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.

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


**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 Ax 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.


**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.
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

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
Section #1 Identifying Information

1. Today's Date: October 21, 2013

2. First Name Eric   Last Name Kossoff Degree MD

3. Are you the Main Assigned Author? ☒ Yes   ☐ No

If no, enter your name as co-author:

4. Manuscript/Article Title: Danger in the pipeline for the ketogenic diet?

5. Journal Issue you are submitting for: 14.6

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

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* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.
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* This means money that your institution received for your efforts.
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