



Danger in the Pipeline for the Ketogenic Diet?

The Impact of the Ketogenic Diet on Arterial Morphology and Endothelial Function in Children and Young Adults With Epilepsy: A Case-Control Study.

Coppola G, Natale F, Torino A, Capasso R, D'Aniello A, Pironti E, Calabro R, Verrotti A. *Seizure* 2013;23:260–265.

PURPOSE: The present study aimed to assess the impact of the ketogenic diet on arterial morphology and endothelial function of the big vessels of the neck and on cardiac diastolic function, in a cohort of epileptic children and young adults treated with the ketogenic diet. **METHODS:** Patients were recruited based on the following inclusion criteria: (1) patients who were or had been on the ketogenic diet for a time period of at least six months. Each patient underwent measurement of carotid intima media thickness, carotid artery stiffness, echocardiography, and diastolic function assessment. Patients with drug resistant epilepsy, matched for number, age and sex and never treated with ketogenic diet, were recruited as controls. **RESULTS:** The population study was composed by 43 epilepsy patients (23 males), aged between 19 months and 31 years (mean 11 years). Twenty-three patients were or had been treated with ketogenic diet, and 20 had never been on it (control group). Subjects treated with the ketogenic diet had higher arterial stiffness parameters, including AIx and b-index and higher serum levels of cholesterol or triglycerides compared to those who had never been on the diet (control group) ($p < 0.001$). **CONCLUSIONS:** Arterial stiffness is increased in children and young adults treated with the ketogenic diet, before the increase of the intima media thickness. This supports that arterial stiffness is an early marker of vascular damage.

Effects of Ketogenic Diet on Vascular Function.

Kapetanakis M, Liuba P, Odermarsky M, Lundgren J, Hallbook T. *Eur J Paediatr Neurol* 2014;18:489–494.

BACKGROUND: Ketogenic diet is a well-established treatment in children with difficult to treat epilepsy. Very little is known about the long-term effects on vascular atherogenic and biochemical processes of this high-fat and low carbohydrate and protein diet. **METHODS:** We evaluated 26 children after one year and 13 children after two years of ketogenic diet. High resolution ultrasound-based assessment was used for carotid artery intima-media thickness (cIMT), carotid artery distensibility and carotid artery compliance. Blood lipids including high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol, (LDL-C), total cholesterol (TC), apolipoprotein A (apoA), apolipoprotein B (apoB) and high-sensitivity C-reactive protein (hsCRP) were analysed. **RESULTS:** A gradual decrease in carotid distensibility and an increase in LDL-C, apoB and the TC:LDL-C and LDL-C:HDL-C ratios were seen at three and 12 months of KD-treatment. These differences were not significant at 24 months. cIMT, BMI and hsCRP did not show any significant changes. **CONCLUSIONS:** The initial alterations in lipids, apoB and arterial function observed within the first year of KD-treatment appear to be reversible and not significant after 24 months of treatment.

Commentary

The popularity of ketogenic diets for children and adults with epilepsy in the modern era is at an all-time high. Effective in approximately half of those who try them, it is difficult to argue dietary therapy should be offered earlier in the course of refractory epilepsy. The recent emergence of alternative variants of the diet, computer programs for recipe building, and

creative dietitians and parents have made dietary therapies easier and more palatable than ever before (1, 2).

Unfortunately, these medical treatments have very real side effects. Several are more benign and often treatable, including constipation, hypoglycemia, and gastroesophageal reflux (3). However, others such as kidney stones, growth disturbance, and acidosis can be potentially more problematic (3). Many parents and patients are particularly concerned about the effects of hypercholesterolemia, especially in the long term (4). It is not unusual for a family to ask: "will my child have a heart attack from this diet?" Preliminary data suggests that although serum lipid values increase in the first several months on the ketogenic diet, they decline to normal values



by 12 months and remain normal on the diet for many years (4, 5). Long-term follow-up of children off the ketogenic diet (now often young adults) has not demonstrated any obvious cardiovascular issues, yet this is hardly proof that no subtle negative impact potentially exists (6).

It is in light of this uncertainty that these two articles were recently published—interestingly, just 4 months apart—and both raise similar concerns. Each study analyzed the short-term effects of the ketogenic diet on vascular function, as measured noninvasively by carotid artery ultrasound. Dr. Kapetanakis and his team from Sweden, along with Dr. Coppola and his team from Italy, came to quite similar conclusions: the ketogenic diet appears to cause stiffening of the carotid artery wall, but this change appears to both decline over time and be reversible.

In the first study by Kapetanakis, 43 children ages 2–15 years were started on dietary therapy; 84% on a standard 4:1 ratio ketogenic diet. They all had carotid ultrasounds at baseline, 3, 12, and 24 months, along with fasting serum lipid profiles. The carotid arteries were less “distensible” at 3 and 12 months but returned to normal by 24 months, and there was no difference in the intimal wall thickness. Although one might suspect the distensibility would be correlated to total cholesterol or triglycerides, there was no statistical relationship identified.

Dr. Coppola’s team approached this issue slightly differently, by comparing 23 children and adults exposed to the ketogenic diet to 20 control children with epilepsy never treated with dietary therapy. Unlike the study from Sweden, this study examined only carotid artery function at one time point compared to longitudinally. Results were highly similar: those patients treated with dietary therapy had decreased carotid distensibility but no change in the actual artery thickness. In addition, those who had stopped the ketogenic diet in the more distant past (defined as >3 years) had a return to normal values. Some markers of carotid distensibility did “weakly” correlate with total cholesterol and triglyceride elevations, but no other obvious predictors were found.

Both research groups appropriately highlighted in their discussion sections that the potential risks of dietary therapy must always be balanced with the potential value for seizure control. None of the children or adults in these studies had any reported clinical symptoms, and many were doing well from a seizure perspective. However, this new information does raise concerns about negative effects of dietary therapy on blood vessel functioning, even if only in the short term. There may be some value in aggressive management of hypercholesterolemia should this truly be a risk factor for this abnormality (7). The use of statin medications in patients on ketogenic diets has yet to be explored. Providing diets with less fat, such as the modified Atkins diet and low glycemic index treatment, may

have less of an impact on lipids (1, 2). Lastly, even though the study from Sweden suggested that carotid stiffness may improve after 12 months of dietary therapy, it would seem logical, based on the Italian results, to consider diet discontinuation at 1–2 years if medically indicated to allow blood vessels to normalize. For some conditions such as infantile spasms, 6 months only of dietary therapy may be sufficient (8).

Obviously, it is too early to sound any alarm on the effects of diets on blood vessels. However, it serves to highlight the need for more studies examining potential silent adverse effects. Selenium deficiency in ketogenic diet patients may cause prolonged QT intervals and lead to cardiomyopathy (9). Vitamin D deficiency and acidosis can affect bone mineral density and eventually lead to fractures (10). Cardiovascular disease should be no exception, and as more adults start dietary therapies, there will likely be more studies such as this in the “pipeline.”

by Eric Kossoff, MD

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