BAU-Medicine

Sheet no.8

Lecture Date: 5th Jan 2021

Lecture Title: Glucose Homeostasis 2

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دعاء لأخينا رشيد:
اللهم ارحمه واغفرله وآنس وحشته
ووسع قبره اللهم اجعل عيده في الجنة
أجمل، اللهمّ اجعل قبره روضةً من
رياض الجنّة، ولا تجعله حفرةً من حفر
النّار.

It'll be better for you to watch the lecture, don't worry it's easy and mostly stuff we already know but it'll help with understanding the doctor's view better and this sheet will be even easier with it

Glucose homeostasis

Let's discuss insulin deficiency and its effects on carbohydrates, fat, and protein metabolism:

1. Carbohydrates:

   In the absence of insulin there is a significant decrease in intracellular glucose thus decreased utilization of glucose this will force the cell to activate "alternative" pathways to get energy, those being fatty acids and amino acids pathways (marked as red arrows in the picture below)

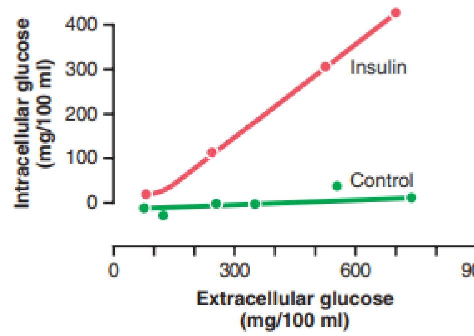
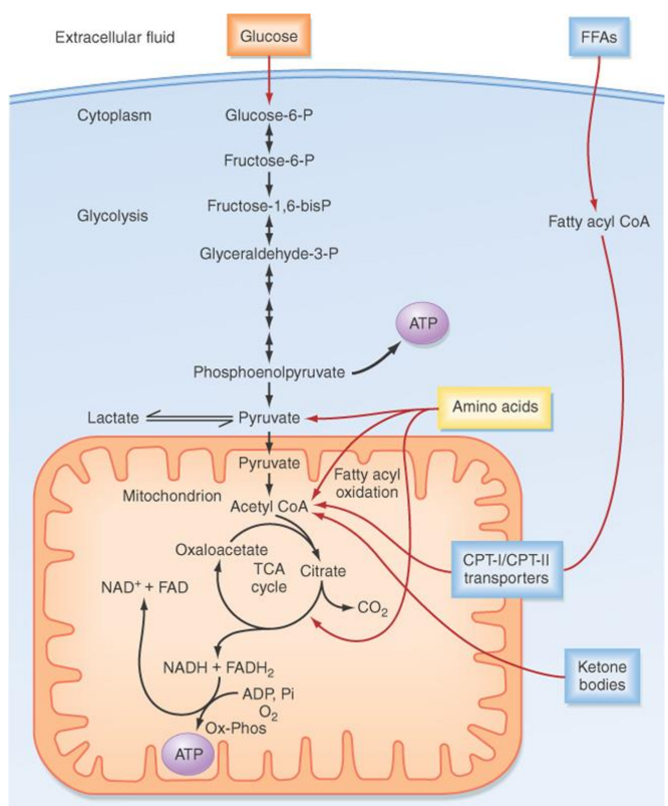


Figure 79-4. The effect of insulin in enhancing the concentration of glucose inside muscle cells. Note that in the absence of insulin (control), the intracellular glucose concentration remains near zero, despite high extracellular glucose concentrations. *(Data from Eisenstein AB: The Biochemical Aspects of Hormone Action. Boston: Little, Brown, 1964.)*

2. Fat:

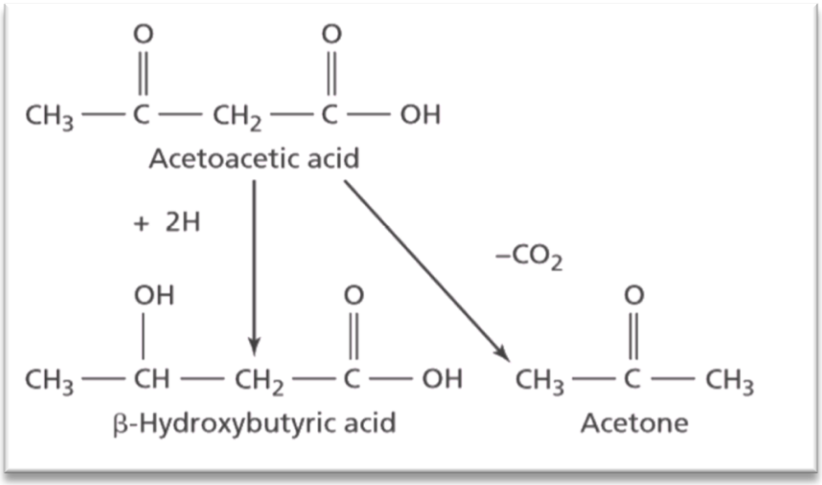
   Insulin deficiency will increase the use of fatty acids for energy and this is how:

   Insulin is a regulator for the hormone-sensitive lipase; which breaks down fat; when insulin levels are high this enzyme is suppressed but once insulin levels drop this enzyme becomes strongly activated in adipose tissue which will increase fatty acids concentration in plasma. This has a lot of effects throughout the body, one of them is increasing the concentrations of cholesterol and phospholipids in plasma, this happens because of the excess of fatty acids in plasma promotes liver conversion of fatty acids into these products which are then discharged into the blood in lipoproteins thus increasing their concentration too.



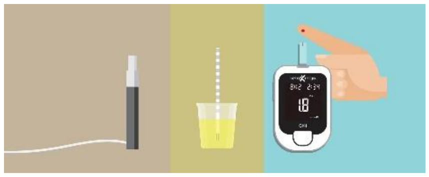
(Modified from Porterfield SP, White BA: Endocrine Physiology, 3rd ed. Philadelphia, Mosby, 2007.)

Also while on the subject, as we know the main product of fat metabolism is Acetyl-CoA, which will be formed in excessive & uncontrolled amounts to compensate for the relatively low intracellular glucose caused by insulin deficiency, this excess Acetyl-CoA will be converted into large amounts of Acetoacetic acid which in turn will be converted into:



A. β-Hydroxybutyric acid: which will when produced in high amounts cause acidosis, which has A LOT of effects on various body organs like the lungs for example.
B. Acetone: which will cause ketosis

These are called ketone bodies and the can be detected in breath, blood, and urine.



This effect is also what happens in increased growth hormone secretion because GH decreases glucose utilization in the cells thus relatively decreased intracellular glucose concentration and so on (the above process repeats)

3. Protein:

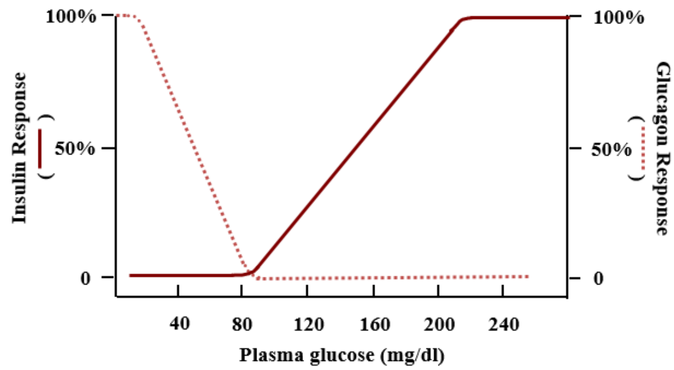
Insulin stimulates the transportation of amino acids into the cells, it increases messenger RNA translation and transcription of selected DNA genetic sequences and it inhibits protein catabolism while also depressing gluconeogenesis rate.
In insulin deficiency all the processes mentioned above will be REVRSED;
Insulin is said to stimulate all anabolic enzymes while it inhibits catabolic enzymes so in insulin deficiency there will be less amino acid uptake so less protein synthesis, less glucose uptake which will decrease glycogen synthesis and stimulate fat metabolism and increased protein breakdown.

Insulin absence is said to have a catabolic effect while its presence is said to have an anabolic effect.

Glucagon

Glucagon is a hormone secreted by alpha cells of the pancreas when blood glucose levels drop

In people who eat 3 meals/day, glucagon functions for only short periods of time throughout the day but in states of fasting or starvation (poor-fed states) the effect of glucagon is highly pronounced and that is important to keep blood glucose within normal levels which will be discussed in a bit in more details.



Miscellaneous notes about this table:

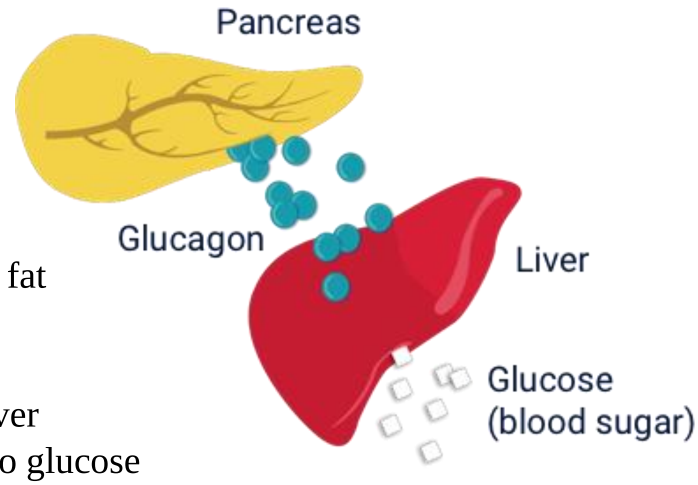
1. Somatostatin is ALWAYS inhibitory and it's responsible for insulin-glucagon balance.

Factors Affecting Glucagon Secretion

Stimulation	Inhibition
Hypoglycemia	Glucose
Amino acids Arginine Alanine	Somatostatin Insulin (direct effect)
Gastrointestinal hormones Cholecystokinin (CCK) Gastrin	Gastrointestinal hormones Secretin Glucagon-like peptide-1 (GLP-1)
Fasting	Free fatty acids
Exercise	Ketoacids
Neural influences Vagal activity-acetylcholine Sympathetic activity- β-adrenergic stimulation (norepinephrine, epinephrine)	Neural influences α-adrenergic stimulation

2. Regarding amino acids, you can notice that 2 specific ones are mentioned; Arginine and Alanine; when we consume a protein portion it's normally a mixture of different amino acids at once thus it's hard to determine which amino acid affects what, so these conclusions were obtained from injecting a subject with a specific amino acid and studying its effect.

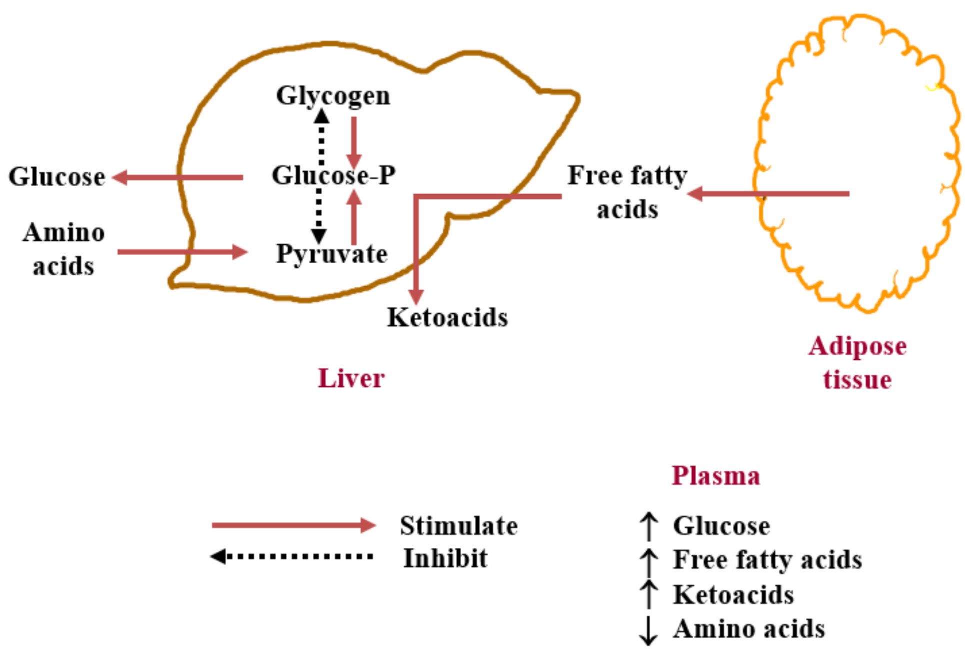
Glucagon Function:



1. RAISE PLASMA'S GLUCOSE LEVELS
2. Breakdown of liver glycogen (GLYCOGENOLYSIS)
3. Increased gluconeogenesis in the liver from fat and proteins.
4. Activates adipose cell lipase
5. Inhibits the storage of triglycerides in the liver
6. Promoted rapid conversion of amino acids to glucose

Metabolic Effects of Glucagon:

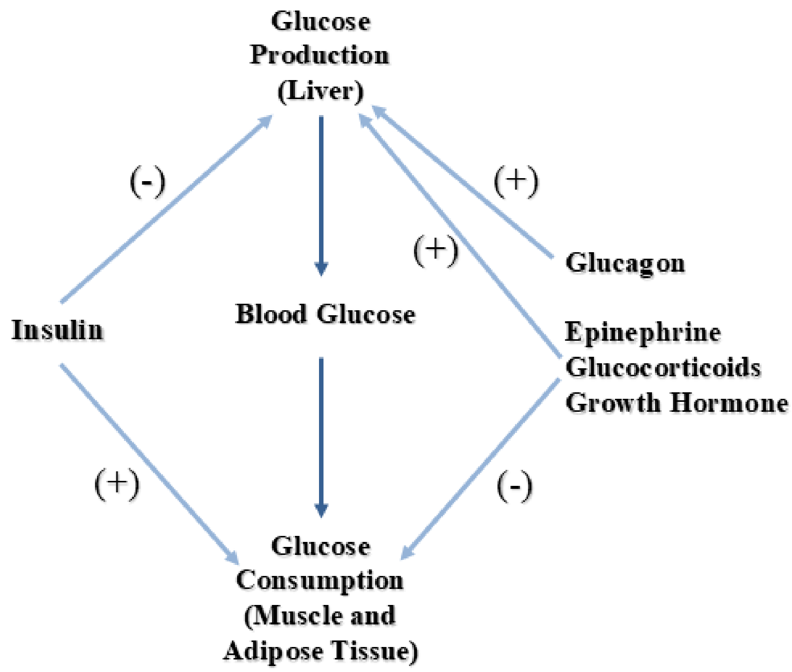
Pay attention to everything in this picture, especially what happens in plasma.



Hormonal Interactions in the Maintenance of Blood Glucose Concentration

Sources of glucose:

a. Exogenous from meals
b. Endogenous from glycogenolysis or gluconeogenesis.



Q: In our day-to-day life we get glucose from our meals, but what if there wasn't an exogenous source of glucose? What will happen then? And how will we get the energy we need?

A: our liver will be responsible of providing us with the glucose we need either by glycogenolysis or by gluconeogenesis, this process is highly regulated by different hormones; as follows:

1. In well-fed states:
   Insulin inhibits glucose production by the liver by stimulating glycogenesis

2. In fasting/starvation:
   Glucagon: stimulates glucose production to raise blood glucose either by glycogenolysis or gluconeogenesis either using fats or amino acids
   Epinephrine, glucocorticoids, and GH: increase glucose production by the liver in the same manner as glucagon.

3. While sleeping:
   There is no exogenous glucose so they body has to compensate to keep glucose levels relatively normal, as we've mentioned before GH secretion is increased while sleeping, and so is glucocorticoids and glucagon, which will collectively increase glucose production after a

period of sleep. Once there is an exogenous source of glucose, these mechanisms will be suppressed.

GLUCOSE PATTERN IN WELL AND POOR FED STATES

The graph resembles the effects of **starvation** on the food stores of the body: carbohydrates stores will be depleted within a few days, then fat and proteins are the main source of energy

While in fasting the main source of energy are carbohydrates followed by fat followed, to a much lesser extent, by proteins.

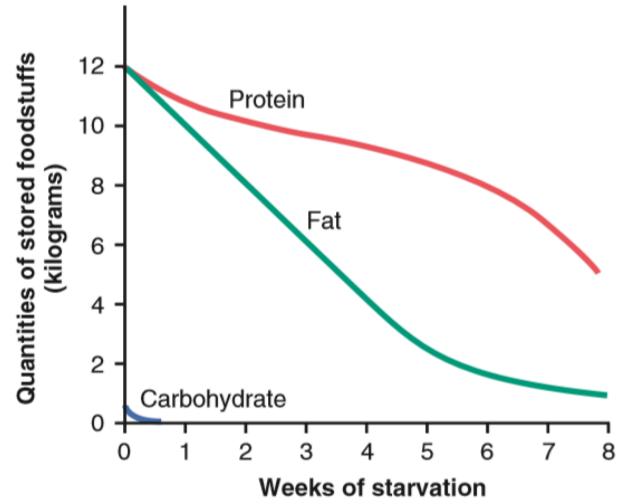
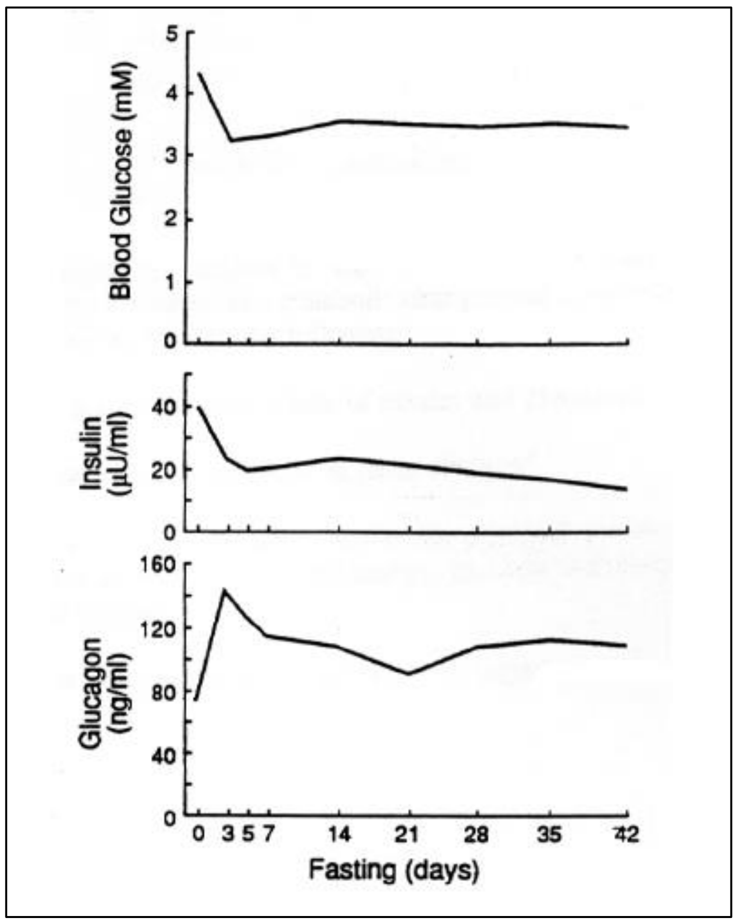


Figure 72-3. Effect of starvation on the food stores of the body.

This graph shows concentrations of glucose, insulin, and glucagon in blood throughout a period of fasting,

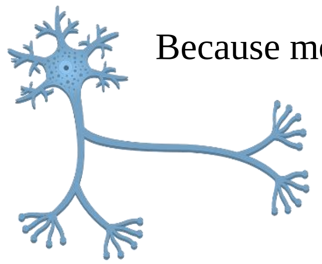
1. Insulin: insulin concentration in blood keeps dropping approaching but never zero, throughout the period cause there is no exogenous glucose to stimulate its secretion.
2. Glucagon: gradually increases and stays high throughout the period to keep the glucose levels in blood "constant" (within normal levels) same behavior is pronounced with GH.
3. Glucose: you may hear the word "increase" used here but it refers to the fact that we kept the glucose level from dropping further, but we really just kept it relatively constant as a result of glucagon, cortisol, and GH effects and



this resembles fasting blood sugar when measured in the morning.

Fasting blood sugar: resembles glucose levels along with low insulin levels and relatively raised glucagon, and diurnal variations of cortisol and GH levels, which will both be high in the morning.

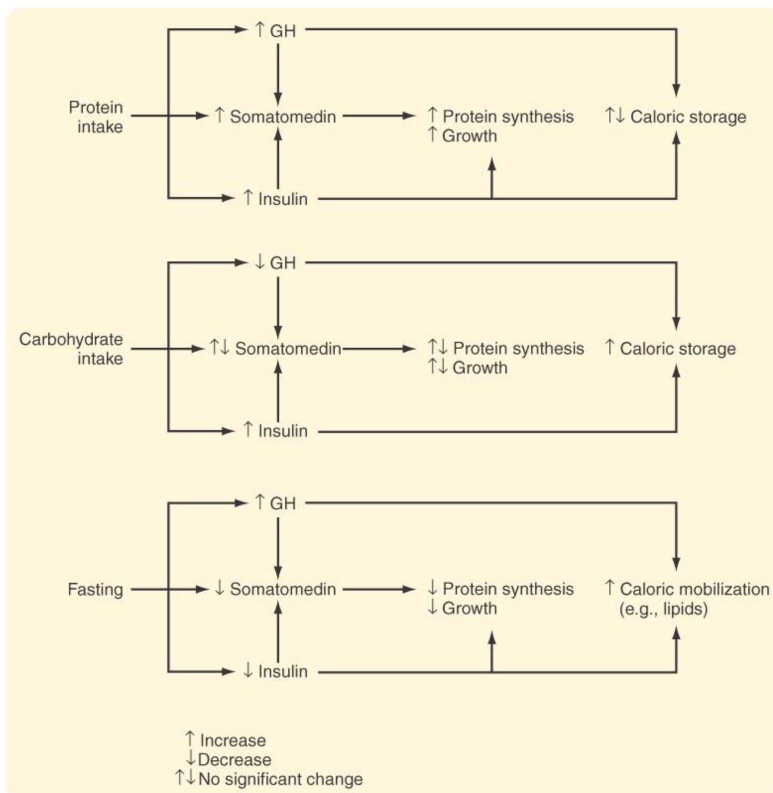
Why is it so important to maintain a relatively constant blood glucose level?



Because most tissues have other sources of energy **but** nerve cells depend entirely on glucose, that's why this process is so important; and if the body fails to keep blood glucose levels within normal this can result in a coma or even death due to nerve cells damage.

This graph was explained extensively before but the doctor explained it again at 24:22

1. **Fasting:** stimulates the secretion of GH and inhibits the secretion of insulin, which has a net effect of decreased somatomedin secretion, therefore decreased protein synthesis and growth even though we have an increased secretion of GH; and that's because we don't have enough carbohydrates and amino acids to initiate protein synthesis and growth so the ultimate goal in this is to increase caloric mobilization and not protein synthesis.
2. **Carbohydrates intake:** stimulates secretion of insulin while inhibiting the secretion of GH this doesn't have a significant effect on somatomedin concentration or protein synthesis and growth



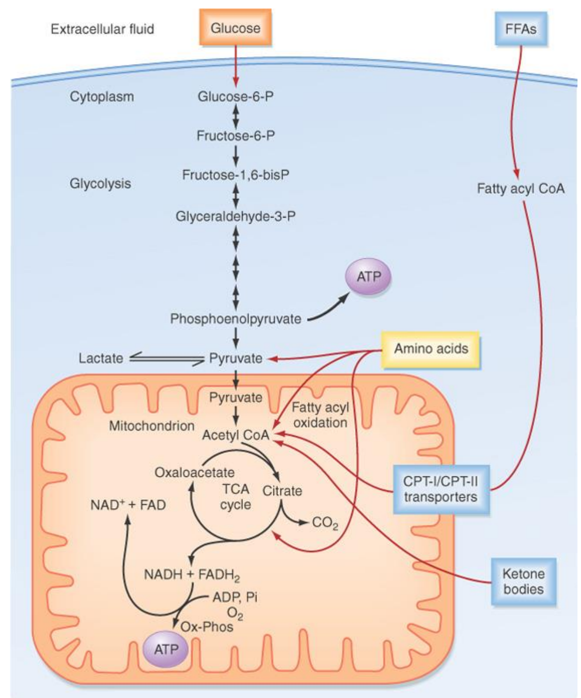
The corner stone for growth is the growth hormone but we also need insulin, cortisol, vitamin D, parathyroid, estrogen, progesterone and many others.

3. **Protein intake:** will stimulate the secretion of both GH and insulin which will have a net effect of increased somatomedin secretion and the subsequent protein synthesis and growth.

EXCERSISE:

In exercise a lot of changes happen throughout the body for example, the heart increases its output to supply the high demand for the now active muscles with oxygen and material to be utilized for energy.

Another worth mentioning aspect of exercise is its effect on insulin, exercising inhibits insulin secretion, this might confuse you at first, don't we need insulin to raise intracellular glucose concentration to be utilized for energy? Well, yes but also no, because membranes of muscle cells become more permeable to glucose while exercising that its transportation across them no longer needs insulin (not insulin-dependent), AND because of the inhibition of insulin secretion; alternative pathways for energy are also activated (fat and protein) this will yield a high amount of energy to be used in active muscles.



(Modified from Porterfield SP, White BA: Endocrine Physiology, 3rd ed. Philadelphia, Mosby, 2007.)

Q: How long should you wait to exercise after eating?

A: At least after 2 hours

Q: Why?

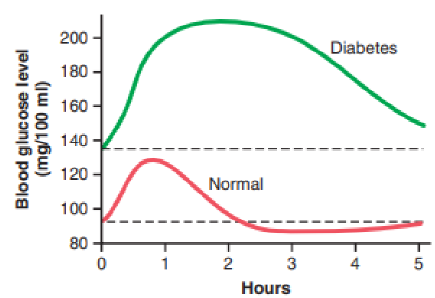


Figure 79-12. Glucose tolerance curve in a normal person and in a person with diabetes.

A: As we know insulin is important to help the influx of glucose into the various types of cells of our body (muscle, adipose tissue, liver, etc.) but while exercising we primarily need glucose for our muscle tissue to be utilized for energy and it's not needed in adipose tissue for example, and as we also know that glucose influx into muscle cells is insulin-independent in exercise so the optimal condition for exercising is when insulin blood levels are low and that occurs about 2 hours after a meal.

If carbohydrates were to be consumed let's say from a soda; which has a high amount of sugar; **WHILE** exercising this will affect this balance, a large amount of exogenous glucose will stimulate insulin secretion which will cause glucose to be transported into other cells rather than it being mainly transported into muscle tissue. This will not be the case if only a small amount of sugar is consumed, because it wouldn't be enough to stimulate the secretion of insulin.

Now, let's take into consideration a healthy person who eats 3 meals/ day, where will he get most of his energy supply?

Most energy will come mainly from carbohydrates (glucose) in the first 2 hours, and then fatty acids will play a larger and larger role the more we spend without eating until it is the main/only source of energy, so the less meals we consume per day the higher dependence on fatty acids to be utilized to provide us with energy (fatty acid utilization is almost 50% if you consume 3 whole meals and this percentage keeps getting higher and higher the less meals you consume)