Chapter 3:
The basics of fuel utilization

Although this chapter does not discuss the ketogenic diet in great detail, the information presented is helpful in understanding the following chapters. There are four primary fuels which can be used in the human body: glucose, protein, free fatty acids, and ketones. These fuels are stored in varying proportions in the body. Overall, the primary form of stored fuel is triglyceride, stored in adipose tissue. Glucose and protein make up secondary sources. These fuels are used in varying proportions depending on the metabolic state of the body.

The primary determinant of fuel utilization in humans is carbohydrate availability, which affects hormone levels. Additional factors affecting fuel utilization are the status of liver glycogen (full or empty) as well as the levels of certain enzymes.

Section 1: Bodily Fuel Stores

The body has three storage depots of fuel which it can tap during periods of caloric deficiency: protein, which can be converted to glucose in the liver and used for energy; carbohydrate, which is stored primarily as glycogen in the muscle and liver; and fat, which is stored primarily as body fat. A fourth potential fuel is ketones. Under normal dietary conditions, ketones play a nonexistent role in energy production. In fasting or a ketogenic diet, ketones play a larger role in energy production, especially in the brain. A comparison of the various fuels available to the body appears in table 1.

Table 1: Comparison of bodily fuels in a 150 lb man with 22% bodyfat

Tissue	Average weight (lbs)	Caloric worth (kcal)
Adipose tissue triglyceride	33	135,000
Muscle protein	13	24,000
Carbohydrate stores		
Muscle glycogen (normal)	00.25	480
Liver glycogen	00.5	280
Blood glucose	00.04	80
Total carbohydrate stores	00.8	840

Source: "Textbook of Biochemistry with Clinical Correlations 4th ed." Ed. Thomas M. Devlin. Wiley-Liss, 1997.

The main point to take from this chart is that carbohydrate stores are minimal in comparison to protein and fat, sufficient to sustain roughly one day's worth of energy. Although stored protein could conceivably fuel the body for far longer than carbohydrate, excessive protein losses will eventually cause death. This leaves adipose tissue as the primary depot for long term

energy storage (2). The average person has enough energy stored as body fat to exist for weeks or months without food intake and obese individuals have been fasted for periods of up to one year.

Section 2: Relationships in fuel use

Looking at table 1, it appears that there are least 4 distinct fuels which the body can use: glucose, protein, free fatty acids (FFA), and ketones. However when we look at the relationships between these four fuels, we see that only glucose and FFA need to be considered.

The difference in the proportion of each fuel used will depend on the metabolic state of the body (i.e. aerobic exercise, weight training, normal diet, ketogenic diet/fasting). Exercise metabolism is addressed in later chapters, and we are only concerned here with the effects of dietary changes on fuel utilization.

In general, tissues of the body will use a given fuel in proportion to its concentration in the bloodstream. So if a given fuel (i.e. glucose) increases in the bloodstream, the body will utilize that fuel in preference to others. By the same token, if the concentrations of a given fuel decrease in the bloodstream, the body will use less of that fuel. By decreasing carbohydrate availability, the ketogenic diet shifts the body to using fat as its primary fuel.

Glucose and Protein use

When present in sufficient quantities, glucose is the preferred fuel for most tissues in the body. The major exception to this is the heart, which uses a mix of glucose, FFA and ketones.

The major source of glucose in the body is from dietary carbohydrate. However, other substances can be converted to glucose in the liver and kidney through a process called gluconeogenesis ('gluco' = glucose, 'neo' = new, 'genesis' = the making). This includes certain amino acids, especially alanine and glutamine.

With normal glucose availability, there is little gluconeogenesis from the body's protein stores. This has led many to state that carbohydrate has a 'protein sparing' effect in that it prevents the breakdown of protein to make glucose. While it is true that a high carbohydrate intake can be protein sparing, it is often ignored that this same high carbohydrate also decreases the use of fat for fuel. Thus, in addition to being "protein sparing," carbohydrate is also "fat sparing" (3).

If glucose requirements are high but glucose availability is low, as in the initial days of fasting, the body will break down its own protein stores to produce glucose. This is probably the origin of the concept that low carbohydrate diets are muscle wasting. As discussed in the next chapter, an adequate protein intake during the first weeks of a ketogenic diet will prevent muscle loss by supplying the amino acids for gluconeogenesis that would otherwise come from body proteins

By extension, under conditions of low glucose availability, if glucose requirements go down due to increases in alternative fuels such as FFA and ketones, the need for gluconeogenesis from protein will also decrease. The circumstances under which this occurs are discussed below.

Since protein breakdown is intimately related to glucose requirements and availability, we can effectively consider these two fuels together. Arguably the major adaptation to the ketogenic diet is a decrease in glucose use by the body, which exerts a protein sparing effect (2). This is discussed in greater detail in chapter 5.

Free Fatty Acids (FFA) and ketones

Most tissues of the body can use FFA for fuel if it is available. This includes skeletal muscle, the heart, and most organs. However, there are other tissues such as the brain, red blood cells, the renal medulla, bone marrow and Type II muscle fibers which cannot use FFA and require glucose (2).

The fact that the brain is incapable of using FFA for fuel has led to one of the biggest misconceptions about human physiology: that the brain can only use glucose for fuel. While it is true that the brain normally runs on glucose, the brain will readily use ketones for fuel if they are available (4-6).

Arguably the most important tissue in terms of ketone utilization is the brain which can derive up to 75% of its total energy requirements from ketones after adaptation (4-6). In all likelihood, ketones exist primarily to provide a fat-derived fuel for the brain during periods when carbohydrates are unavailable (2,7).

As with glucose and FFA, the utilization of ketones is related to their availability (7). Under normal dietary conditions, ketone concentrations are so low that ketones provide a negligible amount of energy to the tissues of the body (5,8). If ketone concentrations increase, most tissues in the body will begin to derive some portion of their energy requirements from ketones (9). Some research also suggests that ketones are the preferred fuel of many tissues One exception is the liver which does not use ketones for fuel, relying instead on FFA (7, 10,11).

By the third day of ketosis, all of the non-protein fuel is derived from the oxidation of FFA and ketones (12,13). As ketosis develops, most tissues which can use ketones for fuel will stop using them to a significant degree by the third week (7,9). This decrease in ketone utilization occurs due to a down regulation of the enzymes responsible for ketone use and occurs in all tissues except the brain (7). After three weeks, most tissues will meet their energy requirements almost exclusively through the breakdown of FFA (9). This is thought to be an adaptation to ensure adequate ketone levels for the brain.

Except in the case of Type I diabetes, ketones will only be present in the bloodstream under conditions where FFA use by the body has increased. For all practical purposes we can assume that a large increase in FFA use is accompanied by an increase in ketone utilization and these two fuels can be considered together.

Relationships between carbohydrates and fat

Excess dietary carbohydrates can be converted to fat in the liver through a process called de novo lipogenesis (DNL). However short term studies show that DNL does not contribute

significantly to fat gain in humans. As long as muscle and liver glycogen stores are not completely filled, the body is able to store or burn off excess dietary carbohydrates. Of course this process occurs at the expense of limiting fat burning, meaning that any dietary fat which is ingested with a high carbohydrate intake is stored as fat.

Under certain circumstances, excess dietary carbohydrate can go through DNL, and be stored in fat cells although the contribution to fat gain is thought to be minimal (14). Those circumstances occur when muscle and liver glycogen levels are filled and there is an excess of carbohydrate being consumed.

The most likely scenario in which this would occur would be one in which an individual was inactive and consuming an excess of carbohydrates/calories in their diet. As well, the combination of inactivity with a very high carbohydrate and high fat diet is much worse in terms of fat gain. With chronically overfilled glycogen stores and a high carbohydrate intake, fat utilization is almost completely blocked and any dietary fat consumed is stored.

This has led some authors to suggest an absolute minimization of dietary fat for weight loss (15,16). The premise is that, since incoming carbohydrate will block fat burning by the body, less fat must be eaten to avoid storage. The ketogenic diet approaches this problem from the opposite direction. By reducing carbohydrate intake to minimum levels, fat utilization by the body is maximized.

Summary

From the above discussion, we can represent the body's overall use of fuel as:

Total energy requirements = glucose + FFA

Therefore if energy requirements stay the same, a decrease in the use of glucose will increase the use of FFA for fuel. By corollary, an increase in the body's ability to use FFA for fuel will decrease the need for glucose by the body. This relationship between glucose and FFA was termed the glucose-FFA Cycle by Randle almost 30 years ago (17,18).

Section 3: Factors influencing fuel utilization

There are several factors which affect the mix of fuels used by the body. The primary factor is the amount of each nutrient (protein, carbohydrate, fat and alcohol) being consumed and this impacts on the other three factors (16). The second determinant is the levels of hormones such as insulin and glucagon, which are directly related to the mix of foods being consumed. Third is the bodily stores of each nutrient including fat stores and muscle/liver glycogen. Finally the levels of regulatory enzymes for glucose and fat breakdown, which are beyond our control except through changes in diet and activity, determine the overall use of each fuel. Each of these factors are discussed in detail below.

Quantity of nutrients consumed

There are four substances which man can derive calories from: carbohydrate, protein, fats, and alcohol. As stated above, the body will tend to utilize a given fuel for energy in relation to its availability and concentration in the bloodstream.

In general, the body can increase or decrease its use of glucose in direct proportion to the amount of dietary carbohydrate being consumed. This is an attempt to maintain body glycogen stores at a certain level (19). If carbohydrate consumption increases, carbohydrate use will go up and vice versa.

Protein is slightly less regulated (16). When protein intake goes up, protein oxidation will also go up to some degree. By the same token, if protein intake drops, the body will use less protein for fuel. This is an attempt to maintain body protein stores at constant levels.

In contrast, the amount of dietary fat being eaten does not significantly increase the amount of fat used for fuel by the body. Rather fat oxidation is determined indirectly: by alcohol and carbohydrate consumption (15).

The consumption of alcohol will almost completely impair the body's use of fat for fuel. Similarly the consumption of carbohydrate affects the amount of fat used by the body for fuel. A high carbohydrate diet decreases the use of fat for fuel and vice versa (15). Thus, the greatest rates of fat oxidation will occur under conditions when carbohydrates are restricted. As well, the level of muscle glycogen regulates how much fat is used by the muscle (20,21), a topic discussed in chapter 18. Using exercise and/or carbohydrate restriction to lower muscle and liver glycogen levels increases fat utilization (22).

Hormone levels

There are a host of regulatory hormones which determine fuel use in the human body. The primary hormone is insulin and its levels, to a great degree, determine the levels of other hormones and the overall metabolism of the body (2,16,23). A brief examination of the major hormones involved in fuel use appears below.

Insulin is a peptide (protein based) hormone released from the pancreas, primarily in response to increases in blood glucose. When blood glucose increases, insulin levels increase as well, causing glucose in the bloodstream to be stored as glycogen in the muscle or liver. Excess glucose can be pushed into fat cells for storage (as alpha-glycerophosphate). Protein synthesis is stimulated and free amino acids (the building blocks of proteins) are moved into muscle cells and incorporated into larger proteins. Fat synthesis (called lipogenesis) and fat storage are both stimulated. FFA release from fat cells is inhibited by even small amounts of insulin.

The primary role of insulin is to keep blood glucose in the fairly narrow range of roughly 80-120 mg/dl. When blood glucose increases outside of this range, insulin is released to lower blood glucose back to normal. The greatest increase in blood glucose levels (and the greatest increase in insulin) occurs from the consumption of dietary carbohydrates. Protein causes a smaller increase in insulin output because some individual amino acids can be converted to glucose. FFA can stimulate insulin release as can high concentrations of ketone bodies, although to a much lesser degree than carbohydrate or protein. This is discussed in chapter 4.

When blood glucose drops (during exercise or with carbohydrate restriction), insulin levels generally drop as well. When insulin drops and other hormones such as glucagon increase, the body will break down stored fuels. Triglyceride stored in fat cells is broken down into FFA and glycerol and released into the bloodstream. Proteins may be broken down into individual amino acids and used to produce glucose. Glycogen stored in the liver is broken down into glucose and released into the bloodstream (2). These substances can then be used for fuel in the body.

An inability to produce insulin indicates a pathological state called Type I diabetes (or Insulin Dependent Diabetes Mellitus, IDDM). Type I diabetics suffer from a defect in the pancreas leaving them completely without the ability to make or release insulin. IDDM diabetics must inject themselves with insulin to maintain blood glucose within normal levels. This will become important when the distinction between diabetic ketoacidosis and dietary induced ketosis is made in the next chapter.

Glucagon is essentially insulin's mirror hormone and has essentially opposite effects. Like insulin, glucagon is also a peptide hormone released from the pancreas and its primary role is also to maintain blood glucose levels. However, glucagon acts by raising blood glucose when it drops below normal.

Glucagon's main action is in the liver, stimulating the breakdown of liver glycogen which is then released into the bloodstream. Glucagon release is stimulated by a variety of stimuli including a drop in blood glucose/insulin, exercise, and the consumption of a protein meal (24). High levels of insulin inhibit the pancreas from releasing glucagon.

Under normal conditions, glucagon has very little effect in tissues other than the liver (i.e. fat and muscle cells). However, when insulin is very low, as occurs with carbohydrate restriction and exercise, glucagon plays a minor role in muscle glycogen breakdown as well as fat mobilization. In addition to its primary role in maintaining blood glucose under conditions of low blood sugar, glucagon also plays a pivotal role in ketone body formation in the liver, discussed in detail in the next chapter.

From the above descriptions, it should be clear that insulin and glucagon play antagonistic roles to one another. Whereas insulin is primarily a storage hormone, increasing storage of glucose, protein and fat in the body; glucagon's primary role is to mobilize those same fuel stores for use by the body.

As a general rule, when insulin is high, glucagon levels are low. By the same token, if insulin levels decrease, glucagon will increase. The majority of the literature (especially as it pertains to ketone body formation) emphasizes the ratio of insulin to glucagon, called the insulin/glucagon ratio (hG ratio), rather than absolute levels of either hormone. This ratio is an important factor in the discussion of ketogenesis in the next chapter. While insulin and glucagon play the major roles in determining the anabolic or catabolic state of the body, there are several other hormones which play additional roles. They are briefly discussed here.

Growth hormone (GH) is another peptide hormone which has numerous effects on the body, both on tissue growth as well as fuel mobilization. GH is released in response to a variety of stressors the most important of which for our purposes are exercise, a decrease in blood glucose, and carbohydrate restriction or fasting. As its name suggests, GH is a growth promoting hormone, increasing protein synthesis in the muscle and liver. GH also tends to mobilize FFA from fat cells for energy.

In all likelihood, most of the anabolic actions of GH are mediated through a class of hormones called somatomedins, also called insulin-like growth factors (IGFs). The primary IGF in the human body is insulin like growth factor-1 (IGF-1) which has anabolic effects on most tissues of the body. GH stimulates the liver to produce IGF-1 but only in the presence of insulin.

High GH levels along with high insulin levels (as would be seen with a protein and carbohydrate containing meal) will raise IGF-1 levels as well as increasing anabolic reactions in the body. To the contrary, high GH levels with low levels of insulin, as seen in fasting or carbohydrate restriction, will not cause an increase in IGF-1 levels. This is one of the reasons that ketogenic diets are not ideal for situations requiring tissue synthesis, such as muscle growth or recovery from certain injuries: the lack of insulin may compromise IGF-1 levels as well as affecting protein synthesis.

There are two thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Both are released from the thyroid gland in the ratio of about 80% T4 and 20% T3. In the human body, T4 is primarily a storage form of T3 and plays few physiological roles itself. The majority of T3 is not released from the thyroid gland but rather is converted from T4 in other tissues, primarily the liver. Although thyroid hormones affect all tissues of the body, we are primarily concerned with the effects of thyroid on metabolic rate and protein synthesis. The effects of low-carbohydrate diets on levels of thyroid hormones as well as their actions are discussed in chapter 5.

Cortisol is a catabolic hormone released from the adrenal cortex and is involved in many reactions in the body, most related to fuel utilization. Cortisol is involved in the breakdown of protein to glucose as well as being involved in fat breakdown.

Although cortisol is absolutely required for life, an excess of cortisol (caused by stress and other factors) is detrimental in the long term, causing a continuous drain on body proteins including muscle, bone, connective tissue and skin. Cortisol tends to play a permissive effect in its actions, allowing other hormones to work more effectively.

Adrenaline and noradrenaline (also called epinephrine and norepinephrine) are frequently referred to as 'fight or flight' hormones. They are generally released in response to stress such as exercise, cold, or fasting. Epinephrine is released primarily from the adrenal medulla, traveling in the bloodstream to exert its effects on most tissues in the body. Norepinephrine is released primarily from the nerve terminals, exerting its effects only on specific tissues of the body.

The interactions of the catecholamines on the various tissues of the body are quite complex and beyond the scope of this book. The primary role that the catecholamines have in terms of the ketogenic diet is to stimulate free fatty acid release from fat cells.

When insulin levels are low, epinephrine and norepinephrine are both involved in fat mobilization. In humans, only insulin and the catecholamines have any real effect on fat mobilization. With insulin inhibiting fat breakdown and the catecholamines stimulating fat breakdown.

Liver glycogen

The liver is one of the most metabolically active organs in the entire body. All foods coming through the digestive tract are processed initially in the liver. To a great degree, the level of liver

glycogen is the key determinant of the body's overall trend to store or breakdown nutrients (25). Additionally, high levels of liver glycogen tends to be associated with higher body fat levels (19).

The liver is basically a short term storehouse for glycogen which is used to maintain blood glucose. The breakdown of liver glycogen to glucose, to be released into the bloodstream, is stimulated by an increase in glucagon as discussed previously.

When liver glycogen is full, blood glucose is maintained and the body is generally anabolic, which means that incoming glucose, amino acids and free fatty acids are stored as glycogen, proteins, and triglycerides respectively. This is sometimes called the 'fed' state (1).

When liver glycogen becomes depleted, via intensive exercise or the absence of dietary carbohydrates, the liver shifts roles and becomes catabolic. Glycogen is broken into glucose, proteins are broken down into amino acids, and triglycerides are broken down to free fatty acids. This is sometimes called the 'fasted' state (1).

If liver glycogen is depleted sufficiently, blood glucose drops and the shift in insulin and glucagon occurs. This induces ketone body formation, called ketogenesis, and is discussed in the next chapter.

Enzyme levels

The final regulator of fuel use in the body is enzyme activity. Ultimately enzyme levels are determined by the nutrients being ingested in the diet and the hormonal levels which result.

For example, when carbohydrates are consumed and insulin is high, the enzymes involved in glucose use and glycogen storage are stimulated and the enzymes involved in fat breakdown are inhibited. By the same token, if insulin drops, the enzymes involved in glucose use are inhibited and the enzymes involved in fat breakdown will increase.

Long term adaptation to a high carbohydrate or low carbohydrate diet can cause longer term changes in the enzymes involved in fat and carbohydrate use as well. If an individual consumes no carbohydrates for several weeks, there is a down regulation of enzymes in the liver and muscle which store and burn carbohydrates (1, 17,18). The end result of this is an inability to use carbohydrates for fuel for a short period of time after they are reintroduced to the diet.

Summary

Although there are four major fuels which the body can use, for our purposes only the interactions between glucose and free fatty acids need to be considered. As a general rule, assuming that the body's total energy requirements stay the same, an increase in glucose use by the body will result in a decrease in the use of fatty acids and vice versa.

There are four major factors that regulate fuel use by the body. Ultimately they are all determined by the intake of dietary carbohydrates. When carbohydrate availability is high, carbohydrate use and storage is high and fat use is low. When carbohydrate availability is low, carbohydrate use and storage is low and fat use is high.

The most basic premise of the ketogenic diet is that the body can be forced to burn greater amounts of fat by decreasing its use of glucose. The adaptations which occur in the body as well as the processes involved are discussed in the next chapter.

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Chapter 4:
Basic ketone physiology

To understand the adaptations which occur as a result of ketosis, it is necessary to examine the physiology behind the production of ketone bodies in the liver. As well, an examination of what ketone bodies are and what ketosis represents is necessary. Finally, concerns about ketoacidosis as it occurs in diabetics are addressed.

Section 1: Ketone bodies

What are ketone bodies?

The three ketone bodies are acetoacetate (AcAc), beta-hydroxybutyrate (BHB) and acetone. AcAc and BHB are produced from the condensation of acetyl-CoA, a product of incomplete breakdown of free fatty acids (FFA) in the liver. While ketones can technically be made from certain amino acids, this is not thought to contribute significantly to ketosis (1). Roughly one-third of AcAc is converted to acetone, which is excreted in the breath and urine. This gives some individuals on a ketogenic diet a 'fruity' smelling breath.

As a side note, urinary and breath excretion of acetone is negligible in terms of caloric loss, amounting to a maximum of 100 calories per day (2). The fact that ketones are excreted through this pathway has led some authors to argue that fat loss is being accomplished through urination and breathing. While this may be very loosely true, in that ketones are produced from the breakdown of fat and energy is being lost through these routes, the number of calories lost per day will have a minimal effect on fat loss.

Functions of ketones in the body

Ketones serve a number of functions in the body. The primary role, and arguably the most important to ketogenic dieters, is to replace glucose as a fat-derived fuel for the brain (3,4). A commonly held misconception is that the brain can only use glucose for fuel. Quite to the contrary, in situations where glucose availability is limited, the brain can derive up to 75% of its total energy requirements from ketone bodies (3).

Ketones also decrease the production of glucose in the liver (5-7) and some researchers have suggested that ketones act as a 'signal' to bodily tissues to shift fuel use away from glucose and towards fat (6). These effects should be seen as a survival mechanism to spare what little glucose is available to the body. The importance of ketones as a brain fuel are discussed in more detail in the next chapter.

A second function of ketones is as a fuel for most other tissues in the body. By shifting the entire body's metabolism from glucose to fat, what glucose is available is conserved for use by the

brain (see chapter 5 for more detail) (6). While many tissues of the body (especially muscle) use a large amount of ketones for fuel during the first few weeks of a ketogenic diet, most of these same tissues will decrease their use of ketones as the length of time in ketosis increases (4). At this time, these tissues rely primarily on the breakdown of free fatty acids (FFA). In practical terms, after three weeks of a ketogenic diet, the use of ketones by tissues other than the brain is negligible and can be ignored.

A potential effect of ketones (discussed further in chapter 5) is to inhibit protein breakdown during starvation through several possible mechanisms, discussed in detail in the next chapter. The only other known function of ketones is as a precursor for lipid synthesis in the brain of neonates (4).

Section 2: Ketogenesis and the two site model

The formation of ketone bodies, called ketogenesis, is at the heart of the ketogenic diet and the processes involved need to be understood. As described in the previous chapter, the primary regulators of ketone body formation are the hormones insulin and glucagon. The shift that occurs in these two hormones, a decrease in insulin and an increase in glucagon is one of the major regulating steps regulating ketogenesis.

A great amount of research has been performed to determine exactly what is involved in ketogenesis. All the research has led to a model involving two sites: the fat cell and the liver. In addition, the enzyme mitochondrial HMG CoA reductase (MHS) has been suggested as a third site of regulation (4,8). For our purposes, MHS and its effects are unimportant so we will focus only on the first two sites of regulation: the fat cell and the liver.

The fat cell

As discussed in the previous chapter, the breakdown of fat in fat cells, is determined primarily by the hormones insulin and the catecholamines. When insulin is high, free fatty acid mobilization is inhibited and fat storage is stimulated through the enzyme lipoprotein lipase (LPL). When insulin decreases, free fatty acids (FFA) are mobilized both due to the absence of insulin as well as the presence of lipolytic (fat mobilizing) hormones such as the catecholamines (9,10). Glucagon, cortisol and growth hormone play additional but minor roles.

Insulin has a much stronger anti-lipolytic effect than the catecholamines have a lipolytic effect. If insulin is high, even though catecholamines are high as well, lipolysis is blocked. It is generally rare to have high levels of both insulin and catecholainines in the body. This is because the stimuli to raise catecholamine levels, such as exercise, tend to lower insulin and vice versa.

Breakdown and transport of Triglyceride (11)

When the proper signal reaches the fat cell, stored triglyceride (TG) is broken down into glycerol and three free fatty acid (FFA) chains. FFA travels through the bloodstream, bound to a

protein called albumin. Once in the bloodstream, FFA can be used for energy production by most tissues of the body, with the exception of the brain and a few others.

FFA's not used for energy by other tissues will reach the liver and be oxidized (burned) there. If there is sufficient FFA and the liver is prepared to produce ketone bodies, ketones are produced and released into the bloodstream.

The fat cell should be considered one regulatory site for ketone body formation in that a lack of adequate FFA will prevent ketones from being made in the liver. That is, even if the liver is in a mode to synthesize ketone bodies, a lack of FFA will prevent the development of ketosis.

The liver

The liver is always producing ketones to some small degree and they are always present in the bloodstream. Under normal dietary conditions, ketone concentrations are simply too low to be of any physiological consequence. A ketogenic diet increases the amount of ketones which are produced and the blood concentrations seen. Thus ketones should not be considered a toxic substance or a byproduct of abnormal human metabolism. Rather, ketones are a normal physiological substance that plays many important roles in the human body.

The liver is the second site involved in ketogenesis and arguably the more important of the two. Even in the presence of high FFA levels, if the liver is not in a ketogenic mode, ketones will not be produced.

The major determinant of whether the liver will produce ketone bodies is the amount of liver glycogen present (8). The primary role of liver glycogen is to maintain normal blood glucose levels. When dietary carbohydrates are removed from the diet and blood glucose falls, glucagon signals the liver to break down its glycogen stores to glucose which is released into the bloodstream. After approximately 12-16 hours, depending on activity, liver glycogen is almost completely depleted. At this time, ketogenesis increases rapidly. In fact, after liver glycogen is depleted, the availability of FFA will determine the rate of ketone production. (12)

The Insulin/Glucagon ratio

With the two regulating sites of ketogenesis discussed, we can return to the discussion of insulin and glucagon and their role in establishing ketosis. When carbohydrates are consumed, insulin levels are high and glucagon levels are low. Glycogen storage is stimulated and fat synthesis in the liver will occur. Fat breakdown is inhibited both in the fat cell as well as in the liver (8).

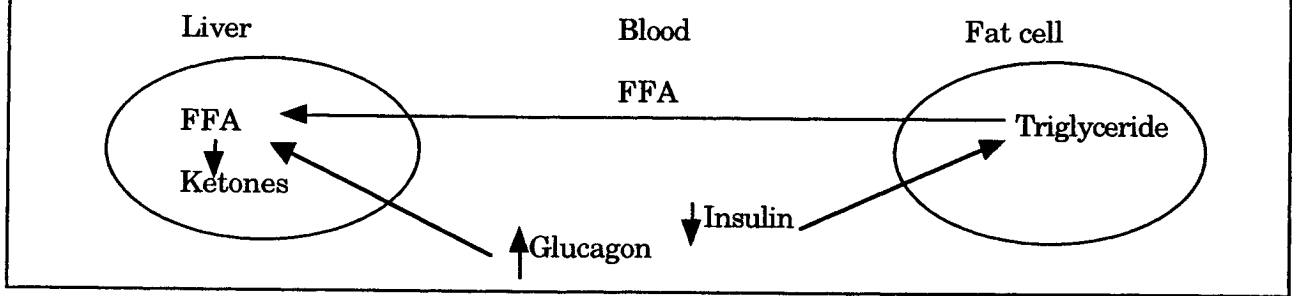
When carbohydrates are removed from the diet, liver glycogen will eventually be emptied as the body tries to maintain blood glucose levels. Blood glucose will drop as liver glycogen is depleted. As blood glucose decreases, insulin will decrease and glucagon will increase. Thus there is an overall decrease in the insulin/glucagon ratio (I/G ratio) (8,14).

As insulin drops, FFA are mobilized from the fat cell, providing adequate substrate for the liver to make ketones. Since liver glycogen is depleted, CPT-1 becomes active, burning the incoming FFA, which produces acetyl-CoA. Acetyl-CoA accumulates as discussed in the section

above and is condensed into ketones.

The liver has the capacity to produce from 115 to 180 grams of ketones per day once ketogenesis has been initiated (4,15-17). Additionally, the liver is producing ketones at a maximal rate by the third day of carbohydrate restriction (16). It appears that once the liver has become ketogenic, the rate of ketone body formation is determined solely by the rate of incoming FFA (12). This will have implications for the effects of exercise on levels of ketosis (see chapter 21 for more details). Figure 1 graphically illustrates the 2 site model of ketogenesis.

Figure 1: The two site model of ketogenesis



Summary

The production of ketone bodies in the liver requires a depletion of liver glycogen and a subsequent fall in malonyl-CoA concentrations allowing the enzyme carnitine palmityl tranferase I (CPT-1) to become active. CPT-1 is responsible for carrying free fatty acids into the mitochondria to be burned. At the same time CPT-1 is becoming active, a drop in blood glucose causes a decrease in the insulin/glucagon ratio allowing free fatty acids to be mobilized from fat cells to provide the liver with substrate for ketone body formation.

Technical note: Malonyl-CoA and Carrntine Palmityl Transferase-1 (CPT-1)

Rather than liver glycogen per se, the primary regulator of ketogenesis in the liver is a substance called malonyl-CoA (8,13). Malonyl-CoA is an intermediate in fat synthesis which is present in high amounts when liver glycogen is high. When the liver is full of glycogen, fat synthesis (lipogenesis) is high and fat breakdown (lipolysis) is low (8).

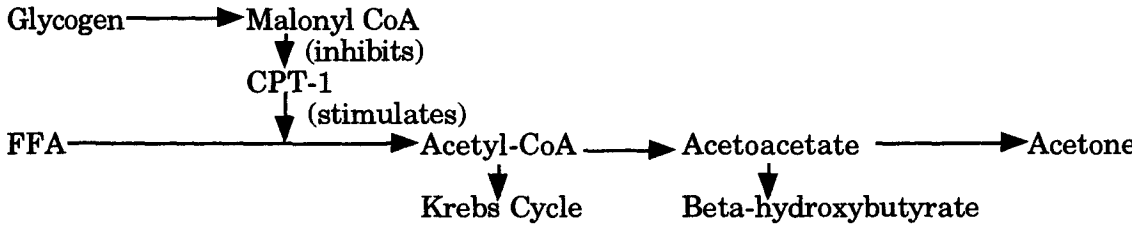
Malonyl-CoA levels ultimately determine whether the liver begins producing ketone bodies or not. This occurs because malonyl-CoA inhibits the action of an enzyme called carnitine palmityl tranferase 1 (CPT-1) both in the liver and other tissues such as muscle (8,13).

CPT-1 is responsible for transporting FFA into the mitochondria to be burned. As FFA are burned, a substance called acetyl-CoA is produced. When carbohydrate is available, acetyl-CoA is used to produce more energy in the Krebs cycle. When carbohydrate is not available, acetyl-CoA cannot enter the Krebs cycle and will accumulate in the liver (figure 2).

As Malonyl-CoA levels drop and CPT-1 becomes active, FFA oxidation occurs rapidly causing an increase in the level of acetyl-CoA. As discussed in the next section, when acetyl-

CoA levels increase to high levels, they are condensed into acetoacetic acid which can further be converted to beta-hydroxybutyrate and acetone, the three major ketone bodies.

Figure 2: **Interrelationship between Malonyl-CoA and CPT-1**



Section 3: Ketosis and Ketoacidosis

Having discussed the mechanisms behind ketone body production, we can now examine the metabolic state of ketosis, and what it represents. Additionally, ketosis is contrasted to runaway diabetic ketoacidosis.

Ketosis is the end result of a shift in the insulin/glucagon ratio and indicates an overall shift from a glucose based metabolism to a fat based metabolism. Ketosis occurs in a number of physiological states including fasting (called starvation ketosis), the consumption of a high fat diet (called dietary ketosis), and immediately after exercise (called post-exercise ketosis). Two pathological and potentially fatal metabolic states during which ketosis occurs are diabetic ketoacidosis and alcoholic ketoacidosis.

The major difference between starvation, dietary and diabetic/alcoholic ketoacidosis is the level of ketone concentrations seen in the blood. Starvation and dietary ketosis will normally not progress to dangerous levels, due to various feedback loops which are present in the body (12). Diabetic and alcoholic ketoacidosis are both potentially fatal conditions (12).

All ketotic states ultimately occur for the same reasons. The first is a reduction of the hormone insulin and an increase in the hormone glucagon both of which are dependent on the depletion of liver glycogen. The second is an increase in FFA availability to the liver, either from dietary fat or the release of stored body fat.

Under normal conditions, ketone bodies are present in the bloodstream in minute amounts, approximately 0.1 mmol/dl (1,6). When ketone body formation increases in the liver, ketones begin to accumulate in the bloodstream. Ketosis is defined clinically as a ketone concentration above 0.2 mmol/dl (6). Mild ketosis, around 2 mmol, also occurs following aerobic exercise. (4). The impact of exercise on ketosis is discussed in chapter 21.

Ketoacidosis is defined as any ketone concentration above 7 mmol/dl. Diabetic and alcoholic ketoacidosis result in ketone concentrations up to 25 mmol (6). This level of ketosis will never occur in non-diabetic or alcoholic individuals (12). A summary of the different ketone body concentrations appears in table 1.

Table 1: Comparison of ketone concentrations under differentconditions

Metabolic state	Ketone body concentration (mmol/dl)
Mixed diet	0.1
Ketosis	0.2
Fasting 2-3 days	1
Post-exercise	Up to 2
Fasting 1 week	5
Ketogenic diet	5-6
Fasting 3-4 weeks	6-8
Ketoacidosis	8+
	Up to 25

Note: Ketone body concentrations are higher in fasting than during a ketogenic diet due to the slight insulin response from eating.

Data is from Mitchell GA et al. Medical aspects of ketone body metabolism. Clinical & Investigative Medicine (1995) 18:193-216; and Robinson AM and Williamson DH. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. Physiol Rev (1980) 60: 143-187.

Ketonemia and ketonuria

The general metabolic state of ketosis can be further subdivided into two categories. The first is ketonemia which describes the build-up of ketone bodies in the bloodstream. Technically ketonemia is the true indicator that ketosis has been induced. However the only way to measure the level of ketonemia is with a blood test which is not practical for ketogenic dieters.

The second subdivision is ketonuria which describes the build-up and excretion of ketone bodies in the urine, which occurs due to the accumulation of ketones in the kidney. The excretion of ketones into the urine may represent 10-20% of the total ketones made in the liver (4). However, this may only amount to 10-20 grams of total ketones excreted per day (17). Since ketones have a caloric value of 4.5 calories/gram, (17) the loss of calories through the urine is only

45-90 calories per day.

The degree of ketonuria, which is an indirect indicator of ketonemia, can be measured by the use of Ketostix (tm), small paper strips which react with urinary ketones and change color. Ketonemia will always occur before ketonuria. Ketone concentrations tend to vary throughout the day and are generally lower in the morning, reaching a peak around midnight (6). This may occur from changes in hormone levels throughout the day (18). Additionally, women appear to show deeper ketone levels than men (19,20) and children develop deeper ketosis than do adults (5). Finally, certain supplements, such as N-acetyl-cysteine, a popular anti-oxidant, can falsely indicate ketosis (4).

The distinction between ketonuria and ketonemia is important from a practical standpoint. Some individuals, who have followed all of the guidelines for establishing ketosis will not show urinary ketones. However this does not mean that they are not technically in ketosis. Ketonuria is only an indirect measure of ketone concentrations in the bloodstream and Ketostix (tm) measurements can be inaccurate (see chapter 15 for more details).

What does ketosis represent?

The development of ketosis indicates two things. First, it indicates that the body has shifted from a metabolism relying primarily on carbohydrates for fuel to one using primarily fat and ketones for fuel (4). This is arguably the main goal of the ketogenic diet: to cause an overall metabolic shift to occur in the body. The reasons this shift may be desirable are discussed in the next chapter.

Second, ketosis indicates that the entire pathway of fat breakdown is intact (4). The absence of ketosis under conditions which are known to induce it would indicate that a flaw in fat breakdown exists somewhere in the chain from fat breakdown, to transport, to oxidation in the liver. This absence would indicate a metabolic abnormality requiring further evaluation.

A major concern that frequently arises with regards to ketogenic diets is related to the slight acidification caused by the accumulation of ketone bodies in the bloodstream. Normal blood pH is 7.4 and this will drop slightly during the initial stages of ketosis.

While blood pH does temporarily decrease, the body attains normal pH levels within a few days (21) as long as ketone body concentrations do not exceed 7-10 mmol (22). Although blood pH is normalized after a few days, the buffering capacity of the blood is decreased (21), which has implications for exercise as discussed in chapters 18 through 20.

There is frequent confusion between the dietary ketosis seen during a ketogenic diet and the pathological and potentially fatal state of diabetic ketoacidosis (DKA). DKA occurs only in Type I diabetes, a disease characterized by a defect in the pancreas, whereby insulin cannot be produced. Type I diabetics must take insulin injections to maintain normal blood glucose levels. In diabetics who are without insulin for some time, a state that is similar to dietary ketosis begins to develop but with several differences.

Although both dietary ketosis and DKA are characterized by a low insulin/glucagon ratio, a non-diabetic individual will only develop ketosis with low blood glucose (below 80 mg/dl) while a Type I diabetic will develop ketosis with extremely high blood glucose levels (Type I diabetics may have blood glucose levels of 300 mg/dl or more) (12).

Additionally, the complete lack of insulin in Type I diabetics appears to further increase ketone body formation in these individuals. While a non-diabetic individual may produce 115-180 grams of ketones per day (4,16), Type I diabetics have been found to produce up to 400 grams of ketones per day (22,23). The drop in blood pH seen in DKA is probably related to the overproduction of ketones under these circumstances (12).

This increase in ketone formation is coupled with an inability in the Type I diabetic to use ketones in body tissues (12). Presumably this occurs because blood glucose is present in adequate amounts making glucose the preferred fuel. Thus there is a situation where ketone body formation is high but ketone body utilization by the body is very low, causing a rapid buildup of ketones in the bloodstream.

Additionally, in non-diabetic individuals there are at least two feedback loops to prevent runaway ketoacidosis from occurring. When ketones reach high concentrations in the bloodstream (approximately 4-6 mmol), they stimulate a release of insulin (8,12). This increase in insulin has three major effects (24). First, it slows FFA release from the fat cell. Second, by raising the insulin/glucagon ratio, the rate of ketone body formation in the liver is decreased. Third, it increases the excretion of ketones into the urine. These three effects all serve to lower blood ketone body concentration.

In addition to stimulating insulin release, ketones appear to have an impact directly on the fat cell, slowing FFA release (12,22). This would serve to limit FFA availability to the liver, slowing ketone body formation. Ultimately these two feedback loops prevent the non-diabetic individual from overproducing ketones since high ketone levels decrease ketone body formation.

Type I diabetics lack both of these feedback loops. Their inability to release insulin from the pancreas prevents high ketone body levels from regulating their own production. The clinical treatment for DKA is insulin injection which rapidly shuts down ketone body formation in the liver, slows FFA release from fat cells, and pushes ketones out of the bloodstream (12). Additionally, rehydration and electrolyte supplementation is necessary to correct for the effects of DKA (12).

The feedback loops present in a non-insulin using individual will prevent metabolic ketosis from ever reaching the levels of runaway DKA (12). Table 2 compares the major differences between a normal diet, dietary ketosis and diabetic ketoacidosis.

Table 2: Comparison of Dietary Ketosis and Diabetic Ketoacidosis

	Normal diet	Dietary ketosis	DKA
Blood glucose (mg/dl)	80-120	65-80	300+
Insulin	Moderate	Low	Absent
Glucagon	Low	High	High
Ketones production (g/day)	Low	115-180	400
Ketone concentrations (mmol/dl)	0.1	4-10	20+

One additional pathological state which is occasionally confused with dietary ketosis is alcoholic ketoacidosis. Alcoholic KA occurs in individuals who have gone without food while drinking heavily (4). Ethanol also has effects on ketone body formation by the liver, causing a runaway ketotic state similar to DKA (25). In contrast to DKA, alcoholic ketoacidosis can be easily reversed by eating carbohydrates as this increases insulin and stops ketone formation (4).

Summary

Ketosis is a metabolic state where ketones and FFA replace glucose as the primary fuel of the body in most tissues. The presence of ketosis indicates that fat breakdown has been activated in the body and that the entire pathway of fat degradation is intact. The lack of ketosis in states such as fasting and a ketogenic diet known to induce ketosis would indicate the presence of a metabolic abnormality.

Ketosis can be delineated into ketonemia, the presence of ketones in the bloodstream, and ketonuria, the presence of ketones in the urine. Clinically, ketosis is defined as a ketone concentration of 0.2 mmol. A ketogenic diet or fasting will result in ketone levels between 4 and 8 mmol. Ketoacidosis is defined as 8 mmol or higher and pathological ketoacidosis, as in diabetic ketoacidosis, can result in ketone concentrations of 20 mmol or greater. Ketoacidosis, as it occurs in Type I diabetics and alcoholics and which is potentially fatal, will not occur in non-diabetic individuals due to built in feedback loops whereby excess ketones stimulate the release of insulin, slowing ketone body formation.

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Chapter 5:

Adaptations to Ketosis

Having discussed the basics of fuel utilization, ketone body formation and ketosis, it is now time to examine in detail the adaptations which occur in shifting the body away from glucose and towards fat metabolism. The primary adaptation occurs in the brain although other systems are affected as well.

There is a common misconception, especially among bodybuilders, that ketosis is indicative of protein breakdown when in fact the exact opposite is the case. The development of ketosis sets in motion a series of adaptations which minimize body protein losses during periods of caloric deprivation. In fact, preventing the development of ketosis during these periods increases protein losses from the body.

The adaptations to ketosis are complex and involve most systems of the body. As with the previous sections, smaller details are ignored for this discussion and interested readers should examine the references provided. Rather, the major adaptations which occur in the body's tissues, especially the brain, liver, kidney and muscle are described.

The adaptations to ketosis have been studied in great depth during periods of total starvation. While this is an extreme state, the lack of food intake makes it simpler to examine the major adaptations. To help individuals understand the adaptations to ketosis, the metabolism of the body is examined during both short and long term fasting. The next chapter discusses the effects of food intake on ketosis, as well as body composition changes. The following sections address in detail the effects of ketosis on glucose/protein requirements as well as the effects on fat and ketone use.

Section 1: An overview of starvation

Starvation and the ketogenic diet

In one sense, the ketogenic diet is identical to starvation, except that food is being consumed. That is, the metabolic effects which occur and the adaptations which are seen during starvation are roughly identical to what is seen during a ketogenic diet. The primary difference is that the protein and fat intake of a ketogenic diet will replace some of the protein and fat which would otherwise be used for fuel during starvation.

The response to total starvation has been extensively studied, arguably more so than the ketogenic diet itself. For this reason the great majority of data presented below comes from studies of individuals who are fasting. With few exceptions, which are noted as necessary, the metabolic effects of a ketogenic diet are identical to what occurs during starvation.

Although it is discussed in greater detail in a later section, the critical aspect of developing ketosis is the quantity of carbohydrates in the diet and carbohydrate restriction mimics the

response seen with total fasting (1-3). The amounts of protein and fat are less critical in this regard (see chapter 9 for more details).

A brief overview of the adaptations to starvation (4)

Before looking in detail at the adaptations to starvation, we will briefly discuss the major events which occur. Starvation can be broken into 5 distinct phases. In the first phase, during the first 8 hours of starvation, the body is still absorbing fuel from previous meals. Within 10 hours after the last carbohydrate containing meal, roughly 50% of the body's total energy requirements are being met by free fatty acids (FFA).

In the second phase, the first day or two of starvation, the body will rely on FFA and the breakdown of liver glycogen for its energy requirements. Liver glycogen is typically gone within 12-16 hours.

In the third phase, during the first week of starvation, the body will drastically increase the production of glucose from protein and other fuels such as lactate, pyruvate and glycerol. This is called gluconeogenesis (the making of new glucose) and is discussed in detail below. At the same time, tissues other than the brain are decreasing their use of glucose, relying on FFA and ketones instead. This helps to spare what little glucose is available for the brain. During this phase, protein breakdown increases greatly.

The fourth phase of starvation is ketosis, which begins during the third or fourth day of starvation, and continues as long as carbohydrates are restricted. The major adaptations during ketosis is increased utilization of ketones by the brain. The final phase, which begins in the second week, is marked by decreasing protein breakdown and gluconeogenesis, as the major protein sparing adaptations to ketosis occur. With the exception of the initial hours of carbohydrate restriction (phases 1 and 2), each of the above phases is discussed in more detail below.

Changes in hormones and fuel availability

Although some mention is made in the discussions below of the adaptations seen during this time period, most of the major adaptations to ketosis start to occur by the third day, continuing for at least 3 weeks (4-6). During the first 3 days of fasting, blood glucose drops from normal levels of 80-120 mg/dl to roughly 65-75 mg/dl. Insulin drops from 40-50 U/ml to 7-10 U/ml (5,7,8). Both remain constant for the duration of the fast. One thing to note is that the body strives to maintain near-normal blood glucose levels even under conditions of total fasting (5). The popularly held belief that ketosis will not occur until blood glucose falls to 50 mg/dl is incorrect. Additionally, the popular belief that there is no insulin present on a ketogenic diet is incorrect (7).

One difference between fasting and a ketogenic diet is that the slight insulin response to dietary protein will cause blood glucose to be maintained at a slightly higher level, approximately 80-85 mg/dl (1). This most likely occurs due to the conversion of dietary protein to glucose in the liver.

At the same time that insulin and glucose are decreasing from carbohydrate restriction, other hormones such as glucagon and growth hormone are increasing, as are the levels of adrenaline and noradrenaline (7,10-12). Cortisol may actually decrease (13). This increases the rate of fat breakdown and blood levels of FFA and ketones increase (6,8,10,14,15).

Although the liver is producing ketones at its maximum rate by day three (14), blood ketone levels will continue to increase finally reaching a plateau by three weeks (6). The decrease in blood glucose and subsequent increase in FFA and ketones appear to be the signal for the adaptations which are seen, and which are discussed below (16).

In addition to increases in FFA and ketones, there are changes in blood levels of some amino acids (AAs). Increases are seen in the the branch chain amino acids, indicating increased protein breakdown (1, 17-19). As well, there are decreases in other AAs, especially alanine (1, 10,17-19) This most likely represents increased removal by the liver but may also be caused by decreased release of alanine from the muscles (16). This is discussed in further detail in section 3. Changes in levels of the other amino acids also occur and interested readers should examine the references cited. Blood levels of urea, a breakdown product of protein also increase (1). All of this data points to increased protein breakdown during the initial stages of starvation.

By the third day of carbohydrate restriction, the body is no longer using an appreciable amount of glucose for fuel. At this time essentially all of the non-protein energy is being derived from the oxidation of fat, both directly from FFA and indirectly via ketone bodies (20).

Section 2: Changes in ketone and fat usage during starvations

The changes which occur in ketone and FFA utilization during starvation are different for short and long term starvation. Both are discussed below.

Fat and ketone use during short term starvation

Measurements of fuel use show that approximately 90% of the body's total fuel requirements are being met by FFA and ketones by the third day (20). After three weeks of starvation, the body may derive 93% of its fuel from FFA (10, 21).

For an individual with a metabolic rate of 2700 calories per day, roughly 2400 calories of FFA (approximately 260 grams of fat) are used to fuel the body. Considering that one pound of fat contains 3,500 calories, this represents a loss of almost two-thirds of a pound of fat per day. Smaller individuals with lower metabolic rates will use proportionally less fat. While this extreme rate of fat loss makes starvation attractive as a treatment for obesity, the problems associated with total fasting (especially body protein loss) make it unacceptable.

The main point is that the metabolic state of ketosis causes a large scale shift from glucose to fat metabolism resulting in a much larger oxidation of fat than is seen on a more

'balanced' diet. The ketogenic diet is an attempt to harness this shift to cause maximum fat loss and minimum muscle loss, as discussed in greater detail in the upcoming sections.

Fat and ketone use during long term starvation

Most tissues except the brain, stop using ketones for fuel after the third week of ketosis. This is especially true for skeletal muscle. While muscle initially derives up to 50% of its energy requirements from ketones (22), this drops to 4-6% by the third week of ketosis. (22, 23). This is thought to occur for the following reason.

During the first few days of ketosis, the brain is incapable of using ketones for fuel. By using a large amount of ketones for fuel, skeletal muscle prevents a rapid increase in blood ketone levels, which might cause acidosis. As time passes and the brain adapts to using ketones for fuel, skeletal muscle must stop using ketones for fuel, to avoid depriving the brain of fuel. For all practical purposes, with long term starvation, the primary fuel of all tissues except the brain (and the others mentioned in section 3) is FFA, not ketones.

Section 3: Changes in Glucose and Protein Use During Starvation

At the same time that FFA and ketone use is increasing, the body's use of glucose and protein are going down. This is a critical adaptation for two reasons. First and foremost, there are tissues in the body which can not use FFA for fuel, requiring glucose. By decreasing their use of glucose, those tissues which do not require glucose for energy spare what little is available for the tissue which do require it. Thus, there is always a small requirement for glucose under any condition. As we shall see, this small glucose requirement can easily be met without the consumption of carbohydrates.

The second reason is that a reduction in protein losses is critical to survival during total starvation. The loss of too much muscle tissue will eventually cause death (6). From a fat loss standpoint, the 'protein sparing' effect of ketosis is also important to prevent lean body mass losses.

To examine the adaptations to ketosis in terms of glucose and protein, we first need to discuss which tissues do and do not require glucose. Then the adaptations which occur during starvation, in terms of the conservation of glucose, can be examined.

Which tissues use glucose?

All tissues in the body have the capacity to use glucose. With the exception of the brain and a few other tissues (leukocytes, bone marrow, erythrocytes), all tissues in the body can use FFA or ketones for fuel when carbohydrate is not available (5,23).

Under normal dietary conditions, glucose is the standard fuel for the brain and central

nervous system (CNS) (24,25). The CNS and brain are the largest consumers of glucose on a daily basis, requiring roughly 104 grams of glucose per day (5,25).

This peculiarity of brain metabolism has led to probably the most important misconception regarding the ketogenic diet. A commonly heard statement is that the brain can only use glucose for fuel but this is only conditionally true. It has been known for over 30 years that, once ketosis has been established for a few days, the brain will derive more and more of its fuel requirements from ketones, finally deriving over half of its energy needs from ketones with the remainder coming from glucose (6,26,27).

As a few tissues do continue to use glucose for fuel, and since the brain's glucose requirement never drops to zero, there will still be a small glucose requirement on a ketogenic diet. This raises the question of how much glucose is required by the body and whether or not this amount can be provided on a diet completely devoid of carbohydrate.

How much carbohydrate per day is needed to sustain the body?

When carbohydrate is removed from the diet, the body undergoes at least three major adaptations to conserve what little glucose and protein it does have (5). The primary adaptation is an overall shift in fuel utilization from glucose to FFA in most tissues, as discussed in the previous section (5,6). This shift spares what little glucose is available to fuel the brain.

The second adaptation occurs in the leukocytes, erythrocytes and bone marrow which continue to use glucose (6). To prevent a depletion of available glucose stores, these tissues break down glucose partially to lactate and pyruvate which go to the liver and are recycled back to glucose again (5,6). Thus there is no net loss of glucose in the body from these tissues and they can be ignored in terms of the body's carbohydrate requirements.

The third, and probably the most important, adaptation, occurs in the brain, which shifts from using solely carbohydrate for fuel to deriving up to 75% of its energy requirements from ketones by the third week of sustained ketosis. (5,6,26) As the brain is the only tissue that continues to deplete glucose in the body, it is all we need concern ourselves with in terms of daily carbohydrate requirements.

The brain's glucose requirements

In a non-ketotic state, the brain utilizes roughly 100 grams of glucose per day (5,25). This means that any diet which contains less than 100 grams of carbohydrate per day will induce ketosis, the depth of which will depend on how many carbohydrates are consumed (i.e. less carbohydrates will mean deeper ketosis). During the initial stages of ketosis, any carbohydrate intake below 100 grams will induce ketosis (28). As the brain adapts to using ketones for fuel and the body's glucose requirements decrease, less carbohydrate must be consumed if ketosis is to be maintained.

The question which requires an answer is this: What sources of glucose does the body have other than the ingestion of dietary carbohydrate? Put differently, assuming zero dietary carbohydrate intake, can the body produce enough glucose to sustain itself?

Please note that the following discussion is only truly relevant to individuals on a Standard Ketogenic Diet (SKI)) who are not exercising. However the same information also applies to individuals using a TKD or CKD as some period is spent in ketosis. The impact and implications of exercise on carbohydrate requirements is discussed in later chapters.

Sources of glucose in the body during short term ketosis

The easiest way to examine the body's requirements for glucose is to look at the effects of complete fasting in both the short term (a few hours to 3 weeks) and the long term (3 weeks and up). The few differences between complete fasting and a ketogenic diet are discussed afterwards.

Liver glycogen and gluconeogenesis

The initial storage depot of carbohydrate in the body is the liver, which contains enough glycogen to sustain the brain's glucose needs for approximately 12-16 hours (4). We will assume for the following discussion that liver glycogen has been depleted, ketosis established, and that the only source of glucose is from endogenous fuel stores (i.e. stored body fat and protein). The effects of food intake on ketosis is discussed in chapter 9.

After its glycogen has been depleted, the liver is one of the major sources for the production of glucose (gluconeogenesis) and it produces glucose from glycerol, lactate/pyruvate and the amino acids alanine and glutamine (5,6,25) The kidney also produces glucose as starvation proceeds (8).

Glycerol comes from the breakdown of adipose tissue triglyceride, lactate and pyruvate from the breakdown of glycogen and glucose, and alanine and glutamine are released from muscle. Since we are ultimately concerned with the loss of muscle tissue during ketosis, gluconeogenesis from alanine and glutamine are discussed further.

Protein breakdown

With the induction of starvation, blood alanine/glutamine levels both increase significantly, indicating an increase in muscle protein breakdown (6,19). Alanine is absorbed by the liver, converted to glucose and released back into the bloodstream. Glutamine is converted to glucose in the kidney (8). There are also increases in blood levels of the branch-chain amino acids, indicating the breakdown of skeletal muscle (18).

During the initial weeks of starvation, there is an excretion of 12 grams of nitrogen per day. Since approximately 16% of protein is nitrogen, this represents the breakdown of roughly 75 grams of body protein to produce 75 grams of glucose (6). If this rate of protein breakdown were to continued unchecked, the body's protein stores would be depleted in a matter of weeks, causing death.

After even 1 week of starvation, blood alanine levels begin to drop and uptake by the kidneys decreases, indicating that the body is already trying to spare protein losses (19). During

longer periods of starvation, blood levels of alanine and glutamine continue to decrease, as does glucose production by the liver (6,21). As glucose production in the liver is decreasing, there is increased glucose production in the kidney (21).

Because of these adaptations, nitrogen losses decrease to 3-4 grams per day by the third week of starvation, indicating the breakdown of approximately 20 grams of body protein (6). With extremely long term starvation, nitrogen losses may drop to 1 gram per day (7), indicating the breakdown of only 6 grams of body protein. However at no time does protein breakdown decrease to zero, as there is always a small requirement for glucose (10). As we shall see in a later section, the development of ketosis during starvation is critical for protein sparing.

Fat breakdown

The glycerol portion of triglycerides (TG) is converted to glucose in the liver with roughly ten percent of the total grams of TG broken down (whether from body fat or dietary fat) appearing as glucose (25,29). An average sized individual (150 lbs) may catabolize 160-180 grams of fat per day which will yield 16-18 grams of glucose (10). Obviously a larger individual would oxidize more fat, producing more glucose. The amount of glycerol converted to glucose is fairly constant on a day-to-day basis and will depend primarily on metabolic rate.

Protein and fat

Excluding the glucose made by recycling lactate and pyruvate, the body will produce the 100 grams of glucose which it needs from the breakdown of approximately 180 grams of TG and 75 grams of muscle protein (see Table 1) (6).

Table 1: Sources of glucose during **the initial** stages **of starvation**

Glucose produced (grams)	Source
	Amount of carbohydrate required by brain
-400	Breakdown of 180 grams of TG
18	Breakdown of 75 grams of protein
75	Total carbohydrate produced per day
93	in the liver

Production of glucose during long term starvation

As long term adaptation to ketosis continues, there are a number of adaptations which occur to further spare glucose. From the third day of ketosis to three weeks of fasting, the brain gradually increases its use of ketones for fuel, ultimately deriving up to 75% of its total energy from ketones (6,26). This shift to using ketones by the brain means that only 40 grams of glucose per day is required, the remaining 60-75 grams of energy being provided by ketones (26). This means that less protein must be broken down to produce glucose. Since TG breakdown will

still provide 18 grams of glucose per day, protein breakdown will only be 20 grams per day (see table 2 on the next page) (6). As stated previously, is appears the primary purpose of ketones in humans is to provide the brain with a non-glucose, fat-derived fuel for the brain (27,30).

Summary

The implication of the adaptations discussed above is that the body does not require dietary carbohydrates for survival (exercise and muscle growth are a separate issue). That is, there is no such thing as an essential dietary carbohydrate as the body can produce what little glucose it needs from other sources.

Of course, the price paid is the loss of body protein, which will ultimately cause death if continued for long periods of time. This loss of body protein during total starvation is unacceptable but the above discussion only serves to show that the body goes through a series of adaptations to conserve its protein. As we see later in this chapter, the addition of dietary protein will maintain ketosis, while preventing the breakdown of bodily protein. In brief, rather than break down bodily protein to produce glucose, the body will use some of the incoming dietary protein for glucose production. This should allow maximal fat utilization while sparing protein losses.

Table 2: Sources of glucose during long term starvation

Source	Glucose produced (grams)
Amount of carbohydrate required by brain	40
Breakdown of 180 grams of fat	18
Breakdown of 20 grams of protein	20
Total carbohydrate produced per day in the liver and kidney	38

Section 4: Ketosis and protein sparing

Having quantitatively examined the adaptations which occur in terms of glucose use and nitrogen losses during starvation, the mechanisms behind the 'protein sparing' effect of ketosis can now be discussed.

The question which needs to be answered is what mechanisms exist for ketones (or ketosis) to spare protein. There are at least four possible mechanisms through which ketogenic diets may spare protein, three of which are well established in the literature, the fourth less so. They are discussed in more detail below.

Decreasing the body's glucose requirements

This is arguably the primary mechanism through which ketosis spares nitrogen losses. This adaptation is discussed in detail in the previous sections and is well established in the

literature. To briefly recap, by shifting the body's overall metabolism to fat and ketones (especially in the brain), less protein is converted to glucose and protein is spared (6,27). This mechanism is not discussed in further detail here.

It should be noted that preventing the development of ketosis, either with drugs or with the provision of too much dietary carbohydrate, maintains the nitrogen losses during starvation (31).

That is, the development of ketosis is a critical aspect of preventing excessive nitrogen losses during periods of caloric insufficiency. This suggests that non-ketogenic low-carbohydrate diets (frequently used by bodybuilders) may actually cause greater protein losses by preventing the body from maximizing the use of fat for fuel, which is addressed in chapter 6.

Decreased nitrogen excretion via the kidney

The kidney is a major site of ketone uptake and the build-up of ketones in the kidney has at least two metabolic effects (32). The first is an increase in urinary excretion of ketones, which can be detected with Ketostix (tm). The second is an impairment of uric acid uptake, which is discussed in chapter 7.

The excretion of ketones through the kidneys has an important implication for nitrogen sparing. The kidney produces ammonia, which requires nitrogen, as a base to balance out the acidic nature of ketones and prevent the urine from becoming acidic. This is at least one possible site for an increase in protein losses during ketosis (32). In all likelihood, the increased excretion of ammonia may be the basis of the idea (long held in bodybuilding) that ketone excretion is indicative of protein loss.

As ketosis develops, however, there is an adaptation in the kidney to prevent excessive ammonia loss. As blood ketone concentrations increase, the kidney increases its absorption of ketones. If this increased absorption was accompanied by increased ketone excretion, there would be further nitrogen loss through ammonia production.

However urinary excretion of ketones does not increase, staying extremely constant from the first few days of ketosis on. Therefore, most of the ketones being absorbed by the kidney are not being excreted. The resorption of ketones appears to be an adaptation to prevent further nitrogen losses, which would occur from increasing ammonia synthesis (16,32). This adaptation has the potential to spare 7 grams of nitrogen (roughly 42 grams of body protein) per day from being lost (32).

Directly affecting protein synthesis and breakdown

As stated, it is well established that protein breakdown decreases during the adaptation to total starvation and one of the mechanisms for this decrease is a lessening of the brain's glucose requirements. It has also been suggested that protein sparing is directly related to ketosis (5,26). As well, many popular authors have suggested that ketones are directly anti-catabolic but this has not been found in all studies.

As described previously, muscles will derive up to 50% of their energy requirements from ketones during the first few days of ketosis. However this drops rapidly and by the third week of

ketosis, muscles derive only 4-6% of their energy from ketone bodies (22). This becomes important when considering the time course for nitrogen sparing during ketosis.

Infusion studies

Several studies have examined the effects on protein breakdown during the infusion of ketone bodies at levels that would be seen in fasting or a ketogenic diet. Of these studies, three have shown a decrease in protein breakdown (33-35) while two others have not (36,37). One study suggested that ketones were directly anabolic (38). One oddity of these studies is that the infusion of ketones (usually as a ketone salt such as sodium-acetoacetate) causes an increase in blood pH (36,38), contrary to the slight drop in blood pH which normally occurs during a ketogenic diet.

At least one study suggests that the rise in pH is responsible for the decrease in protein breakdown rather than the ketones themselves (36); and sodium bicarbonate ingestion can reduce protein breakdown during a ketogenic diet (39). However, since blood pH is normalized within a few days of initiating ketosis, while maximal protein sparing does not occur until the third week, it seems unlikely that changes in blood pH can explain the protein sparing effects of ketosis.

It should be noted that these studies are different than the normal physiological state of ketosis for several reasons. First and foremost, the mixture of ketone salts used is not chemically identical to the ketones that appear in the bloodstream. Additionally, the increase in pH seen with ketone salt infusion is in direct contrast to the drop in pH seen on a ketogenic diet suggesting a difference in effect. Therefore, ketones produced during metabolic ketosis may still have a direct anti-catabolic effect.

Possibly the biggest argument against the idea that ketones are directly anti-catabolic is the time course for changes in nitrogen balance. Most of the infusion studies were done on individuals who had been fasting for short periods of time, overnight or a few days. The major decrease in nitrogen sparing does not occur until approximately the third week of ketosis, at which time muscles are no longer using ketones to any significant degree (22,40). All of the above data makes it difficult to postulate a mechanism by which ketones directly affect muscle protein breakdown. In all likelihood, contrary to popular belief, ketones are not directly anti-catabolic.

Affecting thyroid levels

A fourth possible mechanism by which ketosis may reduce protein breakdown involves the thyroid hormones, primarily triiodothyronine (T3). T3 is arguably one of the most active hormones in the human body (42-44). While most think of T3 simply as a controller of metabolic rate, it affects just about every tissue of the body including protein synthesis. A decrease in T3 will slow protein synthesis and vice versa. As a side note, this is one reason why low carbohydrate diets are not ideal for individuals wishing to gain muscle tissue: the decrease in T3 will negatively affect protein synthesis.

The body has two types of thyroid hormones (42). The primary active thyroid hormone is T3, called triiodothyronine. T3 is responsible most of the metabolic effects in the body. The other thyroid hormone is T4, called thyroxine. Thyroxine is approximately one-fifth as metabolically active as T3 and is considered to be a storage form of T3 in that it can be converted to T3 in the liver.

T3 levels in the body are primarily related to the carbohydrate content of the diet (44-46) although calories also play a role (47-49). When calories are above 800 per day, the carbohydrate content of the diet is the critical factor in regulating T3 levels and a minimum of 50 grams per day of carbohydrate is necessary to prevent the drop in P3 (44,48,49). To the contrary, one study found that a 1500 calorie diet of 50% carbohydrate and 50% fat still caused a drop in T3, suggesting that fat intake may also *affect thyroid* hormone metabolism (50).

Below 800 calories per day, even if 100% of those calories come from carbohydrate, T3 levels drop (47). Within days of starting a ketogenic diet, T3 drops quickly. This is part of the adaptation to prevent protein losses and the addition of synthetic T3 increases nitrogen losses during a ketogenic diet (1). In fact the ability to rapidly decrease T3 levels may be one determinant of how much protein is spared while dieting (51).

Hypothyroidism and euthyroid stress syndrome (ESS)

There are two common syndromes associated with low levels of T3 which need to be differentiated from one another. Hypothyroidism is a disease characterized by higher than normal thyroid stimulating hormone (TSH) and lower levels of T3 and P4. The symptoms of this disease include fatigue and a low metabolic rate.

The decrease in P3 due to hypothyroidism must be contrasted to the decrease seen during dieting or carbohydrate restriction. Low levels of T3 with normal levels of T4 and TSH (as seen in ketogenic dieting) is known clinically as euthyroid stress syndrome (ESS) and is not associated with the metabolic derangements seen in hypothyroidism (1). The drop in T3 does not appear to be linked to a drop in metabolic rate during a ketogenic diet (17,52).

As with other hormones in the body (for example insulin), the decrease in circulating T3 levels may be compensated for by an increase in receptor activity and/or number (1). This has been shown to occur in mononuclear blood cells but has not been studied in human muscle or fat cells (53). So while T3 does go down on a ketogenic diet, this does not appear to be the reason for a decrease in metabolic rate.

Summary

The primary adaptation to ketosis (as it occurs during total starvation) is a gradual decrease in the body's glucose requirements with a concomitant increase in the use of free fatty acids and ketones. The main adaptation which occurs is in the brain which shifts from deriving 100% of its fuel from glucose to deriving as much as 75% of its total energy requirements from ketones. Thus the commonly stated idea that the brain can only use glucose is incorrect.

A large increase in the breakdown of body protein during the initial stages of starvation provides the liver and kidney with the amino acids alanine and glutamine to make glucose. However, there is a gradual decrease in protein breakdown which occurs in concert with the decreasing glucose requirements.

Although the exact mechanisms behind the 'protein sparing' effect of ketosis are not entirely established, there are at least four possible mechanisms by which ketogenic diets may spare protein. These include decreased glucose requirements, decreased excretion of ketones from the kidneys, a possible direct effect of ketones on protein synthesis, and the drop in thyroid levels seen during starvation.

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