I. Interrelationship between different metabolic pathways

Energy is obtained from the oxidation of the macronutrients carbohydrate, fat and protein. The end products of fat and carbohydrate metabolism are carbon dioxide, water and energy only. The catabolic oxidation of carbohydrates (glycolysis, citric acid cycle, and oxidative phosphorylation), fatty acids, lipids, ketone bodies, and amino acids, all lead eventually to the production of ATP coupled to all of these processes is the need to eliminate waste products, including CO_2 ,water, and urea (urea cycle) but also creatinine, uric acid and ammonia). About 80% of urinary nitrogen is normally present as urea. These concepts are summarized in Figure 1.

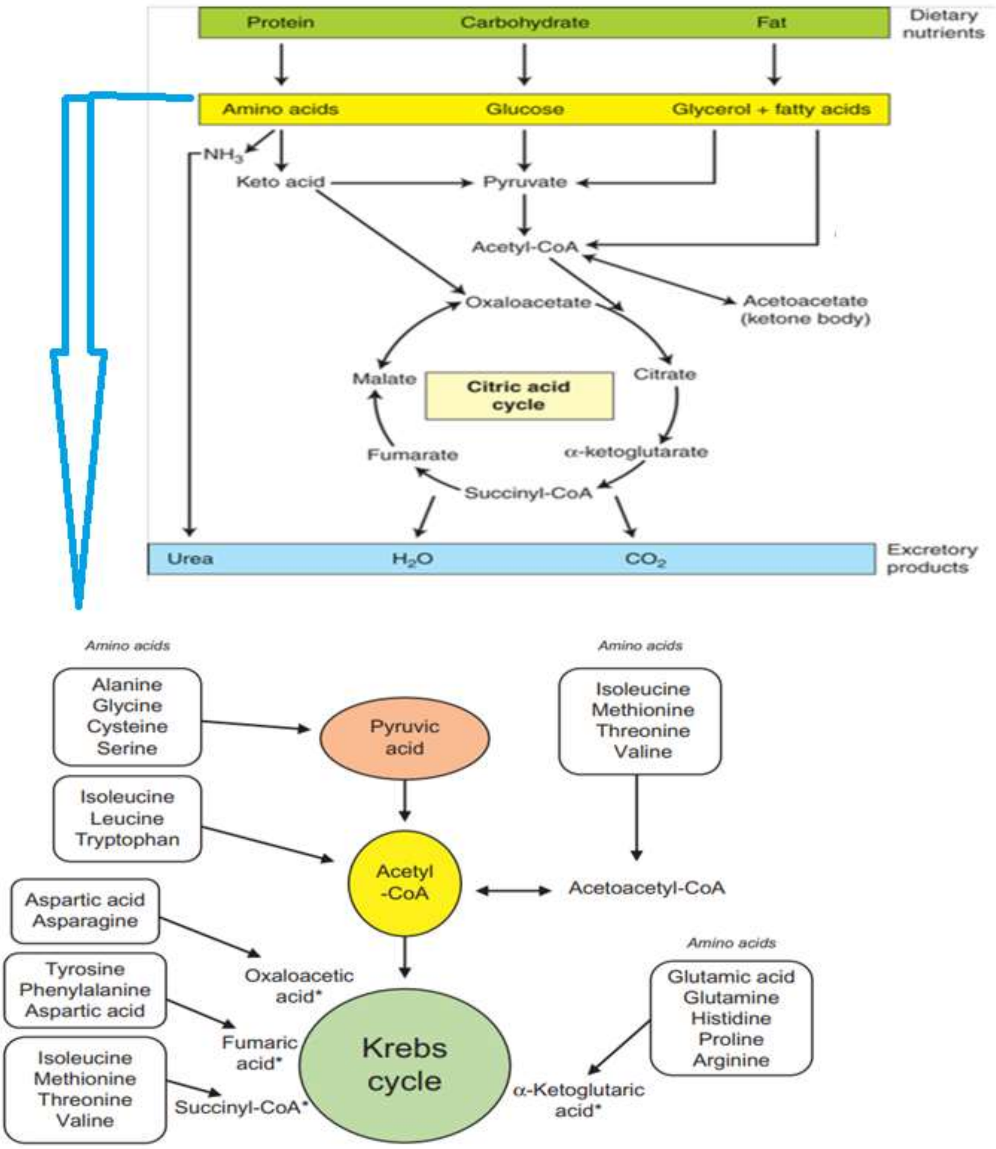

Figure 1: Enter of the macronutrients into the major energy metabolism pathways

I.1. Energy release

I.1.1.Carbohydrates metabolism pathway

The principal carbohydrate is glucose, but other monosaccharides include fructose and galactose. Glucose is absorbed from the gastrointestinal tract via the portal vein. It passes to the general circulation where it is metabolized in the tissues, or may be stored as glycogen, particularly in muscle and liver. In starvation, most tissues, including muscle (both skeletal and cardiac), can obtain their energy needs from fatty acids alone, but some, such as the central nervous system and red blood cells, are obligatory users of glucose.

Glucose is oxidized via two sequential metabolic pathways: the glycolytic pathway, which occurs in the cytoplasm; and the Krebs cycle, which takes place in the mitochondria. With carbohydrates, pyruvate is transported across the inner mitochondrial membrane and is then oxidatively decarboxylated to acetyl CoA. This reacts with the four-carbon acid oxaloacetate to produce the six-carbon tricarboxylic acid citrate. A number of other intermediate compounds are generated (α-ketoglutarate, succinyl CoA, succinate, malate, fumarate) but the oxidation of the acetyl groups to carbon dioxide is coupled to the reduction of NAD and FAD to NADH and $FADH_2$, which enter the respiratory chain to produce ATP.

I.1.2. Lipid metabolism pathway

When the triglyceride is hydrolyzed in the adipocyte or skeletal muscle during exercise, the glycerol can converted to glucose in a process of gluconeogenesis, which is first converted to dihydroxyacetone phosphate and then to glyceraldehyde-3-phosphate. Then the glycerol becomes available to the citric acid cycle and subsequently is metabolized into NADH and ATP. The three free fatty acids of the triglyceride enter the beta-oxidation biochemical pathway located in the mitochondrial matrix.

The result of beta-oxidation pathway reaction is conversion of the carbons of the fatty acid into acetyl-CoA. The acetyl-CoA produced enters the Krebs cycle and ATP is produced in the electron transport chain. The reactions in beta-oxidation also directly generate NADH and $FADH_2$, which are used by the electron transport chain in redox reactions to produce additional ATP. Lipid energy metabolism in this way is a high yield but slow rate process for ATP production.

I.1. 3. Protein metabolism pathway

The amino acids in the pool can be used as a source of energy in the form of ATP. Amino acids are not a primary source of energy, but under certain circumstances such as when caloric intake of food is limited (low energy availability), amino acids can be metabolized and ATP produced. Interconversions can take place between amino acids and products of fat and carbohydrate metabolism involving transfer of the amino groups to other keto acids by transamination or oxidative deamination can take place with the formation of NH_4 which is in equilibrium with ammonia.

Most of the NH_4 formed by deamination in the liver is converted to urea excreted in urine (urea cycle). Removal of the amino group from amino acids produces the corresponding keto acids, most of which undergo oxidative metabolism via pyruvate or the various intermediates in the TCA cycle. Some amino acids are ketogenic in that their keto acids are converted to acetoacetate, but most are glucogenic and are converted to glucose via gluconeogenesis such as alanine.

I.2. Key biomecules

Several key biomolecules such as glucose-6-phosphate (G6-P), pyruvate, and acetyl coenzyme A or acetyl-CoA link the biochemical pathways for carbohydrates, lipids, and proteins. G6-P acetyl CoA and pyruvate link the anabolic and catabolic pathways of carbohydrate and fat metabolism to maintain a constant supply of energy to maintain homeostasis under constantly changing conditions (Figure 2).

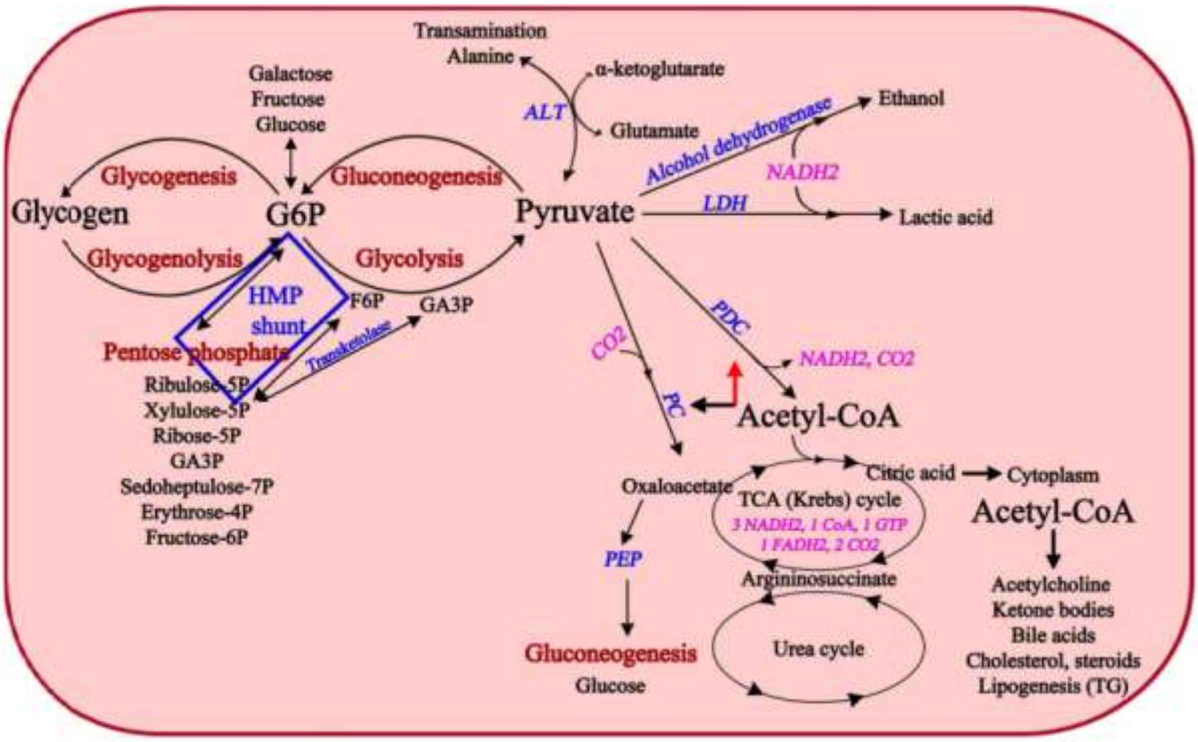

Figure 2: Presentation of the linking role of pyruvate, G6P and acetyl-CoA in carbohydrate and lipid pathways.
ALT: alanine transaminase; **LDH**: lactate deshydrogenase; **PDC**: pyruvate deshydrogenase; **PC**: pyruvate carboxylase; **PEP**: phosphoenolpyruvate; **HMP shunt**: hexose monophosphate shunt. **TG**: triglycerides.

I.2.1. Glucose-6-phosphate

After the ingestion of carbohydrates, glucose taken up by the liver is converted to G6-P by glucokinase. This phosphorylation uses one ATP molecule and traps the glucose within liver cells. Subsequently, G6-P is metabolized via one of the following three pathways (Figure 3):

a) **Glycogenesis** for the storage of carbohydrates as glycogen,
b) **Glycolysis** for the production of ATP,
c) **Pentose phosphate pathway (PPP)** for the production of NADPH and five-carbon sugars (pentose).

The pathway chosen depends upon the activation state of key enzymes (glycogen synthase and phosphofructokinase-1), substrate availability (G6-P, ATP, and $NADP^+$), and allosteric effectors such as ATP, adenosine monophosphate (AMP), fructose 2, 6-bisphosphate (F2, 6BP), and citrate. The key enzymes in glycogenesis and glycolysis are predominantly regulated by hormone-stimulated, covalent modification (phosphorylation or dephosphorylation). In contrast, the pentose phosphate pathway is primarily regulated by the availability of G6-P and $NADP^+$.

In feeding periods, glucose can be oxidized to CO_2 through a series of metabolic pathways, namely glycolysis in the cytosol, followed by the tricarboxylic acid cycle and the respiratory chain in the mitochondria. The first step of glycolysis is the isomerization of G6P into fructose-6 phosphate to produce triose-phosphate, then resulting in the generation of 2 pyruvate molecules and a small amount of ATP (net gain of 2 ATP molecules). Glycolysis supplies 3 carbon-compounds, such as triose-phosphate, pyruvate and lactate that can be used to maintain cellular homeostasis and produce biomass. The oxidation of pyruvate then generates the bulk of ATP under aerobic conditions is summarized in (Figure 3).

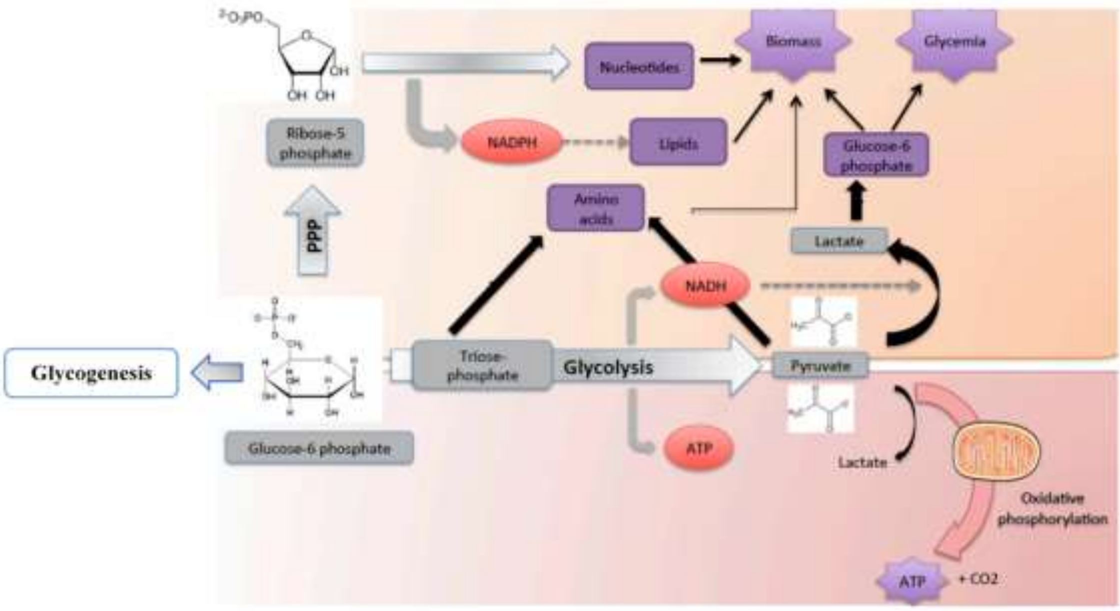

Figure 3: Glucose-6 phosphate: a source of energy and carbon skeletons.

When ATP and citrate concentrations are high, phosphofructokinase-1 is allosterically inhibited, slowing down the committed step of glycolysis (the production of fructose 1,6-bisphosphate) leading to increased concentrations of G6-P. First, G6-P is a positive allosteric effector of glycogen synthase, leading to the formation of glycogen or glycogenesis. Second, G6-P indirectly inhibits glycogen phosphorylase thereby inhibiting glycogenolysis or glycogen degradation.

Alternatively, when the ratio of $NADP^+$/ NADPH is high, meaning low levels of NADPH relative to $NADP^+$, indicates that the cell is in a state of oxidative stress or is lacking the reducing power required for essential biological processes. G6-P can be shuttled into the pentose phosphate pathway to generate NADPH (reducing power). PPP is an important metabolic pathway known to provide reducing equivalents (NADPH) for anabolism and it plays a pivotal role in counteracting oxidative stress and to synthesize a number of biomolecules by biosynthetic pathways such as, fatty acids, cholesterol. Indeed, during oxidative stress, NADPH is needed for the generation of reduced glutathione. Excess ribose- 5-phosphate not required for nucleotides synthesis returns to the glycolytic pathway as fructose-6-phosphate and phosphoglyceraldehyde.

Under conditions where the ratio of $NADP^+$/ NADPH is low, meaning high levels of NADPH relative to $NADP^+$, the pentose pathway will not operate regardless of the concentration of G6-P.

I.2.2. Pyruvate

Pyruvate can be converted into four different substrates: lactate, alanine, oxaloacetate, and acetyl-CoA, depending upon the energy needs of a cell (Figure 3). The pyruvate is subsequently treated aerobically or anaerobically.

- If sufficient oxygen is present for aerobic conversion, pyruvic acid is further metabolically transformed into acetyl-CoA. Pyruvate decarboxylation or oxidative decarboxylation reaction is the linker between glycolysis and the Krebs cycle and is catalyzed by pyruvate dehydrogenase complex (PDC). In this process, two pyruvic acids of the glycolysis pathway are consumed to produce two molecules of acetyl-CoA and 2 $NADH_2$. $NADH_2$ is consumed in the oxidative phosphorylation reaction. Acetyl-CoA is either used in the Krebs cycle and oxidative phosphorylation reaction in mitochondria for full oxidization of glucose or is converted to citrate. Citrate is exported to the cytosol for biosynthesis of fatty acid. In the Krebs cycle, two pyruvates of glycolysis are degraded to release their energy in the form of 2 GTP and the reduced forms of high energy molecules (6 $NADH_2$ and 2 $FADH_2$). $NADH_2$ and $FADH_2$ are consumed in the oxidative phosphorylation process of the mitochondria. Therefore, the reducing potentials of the $NADH_2$ and $FADH_2$ are converted to chemical energy in the form of $NADH_2$ is equal to 3 ATP and the energy of $FADH_2$ is equal to 2 ATP.

- In anaerobic states (heavy exercise or cells without mitochondria), pyruvate is converted to lactate through a bilateral reaction catalyzed by lactate dehydrogenase (LDH) and consumption of one molecule $NADH_2$. Lactate is transferred to the liver for gluconeogenesis and glucose production to be used again in the glycolysis pathway (Cori cycle)

Furthermore, Oxaloacetic acid (OAA) synthesis after carboxylation by pyruvate carboxylase (PC). OAA can be consumed in either the Krebs cycle or the gluconeogenesis. In addition in bacteria, ethanol synthesis (alcoholic fermentation) via using alcohol dehydrogenase and $NADH_2$. Pyruvate can also be converted in muscle tissue to the amino acid alanine via the alanine transaminase (ALT) reaction (transamination). In a manner analogous to the Cori cycle, the glucose alanine cycle or Felig cycle then converts this alanine back to pyruvate in the liver where it is used to produce new glucose via gluconeogenesis as a source of energy for anaerobic glycolysis in muscle.

Cori cycle and glucose-alanine cycle are the cycles that link glucose production in the liver to energy production in other tissues. In the Cori cycle, bilateral association between glycolysis in the skeletal muscle cells with gluconeogenesis in the hepatocytes is shown. Waste product of the skeletal muscles (lactate) is used in the hepatocytes to produce glucose for consumption as energy in the skeletal muscle. In the glucose-alanine cycle, the nitrogen product of non-hepatic tissues, produced from transamination reaction and amino acid production, is transferred to the hepatocytes to be used for either gluconeogenesis and glucose production or excretion as urea (Figure 4).

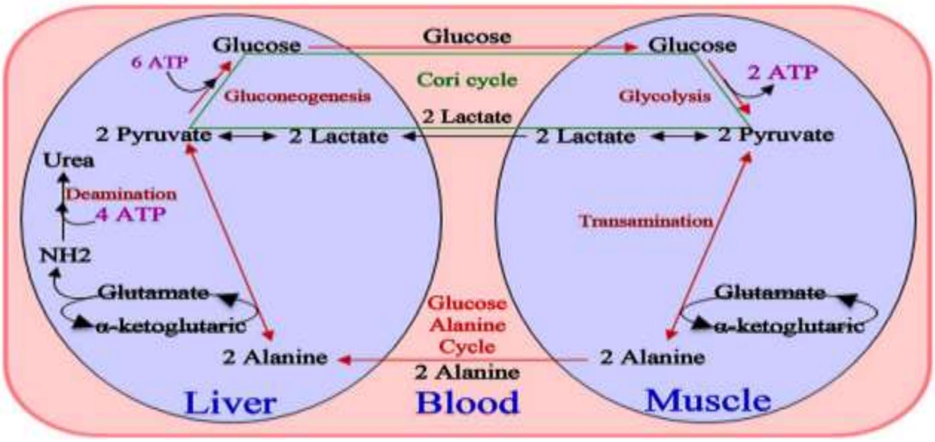

Figure 4: Cori cycle and glucose-alanine cycle.

I.2.4. Ribose 5 phosphate

Excess ribose5-phosphate not required for nucleotide synthesis returns to the glycolytic pathway as fructose-6-phosphate and phosphoglyceraldehyde.

I.2.4. Acetyl CoA

Carbohydrates, lipids and amino acids are the substrates which produce acetyl-CoA. Acetyl-CoA is used in different biochemical pathways including (Figure 5):

a) The Krebs cycle to produce H_2O, CO_2 and energy via the citric acid cycle and oxidative phosphorylation,

b) Biosynthesis of cholesterol, squalene, bile acids, vitamin D3 and steroidal hormones such as estrogen, progesterone, testosterone and adrenal hormones,

c) Synthesis of fatty acids,

d) Synthesis of ketone bodies such as acetone, beta-hydroxybutyric acid and acetoacetic acid, in the liver in starvation and the diabetic states

e) Synthesis of acetylcholine that is the carrier of nerve impulses

f) Acetyl donor for the acetylation of many proteins including histones and transcription factors.

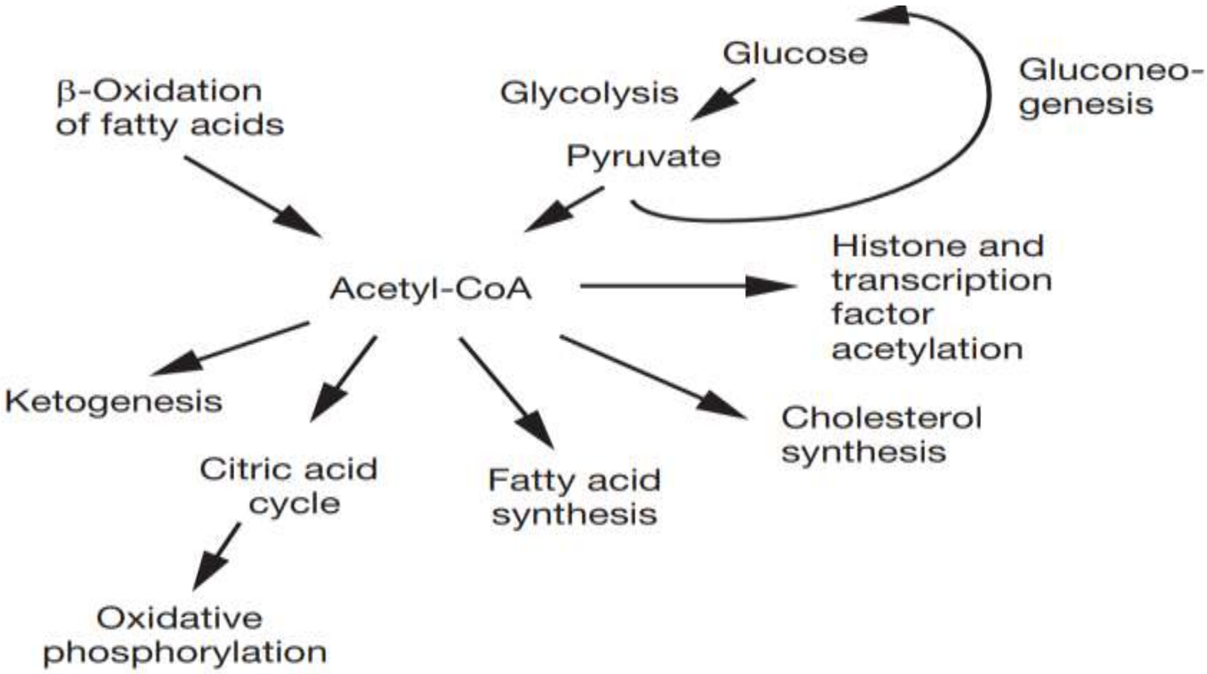

Figure 5: Acetate metabolism