UNIVERSITY OF PNG
SCHOOL OF MEDICINE AND HEALTH SCIENCES
DIVISION OF BASIC MEDICAL SCIENCES
DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
GLUCOSE HOMEOSTASIS – (Diabetes Mellitus Part 1): An Overview

WHAT IS HOMEOSTASIS?

- Homeostasis is a fundamental characteristic of living organisms
- Homeostasis (Homeostatic control): Condition in which disturbances to systems by stimuli are minimized, because the stimulus is able to start a series of events that can restore the system to the original state
    - Simply means: maintenance of a relatively constant internal environment within tolerable limits
- Break down in the Homeostatic mechanisms may lead to disease.

What systems are involved in homeostatic regulation (give an example)?

- Endocrine system, Nervous system, Immune system, etc. are responsible for mediating both detection and response to homeostatic changes from the level of the cell to that of the whole organism
- An example of Homeostatic control:
    - Maintenance of Glucose level in Blood.
        - Under the control of numerous exquisitely sensitive Homeostatic mechanisms
            - One of the major mechanisms involves: Cells of the Endocrine pancreas, their detection of blood glucose level, and the hormones (Insulin and Glucagon) that they secrete
    - Defects in this homeostatic mechanism are responsible for one of the major challenges to human health – **Diabetes Mellitus**.

Why the need for adequate amount of Glucose in the Blood?

- Under normal Physiological conditions:
    - Brain and the rest of the Nervous tissue utilize Glucose as Major Substrate for Energy production
    - Brain still requires Glucose during prolonged fasting
    - Mature RBC do not contain Mitochondria, thus energy is obtain via Anaerobic Glycolysis
    - In RBC 2,3-Bis-Phosphoglycerate is required for effective transport of O_2
    - Skeletal muscle during heavy exercise utilizes Muscle Glycogen and Blood Glucose for Energy production

- **It is essential that Glucose is always available in adequate amount in the blood, because Brain and Red Blood Cells utilize glucose almost exclusively as major substrate for energy**

How does dietary intake of Glucose relate to Insulin level in blood?

- Glucose level increases in the blood shortly after dietary intake (following a meal).
  - Within 2 to 3 hours after consumption of the meal, blood glucose level should be restored to the Pre-prandial level
- Increase in blood glucose level after a meal is immediately followed by increase in Blood Insulin level (See **Fig. 1**.)
- **Figure 1** shows schematic representation of the relationship between Plasma Glucose and Plasma Insulin levels during periods of Eating and Fasting

TAKE NOTE:

- Insulin secretion is stimulated by several events that are associated with Glucose intake.
- Elevated blood glucose directly stimulates Pancreatic Insulin release from the Beta cells (Islets of Langahan) in the Pancreas
- Insulin release is also stimulated by other components of the typical diet, (notably **Leucine** and **Arginine** derived from the digestive hydrolysis of protein in the diet)
- Digestive process stimulates the release from the GIT of Gastrin, Pancreozymin, Cholecystokinin, and the Glucagon-like Gastrointestinal peptide Glicentin
  a. These hormones appear to feed forward to the Pancreatic β-cell and stimulate insulin release in an anticipatory manner
- Insulin release is also under Neural Control, possibly also as an anticipatory event.

How does the composition of the meal affect blood levels of Insulin and Glucagon?

- Blood levels of both Insulin and Glucagon are changed after consumption of a meal
  - Magnitude and direction of the change depends on composition of the meal
- For a meal containing mainly Carbohydrate:
  - Glucagon level in blood will fall because of:
    - Direct Inhibition of the Alpha-cells in Islets by high glucose level, and
    - Increase in the release of Insulin from Beta cells in the Islets
- For a meal containing High Protein and Low Carbohydrate:
  - Glucagon level in blood will increase as a consequence of Amino Acid Influx
- For a Typical meal that contains both Carbohydrate and Protein:
  - Insulin level in blood may increase compared to Glucagon level

HOW DOES THE BODY NORMALLY DISPOSE OF HIGH DIETARY GLUCOSE?

What is the role of the Liver in the disposal of high dietary glucose?

- After a period of fasting, such as overnight fasting, substantial amount of Carbohydrate consumed in the diet is converted to Hepatic Glycogen
- Liver is the first important site for metabolism of Ingested Glucose
  - Liver is freely permeable to glucose, it extracts about 50% of the digested Carbohydrate
  - Glucose transporter in Liver is GLUT 2

    - GLUT 2 is not sensitive to Insulin
- In Hepatocytes Glucose is first converted to G-6-P (by Glucokinase) and then via G-1-P to Glycogen
- Insulin promotes Glycogen formation in Hepatocytes via activation of Glycogen Synthase
- Glycogen Synthase promotes storage of Glucose as Hepatic Glycogen until the Hepatocytes have restored their optimal level of Glycogen
- Signal for termination of the synthesis of Glycogen is the level of Glycogen itself, which acts by inhibiting Glycogen Synthase Phosphatase
- After filling up of Hepatic Glycogen store, Glucose remaining in blood is distributed to other tissues

What is the role of the Muscle in disposal of dietary glucose after the action of the liver?

- Insulin directly stimulates the uptake of glucose into muscle cells
    - Glucose transporter in muscle is GLUT 4, which is sensitive to Insulin
- Glucose taken up is used to replenish Glycogen store in muscle
- Extra glucose in muscle is used for Protein Synthesis, so as to replenish those proteins that might have been degraded for Gluconeogenesis during the period of fasting

What happens to the glucose remaining in blood after Liver and Muscle tissues have extracted and stored enough glucose as Glycogen?

- With the exception of the **Brain, Liver, and Blood cells**, Insulin directly stimulates the uptake and use of Glucose by most cells of the body
- Liver plays a major role in converting excess glucose into Triacylglycerols (Triglycerides), packaging them into VLDL and exporting the VLDL to Adipose tissue
- As a consequence, much of the glucose in excess of that needed to restore Glycogen levels in the Liver and Muscle ends up as Triacylglycerols stored in Adipocytes
- Insulin is the Primary signal for conversion of excess glucose to Triacylglycerols for storage in Adipocytes

SUMMARY OF DISPOSAL OF HIGH DIETARY GLUCOSE:

Summary of disposition of high dietary glucose is as follows:

- Optimal amount of glucose is stored as Glycogen in Liver and Muscle
- Remaining glucose in Blood is used for other biosynthetic purposes and any excess is then converted into Fatty acids and stored as Triacylglycerols
- Although the Glucose level in systemic blood may be elevated, it does not exceed the Renal Threshold (about 200mg/dl or 11mmol/L) therefore, Glucose does not spill into the urine
- Insulin plays pivotal role in disposal of high blood glucose by stimulating a range of Anabolic processes in addition to those of Glycogen, Protein and Triacylglycerol synthesis

- Insulin does so by a variety of Regulatory mechanisms, which may involve either the modification of key regulatory enzymes and/or regulation of their synthesis

- **In addition to the role of Insulin is the absence of the Insulin "Counter-Regulatory" Hormones – Glucagon, Glucocorticoids and Catecholamines**

REGULATION OF BLOOD GLUCOSE DURING FASTING

How is Blood Glucose level regulated during fasting?

- In a 'healthy" individual, blood glucose level usually remains constant, even if no food is consumed within a 24-hour period
- During prolonged fasting:
  - Blood glucose level usually decreases only slightly, but is within normal range
  - Brain and RBC are still actively metabolizing glucose, thus the blood glucose that is utilized must be replenished

- Liver is the major source for the Glucose that keeps blood glucose level within normal range during period of fasting
- This is done:
  - Initially by bread down of Glycogen stored in the Liver (Hepatic Glycogenolysis),
  - Later by contribution from Gluconeogenesis (synthesis of Glucose from Non-carbohydrate sources) in the liver

What is the role of the Liver in regulating blood glucose during fasting?

Glycogenolysis (Glycogen breakdown):

- Glycogen stored in Hepatocytes (about 5 to 10% wet weight of liver) is mobilized and used up within the first 24 to 36 hours of fasting
- First positive signal for stimulation of Glycogenolysis in Hepatocytes is Increase plasma level of **Glucagon**, which is secreted in response to Hypoglycemia
- Second positive signal is the **absence of Insulin** (Hypoglycemia)

- During Hepatic Glycogenolysis:
  - Glucose-1-Phosphate (G-1-P) is produced from Glycogen
  - G-1-P is then converted to Glucose-6-Phosphate (G-6-P)
  - G-6-P is then converted to Glucose by **Glucose-6-Phosphatase**
  - Glucose molecules formed in the Hepatocytes are released into the blood to maintain normal blood Glucose level

- **Glucagon and Insulin tightly regulates Glycogen breakdown to Glucose that directly maintains the level of Glucose in Blood**
- **In the initial phases of starvation/fasting this is the major Glucose-producing mechanism**
- Hepatic Glycogenolysis is also regulated by Catecholamines (Adrenaline and Noradrenaline)

- Catecholamine release is a less sensitive hypoglycemic signal compared to Glucagon, but it does play a significant role in stimulating hepatic Glycogenolysis in circumstances of additional stress and marked Hypoglycemia

Gluconeogenesis (synthesis of glucose from non-carbohydrate sources):

- As hepatic Glycogen stores become depleted during fasting (or starvation) the other significant source of Glucose is Gluconeogenesis
- Sites of Gluconeogenesis and sources of precursors depend upon the duration of Caloric deprivation
- Although the Kidney assumes importance as a source of new glucose during protracted starvation, during brief fasting at least 90% of total Gluconeogenesis occurs in the Liver

What is the role of Skeletal Muscle in regulating blood glucose during fasting?

- Glycogen content in Skeletal muscle (about 1% wet weight) is lower that in the liver, however because the total mass of skeletal muscle is much higher than that of liver, the total Glycogen content in skeletal muscle is much higher than the total Glycogen content in the Liver
- Glycogen in skeletal muscle is not readily available to maintain blood glucose concentration
- Muscle tissue does not contain **Glucose-6-Phosphatase**, and thus cannot convert Glucose-6-Phosphose to Glucose
- Muscle does not play any significant role in maintaining blood glucose level
- Under Anaerobic conditions the muscle converts Glucose to Lactate, which is released in the blood picked up by the Liver and converted to Glucose (Cori Cycle)

What primary signals attune the body to the status of Gluconeogenesis?

- Primary signals that attune the body to the status of Gluconeogenesis are as follows:

Glucagon – as an Acute Modulator:

- Actions of Glucagon are directed towards increasing blood glucose from Low to Normal: Thus
    - In Hepatocytes:
        - Glucagon stimulates Glycogen breakdown to Glucose to maintain blood glucose level
        - Glucagon stimulates the formation of Glucose from Gluconeogenic intermediates, and
    - In Adipocytes:
        - Glucagon stimulates Triacylglycerol and Fatty acid breakdown and their Oxidation, and also provide substrates for Gluconeogenesis

Absence of Insulin:
Actions of Insulin are directly opposite to those of Glucagon

(See Fig 2: STOP – GO ACTION OF INSULIN)

- Insulin stimulates:
  - Glycogen synthesis,
  - Glycolysis, and
  - Biosynthesis of fatty acids

Glucocorticoids (e.g. Cortisol) – as Chronic Modulators:

Glucocorticoid actions are more complex than either Insulin or Glucagon

- In simple terms:
  - Glucocorticoids stimulate:
    - Fatty acid breakdown
    - Gluconeogenesis,
    - Rate of Hepatic Glycogen synthesis
  - Glucocorticoids are one of the major signals for the degradation of muscle proteins, with the amino acids serving as precursors for Gluconeogenesis

SUMMARY:

- Tissues involved in Glucose conservation: **Liver, Skeletal Muscle and Adipose Tissue**
- Glucagon actions are essentially restricted to Liver and Adipose tissue **WHY??**
  - Glucagon stimulates Glycogen breakdown and Gluconeogenesis in Hepatocytes
  - Glucagon stimulates breakdown of Triglycerides in Adipose tissues producing substrate for Gluconeogenesis in Hepatocytes
- Glucocorticoids activate hepatic Gluconeogenesis synergistically with Glucagon
- A major site of Glucocorticoids actions is on Skeletal Muscle;
- Presence of Glucocorticoids and the Absence of Insulin are Primary signals for enhanced Protein degradation
- Effects of Glucocorticoids are long term,
- Effects of Glucagon are moments to moment

Five Phases of Glucose Homeostasis:

For convenience Glucose Homeostasis can be divided into Five Phases as shown in **Fig. 3**.

GENERAL CONCEPTS: **Understanding Glucose Homeostasis:**

Balancing Act: Hypoglycemia and Hyperglycemia:

- Glucose Homeostasis involves extensive contributions from various metabolic tissues (**Liver, Skeletal muscle, Adipose tissue, etc.**) tightly regulated and balanced by the Metabolic Endocrines
- Hypoglycemia and Hyperglycemia refers to circumstances when this balance is disturbed, giving uncharacteristically Low and High Blood Glucose concentrations, respectively

- Circumstances that give rise to Hypoglycemia or Hyperglycemia can generally be divided in three categories, namely:
  - Factors related to effective Insulin concentration,
  - Insulin Counter-Regulatory Hormones
  - Sources of Fuel for the tissues

Insulin Counter-Regulatory Hormones:

- Insulin Counter-Regulatory Hormones, (Glucagon, Catecholamines, Glucocorticoids and Growth hormones) antagonizes the actions of Insulin
- Each is elevated in plasma in response to Hypoglycemia

References:

1. WWW.zonehome.com/met/metglucose.html
2. WWW.niko.unl.edu/bs101/notes/lecture12.html
3. WWW.mun.ca/biochem/courses/1430/diabetes.html
4. Textbook of Biochemistry with clinical correlations, ed. Delvin T. M. 4th Edition pages 536 to 540.

Fig. 1: RELATIONSHIP BETWEEN PLASMA GLUCOSE AND INSULIN LEVEL

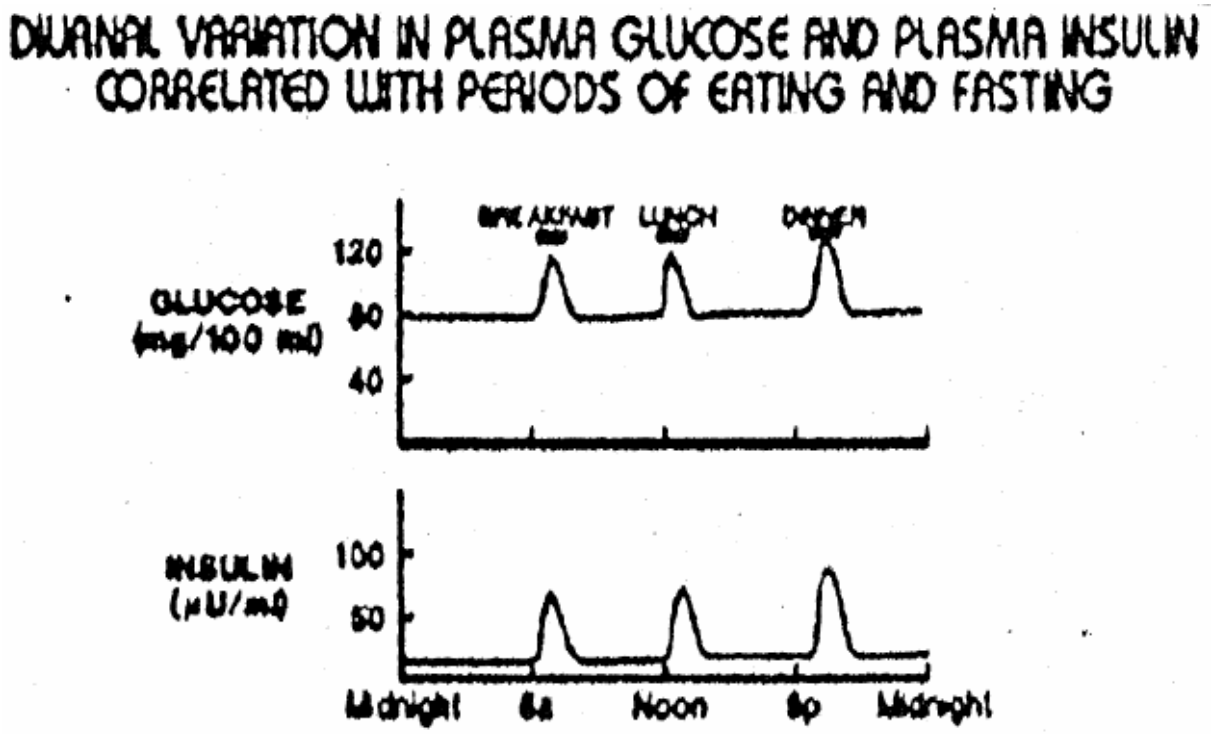


Fig. 2: STOP-GO ACTIONS OF INSULIN & GLUCAGON

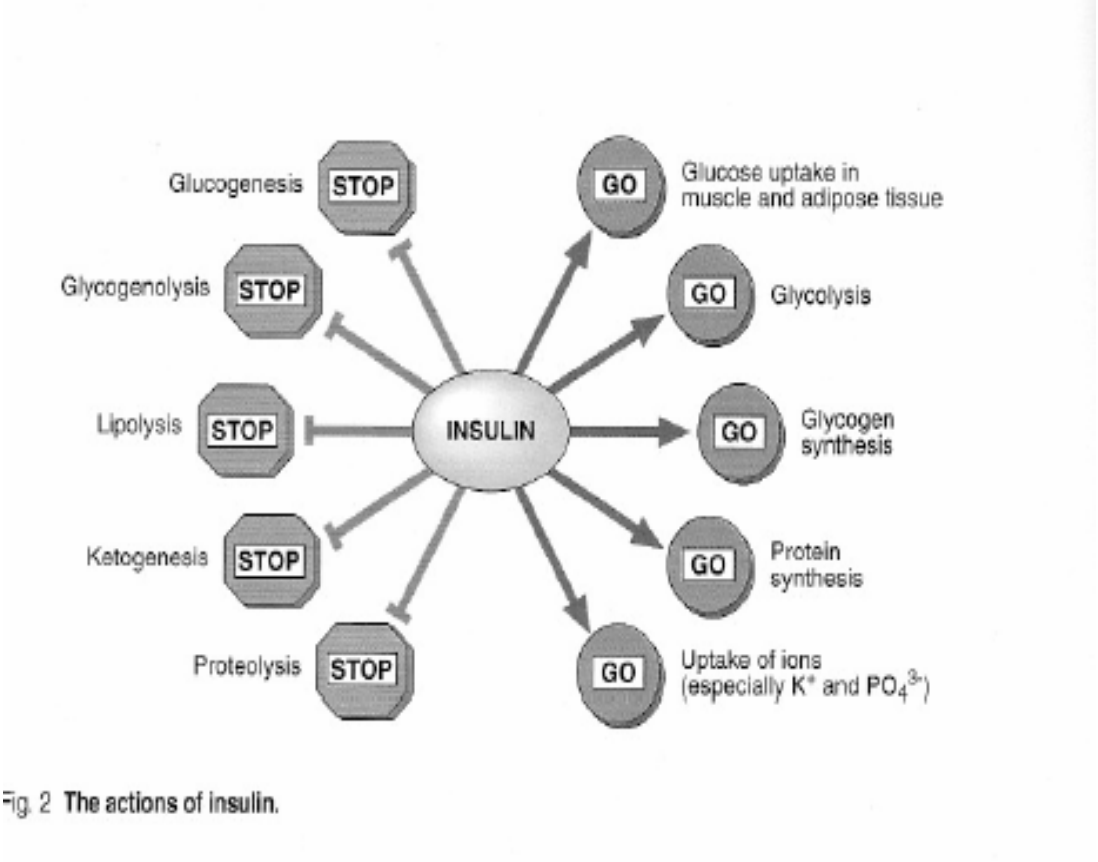
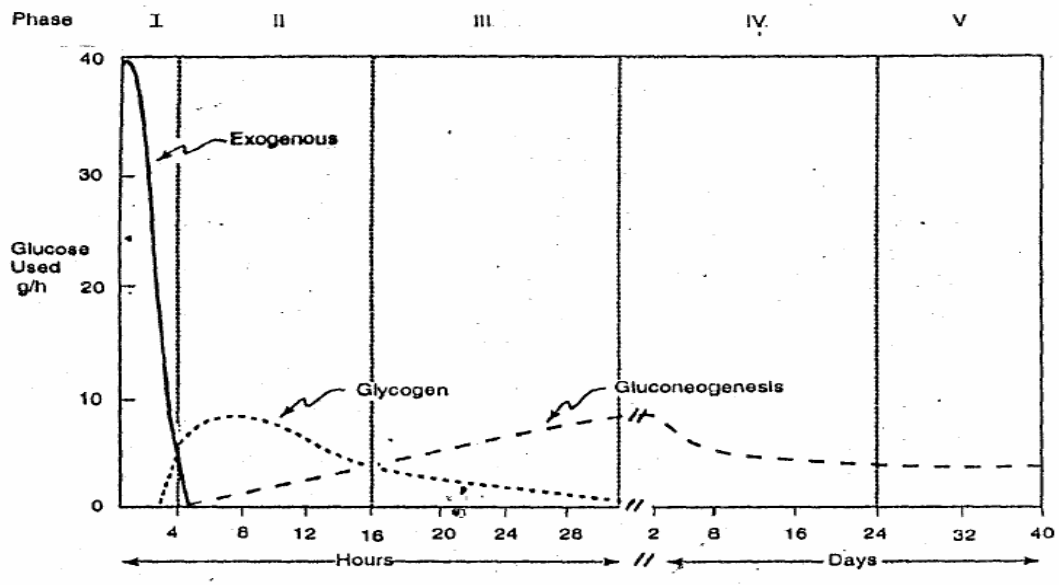


Fig. 2 **The actions of insulin.**

Fig 3: FIVE PHASES OF GLUCOSE HOMEOSTASIS IN HUMANS



Phase	ORIGIN OF BLOOD GLUCOSE	TISSUES USING GLUCOSE	MAJOR FUEL OF BRAIN
I	Exogenous	All	Glucose
II	Glycogen Hepatic gluco–neogenesis	All except liver. Muscle and adipose tissue at diminished rates	Glucose
III	Hepatic gluconeogenesis Glycogen	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Glucose
IV	Gluconeogenesis, hepatic and renal	Brain, RBCs, renal medulla. Small amount by muscle	Glucose, ketone bodies
V	Gluconeogenesis, hepatic and renal	Brain at a diminished rate, RBCs, renal medulla	Ketone bodies, glucose

Fig 8

FIGURE ~~1-10~~
The five phases of glucose homeostasis in humans.
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