Obesity Paradox − The Controversial Role of Body Mass Index and Plasma Adiponectin in Coronary Artery Disease and Acute Coronary Syndrome

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Body mass index (BMI) is an anthropometric index used to evaluate a person's weight. In the general population, higher BMI is associated with more adverse outcomes as well as cardiovascular risk factors. The current clinical guidelines suggest weight control within desirable BMI as 18.5 to 24.9 kg/m^2. In the event of coronary artery disease or acute coronary syndrome, the impact of BMI on clinical outcomes still remains controversial. Some studies have demonstrated that overweight and obese patients had better prognosis than normal weight patients. Adiponectin, a secretory protein produced by adipocytes and inversely proportional to BMI, is a possible mediator for the so-called "obesity paradox", a term for the obese-protective phenomenon. Lower plasma adiponectin is associated with the progression of coronary artery disease. However, in the presence of acute coronary syndrome, patients with higher plasma adiponectin could be associated with adverse outcomes. Further studies including serial change of plasma adiponectin, or the use of other methods to discriminate lean and fat body mass are necessary to investigate this seemingly contradictory topic.

Key Words: Adiponectin • Body mass index • Obesity paradox

INTRODUCTION

A person's weight can be evaluated clinically by body mass index (BMI), an anthropometric index defined as weight in kilograms (kg) divided by the square of the height in meters (m^2).[1] According to global estimates from the World Health Organization (WHO), obesity is becoming a prevalent problem because the incidence rate of obesity in the general population has been progressively increasing, not only in Western countries but also in predominantly Asiatic areas areas − including Taiwan and China.[1-5] Besides, obesity is associated with increased morbidity and overall mortality, as well as with cardiovascular risk factors such as diabetes, hypertension and hyperlipidemia.[6-8] This review will address the current understanding of the impact of BMI on patients presenting with coronary artery disease (CAD), especially those with acute coronary syndrome (ACS).

Increasing body mass index is a prevalent issue in general population

BMI is an anthropometric index which is calculated as a person's weight in kilograms (kg) divided by the square of height in meters (m^2). According to the definition of World Health Organization (WHO), adult BMI $\geq$ 25 is overweight, and $\geq$ 30 indicates obesity (Table 1).[1] In the United States, incidence rates of overweight and

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obesity have increased 2 to 3-fold over the past 50 years.[3] Worldwide, the obesity rate in the general population has doubled since the 1980s. In a recent report derived from WHO global estimates,[2] over 10 percent of the world's adult population is obese. The classification of BMI in Taiwan is different from that used by the WHO (Table 2).[4] In Taiwan, the normal weight is defined as 18.5-23.9 in BMI while it is 18.5-24.9 according to the WHO criteria (Table 1, 2). According to a report released arising from the 2011 Nutrition And Health Survey In Taiwan (NAHSIT), the prevalence of overweight and obesity status in Taiwan was more than 50% for male and 36% for female.[5] Comparing the Taiwanese data with data from other countries, the prevalence of obesity in Taiwan is higher than in many other Asian countries, but less than in the West. Based on this larger trend of an increasing incidence of obesity worldwide, we should face up to the impact of BMI on public health in Taiwan.

Obesity is a risk factor for the development of coronary artery disease

A number of studies have demonstrated that obesity is associated with increased morbidity and overall mortality, as well as with CAD risk factors such as diabetes, hypertension and hyperlipidemia.[6-8] Therefore, the American Heart Association and American College of Cardiology guidelines have listed obesity as a major modifiable cardiovascular risk factor.[9] These guidelines also recommend weight management by measuring the BMI and waist circumference, and suggest a desirable BMI range as 18.5 to 24.9 kg/m^2.

There are several pathways to explain how obesity increases the risk of CAD and adverse cardiovascular events. Obesity enhances free fatty acid metabolism, reduces insulin sensitivity, increases sympathetic activities, promotes systemic inflammation, and induces a

hypercoagulable state; all of these factors contribute to the development and progression of CAD.[10] One potential mediator of the aforementioned effects is adiponectin, which is a protein mainly secreted by adipocytes.

Adiponectin is predominately produced by adipose tissue. Recent studies suggest that it could be also synthesized and secreted by cardiomyocytes, especially upon stimulation such as with angiotensin II.[11,12] The adiponectin gene is located on chromosome 3q27 in humans and consists of 247 amino acids.[11,13] The primary role of adiponectin is to exert response to extracellular stimuli and metabolic changes. In rodents, the major effect of adiponectin is to increase fatty acid oxidation in muscle, resulting in improved insulin sensitivity.[14] Although mainly produced by adipocytes, plasma adiponectin levels are inversely proportional to BMI and visceral adiposity.[15-17] Hypoadiponectinemia in obese individuals and those with type 2 diabetes is associated with insulin-resistance and increased plasma C-reactive protein.[16] It was shown that plasma adiponectin levels < 4.0 μg/ml may have a 2-fold increase in the prevalence of CAD.[17] In our recent animal study, administration of globular adiponectin improved high glucose-impaired endothelial progenitor cell functions in vasculogenesis by up-regulation of endothelial nitric oxide synthase (eNOS) activity.[18] These findings may explain some of the putative anti-atherogenic, vasoprotective properties of adiponectin and provide a potential therapeutic rationale of adiponectin for vascular repair in type 2 diabetic subjects.

However, plasma adiponectin level may not be universally reduced in the presence of different cardiovascular risk factors. In non-diabetic hypertensives, plasma adiponectin level is generally reduced in those subjects with metabolic syndrome.[19] Furthermore, plasma adiponectin level may not be associated with endothelial

Table 1. Classification of adult body mass index (BMI) in World Health Organization

Classification	BMI (kg/m^2)
Underweight	< 18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Class I obese	30.0-34.9
Class II obese	35.0-39.9
Class III obese	≥ 40

Table 2. Classification of adult BMI in Taiwan

Classification	BMI (kg/m^2)
Underweight	< 18.50
Normal weight	18.5-23.9
Overweight	24.0-26.9
Mild obese	27.0-29.9
Moderate obese	30.0-35.9
Severe obese	≥ 35

dysfunction in hypertensive subjects without type 2 diabetes.[20] Thus, it remains to be investigated whether low plasma adiponectin levels may directly contribute to the acceleration and progression of atherosclerosis in non-diabetic patients with obesity and/or metabolic syndromes.

The relation of BMI to acute coronary syndrome remains controversial

Once CAD occurs, obesity may have an impact on overall and cardiovascular mortality. In fact, a number of epidemiological studies have suggested that obesity may provide "protection" in some major cardiovascular diseases. For example, in patients with heart failure,[21] atrial fibrillation,[22] and sudden cardiac death,[23] clinical outcomes and survival have been shown to be more favorable among obese patients than among those of normal weight. This phenomenon led to the proposal of the "obesity paradox". In a meta-analysis study from heart failure patients reported by Oreopoulos et al., compared to individuals with normal weight, both overweight and obesity were associated with lower all-cause mortality [relative risk (RR) 0.84, 95% confidence interval (CI) 0.79-0.90 of overweight; RR 0.67, 95% CI 0.62-0.73 of obesity] as well as cardiovascular mortality (RR 0.81, 95% CI 0.72-0.92 of overweight; RR 0.60, 95% CI 0.53-0.69 of obesity).[21] In patients of atrial fibrillation, a post-hoc analysis from the AFFIRM study revealed overweight and obesity were associated with lower all-cause mortality as compared with normal weight [hazard ratio (HR) 0.64, 95% CI 0.48-0.84, p = 0.001 for overweight; HR 0.80, 95% CI 0.68-0.93, p = 0.005 for obese]. Overweight and obese patients also had lower cardiovascular mortality on multivariate analysis (HR 0.40, 95% CI 0.26-0.60, p < 0.001 of overweight; HR 0.77, 95% CI 0.62-0.95, p = 0.01 of obesity).[22]

Although the manifestation of a "protective phenomenon" of higher BMI is obvious in some major cardiovascular diseases, the relation between obesity and prognosis in patients with established CAD has revealed contradictory results.[24-28] In Martin et al.'s report,[24] obesity is associated with a significant increase in target vessel revascularization following by percutaneous coronary intervention (PCI), especially in patients < 65 years of age (BMI > 30 vs ≤ 30 kg/m^2: 12.3% vs. 8.4%, p = 0.003). Other long- and short-term ischemic events are similar in obese and non-obese patients. However, in recent study reported by Bashey et al., overweight and obese patients had higher incidence rates of metabolic abnormalities but better prognosis after elective PCI. In this study, all-cause mortality per 1000 person-years of BMI levels of 18.5-25.0, 25.0-29.9 and 30.0-34.9 kg/m^2 were 55.5%, 33.7%, and 28.3%, respectively.[28] After adjustment for metabolic abnormalities and compared to those BMI of normal weight, patients with BMI of overweight and obesity had a lower hazard ratio for all-cause mortality.[28]

Studies on the obesity paradox in patients presenting with ACS have revealed controversial results.[29-32] Rana et al. reported that BMI appeared to have an inverse relation with post-myocardial infarction death. In this study, after adjusting age, sex, and race, all-cause mortality rate was higher in overweight and obese patients (HR 0.96, 95% CI 0.74-1.26 of overweight; HR 1.44, 95% CI 1.04-2.01 of class I obese; HR 1.62, 95% CI 1.02-2.57 of class II and III obese).[29] On the other hand, in Wells et al.'s report for patients with acute myocardial infarction (AMI), there were no statistically significant associations between BMI and outcomes (in AMI), including morbidity, mortality, and length of stay.[30] In-hospital mortality in BMI < 20, 20-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m^2 were 18%, 8%, 7%, 11%, 4.8% (p = 0.515), respectively; all-cause mortality rates were 0%, 1.6%, 1.0%, 1.5%, 0% (p = 0.918), respectively.[30] The authors concluded that obesity does not adversely influence clinical outcomes in AMI. However, in a recent study analyzing 50149 patients with ST-elevation myocardial infarction (STEMI), rates of adverse outcomes were highest among normal-weight patients, lower in overweight and class I to II obese patients, and then increased again in patients with class III obesity.[32] The in-hospital death rate of normal weight, overweight, class I, II, and III obese patients were 7.7%, 5.0%, 4.3%, 4.4%, 6.1%, respectively.[32] After multivariate adjustment, the adjusted odds of death were not significantly different between normal-weight, overweight, and obese patients.[32]

Although the conclusions are in conflict with each other, there are some common features noted in these contradictory studies. First, for patients presenting with CAD or ACS, the average age was younger in the obese BMI groups than in normal weight and underweight

groups. Second, higher BMI was associated with higher incidence rates of metabolic abnormalities such as dyslipidemia, diabetes, and hypertension. Third, the number of patients of overweight and obesity was much more than those of normal weight and underweight.

Does adiponectin play a prognostic role for clinical outcomes in patients with CAD or ACS?

Among patients with established CAD, those with complex coronary lesions had significantly lower plasma adiponectin levels than those with simple lesions.[33,34] Although a lower plasma adiponectin level appears to be associated with progression of atherosclerosis and greater coronary lesions complexity, if raised in patients with CAD, it becomes associated with an increased risk for cardiovascular events.[35] Pilz et al. have shown that a relatively higher plasma adiponectin level in CAD patients could independently predict adverse cardiovascular events.[36] Wilson et al. measured plasma adiponectin in 3931 patients stabilized following ACS and assessed the relationship following a 2-year outcome overview. In this study, adiponectin greater than the median (4477 ng/mL) was independently associated with an increased risk of death or recurrent myocardial infarction (HR 1.60, 95% CI 1.29-1.97, p < 0.001).[37] The authors concluded that higher plasma adiponectin level after ACS is independently related to a higher risk of future adverse events.

Although a large number of studies have shown the relationship between plasma adiponectin levels and the prognosis of ACS, it remains uncertain whether plasma adiponectin could directly contribute to the development of the "obesity paradox". Future clinical studies are required to clarify these issues.

Possible clinical explanations for obesity paradox in patients of ACS

There are some clinical clues proposed for the "obesity paradox".[38] First, patients with lower BMI are older and may have other systemic illness. Therefore, a portion of the mortality rate might be attributable to noncardiac reasons. Obese patients tended to have better left ventricular ejection fraction and renal function, which exert a potentially positive effect on patient prognosis. Second, lower BMI has been related to lower lean mass, a condition known as sarcopenia. Patients with

sarcopenia may have a limited exercise capacity and reduced mobility, both conditions which are associated with increased total mortality. Small increments of BMI as seen in overweight and mildly obese patients can be due to a preserved or increased lean mass with little elevation in body fat. Preserved or increased lean mass have been associated with an improved capacity to deal with the stress of ACS and PCI. This implies the use of BMI as a measuring tool has a poor ability to discriminate lean and fat body mass. Third, overweight and obese patients are often younger in age. However, younger age at presentation may have provided the survival benefit in the obese patients. Furthermore, these patients might receive more aggressive treatment after presenting with CAD or ACS. Fourth, low and normal BMI groups were associated with a lower prevalence of established metabolic abnormalities. Therefore, these BMI groups were less likely to be a target of aggressive secondary prevention therapies for modifying cardiovascular risk factors – such as healthy diet and exercise, cholesterol reduction, or treatment for diabetes and hypertension.

Recent novel studies of the obesity paradox and adiponectin in Taiwan

In Taiwan, both the BMI definition of obesity and the distribution of BMI in the general population are different from that common definition typically used in Western countries. It could prove interesting and medically beneficial to further explore and investigate the obesity paradox and adiponectin in Taiwan. We have recently measured plasma adiponectin for 962 participants from 302 families, and investigated the association of adiponectin (*ADIPOQ*) gene with the phenotypes of hypertension and metabolic syndrome in a primary prevention cohort.[39] In this study, metabolic syndrome could be linked to decreased plasma adiponectin values. Furthermore, plasma adiponectin was significantly lower in patients with metabolic syndrome with hypertension component (9.3 ± 0.47 µg/ml), as compared to that in hypertension alone (13.4 ± 0.74 µg /ml) and that in metabolic syndrome without hypertension (11.9 ± 0.60 µg/ml, p < 0.05).[39] It was also demonstrated that *ADIPOQ* genetic variants were selectively and specifically associated with the concomitant presence of metabolic syndrome and hypertension, suggesting a poten-

tial genetic linkage between metabolic syndrome and hypertension.[39] Accordingly, it seems that the genetically determined plasma adiponectin level could be a particular marker for the presence of metabolic syndrome with hypertension.

On the other hand, we also found that in 96 patients with chronic heart failure, circulating concentrations of adiponectin increased with the severity of heart failure; additionally, higher plasma adiponectin levels were predictive for the development of major adverse cardiac events (MACE) (with MACE vs. without MACE: 23133 ± 15519 vs. 15289 ± 12258 ng/ml, p = 0.009).[19] Besides, we have further shown that BMI was inversely associated with plasma adiponectin (γ = -0.203, p = 0.003) and the prognosis of patients with CAD who underwent coronary artery bypass grafting (CABG).[40] In this study, patients with BMI < 25 kg/m^2 had a decreased event-free survival when compared to those with BMI ≥ 25 kg/m^2. After accounting for age, sex, manifest acute coronary syndrome, glomerular filtration rate, and left ventricular ejection fraction, BMI remained inversely correlated with cardiovascular mortality in the study population. [HR and 95% CI per 1 kg/m^2: 0.912 (0.833 to 0.998)].[40] It was also shown that higher plasma adiponectin was adversely related to long-term prognosis after CABG (survivor vs. non-survivor: 6.59 ± 4.48 mg/L vs. 10.07 ± 7.32 mg/L, p < 0.001).[40] Altogether, our findings in heart failure and CAD are in concordance with those findings of Pilz et al. in CAD patients, and those of Wilson et al. in ACS patients.[37] It seems that in these secondary prevention cohorts, higher plasma adiponectin level could be an indicator of a higher risk of future adverse events, which could be significantly different from the association of reduced plasma adiponectin level with the cluster of cardiovascular risk factors including metabolic syndrome and hypertension in the primary prevention cohort. It is also interesting that, consistent with the so-called "obesity paradox", increased BMI could be a protective indicator of adverse events after CABG in our CAD patients.

CONCLUSIONS

As one of the common measurements of obesity, BMI is a prevalent term used to describe what can only be characterized as an obese population which is increasing progressively. BMI is associated with overall mortality in the general population, as well as cardiovascular risk factors such as dyslipidemia, hypertension, and diabetes. However, it remains controversial whether the "obesity paradox" exists among patients presenting with CAD or ACS. Though suggested as a potential mediator of the "obesity paradox", the potential mechanistic role of adiponectin should be further investigated for the development and progression of atherosclerosis in obese subjects. Besides, improved and novel methods to precisely discriminate between lean and fat body mass are also necessary to further clarify the real presence of the "obesity paradox".

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