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**PRIMARY OBESITY**

This is a state of excess adipose tissues in the body, it is not caused by clinical conditions.

Primary obesity has been said to affect 5-30% of the adult population.

The case of primary obesity is reported to be higher among the poor in the society and lower among the average and rich.

Metabolic diseases most associated with primary obesity contribute to atherosclerosis, hypertension, dyslipidemia, diabetes type II, hyperandrogenemia in women and hypoandrogenemia

/hyperestrogenemia in men

**How Drug Therapy And Congenital Syndrome Affects Secondary Obesity**

Drug-induced weight gain is a serious side effect of many commonly used drugs leading to noncompliance with therapy and to exacerbation of comorbid conditions related to obesity. Improved glycemic control achieved by insulin, insulin secretagogues or thiazolidinedione therapy is generally accompanied by weight gain. It is a problematic side effect of therapy due to the known deleterious effect of weight gain on glucose control, increased blood pressure and worsening lipid profile. Weight gain may be lessened or prevented by adherence to diet and exercise or combination therapy with metformin. Weight gain is also common in psychotropic therapy. The atypical antipsychotic drugs (clozapine, olanzepine, risperidone and quetiapine) are known to cause marked weight gain. Antidepressants such as amitriptyline, mirtazapine and some serotonin reuptake inhibitors (SSRIs) also may promote appreciable weight gain that cannot be explained solely by improvement in depressive symptoms. The same phenomenon is observed with mood stabilizers such as lithium, valproic acid and carbamazepine. Antiepileptic drugs (AEDs) that promote weight gain include valproate, carbamazepine and gabapentin. Lamotrigine is an AED that is weight-neutral, while topiramate and zonisamide may induce weight loss.

Many commonly used medications may cause weight gain. The amount of weight gained may vary depending on the patient and type of medication.

Mechanisms for weight gain can be through:

* Stimulation of appetite
* Stimulation of fat storage
* Slowed metabolism
* Fluid retention
* Impaired exercise tolerance

In many cases, there might be an alternative medication with less effect on weight; in other cases the medications that cause weight gain may be preferable to alternatives. As many of these medications may be life-sustaining, patients should be advised against stopping any of these medications without first consulting their provider. The risks of stopping or changing medication should be balanced against the risks of obesity and related co-morbidities.

Knowing which medications may adversely affect weight will help both the patient and provider monitor any change in weight. It is important to note that not all patients respond similarly to these medications.  It is also important to evaluate any supplements and over-the-counter medications the patient may be using as well.

The following classes of medications are associated with weight gain:

* Anti-depressants, anti-anxiety, mood stabilizers:
  + Selective serotonin reuptake inhibitors (SSRIs): Paxil, Zoloft, Celexa, Prozac
  + Older anti-depressants: Amitriptyline, Imipramine, Nortriptyline, Trazodone, Monoamine oxidase inhibitors (MAOIs)
  + Lithium
  + Benzodiazepines
* Antipsychotics:
  + Olanzapine, Clozapine, Risperidone, Quetiapine, Aripiprazole, Haloperidol
* Diabetes medications:
  + Insulin: Both short- and long-acting
  + Sulfonylureas: Glimepiride, Glipizide, Glyburide
  + Thiazolidinedione: Pioglitazone
  + Other: Nateglinide, Repglinide
* Steroid hormones:
  + Synthetic progestins: Medroxyprogesterone, Norethindrone, Levonorgestrel
  + Contraceptives: Oral contraceptive pills, Nexplanon
  + Corticosteroids: Prednisone, Methylprednisolone, Prednisolone
  + Chemotherapy: Tamoxifen, Arimidex
* Anticonvulsants, anti-migraine, neuropathic pain:
  + Gabapentin, Pregabalin, Valproic acid, Carbamazepine, Divalproex
* Opioids: All opioids may decreased metabolic rate and exercise tolerance
* Anti-hypertensive:
  + Beta-blockers: Atenolol, Metoprolol, Propranolol, Acebutolol
  + Alpha-blockers: Clonidine
  + Calcium channel blockers: Nisoldipine
* Antihistamines: Diphenhydramine, Fexofenadine, Cetirizine, Ranitidine, Azelastine
* Other:
  + Hypnotics: Remeron, Zolpidem, Doxepin
  + Anti-retroviral
* If any of these medications need to be used and no alternative available, it is important to reassure the patient that weight loss and maintenance is still possible despite the effect of the medication.

**Cancer And Its Molecular Basis**

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. Several of the oncogenes discussed below, including the p53, c-fms, and Ras genes, can be activated by point mutations that lead to aminoacid substitution in critical portions of the protein

**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.

**Growth factors and their receptors**

Growth factors (GFs) play an important physiological role in the normal process of growth control aimed at maintaining tissue homeostasis. They transmit growth signals from one cell to another. These signals are sensed on the cell surface by specific growth factor receptors (GFRs). GFRs transfer the growth signal via signalling pathways to activate target molecules that promote proliferation

The mitogen (or growth factor) binds to its receptor, a receptor tyrosine kinase. Tyrosine phosphorylation of the receptor leads to activation of several docking proteins, and eventually to the activation Ras, bound to the inside of the cell membrane. Active Ras in turn activates the MAP kinase signalling cascade, beginning with Raf. The final MAP kinase in this sequence activates several target proteins, for example a transcription factor that activates expression of the Myc gene. Myc itself is a transcription factor that activates the expression of cell cycle regulatory genes.

**Other elements of cell signalling**

An alternative strategy by which cancer cells can become GF independent involves constitutive activation of internal signalling components. For example, the Ras protein in normal cells is switched off and does not signal unless a GFR becomes activated, which through a series of intermediaries, is able to activate the Ras protein, converting it from its quiescent state to an active, signal-emitting state. Thereafter, the Ras protein is able to release further downstream signals that are capable of inducing proliferation. In cancer cells, this signalling pathway is deregulated because structurally altered Ras proteins are able to continuously send growth stimulatory signals into the interior of the cell in the absence of GFs.

**Genes frequently mutated in cancer**

The genes that have been implicated in carcinogenesis are divided into two broad categories oncogenes (‘cell accelerators’) and tumour suppressor genes (‘cell brakes’) but also include DNA repair genes

### Cellular oncogenes

Genes that promote autonomous cell growth in cancer cells are called oncogenes, and their normal cellular counterparts are called proto-oncogenes. Proto-oncogenes are physiologic regulators of cell proliferation and differentiation while oncogenes are characterised by the ability to promote cell growth in the absence of normal mitogenic signals. Their products, oncoproteins, resemble the normal products of proto-oncogenes with the exception that oncoproteins are devoid of important regulatory elements. Their production in the transformed cells becomes constitutive, that is, not dependent on growth factors or other external signals. Proto-oncogenes can be converted to oncogenes by several mechanisms including point mutation and gene amplification resulting in:

* Overproduction of growth factors
* Flooding of the cell with replication signals
* Uncontrolled stimulation in the intermediary pathways
* Cell growth by elevated levels of transcription factors

The RAS oncogene is the most frequently mutated oncogene in human cancer. It encodes a GTP-binding protein Ras that functions as an on-off ‘switch’ for a number of key signaling pathways controlling cellular proliferation. In a normal cell, Ras is transiently activated and recruits Raf, to activate the MAP-kinase pathway to transmit growth-promoting signals to the nucleus. The mutant Ras protein is permanently activated leading to continuous stimulation of cells without any external trigger

**Tumor suppressor genes**

Tumor suppressor genes encode proteins that are:

* receptors for secreted hormones that function to inhibit cell proliferation
* negative regulators of cell cycle entry or progression
* negative regulators of growth signaling pathways (e.g. APC or PTEN)
* checkpoint-control proteins that arrest the cell cycle if DNA is damaged or chromosomes are abnormal
* proteins that promote apoptosis DNA repair enzymes.

The transformation of a normal cell to a cancer cell is accompanied by the loss of function of one or more tumor suppressor genes and both gene copies must be defective in order to promote tumor development

Causes Of Cancer

### Mutations and cancer

Cancer development is based on the accumulation of somatic mutations over lifetime. Germ line mutations are typically not involved, but in very rare cases of inherited cancer predisposition, they are contributing to disease progression.

Typically the basal mutation rate is low in humans, but it may be enhanced through one of the three following groups of environmental carcinogens: chemical mutagens, radiation and tumor viruses. Exposure to mutagens or radiation greatly increases the mutation rate and thus the probability of developing cancer.

Chemical mutagens comprise a quite disparate group of chemicals that modify DNA through a range of mechanisms, such as alkylation or deamination of DNA bases, or through intercalation between base pairs and formation of DNA adducts (e.g. aromatic hydrocarbons). Oxidative damage may also affect DNA integrity.

X-rays and radioactive radiation tend to induce DNA double-strand breaks, whereas UV radiation results in the formation of pyrimidine dimers, by cross-linking of adjacent pyrimidine bases.

### Viral causes of cancer

Certain viruses, derived from quite different taxonomic groups are able to induce cancer development. We distinguish the highly **oncogenic viruses**, which contain **viral oncogenes** in their genomes that are in most cases derived from cellular proto-oncogenes, whereas **slowly transforming viruses** do not contain such genes. They tend to use one of the following mechanisms to stimulate proliferation of their host cells:

* Insertion of a strong promoter in the vicinity of a host cell proto-oncogene
* Expression of proteins that neutralize host cell tumor suppressor proteins
* Expression of proteins that prevent or delay apoptosis

Characteristics of viral carcinogenesis include:

* Tumor viruses often establish persistent infections in the human host
* Host factors are important determinants of virus-induced carcinogenesis
* Viruses are rarely complete carcinogens; they require additional factors to fully activate carcinogenesis.