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 Assignment

1. What do you understand by primary obesity ?

2. How does drug therapy and congenital syndrome affect secondary obesity ?

3. Discuss the aetiology of cancer and it’s molecular basis ?

 Answers

1. Obesity is a medical condition in which excess body fat has

 accumulated to an extent that it may have a negative effect on health. 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.

1. 2. Secondary obesity means that you have a medical condition that has caused you to gain weight.

There are some congenital conditions that can lead to secondary obesity such as;

• Hypothyroidism: it is associated with decreased thermo genesis, decreased metabolic rate, and has also been shown to correlate with a higher body mass index (BMI) and a higher prevalence of obesity.

• Polycystic ovarian syndrome (PCOS): is a condition that affects a woman's hormone levels. Women with PCOS produce higher than normal amounts of male hormones. This hormone imbalance causes them to skip menstrual periods and makes it harder for them to get pregnant. Polycystic ovary syndrome is a condition that can affect a woman's ability to produce eggs. PCOS is linked with higher levels of circulating insulin, which is characteristic in type 2 diabetes

• Cushing disease: it is a condition in which the pituitary gland releases too much adrenocorticotropic hormone (ACTH). The pituitary gland is an organ of the endocrine system. Cushing disease is a form of Cushing syndrome. Cushing disease can occur if you have high stress levels of the stress hormone cortical, in your blood. Cortisol increases our blood pressure and blood glucose levels and is one complication which can result from untreated Cushing's syndrome.

• Obesity is fairly significant in individuals with congenital syndrome such as heart disease. Obesity can also serve as a risk factor to hypertension. Pregnancy obesity can also serve as a risk factor to malformations on the fetus. Maternal obesity is associated with an increased risk for congenital anomalies. Obese women were more likely to have an infant with spinal bifida, omphalocele, heart defects and multiple anomalies. Overweight women were more likely to have infants with heart defects and multiple anomalies.

There are some certain kinds of medications that can induce diabetes but can be reversed when the drugs are discontinued. There are some drugs known to induce diabetes such as;

• Corticosteroid

• Thiazide diuretics

• Beta-blockers

• Antipsychotics

• Statins

Corticosteroid: This is a powerful drug used to treat symptoms like inflammation caused by rheumatoid arthritis and lupus.

However, particularly if corticosteroids are taken over longer periods of time, steroid treatment can sometimes lead to the development of type 2 diabetes permanently. Whilst on steroid medication, you may need to take diabetes medication which may include insulin. When you come off the steroids course of treatment, you may be able to go onto less strong diabetes medication or come off blood glucose lowering medication altogether. From my general understanding steroids can lead to type 2 diabetes.

Effect of drug therapy on secondary obesity

The pharmacological treatment for obesity has attracted much attention from both clinicians and patients, although the amount of extra weight loss attributable to it is modest (<5 kg at 1 year). Nevertheless, this amount of weight loss has been shown to improve insulin sensitivity, glycaemic control, dyslipidaemia and hypertension in overweight patients. A major goal of weight management is to improve cardiovascular risks so that the overall obesity-related morbidity and mortality can be reduced. Therefore, drugs for obesity are expected to demonstrate these additional benefits.

While there are many factors which contribute to obesity, the balance between calorie intake and energy expenditure is crucial in determining a person's weight. Drug treatment of obesity can be classified into three groups based on different mechanisms of action: drugs that reduce food intake; drugs that interfere with fat absorption; and drugs that increase energy expenditure and thermogenesis.

a. Drugs that reduce food intake

This class of medication used for weight control acts primarily on neurotransmitters of the central nervous system to reduce food intake. This class of drugs includes noradrenergic drugs, serotonergic drugs, serotonergic and adrenergic drugs, drugs binding to the γ-aminobutyric acid receptors or the cannabinoid receptors, and some peptides that reduce appetite or elicit a feeling of satiety. Noradrenergic drugs release norepinephrine (noradrenaline) or block its uptake into neurons to affect food intake. Norepinephrine is released from stores in the presynaptic vesicles, and then reduces food intake by acting on β-adrenergic receptors in the perifornical hypothalamus. These drugs include phenylpropanolamine, amphetamine, phentermine and diethylpropion. Phenylpropanolamine has been withdrawn because of its association with an increased risk of haemorrhagic stroke. Amphetamine is potentially addictive and is therefore not recommended for the treatment of obesity. Phentermine and diethylpropion, which stimulate the release of norepinephrine, are sympathomimetic amines like amphetamine. However, unlike amphetamine, they have little or no effect on dopamine release at the synapse.

b. Drugs which interfere with fat absorption

Orlistat is a reversible gastrointestinal lipase inhibitor which inactivates hydrolyzation of dietary fat and prevents absorption of dietary fat by approximately 30%, thus reducing the calorie intake of the patient. Orlistat is the medication, other than sibutramine, currently approved for the long-term management of obesity. In February 2007, a reduced-strength version of orlistat was approved for over-the-counter use by USFDA. A meta-analysis of 29 studies of orlistat for weight loss in adults reported that the pooled mean weight loss was 2.59 kg at 6 months and 2.89 kg at 12 months. A number of clinical trials including the 4-year XENical in the prevention of diabetes in obese subjects (XENDOS) study demonstrated that orlistat-treated patients had statistically significant reductions in waist circumference, total and LDL-C, blood pressure and improvements in blood glucose concentrations and insulin resistance when compared with patients on placebo and diet only.

c. Drugs which increase energy expenditure and thermogenesis

Ephedrine and caffeine belong to this category. One long-term placebo-controlled clinical trial with ephedrine, caffeine or their combination showed that the combination of ephedrine and caffeine had greater effect on weight loss than either when used alone. These substances are contained in some health supplements. However, the USFDA has not approved the combination of ephedrine and caffeine as a weight-reducing treatment.

Effect of congenital syndrome on secondary obesity.

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

a. A deficiency in thyroid hormone (hypothyroidism)

According to common perception, hypothyroidism is held responsible for obesity. However, linking them causally is controversial. Overt hypothyroidism is associated with modest weight gain, but there is a lack of clarity regarding subclinical hypothyroidism. Novel view indicates that changes in thyroid-stimulating hormone (TSH) could well be secondary to obesity. The increasing prevalence of obesity further confounds definition of normal TSH range in population studies. Thyroid autoantibody status may help in establishing the diagnosis of subclinical hypothyroidism in obesity. High leptin levels may play a role in the hyperthyrotropinemia of obesity and also increase susceptibility to thyroid autoimmunity and subsequent hypothyroidism. There is at most a modest effect of L-T4 treatment in overt hypothyroidism in inducing weight loss; benefit in subclinical hypothyroidism is not established with no data supporting thyroid hormone use in euthyroid obese patients.

When your thyroid makes less of its hormones, your metabolism slows down. 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.

b. Polycystic ovarian syndrome (PCOS):

Since its original description in 1935 by Stein and Leventhal, obesity has been recognized as a common feature of the polycystic ovary syndrome (PCOS). In the United States, some studies report that the prevalence of overweight and obesity in women with PCOS is as high as 80%. Outside the U.S., the prevalence of obesity in affected women is lower, although it has increased over time, with studies reporting rates as low as 20%. Differences in the diagnostic criteria for PCOS account for some of this difference in prevalence rates. However, even when comparable diagnostic criteria are applied, both the prevalence and severity of obesity are lower in women with PCOS outside the U.S. This observation suggests that environmental factors, such as lifestyle, contribute to development of obesity in PCOS. The consistent association between PCOS and obesity suggests a biologic basis for this observation. Moreover, obesity exacerbates many of the reproductive and metabolic abnormalities associated with PCOS. This review explores the available data on the mechanisms of this association. 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.

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

3. Cancer is a disease caused by genetic changes leading to uncontrolled cell growth and tumor formation. The basic cause of sporadic (non-familial) cancers is DNA damage and genomic instability. A minority of cancers are due to inherited genetic mutations. Etiologies of cancer can be defined as the causes or cofactors of cancer.

Aetiology of Cancer:

The majority of cancers, are due to genetic mutations from environmental and lifestyle factors. The remaining are due to inherited genetics. Environmental refers to any cause that is not inherited genetically, such as lifestyle, economic, and behavioral factors and not merely pollution. Common environmental factors that contribute to cancer death include tobacco, diet and obesity, infections, radiation (both ionizing and non-ionizing, up to 10%), lack of physical activity, and pollution. Psychological stress does not appear to be a risk factor for the onset of cancer, though it may worsen outcomes in those who already have cancer.

It is not generally possible to prove what caused a particular cancer because the various causes do not have specific fingerprints. For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, the cancer may have developed for one of those reasons. Excepting the rare transmissions that occur with pregnancies and occasional organ donors, cancer is generally not a transmissible disease.

Environmental Factors that cause cancer.

• Chemicals

The incidence of lung cancer is highly correlated with smoking. Exposure to particular substances have been linked to specific types of cancer. These substances are called carcinogens. Tobacco smoke, for example, causes 90% of lung cancer. It also causes cancer in the larynx, head, neck, stomach, bladder, kidney, esophagus and pancreas. Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons. Tobacco is responsible for about one in five cancer deaths worldwide and about one in three in the developed world. Cancers such as lung cancer and mesothelioma can come from inhaling tobacco smoke or asbestos fibers, or leukemia from exposure to benzene.

• Diet and exercise

Diet, physical inactivity and obesity are related to up to 30–35% of cancer deaths. Physical inactivity is believed to contribute to cancer risk, not only through its effect on body weight but also through negative effects on the immune system and endocrine system. More than half of the effect from diet is due to overnutrition (eating too much), rather than from eating too few vegetables or other healthful foods. Some specific foods are linked to specific cancers. A high-salt diet is linked to gastric cancer. Aflatoxin B1, a frequent food contaminant, causes liver cancer. Betel nut chewing can cause oral cancer. National differences in dietary practices may partly explain differences in cancer incidence. For example, gastric cancer is more common in Japan due to its high-salt diet while colon cancer is more common in the United States. Immigrant cancer profiles mirror those of their new country, often within one generation.

• Infection

Worldwide approximately 18% of cancer deaths are related to infectious diseases. Viruses are the usual infectious agents that cause cancer but cancer bacteria and parasites may also play a role.

a. Oncoviruses (viruses that can cause cancer) include human papillomavirus (cervical cancer), Epstein–Barr virus (B-cell lymphoproliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpesvirus (Kaposi's sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma) and human T-cell leukemia virus-1 (T-cell leukemias).

b. Bacterial infection may also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma.

c. Parasitic infections associated with cancer include Schistosoma haematobium (squamous cell carcinoma of the bladder) and the liver flukes, Opisthorchis viverrini and Clonorchis sinensis (cholangiocarcinoma).

Therefore;

Bacteria and viruses can cause cancer:

▪ Helicobacter pylori (H. pylori, which causes gastritis)

▪ HBV, HCV (hepatitis viruses that cause hepatitis)

▪ HPV (human papilloma virus, papilloma virus, which causes changes eg. Cervical cells)

▪ EBV (Epstein-Barr virus, the herpes virus that causes inflammation of the throat lymphoid).

• Radiation

Radiation exposure such as ultraviolet radiation and radioactive material is a risk factor for cancer. Many non-melanoma skin cancers are due to ultraviolet radiation, mostly from sunlight. Sources of ionizing radiation include medical imaging and radon gas. Ionizing radiation is not a particularly strong mutagen. Medical use of ionizing radiation is a small but growing source of radiation-induced cancers. Ionizing radiation may be used to treat other cancers, but this may, in some cases, induce a second form of cancer. It is also used in some kinds of medical imaging.

Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies. Clear evidence establishes ultraviolet radiation, especially the non-ionizing medium wave UVB, as the cause of most non-melanoma skin cancers, which are the most common forms of cancer in the world.

Non-ionizing radio frequency radiation from mobile phones, electric power transmission and other similar sources has been described as a possible carcinogen by the World Health Organization's International Agency for Research on Cancer.[62] Evidence, however, has not supported a concern. This includes that studies have not found a consistent link between mobile phone radiation and cancer risk.

• Heredity

The vast majority of cancers are non-hereditary (sporadic). Hereditary cancers are primarily caused by an inherited genetic defect. Some of these syndromes include: certain inherited mutations in the genes BRCA1 and BRCA2 with a more than 75% risk of breast cancer and ovarian cancer and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), which is present in about 3% of people with colorectal cancer, among others. Statistically for cancers causing most mortality, the relative risk of developing colorectal cancer when a first-degree relative (parent, sibling or child) has been diagnosed with it is about 2.The corresponding relative risk is 1.5 for lung cancer, and 1.9 for prostate cancer. For breast cancer, the relative risk is 1.8 with a first-degree relative having developed it at 50 years of age or older, and 3.3 when the relative developed it when being younger than 50 years of age.

Taller people have an increased risk of cancer because they have more cells than shorter people. Since height is genetically determined to a large extent, taller people have a heritable increase of cancer risk.

• Physical agents that cause cancer

Some substances cause cancer primarily through their physical, rather than chemical, effects. A prominent example of this is prolonged exposure to asbestos, naturally occurring mineral fibers that are a major cause of mesothelioma (cancer of the serous membrane) usually the serous membrane surrounding the lungs. Other substances in this category, including both naturally occurring and synthetic asbestos-like fibers, such as wollastonite, attapulgite, glass wool and rock wool, are believed to have similar effects. Non-fibrous particulate materials that cause cancer include powdered metallic cobalt and nickel and crystalline silica (quartz, cristobalite and tridymite). Usually, physical carcinogens must get inside the body (such as through inhalation) and require years of exposure to produce cancer.

Physical trauma resulting in cancer is relatively rare. Claims that breaking bones resulted in bone cancer, for example, have not been proven. Frequent consumption of scalding hot tea may produce esophageal cancer. Generally, it is believed that cancer arises, or a pre-existing cancer is encouraged, during the process of healing, rather than directly by the trauma. However, repeated injuries to the same tissues might promote excessive cell proliferation, which could then increase the odds of a cancerous mutation. Chronic inflammation has been hypothesized to directly cause mutation. Inflammation can contribute to proliferation, survival, angiogenesis and migration of cancer cells by influencing the tumor microenvironment. Oncogenes build up an inflammatory pro-tumorigenic microenvironment.

• Hormones

Some hormones play a role in the development of cancer by promoting cell proliferation. Insulin-like growth factors and their binding proteins play a key role in cancer cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis.

Hormones are important agents in sex-related cancers, such as cancer of the breast, endometrium, prostate, ovary and testis and also of thyroid cancer and bone cancer. Other factors are relevant: obese people have higher levels of some hormones associated with cancer and a higher rate of those cancers. Women who take hormone replacement therapy have a higher risk of developing cancers associated with those hormones. On the other hand, people who exercise far more than average have lower levels of these hormones and lower risk of cancer. Osteosarcoma may be promoted by growth hormones. Some treatments and prevention approaches leverage this cause by artificially reducing hormone levels and thus discouraging hormone-sensitive cancers.

• Autoimmune diseases

There is an association between celiac disease and an increased risk of all cancers. People with untreated celiac disease have a higher risk, but this risk decreases with time after diagnosis and strict treatment, probably due to the adoption of a gluten-free diet, which seems to have a protective role against development of malignancy in people with celiac disease. However, the delay in diagnosis and initiation of a gluten-free diet seems to increase the risk of malignancies. Rates of gastrointestinal cancers are increased in people with Crohn's disease and ulcerative colitis, due to chronic inflammation. Also, immunomodulators and biologic agents used to treat these diseases may promote developing extra-intestinal malignancies.

Some drugs may increase the risk of cancer:

▪ certain antineoplastic agents

▪ certain hormones

▪ medicines that cause immune deficiency

Molecular Basis of Cancer:

Cancer is a group of diseases characterized by an autonomous proliferation of neoplastic cells which have a number of alterations, including mutations and genetic instability. Cellular functions are controlled by proteins, and because these proteins are encoded by DNA organized into genes, molecular studies have shown that cancer is a paradigm of acquired genetic disease. The process of protein production involves a cascade of several different steps, each with its attendant enzymes, which are also encoded by DNA and regulated by other proteins. Most steps in the process can be affected, eventually leading to an alteration in the amount or structure of proteins, which in turn affects cellular function. However, whereas cellular function may be altered by disturbance of one gene, malignant transformation is thought to require two or more abnormalities occurring in the same cell. Although there are mechanisms responsible for DNA maintenance and repair, the basic structure of DNA and the order of the nucleotide bases can be mutated. These mutations can be inherited or can occur sporadically, and can be present in all cells or only in the tumor cells. At the nucleotide level, these mutations can be substitutions, additions or deletions.