Obesity and Cardiovascular Disease – Beyond Body Weight and Energy Balance

Katharina Lechner¹,², MD; Ronald M Krauss³, MD

Author Affiliations:
¹ German Heart Centre Munich, Technical University Munich, Germany
² DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
³ University of California, San Francisco, San Francisco, California, USA

Corresponding author:
Dr. med. Katharina Lechner
Department of Cardiology, German Heart Centre Munich, Technical University Munich
Lazarettstraße 36 · 80636 Munich, Germany
Phone: +49 089 1218 0 · Fax: +49 089 1218 0 · E-mail: contact@katharinalechner.net

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Obesity is a serious public health issue with complications that burden healthcare systems worldwide. While there is abundant evidence for harmful effects of obesity on atherosclerotic cardiovascular disease (ASCVD) risk, there have also been arguments that its effect is neutral. The definition of obesity might lie at the core of the confusion of the disparate effects of obesity on ASCVD risk, as body mass index (BMI), the traditional anthropometric index used to define obesity, disregards the proportion of lean body mass to fat mass, as well as adipose tissue distribution and phenotype. These are important determinants of cardiometabolic health and result in considerable individual metabolic heterogeneity among individuals with any given body weight. Therefore, the focus on weight loss per se might not represent the optimal clinical care path to combat the twin pandemics of obesity and ASCVD. Moreover, dietary strategies to achieve weight loss are problematic if they do not address important hormonal responses to food cues that modulate satiety or if they disregard the role of food matrix that can impact health across the spectrum of BMI. Recently, alternative concepts have been proposed that focus on diet quality rather than solely on energy balance, on increasing cardiorespiratory fitness/reducing sedentary behavior, and on other factors such as restorative sleep patterns and minimization of stress which have been shown to favorably affect body composition and metabolic phenotype even in the absence of weight loss.

In this issue of the European Journal of Preventive Cardiology, a position paper on behalf of the World Heart Federation and the World Obesity Federation reviews the relation of obesity to ASCVD risk and presents management strategies. We commend these groups for raising awareness of this important issue within the preventive cardiology community. Notably, the authors review the unequivocal evidence that markers for truncal adiposity such as waist circumference provide independent and additive information to body weight/BMI for predicting
morbidity and risk of death.\textsuperscript{6} Waist circumference is a surrogate for the presence of the accumulation of dysfunctional ectopic adipose tissue in organs such as the liver, pancreas and pericardium.\textsuperscript{4} This lies at the core of a cluster of local and systemic traits that have been linked to ASCVD, and include an atherogenic lipoprotein pattern as well as insulin resistance, compensatory hyperinsulinaemia, and type 2 diabetes (T2D).\textsuperscript{4} Consistent with this notion, mobilization of ectopic fat depots in liver, pancreas and pericardium has been associated with amelioration of ASCVD risk factors independent of body weight.\textsuperscript{7} Hence management of truncal obesity has been suggested as a “vital” clinical target in a recent Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity.\textsuperscript{6} With respect to management strategies, and specifically regarding dietary advice, the authors state that while diets rich in vegetables, fruits and fiber, with lower amounts of red meat, are generally considered as promoting cardiovascular health, much controversy remains regarding specific dietary interventions for preventing and managing ASCVD risk associated with excess adiposity.

We are of the opinion that dietary policies for the management of obesity during the past decades have limitations and that alternative strategies should be considered. First, there is no compelling evidence that calorie- and nutrient-based approaches, with one of the major components being restriction of dietary (in particular, saturated) fat, have substantially reduced cardiometabolic disease burden.\textsuperscript{5} Another major limitation is that a simple energy balance model of obesity disregards the complex and weight-independent effects of food matrix and dietary patterns on metabolic and hormonal responses related to satiety and other intermediary pathways relevant to cardiovascular and overall health.\textsuperscript{5,8} According to the alternative carbohydrate-insulin model, the hormonal responses to highly processed carbohydrates shift energy partitioning from fuel oxidation toward energy deposition in adipose tissue.\textsuperscript{8} In turn, dietary carbohydrate restriction, by
lowering insulin levels, may favor fat mobilization. Supporting this hypothesis, Gepner et al. reported that in the CENTRAL-MRI trial a Mediterranean low carbohydrate dietary pattern was superior to a low fat diet in mobilizing fat depots in liver, pancreas and pericardium in patients with truncal adiposity and/or atherogenic dyslipidemia. Interestingly, amelioration of lipid traits related to ASCVD risk (elevated triglycerides and triglyceride/high-density lipoprotein cholesterol ratio) correlated with reductions in visceral/hepatic fat, but not with BMI per se, supporting the notion that preferential mobilization of visceral/ectopic fat can improve cardiovascular risk factors in individuals with obesity. Thus, a focus on limiting carbohydrate intake, particularly highly processed grains and added sugar, provides an alternative approach to the current “eat less – exercise more” strategy for treatment of obesity and related ASCVD risk.

There has been concern that low carbohydrate intake, and particularly extreme restriction that induces nutritional ketosis, has the potential to raise LDL-cholesterol (LDL-C) levels. However, in evaluating the potential impact of this increase on ASCVD risk a more nuanced view should be taken based on the effects of dietary carbohydrate on the overall lipoprotein profile. Atherogenic dyslipidemia, a lipoprotein pattern strongly associated with ASCVD risk, is pathophysiologically linked to relative overconsumption of dietary sugars/starches (i.e. above levels that can be directly oxidized), particularly in the presence of pre-existing (hepatic) insulin resistance. This promotes increased hepatic de novo lipogenesis and reduced long chain fatty acid oxidation, resulting in secretion of large very low-density lipoprotein particles enriched in ApoC3 and palmitic acid (C16:0) that are precursors of atherogenic remnant lipoproteins and cholesterol depleted small, dense LDL particles. Both C16:0 and ApoC3 contribute to vascular inflammation through activation of toll-like receptor 2/4 and subsequent NLRP3-inflammasome activation. Dietary carbohydrate restriction has the potential to reverse this coordinated pattern of lipoprotein abnormalities. For example, in 262 individuals living with T2D [baseline mean
(SD) age 54 (8) year, BMI 40.4 (8.8) kg/m²), a very low carbohydrate dietary pattern resulting in nutritional ketosis reduced body weight, reversed atherogenic dyslipidemia in the majority, and reduced inflammatory biomarkers of ASCVD risk after one year. While an increase in LDL-C of about 10% was observed in this study, there was no increase in atherogenic lipoproteins as assessed by plasma apoB concentration and total LDL particle number. After two years, a sustained improvement in the atherogenic lipid and lipoprotein profile was observed in a subgroup analysis of this study. This reiterates the importance of assessing lipid and lipoprotein markers beyond LDL-C for risk stratification in patients with truncal obesity and provides a perspective on atherogenic lipoprotein pattern as a key modifiable component in ASCVD prevention.

In conclusion, the presence of truncal adiposity deserves a comprehensive cardiovascular risk assessment. Management should involve a multidisciplinary approach aimed at implementing personalized eating patterns and increasing physical activity, as well as providing psychosocial assessment and guidance that may mitigate behavioral and physiologic responses to stress. Public health initiatives aimed at decreasing sedentary time at work and the burden of environmental stressors such as non-physiological light exposure (i.e. blue light) and nighttime noise and air pollution can further ameliorate risk factors for obesity and ASCVD.

**Author contribution**

K.L. did the literature search, and drafted the manuscript. Ronald M Krauss revised and edited the manuscript. Both authors approved the final version of this manuscript.

**Declaration of conflicting interests**

KL has no conflict of interest to declare. RMK is a scientific advisor for Virta Health and receives grant support from Quest Diagnostics.
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