

MALIGNANT CACHEXIA (CACHEXIA – ANOREXIA SYNDROME): Overview

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What do you understand by Cachexia?

- **Cachexia:**
 - Complex metabolic status with progressive weight loss involving Adipose Tissue and Skeletal Muscle,
 - Condition of Severe Malnutrition and Negative Nitrogen Balance characterized by:
 - Anorexia,
 - Weight loss
 - Skeletal Muscle wasting;
 - Visceral Proteins (Liver, Kidney and Heart) are not wasted;

- **Cachexia:**
 - Usually associated with chronic infections and malignant conditions,
 - May occur after extensive Traumatic Injury or Sepsis, in aging persons with Failure to Thrive Syndrome,
 - Represents clinical consequence of chronic, systemic inflammatory response, with high hepatic synthesis of Acute-Phase Proteins:
 - These are proteins that respond to tissue injury,
 - This may cause depletion of Essential Amino Acids,

- Metabolic & Behavioural changes in Cachexia are associated with patient complaints of:
 - Weakness, Fatigue, Pain,
 - Gastrointestinal distress,
 - Sleep/Wake disturbance,
 - Shortness of breath,
 - Lethargy,
 - Depression,
 - Malaise,
 - Fear of being a burden on family members;
- **Cachexia is often associated with Anorexia;**

What is Anorexia?

- **Anorexia:** loss of appetite or desire to eat;
 - It leads to decreased nutrient intake triggering malnutrition and progressive deterioration with muscle wasting,
- Anorexia may occur in cancer patients;
- It may occur early in the disease process or later as the tumour grows and metastasizes;

Is Anorexia the same as Cachexia?

- Anorexia is not the same as Cachexia;
- Cachexia may occur in individuals consuming adequate calories and protein but experiencing Malabsorption of nutrients;

Is malignant Cachexia the same as simple starvation?

- Malignant Cachexia is not the same as simple starvation,
- Most individuals tend to adapt to starvation by decreasing their Basal Metabolic Rate (BMR);
- BMR can be **Increased, Decreased** or **Normal** in patient with Malignant Cachexia;

What are the causes of malignant cachexia?

- Specific causes are not fully known:
- Several contributing factors have been suggested:
 - Decreased appetite,
 - Decreased food intake,
 - Production of Catabolic Factors secreted by certain Tumours,
 - Production of Autoimmune Cytokines;

IMPORTANT TO NOTE

- Loss of taste and malaise that accompanies many malignant diseases may contribute to poor food intake leading to malnutrition, but these factors do **not fully** explain the metabolic changes in malignant Cachexia;
- Most tumours exhibit high rates of Glycolysis and release Lactate in presence of Oxygen, however the energy requirement of tumour does not explain weight loss because weight loss occurs in both large and small tumours;

What is Cachexia-Anorexia Syndrome (CAS)?

- **Cachexia-Anorexia Syndrome (CAS):**
 - Catabolic state that causes weight loss in patients with advance cancer;
 - Catabolic status in which severe weight loss cannot be attributed only to low caloric intake;
- In a patient with CAS, even with adequate nutrition, weight loss may occur because the body cannot utilize the nutrients from the diet properly,
- CAS may be due to Chemical Messengers (Cytokines), produced by Tumour and Immune System;

What chemical messengers are involved in CAS?

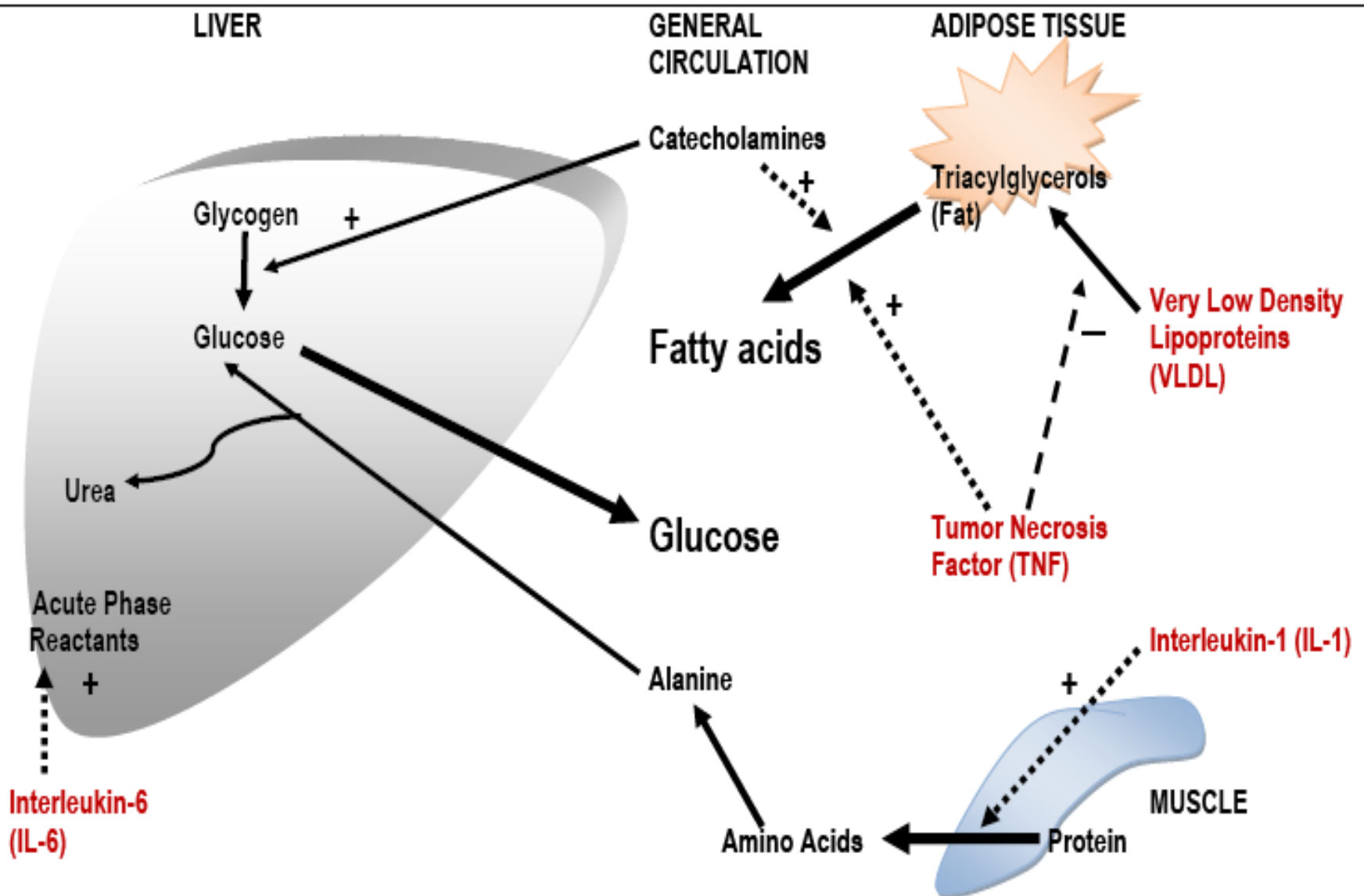
- Chemical Messengers (Cytokines) include (but not limited to):
 - Tumour Necrosis Factor-Alpha (TNF-alpha),
 - Interleukin-1 (IL-1),
 - Interleukin-6 (IL-6),
 - Interferon-gamma,
 - Proteolysis Inducing Factor (PIF),
 - Lipid Mobilizing Factor (LMF),
 - Brain Derived Neurotropic Factor

What are some functions of the Cytokines?

- **Interleukin-1 (IL-1):**
 - Activates Proteolysis in Skeletal Muscle,
- **Interleukin-6 (IL-6):**
 - Stimulates synthesis in liver of Acute Phase Reactants (APR),
 - Acute phase reactants include:
 - Fibrinogen,
 - Complement Proteins,
 - Some Clotting Factors,
 - Alpha-Macroglobulin (involve in defence against injury and infection);

- **Tumour Necrosis Factor-alpha (TNF-alpha):**
 - 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,
- These cytokines appear responsible for much of the wasting in chronic infections and malignancy,
- **Fig. 1: Schematic diagram: effect of Stress on metabolism, showing actions of Cytokines (IL-1, IL-6, TNF) & Catecholamines**

Fig. 1: Effect of Stress on metabolism, showing actions of Cytokines (IL-1, IL-6, TNF) & Catecholamines



IMPORTANT TO NOTE

- CAS may occur because of the effect of chemical messengers on the:
 - Brain,
 - General Body Metabolism,
 - Skeletal Muscle;
- **Actions of some chemical messengers:**
 - Act on Hunger Centers in the Hypothalamus and Frontal Cortex to dull the sensitivity of the brain to hunger signals from the body,
 - Inhibit the ability of the brain to generate appetite;

What are some specific actions of chemical messengers?

- Chemical messengers act on:
 - Liver, Pancreas and Peripheral Tissues,
- Causing abnormalities in the metabolism of
 - Carbohydrates, Fats and Proteins
- Most significant of these is increase in skeletal muscle breakdown;

What are some unique metabolic changes that occur in patients with CAS?

- During CAS instead of using Fat for energy production, the body uses Skeletal Muscle Protein (**failure of Protein Sparing effect**), (**Fig. 2: Cori Cycle & Alanine Cycle**)
- During CAS the Liver continues to produce abnormally large number of "Acute Phase Proteins";
- Normal body adaptation to starvation (decreased BMR and Preferential use of Fat as energy source) does not occur in a patient with CAS;
- Instead, there is increased in BMR;
- When at rest, a patient with CAS uses more Calories than an healthy individual of the same height and weight;

Fig. 2: Metabolic relationship of Liver and Muscle in Cori Cycle (Lactic acid cycle) and Alanine Cycle

