Journal of Geriatric Cardiology | JGC

EDITORIAL

J Geriatr Cardiol 2026; 23(5): 275–283

Ketogenic diet, cardiometabolic diseases and aging

Giuseppe Cioffi[1,✉], Gianluigi Cuomo[2], Raffaele Carluccio[3], Crescenzo Testa[4], Anna Di Lorenzo[5], Luigi De Vito[6], Valentina Parisi[1], Maddalena Conte[1], Dario Leosco[1], Francesco Giallauria[1]

1. Department of Translational Medical Sciences, "Federico II" University of Naples, Via Sergio Pansini 5 (80131), Naples, Italy; 2. "Ospedale del Mare" Hospital of Naples, Via Enrico Russo 11 (80147), Italy; 3. Department of Advanced Biomedical Sciences CardioPath Program, "Federico II" University of Naples, Via Sergio Pansini 5 (80131), Naples, Italy; 4. Department of Medicine and Surgery, University of Parma, Parma, Italy; 5. Outpatient Specialist at "Polo del Sollievo" Hospice ASLNa2Nord, Via Nicola Amore (80020) Casavatore, Naples, Italy; 6. Department of internal Medicine and Clinical Complexity, Federico II University Hospital, Via Sergio Pansini 5 (80131) Naples, Italy

✉ Correspondence to: gcioffi316@gmail.com

https://doi.org/10.26599/1671-5411.2026.05.005

ABSTRACT The ketogenic diet (KD), characterized by a high-fat, moderate-protein, and low-carbohydrate macronutrient composition, has gained growing interest as a potential nutritional approach to cardiometabolic diseases and aging. Emerging evidence suggests that ketone bodies, particularly β-hydroxybutyrate, act not only as alternative energy substrates but also as signaling molecules that influence vascular, metabolic, and epigenetic pathways. This review summarizes current knowledge on the cardiovascular and metabolic implications of KD, emphasizing endothelial function, cardiac energy metabolism, lipid profile, and blood pressure regulation. Experimental and clinical data indicate that KD enhances endothelial antioxidant capacity via Nrf2 activation and eNOS upregulation, reduces cellular senescence, and modulates epigenetic regulators such as histone β-hydroxybutyrylation and SIRT1. In heart failure, acute ketone supplementation improves cardiac output and energetics, while chronic adherence to KD may impair hepatic ketogenesis and lipid homeostasis, potentially offsetting its benefits. Evidence in hypertension and dyslipidemia remains controversial, with short-term improvements often contrasted by long-term elevations in LDL cholesterol and arterial stiffness. In patients with type 2 diabetes, KD promotes glycemic control and insulin sensitivity, yet the sustainability and cardiovascular safety of prolonged use are uncertain. Overall, KD represents a promising but complex therapeutic tool whose efficacy depends on individual metabolic context, diet composition, and duration. A balanced, intermittent, or cyclic ketogenic approach may offer a safer strategy to harness its cardiometabolic and anti-aging benefits.

The ketogenic diet is one of the newest nutrition regimens consisting of high fats, medium proteins, and very low carbohydrates, about approximately 55%-60% fat, 30%-35% of protein, and 5%-10% of carbohydrates (i.e., 30 g per day of carbohydrates are included in a Ketogenic Diet a 2000 Kcal per day diet).[1] The traditional KD is structured in 4: 1 ratio of fats to carbohydrates and protein with 90% of calories coming from fat, 8% from protein, and 2% from carbohydrates.[2] Nowadays, there are some alternative protocols with 3: 1 KD, 2: 1 KD, and 1: 1 KD. Also modified Atkins diet (MAD) or medium-chain triglyceride ketogenic diet (MCTKD) is largely used. Born as a therapeutic diet for pediatric epilepsy, the ketogenic diet is now adopted especially as quite effective in short-run rapid weight loss. The rationale of this regimen is the enhancement of gluconeogenesis and ketogenesis caused by the significant reduction of insulin secretion by the pancreas given by the deprivation of carbohydrates introit and therefore glucose. When serum glucose concentration keeps going down and availability drops further, ketone bodies Acetone, Acetoacetic acid (AcAc), Beta-hydroxybutyrate (BHB) mostly replace glucose and become the primary source of energy; being easily used by the heart and muscle tissue. Also, brain uses KBs due to their ability to cross the blood-brain barrier. Ketone bodies are linked with many mammals' metabolic pathways such as gluconeogenesis, B-oxidation (FAO), lipogenesis, tricarboxylic acid cycle (TCA), and biosynthesis of sterols. Mammals predominantly produce ketones in the liver, starting from Acetyl - CoA derived from Fatty-Acid-Oxidation. KB are transported to extrahepatic tissues to finish oxidation and produce ATP. Under physiological conditions, plasma levels of KB are around

0.05-01mM but prolonged exercise, starvation, and carbohydrate restriction/ ketogenic diet, or insulin deficiency can enhance levels reaching 5–7 mmol.[3] Different ketone levels can have different implication for body's health (Figure 1).

KETOGENIC DIET AND ENDOTHELIAL PROLIFERATION PATHWAYS

Aging is a risk factor for cardiovascular disease and preventing vascular aging represents a tool for cardiovascular dysfunctions. A very low-carbohydrate and high-saturated-fat diet, especially BHB impacts vascular function and vascular blood flow. The reduction of brain injury and neurological dysfunction after brain ischemia and the higher reperfusion recovery of coronary flow seems to be approved, for example, as an effect of KD.[2] Antioxidant effects on endothelial cells through the activation of Nrf2 transcription factor,[4] the reduction of mTOR expression, and increasing eNOS levels are some of the vascular benefits of the Ketogenic Diet.[5] However, the result for big vessels such as carotid and aortic arteries is not so clear. Serum lipid levels seem not to significantly affect carotid intima-media thickness or aortic strain, distensibility, and elastic properties[6] as emerged from studies regarding KD on Vascular structure and functions in Pediatric Epilepsy. But on the other hand, Coppola, *et al.*[7] described higher arterial stiffness parameters and also higher cholesterol and triglycerides levels. The focus should be on endothelium senescence and the role of ketone bodies on it. Cellular senescence plays a role in tissue fibrosis protection, tissue remodeling and vascular disease.[8] In particular, BHB decreases the secretory phenotype of vascular cell senescence[9] (Figure 2). There are a lot of beneficial effects of calorie restriction on prolonging life and delay aging.[10] BHB can prevent replicative senescence in vascular cells reducing IL-1a and enhancing Oct4A levels by the stabilization of Oct4A' s mRNA; in fact, KB binds hnRNP A1, a nuclear ribonucleoprotein implicates in Oct4A transcription. Interesting is the expression of Succinyl-CoA:3-oxoacid-CoA transferase (SCOT) the enzyme of ketone body oxidation of the cardiac endothelial cells.[11] Endothelial cells use ketone bodies to enhance cell proliferation, vessel sprouting and angiogenesis. KB induce the expression of antioxidant defense system genes (Nrf2 and HO-1)[12] and, in mice model, improve hearth function with endothelial-specific Notch inhibition.[13]

EPIGENETIC EFFECTS OF KETONE BODIES ON CARDIOMETABOLIC DISEASE (CMDs)

Epigenetic modification of histones proteins is linked to gene expression without any change in DNA sequence. This control mechanism involves histone methylation and acetylation, and noncoding RNAs. For example, epigenetic alterations, such as DNA methylation (CpG cytosine-guanine dinucleotide sites), contribute to the development of chronic and cardiovascular diseases and could be linked to 16 pathways related to cardiovascular disease.[14] Today, we know that a methylation-based risk score should be used in patients at risk for CVD. A decrease in DNA methylation is linked to hypertension,[15] and human atherosclerotic lesions.[16] It is interesting to note that DNA methylation may also affect the inflammatory response associated to CV risk through the regulation of adhesion and migration of soluble molecules that direct blood leukocytes in

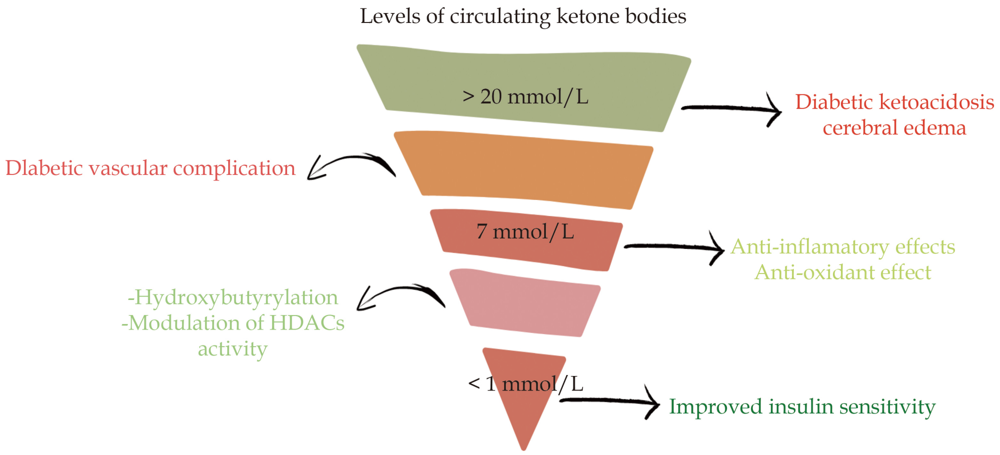

Figure 1 **Different effects of ketobe bodies plasma levels.**

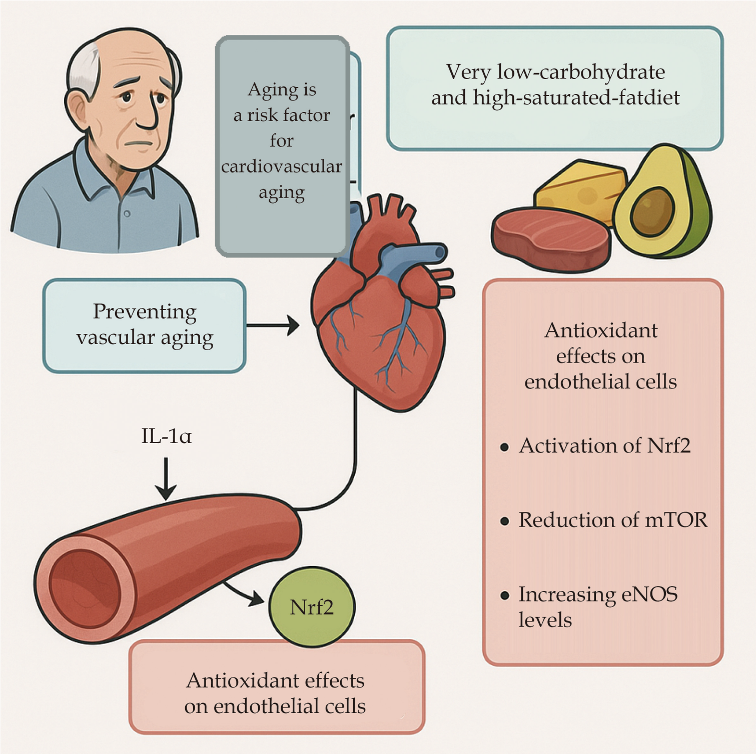

Figure 2 **Effects of ketogenic diet on vascular senescence.**

vascular tissue.[17] For example, a genome-wide decrease of DNA methylation emerged in epileptic patients on KD;[18] BHB has been shown to activate methyltransferase 3 (CMT3) and inhibit DDM1, a regulator of DNA methylation,[19] BHB was initially identified as an inhibitor of histone deacetylases (HDACs), although this was not confirmed by recent data from Chriett, *et al.*[20] Experiment on endothelial cells (HMEC-1) showed indeed that BHB did not increase histone acetylation, but did not inhibit histone deacetylase catalytic activity.[20] Recently, studies showed a synergic epigenetic regulation between KB and SIRT1 on metabolic health. First of all, we should talk about a new type of histone epigenetic modification, post-translational modification (PTM; lysine b-hydroxybutyrylation or Kbhb); it's the key mechanism for epigenetic regulation which alters the activity of metabolic modulators. PTM occur on histone lysines and cellular protein including p53.[21,22] The enhancing levels of lysine b-hydroxybutyrylation (Kbhb) modification of core histones H3 (H3K9BHB) resulted during starvation, is specifically associated with genes upregulation in starvation-responsive metabolic pathways. PTMs represent a new way of approaching to study chromatin regulation and the multiple BHB functions in human pathophysiological states. SIRTs are class III nicotinamide-adenine-dinucleotide (NAD^+)-dependent histone deacetylase (HDACs). We know that $NAD^+/NADH$ ratio is significantly modified depending on the energy fuel available, glucose or BHB. The production of two moles of acetyl-CoA using BHB use only one mole of NAD^+ *vs.* four moles used by glucose as an energy source. This excess of NAD^+ availability resulting from ketogenic diet exerts a positive influence on redox state of cells and modulates (NAD^+)-dependent enzymes such as sirtuins, involved in deacetylation process.[23] SIRT1 and ketone bodies plays a protective adaptive cellular response such as inflammation attenuation, mitochondrial biogenesis, DNA repair and autophagy and fatty acid oxidation.[24] Both KBs and SIRT1 works on PGC1-a promoting the oxidation of fatty acids with the metabolic shift from glucose homeostasis (Figure 3). The KD shows promising applicability in the field of CMDs by regulating key metabolic through the interference for example with PGC1a and PPARa (Figure 4).

KD EFFECTS IN HEART FAILURE

Recent studies suggested a relationship between increasing cardiac ketone oxidation and the improvement of heart function.[25] Increased KB levels can be achieved with some strategies, also the administration of a ketogenic diet.[26] Acute infusion of BHB in patients with heart failure with reduced ejection fraction (HFrEF) improves contractile function,[27] and can also reduce cardiac remodeling, as demonstrated in rat models with heart failure.[28] Ketone bodies are an important fuel source for the heart,[29] and have a cardioprotective role. Nielsen, *et al.*[29] demonstrated that BHB infusion in HFrEF patients improves ejection fraction and cardiac output by 2.0 L/min and EF by 8% with a concomitant reduction of systemic vascular resistance by 30%. In cardiomyocytes, BHB regulates PI3K/Akt pathway to ameliorate cell apoptos-

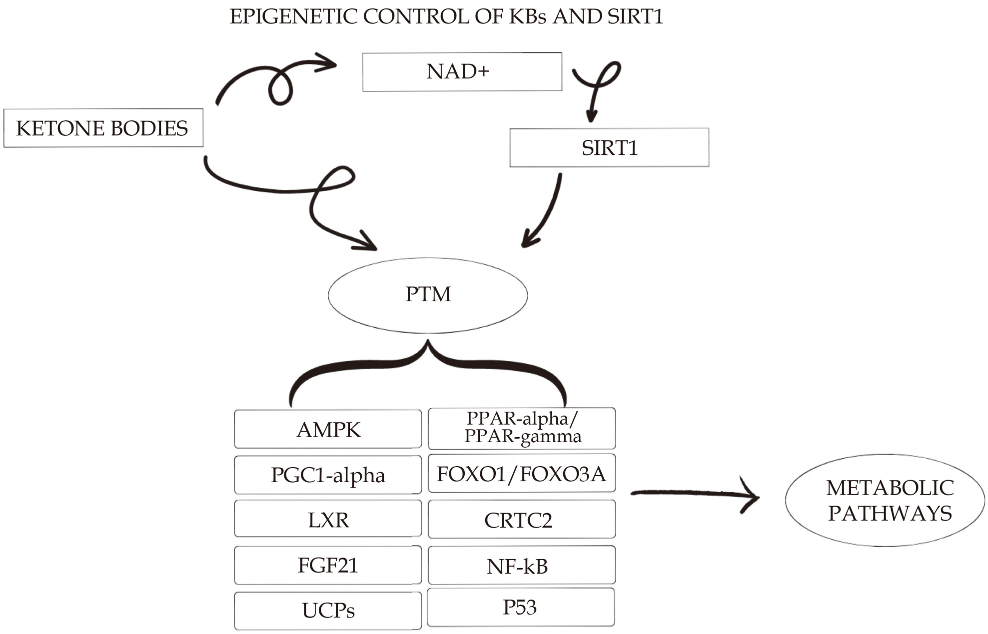

Figure 3 Ketone bodies epigenetic effects on major metabolic pathways.

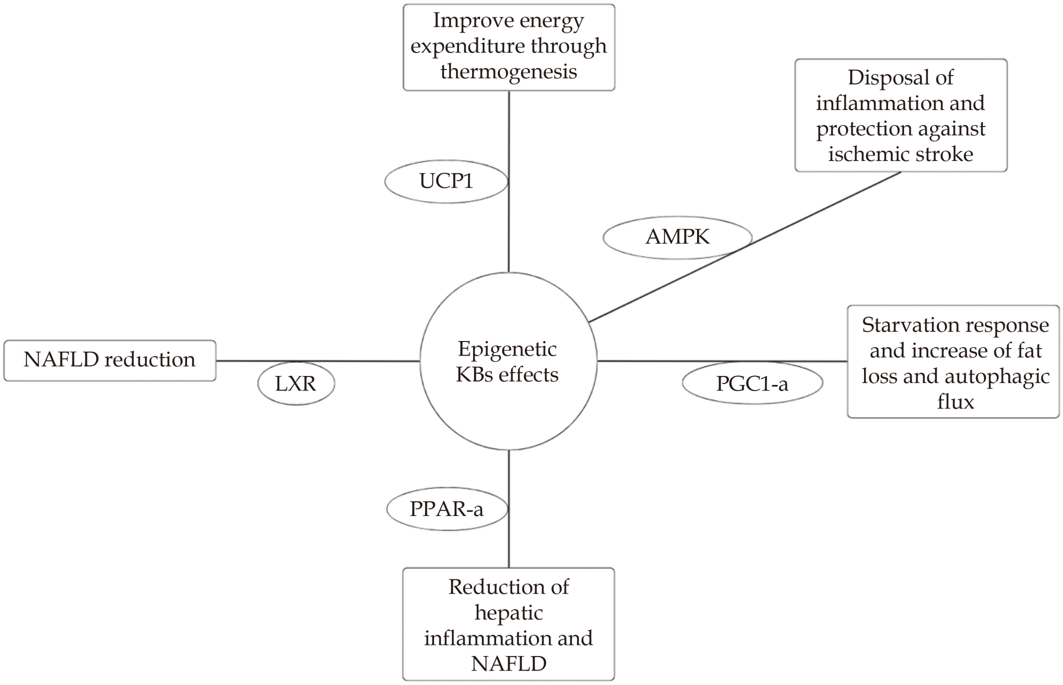

Figure 4 KBs epigenetic effects through the interference with AMPK, PGC1-a, PPAR-a, LXR and UCP1.

is and can also lead to myocardial fibrosis through HDAC2 inhibition, influencing mitochondrial[30] biogenesis and cell respiration.[2] The heart has a strong metabolic system using almost all the substrates such as fatty acids, carbohydrates, lactate, and ketone bodies too. When the heart starts to derange the substrate utilization this phenomenon has a causal role in the development of heart failure and so, for this reason, reset cardiac substrate preference is demonstrated to be a good strategy for cardiac disease treatment.[31–32] Today, we know that the infusion of BHB show good effects improving cardiac function in failing heart involving the expression of genes used to normalize myocardial ATP production.[28] The real problem is that chronic KD feeding failed to protect the heart against heart failure[33] causing the impairment of the liver ketogenesis capacity. A chronic KD diet is not a reliable strategy for cardioprotection during HF and also for adverse effects like cardiac arrhythmias, bone fracture, headache, and weakness[34] and can be also associated with fatty acid metabolic disorders including increasing lipids level circulation. Lipid homeostasis is important and fatty acid metabolic diseases are a risk factor for cardiovascular disease. Recently, a new point of view has been proposed demonstrating that an alternate-day ketogenic diet and not continuous regimen has the potential to protect against heart failure and changes in cardiac structure.[35] Interesting is also the relationship between the mitochondrial pyruvate carrier (MPC) required for pyruvate metabolism and downregulated in failing human hearts, and ketogenic diet. This carrier is composed of two proteins known as MPC1 and MPC2. The loss of mitochondrial pyruvate utilization drives dilated cardiomyopathy and, in animal models MPC2$^{-/-}$, a ketogenic diet completely prevented or reversed cardiac remodeling and dysfunction.

KD show good result to prevent further remodeling in ischemic and pressure-overload mouse hearth failure model.[36]

KD AND HYPERTENSION

The relationship between hypertension and KB plasma levels needs more studies to be explored. Data on the relationship between KD and hypertension are sparse; however, some preliminary report found that KD may be a good adjunctive tool for blood pressure control in many ways. Castellana, *et al.*[37] talked about good effects on the management of hypertension, TDM2, and Dyslipidemia. The establishment of VLCKD can significantly lower SBP in three months follow-up as Cicero, *et al.*[38] demonstrated. VLCKD is characterized by low-fat, low-carbohydrates and 1.2–1.5 g/kg of protein of ideal body weight. VLCKD probably may be a good middle-term strategy showing a significant reduction of body weight from baseline to 4 weeks of (−7/−5kg, $P <$ 0.001) and continuous weight loss until 12 weeks, but after this period no changes have been observed. The same for SBP, with a reduction (−10.5 ± 6.4 mmHg, $P <$ 0.001) but no changes after 1 year of observation.[38] Interestingly, integration with 1,3-butanediol, a ketone precursor, showed strong evidence to reduce hypertension.[39] Another study demonstrates that after 5 weeks of fasting for 18 h in prediabetic men there's a reduction of SBP of 11 ± 4 mmHg and DBP of 10 ± 4 mmHg.[40] Intermittent fasting has elements of KD but may be more beneficial because of KD's high consumption of animal fats, which higher levels of trimethylamine N-oxide associated with cardiovascular risk. Not everything that glitters is gold. In animal models (hypertensive rats) 4 weeks of KD is demonstrated to enhance hypertension, increasing IL1-b and TNF-a expression and decreasing CD31 and eNOS, causing thickness and impaired endothelium-dependent relaxation.[41] Maybe intermittent fasting could be safer and helpful in this cohort.

KD AND SERUM LIPIDS LEVELS

The effect of KB on serum lipids has been largely investigated; 6- week of KD is able to decrease serum triglyceride and fasting serum insulin concentrations and also increase HDL cholesterol but here are no significant direct effects of LDL cholesterol and oxidized LDL.[42] We can highlight that short-term KD can have cardiometabolic effects on CVD risk profile, improving lipid disorders and atherogenic dyslipidemia. Indeed, a meta-analysis confirmed that triglycerides increased in 1 mg/dL for every 1% of energy derived from saturated fat replaced with carbohydrate. For what concerns long-term administration (12 months), KD showed a significant elevation in serum LDL cholesterol and triglyceride.[6] Three studies showed a *U*-shaped curve of overall mortality according to the ratio of carbohydrate intake.[43] The National Lipid Association (NLA), studied VLCD/KDs and in 4 of 7 studies, participants had higher LDL-C, increasing to 6 of 7 in TDM2.[44]

EFFECT OF KD IN T2DM PATIENTS

Since 2019, the American Diabetes Association (ADA) included low-carbohydrate diet in therapy strategies for diabetic patients based nutritional ketosis power to reduce hypoglycemic agents in diabetic patients[45] and KD provides energy through fat oxidation. Blood ketone bodies remains at 0.5–3.0 mmol/L with a reduction of blood glucose. The restriction of carbohydrates reduces the absorption of monosaccharides reducing blood glucose fluctuation, postprandial glucose levels and regulating glucose metabolism.[46–47] A reduction of about 14%–37% of micro- and macro-vascular complications, respectively, is observed through a reduction of HbA1c by 1%. The KD dietary regimen administration shows a significant reduction of Hb1ac, about −0.6% to −3.3%, with a reduction of < 1.5% in the majority of the studies.[48] However, low-carbohydrate diets (LCD) are able to show a significant reduction in A1c only in studies of short duration,[44] and the benefits in diabetes occur but not reverse the disease state. We know that hyperinsulinemia and hyperglycemia are two important cardiovascular risk factors; in fact, insulin function is also related to lipid uptake, lipolisis and lipogenesis.[49] Hyperinsulinemia is linked to increased levels of free IGF-1 that have mitogenic and antiapoptotic properties. A U-shaped association has been reported between IGF-1 and nonfatal CVD events in elderly men.[50] KD shows improvement in glycemic parameters after two weeks and continued in long-term administration (56 weeks);[51] differently towards nondiabetic patients who develop an increase in total cholesterol and LDL levels during long-term administration of KD, in diabetic patients a KD for 4 days and up to 2 years led to a good improvement of lipid asset lowering triglyceride and higher HDL levels.[52] Another tool is to improve insulin resistance in diabetes treatment, especially in obese patients. It is interesting to observe that in newly diagnosed patients with T2DM a periodic KD regimen can reduce fasting insulin more than a healthy diabetic diet,[53] and for patients already on insulin treatment, 70%–90% of them reach the goal of no longer taking insulin after one year of KD.[54] For what concerns insulin resistance, HOMA-IR is considered as an indicator to evaluate it and decreased by about 2.0 after KD consumption for 6 weeks;[55] this is linked to the reduction in body weight. The ketogenic diet is also largely studied in obese patients. The recommendation is to use a maximum of a 12-week weight loss program with VLCKD.[56] Obesity is strictly linked to insulin resistance through chronic low-grade inflammation mediated by endoplasmic (ER) stress, mitochondrial dysfunction, and hyperinsulinemia.

KETOGENIC DIET AND AGING

Caloric restriction, Mediterranean diet and ketogenic diet seem to be associated with healthy aging, modulating in particular the mTORC1/AMPK pathway.[57] Dietary restriction and low caloric intake showed good results in life span expectancy and longevity.[58] The anti-aging effects are promoted by multiple mechanisms: oxidative stress homeostasis,[59] gut microbiota,[60] cellular senescence[61] and inflammation with cellular repair. There are several molecular mechanisms underlying aging, influencing the rate of aging and lifespan. mTORC1, a serine /threonine kinase, has been demonstrated to be related to extended lifespan. The central target of aging regulation and lifespan is the rapamycin (TOR) signaling pathway. Caloric restriction can influence energy pathways mediated by cAMP-responsive element binding protein (CREB) and AMP-Activated protein kinase (AMPK), as the pro-growth of the mTOR pathway. KB has a neuroprotective effect on aging brain cells,[62] reducing inflammation and enhancing mitochondrial function; probably beneficial in neurodegenerative disorders such as Alzheimer's disease[63–64] and Parkinson's disease.[64] For what it concerns, cardiovascular aging effects of KD, debating results on blood lipids and cardiovascular risk are present. The utilization of KD in the elderly population for now seems to have little applicability cause of the lack of evidences in this cluster of patients. Often results in decreased appetite and potential gastrointestinal issues. However, this kind of diet is strongly associated with a reduction in triglyceride levels, weight loss, and increased HDL cholesterol and other cardiovascular potential benefits. The reduction of glucose and insulin levels decreases mTORC1 activity, promoting autophagy and helping cellular detoxification and longevity.

DISCUSSION

The rising interest in the KD as a therapeutic and preventive strategy for cardiometabolic diseases has stimulated increasing scientific attention. While a growing body of evidence highlights the beneficial effects of KD, several aspects remain controversial and require further clarification, particularly regarding long-term cardiovascular safety.

On the vascular level, ketone bodies, especially β-hydroxybutyrate (BHB),[65] appear to exert protective effects, primarily through activation of antioxidant pathways such as Nrf2 and upregulation of endothelial nitric oxide synthase (eNOS), alongside inhibition of mTOR signaling. These mechanisms contribute to improved redox homeostasis, reduced endothelial senescence, and enhanced vascular function, especially within the microcirculation. However, data concerning macrovascular function remain inconsistent, with some studies suggesting increased arterial stiffness and adverse lipid alterations following prolonged KD, particularly in specific populations such as children with refractory epilepsy.

From an epigenetic perspective, BHB acts as a signaling molecule capable of modulating gene expression via histone post-translational modifications, notably lysine β-hydroxybutyrylation (Kbhb), and by increasing NAD^+ levels, thereby activating sirtuin pathways (e.g., SIRT1). These processes have been associated with beneficial effects on mitochondrial function, inflammation, and cellular aging, suggesting a potential role of KD in cardiovascular protection through epigenetic remodeling.

In the setting of heart failure, the failing myocardium exhibits a metabolic shift toward ketone utilization as an alternative energy substrate. Acute administration of BHB in patients with HFrEF has shown improvements in cardiac output and vascular resistance, yet long-term adherence to KD may impair endogenous ketogenesis and lead to deleterious effects. Intermittent or alternate-day ketogenic strategies might represent a promising compromise, although clinical validation remains limited.

Concerning blood pressure, data are scarce and conflicting. While short-term studies suggest a reduction in systolic pressure, particularly with very low-calorie ketogenic diets (VLCKD), other reports indicate a possible increase in arterial pressure and endothelial dysfunction with prolonged KD exposure, especially in animal models. These discrepancies emphasize the importance of dietary composition and duration, as well as individual patient characteristics.

The impact of KD on lipid profiles remains a debated issue. Although initial improvements in triglyceride levels and HDL cholesterol have been documented, several studies report elevations in total and LDL cholesterol following prolonged KD, particularly in non-diabetic individuals. Such findings raise concerns regarding atherogenic risk, suggesting that fat quality and metabolic context play a critical role in modulating lipid responses.

In type 2 diabetes mellitus, KD has demonstrated robust short-term efficacy in improving glycemic control, insulin sensitivity, and medication de-escalation. These effects appear more pronounced in newly diagnosed patients and may persist even with intermittent adherence. Nevertheless, the long-term cardiometabolic impact, especially in relation to lipid metabolism and vascular health, remains to be fully elucidated.

In summary, while KD represents a potentially valuable nutritional intervention in cardiometabolic diseases, its implementation requires careful consideration of individual metabolic profiles, treatment duration, and dietary composition. Future studies should focus on defining patient subgroups most likely to benefit from KD, as well as on optimizing protocols through intermittent or cyclic approaches, with particular attention to long-term safety[66] and cardiovascular outcomes.

CONCLUSIONS

The ketogenic diet emerges as a powerful, albeit complex, tool in the arsenal against cardiometabolic diseases. Its multifaceted effects—ranging from antioxidant and anti-inflammatory actions to epigenetic remodeling and metabolic reprogramming—underscore its therapeutic potential. Yet, like any potent intervention, its benefits are counterbalanced by unanswered questions, particularly concerning long-term cardiovascular safety. The diet's impact appears highly context-dependent, influenced by individual metabolic profiles, duration of adherence, and dietary composition.

To harness the full potential of KD while minimizing risks, a personalized and flexible approach is paramount. Intermittent or cyclic ketogenic strategies may offer a promising middle ground, preserving metabolic benefits while mitigating adverse effects. Ultimately, the future of KD lies not in one-size-fits-all prescriptions, but in targeted, evidence-based applications that respect the nuanced interplay between nutrition, metabolism, and cardiovascular health. As research continues to unfold, KD could evolve from a dietary trend into a cornerstone of precision medicine.

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Please cite this article as: Cioffi G, Cuomo G, Carluccio R, Testa C, Lorenzo AD, Vito LD, Parisi V, Conte M, Leosco D, Giallauria F. Ketogenic diet, cardiometabolic diseases and aging. *J Geriatr Cardiol* 2026; 23(5): 275–283. DOI: 10.26599/1671-5411.2026.05.005