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Medicine and Surgery

BCH 313: Medical Biochemistry

Assignment

**Question 1**

**What do you understand by primary or simple obesity?**

Primary 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) and further evaluated in terms of fat distribution via the waist to hip ratio and total cardiovascular risk factors.

In primary obesity, the excess accumulation of fat is as a result of low insulin production of the body or reduced response to the insulin hormone without any underlying condition affecting it. Any underlying condition that leads to weight gain and affects the weight regulating system of the body is categorized as secondary obesity e.g endocrine conditions, hypothalamic conditions and congenital disorders.

**Question 2**

**How does congenital syndrome and drug therapy affect obesity?**

Obesity is a major risk factor for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Drugs such as steroids and some antidepressants may also cause weight gain. It is essential that the medications are used in conjunction with healthy eating; physical activity, and behavior modification, as medication usage without such changes are generally ineffective. The decision to initiate drug therapy in overweight individuals should be made after consideration of the risks and benefits and the goals of drug therapy should be clear.

The goal of drug therapy for overweight individuals is long-term weight reduction and improvement in overall health. In short-term, 6 to 12 months of clinical trials evaluating drug therapy, weight loss of 4 to 8 percent is typical. Upon initiation of anti-obesity medication, several things must be noted. First, not every drug works for every patient; individual responses vary widely. Second, when the maximal therapeutic effect is achieved, a plateau is reached and weight loss ceases. Finally, when drug therapy is discontinued, weight gain can be expected. Unfortunately, there is still no ideal drug for the treatment of obesity and the current ones are very strictly evaluated. The anti-obesity drug therapy should target patients that have previously failed to lose weight with lifestyle interventions, with BMI ≥30 kg/m2, or those with BMI ≥27 kg/m2 plus concomitant obesity related risk factors or diseases.

The mandatory statement is that lifestyle modifications including dietary habits modification, physical therapy and behavioral therapy are the basis of all weight loss strategies. If the patient is not losing weight using these methods (at least 0.45 kg/week during 6 months), drug therapy should be considered. Available drugs treating obesity could be divided into three categories.

* The first one is the group of drugs that suppress appetite (eg. sibutramine)
* the second is the group of drugs that interfere with digestion (eg. orlistat)
* the third category is an inhomogeneous group of drugs that are actually used for other indications than weight loss, but with a concomitant weight loss effect. Such drugs are for example incretins used in the treatment of diabetes (eg. exenatide, liraglutide), antiepileptic drugs (eg. topimarate) and antidepressants (eg. fluoxetin, sertaline).

Orlistat is a pancreatic lipase inhibitor that blocks the absorption of up to one-third of ingested fat with minimal systemic absorption. Orlistat therapy reduces weight to a modest extent but also the incidence of diabetes beyond the result achieved with lifestyle changes. The possible explanation is the fact that apart from decreasing insulin resistance as a result of weight loss, orlistat may increase postprandial GLP-1 levels acting in gut only. Indirectly, it enhances insulin secretory response to the meal. The most common side effects are diarrhoea and steatorrhea that could be minimized by maintaining a strict low fat diet (<30% of diet). Therapy with orlistat must be controlled and re-evaluated. it should be continued beyond 3 months only if the person has lost at least 5% of the initial body weight since starting drug treatment. Co-prescribing orlistat with other drugs for weight reduction is not recommended.

Incretins are substances secreted form the gut after the meal. The incretin hormones glucagon-like peptide-1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) are released from intestinal cells in response to glucose ingestion. They are degraded quickly in bloodstream by the dipeptidyl-peptidase 4 (DPP4) enzyme. GLP1 is the most investigated incretin and the target of medical therapy. GLP1 reduces gastric emptying, lowers appetite by promoting satiety via hypothalamic receptors and reduces food intake. In this way, GLP1 action leads to substantial and sustained weight loss. There are two types of drugs currently on the market that imitate GLP1 action: DPPP4 inhibitors (drugs that inhibit the action of GLP1 degrading enzyme) and incretin mimetics or analogues (drugs with similar structure to GLP1, only resistant to DPP4). Only incretin mimetics or analogues have weight loss effect, while DPP4 inhibitors do not. The first approved drug using the "incretin effect" was exenatide, an incretin mimetic, followed by liraglutide, an incretin analogue, as the second one. The main problem of this type of drugs is subcutaneous administration. Current indication for prescribing these types of drugs is treatment of obese patients with type 2 diabetes mellitus, not obesity alone. The side effects include nausea, vomiting, and rarely pancreatitis.

Fluoxetine is an antidepressant drug from the group of selective serotonin reuptake inhibitors. Since depression as a disease is strongly associated with obesity and many drugs treating depression finally result in weight gain, such a drug is more than welcome in psychiatry. Long-term studies with fluoxetine have shown significant weight loss, but the drug is still primarily indicated for depressive disorders. There are some speculations that fluoxetine contributes to weight loss by increasing resting energy expenditure. Some studies attribute such a weight loss effect also to sertraline, an antidepressant drug also from the group of selective serotonin reuptake inhibitors. Both sertraline and fluoxetine have shown to be effective in therapy of overweight patients with binge eating disorder.

Obese patients without comorbidities and BMI more than 30 kg/m2 could get orlistat, but only if they have failed to lose weight with lifestyle intervention. The patients with hypertension, dyslipidemia, coronary heart disease, and type 2 diabetes or sleep apnoea could get orlistat if their BMI is higher than 27 kg/m2. Obese type 2 diabetic patients without a previous history of pancreatitis and normal renal function who have failed to achieve satisfactory glucose regulation with oral antidiabetic drug are candidates for incretin mimetic or analogue (upon consultation with endocrinologist). An obese patient with a history of epileptic attack is candidate for topimarate (upon consultation with neurologist). A depressive obese patient, especially one having so called binge eating disorder could get fluoxetine or sertaline (upon consultation with psychiatrist).

**Obesity and Congenital syndromes**

Constitutional obesity and mental retardation co-occur in several multiple congenital anomaly syndromes, including Prader–Willi syndrome, Bardet–Biedl syndrome, Cohen syndrome, Albright hereditary osteodystrophy, and Borjeson–Forssman–Lehmann syndrome as well as some rarer disorders. Life span for children with congenital heart disease is less than normal. Congenital and acquired coronary disease and underlying vascular abnormalities in childhood are likely to be exacerbated by obesity, which is independently associated with endothelial dysfunction and hypertension. Activity restriction in children with congenital heart disease was associated with the development of obesity. Even children who were of healthy weight at baseline had a higher risk of becoming obese over time if their activity was restricted. Physical activity limitation is a risk factor unique to children with heart disease. Importantly, physical activity restrictions in children with heart disease are not solely determined by practitioner recommendations. Indeed, these limitations may sometimes be initiated by parents or be self-imposed. Children with heart disease are often sedentary even when not limited by their physiology.

Massin in a study reported recently that children who had undergone the arterial switch operation were much less likely than their peers to participate in moderate or vigorous activity even when no restrictions had been placed by their cardiologists. Decreased activity may lead to deconditioning, decreased exercise capacity, and lower quality of life. A sedentary lifestyle associated with congenital heart disease is known to carry into adulthood and predict increased morbidity and mortality in this population. Several recent studies have shown the benefits of physical training programs in both adults and children with congenital heart disease.Practitioners may need to refocus counselling during outpatient visits, providing careful instructions for appropriate and safe exercise regimens with regard to the underlying condition, in addition to more traditional counselling regarding exercise restrictions. Given the fact that patients with acquired and congenital heart disease have not escaped the epidemic of obesity, it is especially important for practitioners to adapt current activity guidelines

Genes and behavior may both be needed for a person to be overweight. In some cases multiple genes may increase one’s susceptibility for obesity and require outside factors; such as abundant food supply or little physical activity. Families can’t change their genes but they can change the family environment to encourage healthy eating habits and physical activity. Those changes can improve the health of family members—and improve the family health history of the next generation.

**Question 3**

**Outline the aetiology of cancer and its molecular basis?**

Neoplasia is an abnormal mass or tissue, the growth of which exceeds and is uncoordinated with that of normal tissue and persists in an excessive manner even after cessation of stimuli which caused the change.

Cancer is caused by genetic mutations, these genetic mutations usually result in altered proteins. These mutations are from DNA mutating agents such as chemicals, radiations, viruses etc., which causes a normal cell to have a damaged DNA. the DNA could repair itself through the stages of the cell cycle, however in cancer the damaged cell does not die or get repaired.

Failure of the DNA repair causes mutations in the genome of the somatic cells, these mutations are common in somatic cells then in the germ cells, would cause:

1. Activation of growth promoting oncogenes
2. Inactivation of tumor suppressing genes
3. Alteration in genes that regulate apoptosis

This would lead to unregulated cell division and decreased apoptosis, eventually the damaged cell would increase and proliferate, there would be added mutations, growth of new blood vessels that aid to increase the life of the cancerous cell, tumor progression and then malignant neoplasms leading to invasion and metastasis of the cancer.

**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:

* Chemical carcinogens (tobacco, asbestos, etc.)
* Radiation (UV, ionising)
* Oncogenic viruses

Other risk factors

* Diet
* Chronic infections [helicobacter pylori (stomach), hepatitis C and B viruses (liver), human papillomaviruses (HPV)]
* Genetic predisposition

**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) agent
* 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.

**Radiation carcinogenesis**

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

The melanin pigment in melanocytes provides protection against UV-radiation. Therefore, malignant melanoma occurs more rarely in people with dark skin than in fair-skinned individuals. Albinos and patients with xeroderma pigmentosum (defect of a DNA-repair gene) are at extremely high risk of developing UV-related tumours.

**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)

Hierarchy of radiation sensitivity between different organs:

1. Testis/ovaries
2. Bone marrow (leukaemia)
3. Thyroid gland
4. Gastro-intestinal tract
5. Breast
6. Lung
7. Salivary gland tissues
8. Skin
9. Bone

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. Also 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:

* Acute transforming retroviruses
* 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. HPV gene sequences can be detected in some oropharyngeal carcinomas, particularly those of the tonsils and the larynx.

**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). CDKs are ‘master protein kinases’ that drive progression through the different phases of the cell cycle by phosphorylating and activating other downstream kinases. CDK activity is dependent on the presence of activating subunits called cyclins which are synthesised and degraded in a cell cycle-dependent manner. Cyclin-CDK complexes are further tightly regulated by CDK inhibitors.

The re-entry of cells into the cell cycle is decided at the restriction point (R point). This decision is influenced by extracellular mitogenic signals which are transmitted via signalling pathways to key regulatory proteins, such as transcription factors (e.g. E2F) in the nucleus. These regulatory proteins ultimately activate the S-phase CDKs, which trigger the start of DNA synthesis.

In normal cells, activation of another transcription factor, p53, often referred to as the ‘guardian of the genome’, can impose cell cycle arrest and induce apoptosis (programmed cell death) through its ability to:

* induce the expression of cell cycle inhibitors to prevent proliferation of a cell until any damage has been repaired or
* Initiate apoptosis, if the genomic damage is too great and cannot be repaired.

In >50% of all human tumours the p53 pathway is aberrant. Inactivation of the p53 protein renders it unable to signal and activate the cell’s apoptotic machinery resulting in increased survival of cancer cells.

**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. Unlike normal cells that lack detectable levels of telomerase activity, approximately 90% of human tumours consist of cells that contain an active telomerase enzyme.