

NUTRITION & MALIGNANCY: An Overview

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Malignancy and Weight loss (Cachexia)

- Weight loss (Cachexia) caused by decrease in body fat and wastage of muscles occurs to varying degree in patients with malignancy;
- Multiple vitamin deficiencies occurs in some patients with malignancy;
- Unexplained weight loss may be a sign of malignancy,
- Some clinical features of malignancy include:
 - Anorexia,
 - Lethargy,
 - Weight loss,
 - Muscle weakness,
 - Anemia and Pyrexia

How does weight loss in malignancy affect muscle mass?

- Weight loss in malignancy is mainly from Skeletal Muscle and Adipose Tissue, with relative Sparing of Visceral Proteins (liver, kidney, and heart);
- **Malignancy results in:**
 - Increased turnover of whole body protein,
 - Increased rate of protein synthesis in the Liver,
 - Decreased rate of synthesis in skeletal muscle with corresponding increase in net degradation of skeletal muscle protein

What factors are responsible for weight loss in malignancy?

- Biochemical basis for weight loss is due to many factors:
- Loss of Taste and Malaise that accompanies many malignant diseases may contribute to Poor Food Intake leading to malnutrition,
- Some patients may have Negative Nitrogen Balance,
- Others in Positive Nitrogen Balance may show Caloric Deficit,
- **In weight loss accompanying malignant diseases, Caloric Expenditure may remain high, with an Elevated Basal Metabolic Rate despite reduced dietary intake;**
 - An indication of profound Systemic metabolic derangement in affected individuals

What causes the imbalance in caloric intake and energy requirement in malignancy?

- In malignancy there is Imbalance between Dietary Calorie Intake and body Energy Requirements; this is due to combination of factors:
 - Inadequate food intake,
 - Impaired digestion and absorption,
 - Competition between host and tumour for nutrients:
 - Growing tumour has high metabolic rate that deprives the body of nutrients,
 - Increased energy requirement of the cancer patient:
 - Reaction of the host to the tumour is similar to the metabolic response to stress and injury, (i.e., increased metabolic rate and altered tissue metabolism)

How does stress influence metabolic changes in malignancy?

- Cancer is Physiological Stress on the organism, other Physiological Stress are:
 - Injury,
 - Surgery,
 - Renal Failure,
 - Burns,
 - Infections
- Malignancy may result in:
 - Increase rate of Infection,
 - Dysphagia,
 - Persistent vomiting,
 - Diarrhoea,
- All of these may contribute to cancer Cachexia;

- Different types of stress can cause increase blood levels of Hormones (Insulin Counter Regulatory Hormones):
 - Cortisol,
 - Glucagon,
 - Catecholamines,
 - Growth hormones;
- Some patients may develop **Insulin Resistance**, resulting in elevated levels of:
 - Basal Metabolic Rate,
 - Blood Glucose,
 - Free Fatty Acid

- Intracellular Muscle Glutamine Pool is reduced, resulting in reduced protein synthesis and increased protein breakdown;
- Management of such patients may include replacing Amino Acids, Glucose, and Fat by infusing solutions of these nutrients Intravenously ;
 - Such solutions usually lack Glutamine, Tyrosine, and Cysteine because of stability and solubility constraints;
- Supplementation of these amino acids, by using more stable Dipeptides, may help to reverse the catabolic state resulting in Cachexia;

What factors are responsible for metabolic changes in malignancy?

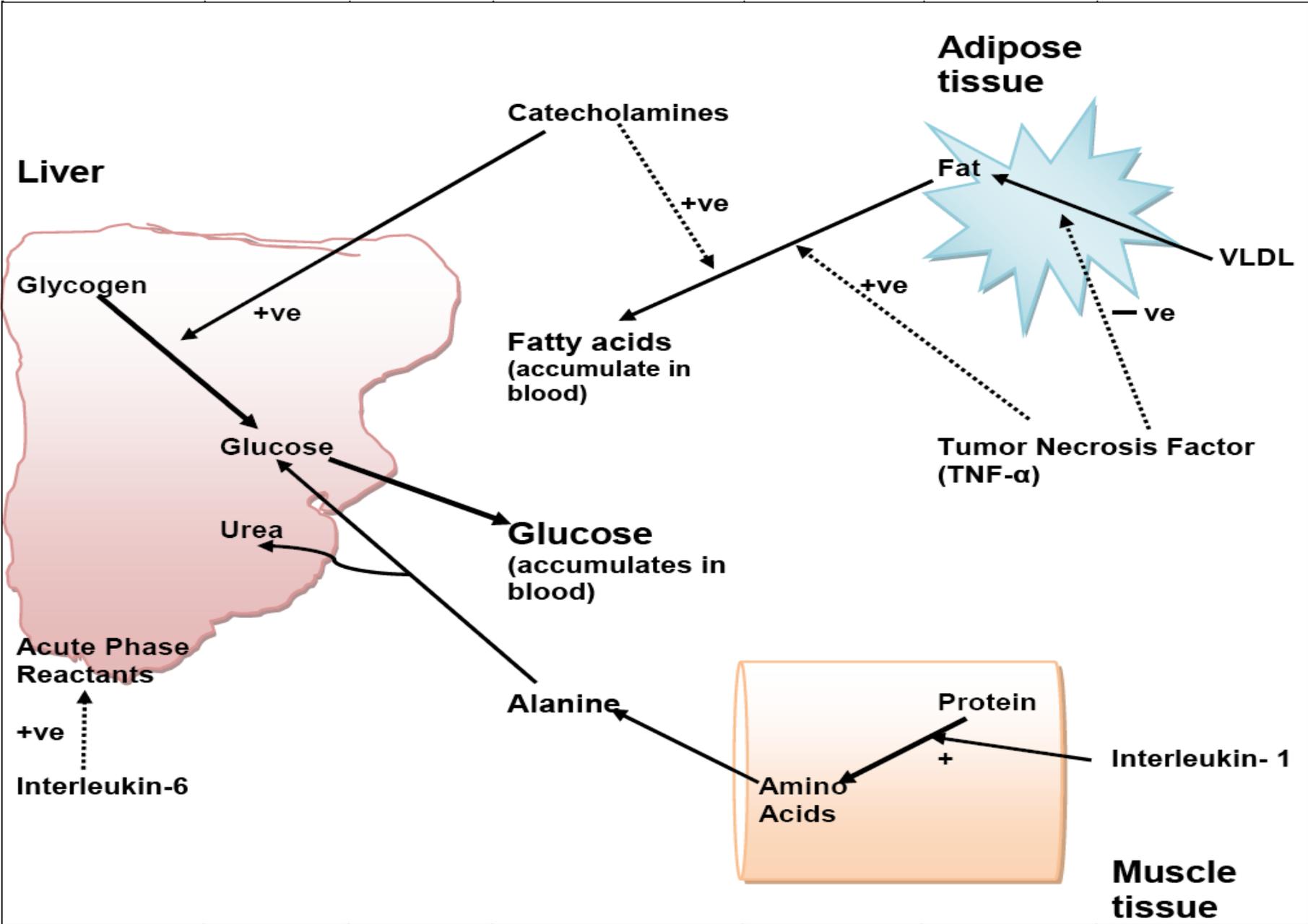
- Malignant cells secrete, or cause the release of, Humoral agents (**Cytokines**) that mediate metabolic changes, which may result in weight loss;
- Negative Nitrogen Balance that occurs in injured or infected patients is mediated by Cytokines (produced by Monocytes and Lymphocytes); Examples of Cytokines:
 - **Interleukin-1,**
 - **Interleukin-6,**
 - **Tumour Necrosis Factor- α (TNF- α)**
- Cytokines:
 - Regulate immune responses,
 - Responsible for causing fever,
 - Causes Cachexia in chronic infections and malignancy;

What are some of the specific functions of Cytokines?

- **Interleukin-1:**
 - Activates breakdown of proteins in skeletal muscle;
- **Interleukin-6:**
 - Stimulates synthesis of Acute Phase Reactants in Liver;
- Examples of Acute Phase Reactants include:
 - Fibrinogen,
 - Complement proteins,
 - Some Clotting Factors,
 - α_2 -macroglobulin, which are presumed to play a role in defense against injury and infection

- **TNF- α :**
 - Suppresses Synthesis of Fat in Adipose Tissue,
 - Prevents uptake of circulating fat by inhibiting Lipoprotein Lipase,
 - Stimulates Lipolysis,
 - Inhibits release of Insulin,
 - Promotes Insulin Resistance;

EFFECT OF STRESS ON METABOLISM



Indicate some special features of cancer cells:

- Cancer cell results from permanent genetic change (Malignant Transformation) in normal cell;
- It may be triggered by:
 - External physical agency, such as: X-Rays
 - Excess Ultraviolet Irradiation from Sunlight,
 - Carcinogenic (cancer causing) chemical agents
- Cancer cells tend to grow aggressively and do not obey normal patterns of tissue formation;

- Abnormal growth pattern is usually disruptive and tends to interfere with normal activities of adjacent cells and tissues;
- Contact inhibition signals are lacking in cancer cells;
- Cancer cells consume less Oxygen than normal cells;
- Cancer cells utilizes about 5 to 10 times more Glucose compared to normal cells,

What is unique in metabolism of Glucose in cancer cells?

- Cancer cells have a distinctive type of metabolism:
- They have all the Glucose metabolism enzymes, but **cannot** link Glycolytic pathway and TCA Cycle;
- Normal Allosteric Factors regulating rate of Glycolysis to match rate of utilization of Pyruvate by TCA cycle are defective or altered in cancer cells;
- This phenomenon is explained by “**Warburg Effect**”, which is different from “Pasteur effect”

Briefly explain Pasteur effect and Warburg Effect

What is Pasteur Effect?

- Rate of Glycolysis is reduced in the presence of Oxygen;

What is Warburg Effect?

- In cancer cells, availability of oxygen does not affect the rate of Glycolysis;
- In the present of Oxygen:
 - Normal cells utilize Aerobic Metabolism to generate energy;
 - Cancer cells utilizes Anaerobic Metabolism, consuming large amount of Glucose to generate energy releasing large amount of Lactate in blood;
 - Cancer cells **do not** make use of Oxidative Phosphorylation;

- Cancer cells convert Glucose into Lactic acid in the presence of O_2
- Most important systemic effect of this Metabolic Imbalance in Cancer Cells is the utilization of large amount of Blood Glucose and the release of correspondingly large amounts of Lactic Acid into the Blood;
- Lactic Acid is taken up by Liver and converted to Glucose via Gluconeogenesis;
- Glucose formed is then released into the Blood;

Why are cancer cells called “Metabolic Parasites”?

- Cancer cells convert Glucose to Lactic acid in presence of Oxygen;
- Lactic acid is released in blood, picked up by Liver for conversion to Glucose via Gluconeogenesis;
- Conversion of Lactic acid to Glucose in Liver uses **6 ATP**;
- Cancer cell produces net of **2 ATP** per Glucose converted into Lactic acid;
- Thus, to convert Lactic acids produce by cancer cell to Glucose the Liver needs to provide an additional **4 ATP**;
- Therefore, Cancer cell is a Metabolic Parasite that depends on Liver for substantial part of its energy;

- Cancer cells are Metabolic Parasites because:
 - They utilize abnormally large amounts of Glucose, which in the presence of Oxygen, are converted into Lactic acid that is released in blood,
 - Lactic acid is then converted back to blood Glucose via Gluconeogenesis in the liver at a large net cost in the ATP stores in the body;
- Cancer cells cause considerable metabolic drain on host, in addition to causing other local and systemic problems;