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DIABETES, OBESITY AND CANCER

**Question**

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.

**Answer**

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

In **primary obesity**, there is adiposopathy (or “sick fat”) which defined as “pathologic adipose tissue anatomic/functional disturbances promoted by positive caloric balance in genetically and environmentally susceptible individuals that results in adverse endocrine and immune responses that may cause or worsen metabolic disease”.

Therefore, obesity can be classified as a primary disease since the adiposopathy determines the dysregulation of 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.

**Secondary obesity** means that a person has a medical condition that has caused them to gain weight. These diseases include endocrine disorder, hypothalamic disorders and some congenital conditions. Some of the more common endocrine disorders include hypothyroidism and polycystic ovarian syndrome (PCOS). There are also rare causes of secondary obesity like Cushing’s disease (hypercortisolism), hypothalamic injury or disorders and genetic mutations.

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

Some of the congenital syndromes associated with obesity are Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome, Albright hereditary osteodystrophy, Alström syndrome, WAGR (Wilms’ tumor, aniridia, genitourinary anomalies, and retardation) syndrome and Borjeson-Forssman-Lehmann syndrome as well as some rarer disorders.

The development of obesity in syndromic conditions typically occurs after infancy. These syndromes are characterized by cognitive impairment, dysmorphic features, and anomalies of major organs.

In Prader-Willi syndrome (PWS), there is functional absence of paternal allele of 15q11-13 and birth weight is normal or slightly low, and infants fail to gain weight, often requiring tube feedings, due to hypotonia and poor suck. Following a period of limited catch-up weight gain from 6 to 18 months, children develop an insatiable appetite, resulting in obesity by age 6. They have relatively high ghrelin levels.

Bardet-Biedl syndrome is a heterogeneous autosomal recessive disorder caused by a defect in one of 15 genes involved in ciliary function. Energy dysregulation is thought to arise from defective leptin activity. Complications from morbid obesity and renal disease are the most common causes of mortality.

Alström syndrome is caused by a mutation in ALSM1, resulting in defective ciliary function. Children typically develop obesity by age 5 years. There is a high incidence of type 2 diabetes, which occurs in up to 70% of individuals by age 20 years.

Albright’s hereditary osteodystrophy is caused by a mutation in GNAS1, leading to a defect in the alpha subunit of G proteins (Gαs) coupled to transmembrane receptors. Excess weight gain may occur during infancy and is thought to arise from Gαs deficiency in imprinted regions of the hypothalamus.

WAGR syndrome, characterized by Wilms’ tumor, aniridia, genitourinary anomalies, and mental retardation, is caused by deletion on 11p14.1, located near the gene responsible for brain-derived neurotrophic factor (BDNF) production. BDNF is regulated by nutritional status and MC4R signaling and is expressed in the hypothalamus, where it facilitates neuronal proliferation, survival, and differentiation. The majority of patients with WAGR and BDNF deletions are obese.

Environment, behavior and genetic traits all influence body weight. The final common pathway for each of these disparate factors, however, is changes in energy intake or energy expenditure. Obesity results from energy imbalance sustained over several years, and obesity treatments can work only by reversing this. Accordingly, all anti-obesity agents have at least one of the following effects:

* Reduce food intake or nutrient absorption.
* Increase resting or activity-related energy expenditure.

Appetite reduction is the primary weight loss mechanism for the majority of current agents.

Pharmacotherapy is a second step in the treatment of obesity, approved only when weight loss targets were not reached through lifestyle intervention. During the history of anti-obesity drugs, many of them were withdrawn because of their side effects. Orlistat deactivated intestinal lipase and inhibits intestinal fat lipolysis. It is the only drug on the European market approved for the treatment of obesity. Orlistat therapy reduces weight to a modest extent, but it reduces the incidence of diabetes beyond the result achieved with lifestyle changes. The new combination of topimarate and fentrmine is approved in the US. Combining different weight loss agents with different mechanisms of action is appealing for two reasons: first, it is less likely to be hindered by redundancy and compensation in appetite regulatory pathways; and second, it enables each component to be given at lower dose to reduce side effects.

The arcuate nucleus of the hypothalamus plays a critical role in appetite regulation. It contains two key populations of neurons, which project to other hypothalamic nuclei and distant brain regions to alter feeding behavior —one co-expresses agouti-related peptide (AgRP) and neuropeptide Y (NPY), which increase food intake, and the other co-expresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which inhibit food intake. Because of the semipermeable blood-brain barrier in this region, peripheral signals indicative of energy balance—including glucose, insulin, leptin, a number of gut-derived factors including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), oxyntomodulin and ghrelin—can directly interact with these neurons and influence feeding behavior.

POMC neuronal activity is also modulated by dopaminergic and serotoninergic signaling from other brain regions and is therefore affected by a number of central nervous system (CNS) drugs that cat on these neurotransmitters. Appetite is regulated not just by physiological energy status but also by environmental and emotional cues, such as sight and smell of food. These reward-associated stimuli are integrated by the mesocorticolimbic reward system, with dopaminergic neurons originating in the ventral tegmental area (VTA) projecting to the nucleus accumbens and the prefrontal cortex, where they influence feeding behavior. Modulation of signaling in the dopaminergic reward system is also suggested as additional mechanism for the action of some appetite suppressants.

Weight loss agents are generally licensed for use in patients with a BMI≥30kg/m2, or ≥27-28 kg/m2 in those with an obesity- associated comorbidity. The choice of agent should reflect patient preference, relative co-indications (such as diabetes for liraglutide) and contraindications (such as seizure disorders for bupropion/naltrexone), and relative efficacy. Weight loss should be accessed at 3 months, and the treatment should be discontinued or substituted if at least 5% weight has not been achieved.

1. **Outline the aetiology of cancer and its molecular basis.**

The substances that cause cancer are called carcinogen may be a chemical substances, such as certain molecules in tobacco smoke. The cause of cancer may be environmental agents, viral or genetic factors. Cancer risk factors can be divided into the following groups:

* **Biological or internal factors**, such as
* Age,
* Gender,
* Inherited genetic defects and
* Skin type.
* **Environmental exposure**, for instance to
* Ionizing radiation such as Radon, uranium, radiation from alpha, beta, gamma and
* UV radiation, and
* Fine particulate matter,
* Non-ionizing radio frequency radiation from mobile phones, electric power transmission.
* **Occupational risk factors**, including
* Carcinogens such as many chemicals (such as tar and pith, polynuclear hydrocarbons, plastic chemicals such as vinyl chloride),
* Radioactive materials and asbestos fibers
* **Lifestyle-related factors,** that cause cancer include:
* Tobacco,
* Alcohol,
* Diet: Studies show that individuals that eat red or processed meat have a higher risk of developing breast cancer, prostate cancer, and pancreatic cancer,
* UV radiation in sunlight,
* Some food-related factors, such as nitrites and poly aromatic hydrocarbons generated by barbecuing food.
* **Bacteria and Viruses** can cause cancer:
* Helicobacter pylori ( H. pylori, which causes gastritis)
* HBV, HCV ( hepatitis viruses that cause hepatitis)
* HPV (human papilloma virus, papilloma virus, which causes changes e.g. Cervical cells)
* EBV( Epstein-Barr virus, the herpes virus that causes inflammation of the throat lymphoid)
* **Drugs** may increase the risk of cancer:
* Certain antineoplastic agents
* Certain hormones
* Medicines that cause immune deficiency

**Molecular Basis of Cancer**

Discussion of the causes necessarily involves an examination of the molecular machinery in cells that guides the basic processes of proliferation (increase in cell number by cell division), differentiation (cell specialization into different tissue types), and apoptosis (programmed cell death). Those processes are guide by two innate programs in cells, the genetic code and the epigenetic code. In cancer, each of those codes ultimately becomes altered regardless of whether the disease originated with an external or internal factor. Cancer, once manifest, becomes an inherited disease of the cell and is therefore self-perpetuating.

The hereditary nature of cancer at cellular level explains why alterations have been found in both the genetic and the epigenetic codes in tumor cells. The number of alterations seen in the coded programs increases as tumors progress to more advanced stages. One way to envision a cancer cell is a cell that has been rewired the normal control circuits for proliferation, differentiation, and death. The resulting alterations in the circuits’ functions, which are encoded by the genetic sequences and by the epigenetic configuration, enable the cell to escape programmed controls.

The genetic program, common to all cells in the body (whether noncancerous or cancerous), is found in the DNA sequence, which is packaged in chromosomes in the cell nucleus. Each person has a unique DNA sequence that is composed of approximately three billion base pairs (units of DNA) organized into roughly 25,000 genes. Some of the gene products that have been linked to cancer are organized in groups (pathways), which form networks that transmit information inside the cell and stimulate responses to changes in the cell’s environment.

The epigenetic code is responsible for providing cells with the memory of their particular specialization—for example, being part of the brain, the liver, or skin. The epigenetic code is embodied in chemical changes to DNA and in chemical and structural modifications of chromatin (the protein-DNA fibres in the nucleus that when condensed form the chromosomes). Modification of chromatin, such as when methyl groups attach to proteins in the chromatin structure, holds the fibre in a less-condensed state and causes genes in the affected area to become or remain active. The resulting patterns of gene expression dictate and maintain cell differentiation.

The billions of cells that make up a tumor are descended from a single cell, in which disturbance of the genetic and epigenetic codes caused remodeling of the control circuits that governed that cell’s existence. A single damaging genetic or epigenetic event, however, is not enough to convert a healthy cell to a cancer cell. Rather, several assaults must be inflicted upon the DNA or chromatin of a cell in order for it to become cancerous. The first of those, the damage that instigates transformation, is known as initiation. Ensuing damage that advances transformation is known as promotion. Initiation and promotion together are required for causing cancer. In many cases that is a slow process that takes years.

Among the hallmarks of cancer are:

* Increased proliferative activity,
* Evasion of growth suppression,
* Resistance to cell death
* Acquired immortality
* Acquired ability to spread to and invade distant tissues and invade distant tissues and to stimulate angiogenesis (the formation of blood vessels).

Proto-oncogenes (cells that have potential to mutate into cancer-causing genes), which encourage cell growth, and tumor suppressor genes, which inhibit it are frequent targets of agents known to cause cancer, including chemicals, viruses, and radiation. Such agents exerts their effects by inducing changes in those genes encode. Mutation that convert proto-oncogenes to oncogenes tend to overstimulate cell growth, keeping the cell active when it should be at arrest, whereas mutations in tumor suppressor genes eliminate necessary brakes on cell growth, also keeping the cell constantly active. If the cell’s repair mechanisms are faulty, mutations will accumulate, and genetic damage that has not been repaired will be reproduced and passed to all daughter cells whenever the cell divides. In this way malfunctioning DNA repair machinery contributes to the genesis of some cancers.

In cancer cells, the execution program of cell death is rendered inoperative following mutation of a protein, p53, which occurs in about half of all cancers. Cells can acquire immortality by bypassing senescence, which normally marks the end of a cell’s functional existence. That is achieved by acquiring mutations that prevent the shortening of the ends of the chromosomes, or telomeres. The progressive shortening of telomeres bring the cell closer to death.