Name: - Adebamiro Adedoyin .F.

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BCH 313 Assignment; - Diabetes, Obesity, and Cancer.

Course Title: - Medical Biochemistry IV

1) Primary Obesity: -

   Primary obesity is due to excessive energy intake and too little consumption of this energy. Patients with this have no underlying condition that lead to obesity. It has the largest population in all types of Obesity and is also called Diet-Induced obesity.

2) Effect of congenital syndrome on obesity: -

   Several genes have the potential to cause obesity in humans, e.g. mutation in leptin gene (ob gene) results in obesity. A peptide hormone 'leptin' released from the adipocytes is a product of gene 'ob gene'. Leptin leads to suppression of food intake. Grossly obese people have a failure in the production of leptin.

   Congenital diseases, also known as Birth defects, are conditions present at birth regardless of the cause. Examples include; Fragile X syndrome, Down syndrome, Prader Willi syndrome, Lawrence-Moon-Bardet syndrome and so on. Some congenital diseases present obesity as a symptom. Another example of such a disease other than the mutated leptin gene is Prada Willi syndrome. Children with this syndrome present a metabolic rate that is lower than the normal and mental problems such as a constant sense of hunger among other symptoms. Metabolism or Metabolic rate is defined as the series of chemical reactions in a living organism that create and breakdown energy necessary for life. In other words, it is the rate at which the body expands energy or burns calories. A high

metabolism means that more calories is needed to maintain weight. However, a person with a low or slow metabolism will burn fewer calories at rest and during activity and therefore has to eat less to avoid becoming overweight.

In Prader Willi syndrome, one of the symptoms is a constant sense of hunger which will result compulsive overeating. Because of their slow metabolic rate, they become overweight. Although this is true for Prader Willi syndrome, it is not the same for all congenital diseases that present obesity as a symptom. Other examples of congenital diseases that present obesity as a symptom include: -

- Lawrence-Moon-Bardet syndrome:-

  People with this disorder become obese as a result of leptin resistance in fat cells (leptin is responsible for decrease in the number of adipocytes). Because the adipocytes do not respond to leptin, they continue to increase in number and lead to obesity.

- Down syndrome: -

  Obesity in Down syndrome occurs due to leptin resistance in fat cells also.

- Pseudohypoparathyroidism: -

  People with this disorder become obese as a result of leptin deficiency.

- Cohen syndrome: -

  Obesity occurs in this syndrome as a result of increased response of adipocytes to insulin.

- Turner syndrome: -

Obesity occurs in this syndrome occurs due to insulin resistance. Excess insulin due to insulin resistance can lead to weight gain and eventually obesity.

Effect of drug therapy on obesity: -

Medication such as antidepressants, antipsychotic, diabetes medication, and generally drugs in the class known as Thiazolidinediones (TZDs) can lead to weight gain and increase in fat. This eventually will result in obesity. As in the case of congenital diseases, how these drugs will produce obesity is different. TZDs are oral anti-diabetic drugs that act as insulin sensitizers. It improves glycemic control and insulin sensitivity in patients with type II diabetes, despite their potential to cause weight gain. Studies have attempted to elucidate the mechanisms behind the apparent paradox of TZDs improving insulin sensitivity while causing weight gain. Data indicate that with TZD treatment, there is a favourable shift in fat deposition from visceral to subcutaneous adipose depots that is associated with improvements in hepatic and peripheral tissue sensitivity to insulin. Although weight gain may occur with TZD therapy, it is not inevitable. Experts do not fully understand why antidepressants lead to weight gain in some people. One theory is that both metabolism and hunger levels may be affected.

Antidepressants interfere with serotonin, the neurotransmitter that regulates anxiety and mood while also controlling appetite. In particular, these changes may increase cravings for carbohydrate-rich foods such as bread, pasta, and desserts. Also, depression itself may cause weight gain in some people and weight loss in others. When people are depressed, their appetites are affected. In some people, this may make them hungrier while others lose their appetite. It may be the

case that when antidepressants take effect, a person's usual appetite returns and this has an impact on their weight.

3) Aetiology of Cancer: -

There are various factors that cause cancer. These include;

(a) Predisposing Factors: - these are factors that could develop overtime or are inherited.

- Age: Cancer can develop in any age, though it is most common in those over 55 years of age. Certain cancers are particularly common in children below 15 years of age. This include;
  -Retinoblastomas
  -Neuroblastomas
  -Wilms' tumours
  -Certain tumours of haemopoietic tissues as lymphomas and Leukaemias
  -Sarcomas of bones and skeletal muscles.
- Heredity: Heredity plays an important role in carcinogenesis. Certain precancerous conditions are inherited. Examples are:
  -Susceptibility to childhood retinoblastomas is inherited as an autosomal dominant trait and approximately 40 per cent of retinoblastomas are familial.
  -Susceptibility to multiple colonic polyposis is inherited as autosomal dominant trait and almost all cases develop into adenocarcinomas in later life.
  -Chromosomal DNA instability may be inherited as an autosomal recessive trait. Conditions are characterised by some defect in DNA repair.
  -In xeroderma pigmentosa, a skin condition, the affected individuals develop carcinomas of skin in areas exposed to UV rays of sunlight.

- Environmental factors: Statistically it has been shown that 80 per cent of human cancers are caused by environmental factors, principally chemicals, through
  -Lifestyle: Cigarette smoking, tobacco chewing.
  -Dietary: Groundnuts and other foodstuffs infected with fungus like Aspergillus produce aflatoxin B1 which is carcinogenic.
  -Occupational: Asbestos, benzene, naphthylamines, beryllium, etc.
  -Latrogenic: Certain therapeutic drugs may be carcinogenic.
- Acquired precancerous disorders: Certain clinical conditions are associated with increased risk of developing cancers. Examples are:
  -Leukoplakia of oral mucosa and genital mucosa developing into squamous cell carcinomas.
  -Cirrhosis of liver: A few cases can develop hepatoma (hepatocellular carcinoma).
  -Ulcerative colitis: Can produce adenocarcinoma of colon.
  -Carcinoma in situ of cervix: Can produce squamous cell carcinoma of cervix.

  (b)Carcinogenic Agents (Agents Causing Cancer):
  Carcinogens that cause cancer can be divided into three main broad groups:
- Physical: Radiant energy
- Chemicals: Variety of chemical compounds can cause cancer. Some of these can act directly and others can act as procarcinogens
- Biological: Oncogenic viruses.

  <u>Rare causes of cancer include: -</u>
- Organ transplantation:-

The development of donor-derived tumors from organ transplants is exceedingly rare. The main cause of organ transplant associated tumors seems to be malignant melanoma, which was undetected at the time of organ harvest. There have also been reports of Kaposi's sarcoma occurring after transplantation due to tumerous outgrowth of virus-infected donor cells.

- Trauma:-

  Physical trauma resulting in cancer is relatively rare. Claims that braking bones resulted in bone cancer, for example, have never been proven. Similarly, physical trauma is not accepted as a cause for cervical cancer, breast cancer, or brain cancer. One accepted source is frequent, long-term application of hot objects to the body, such as those produced by kanger and kairo heaters (charcoal hand warmers), may produce skin cancer, especially if carcinogenic chemicals are also present.

  Frequently drinking scalding hot tea may produce oesophageal cancer. Generally, it is believed that the cancer arises, or a pre-existing cancer is encouraged, during the process of repairing the trauma, rather than the cancer being caused directly by the trauma. However, repeated injuries to the same tissues might promote excessive cell proliferation, which could then increase the odds of a cancerous mutation.

- Maternal-fetal transmission:-

  In the United States, approximately 3,500 pregnant women have a malignancy annually, and transplacental transmission of acute leukemia, lymphoma, melanoma, and carcinoma from m other to fetus has been observed. Excepting the rare transmissions that occur with pregnancies and only a marginal few donors, cancer is generally not a transmissible disease. The main reason for

this is tissue graft rejection caused by major histocompatibility complex (MHC) incompatibility.

In humans and other vertebrates, the immune system uses MHC incompatibility to differentiate between “self” and “non-self” cells because these antigens are different from person to person. When non-self antigens are encountered, the immune system reacts against the appropriate cell. Such reactions may project against tumor cell engraftment by eliminating implanted cells.

Molecular basis of cancer: -

Cancer is a disease of uncontrolled growth and proliferation whereby cells have escaped the body’s normal growth control mechanisms and have gained the ability to divide indefinitely. 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’.

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. 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.

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. 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.

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.

Steps that characterise normal cell proliferation include:

- The binding of a GF to its specific receptor on the cell membrane
- Transient and limited activation of the GFR, which, activates several signal-transducing proteins (e.g. Ras) on the inner leaflet of the plasma membrane
- Transmission of the signal by signal transduction molecules, either to cytosolic targets or to the nucleus where they activate transcription of specific genes
- Entry of the cell into the cell cycle, ultimately resulting in cell division.

This pathway is often derailed in cancer and allows wayward cells to generate their own internal signals that stimulate proliferation and become independent of their environments. Cancer cells are able to induce their own growth stimulatory signals when mutations in the GFR gene occur, which facilitates activation in the absence of GFs or when overproduction of GFs results in an autocrine signalling loop.

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.