Potential Applications of the Ketogenic Diet in Disorders Other Than Epilepsy

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1. INTRODUCTION

Starvation is associated with many drastic or extreme changes in energy metabolism and hormonal levels. Thus, it is not surprising that mimicking this process with the ketogenic diet (KD) may yield a wide range of effects, some potentially deleterious, others having benefits. Use of the KD in intractable epilepsy has increased the comfort level and general experience with the diet and is opening doors to potential new applications. None of these applications is as well studied or as well established as the anticonvulsant potential of the KD. Currently, all the applications discussed in this chapter are highly experimental.

2. FACILITATED GLUCOSE TRANSPORTER PROTEIN TYPE I DEFICIENCY

Under normal conditions, glucose is the preferred brain fuel source. However, glucose is polar and cannot diffuse unaided across the blood–brain barrier; it must be transported across the membrane through a special transporter. In a family of glucose transporters, a single protein transports glucose across the blood–brain barrier—the facilitated glucose transporter type I protein (GLUT1) (1). In 1991 a rare genetic disorder was described in which infants present with seizures, developmental delay, acquired microcephaly, hypotonia, and motor problems (2). Importantly, there is low cerebrospinal fluid glucose (hypoglycorrachia) in the setting of normal plasma glucose (2). Other than a wide range of infections and lupus erythematosus, there are no other causes of isolated hypoglycorrachia (1). The cause of this disease is absence of GLUT1 (3–6).

The KD has been recommended as the major treatment for GLUT1 deficiency. Patients with this disorder achieve prompt control of seizures once placed on the diet (4,7). However, other symptoms of GLUT1 deficiency, such as cognitive delay, do not appear to be affected by the KD (4,7). The ketogenic diet is believed to work by converting brain energy metabolism from being glucose based to being based on ketone bodies.
3. MANIC–DEPRESSIVE ILLNESS

Bipolar, or manic–depressive, illness has been likened to a “slow seizure” (8), and indeed all the accepted mood-stabilizing medications for this disorder either are antiepileptic drugs (valproate, carbamazepine, lamotrigine) (9) or have a seizure-reducing potential (lithium) (10,11). Similarly, electroconvulsive therapy (ECT) and vagus nerve stimulation (VNS), both of which increase the seizure threshold (12,13), are useful in treating bipolar illness (14–16). Thus, anticonvulsant activity appears to be related to mood-stabilizing activity. However, anticonvulsant activity alone is insufficient. The anticonvulsant gabapentin actually worsens manic symptoms (17).

Excessive intracellular sodium accumulation has been linked with both mania and depression (18–20). One of the commonalities of effective mood-stabilizing agents appears to be their ability to inhibit sodium entry or accumulation in an activity-dependent manner (9).

The KD induces a mild extracellular acidosis, at least in the periphery. The excess of extracellular hydrogen ions would be expected to reduce intracellular sodium concentration through the sodium–proton counterexchange system (21,22). Additionally, acidosis has been associated with a reduction of neuronal excitability and activity of excitatory neurotransmitters (23–26). However, despite such conjecture, there is no direct evidence that brain pH changes are induced by the KD (27,28).

Finally, mania and bipolar depression have been associated with both global and focal reductions in glucose utilization (29–33). The KD appears to increase available energy in the form of adenosine triphosphate (34).

These observations have been proposed to suggest a clinical utility of the KD in the management of bipolar illness (35). However, one case report of a treatment-resistant bipolar woman placed on the diet for a month (but never achieving ketosis) was negative (36).

4. RISKS FOR OBESITY, DIABETES, AND CARDIOVASCULAR DISEASE

4.1. Obesity

Obesity is a major public health problem in the United States, with an increasing prevalence in both adults (37,38) and children (39). Obesity increases the risk of morbidity and mortality from associated diseases such as diabetes, hypertension, coronary heart disease, and cancer (40–42). Diets have been the traditional approach to dealing with excessive weight. Robert Atkins (43) popularized the use of the ketogenic diet to deal with weight gain. This type of ketogenic diet is a low-carbohydrate but high-protein formulation and consequently is fundamentally different from diets used for seizure control.

The Atkins diet is based on the premise that control of insulin is essential for weight loss and associated beneficial effects in reduction of diabetes and cardiovascular risk. By reducing carbohydrate intake to a negligible level, the diet attempts to eliminate insulin fluctuations that might occur after a typical meal. It is important to note that while this diet does not limit protein intake, many amino acids can be incorporated into the glycolysis pathways and thus can influence insulin secretion. However, this is not true for fatty acids. Consequently, a low-protein ketogenic diet is more likely to achieve the hypothesized goals of the Atkins diet than the widely used Atkins-type diet itself.