L5

Revised by

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Metabolic response to injury

Objectives:

- No Objectives in the slides.

Color index:

Main Text
Textbook
Males slides
Important
Females slides
Golden notes
42 Doctor note
Extra
41,39 Doctor notes

Editing file

Mediating the Response

overview

- After injury eg: (surgery), aggressive local and systemic mechanisms takes place to return the body into the preinjury state. While these mechanisms are vital for survival in the wild, in the context of surgical injury they can be harmful.
- Metabolic response is primitive response designed for us before modern medicine so we can survive if we got injured in wild or desert because of this response.
- With trauma patients and surgical patients we interfere by supplementing nutrients and blunting the body's response to injury to avoid the consequences like (muscle wasting) and give much better results .This response is GRADED according to the type of injury
- When the patient undergoes a period of starvation or trauma (including surgery) the metabolism of substrates and micronutrients gets affected,also if the body gets injured it will react to it in a harmful way that may affect the person life and it will increase the morbidity مافي شي ببلاش

Features of The Metabolic Response to Injury

- The response to trauma follows an Ebb & Flow pattern. The ebb phase occurs immediately after trauma and lasts from 24-48 hours followed by the flow phase. After this, comes the anabolism phase and finally, the fatty-replacement phase

Ebb

- (**during** the injury)**energy expenditure goes way down** to conserve energy[1].
- It helps in surviving but may lead to permanent tissue damage,(bleedingفي صحراء) this phase will reduces the CO/BP so vessels will not get the blood and then reduce the bleeding .
- Characterized by **hypovolemic shock**. (because of bleeding)
- **Priority is to maintain life/homeostasis by[1]:**

↓Cardiac output

↓Oxygen consumption

↓Blood pressure

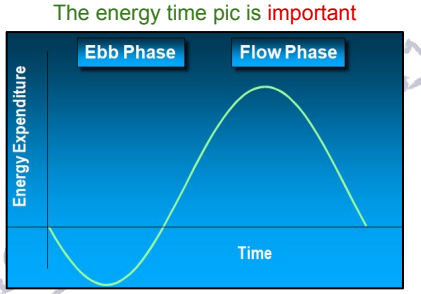
↓Tissue perfusion

↓Body temperature

↓Metabolic rate

Trauma causes major alterations in energy and protein metabolism.

The energy time pic is important



Our aim is to:

➔ Blunt EBB phase as it will lead to further tissue damage

➔ Supplement patients in Flow phase to assure healing and prevent complications

Flow[2]

- **After** surgery/ injury when the body senses that the active insult is gone and it's time to **rebuild**, the **energy expenditure goes way up** in the flow phase to rebuild what has been damaged. in this phase there's rebuilding of muscle and fat ((restore)).
- we need to detect this stage to supply the patient with enough nutrients and energy to support the rebuilding process, otherwise,patients will burn their energy sources leading to inability to re-heal and many other complications.
  - Burn is one of the worst and we try to support the patient during the flow phase
- These hormones and substance released from the body to Breakdown muscle for AA & GLU to repair the injury site
- ↑Catecholamines
- ↑Glucocorticoids
- ↑Glucagon
- Release of cytokines, lipid mediators
- Acute phase protein production (inflammation for scar formation or infection prevention)

1. these changes are essential for survival however they come with consequences, for example the low cardiac output can cause an injury to the kidney. therefore it's recommended to interfere in this phase so the body can emerge in a much better condition with minimal consequences.مافي شي ببلاش
2. **The flow phase may be subdivided into two parts:**

A- initial Catabolic phase: lasts about a week, characterized by: 1-high metabolic rate 2-breakdown of protein and Fat 3-A net loss of nitrogen (negative nitrogen balance) 4-weight loss.

B- Anabolic phase: lasts for 2-4 weeks, protein and fat are stored, positive nitrogen balance and weight gain.

- Surgery is an injury but it is a "controlled injury" because they manage to control the body to response to it.
- It is important to understand metabolic response to:
  - Blunt metabolic response in injury or surgery by interventions and medications.
  - Augment anabolic response, thus helping the body to heal with no permanent sequelae.
- sometimes if the injury is sustained (e.g. multiple surgeries, multiple infections) the patient will continue to be in the Ebb phase for an extended period of time before going to the flow phase

Mediating the Response

Factors mediating the metabolic response to injury:

- The metabolic response is a complex interaction between many body systems:

The Acute Inflammatory Response

- when you get injured(hypoxia, bacteria,etc) or there's a resection or incision Cellular activation (cells die by this injury and release mediators).
- Inflammatory mediators (TNF, IL1,TF, PAF, etc[4]).
  - At the site of injury:
  - Macrophages releases[1]:
    - IL-8 -> attracts more macrophages and neutrophils.
    - IL-1, IL-6, TNF alpha -> activate the macrophages and neutrophils.
      - Inflammatory substances (complement, prostaglandins and free radicals) are released
  - anti-inflammatory substances[2] (antioxidants, protease inhibitors and IL-10) are released
- These mediators will cause the Paracrine vs endocrine effects and release some hormones to prepare the body for the stress that will happen after the injury (cortisol secretion, release of NE & Epinephrine, activation of renin-angiotensin system in addition to the activation of the autonomic nervous system).

The Endothelium

- One of the most important cells that mediate this response is the endothelium of the vessel when you injured it.
- When cells in the vessels get exposed due to injury all blood cells will be activated (WBCs/platlet/ macrophages)
- Selectins, Integrins and ICAMs.[5]
- Nitric Oxide into the circulation
- Tissue Factor (Activate the extrinsic coagulation pathway and limits the bleeding).[3]
- Vasodilation might cause edema due to protein leak

1. these cytokines act locally, they can cause systemic effects, Eg: IL-1 causes fever.
2. The clinical condition of the patient depend upon the balance between inflammatory and anti-inflammatory substances.
3. If the inflammatory response become generalized, there is a risk of disseminated intravascular coagulation (DIC).
4. Inflammatory mediators IL2, IL3, IL4 and IL6,
5. Inflammatory markers which play a role in chemotaxis
6. Nitric oxide (Causes vasodilation and accumulation of WBC's and promote healing).

Mediating the Response

Afferent nerve stimulation 1

- Impulses from afferent nerve fibers reaches the thalamus and causes:
  - sympathetic nervous system activation and hormones from adrenal medulla:
    - increase heart rate and cardiac output. That's why the patients who are in pain they have tachycardia and hypertension.
      and they became anxious
    - changes in carbohydrates, fat and protein metabolism.
  - stimulation of other pituitary hormones.

The Endocrine system

- Endocrine system gets activated because the inflammatory mediators along with the SNS factors (NE/E) so there will be a hormonal changes .
- In the states of injury the body tries to survive not to build so (insulin/growth hormone) reduced.
- Changes in the endocrine system (direct stimulation or by feedback) aims to:
  - mediate the initial response.
  - maintain body fluids.
  - conserve energy in the beginning, and direct it where it's needed and return substrate metabolism to normal
- more stress hormones, less anabolic hormones:(any anabolic will decrease)

01 Pituitary gland:

1. **↓GH**
2. **↑ACTH**
3. **↑ADP (ADH)**

02 Adrenal:

1. **↑Cortisol:**
   More stress to generate energy which is required in healing & repairing.
2. **↑Aldosterone:**

03 Pancreas:

1. **↑Glucagon**
   For More energy and repairing
2. **↓Insulin:**

04 Other:

1. **Renin**
2. **Angiotensin**
3. **↓Sex hormones**
4. **↓T4**

1. Epidural or spinal Anesthesia is given to blunt afferent nerve stimulation
2. Afferent nerve stimulation : when the nerve is injured or stimulated by circulating mediators
3. Aldosterone is affected to conserve water and sodium as the body feels that there's hemorrhage somewhere.
4. Insulin and T4 decrease to conserve energy by decreasing the metabolic rate

Consequences of the response

- Limiting injury e.g by vasoconstriction
- Initiation of repair processes e.g directing platelets and forming clots
- Mobilization of substrates (glucagon and amino acid secretion increases).
- Prevention of infection penetration to the skin[1] increases the risk for infections, that's why WBC count increases after surgery & trauma along with complimentary immunity
- Distant organ damage.[2]

Hypovolemia:

- **Reduced circulating volume often characterises moderate to severe injury, and can occur for a number of reasons:**
  - loss of blood (hemorrhage).
  - loss of electrolyte containing water (vomiting, diarrhea and sweating).
  - loss of water (prolonged exposure of viscera during surgery).
  - loss of protein rich fluid into the interstitial space(increased capillary permeability).

- **The neuroendocrine response attempt to control hypovolemia by:**
  - Fluids conserving measures (ADH and Aldosterone).
  - blood flow conserving measures by increasing HR, CO and vasoconstriction (sympathetic activation)

Increased energy metabolism and substrate cycling:

- **although physical activity decreases after surgery, overall energy expenditure rises up to 50% due to:**
  - Increased thermogenesis (mild pyrexia).
    - BMR increases by 10% for each 1C°
  - Increased Basal Metabolic Rate BMR.

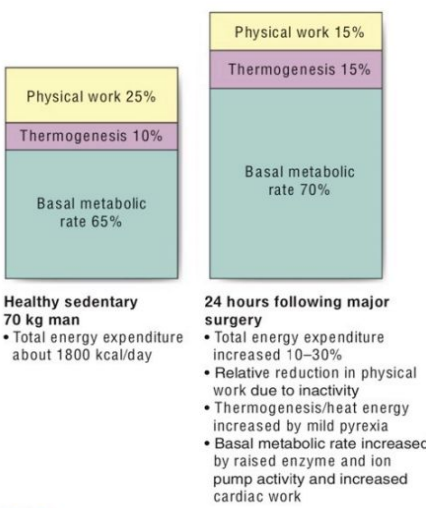


Fig. 1.4 Components of body energy expenditure in health and following surgery.

1-Major defensive organ is broken so bacteria can get in and out freely so you want to have ready immune systems to fight bacteria and give prophylaxis prior to surgery.
2-Examples of distant organ damage; damage to the kidney and the gut when the blood is being shunted to the area of the injury.

Consequences of the response

Catabolism and Starvation:

- Following surgery, Catabolism is mediated by catecholamines, proinflammatory cytokines and hormones

★ It will affect the metabolism of:

01

Carbohydrate

- **increase blood glucose (hyperglycemia[1]) which is caused by:**
  - glycogenolysis by (glucagon and catecholamines).
  - gluconeogenesis by (cortisol).
  - Insulin resistance.

02

Fat

- **Breakdown of triglycerides into glycerol and FFAs by:**
  - catecholamines.
  - cortisol.
  - glucagon.

03

Protein

- **Breakdown of skeletal muscles (loss of muscle mass) into amino acids to be used for:**
  - gluconeogenesis.
  - the production of acute phase proteins eg: (C-reactive protein, alpha1 Antitrypsin)

- **Starvation is caused by:**
  - Fasting prior to surgery[2]
  - loss of appetite after surgery.
  - Fasting after surgery (if the surgery involves the gastrointestinal tract).
  - Reduced nutritional intake because of the illness requiring treatment

Acute starvation phase

- Characterized by:
  - glycogenolysis and gluconeogenesis.
  - Lipolysis and FFAs release.

VS

Chronic starvation phase[3]

- Lipolysis and FFAs release.
- Ketones production and use for energy in the brain (conserving muscles).
- Reduction in energy expenditure (compensated starvation).

1. Severe hyperglycemia may increase morbidity and mortality in surgical patients and glucose levels should be controlled in the perioperative setting.
2. Important to empty the stomach so when we give anesthesia food won't regurgitate to the lungs, but we should let him drink fluids to minimize the starvation and catabolic effect during surgery.
3. If fat stores are depleted, and the individual is close to death → muscles are used as final energy source.

Consequences of the Response:

Changes in Red Blood Cell synthesis and coagulation:

- **Anemia is common after major surgery or trauma because of bleeding.**
- **Blood transfusion to correct anemia is not required unless hemoglobin concentration is below 80 g/L.**
- **After tissue injury, blood becomes hypercoagulable because of:**
  - Activation of coagulation cascade following endothelial injury.
  - Platelet activation by mediations e.g: (cytokines).
  - Venous stasis due to hypovolemia and immobility.
  - increased concentrations of circulating procoagulant factors (e.g. fibrinogen)
  - Decreased concentrations of circulating anticoagulants (e.g. Protein C)

Anabolism:

- **Involves re-gaining weight, skeletal muscle mass and fat stores.**
- **Occurs after the inflammatory mediators are no longer produced.**
- **Adequate nutritional support and early mobilization also appear to be important in promoting enhanced recovery after surgery (ERAS).**
- **Hormones contributing to anabolism are:**

01 **Insulin**

02 **Growth Hormone**

03 **Androgens**

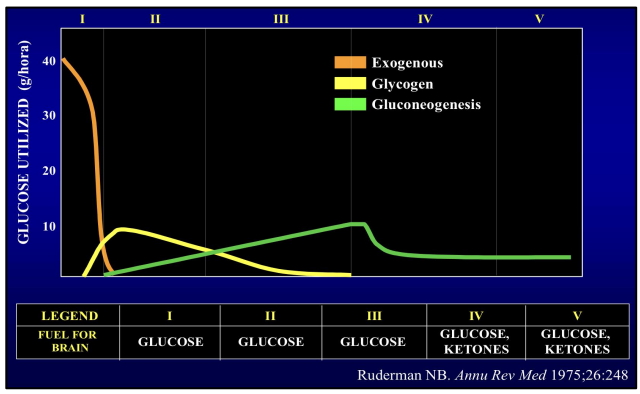
04 **Insulin like growth factor.**

Starvation & Injury

Metabolic Response to Fasting:

- the body's response to starvation is different from its response to injury.
- when you're fasting your glucose utilization goes down.
- after 40 days of starvation the body starts using ketones for energy.
- we need to keep the patient in stage 1 by supplementing the patient with enough nutrients.

- Initially in stage 1 the exogenous glucose is the main fuel for the brain (carbohydrate deposits)
- In stage 2 and 3 the glucose falls and the brain needs to rely on another source for energy. Glucagon will be secreted to breakdown Glycogen and convert it into glucose .
- In stage 4 the glycogen store gets depleted and gluconeogenesis takes over. muscle breakdown increases to release amino acids (which are needed for gluconeogenesis) that's why this stage needs to be avoided bcs it lead to muscle wasting . (in stage 4 and 5 there's not much glucose left and the brain starts to suffer).

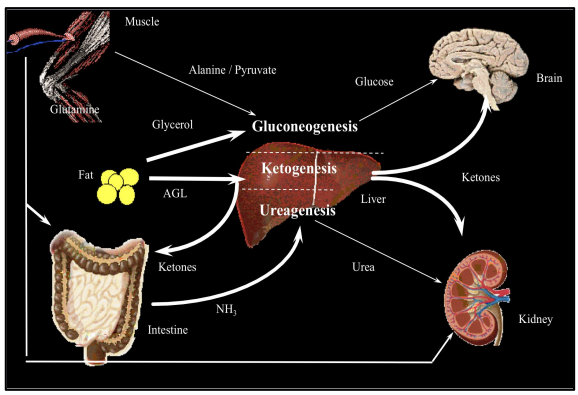


Ruderman NB. *Annu Rev Med* 1975;26:248

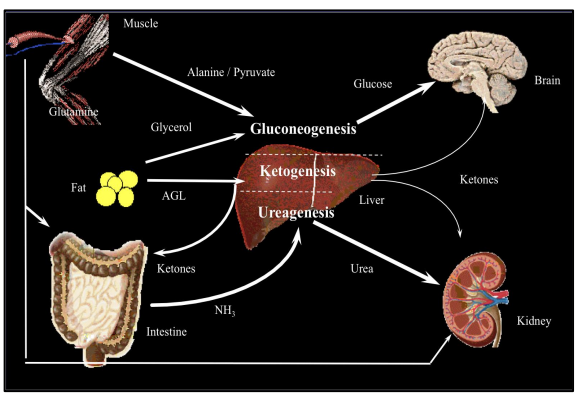
Starvation:

- Metabolic rate decreases significantly in comparison with fasting.

- ketones can be used everywhere **EXCEPT the brain. The brain needs to rely on glucose** for an extended period of time, but after 40 days it will use it.
- Amino acids come from the muscles only which will lead to breaking them down



Early Stage



Late Stage

- There's breakdown of fat and muscle (muscles are more accessible than fat).
- Muscle wasting is an indicator to initiate rehabilitation as its difficult to regain muscle fibers again unlike fat.
- Using of ketones along with glucose by the brain for energy(chronic starvation).

- In the early stage more urea is going to the kidney.

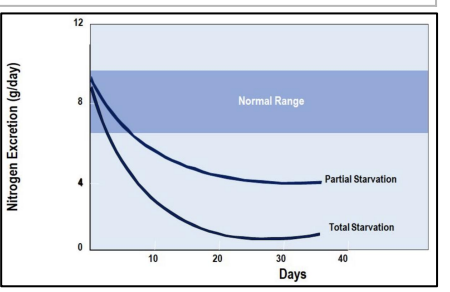
Starvation & Injury

Metabolic Response to Starvation:

- Initially NE from sympathetic nervous system goes down significantly, however NE secretion from the adrenal gland goes up.
- Thyroid hormones goes down to conserve energy.

Hormone	Source	Change in Secretion
Norepinephrine	Sympathetic Nervous System	↓↓↓
Norepinephrine	Adrenal Gland[1]	↑
Epinephrine	Adrenal Gland[1]	↑
Thyroid Hormone T4	Thyroid Gland (changes to T3 peripherally)	↓↓↓

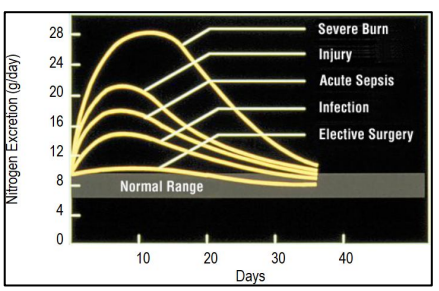
Energy Expenditure in Starvation:



- in starvation mode, energy expenditure goes **down** and it reaches a **plateau** after a month.
- Nitrogen excretion is an indicator of catabolic rate and how much muscle was wasted.
- This is an important difference between starvation and injury, seeing that it doesn't happen in injuries (Epp/flow)

- the more you are in the starvation mode (not injury only starvation) the more your energy expenditure goes down. (the diet with only reducing eating isn't useful because you will reduce your energy expenditure) **Important**

flow phase



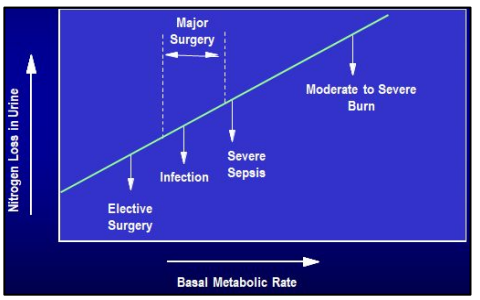
- This graph illustrates nitrogen losses in relation to trauma. With respect to protein, the greater the trauma, the greater the effect on the nitrogen balance. Similar to metabolic rate, patients experience nitrogen losses according to the severity and duration of the trauma.
- The normal range is indicated by the shaded area. The amount of protein requirement relative to calories increases in patients with metabolic stress.
  - The worse the injury is, the worse the catabolic state, energy expenditure and nitrogen excretion[3]
  - In elective surgery the response is blunted (with proper Anesthesia, enough nutrition and hydration with clear liquids) to avoid unnecessary tissue injuries and minimize the harm.

1. Adrenal NE and EP are considered as “stress hormones”, There level rises in starvation to increase the mobilization of fuel sources
2. An example of partial starvation: a patient who develops post surgical complications that would last for days to weeks making him unable to eat.
3. For example, burn victims need immediate fluid treatment and monitoring of nitrogen balance otherwise they fail to heal and they enter the catabolic state.

Starvation & Injury

Energy Expenditure in Starvation:

- the amount of nitrogen the patient loses in the urine is an indicator of how bad the injury is and how aggressive the patient's response is



Comparing Starvation & Injury:

- **The body adapts to starvation, but not in the presence of critical injury or disease.**

IMPORTANT	Starvation	Trauma or Disease
Metabolic Rate	↓	↑↑[1]
Body Fuels	Conserved	Wasted[2]
Body Proteins	Conserved	Wasted[2]
Urinary Nitrogen	↓	↑↑
Weight Loss	Slow	Rapid

- **The metabolic response to starvation can be contrasted to trauma or disease:**
  - Metabolic rate drops during starvation, while in trauma patients it rises in proportion to the trauma severity[3].
  - Body fuels and body proteins are conserved during starvation[4], but are wasted during trauma.
  - Urinary nitrogen values fall with inadequate protein and calorie intake, but increase in response to metabolic stress. We measure it to calculate the loss and supply the patient with nutrition
  - Weight loss is slow in underfed patients but rapid in trauma patients.
  - Changes in body composition with trauma usually occur two to three times faster than during starvation.

1. Initially in the Ebb phase it decreases but later on as the patient enters the flow phase the metabolic rate increases.
2. first the body will try to conserve them but after 48 hours they get used immediately for repair and healing. Specially muscles as they're easy to break but difficult to rebuild
3. to achieve better outcomes after a surgery or a trauma we have to blunt the Ebb phase (to avoid hypovolemic shock, hypotension, and reduced tissue perfusion by giving the patient enough blood, stopping the bleeding and supplying the patient with enough oxygen) and support the flow phase by giving them extra nutrition according to the patient own BMR
4. if the starvation is persistent they get wasted.

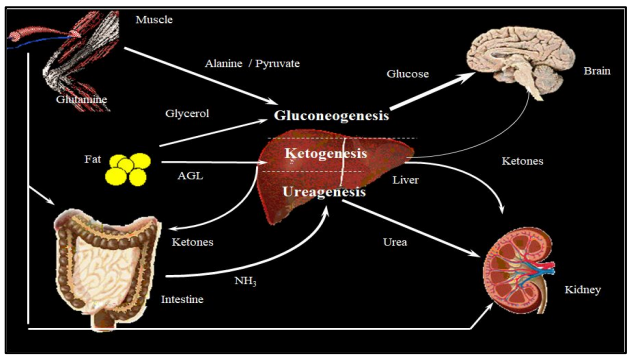
The effect of injury

Metabolic Changes after Injury:

Endocrine Response

- Fatty Deposits → Fatty Acids
- Liver & Muscle (glycogen) → Glucose
- Muscle (amino acids) → Amino Acids

- **Endocrine** response in the form of increased catecholamines, glucocorticoids and glycogen, leads to mobilization of tissue energy reserves. These calorie sources include fatty acids and glycerol from lipid reserves, glucose from hepatic glycogen (muscle glycogen can only provide glucose for the involved muscle) and gluconeogenic precursors (eg, amino acids) from muscle.
- **The** response to trauma includes a breakdown of muscle tissue. This mechanism provides amino acids for gluconeogenesis and for synthesis of proteins involved in immunologic response and tissue repair. However, this process can lead to a loss of body mass, most notably body protein.



- **Prolonged** metabolic stress without provision of adequate calories and protein leads to impaired body functions and ultimately malnutrition.

Modifying the Response:

*This is the purpose of the lecture

Medication
(Before or after injury)

- To blunt inflammatory response and the sympathetic system with pain meds, prophylactic antibiotics..etc

Nutritional status

- It's an absolute requirement that the patient be in a well nutritional status before any elective surgery, otherwise supplements are needed. (Prehabilitation)

Severity of injury

- Perform minimally invasive surgeries with meticulous technique

Temperature

- Prevent hypothermia which leads to coagulopathies.

Hypothermia results in worsening acidosis, which both contribute to the severity of coagulopathy. A worsening coagulopathy results in continued hemorrhage

Hypothermia→coagulopathy →bleedings → injury → increase metabolic rate

Anesthetic technique

- Even the patient is sleep or underwent general anaesthesia we give epidural anaesthesia to prevent metabolic response mediated by nervous system

The doctor's summary

- Injury (Trauma or Surgery) leads to a metabolic response.
- Metabolic response to injury is an adaptive and graded response.
- Metabolic response could overwhelm the body and lead to increased morbidity and mortality.
- We can modify the metabolic response before by optimise patient condition and sometimes after injury.
- The body responds differently to starvation and trauma. Starvation is associated with a decreased metabolic rate, which allows the body to adapt to reduced intake. After trauma, metabolic changes are associated with increased nutritional requirements. If nutritional requirements are not met during trauma, loss of protein and body mass can produce significant impairment.
- Metabolism of substrates and micronutrients is altered by starvation and trauma. During periods of starvation, metabolic processes slow down to conserve energy and adapt to calorie deprivation. After trauma, the body's hormonal situation changes, increasing the demand for energy, proteins, and micronutrients. If nutritional requirements are not recognized and met during starvation or trauma, there may be a loss of body mass, body protein, and impairment or loss of body functions.

Summary

- **Our aim is to blunt EBB phase as it will lead to further tissue damage and supplement patients in Flow phase to assure healing and prevent complications**

Ebb phase

↓Cardiac output ↓Oxygen consumption
↓Blood pressure ↓Tissue perfusion
↓Body temperature ↓Metabolic rate

VS

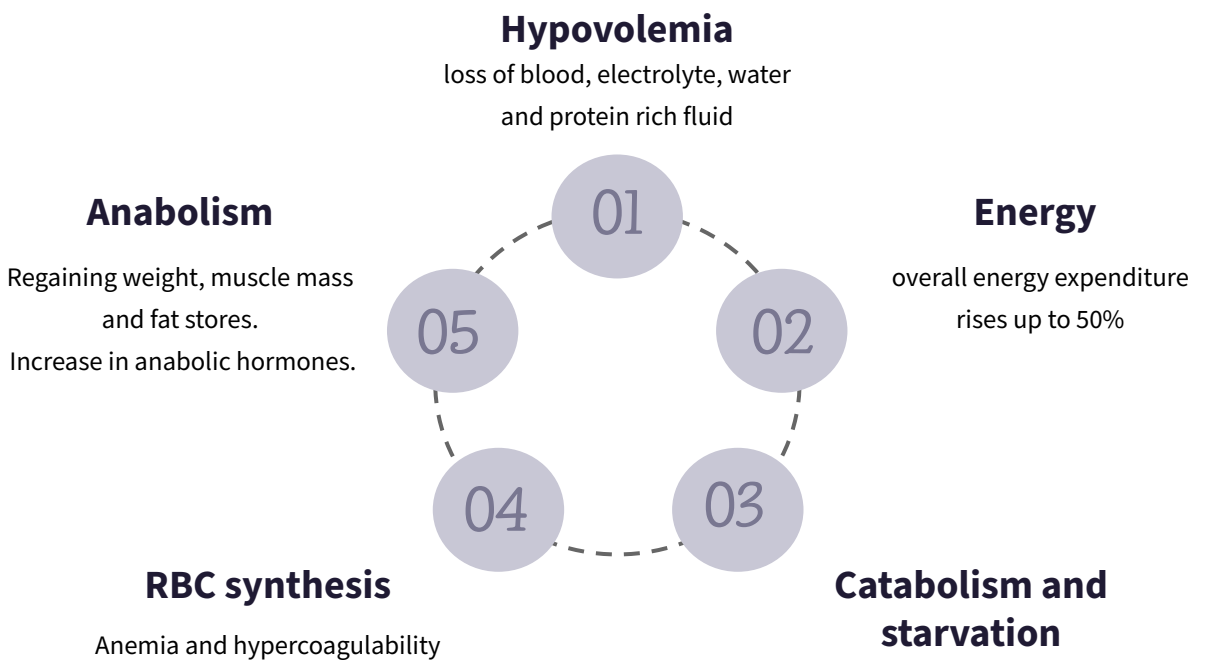
Flow phase

↑Catecholamines
↑Glucocorticoids
↑Glucagon
Release of cytokines, lipid mediators
Acute phase protein production

	Response
Acute Inflammatory Response	• Cellular activation. • Inflammatory mediators (TNF, IL1,IL2, IL3, IL4 and IL6). • Paracrine vs endocrine effects.
Endothelium	• Selectins, Integrins and ICAMs. • Nitric Oxide > vasodilation > edema. • Tissue Factor > coagulation > DIC.
Afferent nerve stimulation	• Sympathetic nervous system activation. • Release of hormones from adrenal medulla. • Stimulation of other pituitary hormones.
Endocrine system	• More stress hormones, less anabolic hormones: ○ Pituitary gland: GH, ACTH and ADH. ○ Adrenal: cortisol, aldosterone. ○ Pancreas : glucagon,↓Insulin. ○ Other: renin, angiotensssion,↓sex hormone,↓T4.

Summary

- The metabolic response **limits the injury** and **initiate the repair process** by **mobilizing substrates**. Help in **preventing the infections** but could cause **distance organ damage**.
- More consequences:



	Starvation	Trauma or Disease
Metabolic Rate	↓	↑↑
Body Fuels	Conserved	Wasted
Body Proteins	Conserved	Wasted
Urinary Nitrogen	↓	↑↑
Weight Loss	Slow	Rapid

- Modifying the metabolic response done through:

Quiz!

Q1: A 30 year old man had a successful cholecystectomy, which of the following hormones do you expect to increase in his case?

1. Insulin
2. Thyroid hormones
3. Cortisol
4. none

Q2: In the early stage of starvation which of the following uses glucose?

1. kidney
2. muscle
3. skin
4. brain

Q3: What are the hormonal changes that happen during starvation?

1. Initial increase in thyroid hormone levels and decreased norepinephrine and epinephrine levels
2. Initial decrease in norepinephrine levels and later an increase in norepinephrine and epinephrine with decreased thyroid hormone levels
3. Initial decrease in thyroid hormone and later an increase in it's level with continuous decrease in norepinephrine and epinephrine levels
4. Continuous increase in norepinephrine levels and later an increase in thyroid hormone levels

Q4: Counter regulatory hormones in response to metabolic response to injury are all except.

1. Glucocorticoids
2. Catecholamines
3. Thyroid hormones
4. Glucagon

Q1) **3**/ Q2) **4**/ Q3) **2**/ Q4) **3**

Quiz!

Q5: What is the main physiological role of the ebb phase?

1. Conserving energy stores
2. Increasing metabolic rate
3. Replacement of lost tissue
4. increase blood pressure

Q6: The flow phase is characterized by?

1. conserving energy
2. Increased insulin secretion
3. Increased glucagon secretion
4. Decreased catecholamines secretion

Q7: what happens to urinary nitrogen in trauma or disease is?

1. increased
2. decreased
3. unchanged
4. none

Q8: In stress response, which of the following statements are false?

1. It is graded.
2. Metabolism and nitrogen excretion are related to the degree of stress.
3. In such a situation there are physiological, metabolic and immunological changes.
4. The changes cannot be modified.

Q5) **1**/ Q6) **3**/ Q7) **1**/ Q8) **4**

القادة

رزان المهنا　　في الدوسري　　محمد الغامدي

نوف الضلعان　　وعد أبو نخاع

الأعضاء

ولاء المطوع　　سعد المقرن　　عبدالرحمن بن عتيق

حسبي الله لا إله إلا هو عليه توكلت وهو رب العرش العظيم.
اللهم إني أستودعك ما قرأت وما حفظت وما تعلمت فرده لي عند حاجتي إليه إنك على كل شيء قدير.

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