Trends in Cardiovascular Medicine 29 (2019) 226–227

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

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

Editorial Commentary: The obesity paradox in cardiovascular disease: Deeper phenotyping to get to the heart of the matter

Abbi Lane-Cordova

Department of Exercise Science, Arnold School of Public Health, University of South Carolina at Columbia, Columbia, SC 29201, USA

The review by Xia, Lloyd-Jones, and Khan in this issue of *Trends in Cardiovascular Medicine* provides insight regarding the obesity paradox. The *obesity paradox* refers to the paradoxical yet consistently replicated observation that individuals with cardiovascular disease (CVD) classified as overweight/obese according to body mass index (BMI) tend to live longer than normal-weight individuals [1].

As noted by Xia et al. [1], using BMI to classify individuals as overweight or obese has major limitations. First, BMI fails to distinguish between fat versus lean mass. The distinction is important because the presence of more muscle mass may indicate less unintentional weight loss prior to study enrollment, or (like excess fat stores), provide additional metabolic reserve after CVD diagnosis. Simply determining whether total or regional amounts of lean mass modify the obesity paradox will be an important initial step. However, there is heterogeneity in muscle biochemical and functional properties, termed "muscle quality". Molecular markers of muscle quality, such as markers of mitochondrial biogenesis and fat transport and oxidation, can be measured using invasive muscle biopsy techniques [2]. But standard physical performance tests provide a non-invasive, real-life index of muscle quality and function that have been associated with CV outcomes [3]. In a study of 1506 men with existing hypertension, muscular strength, an index of muscle quality, was inversely associated with all-cause mortality [4]. Quantification of muscle mass and the inclusion of muscle biopsies or physical performance tests in cohorts of individuals with CVD are needed to determine whether muscle mass and/or quality modify the obesity paradox.

Second, BMI offers no information about regional fat distribution or fat characteristics. Like the differences in muscle tissue, several recent studies have suggested that all adipose tissue is not the same. Dysfunctional adiposity, defined as visceral fat and evidence of insulin resistance, was associated with new-onset prediabetes and diabetes in a study of 732 adults with obesity [5], but total body fat and BMI were not linked to incident diabetes in the same study. Centrally-distributed adipose tissue, measured with a CT scan, was also associated with excess CV mortality and CV risk factor abundance in the Framingham cohort [6,7]. Waist circumference was an independent predictor of mortality across BMI categories in patients with end-stage renal disease, providing further support for the idea that patterns of fat distribution matter in chronic disease states [8]. Adipose tissue functions as an endocrine organ, and inflammatory and hypoxic proteins and adipokines secreted in varying concentrations from different fat depots have robust and largely negative systemic effects. The differential associations between central/visceral versus subcutaneous fat and mortality may be attributable to pro-inflammatory or otherwise undesirable endocrine properties of visceral versus subcutaneous fat depots [9].

Xia et al. [1] also discuss the poorly understood relationship between obesity, cardiorespiratory fitness, physical activity, and mortality in individuals with CVD. For example, a recent study of 774 black and white men and women detected an obesity paradox in heart failure patients with low exercise capacity ($\leq$4 METS) but found that the obesity paradox did not exist in heart failure patients with an exercise capacity $\geq$4 METS [10]. The investigations included in the review in this issue also detected the obesity paradox in low-fit or sedentary individuals. Patients with both lower BMI and low fitness might be fundamentally different, sicker patients, who have a more aggressive disease course or have endured a longer duration of disease. Low BMI-low fit patients might have less favourable body composition or poorer muscle and fat quality. Deeper phenotyping of muscle and fat tissue and exercise capacity is needed to better understand the obesity paradox in CVD and inform treatment.

Whether increasing physical activity and/or improving fitness, independent of changes in body weight, improves outcomes in individuals with CVD is not known, though Vanhees, et al., found that every 1% improvement in fitness achieved during a 3-month cardiac rehabilitation program was associated with a 2% lower hazard ratio of cardiovascular mortality in men with coronary disease [11]. Regular exercise participation has measurable effects on body composition, muscle quality, and non-traditional CVD risk factors, such as autonomic and endothelial function [12,13], that are also associated with mortality. Thus, performing physical activity or improving fitness might increase survival in individuals with CVD even without changing BMI [14]. Along these lines, there have been few randomized, controlled studies of intentional weight loss in patients with CVD. A study of patients with atrial fibrillation found that sustained weight loss, induced by diet and exercise, was associated with better survival [15]. When bigger doses of exercise were used to induce significantly greater weight loss in patients participating in a cardiac rehabilitation program, the group

E-mail address: lanecord@mailbox.sc.edu

https://doi.org/10.1016/j.tcm.2018.08.010

that performed the biggest exercise dose and experienced the most weight loss achieved parallel, graded improvements in endothelial function, measured in-vivo with flow-mediated dilation [16]. These results suggest that increasing physical activity, improving fitness, or intentional weight loss might improve outcomes in individuals with CVD via multiple potential pathways, but larger trials in diverse populations and women are needed.

Finally, however perplexing the obesity paradox may be, there is no paradox in prevention. While the current review offers explanations for the obesity paradox in individuals with CVD, the authors also emphasize that there is no doubt that obesity increases the risk of CVD in the first place. Public health efforts should focus on life-long achievement and maintenance of a favourable BMI and adoption of favourable lifestyle factors, especially regular exercise.

Acknowledgments

ALC is funded by the American Heart Association (18CDA34110038).

References

[1] Xia JY, Lloyd-Jones JY, Khan SS. Association of body mass index with mortality in cardiovascular disease: new insights into the obesity paradox from multiple perspectives. Trends Cardiovasc Med 2018 in press.
[2] Mulya A, Haus JM, Solomon TP, Kelly KR, Malin SK, Rocco M, et al. Exercise training-induced improvement in skeletal muscle PGC-1alpha-mediated fat metabolism is independent of dietary glycemic index. Obes (Silver Spring) 2017;25(4):721–9.
[3] Chainani V, Shaharyar S, Dave K, Choksi V, Ravindranathan S, Hanno R, et al. Objective measures of the frailty syndrome (hand grip strength and gait speed) and cardiovascular mortality: a systematic review. Int J Cardiol 2016;215:487–93.
[4] Artero EG, Lee DC, Ruiz JR, Sui X, Ortega FB, Church TS, et al. A prospective study of muscular strength and all-cause mortality in men with hypertension. J Am Coll Cardiol 2011;57(18):1831–7.
[5] Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. JAMA 2012;308(11):1150–9.
[6] Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. J Am Coll Cardiol 2013;62(10):921–5.
[7] Lee JJ, Pedley A, Hoffmann U, Massaro JM, Levy D, Long MT. Visceral and intrahepatic fat are associated with cardiometabolic risk factors above other ectopic fat depots: the framingham heart study. Am J Med 2018;131(6):684–92 e12.
[8] Postorino M, Marino C, Tripepi G, Zoccali C, Group CW. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. J Am Coll Cardiol 2009;53(15):1265–72.
[9] Kwon EY, Shin SK, Cho YY, Jung UJ, Kim E, Park T, et al. Time-course microarrays reveal early activation of the immune transcriptome and adipokine dysregulation leads to fibrosis in visceral adipose depots during diet-induced obesity. BMC Genomics 2012;13:450.
[10] McAuley PA, Keteyian SJ, Brawner CA, Dardari ZA, Al Rifai M, Ehrman JK, et al. Exercise capacity and the obesity paradox in heart failure: the fit (henry ford exercise testing) project. Mayo Clin Proc 2018;93(6):701–8.
[11] Vanhees L, Fagard R, Thijs L, Amery A. Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. Am J Cardiol 1995;76(14):1014–19.
[12] Fu Q, Levine BD. Exercise and the autonomic nervous system. Handb Clin Neurol 2013;117:147–60.
[13] Walker AE, Kaplon RE, Pierce GL, Nowlan MJ, Seals DR. Prevention of age-related endothelial dysfunction by habitual aerobic exercise in healthy humans: possible role of nuclear factor kappaB. Clin Sci (Lond) 2014;127(11):645–54.
[14] Pedersen BK. Body mass index-independent effect of fitness and physical activity for all-cause mortality. Scand J Med Sci Sports 2007;17(3):196–204.
[15] Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015;65(20):2159–69.
[16] Ades PA, Savage PD, Lischke S, Toth MJ, Harvey-Berino J, Bunn JY, et al. The effect of weight loss and exercise training on flow-mediated dilatation in coronary heart disease: a randomized trial. Chest 2011;140(6):1420–7.