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ANATOMY

BCH 308

Questions

- What do you understand by primary obesity?
- How does drug therapy and congenital syndrome affect secondary obesity?
- Discuss the etymology of cancer and its molecular basis

ANSWER

1. Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health. It is defined by body mass index (BMI). Primary Obesity is a medical condition in which excess body fat has accumulated to an extent that it may have a negative effect on health. People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30 kg/m2; the range 25–30 kg/m2 is defined as overweight. Obesity is most commonly caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility. In the world wide, obesity represents one of the major public health issue associated with increased morbidity and mortality. Overweight or obesity, significantly increases the likelihood of various diseases and conditions, such as: arterial hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, cerebral vasculopathy, gallbladder lithiasis, arthropathy, ovarian polycytosis, sleep apnea syndrome, and some neoplasms. Primary obesity is simply obesity caused by the accumulation of excess body fat due to increased energy intake and decreased energy expenditure.

2. How Drug Therapy affect Secondary Obesity**:**

Sometimes it is not the drug itself causing weight gain; however, it is the side-effects from the drug. Some drugs stimulate arcuate nucleus of the hypothalamus causing a large appetite, and as a result, more food is been consumed. Others

may affect how your body absorbs and stores glucose, which can lead to fat deposits in the midsection of your body.

Drug-induced weight gain is a serious side effect of many commonly used drugs leading to noncompliance with therapy and to exacerbation of comorbid conditions related to obesity. Improved glycemic control achieved by inssulin, insulin secretagogues or thiazolidinedione therapy is generally accompanied by weight gain. It is a problematic side effect of therapy due to the known deleterious effect of weight gain on glucose control, increased blood pressure and worsening lipid profile.

The atypical antipsychotic drugs (clozapine, olanzepine, risperidone and quetiapine) are known to cause marked weight gain. Antidepressants such as amitriptyline, mirtazapine and some serotonin reuptake inhibitors (SSRIs) also may promote appreciable weight gain that cannot be explained solely by improvement in depressive symptoms. The same phenomenon is observed with mood stabilizers such as lithium, valproic acid and carbamazepine.

How congenital syndrome affects Secondary Obesity**:**

Some of the most common endocrine disorders that can contribute to secondary disorder include:

- A deficiency in thyroid hormone (hypothyroidism) and
- Polycystic ovarian syndrome (PCOS).

There are also some rare causes of secondary obesity like Cushing's disease (hypercortisolism), hypothalamic injury or disorders, and genetic mutations.

- Hyperthyroidism:

When your thyroid makes less of its hormones - as it does in hypothyroidism - your metabolism slows down. The more severe your hypothyroidism is, the more weight you'll gain. Some of the weight gain is fat, which may lead to obesity along the line but much of it is fluid buildup from the effects of an underactive thyroid on your kidney function.

- Polycystic ovarian syndrome: PCOS can cause missed or irregular menstrual periods, excess hair growth, acne, infertility, and weight gain. Women with PCOS may be at higher risk for type 2 diabetes, high blood pressure, heart problems, and endometrial cancer.

3. Etymology of cancer: Cancer is derived from a Latin word meaning "Malignant tumor" and also derived from the Greek word karkinos which also means "Tumor" Cancer risk factors

As a rule, carcinogenesis is a process caused not by a single factor but by collaborative action of several agents.

Major carcinogenic factors:

1. Chemical carcinogens (tobacco, asbestos, etc.)
2. Radiation (UV, ionising)
3. Oncogenic viruses

Other risk factors

1. Diet
2. Chronic infections [helicobacter pylori (stomach), hepatitis C and B viruses (liver), human papillomaviruses (HPV; cervix, oral?)]
3. Genetic predisposition

Smoking, which is responsible for approx. 25-30% of all cancer deaths, is the preventable risk factor with a major significance. Diet is, presumably, a similarly significant risk factor. Approx. 20-40% of all cancer deaths are caused by an unbalanced diet, ie general over-nutrition, too many animal fats, and reduced intake of certain vitamins, minerals and fibres of fresh fruit and vegetables. Further risk factors include infections, genetic predisposition, alcohol abuse, occupational exposition to carcinogenic agents and environmental effects, such as solar irradiation as well as indoor exposition to radon, and passive smoking.

Chemical carcinogens

The carcinogenic effect of all chemical substances is based on their ability to react with intracellular macromolecules, especially DNA and RNA, and thus induce malfunctions in the cells. The primary targets of chemical carcinogens are the oncogenes and tumour suppressor genes. Chemical carcinogens are broadly divided into two classes: complete (initiator + promoter) and the more frequently occurring incomplete (only initiator) agents. Their action may be direct or indirect (procarcinogens – activation after metabolic conversion). The carcinogenic effect of pro-carcinogens is primarily dependent on the site of their metabolic conversion. With ubiquitary enzymes, carcinogenesis occurs at the site of entrance (e.g. benzo[a]pyrene in tobacco smoke, metabolic conversion in the lungs, bronchial carcinoma). Substances that require organ-specific enzymes for metabolic conversion, e.g. aromatic amines (conversion at first in the liver, then in the kidney, carcinogenic effect only in the urinary bladder) will induce malignancy far away from the entrance.

Risk behaviour: Smoking and chronic alcohol abuse

Tobacco is by far the most important risk factor for oral cancer and pre-cancer. Tobacco is smoked, chewed or sniffed worldwide. Processed tobacco contains at least 3050 compounds, many of which are toxic and/or carcinogenic. Besides aromatic hydrocarbons (e.g. benzo[a]pyrene), the tobacco-specific N-nitrosamines (TSNA) are the major carcinogens. TSNAs are causative agents for oral cancer and precancer (oral leukoplakias). Cigarette smoke is also directly associated with the development of laryngeal and bronchial carcinoma. Moreover, about one third of all cancer-related deaths worldwide are attributed to smoking. Smokers have a significantly increased risk of developing cancer, not only in the upper and lower respiratory tract but also in the following organs:

- Stomach
- Esophagus
- Bladder
- Kidney

- Pancreas
- Uterine cervix
- Breast
- Colon

While most people are aware of the dangers of smoking, awareness of the consequences of alcohol abuse for the development of malignant tumours, particularly oral and pharyngeal carcinomas, is lacking. The risk for smokers who do not drink alcohol is twice to four times as high as that for non-smokers; this risk is increased 5 to 15-fold with excessive smoking and alcohol consumption (alcohol increases the permeability of the oral mucosa, thus intensifying the carcinogenic effect of smoking). Three glasses of wine a day are also supposed to increase the risk in non-smokers by factor. Results of a metaanalysis of all epidemiological data available so far on the hazardous effects of mild, moderate, or heavy chronic alcohol abuse suggest an increasing rate of cancer. Every drink taken on an average daily basis (mean alcohol content approx. 10 g) increases the risk of a malignancy by 5 to 30%, with the highest risk being that of oral, pharyngeal, or oesophageal tumours (Longnecker MP & Engner S. 1996)

Radiation carcinogenesis

All types of shortvawe radiation, especially ionising radiation, can cause cancer. Principally, the effects of ionising radiation and ultraviolet rays are distinguished.

Mechanism of damaging action

The carcinogenic effect of radiation is related to its mutagenic effects, e.g. damage to DNA through the surrounding hydrogen molecules. Water molecules will be split by photons into free radicals (H+,OH-,e-) which will finally damage the DNA.

The radiation energy

- Causes chromosome breakage, translocation and point mutations
- Changes the protein structure
- Inactivates enzymes
- Destroys membranes.

Ultraviolet rays (UV)

Effect of UV rays on skin:

- Inactivation of enzymes
- Inhibition of cell division
- Activation of T-suppressor cells
- Activation of tumour suppressor gene p53
- Induction of mutations
- Cell death

The most common types of UV-induced skin tumours are:

- Squamous cell carcinoma (epidermis)
- Malignant melanoma (melanocytes)
- Basocellular carcinoma (pluripotent stem cell?)

Ionising radiation (alpha, beta and gamma rays)

- Alpha rays consist of protons and neutrons
- Beta rays consist of electrons
- Gamma rays include photons and X-rays

The carcinogenic effect of ionising radiation depends on:

- Type of radiation (alpha rays are more dangerous than gamma)
- Dose-incidence relation
- DNA-repair mechanisms
- Host factors (age, immune status, hormones, tissue characteristics)

Survivors of radiation catastrophes (Hiroshima, Nagasaki, Chernobyl) disclosed a markedly increased incidence of: myeloid leukaemia (bone marrow), carcinomas of the thyroid gland, breast and lung.

- Many physicians from the early X-ray era died of radiation-induced cancers.

Oncogenic viruses

RNA viruses

The oncogenic RNA viruses are referred to as retroviruses since they contain a reverse transcriptase (in the infected cell, a virus DNA is synthetised by the virus RNA which will be incorporated into the host genome).

Two types are distinguished:

1. Acute transforming retroviruses
2. Slow transforming retroviruses

Human retrovirus infections (tumours)

- Human T-cell leukaemia/lymphoma virus (HTLV) type I and III
- HTLV-III is identical with the causative agent of AIDS (HIV=human immunodeficiency virus). Its association with human malignancies is indirect: Kaposi's sarcoma, malignant non-Hodgkin lymphomas, leukaemias.

Despite their high number, the role of retroviruses in human carcinogenesis has so far only been proved in the above-mentioned two tumours.

Oncogenic DNA viruses

They are mainly responsible for the development of malignant tumours in humans. Some viruses are particularly characteristic for certain diseases. The mechanisms of the neoplastic effect of DNA viruses are manifold: some of them, like HPV, include transforming sequences (oncogenes) which will be incorporated into the host genome, others have an indirect effect.

Molecular basis of cancer

It is a multi-step process that requires the accumulation of many genetic changes over time. These genetic alterations involve activation of proto-oncogenes to oncogenes, deregulation of tumour suppressor genes and DNA repair genes and ‘immortalisation’.
Cell cycle regulation and the importance of apoptosis In normal cells, proliferation and progression through the cell cycle is strictly regulated by groups of proteins that interact with each other in a specific sequence of events. Checkpoints ascertain that individual stages of the cell cycle are completed correctly and ensure that incompletely replicated DNA is not passed onto daughter cells. Core to this control system are cyclin-dependent kinases (CDKs).

Cell immortalisation and tumourigenesis

Immortalisation is defined as the acquisition of an infinite lifespan. Normal mammalian somatic cells proliferate a limited number of times before undergoing senescence. Senescent cells may remain metabolically active even though they have permanently ceased proliferation. Immortalisation is an essential step in the malignant transformation of normal cells and can be attributed, in part, to the presence of telomerase, the enzyme responsible for maintaining telomeres at the ends of chromosomes. By extending telomeric DNA, telomerase is able to counter the progressive telomere shortening that would otherwise lead to cell death.