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

Obesity results when caloric intake exceeds energy expenditure. A crude population measure of obesity is the body mass index (BMI), a person’s weight (in kilograms) divided by the square of his or her height (in metres). A person with a BMI of 30 or more is generally considered obese.

1. **HOW DOES CONGENITAL SYNDROME AND DRUG THERAPY AFFECTS 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 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.

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.

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).

I**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 orlistatmust be controlled and re-evaluated. According to the National Institute for Health and Clinical Excellence (NICE) guidelines, 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 incretinmimetics or analogues (drugs with similar structure to GLP1, only resistant to DPP4). Only incretinmimetics 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.

**Which patients should be treated with what kind of anti-obesity 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 childrenwith congenital heart disease is less than normal. Congenital and acquired coronary disease andunderlying 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.

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.

However genes can directly cause obesity in specific disorders such as Bardet-Biedl syndrome and Prader-Willi syndrome. Prader-Willi syndrome, the commonest obesity syndrome is due to loss of imprinted genes on 15q11-13.

3. OUTLINE THE AETIOLOGY OF CANCER AND ITS MOLECULAR BASIS.

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
4. Smoking
5. Alcohol abuse
6. Environmental effects

**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

**Major chemical carcinogens in humans**

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| Carcinogenic substance | Tumour | Source |
| *Direct-acting carcinogens* |
| *Alkylating agents:* |   |   |
| Cyclophosphamide | Leukaemia, lymphoma | Cytostatic drugs |
| *Indirect-acting carcinogens* |
| *Polycyclic aromatic hydrocarbons*: |   |   |
| Carbon black, tar, mineral oilsbenzo[a]pyrene | Skin cancerBronchial carcinoma | Occupational exposition,Cigarette smoke |
| *Aromatic amines, azo dyes:* |   |   |
| 2-naphthylaminebenzidine (butter yellow)2-acetylaminofluorene | Urinary bladder cancerLiver cancer | Rubber industryDye industry |
| *Nitrosamines and nitrosamides:* |   |   |
| Dimethyl-,Diethylnitrosamine | Stomach, colon, liver cancer | Nitrates and nitrites in food (preservatives),Fertilisers,Tobacco smoke |
| *Organic substances/solvents:* |   |   |
| Vinyl chloridebenzene | Liver angiosarcoma, glioblastoma,Leukaemia | PVC productionChemical industry |
| *Anorganic substances:* |   |   |

**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?)

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 xerodermapigmentosum (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

**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. HPV gene sequences can be detected in some oropharyngeal carcinomas, particularly those of the tonsils and the larynx. Their role in the development of these tumours is the subject of research.

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| Virus family | Type | Tumour |
| Papavo Virus | Human Papilioma Virus: | Verruca vulgaris |
| Different types (1, 2, 4, and 7) |
| Types 6, 8, 11 (low-risk) | Genital warts (condylomaacuminatum)Laryngeal papilloma |
| Types 16, 18, 31, 33 (high-risk) | Cervical carcinomaOro-pharyngeal carcinomaLaryngeal carcinoma |
| Herpes viruses | Type 2 herpes-simplex virus(HSV-2) | Cervical carcinomaVulvar carcinoma |
| Epstein-Barr virus(EBV) | Malignant B-cell lymphoma(Burkitt-lymphoma)Hodgkin lymphomaNasopharyngeal carcinoma |
| Human herpes virus 8(HHV-8) | Kaposi's sarcoma |
| Hep-a-DNA viruses | Hepatitis B virus (HBV) | Hepatocellular carcinoma |
| Hepatitis C virus | Hepatocellular carcinoma |

**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’.

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 (refer to Figure 3, Section 2). 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.