The Ketogenic Diet for Type 1 Diabetes

Technical Notes

These technical notes are related information provided to those who have purchased a copy of *The Ketogenic Diet for Type 1 Diabetes*, an e-book by Ellen Davis, MS and Keith Runyan, MD offered at www.ketogenic-diet-resource.com. Printed copies of the same book can be found on Amazon.com.

Tech Note 1— The Discovery of Insulin and Changes to Diabetes Treatment

> Dietetic treatment is of the first importance. The carbohydrates taken in the food are of no use to the body and must be removed by the kidneys thereby entailing polydipsia, polyuria, pruritus, and renal disease.
>
> Dr. Elliott Proctor Joslin
> *Joslin Diabetic Diet*, 1923

Before the arrival of insulin as a viable treatment for diabetes in 1923, physicians counseled people with diabetes to avoid carbohydrates and follow what is now called a ketogenic diet. Patients were told to follow a "strict diet: meat, poultry, game, fish, clear soups, gelatin, eggs, butter, olive oil, coffee, tea." The table below from the American Diabetes Association's Nutrition Recommendations and Principles for Diabetes Mellitus in 2000 shows that as time progressed, dietary restrictions were relaxed.

Year/Diet	Distribution of calories (%)		
	Carbohydrate	Protein	Fat
Joslin Diet	2	17	75
1921	20	10	70
1950	40	20	40
1971	45	20	35
1986	≤60	12-20	<30
1994	varies	10-20	<10 saturated

This change in dietary recommendations had negative consequences for diabetic patients. A 1960 study by Johnsson et al looked at the prevalence of diabetic complications in patients on the strict dietary guidelines before insulin's widespread usage and compared it to the complications incidences in a later group of patients following a relaxed diet that included more

carbohydrate and used insulin to lower blood sugar. They found the rates of diabetic retinopathy and nephropathy were much higher in the group following the high-carb diet, despite the addition of insulin to manage blood sugar.

Tech Note 2—Lipid-Heart Hypothesis

The idea that a "healthy diet" should be high in grains and starches, low in total and saturated fat, and supplemented with vegetable oils high in polyunsaturated fats was a new concept in the mid 1950s and was based on Ancel Keys's untested lipid-heart hypothesis. His idea was crafted from epidemiological studies that examined dietary-fat intake and cardiovascular disease (CVD) deaths. Intake of refined starches and sugar was not specifically examined, only total carbohydrates. These types of studies can at best only determine associations and not causation. Subsequently, multiple clinical trials were conducted to determine if the new low-fat diet would actually reduce CVD. The studies had mixed results, with some outcomes showing improvements in CVD events or deaths and other outcomes showing no improvement in CVD or showing an increase in cancer and non-cardiac deaths. The authors emphasized positive results in the abstract and conclusions, and they buried or made superficial reference to negative findings. If the trial results were outright negative, they delayed publication, didn't publish it at all, or pointed out other published studies that showed the positive results they wished to emphasize.

The bottom line is this: the low-fat diet has never been shown to lengthen life and, at best, changes the cause of death from CVD to other causes, including cancer, suicide, and homicide, to name a few.

Observational studies reveal associations, while clinical trials are more capable of revealing causation. A common example of association is between fires and firemen being present at the scene. Would you think that firemen, by virtue of being there, were actually causing a fire? Well, using Ancel Keys's approach, one might be led to arrive at such a conclusion. Using his persuasive personality, he was able to convince other influential physicians at the American Heart Association to make recommendations that Americans should change their diet based on suggestive data.

When George McGovern formed a committee to draft dietary guidelines to address what appeared to be an increasing prevalence of coronary artery disease, they sought the opinion of leading nutrition scientists as to what comprised a healthy diet. There was no consensus on this topic. Many sided with Keys's lipid-heart hypothesis, including Jeremiah Stamler and Mark Hegsted. But Pete Ahrens, Sir John McMichael, and John Yudkin thought that refined carbohydrates and sugar were the more likely dietary evils and believed that guidelines, as conceived, had "potential harm."

Senator George McGovern announced publication of the first *Dietary Goals for the United States* on January 14, 1977. These guidelines certainly gave the food industry an authoritative backing behind the creation of many new food products containing cheap and refined grains, starches, sugars, and vegetable oils to replace animal fats high in saturated fat and cholesterol. Since vegetable oils are liquid at room temperature, the industry hydrogenated them to mimic saturated fats, which are solids at room temperature (e.g., Crisco). This created a new problem called trans fats. These unnatural fats rarely exist in nature and have since been associated with heart disease, ironically causing the very problem they were supposed to prevent!

The dietary guidelines did however recommend limiting sugar in the diet, while the media and food industry's advertisements emphasized the low-fat aspect of their products. In order to make the lower-fat products palatable, sugar was added in increasing amounts over the years. In the mid to late 1970s, just as the public was becoming concerned about the effect of sugar in the diet, high-fructose corn syrup was developed and marketed as a new sweetener, despite it being almost identical to sugar. An obesity and diabetes pandemic followed—not surprising, given what we know about how the body deals with refined carbohydrates and sugar. For more information on this topic, we recommend reading *Good Calories, Bad Calories* by Gary Taubes or *The Big Fat Surprise by* Nina Teicholz.

Tech Note 3— Research Evidence on Ketones as an Alternate Fuel

Ketones are beneficial in many ways, but they are perhaps the most misunderstood compounds in medicine. Medical-school biochemistry textbooks only touch on ketone metabolism, which explains why most physicians are not familiar with its benefits.

There are three ketones or ketone bodies. They are acetoacetate (AcAc), beta-hydroxybutyrate (BHOB), and acetone. BHOB can be thought of as a transportable form of AcAc. Once BHOB arrives to the cellular mitochondria in any tissue that can utilize it, it is first converted to AcAc before being used to produce ATP, which is the universal fuel of all cells.

In an important study by Ernest J. Drenick et al, obese non-diabetic subjects first demonstrated the typical symptoms of hypoglycemia after insulin was administered before fasting. After these people fasted for two months, their BHOB levels were on average 8 mM. Insulin was administered again during this fasting phase, and the mean BHOB level dropped to 6.7 mM, while blood glucose dropped to 36 mg/dL (2 mmol/L), which in a carb-adapted brain would set off serious alarms. Amazingly, the subjects had *no symptoms of hypoglycemia*, even though they had the same degree of hypoglycemia that had previously led to severe hypoglycemic symptoms before fasting.

It was the keto-adaptation and the blood BHOB and AcAc levels that occurred during fasting that protected their brains against symptoms of hypoglycemia. The discussion section of the study mentioned above is particularly pertinent. The authors write:

> Previously, it was not known if the fasted human brain could tolerate an acute fall in glucose concentrations to very low levels without the development of hypoglycemic manifestations. Satisfactory evidence for such an adaptation had to be sought in subjects who had actually experienced symptomatic hypoglycemic reactions before fasting but proved insensitive to the stress of equally severe hypoglycemic episodes after fasting. The findings of this study suggest a possible clinical application. Brittle diabetics, subject to recurrent symptomatic insulin reactions, may possibly benefit from eating ketogenic diets.

Brittle diabetes, also called labile diabetes, is an older term used to describe a person with poorly controlled diabetes due to lack of understanding and motivation to check blood glucose frequently, follow a consistent diet (even if high carb), or, take insulin carefully and consistently. They display frequent life-threatening extremes of both high and low blood sugars with frequent hospitalizations and multiple long-term complications. The authors of the study hypothesized that ketones might prevent the symptoms of hypoglycemia. Areas of current research include administering ketone salts or esters and medium-chain triglycerides (which can be converted to ketones by the liver) as means to increase blood-ketone levels. However, we are not aware of any studies using the ketogenic diet for the same purpose. On a side note, the cause of brittle diabetes is controversial with some people reporting swings in blood sugar even when practices are in place to control blood-sugar extremes. Emotional stress may be involved or there may be a combination of several physical factors involved.

Another study published in 1987 tested the effect of a 72-hour fast on mental alertness after insulin-induced hypoglycemia. Eight normal-weight, healthy males had tests of mental function before and after insulin-induced hypoglycemia after 12 hours and 72 hours of fasting. The authors wrote:

> In conclusion, mental alertness was reduced by moderate hypoglycaemia after an overnight fast while similar hypoglycaemia did not reduce mental alertness after prolonged fasting. This may illustrate a decrease of the glucose dependency of the central nervous system during prolonged fasting.

These studies of protection from the symptoms of hypoglycemia by ketosis in prolonged fasting may or may not be applicable to those in nutritional ketosis since it has not been formally studied.

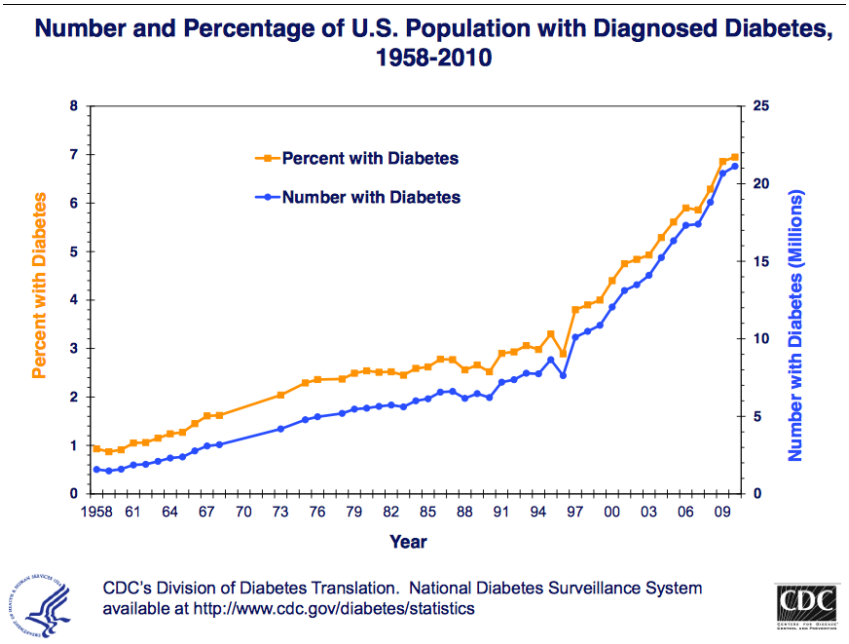
Tech Note 4—Ketogenic Diet Effect on Markers of Inflammation

The ketogenic diet has positive effects on markers of inflammation. Inflammation is thought to be an important component of the initiation and progression of atherosclerosis and CVD, insulin resistance, metabolic syndrome, type 2 diabetes, cancer, and likely many of the diseases of Western civilization. Most clinical laboratories can measure these three inflammatory markers: high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α). Many others have been measured in research studies of the ketogenic diet. The following is from this important study by Cassandra E. Forsythe et al:

> Acute ingestion of carbohydrate clearly induces an increase in reactive oxygen species and activation of pro-inflammatory pathways, and isocaloric high-carbohydrate and high glycemic diets are associated with increased biomarkers of inflammation. In the context of hypocaloric diets, we showed that reducing dietary total and saturated fat only had a small effect on circulating inflammatory markers whereas reducing carbohydrate led to considerably greater reductions in a number of proinflammatory cytokines, chemokines, and adhesion molecules.

Tech Note 5— Why Diabetes Is on the Rise and the Associated Costs

The figure at right, from the Centers for Disease Control website, shows the alarming rise in diabetes prevalence in the United States from 1958 to 2010. According to the International Diabetes Federation 2013 report, "Today, there are 382 million people living with diabetes, but almost half are not aware of it. A further 316 million with impaired glucose tolerance are at high risk of developing diabetes—an alarming number that is set to reach 471 million by 2035." Five percent of those with diabetes have T1DM, 90%-–92% have T2DM, and the remaining 3%–5% have other types of diabetes including cases where



disease, alcohol, drugs, infection, trauma, or surgery has damaged the pancreas. Included in this small group is gestational diabetes, which is diabetes that has was diagnosed during pregnancy with return to a normal metabolic state after delivery.

You may wonder why diabetes and many other chronic diseases are increasing in prevalence at such a rapid pace? We think the carbohydrate hypothesis best explains the current pandemic of obesity and diabetes and explains why heart disease and cancer are the leading causes of death in the United States.

The carbohydrate hypothesis states that the introduction of man-made dietary refined starches (e.g., wheat flour, corn starch, polished rice, cereals) and sugars (e.g., cane and beet sugar, high-fructose corn syrup) to any population causes numerous previously rare chronic diseases including dental caries, appendicitis, peptic-ulcer disease, and, after longer periods of time, obesity, diabetes, cardiovascular disease, and cancer. For the past fifty years, medical scientists have focused their research efforts on testing the lipid-heart hypothesis, which states that dietary saturated fat causes elevated blood cholesterol, which in turn causes heart disease. Unfortunately, the proponents of the lipid-heart hypothesis, beginning with Ancel Keys, PhD, in the early 1950s were so convinced it was correct that Keys, Paul Dudley White, MD, Louis N. Katz, MD, Howard B. Sprague, MD, and Jeremiah Stamler, MD, among others, convinced the American Heart Association in 1960 to promote the low-saturated-fat diet before any clinical trials had shown positive results. Subsequent clinical trials were completed that showed marginal reduction in CVD events or deaths but no reduction in overall deaths. Reports of the results invariably emphasized the positive CVD findings, when what most people wanted to know was, "Will I live a longer and healthier life if I follow the low-fat diet, stop smoking, lower my blood pressure, lose weight, and so on?"

We recommend Gary Taubes's book, *Good Calories, Bad Calories*, for those interested in learning more about this topic. In 1977, the United States Department of Agriculture, under the direction of Senator George McGovern, released the Dietary Goals for Americans detailing a low-saturated-fat, higher-polyunsaturated-fat, high-carbohydrate diet in hopes of decreasing heart disease deaths, despite objections from leading scientists pointing to the lack of evidence for such a widespread recommendation. Since the 1960s, numerous clinical trials have failed to show an improvement in total mortality from implementation of the low-fat diet. Rather, the studies emphasize the small reduction in cardiovascular events (heart attacks) and deaths in some of the trials, and gloss over the total mortality problem. What we have observed since the low-fat, high-carbohydrate dietary recommendation is a threefold increase in obesity and a sevenfold increase in diabetes since 1960. Hopefully, in our lifetimes, the carbohydrate hypothesis will be tested. The purpose in doing clinical trials is to determine the long-term disease outcomes of following a low-carb diet compared to the low-fat diet. In the meantime, we cannot ignore the results of randomized controlled trials showing the effectiveness of a low-carb or ketogenic diet in treating diabetes. Completely removing refined starches and sugars and limiting total

carbohydrates is without question a more effective therapy for diabetes when compared to the low-fat diet.

Diabetes is a costly disease to care for, especially when it is not well controlled, since the majority of the cost is associated with treating the complications of diabetes. Twenty percent of all health care dollars are spent on people with diabetes. Diabetes is the leading cause of blindness, kidney failure, and non-traumatic lower-limb amputations. The leading causes of death for people with diabetes are heart disease and stroke. In fact, at least 65% of people with diabetes die from some form of heart disease or stroke.

Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are thought to be separate diseases with different etiologies, however, both T1DM and T2DM are increasing in prevalence during the same time span beginning in the 1960s and continuing up to today, suggesting that some common environmental factor(s) may be at play. Our nation's current dietary pattern is a very likely candidate for one of these environmental factors.

Tech Note 6— Type 1 Diabetes Mellitus, Autoimmune Conditions, and Diabetic Ketoacidosis

T1DM is an autoimmune disease affecting children and adolescents that results in destruction of the pancreatic β-cells that produce and release insulin in response to the blood-glucose concentration. Approximately 5%–10% of people with diabetes have T1DM. The following autoimmune diseases are more common in people with T1DM than in the general population: celiac disease, gluten sensitivity, pernicious anemia, Addison's disease, and autoimmune thyroid disease.

The causes of autoimmune diseases are not exactly known, nor are the exact environmental and immune factors that result in an autoimmune β-cell attack. In the case of T1DM, there appears to be a mix-up in the immune system's ability to properly distinguish foreign substances such as bacteria, viruses, wheat gluten, and possibly milk protein from normal internal structures like the pancreatic β-cells and insulin itself. Exposure to these foreign substances activates the body's immune system to produce antibodies directed against both insulin and the insulin producing β-cells. Once tagged by the antibodies, other immune cells, including T-cells and macrophages, target and destroy the β-cells. Breast-feeding decreases the risk of a child developing T1DM, which is indirect evidence for the involvement of consuming cow's milk (casein) and infant formula (sugar, vegetable oils) in the development of T1DM. In response to one or more of these environmental antigens, the immune system then mounts an attack against the β-cells and eventually destroys them. This destructive process can proceed quickly or take many years.

Experimental research in modulating the immune system to reduce the anti-β-cell and anti-insulin-antibody formation is ongoing. Relatives of persons with T1DM should be tested for the autoantibodies commonly found in individuals with T1DM. At the time of this writing, this can be done without cost through Type 1 Diabetes TrialNet. Relatives of individuals with T1DM are fifteen times more likely to develop T1DM than the general population. Early diagnosis and treatment of T1DM may limit acute complications and extend long-term endogenous insulin production.

Approximately 50% of the genetic risk for T1DM can be attributed to the human leukocyte antigen (HLA) gene region. The highest risk HLA DR3/4 DQ8 genotype has been shown to be highly associated with β-cell autoimmunity. The first antibodies described in association with the development of T1DM were islet-cell autoantibodies. Subsequently, antibodies to insulin, glutamic acid decarboxylase (GAD65), protein tyrosine phosphatase (IA2 or ICA512), and ZnT8 (zinc transporter 8) have all been defined. Ninety percent or more of persons with new-onset T1DM are found to express one or more types of islet autoantibodies. Islet-cell cytoplasmic autoantibodies (ICA) and GAD65 are the most common, being found in 70% to 80% of new-onset T1DM patients. Insulinoma-associated-2 autoantibodies (IA-2A) are less common, occurring in approximately 60% of T1DM patients at disease onset. In children with new-onset disease, insulin autoantibodies (IAA) are present in about 50%. of patients. However, IAA are uncommon in adults. These antibodies can be present for months and years before and for several months after the diagnosis of T1DM, but tend to decline with time. Only about 10% of individuals who are diagnosed with T1DM have a family history of the disease.

Glucose intolerance develops when about 50% of the β-cells have been destroyed. Symptoms of diabetes develop after destruction of 80%–85% of the β-cells. The first manifestation is glucose intolerance (abnormal increase in blood glucose after a carbohydrate-containing meal or during an oral glucose-tolerance test) and later, fasting hyperglycemia develops, but if the elevation is mild, there may not be any symptoms. Once hyperglycemia becomes persistent, and especially when the blood glucose exceeds 250 mg/dL [13.9 mmol/L], the kidney's ability to reabsorb the filtered glucose is exceeded, and glucose is excreted in the urine. This causes two problems:

First, glucose is a source of energy that is now being excreted unused into the urine. The release of fatty acids from adipose tissue and the inability to store fat, plus the inability to make proteins combined with the impaired ability to transport glucose into cells results in wasting of all tissues with significant weight loss.

Second, the presence of glucose in the urine causes more urine volume to be excreted, called osmotic diuresis, which acts like a potent diuretic. This causes excessive urination (polyuria) that, in turn, stimulates thirst with an increase in fluid intake (polydipsia). It is not uncommon that people with undiagnosed diabetes have cravings for sweet foods like ice cream,

candy, and sweet drinks like fruit juice, cola, or tea. Because insulin is absent, the blood glucose can't be moved into cells for utilization, and the body and brain sense a lack of available glucose despite excess quantities in the bloodstream. The impaired ability to utilize fuels (glucose, fat, and protein) causes fatigue and hunger. Thus, individuals with T1DM usually present with these five symptoms: weight loss, fatigue, hunger, polyuria, and polydipsia. Many other signs and symptoms can occur, depending on how long blood glucose has been elevated. These symptoms include blurred vision, numbness of skin, erectile dysfunction, and unexplained infections.

Diabetic ketoacidosis (DKA) is a serious and potentially life-threatening acute complication of diabetes. It is the initial manifestation of T1DM in 30%–40% of children and 20% of adults. Precipitating factors for DKA include infections, intercurrent illnesses, psychological stress, and poor compliance with insulin therapy. Urinary tract infection, pneumonia, and other infections account for 30%–50% of cases. Although DKA is a life-threatening condition and 2%–5% die despite treatment, the great majority recovery completely if medical attention is sought early.

Tech Note 7— Type 2 Diabetes Mellitus: Refined-Carbohydrate Disease and Insulin Resistance

> In general, numerous weighty opinions favor the importance of sugar in the causation of various symptoms or complications of diabetes … The consumption of sugar is undoubtedly increasing. It is generally recognized that diabetes is increasing, and to a considerable extent, its incidence is greatest among the races and the classes of society that consume most sugar. There is a frequently discussed, still unsettled, question regarding the possible role of sugar in the etiology of diabetes. The general attitude of the medical profession is doubtful or negative as regards statements in words. There are not so many positive open accusations against sugar in the etiology of the disease as there are against it in the etiology of all the complications. But the practice of the medical profession is wholly affirmative. Any patient with even an unimportant reduction of the assimilation-limit for sugar, in the absence of any too-obvious cause, will be advised not to overstep that limit.
>
> Frederick Allen, Studies Concerning Glycosuria and Diabetes, 1913.
> (Credit to Gary Taubes, *Good Calories, Bad Calories*, 2008.)

In 1913, eight years before the discovery of insulin, the medical profession agreed that a patient with any degree of carbohydrate intolerance would be advised not to exceed it. In other words, persons with diabetes mellitus were advised to avoid sweets and starches. Hindu physicians recognized T2DM two thousand years ago as a disease of the rich, as the rich were the ones who could afford to buy and consume the newly imported sugar, flour, and rice from New Guinea. It was formerly called non-insulin-dependent diabetes mellitus. As illustrated

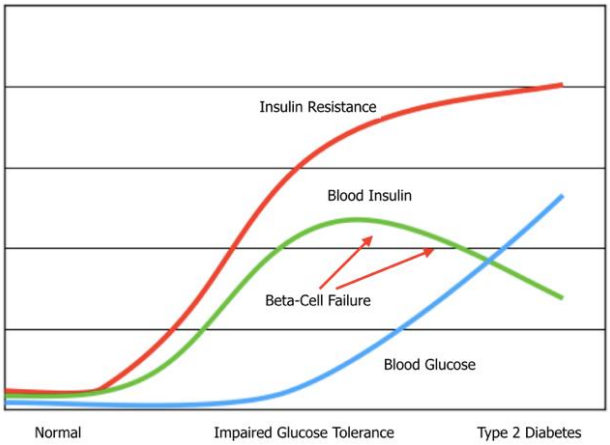
above from *Studies Concerning Glycosuria and Diabetes* by Frederick Allen in 1913, T2DM has been suspected for the past hundred years to be caused by or at least associated with increased consumption of sugar and refined carbohydrates like flour, rice, and fruit preserves.

T2DM is a complex disorder because its exact cause is unknown. The link between the development of type 2 diabetes and obesity with the introduction and increase over time of dietary refined carbohydrates and sugars is hard to ignore. This association does not prove causation, however, there must be a reason for the marked increase in prevalence of both T2DM and obesity in the United States and most of the developed world. George Campbell, MD, a South African diabetologist in the 1950s, studied diabetes in the Zulu people of South Africa over a ten-year period. He never saw a case of diabetes among the rural Zulus. He was the first to observe an incubation period of about twenty years in eighty Zulu diabetics after exposure to excessive sugar consumption, which he defined as 70 lbs/capita/year. By comparison, the United States total sweetener consumption was 152 lbs/capita/year in the year 2000.

Campbell and Peter Cleave published *Diabetes, Coronary Thrombosis and the Saccharine Disease*, 1966, in which they argued that all the chronic diseases of Western societies were manifestations of a single disorder, namely "refined-carbohydrate disease." These Western refined foods (sugar, molasses, fruit preserves, white flour, and white rice) were desirable because they could be transported around the world without spoiling or being consumed by rodents and insects on the way.

Rosalyn Yalow, PhD, and Salomon Berson, MD, described a radioimmunoassay for measuring insulin in the blood of humans in 1959. Using this technique, they were able to measure blood-insulin levels in adults with diabetes and found, for the first time, that individuals with T2DM had elevated blood-insulin levels (hyperinsulinemia), certainly an unexpected finding since until that time it was assumed that all diabetics had reduced insulin levels. It was the finding of elevated insulin levels in T2DM that led to the realization that the primary defect in T2DM is insulin resistance. Hyperglycemia in the fasting state is directly related to increased hepatic-glucose production due to hepatic insulin resistance, and insulin resistance is a state of carbohydrate intolerance.

In the postprandial state (after a meal), further hyperglycemia results from the combination of insufficient suppression of hepatic-glucose output and defective insulin-stimulated glucose uptake in target tissues, particularly skeletal muscle due to insulin resistance of the muscle. After years of T2DM, abnormal islet-cell function becomes a key and requisite feature of T2DM, as the



pancreas is no longer able to secrete enough insulin to keep pace with insulin resistance. In early disease stages, insulin production is normal or increased in absolute terms, but disproportionately low for the degree of insulin resistance, which is typically increased as shown in figure above.

In T2DM, the ability of the pancreatic β-cells to release adequate insulin in phase with rising blood glucose is profoundly compromised. This functional β-cell failure is the main quantitative determinant of hyperglycemia and progresses over time. In addition, in T2DM pancreatic alpha cells secrete excessive glucagon, further promoting hepatic-glucose production. Importantly, β-cell dysfunction is not necessarily irreversible. Enhancing insulin action by reducing insulin resistance relieves the demand on β-cells. Insulin resistance in target tissues (liver, muscle, adipose tissue, myocardium) is a prominent feature in most individuals with T2DM, especially the obese. This results in both glucose underutilization and overproduction.

Interestingly, not all insulin-responsive cells become resistant to the same extent. Skeletal muscle appears to develop insulin resistance before adipose or hepatic tissue. The ability to convert blood glucose to fat in the adipose tissue temporarily ameliorates glucose intolerance. In other words, becoming obese can actually prevent or slow the development of diabetes. Of course, becoming obese is not a solution to glucose intolerance, but it does explain the close connection between obesity and T2DM and has been termed "diabesity." Blood fatty acids increase in diabetes and in the milieu of hyperinsulinemia promotes fatty acid deposition in liver and adipose tissue resulting in non-alcoholic fatty liver disease and obesity.

One serious acute complication of T2DM is called hyperglycemic hyperosmolar syndrome (HHS). HHS is the initial manifestation of diabetes in 7%–17% of patients. Infection is the major precipitating factor, occurring in 30%–60% of patients. Urinary-tract infection and pneumonia are the most common infections that precipitate HHS. In many instances, an acute illness such as a cerebrovascular accident or myocardial infarction provokes the release of counterregulatory hormones, including glucagon, cortisol, epinephrine, and growth hormone, which stimulate overproduction of glucose, resulting in hyperglycemia. Certain medications that precipitate diabetic ketoacidosis may also precipitate HHS, including glucocorticoids, thiazide diuretics, dilantin, and beta-blockers. The mortality rate for HHS is about 15% due to the seriousness of the precipitating cause rather than the metabolic disturbance (i.e. hyperglycemia).

Tech Note 8—About Glucagon and Amylin

Glucagon is a hormone secreted by pancreatic alpha cells. Glucagon opposes many of the actions of insulin. It stimulates glycogenolysis (the breakdown of glycogen to glucose), gluconeogenesis (the production of glucose from glycerol and amino acids), fatty acid oxidation (burning fatty acids), and ketogenesis. Glucagon secretion by the pancreatic alpha cells is normally stimulated by hypoglycemia in the milieu of reduced insulin secretion by functioning beta-cells. In insulin-dependent diabetes, hyperinsulinemic hypoglycemia inhibits glucagon

secretion and therefore blocks the normal mechanism by which glucagon increases blood glucose. Glucagon is also available as an injectable medication to rescue the impaired diabetic having a severe hypoglycemic episode.

Amylin is another hormone secreted by the β-cells of the pancreas. Its secretion is stimulated by glucose, and it is co-secreted with insulin in a ratio of 100:1. Amylin slows the rate of appearance of glucose in the blood after eating by slowing down gastric emptying and inhibiting digestive secretions including gastric acid, pancreatic enzymes, and bile. It also inhibits appetite resulting in reduction of food intake as well as inhibiting glucagon secretion. A synthetic analog of amylin, pramlintide (brand name Symlin), is available by injection for the treatment of T1DM and T2DM. (See Chapter 9 in *The Ketogenic Diet for Type 1 Diabetes*).

Tech Note 9—Adipose Tissue Fatty Acids and Trans Fats

Fat is stored in our body in cells called adipocytes. The fat stored under the skin is called subcutaneous fat and is usually not harmful to our health. Fat stored in and around organs is called visceral or abdominal fat, and is usually associated with T2DM, insulin resistance, and metabolic syndrome. (Picture the typical beer belly and you get the idea.)

The chemical form of fat in the body is called triglyceride, and it's composed of a glycerol molecule bound to three fatty acids. Triglycerides are a very efficient form of energy storage compared to glucose or glycogen. Fat yields 9 kcal per gram when burned, but glycogen, when stored in muscle or liver, must be accompanied by water, so it yields only 1–2 kcal per gram when burned. This explains why fat is our preferred form of energy storage. In fact, a lean body stores about fifty-five times more calories in the form of fat than glucose.

Fatty acids are categorized by the number of carbon molecules: short chains have 3–6 carbons, medium chains have 8–12 carbons, and long chains have 14–24 carbons. Fatty acids are also categorized by their degree of saturation. The degree of saturation indicates the presence or absence of double bonds between the carbon atoms. Saturated fatty acids (SFA) have no double bonds, monounsaturated fatty acids (MUFA) have one double bond, and polyunsaturated fatty acids (PUFA) have two or more double bonds. The term unsaturated fatty acid refers to fatty acids with one or more double bonds and, thus, includes both MUFA and PUFA.

Most fats found in the diet are mixtures of SFA, MUFA, and PUFA, each of varying carbon molecule lengths. In general, fats composed of more SFA have higher melting points, and those composed of more PUFA have lower melting points. That's why at room temperature lard is a solid but olive oil is a liquid. The body takes advantage of this property and can synthesize SFA, MUFA, and PUFA as needed depending on the environmental temperature. After all, you wouldn't want your body fat to solidify in cold weather!

SFA and MUFA are, for the most, part fatty acids that are burned (oxidized) for energy purposes, particularly when one is fat-adapted while consuming a ketogenic diet. Fat in the diet is the best source of energy and does not create metabolic derangements that occur when carbohydrates are the primary energy source.

Our bodies can synthesize almost all fatty acids except for two. These are called essential fatty acids. The parent molecules are linoleic acid (an omega-6 fatty acid) and alpha-linolenic acid (an omega-3 fatty acid). Both types of essential fatty acids can be metabolized in pathways that produce prostaglandins, physiologically active compounds that can have diverse hormone-like effects. The products of alpha-linolenic acid such as DHA and EPA are important for brain and heart health.

Trans Fat (TFA)

Trans fatty acids are hydrogenated or partially hydrogenated "vegetable" oils like soybean, cottonseed, and others. Fatty acids in these oils are mainly PUFA and are susceptible to spoilage on a grocery store shelf due to the more chemically reactive double bonds. The process of adding hydrogen (hydrogenation) to the double bonds of a MUFA or PUFA is not specific as to its orientation. Thus, one of the natural "cis" chemical bonds is replaced by an unnatural and unhealthy trans fatty acid bond.

Vegetable oils were originally introduced by the US food industry as a cheap substitute for animal fats like tallow and lard. In 1961, the American Heart Association (AHA) officially endorsed a low-fat diet recommending that we replace saturated fat with polyunsaturated and hydrogenated vegetable shortenings. This was done at the urging of AHA board members Ancel Keys and Jeremiah Stamler. The US food industry capitalized on this opportunity by creating more processed food products that utilized vegetable fats.

> In the 1990s, both the Food and Drug Administration (FDA) and the US processed-food industry became aware of the harmful effects of TFA. In 2003, the FDA required labeling of foods with TFA content, however, it provided this stipulation: *"If a serving contains less than 0.5 gram, the content, when declared, must be expressed as 0 g."*

Thus, by making the serving size small, significant amounts of TFA could be consumed by the unsuspecting consumer. The fast-food and processed-food industries have been reducing trans fats in their offerings, and the FDA is on the verge of completely eliminating them from the food supply. Since food industries are still operating under the misconception that naturally sourced saturated fats are undesirable, they are searching for substitutes that use vegetable oils, and new choices will likely be introduced to the food supply without adequate testing, just as in the case of trans fats. For this and other reasons, avoiding fast foods and processed foods is the safest bet.

Tech Note 10—Harmful Effects of Excess Sugar and Fructose Consumption

Fructose is a monosaccharide found naturally in fruit. The amount of fructose in fruit crops has increased as they have been bred to be sweeter. The largest increase in fructose consumed in Western societies comes not from fruit but from sucrose (table sugar from cane sugar or beet sugar) and high-fructose corn syrup (HFCS).

The process of creating HFCS was invented in Japan in 1965 and was introduced to the American market in the mid to late 1970s. HFCS is significantly cheaper to produce compared with cane or beet sugar and was quickly adopted by the processed-food and soft-drink industries. The US government sweetens the deal by subsidizing corn production. Corn is now the most heavily subsidized crop in the United States, with millions of dollars being paid out to farmers to continue growing corn, even when they lose money doing so.

HFCS can be made in any ratio of fructose to glucose, but the most commonly used formulation is 55% fructose and 42% glucose. This ratio is chosen because it has the same degree of sweetness as sucrose, which is 50% fructose and 50% glucose. Keep in mind that refined sugar and pure fructose have absolutely no nutrients, no vitamins, no antioxidants, no electrolytes, and no minerals. And while sucrose, or white sugar, is often referred to as "empty calories," its fructose component is metabolically much worse.

Fructose is metabolized differently than glucose. It is rapidly absorbed from the intestine and does not directly stimulate blood sugar or insulin the way glucose does. This is because rather than entering the whole body's blood supply, fructose is sent directly to the liver, the primary organ capable of metabolizing it. Hence, the reduced effect of fructose on blood sugar and insulin levels comes at the expense of the liver. It was this peculiarity of fructose that led the American Diabetes Association (ADA) to advocate its use as a sweetener for those with diabetes based on studies like these. This is currently what the American Diabetes Association has to say about including sugar in the diet of a person with diabetes:

> Now experts agree that you can substitute small amounts of sugar for other carbohydrate-containing foods into your meal plan and still keep your blood-glucose levels on track. In the past, people with diabetes were told to completely avoid sugar.

When fructose is ingested in significant amounts in the diet during short-term studies, there are several adverse effects that develop in susceptible people.

- Overproduction of uric acid from fructose consumption leads to gout and hypertension.
- Overproduction of saturated fatty acids (SFA) leads to dyslipidemia characterized by increased triglycerides, very low density lipoprotein (VLDL), and small, dense low-

density lipoprotein particles (sdLDL), and decreased high-density lipoprotein (HDL), all of which are known to increase the risk of developing cardiovascular disease (CVD), including heart attack and stroke.

- An increase in insulin resistance and hyperinsulinemia that can lead to metabolic syndrome and T2DM.
- An increase in systemic inflammation, which is suspected to be the initiating event in development of CVD and many other disease states.
- Reduction in leptin levels, development of leptin resistance, stimulation of appetite with subsequent weight gain, and obesity.
- An increase in non-alcoholic fatty-liver disease (NAFLD), which can lead to inflammation and swelling (steatohepatitis) and eventually cirrhosis and liver failure, need for liver transplantation, or even death.

This is the bottom line: Both sugar (sucrose and sugar by any other name) and fructose in refined form or in significant quantities can cause terrible metabolic damage, particularly for persons with diabetes. We recommend that these foods be avoided as much as possible.

Tech Note 11— Hemoglobin A1c (HbA1c): Only a Rough Indicator of Average Blood Glucose

In this study based on data from The Diabetes Control and Complications Trial (DCCT), 1,439 patients had regular glucose measurements seven times per day that could be compared with their HbA1c. However, in a graph from the study, you can see the regression equation was glucose (mg/dL) = 35.6 * HbA1c – 77.3, with $R^2 = 0.67$, which is not a good correlation. This means that 67% of the variability among the observed values of estimated average glucose (mg/dL) is explained by the linear relationship between estimated average glucose (mg/dL) and HbA1c (%). Conversely that means 33% of the variability is due to several factors including an inherent or genetic difference in glycation, a difference in red blood cell life span, age, race, sex, and other influences. From the data in Figure 1 of the study, diabetics with mean plasma glucose of 214 mg/dL (11.9 mmol/L) had HbA1c ranging from 6.2% to 12.4%, while diabetics with mean plasma glucose of 115 mg/dL (6.4 mmol/L) had HbA1c ranging from 5.4% to 8.6%.

It should be clear that HbA1c for a given individual is only a rough indicator of average blood glucose or glycemic control.

Another study that determined a linear regression equation in both normal controls and patients with T1DM and T2DM between their average blood-glucose values and their HbA1c results. Each subject obtained approximately 2,700 glucose values during the three-month study, and they were correlated with the HbA1c. Figure 1 from the study shows the average glucose (mg/dL) as a function of HbA1c. Subjects with mean plasma glucose of 84 mg/dL (4.6 mmol/L)

had HbA1c ranging from 4.6% to 5.5%. The regression equation derived in this study is as follows: average glucose (mg/dL) = 28.7 * A1C 46.7 with an $R^2 = 0.84$, $P < 0.0001$. This is a better correlation as compared with the previous study.

Of note, the mean ± SD (standard deviation) HbA1c of the eighty non-diabetic subjects was 5.2 ± 0.3%. This shows that HbA1c varies from one person to another despite the same average blood glucose. That means HbA1c is not an exact surrogate for average blood glucose, and HbA1c cannot be exactly translated to an average blood glucose using the linear regression model. Some laboratories, when reporting HbA1c on your lab results, also report an estimated average blood glucose using one of these regression equations.

If you are interested in exploring some of the reasons why HbA1c is not solely determined by average blood glucose, we refer you to the following: study, study, study, study, study, study.
