Obesity and Coronary Heart Disease: Epidemiology, Pathology, and Coronary Artery Imaging

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ABSTRACT: Overweight and obesity contribute to the development of cardiovascular disease (CVD) in general and coronary heart disease (CHD) in particular in part by their association with traditional and nontraditional CVD risk factors. Obesity is also considered to be an independent risk factor for CVD. The metabolic syndrome, of which central obesity is an important component, is strongly associated with CVD including CHD. There is abundant epidemiologic evidence of an association between both overweight and obesity and CHD. Evidence from postmortem studies and studies involving coronary artery imaging is less persuasive. Recent studies suggest the presence of an obesity paradox with respect to mortality in persons with established CHD. Physical activity and preserved cardiorespiratory fitness attenuate the adverse effects of obesity on CVD events. Information concerning the effect of intentional weight loss on CVD outcomes in overweight and obese persons is limited. (Curr Probl Cardiol 2020;00:100655.)

It has become increasingly apparent during the past half-century that a relationship exists between overweight (OW)/obesity and cardiovascular (CV) disease (CVD), particularly coronary heart disease (CHD).[1-20] CHD may be characterized as coronary artery disease (CAD) and its complications.[1-20] OW and obesity are closely associated with multiple traditional and nontraditional (novel) risk factors for CVD.[1-9,11-20] The metabolic syndrome (MetS) refers to a clustering of risk factors

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for CVD. Patients with the MetS are a particularly high risk for CHD.[1-9,11-20] This review discusses the relation of OW and obesity to CVD and CHD based on epidemiologic and pathologic studies and on studies involving coronary artery imaging. It also provides evidence supporting the existence of an obesity paradox related to CHD. Finally, it describes the effects of physical activity, cardiorespiratory fitness (CRF), and intentional weight loss on CVD and CHD outcomes in patients who are OW or obese.

DEFINITIONS

The World Health Organization and related classifications of body weight, criteria for central (abdominal, visceral) obesity based on waist circumference (WC) and waist-hip ratio (WHR), and the most commonly-used criteria for the MetS are summarized in Table 1.[1,10-12,15-20]

OBESITY AND CVD

Risk Factors for CVD

There are a multiple genetic, physiological, and biochemical mechanisms that facilitate to the development of atherosclerotic vascular disease and by

Table 1. Commonly-used classifications and criteria associated with overweight and obesity

World Health Organization body weight classification*	
Underweight	<18.5 kg/m^2
Normal weight	18.5-24.9 kg/m^2
Overweight	25.0-29.9 kg/m^2
Class I obesity	30.0-34.9 kg/m^2
Class II (severe) obesity	35.0-39.9 kg/m^2
Class III (morbid, extreme) obesity	≥40.0 kg/m^2
Class IV (super) obesity	≥50.0 kg/m^2
Commonly-used markers of central obesity	
Waist circumference	≥102 cm in men; ≥88 cm in women
Waist-hip ratio	>1.0 in men; >0.8 in women
Metabolic syndrome (3 of the following 5 required):	
Waist circumference	≥102 cm in men; ≥88 cm in women
Blood pressure	≥130/85 mmHg
Serum triglyceride level	≥150 mg/dL
Serum HDL cholesterol level	<40 mg/dL in men; <50 mg/dL in women
Serum glucose level	>110 mg/dL

Table adapted from refs.[1,10-12]
Abbreviations: kg/m^2, kilograms per meter squared; cm, centimeters; mmHg, millimeters of mercury; mg/dL, milligrams/deciliter; HDL, high density lipoprotein.
*Body weight was expressed as body mass index (BMI).

extension CHD.[1-9,11-20] Traditional CVD risk factors associated with OW and obesity include type 2 diabetes mellitus (DM), hypertension, and various dyslipidemias (including elevated serum triglyceride levels, low serum levels of high-density lipoprotein, and increased serum levels of small dense low-density lipoprotein and apoprotein B.[1-6,11-20] Nontraditional or novel CVD risk factors associated with OW and obesity include insulin resistance, hyperinsulinemia, endothelial dysfunction, various inflammatory markers, and a variety of pro-thrombotic factors (increased serum fibrinogen levels, von Willebrand's factor, plasminogen activating factor-1, clotting factors VII and VIII).[1,11,16-20] Central obesity is key component of the MetS, which itself is an important risk factor for CVD including CHD.[1,15-20] The 27th Bethesda Conference classified obesity as an independent risk factor for CVD.[20]

EPIDEMIOLOGIC STUDIES

The relation of obesity to CVD has been the focus of numerous epidemiologic studies. Most commonly, they have attempted to determine the relationship of obesity to the risk of CVD or the risk of CHD. Some of these studies included risk assessment for cerebrovascular disease.

Relation of OW and Obesity to CVD and CHD: General Body Weight Indices

The Framingham Heart Study has proven to be a rich source of data concerning the relation of OW and obesity to CVD risk including CHD risk. The earliest of these trials was reported by Hubert et al and involved 2252 men and 2818 women (age range: 28-62 years, follow-up: 26 years).[21] Minimum relative weight was found to be a risk factor for CHD and stroke independent of risk factors such as age, cholesterol level, systolic blood pressure, left ventricular hypertrophy, and glucose intolerance. In a study of 597 men and 1126 women (age range: 55-65 years, follow-up: 23 years), Harris et al identified a "U" shaped mortality curve for body mass index (BMI).[22] In a trial of 2039 men and 2871 women (age range: 35-70 years, follow-up: 24 years), Kannel et al noted that the risk of CVD occurred in patients with abdominal and general obesity in a linear fashion.[23] In an update of this study, Kannel et al reported that after 26 years of follow-up, each standard deviation of relative weight gain predicted an increased risk of CHD and stroke of 15% in men and 22% in women.[24] In this study, optimal BMI for avoidance of CVD was 22.6 kg/m^2 in men and 21.1 kg/m^2 in women. Wilson et al showed that OW or obesity determined by BMI in men and women (age range: 35-75 years) followed for up to 44 years was associated with an increased incidence of CVD.[25]

Another large epidemiologic trial, the Nurse's Health Study, also provided a wealth of information concerning the relation of body weight to CVD, particularly CHD. Manson et al studied 115,886 women (age range: 30-56 years, follow-up: 8 years).[26] These investigators noted a link between obesity and the risk of CHD. A subsequent study showed that CHD mortality was less than that reported for women in the general US population.[27] In a study by Willett et al of middle-aged women followed for 14 years, the highest BMI within the range of weight gains after 18 years of age predicted elevated risk of CHD.[28] Rexrode et al studied 44,702 women followed for 12 years.[29] This study showed that women who were nonsmokers and whose BMI was $\geq$32 kg/m^2 had a relative risk of CVD mortality of 4.1 compared to women whose BMI was $<$19 kg/m^2. Cho et al noted that weight gain before the onset of DM was associated with increased risk of CHD in 5897 women (follow-up: 12 years, after adjustment for BMI and selected CVD risk factors.[30]

Baik et al studied 39,756 males (age range: 40-75 years, follow-up: 10 years) as part of the Health Professionals Follow-up Study.[31] The risk of CVD mortality rose progressively with increasing BMI in men $<$65 years old. In a previous study these investigators showed that in men $\geq$65 years old no association between BMI and CVD mortality was noted.[31]

A study by Field et al combined subgroups from the Nurse's Health Study and the Health Professionals Follow-up Study.[32] The study population consisted of 77,690 women and 40,060 men (follow-up: 10 years). In this study the risk of CHD or stroke rose in patients with increasing severity of OW or obesity. The first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study evaluated the relation between body weight and risk of CHD in 2 separate reports. In a study of 1259 women (age range: 65-74 years, follow-up: 14 years), a BMI $\geq$29 kg/m^2 was an independent risk factor for CHD.[33] In a second study of 620 men and 960 women (mean age: 77 years, follow-up: 13 years), Harris et al reported that the presence of heavier weight in late middle age was a risk factor for CHD later in life.[34] The presence of heavier weight during older age served as a risk factor for CHD after adjusting for weight loss.

Calle et al studied $>$1,000,000 subjects (follow-up: 14 years).[35] Increased BMI, defined as $>$26.5 kg/m^2 in men and $>$25.0 kg/m^2 in women, predicted CVD in both men and women. In those whose BMI was $>$40 kg/m^2, respective relative risks for CVD in men and women were 2.7 and 1.9.

A retrospective study of 866 African-American men and women followed for 7 years reported by Adams-Campbell et al assessed the relation

of BMI to CAD confirmed by invasive coronary angiography.[36] In this study CAD occurred more frequently in subjects who were OW than in patients with normal weight or in those who were obese.

Zhou et al demonstrated that OW served as an independent predictor of CHD in 14 target populations comprising 1974 men and women (age range: 30-59 years, follow-up: 9 years).[37]

The Manitoba Heart Study comprised 3983 men (mean age at entry: 30.8 years, follow-up: 26 years).[38] There were 390 cases of CHD during follow-up. Elevated BMI was significantly associated with MI, sudden death, and coronary insufficiency. These findings were not apparent until year 16 of follow-up. The presence of OW or obesity was found to be the best predictor of myocardial infarction (MI) after 20 years of observation. Conversely, in the Pooling Project there was no significant age-adjusted or age-associated relation between obesity and CHD in male cohorts.[5]

In a meta-analysis of 8 studies comprising 61,386 adults (follow-up: >10 years), Kramer et al reported approximately 4000 adverse CVD events.[39] Subjects with obesity, but without the MetS had a 24% higher risk of CVD events than participants with normal weight without the MetS. The Copenhagen General Population Study followed 71,527 adults followed for a mean duration of 3.6 years.[40] Adults who were OW or obese with the MetS manifested increased risk for MI (hazard ratios [HR] of 1.26, 95% confidence interval [CI]: 1.0-1.6 in patients who were OW and 1.88, 95% CI: 1.3-2.6 in those who were obese).

Jousilahti et al studied 16,113 Finnish men and women (age range: 30-59 years, follow-up: 15 years).[41] Obesity was found to be an independent risk factor for CHD mortality among men and contributed somewhat less to CHD mortality risk in women.

In the Chicago Western Electric Study 1707 men (age range: 40-55 years), followed for 22 years.[42] After 15 years, all indices of adiposity except for triceps skinfold thickness were significantly related to CHD mortality.

BMI and fat patterning failed to predict CHD mortality in African-American women during a follow-up period of 25-28 years in the Charleston Heart Study.[43] In the Adventist Mortality Study of 12,576 women (age range: 30-74 years, follow-up: 26 years), there was a "U" shaped curve for risk of CHD, hypertensive disease and stroke mortality, particularly during the fifth to seventh decades of life.[44]

In a prospective study of 7735 males (age range: 40-59 years, mean follow-up: 14.8 years), Shaper et al showed that a BMI of 22 kg/m^2 was associated with the lowest risk of CVD mortality.[45]

The Women's Health Australia Project included 13,431 women (age range: from 45 to 49 years) and was designed to assess the relation

between BMI and CVD risk.[46] In this study Brown et al demonstrated that a BMI of 19-24 kg/m^2 was the optimal BMI for minimizing CVD risk. In a retrospective analysis of data that were obtained prospectively, Benedetto et al assessed the relation of BMI categories to early and late mortality after first time isolated coronary artery bypass grafting (CABG).[47] The study population consisted of 3269 subjects with normal weight, 6660 subjects who were OW, 3821 subjects who were obese, and 211 subjects who were morbidly obese. Propensity scoring was used to adjust for potential confounding factors. Early mortality was not affected by the presence of OW, obesity or morbid obesity regardless of the patient's risk profile. OW was not protective against late death compared to normal weight subjects. The obese state was associated with a higher risk for late death (HR: 1.22, 95% CI: 1.07-2.66, $P< 0.006$) and a trend toward late mortality in those with morbid obesity (HR: 1.36, 95% CI: 0.24-2.49).

Relation of Fat Distribution to CVD and CHD Risk

Epidemiologic studies strongly suggest that the presence of central obesity is superior to general indices of body weight (BMI, relative weight) as a predictor of CVD and CHD morbidity and mortality.

In a study of 27,098 adults from 52 countries Yusuf et al showed that BMI was minimally associated with MI after adjustment for other CVD risk factors (odds ratio [OR] of 1.12, 95% CI: 1.03-1.22).[48] In contrast, the ORs for WHR as a predictor of MI were substantially higher (1.90 in the fourth and 2.52 in the fifth quintile). In the INTERHEART Study, WHR was the strongest predictor of MI.[49] In this study, other measures of abdominal obesity were also stronger predictors of MI than was BMI.

A review of relevant studies by Rao et al demonstrated that high BMI and high WHR were independent risk factors for CHD mortality.[50]

Hamer et al combined data from the Health Study of England with data from the Scottish Health Survey (22,308 subjects, mean age: 54 years).[51] Patients who were obese with lower metabolic risk (WC <102 cm for men and <88 cm for women, normotensive, no DM, normal C-reactive protein (CRP), normal high-density lipoprotein cholesterol) had no increase in CVD risk compared to healthy nonobese individuals.

In a case control study of men and women <70 years old (216 cases, 261 controls), increased mid-thigh girth and subcutaneous fat mass appeared to have a protective effect against CHD.[52]

Rexrode et al showed that WHR and WC were independently associated with CHD risk in 44,702 women in the Nurse's Health Study.[53]

Coutinho et al studied 15,547 subjects with CAD to determine the relative associations of BMI and WHR to 5-year survival.[54] The study population consisted of 55% men (mean age: 66 years). A total of 4699 deaths occurred over a median follow-up period of 4.7 years. Those with a normal BMI, but with a high WHR had a higher mortality rate than those with a normal BMI and a normal WHR (HR: 1.10, 95% CI: 1.05-1.17), those who were OW with a normal WHR (HR: 1.20, 95% CI: 1.09-1.31), and those who were obese with a high WHR (HR: 1.27, 05% CI: 1.18-1.39). The p values for all comparisons were <0.0001.

Sharma et al studied 7057 patients >65 years old with known CAD who were at normal weight, but had central obesity (those with a high WHR or high WC).[55] The mean follow-up time was 7.1 years. The highest mortality risk occurred in those with a normal BMI and central obesity (HR: 1.29, 95% CI: 1.14-1.46 for high WHR and HR: 1.29, 95% CI: 1.12-1.50 for high WC). High WHR was predictive of mortality overall (HR: 2.14, 95% CI: 1.93-2.38), but high WC overall was not predictive of mortality. High WHR predicted mortality in both men and women, whereas WC predicted mortality only in men (HR: 1.12, 95% CI: 1.01-1.24).

A study by Zhang et al demonstrated that the relative risk of CVD mortality rose progressively with increasing quintiles of WC (1.00, 1.04, 1.04, 1.28, and 1.99) after adjustment for BMI and selected risk factors for CVD.[56]

The previously-cited study by Baik et al noted that WHR predicted CVD mortality in men ≥65 years of age.[31] In the same group of patients, Rimm et al reported that in those ≥21 years of age, BMI, WHR, and weight gain were associated with increased risk of CAD.[57] In patients 65 years of age or older, WHR was superior to BMI in predicting CAD risk.

In a Brazilian study of 2396 patients reported by Fontela et al, conicity index, BMI, and WC were assessed to determine their relation to CAD mortality.[58] None of these anthropomorphic measurements proved to be independent predictors of CAD mortality.

The Paris Prospective Study consisted of 6718 men (age range: 42-53 years, average follow-up: 6.6 years).[59] Thirteen upper and lower body skinfold thicknesses were measured. Higher ratios of truncal to mid-thigh skinfold thickness were most predictive of CHD, even after adjusting for blood pressure, cholesterol, and DM.

In the Study of Men Born in 1913, 792 were evaluated at 54 years age.[60] Follow-up occurred 13 years later. BMI and skinfold thickness measurements were obtained as was WC. None of these measurements were significantly associated with ischemic heart disease, stroke, and all-cause mortality. In contrast, WHR was significantly associated with

ischemic heart disease and stroke (P= 0.04). Adjustment for traditional CVD risk factors attenuated this association.

Prineas et al assessed the relation between WHR and 4-year risk of fatal CAD in 32,858 women (age range: 55-69 years).[61] In the highest tercile of WHR compared to the lowest tercile of WHR, the relative risk of death from CAD was 3.3 (95% CI: 2.0-5.6). There was a trend towards an increased relative risk when the middle tercile was compared with the lowest tercile. High WHR was, for the most part, an independent risk factor for CAD-related death, although multiple other CVD risk factors were also considered to be important predictors of this endpoint on multivariate analysis.

In a study reported by Jonsson et al, 22,025 Swedish men (age range: 27-61 years) were followed for 23 years.[62] The cumulative mortality rate was 20% (13% for CHD events). The relative risk for CHD events in patients who were OW was 1.26 (95% CI: 1.12-1.37) and was 1.76 (95% CI: 1.49-2.68) in patients who were obese. CHD events and CHD itself were thought to be closely-related to CVD risk factors.

A study of 105,062 US male veterans followed for 23 years reported by Terry et al, the relative risk of ischemic heart disease death per standard deviation of WHR ranged from 1.11 to 1.17 (higher in younger subjects).[63] BMI was not a significant risk predictor for younger subjects, but became a significant risk predictor among veterans 21-30 years of age.

Bengtsson et al reported the results of a study of 1462 randomly selected Swedish women (age range: 38-60 years) who were followed for total mortality over 20 years.[64] WHR was an independent predictor of total mortality and death from MI (relative risk: 1.67, 95% CI: 1.18-2.36).

Lakka et al studied 1346 Finnish men (age range: 42-60 years) with no evidence of CVD at entry.[65] The average follow-up period was 10.6 years, during which time 123 acute CHD events occurred. After adjustment for confounding variables, WHR (P< 0.009), WC (P < 0.010), and BMI (P < 0.013) cumulatively were associated with a nearly 3-fold risk of CHD events. WHR provided additional value beyond BMI, but the converse was not true. Patients with abdominal obesity combined with cigarette smoking and poor cardiorespiratory fitness respectively were shown to have 5.5 and 5.1 times the risk of CHD events.

In a study of 9206 Australian adults (age range: 20-69 years) after adjustment for multiple CVD risk factors, WHR was a dominant and independent predictor of CVD and CHD mortality.[66] WHR was a better predictor than WC and WC was a better predictor than BMI.

Lapidus et al studied 1462 Swedish women (age range: 38-60 years) to assess the relation of the distribution of adipose tissue to the risk of CVD

and death.[67] On multivariate analysis, WHR and WC were associated with 12-year incidence of MI independent of age, BMI, cigarette smoking, dyslipidemias and, and systolic blood pressure.

In a substudy of the Honolulu Heart Study, Curb et al reported that in Japanese-American men, BMI, subscapular skinfold thicknesses centrality index predicted CHD after adjustment for selected CVD risk factors.[68]

A study of 2512 men (follow-up: 14 years) by Yarnell et al demonstrated that subscapular skinfold thickness significantly predicted ischemic heart disease after adjustment for age, smoking, and social status.[69] Other skinfold thickness measurements contributed marginally to ischemic heart disease prediction relative to BMI.

PATHOLOGY

Studies derived from postmortem evaluation have shown mixed results concerning to the relationship between OW/obesity and CHD. The International Atherosclerosis Project (1960-1964).[70] This study contained autopsy data on 350 persons from 6 geographic regions. The study showed that among those who died accidentally there was no relation between any of the weight indices used and the extent of atheromata. In a World Health Organization Study conducted in Europe and reported by Sternby, there was no significant difference in the prevalence of coronary stenosis or the extent of atherosclerosis between normotensive, nondiabetic patients who were obese and subjects at normal weight.[71] In this study, subjects with wasting diseases were excluded. Giertson et al reported no significant difference in the extent of coronary atherosclerosis between 408 patients who were underweight and those who were OW (age range: 15-89 years).[72] A retrospective autopsy study reported by Ackerman et al showed that the degree of coronary atherosclerosis was similar in persons who were OW and persons with average weight.[73]

Yater et al found no significant difference in body weight between 237 men who died of CHD and 297 men who suffered accidental death.[74]

Lee and Thomas reported no significant difference in body weight between 450 persons (age range: 30-60 years) who succumbed to acute MI and persons with average body weight in the general population matched who were for age and sex.[75]

Several studies have described a relation between abdominal panniculus thickness and coronary atherosclerosis. Wilens et al described postmortem findings in 1260 cases. Advanced coronary atherosclerosis occurred twice as often in those with an abdominal panniculus >3 cm as in persons with poor nutritional status.[76] The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study comprised 3000 males and females (age range: 15-34

years), In this study McGill et al described fatty streaks in the right and left anterior descending coronary arteries in adolescents and young men with an increased BMI.[77] Fatty streaks in the right coronary artery were greater in the right coronary artery in young men with a thick abdominal panniculus. There was a trend toward greater fatty streaks in the right coronary artery young women with a thick abdominal panniculus. There was no association between BMI and coronary atherosclerosis in young women. Previously, McGill et al studied 1532 autopsied young persons who died of causes other than CHD. In males, the percentages of fatty streaks and raised right coronary lesions were 2-4 times higher in subjects whose abdominal panniculus thickness was >17 mm compared to males whose abdominal panniculus ≤ 17 mm.[78]

Strong et al reported the results of a study of 1108 males (age range: 13-34 years) who succumbed to diseases other than CHD.[79] A positive correlation was noted between body weight-height indices and raised coronary lesions in white Americans, but not in African-Americans. However, the differences in panniculus thickness between groups were small.

Patel et al reported findings from 672 autopsy cases of men (age range: 25-64 years), 70% of whom suffered accidental death.[80]. There was a weak correlation between abdominal panniculus thickness and raised coronary artery lesions in white men, but not in African-American men.

In a retrospective analysis of medical records of all nonelderly residents of Olmstead County, MN between 1981 and 2009 who died from non-natural causes and who had CAD at autopsy ($n = 545$), Smith et al noted a nonlinear decline in CAD that was associated with a decrease in hypertension.[81] Trends identifying increasing obesity and DM were thought to contribute to the end of the decline in CAD.

In a postmortem evaluation of 110 subjects in which biopsies of subcutaneous fat were acquired Bjurulf et al showed that the severity of coronary atherosclerosis correlated with the size, but not the number of fat cells.[82].

Autopsy findings in a study of 37 Japanese-American men showed a positive correlation between CHD severity and relative weight $>116\%$.[83]

Wilkens et al reported greater severity of CHD on autopsy and a higher incidence of catastrophic CHD events in normotensive men who were obese, but not in women.[84]

INVASIVE ANGIOGRAPHIC AND COMPUTED TOMOGRAPHIC IMAGING

Coronary anatomy has been studied using invasive coronary angiography, computed tomographic coronary angiography and by assessment of coronary artery calcium using computed tomography.

Invasive Coronary Angiographic Studies

The Honolulu Heart Program was a study of 357 men drawn from a cohort of 7591 men without established CHD at entry.[85] Invasive coronary angiography was performed on entry and was repeated during a follow-up period of 20 years. Thirty-five men with <50% stenosis represented controls. There was no significant difference in BMI between controls and subjects with greater degrees of coronary stenosis.

Cramer et al 262 patients with established CHD based on invasive coronary angiography on entry followed by repeat invasive coronary angiography 2-182 months after the initial angiogram.[86] No significant difference in the progression of coronary lesions between those with a relative weight greater than 120% and those with lower relative weights.

Stalls et al consulted an invasive coronary angiographic database of 33,119 patients. They reported that although black subjects had higher frequencies of CVD risk factors and were more commonly morbidly obese, they were significantly less likely to have significant coronary artery stenosis on angiography.[87]

These cross-sectional invasive coronary angiographic studies and others assessing coronary artery stenosis in patients who were OW or obesity showed little or no relation between BMI and severity of CAD.[88-96]

Farhang et al studied 414 patients with suspected CAD who underwent invasive coronary angiography (mean age: 61.2 years, 60.4% male).[97] Severity of CAD was assessed using the Synergy between Percutaneous Intervention with Taxus and Cardiac Surgery (SYNTAX) and Duke scoring systems. There was a negative correlation between BMI and both SYNTAX score and Duke score ($P = 0.001$ for both). There was a positive correlation between WHR and severity of CAD using the Duke score ($P = 0.03$).

To assess the influence of BMI on extent of coronary atherosclerosis in patients at risk for CAD based on CVD risk factors, Rossi et al studied 1299 consecutive patients (69.7% male) who underwent invasive coronary angiography.[90] The study population consisted of patients with normal weight (36.5%) patients who were OW (43.6%) OW, and patients who were obese (19.6%). During a mean follow-up period of 40 months, the patients who were OW or obese had a higher incidence of CHD events than normal weight patients (62.7% in patients who were OW, 74.9%, in patients who were obese and 53.2% in patients with normal weight, ($P < 0.05$).

In a study by Alkawam et al 7567 patients were hospitalized for chest pain and underwent invasive coronary angiography.[98] The study included

414 patients who were obese (BMI ≥30 kg/m^2, 80% of whom had CAD. These patients displayed CAD at a younger age than patients who were not obese (57 years vs 63 years). Of the 332 patients with obesity and CAD 55.4% had obstructive CAD. Traditional CVD risk factors such as male gender and cigarette smoking favored obstructive CAD, whereas dyslipidemia favored nonobstructive CAD.

Cepeda-Valery reported the results of an invasive coronary angiographic study of 95 patients with acute MI assessing the relation of obesity to SYNTAX score and CAD severity.[99] On univariate analysis obesity was associated with a lower SYNTAX score ($P = 0.009$), fewer lesions >50% ($P = 0.03$), and less proximal left anterior descending coronary stenosis ($P = 0.02$), whereas age, cigarette smoking, and DM were significant predictors of more severe CAD. On multivariate analysis obesity remained a significant predictor of less severe CAD including lower SYNTAX score ($P = 0.04$), fewer coronary stenotic lesions >50% ($P = 0.007$), and a lower likelihood of proximal left anterior descending coronary stenosis ($P = 0.03$). Age, cigarette smoking, and DM remained significant predictors of severe CAD.

Computed Tomographic Coronary Artery Imaging Studies

Multiple studies employing computed tomography of the coronary arteries have evaluated the relation of obesity to CAD and CAC. Labounty et al studied 13,874 patients who were suspected of having CAD and who underwent computed tomographic coronary angiography.[100] Subjects with an increased BMI had a greater prevalence, extent and severity of CAD that could not be attributed entirely to CVD risk factors. In this study an independent association existed between BMI and risk of MI.

In the Muscatine Heart Study consisting of 384 males and females (15 years old at entry, follow-up: 15 years), obesity (assessed by BMI and triceps skinfold thickness) was strongly associated with coronary artery calcification (CAC) detected by computed tomography.[101]

In the Dallas Heart Study See et al reported that WHR was the only anthropomorphic measure of obesity associated with CAC on computed tomography (OR: 1.91).[102]

Several studies have utilized the Agaston score derived from cardiac computed tomography to quantify CAC. In a retrospective study of 6661 patients (mean age: 57.1 years), Aljizeeri et al evaluated the association of CAC (Agaston score) and indices of body weight including BMI and % body fat.[103] The study included patients who were underweight (0.1%), patients with normal weight (21.3%), patients who were OW

(39.1%), and patients who were obese (39.4%). An independent association existed between the presence of CAC and BMI (5 kg/m^2 increments, OR: 1.05, 95% CI: 1.00-1.11, P= 0.038) and % body fat (OR: 2.38, 95% CI: 1.05-5.41, P = 0.038). BMI categories and body surface area failed to independently predicted CAC score. Percent body fat predicted CAC score in men, but not in women.

In the Coronary Artery Risk Development in Young Adults (CARDIA) study included 3275 healthy persons who were not initially obese (age range: 18-30 years, follow-up up to 25 years).[104] Assessment for associated risk factors and CAD occurred every 2-5 years. During the follow-up period, 40% of participants developed obesity that was either generalized or abdominal. CAC developed at a rate of 16 per 1000 patient years in patients who were obese for >20 years compared to 11 per 1000 patient years in those who remained nonobese. Ten-year progression of CAC (Agaston score) was seen in 25.2% of those with generalized obesity and in 27.2 % of those with abdominal obesity >20 years. Respective rates of progression in patients who were not obese were 20.2% and 19.5%.

Yoon et al retrospectively studied 1218 subjects who were obese, but metabolically healthy to determine the risk of development of the MetS and progression of CAC score during a median follow-up period of 45 months.[105] Obesity was defined as a BMI ≥25 kg/m^2. Patients who were obese, but metabolically healthy was were classified as class I if there was obesity and one other component of the MetS and class II if there was obesity and no other components of the MetS. CAC at baseline was 0 units for all patients. Metabolically healthy patients without obesity served as the reference group. During the follow-up period, 32.2 % of class I and 10.2% of class II metabolically healthy subjects who were obese developed the MetS (HR: 2.174, 95% CI: 1.513-3.127 for class I and HR: 1.166, 95% CI: 0.434-3.129 for class II patients). Class I patients developed a significant increase in Agaston score (HR: 1.653, 95% CI: 1.144-2.390), whereas class II patients experienced no significant change in Agaston score. In class I patients who maintained metabolic health during follow-up, no significant change in Agaston score was noted.

Chang et al studied 14,828 metabolically healthy adults (no evidence of CVD, MetS absent, homeostatic model assessment normal).[106] The study population consisted of normal individuals and subjects who were metabolically healthy and obese. CAC scores were obtained on all patients. Patients who were metabolically healthy but obese had a higher prevalence of CAC than normal weight subjects. Multivariable analysis showed the CAC ratio of metabolically healthy patients with obesity compared to normal weight subjects (risk ratio: 2, 95% CI: 1.48-3.43) Additional adjustment for

metabolic risk factors weakened this association to the point where CAC score was no longer significantly different between the 2 groups. Thus, the prevalence of CAC is higher in metabolically healthy subjects with obesity, but this appears to be mediated by metabolic risk factors below levels traditionally considered to be abnormal.

THE OBESITY PARADOX AND CHD

There is ample evidence to support the presence of an obesity paradox with regard to total and CHD mortality once CHD is confirmed.[107-131]

Wang et al performed a systematic review and meta-analysis on 1,300,794 patients with data culled from 89 studies to assess the association of BMI to risk of mortality and CV events in patients with CAD during a mean follow-up of 3.2 years.[108] Compared to normal weight patients, underweight status was associated with a significantly higher risk of short-term mortality (relative risk: 2.24, 95% CI: 1.85-2.72) and long-term mortality (relative risk: 1.70, 95% CI: 1.56-1.86). OW was associated with significantly lower short-term mortality risk (relative risk: 0.69, 95% CI: 0.64-0.75) and long-term mortality risk (relative risk: 0.79, 95% CI: 0.74-0.82). Similarly, obesity was associated with significantly lower short-term mortality risk (relative risk: 0.68, 95% CI: 0.61-0.75) and long-term mortality risk (relative risk: 0.79, 95%CI: 0.73-0.85). Long-term benefit of obesity abated after 5 years of follow-up. Patients with class II and class III obesity demonstrated lower short-term mortality risk (relative risk: 0.76, 95% CI: 0.62-0.91), but higher mortality risk after 5 years of follow-up (relative risk: 1.25, 95% CI: 1.14-1.38) compared to normal weight patients. Meta-regression analysis showed attenuation of the inverse risk of obesity on mortality over longer follow-up. Romero-Corral et al performed a systematic review and meta-analysis of 40 studies comprising > 250,000 patients with documented CAD.[109] The referent group in this study consisted of subjects whose BMI ranged from 19.0 to 24.9 kg/m^2 (normal weight). Total mortality was significantly lower in patients who were OW than in those with class I obesity. Patients who were underweight (<19.0 kg/m^2 manifested the highest risk for total mortality among the weight groups studied including those with normal weight. It is of interest that the relative risk for total mortality in patients whose BMI was ≥35 kg/m^2 was not significantly different than that of the referent group. Similar findings were observed in subgroups receiving percutaneous coronary revascularization following acute MI. In the CABG subgroup the relative risks for total mortality in patients who were OW and in those with class I obesity were similar to that of the

referent group, as were the relative risks for total mortality for patients whose BMI was ≥35 kg/m^2 and in those who were underweight. These investigators also assessed the relation of CV mortality to BMI classification. Relative risk of CV mortality was somewhat lower in those who were OW and in those with class I obesity. However relative risks for CV mortality were higher than that of the referent group in patients who were underweight and in those whose BMI was ≥35 kg/m^2.

Das et al reported the results of a study of 50,000 patients with acute ST segment elevation MI.[110] Subjects whose BMI ranged from 30 to 35 kg/m^2 had the lowest mortality risk among the groups studied.

In a study by Kragelund et al, in-hospital adjusted mortality among patients with ST segment or non-ST segment elevation MI was lower in patients whose BMI was ≥40 kg/m^2 than it was in subjects whose BMI was < 40 kg/m^2.[111]

The TARGET trial comprised 4800 patients with CAD who received a bare metal stent and were treated with abciximab or tirofiban.[112] No significant difference in death or MI at 30 days or 180 days was noted between those with and without obesity. In this study target vessel revascularization at 6 months was more common in patients <65 years old with obesity than in any of the other study subgroups.

Multiple studies have reported greater use of percutaneous coronary interventions in patients who were obese than in those who were not obese.[113-121]

In contrast to most studies, Akin et al did not report better outcomes in patients with obesity following percutaneous coronary intervention in a German registry.[122]

Studies assessing the effects of obesity on mortality and other outcomes in patients undergoing CABG have produced variable results. A study of 6068 patients undergoing CABG reported by Habib et al demonstrated that 12-year mortality was similar between normal weight subjects and those whose BMI values ranged from 32 to 36 kg/m^2, but was significantly greater in those whose BMI was ≥ 36 kg/m^2.[123] Terada et al reported lower short-term mortality in patients who were OW receiving CABG compared to patients in other body weight categories.[124] In a study of 4713 patients who were obese, 243 patients who were morbidly obese, and 1014 patients with normal weight who underwent isolated CABG, Kuduvalli et al reported no significant differences in the incidence of mortality, MI, stroke, re-exploration of the thorax, or renal failure during short-term follow-up among the 3 study groups.[125] In a study of 31,021 patients with CHD (follow-up: 46 months) Oreopoulos et al reported that medically-treated patients who were OW or had class I obesity who had significantly lower mortality risk than subjects who were

underweight or those who were at normal weight.[126] In patients undergoing CABG, subjects with a BMI of 35-39.9 kg/m^2 had the lowest mortality rates among the weight groups studied. Other studies have reported similar findings.[47,127-129] In most of these studies, patients with class I and class II obesity were more commonly re-vascularized than other BMI subgroups.

DeSchutter et al studied 519 patients with CHD before and after cardiac rehabilitation (follow-up >3 years).[130] All-cause mortality was highest in the subgroup with the highest CRP level and lower BMI. Higher BMI was associated with lower mortality in the entire study population and was associated with a trend toward lower mortality in the higher and lower CRP subgroups. High body fat was associated with lower mortality in the higher CRP subgroup, but not in the lower CRP subgroup.

The bulk of evidence suggests that in patients with CHD who are OW and in those with class I obesity, mortality rates are similar to or lower than mortality rates of normal weight individuals regardless of the clinical presentation.[107-131] Persons who are underweight have consistently been shown to have the highest risk for mortality. Variability exists regarding mortality among those who are more severely obese.

RELATION OF PHYSICAL ACTIVITY AND CRF TO CVD AND CHD IN PATIENTS WHO ARE OW OR OBESE

Substantial evidence confirms the important impact of physical activity and CRF on the overall incidence of CVD and on all-cause and CVD mortality in patients who are OW or obese.[132-138] Recent studies suggest that CRF may be more important than BMI for predicting prognosis; that is, that patients who are OW or obese with preserved CRF may have a better prognosis than do lean subjects with low CRF.[132-138]

McAuley et al studied 9563 men with CHD (mean follow-up: 33.4 years) matched for age and gender.[136] Subjects in the lowest tercile for CRF were classified as unfit, whereas those in higher terciles were classified as fit. During follow-up, fit patients had a good prognosis with respect to all-cause and CVD mortality regardless of BMI, WC or percent body fat. In the unfit group patients with the lowest BMI, WC and percent body fat had a worse prognosis than those with a greater degree of adiposity.

In a recent study from Norway, 6493 participants with CHD were followed for a median of 12.5 years to assess the impact of physical activity and BMI on all-cause and CVD mortality.[137] Patients who were OW or obese had lower all-cause and CVD mortality than did lower weight subjects indicating an obesity paradox. However, this was observed only in

patients who did not meet international physical activity guidelines. Thus, in this study physical activity was more important than BMI in predicting prognosis. In a follow-up study from the same cohort, 3307 patients with CHD were followed for a mean of 15.7 years.[138] Changes in BMI and physical activity were assessed to determine their effect on all-cause and CVD mortality. Weight loss produced no significant reduction in all-cause or CVD mortality. In fact, there was a reduction in mortality in patients with weight gain whose BMI was normal at baseline. Sustained or increased physical activity over time was associated with decreased all-cause and CVD mortality.

In aggregate, these studies suggest that physical activity and preserved CRF are able to attenuate the adverse effects of OW and obesity on all-cause and CVD mortality.

EFFECTS OF WEIGHT LOSS

Intentional weight loss can favorably modify many of the traditional CVD risk factors related to OW and obesity including hypertension, atherogenic dyslipidemia and type 2 DM.[1-9,11,139] Weight loss also reduces insulin resistance and inflammation, improves endothelial function, and decreases the incidence of the MetS.[1,11,15-19]

The Asia Pacific Cohort Collaboration investigators studied 33 cohorts comprising 310,000 patients. They reported that each 2 kg/m^2 decrease in BMI was associated with a 14% decrease in the risk of CHD. In the Australia/New Zealand cohort, the decrease in CHD risk was 10%.[140]

Pack et al performed a systematic review and meta-analysis of 35,335 patients to determine the importance of weight loss in patients with CAD.[141] The endpoint of the study was a composite of all-cause mortality, CVD mortality, and major adverse cardiac events. The study group was 72% male and had an average age of 64 years. The average BMI was 30 kg/m^2 and the average follow-up period was 3.2 years. Overall, the study group demonstrated a greater risk of the composite endpoint with lack of weight loss (relative risk: 1.30, 95% CI: 1.00-1.69, $P = 0.05$). However, intentional weight loss was associated with improved outcomes (relative risk: 0.67, 95%CI: 0.56-0.80, $P < 0.001$), whereas observational weight loss was associated with worse outcomes (relative risk: 1.62, 95% CI: 1.06-2.08, $P < 0.001$). Although data are limited concerning the effect of intentional weight loss on CVD outcomes these studies suggest that intentional weight loss may improve prognosis in patients with CVD in patients who are OW or obese. However, it is clear further investigations are required to verify the findings in these studies.

CONCLUSIONS

OW and obesity are closely linked to both traditional and novel risk factors for CVD Central obesity is an important component of the MetS. Epidemiologic studies suggest an association between OW/obesity and CVD including CHD and its complications. This is particularly true of patients with central obesity. The evidence is less robust in studies derived from autopsy and coronary angiographic data. Obesity is classified as an independent risk factor of CVD. There is substantial evidence to support the existence of an obesity paradox with respect to total and CVD mortality. Low CRF facilitates the development all-cause and CVD mortality in patients with CHD who are OW or obese. Preserved CRF and physical activity attenuates the adverse effects of OW and obesity on all-cause and CVD mortality. Although intentional weight loss can favorably modify many CVD risk factors, evidence of an association between weight reduction and improvement in CVD outcomes remains sparse.

Authors' contributions

Natraj Katta, MD: conceptualization, data collection, writing of original draft, review and editing; **Troy Loethen, MD:** data collection, writing original draft, review and editing; **Carl J. Lavie, MD:** conceptualization, data collection, writing original draft, review and editing; **Martin A. Alpert, MD:** supervisor, conceptualization, data collection, writing first draft, review and editing.

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