Name: ADENIYI ADERONKE TEMILOLA

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1. What do you understand by primary or simple obesity?

Obesity is the pathological state resulting from the consumption of excessive quantity of food over an extended period of time leading to accumulation of excess fat in the body. It is calculated by 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.

Primary obesity is not associated with clinical condition.

1. How does congenital syndrome and drug therapy affects obesity.

Obesity is one of the major risk factor for a number of chronic diseases such as cardiovascular diseases cancer and diabetes. ***Drugs*** such as antipsychostic hypertension, 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.

Goals of Drug Therapy

The goal of drug therapy for overweight individuals with BMI ≥30 kg/m2, or those with BMI ≥27 kg/m2 plus concomitant obesity related risk factors or diseasesis the 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 % 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. Sadly there is still no ideal drug for the treatment of obesity and the current ones are very strictly evaluated**.** The only drug currently approved in Europe is orlistat, Sibutramine 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. Drugs for treatment of obesity include:

The first one is the group of drugs that interfere with digestion (eg: orlistat).

The second is the group of drugs that supresses appetite (eg: sibutramine)

The third category is an inhomogeneous group of drugs which are used for other indications than weight loss, but with a concomitant weight loss effect. Drugs and there uses in this category include: incretins used in the treatment of diabetes (eg. exenatide, liraglutide), antiepileptic drugs (eg. topimarate) and antidepressants (eg. fluoxetin, sertaline).

***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 the treatment of obese patients with type 2 diabetes mellitus. 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. Most drugs for treating depression results to weight gain, in the case that it may contribute to energy expenditure. Long-term studies with fluoxetine have shown significant weight loss, but the drug is still primarily indicated for depressive disorders. In further studies weight loss effect has been contributed 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.

***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).

***Topiramate*** is originally used to treat epilepsy, indicated as an anticonvulsant. The possible mechanism of action is blockage of Na channels, augmentation of the GABA-A receptor activity, antagonism of AMPA/kainate glutamate receptor, and inhibition of the carbonic anhydrase enzyme. Phentermine is an appetite suppressant, an amphetamine like stimulant. It is mediated through sympathetic pathways. The side effects are loss of appetite and vomiting. However, the worst side effect is its potential to cause psychological dependence which made it rejected because its benefits are far lesser than its loss.

Who should get medical treatment on obesity and which kind of drug? Obese patients without comorbidities and BMI more than 30 kg/m2 could get orlistat, only if they did not lose weight after 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 after consultation of endocrinologist. An obese patient with a history of epileptic attack is candidate for topimarate after consultation with neurologist. A depressive obese patient, especially one having so called binge eating disorder could get fluoxetine or sertaline after consultation with psychiatrist. Obese patients are advised not to take off label product because the substance needs to be identified in the product.

***Congenital syndromes***

Constitutional obesity and mental retardation co-occur in several multiple congenital anomaly syndromes, including Prader–Willi syndrome, Bardet–Biedl syndrome as well as other rare 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.

Massin in a study reported recently that children who had undergone the arterial switch operation were less likely 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. 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. 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 behaviour 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.

Sadly genes can directly cause obesity in specific disorders such as Bardet-Biedl syndrome and Prader-Willi syndrome which is the most common obesity syndrome due to deletion of a part of chromosome 15.

1. Outline the Aetiology of cancer and its Molecular Basis.

Cancer is an uncontrolled growth of abnormal cells (cancer cells/malignant cells/tumor cells) anywhere in the body. There are over 200 types of cancer.

**Risk factors of cancer**

As a rule, carcinogenesis is a process caused by collaborative action of several agents. Major carcinogenic factors include:

Chemical carcinogens (tobacco, asbestos, etc.)

Radiation (UV, ionising)

Oncogenic viruses

Others include: Diet, Chronic infections [helicobacter pylori (stomach), hepatitis C and B viruses (liver), human papillomaviruses (HPV; cervix, oral?)], 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 is caused by an *unbalanced diet* (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 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* (pro-carcinogens: 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 oils benzo[a]pyrene | Skin cancer Bronchial carcinoma | Occupational exposition, Cigarette smoke |
| *Aromatic amines, azo dyes:* |  |  |
| 2-naphthylamine benzidine (butter yellow) 2-acetylaminofluorene | Urinary bladder cancer Liver cancer | Rubber industry Dye industry |
| *Nitrosamines and nitrosamides:* |  |  |
| Dimethyl-, Diethylnitrosamine | Stomach, colon, liver cancer | Nitrates and nitrites in food (preservatives), Fertilisers, Tobacco smoke |
| *Organic substances/solvents:* |  |  |
| Vinyl chloride benzene | Liver angiosarcoma, glioblastoma, Leukaemia | PVC production Chemical industry |
| *Anorganic substances:* |  |  |
| Arsenic | Skin, bronchial, liver cancer | Ore extraction, Heat technology, Construction industry, mining, Fossil fuel refinery |
| Asbestos | Mesothelioma, bronchial carcinoma |
| Chromium | Bronchial carcinoma |
| Nickel | Carcinoma of the nasal cavity |
| *Biological substances:* |  |
| Aflatoxin B1 Diethylstilbestrol | Liver cancer Endometrial cancer | Aspergillus flavus (fungus) Synthetic oestrogen |

**Risk behaviour: Smoking and chronic alcohol abuse**

***Tobacco*** is by far the most important risk factor for oral cancer and pre-cancer. Tobacco contains 3500 compounds which are mainly toxic (carcinogenic). It is smoked, chewed or sniffed worldwide. 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 pre-cancer (*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, oesophagus, bladder, kidney, pancreas, uterine cervix, breast and colon.

A correlation between smoking and *leukaemia* is also discussed. Beside the increased risk of cancer, the hazard of developing diseases of the cardiovascular system and the lungs is generally recognised. The number of tobacco-related deaths in Germany is more than 100,000 per year; approx. 50% of smokers die of smoking-related diseases. The *early starting age* (at present *13.5 years*) gives rise to particular concern.

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).

**Radiation carcinogenesis**

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

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 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, and tissue characteristics).

Hierarchy of radiation sensitivity between different organs: Testis/ovaries; Bone marrow (leukaemia); Thyroid gland; Gastro-intestinal tract; Breast; Lung; Salivary gland tissues; Skin; Bone.

Survivors of radiation catastrophes (Hiroshima, Nagasaki, and 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*

They are referred to as *retroviruses* since they contain a reverse transcriptase (in the infected cell, a virus DNA is synthesised 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 1 and 3. 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.

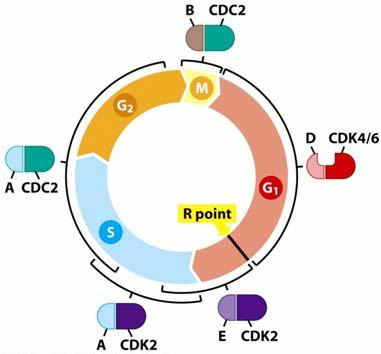
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| Virus family | Type | Tumour |
| Papavo Virus | Human Papilioma Virus: | Verruca vulgaris |
| Different types (1, 2, 4, and 7) |
| Types 6, 8, 11 (low-risk) | Genital warts (condyloma acuminatum) Laryngeal papilloma |
| Types 16, 18, 31, 33 (high-risk) | Cervical carcinoma Oro-pharyngeal carcinoma Laryngeal carcinoma |
| Herpes viruses | Type 2 herpes-simplex virus (HSV-2) | Cervical carcinoma Vulvar carcinoma |
| Epstein-Barr virus (EBV) | Malignant B-cell lymphoma (Burkitt-lymphoma) Hodgkin lymphoma Nasopharyngeal 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’.

**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 (Figure 2). 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.

[](https://wiki.cancer.org.au/oncologyformedicalstudents/File:Cyclins_and_cyclin-dependent_kinases_regulate_cell_cycle.jpg)

**Figure 2: Cyclins and cyclin-dependent kinases (CDKs) regulate the cell cycle.** CDK’s and their regulatory subunits, cyclins (A, B, D & E) tightly control transition through the cell cycle. The brackets indicate the periods in which the cyclin-CDK complexes are active and orchestrate all events necessary in this period. The **restriction point** (R point) is a point in G1 at which the cell becomes ‘committed’ to the cell cycle and after which extracellular proliferation signals are no longer required.

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.