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Ketogenic Diet Prevents Development Of Atherosclerotic Plaques In Apolipoprotein E Knockout Mice

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Higher aldosterone (aldo) levels are associated with increased risk of cardiovascular ischemic events and mortality. It has been demonstrated that aldo accelerates the development of atherosclerosis in apolipoprotein E knockout mice (ApoE KO). Ketogenic diet (KD) positively impacts several cardiovascular risk factors, yet its effect on atherosclerosis is elusive. We hypothesize that KD protects from development of atherosclerotic plaques in ApoE KO mice, a murine model of atherosclerosis. Eight-week-old male ApoE KO mice were fed a KD (90,5% Kcal from fat, 0.4% Kcal from carbohydrate, 9.1% Kcal from protein) or a moderate high fat die (HFD) (42% Kcal from fat, 42.7% Kcal from carbohydrate, 15.2% Kcal from protein) and treated with aldosterone (aldo, 6 μg/mouse per day) or vehicle through osmotic mini-pumps. Cholesterol content was comparable in KD and HFD. After 4 weeks of treatment, in all experimental groups, intraperitoneal glucose tolerance test was performed, and peripheral blood samples were collected. We analysed cryosections of embedded aortic root to quantify the atherosclerotic plaque size, lipid and collagen content. We assessed vascular inflammation in specimens of thoracic aorta by analysing pro-inflammatory (ICAM-1, VCAM-1, IL-6, TNF-α, MCP-1) and anti-inflammatory (Arg-1, RETNLA, CCL5) genes. In ApoE KO mice treated with aldo, KD determined a significant improvement in glucose tolerance, compared to mice fed a HFD, without any significant effect on body weight. Beta-hydroxybutyrate levels were always significantly higher in KD-mice than in AD-mice, confirming nutritional ketosis in KD-mice. Analysis of aortic root showed that aldo treatment determined a significant increase in atherosclerotic plaque size and lipid content in HFD-mice. Such effects were significantly reduced in KD-mice, suggesting a favorable impact of ketosis in preventing atherosclerosis development. Plaque fibrosis did not differ among treatment groups. Finally, we observed a significant reduction in vascular inflammatory markers in KD-mice, when compared to HFD-mice. In particular, KD determined a significant reduction in gene expression of pro-inflammatory markers (ICAM-1, VCAM-1, IL-6, TNF-α, MCP-1) with the concomitant up-regulation of anti-inflammatory markers (Arg-1, RETNLA, CCL5), compared to HFD. The study suggests KD as a potential non-pharmacological approach to prevent the development of atherosclerotic disease in subjects with high cardiovascular risk.

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