high worldwide. Unfortunately, Romania occupies leading places in terms of lung, trachea, colorectal, breast and bronchus cancer (23).

The hormones released by adipokines, leptin and adiponectin are involved in cancer development. Leptin mediates tumor progression by activating AKT (protein kinase B), MAPK (mitogen-activated protein kinase) and STAT3 (signal transducer and activator of transcription proteins) signaling pathways. Adiponectin secreted especially by the visceral adipose tissue, has antitumor properties by activating AMPK (adenosine monophosphate-activated protein kinase) signaling pathways, the anti-inflammatory effects are manifested by inhibiting NF κ B (24,25).

Insulin and IGF-1 (insulin growth factor-1) are involved in the pathogenesis of cancer because it activates the AKT / mTOR signaling pathway, which promotes the growth and proliferation of tumor cells and inhibits cell survival (26).

AKT/mTOR signaling pathway suffers the most mutations in cancer, being a link between obesity and cancer (especially breast and colon) (26-29). Steroid hormones, namely estrogens, progesterone, androgens and adrenal steroids are associated with obesity and the development of certain types of neoplasms in women (30).

Caloric restriction is associated with decreased cancer incidence, which will also lead to decreased AKT / mTOR activation. Tumors with activated PI3K are resistant to caloric restriction (31, 32). Caloric restriction reduces even the incidence of spontaneous tumor development in mice by 55% (22).

In a cohort study conducted by Alicja Wolk and coworkers included 28,129 patients (8165 men, 19964 women) who investigated the incidence of cancer in the period 1965-1993, according to the Swedish National Cancer Registry. The results of the study suggest that obese people have a 33% incidence of cancer, 25% in men and 37% in women.

Increased incidence has been observed for the following types of cancer: small intestine, gallbladder, pancreas, larynx, bladder, uterus, cervix, endometrium, ovary connective tissue, Hodgkin's lymphoma (men) and non-Hodgkin's lymphoma in women (33).

In a study published in 2017 by Chen Y et al. analyzed 31 cohort studies to find an correlation between BMI and breast cancer incidence in postmenopausal or premenopausal women. Studies have shown a positive association between BMI

and an increased incidence of breast cancer in postmenopausal women. No positive correlation was found in premenopausal European women between BMI and breast cancer (34).

A high fiber diet has beneficial effects on the body being involved in metabolism regulation, energy homeostasis and immune function. Fibers are involved in the fight against many disorders such as obesity, diabetes, dyslipidemia, hypertension or colon cancer (35).

CONCLUSIONS

The high consumption of hypercaloric foods leads to obesity. Chronic inflammation and OS induced by obesity cause DNA damage, which is involved in the pathogenesis of cancer. Caloric restriction and a diet rich in fruits and vegetables has beneficial effects on the human body and reduces the incidence of cancer.

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