

MATRIC NO: 17/MHS01/132

LEVEL: 300L

1. WHAT DO YOU UNDERSTAND BY PRIMARY OR SIMPLE OBESITY
2. HOW DOES CONGENITAL SYNDROME AND DRUG THERAPY AFFECTS OBESITY
3. OUTLINE THE AETIOLOGY OF CANCER AND ITS MOLECULAR BASIS.

1. Obesity is a multifactorial pathology that can be related to an altered nutritional behavior or secondary to genetic, hypothalamic, iatrogenic (drug-induced) or endocrine diseases. Adipopathy, being at the base of obesity, is defined as a “pathologic adipose tissue anatomic/functional disturbances promoted by positive caloric balance in genetically and environmentally susceptible individuals that result in adverse endocrine and immune responses that may cause or worsen metabolic disease”. Adipopathy is characterized by adipocyte hypertrophy, visceral adiposity and /or ectopic fat deposition and secretion of hormones, like leptin, and proinflammatory protein, like the overabundance of cytokines, that in turn may lead to metabolic disease. Thus, obesity can be classified as a primary disease because adipopathy determines the abnormal regulation of the metabolic pathways. Metabolic diseases most associated with primary obesity contribute to atherosclerosis, hypertension, dyslipidemia, diabetes type II, hyperandrogenemia in women and hypoandrogenemia/hyperestrogenemia in men.

2A. CONGENITAL SYNDROME

Congenital obesity is the excessive accumulation and storage of fat in the body that is present during infancy and/ or childhood. The following congenital syndromes can contribute to this congenital obesity:

- Obesity due to congenital leptin deficiency
- Prader-Willi Syndrome
- Cohen syndrome
- Bardet-Biedl Syndrome... just to mention a few.

1. OBESITY DUE TO CONGENITAL LEPTIN DEFICIENCY

This is a condition that causes obesity in the first few months of life. Affected individuals are of normal weight at birth but they are constantly hungry and gain weight quickly.

Without effective treatment, these individual's craving for food continues which eventually leads to chronic excessive eating and obesity. Leptin is an adipocyte-derived hormone that plays an important role in energy balance and appetite suppression. Whilst the majority of obese patients manifest hyperleptinemia, patients with Congenital leptin deficiency have undetected levels of leptin in the serum. Congenital leptin deficiency is caused by mutations in the *LEP* gene. This gene provides instructions for making a hormone called leptin, which is involved in the regulation of body weight. Normally, the body's fat cells release leptin in proportion to their size. As fat accumulates in cells, more leptin is produced. This rise in leptin indicates that fat stores are increasing. *LEP* gene mutations that cause congenital leptin deficiency lead to an absence of leptin. As a result, the signaling that triggers feelings of satiety does not occur, leading to the excessive hunger and weight gain associated with this disorder.

2. PRADER-WILLI SYNDROME

Regarding obesity, this syndrome features excessive eating and poor weight gain in childhood. These individuals do not feel satiety after a full meal. Without intervention on their overeating, they are disposed to life-threatening obesity. The obesity associated with PWS results from a chronic imbalance between energy intake and expenditure due to hyperphagia(excessive eating), decreased physical activity, reduced metabolic rate and an inability to vomit. Individuals with PWS have a lower lean body mass contributing to reduced energy expenditure.

3. COHEN SYNDROME

This features truncal obesity of mid-childhood onset with slender arms and legs. Individuals have an increased waist circumference but a normal Body Mass Index (BMI). The increased fat accumulation is due to their lack of the gene responsible for the formation of fat storing cells.

4. BARDET-BIEDL SYNDROME

This features abdominal obesity and insulin resistance. It is due to disturbances in appetite-regulating hormones (ghrelin(obestatin), leptin and adiponectin). Ghrelin is negatively regulated in relation to nutritional status. BBS patients lack the negative regulatory mechanisms of appetite-regulating hormones with respect to nutritional status and exhibit resistance to anorexigenic leptin.

B. DRUG THERAPY

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 state. The amount of weight gain depends both on the dose of the drug and the length of time it is taken.

Weight gain is also common in psychotropic therapy. For example:

- The atypical antipsychotic drugs (clozapine, olanzapine, 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.
- Mood stabilizers such as lithium, valproic acid and carbamazepine.
- Antiepileptic drugs (AEDs) that promote weight gain include valproate, carbamazepine and gabapentin.
- Steroids: Steroid medications such as prednisone are well-known causes of weight gain due to fluid retention and increased appetite. Steroids can also cause a temporary change in body fat distribution, with increased fat in the face, back of the neck, or the abdomen.

3. AETIOLOGY OF CANCER AND MOLECULAR BASIS

Cancer results from factors within the cell itself and external factors from its environment, for example, inherited mutations and mutations as a result of environmental factors. Essentially, they cause the mutation of genes. Therefore, the etiology of cancer is multifactorial, physical, chemical, hormonal, metabolic, genetic and environmental. They all have a role in the development of cancer in that they cause the mutation of genes during replication thereby leading to cancer. Thus, carcinogens (cancer-causing agents) are mutagens and vice-versa., that is, any carcinogen be it physical or chemical will cause DNA damage which leads to mutation and subsequently, CANCER.

Every normal cell has a ***DNA Repair Gene Mechanism*** which corrects defects during replication. Carcinogens and hereditary mutation affects the repair genes thereby resulting in cancer. About 50 percent of human cancer is due to mutation or deletion of the repair gene called **ANTI-ONCOGENE OR ONCOSUPPRESSOR.**

CAUSES OF CANCER

1. **CARCINOGENS:** Physical carcinogens and mutagens like x-rays and gamma rays etc. Chemical carcinogens are aniline, asbestos tobacco etc, food additives and coloring agents...etc
2. **HORMONES:** Steroid hormones are carcinogenic.
3. **HEREDITARY:** Mutated genes causing cancer has 50 percent chance of being passed to offspring. E.g xeroderma pigmentos etc.
4. **ONCOGENIC VIRUSES:** Viruses get integrated into the host' DNA leading to multiplication of viral gene cells overtaking that of the host. E.g epstein-barr virus, HIV etc.

MOLECULAR BASIS OF CANCER

The molecular basis of cancer is seen in the shortening of telomeres on the chromosomes in normal cells. Normal cells replicate and are removed from the system when the need arises by

APOPTOSIS. Cancer cells are able to escape apoptosis of the normal cell cycle, this is possible by use of the enzyme, **TELOMERE POLYMERASE** which lengthens the telomeres on the chromosome. In this way, apoptosis is prevented and the cancer cells are immortalized. Normal cells receive signals for apoptosis but there are chemicals which can destroy these signals hence leading the uncontrollable multiplication of cancer cells.