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**17/MHS01/081**

**BIO 313**

**MEDICAL BIOCHEMISTRY IV**

**QUESTION 1: WHAT DO YOU UNDERSTAND BY PRIMARY OR SIMPLE OBESITY?**

 Simple Obesity also called as primary obesity& is due to excessive energy intake and too little consumption, also known as diet-induced obesity and has the largest proportion in all types of obesity (95%). It is not associated with underlying clinical conditions. Metabolic diseases associated with primary obesity contribute to Hypertension, Diabetes type2, Hyperandrogenemia ,Dyslipidemia, etc

**QUESTIION 2:  HOW DOES CONGENITAL SYNDROME AND DRUG THERAPY AFFECT OBESITY?**

Overweight and obesity are major risk factors 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 which are used in conjunction with healthy eating; physical activity, and behaviour 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.

GOALS OF THERAPY

The goal of any treatment (including drug therapy) for overweight individuals is long-term weight reduction and improvement in overall health.

●Reduce and maintain weight loss – In short-term (6 to 12 months) 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.

During the history, many anti-obesity drugs were introduced and subsequently removed from the market due to various side effects. Unfortunately, there is still no ideal drug for the treatment of obesity and the current ones are very strictly evaluated. The anti-obesity drug/ drug therapy could/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 only drug currently approved in Europe is orlistat, a pancreatic lipase inhibitor. Sibutramine, an appetite suppressant (serotonin-norepinephrine reuptake inhibitor), is off the market since 2010 due to cardiovascular side effects.

The mandatory statement is that lifestyle modifications including dietary habits modification, physical therapy and behavioural 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. The efficacy of the drug should be reconsidered after therapy introduction. In situations when the drug is not efficacious enough, it should be re-evaluated and possibly discontinued.

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);
* and 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).

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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. Contraindications for its use are cholestasis, chronic malabsorption syndrome, and hypersensitivity to orlistat. 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.

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.

Which patients should be treated with what kind of anti-obesity drug?

Who should get medical treatment of obesity and with what kind of drug? 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). Should we encourage obese patients to take off label product, herbs, or unproven substances? There is an easy explanation: if there is no weight loss, there is no sense to take such a product. If an obese patient is losing weight using off label substance, the substance must be identified in the product. Sometimes it is not a harmless one.

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.

**QUESTION 3: OUTLINE THE AETIOLOGY OF CANCER AND ITS MOLECULAR BASIS.**

Causes of cancers necessarily involves an examination of the molecular machinery in cells that guides the basic processes of proliferation (increase in cell number by [cell division](https://www.britannica.com/science/cell-division)), differentiation (cell specialization into different tissue types), and [apoptosis](https://www.britannica.com/science/apoptosis) (programmed cell death). Those processes are guided by two innate programs in cells, the [genetic code](https://www.britannica.com/science/genetic-code) and the [epigenetic](https://www.britannica.com/science/epigenetics) code. In cancer each of those codes ultimately becomes altered regardless of whether the [disease](https://www.britannica.com/science/disease) originated with an external or internal factor. Indeed, a fundamental characteristic of a tumour cell is that it begets a tumour cell. In other words, cancer, once [manifest](https://www.merriam-webster.com/dictionary/manifest), becomes an inherited disease of the cell and is therefore self-perpetuating.

The hereditary nature of cancer at the cellular level explains why alterations have been found in both the genetic and the epigenetic codes in tumour cells. The number of alterations seen in the coded programs increases as tumours progress to more advanced stages. Their existence and accumulation also explain why principles of evolutionary theory provide insights of practical significance for cancer [biology](https://www.britannica.com/science/biology).