COALITION FOR METABOLIC HEALTH

Addressing the Metabolic Drivers of Cardiovascular Disease

Cardiovascular disease (CVD) – heart attacks, strokes, heart failure, and related events, most of which result from atherosclerosis (plaque buildup in the arteries) – is the **leading cause of death** in the United States.[1]

Yet the factors driving CVD often begin long before a heart attack or stroke. Hypertension (high blood pressure), dyslipidemia (unhealthy cholesterol and triglyceride levels), excess weight, and elevated blood glucose are key risk factors that increase the likelihood of CVD – and frequently develop together as part of broader metabolic dysfunction.[2,3,4]

Research indicates that low-carbohydrate and ketogenic therapies can improve several of these interconnected cardiovascular risk factors.[3,5,6] At the same time, no randomized clinical trials have yet followed people on these therapies long enough to determine whether the metabolic improvements ultimately translate into fewer heart attacks, strokes, or cardiovascular deaths.[6,7]

The Rising Burden of Cardiovascular Disease

Cardiovascular disease was responsible for 915,973 U.S. deaths in 2023, representing approximately one in every three deaths.[8] Heart disease and stroke also cost the U.S. healthcare system $223.2 billion annually and account for an additional $191.5 billion in costs associated with premature mortality.[9] The burden is not shared equally. Black adults have the highest prevalence of CVD among major U.S. racial and ethnic groups, at approximately 60% compared with nearly 49% of U.S. adults overall.[8] In 2022, Black adults were 35% more likely than U.S. adults overall to die from CVD.[10] Disparities in cardiovascular outcomes also track closely with social determinants of health, including income, education, food security, and access to care, which are increasingly recognized as important drivers of cardiovascular morbidity and mortality.[9,11]

Where Cardiovascular Risk Begins

CVD is often discussed in terms of individual risk factors such as high blood pressure or cholesterol. Increasingly, however, researchers recognize that many of these risk factors arise from shared metabolic disturbances that begin years before clinical CVD develops.[3,4] One of the most important of these disturbances is insulin resistance, which occurs when cells become less responsive to insulin, prompting the body to produce more of the hormone to manage blood glucose. Over time, this dysfunction is associated with high blood pressure, elevated triglycerides, low HDL-C, chronic inflammation, excess abdominal fat, and more cholesterol-carrying particles that can contribute to plaque buildup. Together, these changes can increase the likelihood that plaque will develop within the arteries, increasing the risk for CVD events.[3,4,12]

Improving the Multiple Drivers of Disease

Because carbohydrate intake is a primary driver of insulin secretion, low-carbohydrate and ketogenic therapeutic approaches have emerged as promising strategies to address the underlying metabolic drivers of CVD rather than individual risk factors in isolation. These therapies are typically defined as less than 130 grams of total carbohydrates per day and less than 50 grams of total carbohydrates per day, respectively.[4]

Research consistently shows that low-carbohydrate and ketogenic therapies improve multiple cardiometabolic risk factors associated with CVD, including body weight, insulin resistance, blood glucose, triglycerides, HDL-C, and blood pressure. These findings have been observed across diverse patient profiles, including adults with obesity, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease (MASLD), as well as adults without established CVD or other diseases – suggesting that carbohydrate reduction may improve cardiovascular risk factors before CVD develops.[3,5,6,12,13,14]

This is consistent with recent clinical guidance from the Obesity Medicine Association, which identifies low-carbohydrate and ketogenic therapeutic approaches as viable nutrition strategies for managing obesity and obesity-related cardiovascular risk factors when implemented as part of comprehensive, individualized care.[15]

Improving the Multiple Drivers of Disease

While findings suggest meaningful improvements in estimated cardiovascular risk as a result of low-carbohydrate and ketogenic nutritional therapies, the interpretation of lipid responses remains an active area of scientific investigation.

Understanding the Cholesterol Question

While low-carbohydrate and ketogenic therapies consistently demonstrate improvements in triglycerides and HDL-C, the effects on LDL-C are variable.[5,6,7,13] In a meta-analysis of 174 randomized trials involving more than 11,000 adults, carbohydrate-reduced diets were associated with a modest average increase in LDL-C, alongside improvements in HDL-C, triglycerides, blood pressure, and body weight. These outcomes were frequently observed among participants with overweight or obesity.[16]

By contrast, a separate meta-analysis of low-carbohydrate interventions found that LDL-C remained stable in groups with overweight or moderate obesity and decreased modestly in groups with more advanced obesity.[17] This variability has prompted growing interest in apolipoprotein B, or ApoB, the primary protein found on the surface of plaque-forming lipoprotein particles, which transport cholesterol and other fats through the bloodstream. Unlike LDL-C, which measures how much cholesterol is being carried in the bloodstream, ApoB estimates the total number of particles capable of entering the artery wall and contributing to atherosclerosis.

Recent studies suggest ApoB may be a more accurate predictor of cardiovascular risk than LDL-C alone, particularly among individuals with insulin resistance, obesity, metabolic syndrome, or elevated triglycerides.[18,19] Adding to the complexity, some studies report favorable changes in ApoB and lipoprotein characteristics despite stable or increased LDL-C. A systematic review found that carbohydrate reduction was associated with fewer small, dense LDL particles and a shift toward larger LDL particles, which some researchers believe may be less likely to contribute to plaque buildup.[20] However, other studies have reported increases in both LDL-C and ApoB among individuals following low-carbohydrate therapies.[6,7]

Understanding the Cholesterol Question

These findings highlight one of the central questions in the cardiovascular nutrition literature: how changes in LDL-C, ApoB, and other lipoprotein markers should be interpreted alongside broader improvements in metabolic health. While low-carbohydrate and ketogenic therapies can improve multiple cardiometabolic risk factors, understanding whether the combined pattern of lipid and metabolic changes ultimately translates into fewer cardiovascular events remains a key area of investigation.

From Risk Factors to Cardiovascular Events

Taken together, the findings highlight the value of more comprehensive cardiovascular risk assessment and evidence-based nutritional interventions as part of routine preventive care.

While research is needed to evaluate their long-term effects on cardiovascular events, low-carbohydrate and ketogenic therapies have consistently demonstrated improvements across multiple cardiometabolic risk factors and may favorably influence many of the metabolic processes that drive CVD. As such, they warrant consideration within broader strategies to improve cardiovascular and metabolic health.

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