Seizure 23 (2014) 260–265

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The impact of the ketogenic diet on arterial morphology and endothelial function in children and young adults with epilepsy: A case–control study

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ARTICLE INFO

Article history:
Received 14 May 2013
Received in revised form 3 December 2013
Accepted 4 December 2013

Keywords:
Ketogenic diet
Arterial morphology
Endothelial function
Carotid artery stiffness

ABSTRACT

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 β-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.
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1. Introduction

The ketogenic diet for the treatment of drug resistant epilepsy is composed of a high amount of lipids, an adequate intake of proteins and a very low percentage of carbohydrates.[1] It is well recognized that the ketogenic diet frequently leads to a wide range of adverse side effects, both early within the first days and late by the end of the first month and on.[2,3]

Among early and/or late adverse effects there is dyslipidemia, consisting of increased triglycerides and/or cholesterol,[3,4] which raises major concerns regarding the potential negative effects on macrocirculation, including the development of atheromasic plates, abnormalities in the vascular parietal elasticity mainly in the heart and brain, and a disorder of intraparenchymal microvascular resistance in the kidney.

Therefore, a relationship between the length of the ketogenic diet and the potential development of such cardiac and vascular adverse events, can be reasonably assumed. Studies on cardiovascular adverse effects arising major concerns upon the use of the ketogenic diet, are so far lacking. Recently, Patel et al.,[5] in a retrospective study on the long-term effects after the ketogenic diet had been discontinued in about one hundred patients, reported that lipids were normal at follow-up, despite most being abnormal while on the ketogenic diet.

On the other hand, Raitakari et al.,[6] found a positive relationship between the exposure to cardiovascular risk in pediatric age between 12 and 18 years, and an increased thickness of the intima and media layers of arterial vessels in adult age. These authors state indeed that exposure to cardiovascular risk factors early in life may induce changes in arteries that contribute to the development of atherosclerosis.

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http://dx.doi.org/10.1016/j.seizure.2013.12.002

The present study aimed to assess the impact of the ketogenic diet on arterial morphology, specifically the development of atheromasic plates, on endothelial function of the big vessels of the neck as well as on cardiac diastolic function, in a cohort of children and young adults who were or had been fed the ketogenic diet.

2. Methods

All patients were followed as outpatients in the Epilepsy Unit of the Clinic of Child Neuropsychiatry of the Second University of Naples, and were recruited in the study in a time period comprised between January 2008 and October 2010.

Inclusion criteria were the following: (1) patients who were or had been on a classical (fat/protein + carbohydrate ratio 4:1) ketogenic diet for a time period of at least six months. This time interval was considered as the minimum treatment period to assess clinical responsiveness to the ketogenic diet. Exclusion criteria were: (1) patients with heart failure, systemic hypertension, diabetes mellitus, thyroid or parathyroid dysfunction; (2) poor compliance from parents/caregivers to participate in the study or from patients to undergo all examinations as requested by the study schedule. Patients with drug resistant epilepsy, matching for number, age and sex and never treated with ketogenic diet, were recruited as controls. The study protocol was approved by the local ethics committee; written informed consent was obtained by parents and, when possible, by patients.

Each patient underwent the following examinations on admission: (1) a blood sample was taken to evaluate white and red cell blood count, alanine and aspartate transaminases, gamma-glutamyltransferase, serum calcium, sodium and potassium, urea, serum creatinine, blood glucose, total and free acylcarnitine, total serum proteins, serum iron, and lipid profile (total cholesterol, high-density (HDL) and low-density (LDL) lipoprotein-cholesterol and triglycerides).

Age at study entry, length of diet treatment, number and type of anticonvulsant drugs, blood levels of each anticonvulsant drug, familial dyslipidemic risk factors, and maximal blood values of lipid profile throughout the diet, were the other parameters considered in all patients.

Serum levels of total cholesterol, triglycerides and lipoprotein fractions were considered in normal, borderline or high range, following Daniels and Greer,[7] In all subjects, anthropometric parameters (height and weight) were measured and body mass index (BMI) was calculated. Furthermore, each patient underwent on admission blood pressure assessment, measurement of carotid intima thickness (IMT), echotracking of the common carotid for the assessment of arterial stiffness, echocardiography and diastolic function assessment by means of standard methodology. Blood pressure was measured after a 5-min rest in supine position, by a digital oscillometric device (Omron model 705 IT; Omron Corporation – Healthcare, Kyoto, Japan) validated for use in children and adolescents. Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as the mean of three blood pressure measurements at rest. Pulse pressure (PP) was calculated as (SBP–DBP). Subjects with abnormal blood pressure values were consequently excluded from the study.

2.1. Measurement of carotid IMT

Measurement of carotid intima media thickness (IMT) and arterial stiffness high-resolution B-mode ultrasound images (Aloka alfa 10; Tokyo, Japan) with a 7–10 MHz linear array transducer were used to measure IMT. Carotid arteries were examined bilaterally in the areas of common carotid (1 cm proximal to the carotid bulb), carotid bifurcation (1 cm proximal to the flow divider) and internal carotid artery (1 cm distal to the flow divider). All measurements were determined manually on the far wall in longitudinal and transverse planes with anterior, lateral and posterior approaches.[8] Two different readings were acquired for each projection. From B-mode images, single video frames were selected for IMT measurements. Intima media thickness (IMT) was defined as the distance between lumen/intima and media/adventitia interfaces. The mean value was calculated for each parameter. Two independent readers, who were blinded with respect to patients' clinical and laboratory profile, made the measurements. The inter- and intra-observer variability was assessed for each measurement from all subjects participating in the study. The inter-observer variability of IMT measurements, evaluated by comparing the values obtained by two sets of scans performed by each reader, was 0 ± 03 mm (coefficient of variation $3 \pm 59\%$). The intra-observer variability was 0 ± 02 mm (coefficient of variation $2 \pm 15\%$).

2.2. Carotid artery stiffness

Subjects were studied after resting supine for 15 min in a temperature-controlled environment. The stiffness parameter β was calculated according to the formula: $\beta = \ln(Ps/Pd)/(Ds - Dd/Dd)$; Ep (pressure-strain elasticity modulus): $Ep = (Ps - Pd)/[(Ds - Dd)/Dd]$; AC (arterial compliance) ($AC = \pi(Ds \times Ds - Dd \times Dd)/[4(Ps - Pd)]$) where Ps and Pd are systolic and diastolic blood pressure in the brachial artery measured by an automated sphygmomanometer (Omron 705CP, Tokyo, Japan), and Ds and Dd are the maximal and minimal diameters of the right common carotid artery measured by e-tracking (ultrasonic high resolution wall tracking Aloka 10, Tokyo, Japan; 7.5 MHz linear array probe). Adjustable gates were positioned at the junctions of the intima and media, and diameter was calculated and displayed in real time as the difference between the displacement waveforms of the anterior and posterior walls. Measurements were taken as a mean of five beats; b was log transformed for analyses, because its distribution was skew. Arterial stiffness was automatically assessed at the common carotid artery 2 cm before the bifurcation by Echo-tracking software (ALOKA Prosound alpha 10 ultrasound machine, Mitakashi, Tokyo, Japan). Echo-tracking system implemented in the ultrasound machine allows accurate measurements of carotid diameter changes, based on radio frequencies (RF) signals, able to detect variations of the arterial diameters with a strictness of 0 ± 01 mm. Arterial pressure waveforms were derived noninvasively by echo tracking from change in carotid diameter over time, and calibrated using SBP and DBP (the software used needs to insert SBP and DBP values in the system of the machine for the calibration). Two sliders (tracking gates) were positioned on a 2D ultrasound image of the common carotid artery, at the front and back walls of the adventitia of the vessel. All acquisitions were synchronized with the electrocardiographic (ECG) signal. The main indices of arterial stiffness b-index, arterial compliance (AC), AIx, local PWV, and Young elastic modulus (Ep) were automatically calculated, as a mean of five beats, according to established formulas. Regarding the AIx (Augmentation Index), it must be noted that the arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. Waves are reflected from the periphery, mainly at branch points or sites of impedance mismatch. In elastic vessels, reflected wave tends to arrive back at the aortic root during diastole. In presence of stiff arteries, the reflected wave arrives back at the central arteries earlier, adding to the forward wave and augmenting the systolic pressure. This phenomenon can be quantified through the Augmentation Index (AIx) defined as the difference between the second and first systolic peaks expressed as a percentage of the pulse pressure.[9]

Arterial compliance (AC) is defined as the change in arterial blood volume for a given change in arterial blood pressure (BP). By simultaneously measuring the diameter of a blood vessel and the

BP in that area, compliance can be directly calculated. Diameters can be measured using ultrasound or magnetic resonance imaging.

The so-called β-index is derived from a logarithmic transformation of the curvilinear relationship between pressure and diameter, as measured using an oscillometer arm cuff and an ultrasound probe. Beta-index is a clinical parameter in what is supposed to be independent of blood pressure.

2.3. Echocardiography

The M-mode echocardiogram was performed by using 3.5 MHz phased array, placed on the III–IV left intercostal space along the parasternal line, with patients supine, in left lateral decubitus and the head of the bed kept at 30°. The end-diastolic measurements of left ventricular internal dimension, left interventricular septum and posterior wall thickness at the QRS peak were measured by using the Penn convention. The left ventricular mass was calculated according to the Devereux formula. Complete 2-dimensional echocardiograms were obtained during normal respiration.

2.4. Diastolic function assessment

The pulsed Doppler sample volume was placed at the mitral valve tips and 5–10 cardiac cycles were recorded from the apical window at a velocity of 100 mm/s. The following parameters of left ventricular diastolic function were determined: early diastolic (E) and late atrial (A) peak velocities (m/s) and their ratio, and E-wave deceleration time (ms). The Doppler tissue imaging (DTI) program was set to the pulsed-wave Doppler mode. Filters were set to exclude high frequency signals, and the Nyquist limit was adjusted to a velocity range of 15–20 cm/s, gains were minimized to obtain a clear tissue signal with minimal background noise. All DTI recordings were obtained during normal respiration. A 5-mm sample volume was placed at the apical 4-chamber view on the lateral corner of the mitral annulus. The resulting velocities were recorded for 5–10 cardiac cycles at a sweep speed of 100 mm/s. The following measurements were determined as diastolic indexes: myocardial early (Em) and atrial (Am) peak velocities (m/s) and their ratio.[10] All echocardiographic and ultrasonographic examinations were recorded on videotape for later playback and analysis and performed by the same experienced physician. For all ultrasonographic examinations, we used the Aloka alfa-10 (Aloka Co., Ltd, Tokyo, Japan) equipped with a variable-frequency phased-array transducer and DTI capabilities.

2.5. Statistical analysis

Continuous variables are expressed as means ± SD and discrete variables as counts and percentages. All statistical analyses were performed by using GB-STAT version 6.50 (Dynamic Microsystems, Inc, Silver Spring, MD, USA). Differences between two groups were assessed by using the Student's *t* test for unpaired data. Comparison of categorical data were made using Fisher's exact test. Pearson correlation coefficient was calculated in order to investigate the linear relationship between stiffness parameters and other variables. Stepwise forward regression analysis was performed to assess which factors independently influence stiffness parameters. Variables selected for inclusion in the models were significant at univariate analysis. Significance was set at $p < 0.05$. Kappa statistic was used to assess inter- and intra-reader variability for echocardiographic and ultrasonographic parameters.

3. Results

The initial data entry comprised 46 patients who fulfilled all the inclusion criteria for enrollment; three patients were excluded from the study because of poor compliance to undergo all the examinations requested by the study schedule.

The population study was consequently composed by 43 patients (23 males, 20 females), aged between 19 months and 31 years (mean 11 years, median 8 years and 4 months).

Patients not treated with ketogenic diet (*20 pts*) (control group):

All patients (9 males, mean age 10 ± 7 years at the time of evaluation) were affected by refractory epilepsy and epileptic syndromes as follows: epileptic encephalopathy (11 pts), symptomatic West syndrome (3 pts), severe myoclonic epilepsy in infancy (3 pts), partial epilepsy (3 pts). No patient had hypercholesterolemia and hypertrygliceridemia.

Patients treated with ketogenic diet (*23 pts*):

All patients (11 males, mean age 11 ± 8 years at the time of evaluation) were affected by refractory epilepsy and epileptic syndromes as follows: epileptic encephalopathy (13 pts), symptomatic West syndrome (2 pts), GLUT1 deficiency (1 pt), severe myoclonic epilepsy in infancy (2 pts), partial epilepsy (5 pts). The age at diet onset was comprised between 3 months and 17 years (mean 5 years and 11 months; median 6 years and 1 months). The time interval between the end of the ketogenic diet and follow-up ranged between 16 months and 6 years (mean 3 years; median 3 years and 2 month). The ketogenic diet lasted from 6 months to 10 years and 7 months (mean 2 years, median 15 month). Triglycerides during the ketogenic diet were over the normal range in 17 patients, with mean value of 267 ± 329 mg/dl (range 81–1403). Thirteen patients (74%) showed both hypercholesterolemia and hypertriglyceridemia.

All but one with Glut-1 deficiency syndrome was taking antiepileptic drugs in combination (mean 2–3 drugs). The drugs most frequently prescribed in both groups were: valproic acid, levetiracetam, topiramate, carbamazepine, phenobarbital, benzodiazepines, zonisamide, and clobazam.

Table 1 reports the demographic and clinical characteristics of patients, from the group treated with ketogenic diet and controls and shows a significant difference in stiffness parameters and cholesterol and triglycerides levels. Subjects treated with ketogenic diet had higher AIx, β-index and levels of blood cholesterol or triglycerides compared to those never treated with ketogenic diet ($p < 0.001$). In these two groups there were no significant differences in fasting blood glucose, serum creatinine, systolic and diastolic blood pressure, pulse pressure, and BMI. Patients treated with KD showed a not significantly increased carotid IMT (*p*: n.s.). Moreover, there were not significant differences in all diastolic parameters (Table 2).

A weak positive correlation was found between β-index and total cholesterol ($p < 0.002$), AIx and triglycerides ($p < 0.003$).

Table 1
Clinical data of patients, including blood pressure values, body mass index, lipid profile, and main vascular parameters, from the group treated with ketogenic diet and controls.

	Ketogenic diet ($n = 23$)	Control group ($n = 20$)	*p*
Age (years) at evaluation	11 ± 8	10 ± 7	0.67
Diet duration (months)	24 ± 29	0	
Systolic BP (mmHg)	105 ± 10	103 ± 8	0.48
Diastolic BP (mmHg)	55 ± 5	53 ± 6	0.2
Pulse pressure	60 ± 4	59 ± 5	0.47
Body mass index (kg/m^2)	20 ± 2	21 ± 3	
Total cholesterol (mg/dl)	224 ± 88	175 ± 55	0.038
Tryglycerides (mg/dl)	267 ± 329	115 ± 25	0.046
Glucose (mg/dl)	70 ± 15	69 ± 18	
AIx (%)	3 ± 2	−8 ± 3	0.001
B-index	5 ± 0.7	3 ± 0.5	0.001
IMT (mm)	0.43 ± 0.08	0.40 ± 0.05	0.1

Legend: BP, blood pressure; AIx and β index, arterial stiffness parameters; IMT, carotid intima thickness. Data are expressed as mean value ± SD.

There was no correlation between other stiffness parameters and BMI, plasma glucose, total cholesterol, HDL cholesterol, triglycerides and serum creatinine levels. Stepwise forward regression analysis was performed with AIx and β-index as a dependent variable and with age, systolic and diastolic blood pressure, pulse pressure, carotid IMT, LVMI, E-wave deceleration time, *E*/*A* and Em/Am ratios and total cholesterol and triglycerides as independent variables. As shown in Table 3, total cholesterol and triglycerides parameter were independently related to β-index and AIx. The inter- and intra-reader variability was good ($k > 0.73$).

In order to find a correlation between vascular parameters and the length of time on KD, patients were divided into 2 subgroups: group 1 (11 pts) (length ≤ 12 months; mean 7.73, median 9.0, ±SD 4.65), and group 2 (12 pts) (length > 12 months; mean 39.5, median 29.5, SD ± 32.26).

The comparison between each sub-group and the control group showed a statistically significant variation in group 1 concerning the parameters AC ($p = 0.004$) and AIx ($p = 0.002$).

In order to find a correlation between vascular parameters' assessment and the time since discontinuation of the KD (free interval), patients were divided into 2 subgroups: group A (10 pts) (free interval ≤36 months; mean 16.20, median 20.0, ±SD 13.95), and group B (13 pts) (free interval >36 months; mean 60.54, median 52.0, SD ±22.51).

The comparison between each sub-group A and B and the control group showed a statistically significant variation in group A concerning the parameter AIx ($p = 0.02$).

Age at follow-up, gender and concomitant antiepileptic drugs were not significantly correlated with changes of the arterial stiffness parameters. In contrast, a significant correlation between b-stiffness and blood levels of total cholesterol was found (Fig. 1), as well as a significant correlation between AIx values and serum triglycerides ($p < 0.001$) (Fig. 2).

4. Discussion

In the present study, we examined children and young adults affected by drug resistant epilepsy treated with ketogenic diet for a mean time period of two years and found that local and systemic arterial stiffness was significantly increased compared with a matched control group, and related to serum cholesterol and triglycerides levels.

This data was independent of age, arterial pressure, gender, and anticonvulsant therapy. Furthermore, left ventricule' relative thickness and diastolic function were worse in patients treated with ketogenic diet than controls.

Further, the echo-color Doppler study did not show any macroscopic finding such as atheromasic plaques, abnormal thickness and echogenicity of the common carotid artery. Nonetheless, there was a significant change of parameters relative to the arterial stiffness, including β-index and Augmentation Index. Of note is that these parameters are specific and sensitive of early functional endothelial damage. Further, in patients with over-the-range cholesterol and triglycerides, the AI index was significantly above the normal range, thus suggesting a potential correlation with the endothelial damage.

Table 2
Comparison of echocardiographic indexes between patients and controls.

	KD	Not KD	*p*
LVDD (cm)	4.33 ± 0.55	4.41 ± 0.44	n.s
LVDS (cm)	2.53 ± 0.45	2.61 ± 0.38	
LVM index (g/m) (2.7)	36.5 ± 10	33.3 ± 5	0.2
RT	39 ± 3	37 ± 5	n.s
E/*A* ratio	2.1 ± 0.3	2.2 ± 0.4	n.s
LV filling pressure (*E*/*E*′)	9 ± 3	8 ± 2	n.s
E deceleration (ms)	133 ± 23	129 ± 25	n.s
IVRT (ms)	63 ± 8	67 ± 9	n.s

Legend: E, early diastolic; A, late atrial; LV, left ventricule; LVDS, left ventricule diameter systole; LVDD, left ventricule diameter diastole; IVRT, isovolumic relaxation time; LVM, left ventricular mass. Data are expressed as mean value ± SD.

Table 3
Multivariate analysis.

Examined variable		β	*t*	*p*
Independent variable				
AIx	Age	2.120624	1.8998	.0799
	Total cholesterol	.01646	.004489	.0016
	Tryglycerides	.017769	.9583	.003
β-index	Age	1.8	1.786	.057
	Total cholesterol	.02231	.003345	.0021
	Tryglycerides	.015676	.8767	.0034

Legend: β standardized regression coefficient, *t* nonparametric *t*-test for beta, *p* value for significance. AIx and β-index, arterial stiffness parameters.

Accordingly, in patients who have been taking the ketogenic diet for longer periods, mild but significant abnormal values of IM-GSM (echogenicity of vessel wall), and β-index and AIx (arterial stiffness), were found. As a result, our patients treated with KD showed a significant increase in arterial stiffness without any change in carotid IMT, thus confirming arterial stiffness as an early marker of cardiovascular damage. So far, data coming from literature on the relationship between ketogenic diet and cardiovascular effects regards substantially the ischemic risk and serum lipid changes. In addition, these studies performed in animals and humans are somewhat controversial. More in detail, Al-Zaid et al.,[11] found that a low carbohydrate ketogenic diet enhances the cardiac tolerance to global ischemia in rats with global ischemic injury, thus suggesting that the low carbohydrate ketogenic diet is functionally cardio-protective. On the contrary, Oishi et al.,[12] found that the ketogenic status in mice fed with the ketogenic diet increases hypofibrinolytic risk by inducing abnormal circadian expression of plasminogen activator inhibitor-1.

Furthermore, Westman et al.,[13] reported that a low carbohydrate ketogenic diet led to beneficial changes in serum lipid subclasses, consisting of a shift from small, dense LDL to large, buoyant LDL, which could lower cardiovascular disease risk, during weight loss in overweight, hyperlipidemic community adult volunteers. Overlapping data were reported by Sharman et al.,[14] in normal-weight men in whom a short-term KD favorably affected serum biomarkers for cardiovascular disease.

More concerns are indeed expressed by Kwiterovich et al.,[15] who found that the ketogenic diet produced significant increases in the atherogenic apoB-containing lipoproteins and a decrease in the antiatherogenic HDL cholesterol.

The vascular changes found in the present study, have to be evaluated in terms of benefit/risk ratio, considering that children

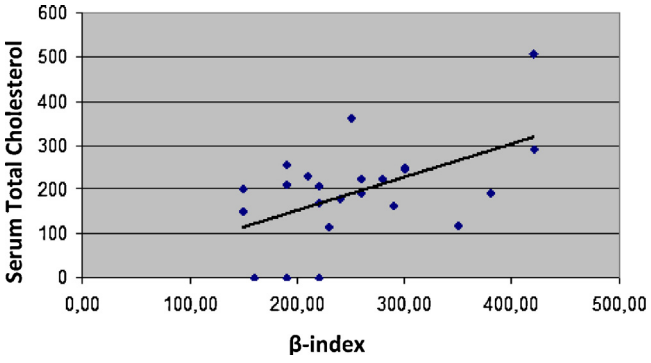

Fig. 1. Relationship between β-index and serum total cholesterol level.

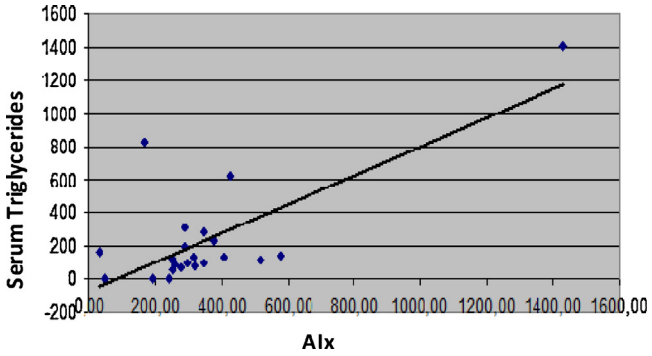

Fig. 2. Relationship between Augmentation Index (AIx) and serum triglycerides.

treated with the ketogenic diet generally suffer from refractory epileptic encephalopathies or congenital metabolic disorders such as GLUT-1 deficiency disorder,[16] for which the diet is a first-choice therapy. Interestingly, predictive value of arterial stiffness is due to structural changes of vessels walls that precede the appearance of echographic lesions including carotid intima thickening and plaques.[17] Disclosing early changes in arterial stiffness may lead to a potential prophylactic drug treatment, including, for instance, ACE-inhibitors or calcium channel blockers.

On this subject, Dahlin et al.,[18] reported the potential efficacy of an early supplementation of the diet with omega-3 fat acid, in the aim of decreasing the omega 6/omega 3 ratio and, accordingly, the cardiovascular risk.

Data show values of Augmentation Index significantly higher in subjects free from ketogenic diet for less than 3 years (mean value 1.4) versus subjects free from ketogenic diet for more than 3 years (mean 5.5) and versus control group (mean 2.1).

Ketogenic diet is known to have effects on lipid metabolism, increasing blood total cholesterol in at least a subset of patients.[15] Hypercholesterolemia has effects on arterial walls, generating early dysfunctions such as arterial stiffness. Our data suggest the possibility that arterial stiffness may regress after more than 3 years free from ketogenic diet. Our hypothesis is that discontinuation of ketogenic diet lowers cholesterol levels, and that a long period of low-to-normal cholesterol can lead to regression of arterial wall early dysfunctions in children and adults with no other cerebrovascular risk factors. Recently Ferrier et al.[19] have demonstrated that intensive reduction of blood cholesterol values can lead to lower arterial stiffness in patients affected by isolated systolic hypertension. Improving the evidence of damage reversibility on arterial walls may be useful in managing patients who have great clinical benefits from ketogenic diet, but tend to develop early arterial walls alterations.

To the best of our knowledge, this is the first study that addressed endothelial function in patients fed the ketogenic diet. However, there are some limitations to be taken into account: (1) it is not a longitudinal study, but patients were compared with sex and age matched control group; (2) the number of patients studied is small, but a good adherence to the study protocol was difficult to obtain; (3) considering this as not an intrapatient longitudinal study, we decided to rule out potential risk factors predisposing to cardiovascular impairment (e.g. arterial hypertension, diabetes mellitus). Although such patients are not excluded from the ketogenic diet in clinical practice.

In conclusion, our data show that arterial stiffness is increased in children and young adults with high level of cholesterol due to the ketogenic diet, before the increase of the intima media thickness. Arterial stiffness is therefore an early marker of vascular damage and indicates risk for later arterial disease.

Furthermore, our study shows that the arterial mechanical impairment, as measured by local β-index and systemic (AIx) stiffness indices, gets worse according to higher plasma cholesterol levels. The finding of slight endothelial changes might justify an early preventive treatment. In case of patients with increased lipid profile on the ketogenic diet, changes in diet regimen such as shifting to a 4:1 to a 3:1 fat/protein plus carbohydrate ratio or increasing polyinsature fat acids amount and/or adding omega-3 compounds, may be tried. In presence of very high lipid profile, ketogenic diet could be quickly withdrawn or alternative treatments including low glycemic index diet or modified Atkins diet might be considered. Indeed, cost/benefit ratio should always guide the clinical approach, even trying to decrease the overall length of diet treatment. Only studies in larger cohorts of patients fed with the ketogenic diet for longer periods, might better clarify the actual impact of this alternative therapy on the endothelial vascular function and its role on inflammation and development of atherosclerotic lesions.

Authors' contributions

Dr. Giangennaro Coppola studied concept and design, critical revision and supervision of the manuscript.

Dr. Natale completed the statistical analysis, did acquisition of data, analysis and interpretation, statistical analysis.

Dr. Annarita Torino, Rosanna Capasso, Alfredo D'Aniello, Claudia Isone, Elena Santoro, Alberto Verrotti did acquisition of data, analysis and interpretation.

All authors report no disclosures.

The study was not industry-sponsored.

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