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Editorial

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The Obesity Paradox: An Epiphenomenon vs. A Clue for the Hidden Pathophysiology of Adiposity

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▸ See the article "Association Between Body Mass Index and Clinical Outcomes According to Diabetes in Patients Who Underwent Percutaneous Coronary Intervention" in volume 53 on page 843.

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Historically, the obesity paradox was first described in 1999 by Fleischmann et al.,[1] who reported a lower risk of mortality with higher body mass index (BMI), and a worse prognosis with lower BMI, among patients undergoing hemodialysis. Subsequently, this "reverse epidemiology," which contrasts against well-established associations between obesity and cardiovascular risk factors, has been observed in patients with various cardiovascular diseases, such as coronary artery disease, heart failure, and peripheral artery disease.[2-5]

Several mechanisms have been proposed to explain this phenomenon (**Figure 1**). Most importantly, possible methodological flaws, such as confounding factors, detection bias, reverse causality, and selection bias, should be considered.[6] Another important aspect is the limitations in BMI as a measurement parameter; BMI does not directly reflect adiposity or fat mass. Nonetheless, several studies have suggested that there may be something more to this famous phenomenon. For example, the role of adiponectin has been suggested as a potential mechanism for this phenomenon; adiponectin is mainly secreted from adipose tissue, exerts protective effects against inflammation, and enhances insulin sensitivity.[7] Although evidence regarding causality is lacking, given lower adiponectin levels in individuals with obesity than in lean individuals, the higher risk of mortality and cardiovascular disease observed in individuals with high adiponectin levels in epidemiological studies suggests that the 'adiponectin paradox' could play a role in the obesity paradox.[8] Further, the complex biology of adipose tissue could play a role in the mechanism underlying the obesity paradox.[9]

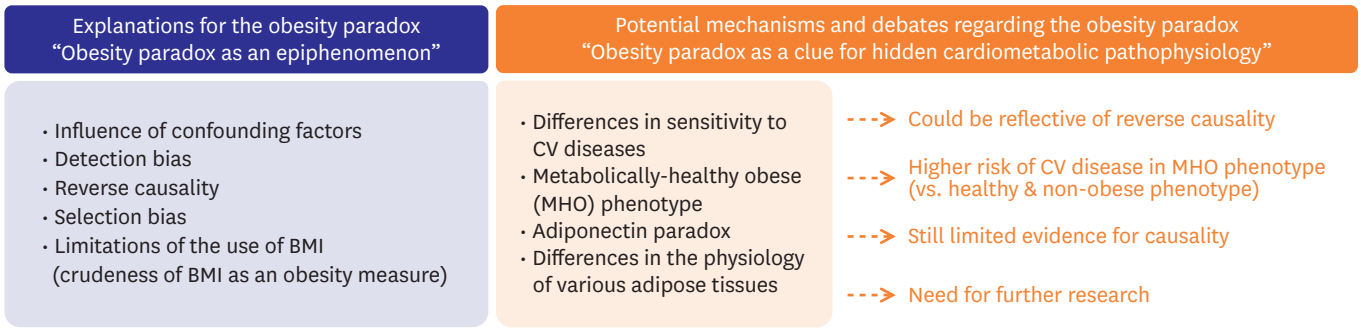

Figure 1. Explanations, potential mechanisms, and debates regarding the obesity paradox.
BMI = body-mass index; CV = cardiovascular.

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Another issue currently debated is the metabolically-healthy obesity (MHO). In individuals with the MHO phenotype, which mainly indicates those with a high BMI but without metabolic syndrome, better cardiorespiratory fitness has been suggested as the key to better clinical outcomes.[9]

A study by Kim et al.[10] in the current issue of the *Korean Circulation Journal* raises another possibility of "hidden modulators" behind the epidemiologic phenomenon of the obesity paradox. The authors investigated the effect of diabetes on the relationship between BMI and clinical outcomes following percutaneous coronary intervention and reported that this relationship differed according to diabetic status. Specifically, a higher risk of cardiovascular events in the underweight group than in the normal weight group was consistently observed regardless of diabetic status. However, a lower risk of cardiovascular events in the overweight to obese group than in the normal weight group was observed only among those with diabetes.

Why does diabetic status matter to the phenomenon of the obesity paradox? The authors suggested a possible influence of inherited sensitivity to cardiovascular diseases among underweight patients with diabetes, advanced age, poor renal function, or fragility, as well as a potential detection bias due to accelerated symptoms of cardiovascular diseases.[10] While methodological biases might still partly explain these findings, they also suggest that there could be some hidden effects of diabetes on the obesity paradox, that is, cardiometabolic modulators play a role.

To better understand the obesity paradox and its clinical consequences, several aspects should be emphasized in future studies. First, the use of direct adiposity measurements may enhance obesity-related research. Secondly, more effort should be made to elucidate the underlying pathophysiology. Third, the individual's cardiometabolic status and level of physical activity should be considered in terms of the MHO phenotype. The current study by Kim et al.[10] draws attention to these issues and facilitates future research to establish more tailored management strategies for obesity.

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