ORIGINAL ARTICLE

The Obesity Paradox of Heart Failure in the Elderly

La paradoja de la obesidad en la insuficiencia cardíaca en ancianos

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ABSTRACT

Background: Multiple studies have demonstrated a "protective" relationship of increased body mass index (BMI) over normal or low BMI in the development and prognosis of heart failure. The BMI categories of the adult population are not adequate in the elderly population. We propose to compare the incidence of global mortality and/or readmission for heart failure during the first year according to the BMI category in this population.
Methods: This was an observational and analytical study of a retrospective cohort of patients ≥ 65 years admitted to the cardiology intensive care unit of Hospital Italiano de Buenos Aires with a diagnosis of Acute Heart Failure Syndrome (AHFS) between January 2013 and December 2017.
Results: The study included 409 patients. The subgroups with higher BMI had lower mortality at one year (Underweight: 53%, Normal weight: 41%, Overweight: 33%, Obese: 27%, p=0.008). In the multivariate analysis, annual mortality HR adjusted for age, gender, readmissions, kidney failure and type of heart failure was 0.51 (95% CI 0.29-0.90) for overweight patients and 0.36 (95% CI 0.19-0.67) for patients with obesity compared with underweight patients. There were no differences in in-hospital mortality or in readmissions at one year between the different BMI subgroups.
Conclusion: In the elderly population with AHFS, the subgroups with higher BMI have a better prognosis during the first year, fulfilling the "obesity paradox".

Key Words: Heart Failure - Obesity Paradox - Body Mass Index – Elderly

RESUMEN

Introducción: Múltiples estudios demostraron una relación "protectora" del índice de masa corporal (IMC) incrementado por sobre el IMC normal o bajo en el desarrollo y el pronóstico de la insuficiencia cardíaca. Las categorías de IMC de la población adulta no son adecuadas en la población anciana. Nos proponemos comparar la incidencia de mortalidad global y de reinternación por insuficiencia cardíaca durante el primer año según la categoría de IMC en esta población.
Materiales y métodos: Estudio observacional y analítico de una cohorte retrospectiva de pacientes mayores de 65 años internados en la unidad de cuidados intensivos cardiológicos del Hospital Italiano de Buenos Aires (HIBA) con diagnóstico de síndrome de insuficiencia cardíaca aguda (SICA) entre enero de 2013 y diciembre de 2017.
Resultados: Se incluyeron 409 pacientes. Los subgrupos con mayor IMC presentaron menor mortalidad al año (peso insuficiente: 53%, normopeso: 41%, sobrepeso: 33%, obesos: 27%, p=0,008). En el análisis multivariado, el HR para mortalidad anual ajustado por edad, sexo, reinternaciones, insuficiencia renal y tipo de insuficiencia cardíaca fue de 0,51 (IC95% 0,29-0,90) en los pacientes con sobrepeso y de 0,36 (IC95% 0,19-0,67) en los pacientes obesos con respecto a los de peso insuficiente. No hubo diferencias en la mortalidad intrahospitalaria ni en las reinternaciones al año entre los diferentes subgrupos de IMC.
Conclusión: En la población de ancianos con SICA, los subgrupos con mayor IMC tienen mejor pronóstico durante el primer año, por lo que se cumple la "paradoja de la obesidad".

Palabras clave: Insuficiencia cardíaca - Paradoja de la obesidad - Índice de masa corporal - Ancianos

INTRODUCTION

Numerous studies have mentioned the role of obesity in heart failure, with altered heart structure and systolic and diastolic function, being also a risk factor for hypertension and coronary heart disease. (1) However, in 2001 Horwich et al. described the "obesity paradox" in a cohort of patients with advanced heart failure, where patients with a body mass index (BMI) >27.8 kg/m^2 had a longer survival time free from heart transplantation than patients with a lower BMI. (2)

Based on this finding, multiple studies demonstrated a "protective" relationship of increased BMI over normal or low BMI in the development and prognosis of heart failure. The pathophysiological mecha-

Rev Argent Cardiol 2021;89:203-208. http://dx.doi.org/10.7775/rac.v89.i3.20233

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Received: 12/14/2020 – *Accepted:* 03/08/2021

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nisms that explain the obesity paradox are not fully clarified.

Recent publications consider that the BMI categories of the adult population are not adequate in the elderly population. In the elderly, it is proposed to consider overweight at a BMI ≥27 kg/m^2 instead of ≥25 kg/m^2 (3)

The obesity paradox in the elderly population with acute heart failure syndromes (AHFS) has not been explored in our region, so we propose to compare the incidence of global mortality and/or readmission for heart failure during the first year according to the BMI category in this population.

METHODS

Study design. This is an observational and analytical study of a retrospective cohort of patients admitted to the cardiology intensive care unit of Hospital Italiano de Buenos Aires (HIBA) with a diagnosis of AHFS.

Eligible Population: Patients affiliated to the HIBA Health Plan admitted to a cardiac intensive care unit with a AHFS diagnosis between January 2013 and December 2017.

Inclusion Criteria: Patients ≥65 years belonging to the HIBA Health Plan, who were admitted to the Cardiology Intensive Care Unit (ICU) of the Cardiology Service of HIBA Central between January 1, 2013 and December 31, 2017, due to any acute heart failure syndrome (acute lung edema, congestive heart failure and low cardiac output or cardiogenic shock) (4)

Exclusion Criteria: Acute ischemic syndromes, Takotsubo syndrome, acute myocarditis and heart transplant patients were excluded, given the different substrate and therapeutic management of these entities, as well as systemic diseases that course with low weight (uncontrolled hyperthyroidism and oncological disease)

Definition of Variables:

Patient stratification: The BMI of each patient was taken from the one registered in the 3 months prior to the index hospitalization. Patients were classified according to the stratification for the elderly proposed by the Spanish Society of Parenteral and Enteral Nutrition (3): underweight: BMI <22 k/m^2, normal weight: BMI = 22-26.9 kg/m^2, overweight: BMI = 27-29.9 kg/m^2 and obesity: BMI ≥ 30 kg/m^2.

Data were collected by a cardiologist, through the review of the electronic medical records, which included clinical and hemodynamic data and complementary studies.

Mortality: All-cause death within 365 days after admission to hospital for AHFS was defined as the primary endpoint. The information was obtained through the review of the medical history and the administrative databases of the health insurance provider.

Readmission: The first readmission for AHFS, defined as unplanned hospitalization that required a >24 h stay, caused by a substantial worsening of the signs and/or symptoms of heart failure, requiring a new admission and administration of intravenous diuretics.

Statistical considerations

Sampling and estimation of sample size

All eligible patients were consecutively included.

Descriptive statistics

Continuous variables were expressed as mean and standard deviation or median and interquartile range, according to the observed distribution. Categorical variables were expressed as absolute and relative frequency.

Analytical statistics

Demographic, clinical and treatment characteristics of the different groups of patients were compared using the chi-square test in the case of categorical variables, or ANOVA or the Kruskal-Wallis test in the case of numerical variables, according to data distribution. The density of annual mortality incidence was estimated in each subgroup and represented using Kaplan-Meier curves. The association between the different subgroups of patients and annual mortality was evaluated applying the Cox proportional hazards model, adjusted for covariates of clinical interest.

A two-tailed p value <0.05 was considered statistically significant. In cases where multiple comparisons were made, the Bonferroni correction was employed. STATA 13.1 software package (Stata Corp, College Station, TX) was used for the analysis.

RESULTS

The study included 409 patients; 12% presented underweight (only 3 patients which had BMI <18.5 kg/m^2 were considered cachectic), 40% normal weight, 24% overweight and 23% obesity. There was a higher percentage of underweight patients among women and patients with obesity had a higher prevalence of diabetes. There were no statistically significant differences in the rest of the risk factors, cardiovascular history or left ventricular ejection fraction (Table 1).

Obese patients presented a mean N-terminal fragment of the prohormone brain type natriuretic peptide (NT pro-BNP) significantly lower than that of the rest of the subgroups.

The subgroups with higher BMI had lower mortality at one year (underweight: 53%, normal weight: 41%, overweight: 33%, obese: 27%, p=0.008). In the univariate analysis, overweight patients had a lower risk of mortality in outpatient follow-up at one year than underweight patients (HR 0.49, 95% CI 0.38-0.85), risk being even lower in obese patients (HR 0.32, 95% CI 0.17-0.59) (Figure 1). In the multivariate analysis, adjusted for age, gender, readmissions, renal failure and type of heart failure, the HR for annual mortality was 0.51 (95% CI 0.29-0.90) for overweight patients and 0.36 (95% CI 0.19-0.67) for patients with obesity compared with underweight patients. (Figure 1)

There were no differences in in-hospital mortality or in readmissions at one year between the different BMI subgroups.

DISCUSSION

The prevalence of obesity has been increasing in the world in the last decades. In 2015, approximately 108 million children and 604 million adults worldwide were obese, representing an increase in the prevalence of obesity in almost all countries since 1980, and a doubling of the prevalence in 70 countries. (1) Numerous studies have mentioned the role of obesity in heart failure, with altered heart structure and systolic and diastolic function; as well as its role as a risk

Table 1.

Population characteristics	Underweight (BMI <22) n=51	Normal weight (BMI 22-26.9) n=164	Overweight (BMI 27-29.9) n=98	Obesity (BMI ≥30) n=96	p
Risk factors					
Age, median (IQR)	87 (82-90)	85 (82–89)	85 (80-88)	81.5 (77-86)	<0.001
Male gender, n (%)	10 (19)	80 (49)	52 (53)	41 (42)	<0.001
Weight (kg), mean (SD)	52 (6)	65 (8)	75 (9)	90 (15)	<0.001
Height (m), mean (SD)	1.58 (0.08)	1.62 (0.09)	1.61 (0.09)	1.62 (0.1)	0.12
BMI, mean (SD)	20.6 (1.1)	24.5 (1.4)	28.5 (0.8)	34.3 (4)	<0.001
Hypertension, n (%)	44 (86)	150 (91)	91 (93)	86 (89)	0.58
Dyslipidemia, n (%)	22 (43)	86 (52)	59 (60)	51 (53)	0.26
Diabetes mellitus, n (%)	5 (10)	29 (18)	19 (19)	31 (32)	0.006
Smoking, n (%)	6 (12)	34 (21)	26 (26)	18 (18)	0.19
CKD, n (%)	7 (13)	42 (25)	27 (27)	26 (27)	0.26
Cardiovascular history					
CHF, n (%)	20 (39.9)	49 (29)	34 (35)	40 (41)	0.24
AMI, n (%)	1 (2)	10 (6)	6 (6)	1 (1)	0.16
CSA, n (%)	0 (0)	2 (1.2)	3 (3.1)	2 (2.1)	0.52
CABG, n (%)	1 (2)	11 (7)	8 (8)	11 (11)	0.2
PCI, n (%)	2 (4)	18 (11)	12 (12)	9 (9)	0.42
Stroke , n (%)	7 (14)	20 (12)	17 (17)	10 (10)	0.52
PAD, n (%)	0 (0)	11 (6.7)	15 (15)	11 (11)	0.009
LVEF					0.7
≥ 50, n (%)	33 (66)	89 (57)	56 (61)	57 (60)	
40-49%, n (%)	10 (20)	27 (17)	17 (18)	19 (20)	
<40%, n (%)	7 (14)	41 (26)	19 (20)	19 (20)	
Biomarkers, n (%)					
USTT, mean (SD)	37 (23)	126 (375)	235 (878)	82 (140)	0.48
NT proBNP, mean (SD)	10 046 (8687)	7587 (7636)	8197 (8304)	5030 (5104)	0.01
Results					
In-hospital mortality, n (%)	1 (2)	11 (7)	6 (6)	8 (8)	0.51
Mortality at 1-year post-discharge, n (%)	27 (53)	68 (41)	32 (33)	26 (27)	0.008
Rehospitalizations, n (%)	22 (43)	51 (31)	31 (31)	30 (31)	0.41

BMI: Body mass index, CKD: Chronic kidney disease, CHF: Congestive heart failure
AMI: Acute myocardial infarction, CSA: Chronic stable angina, CABG: Coronary artery bypass grafting, PCI: Percutaneous coronary intervention, PAD: Peripheral artery disease, LVEF: Left ventricular ejection fraction, USTT: Ultrasensitive Troponin T, NT proBNP: N-terminal fragment of the prohormone brain type natriuretic peptide.

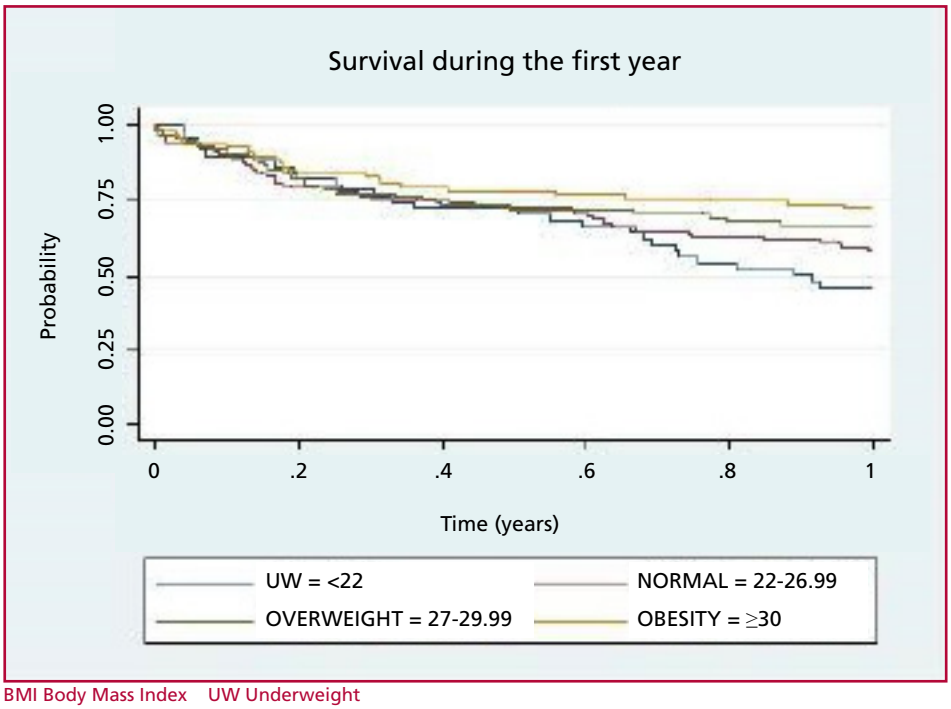
factor for hypertension and coronary heart disease. In 1992, Kasper et al. described the "cardiomyopathy of the obese" based on hemodynamic abnormalities and endomyocardial biopsies of patients with heart failure. (5) In 2002 Kenchaiah demonstrated the relationship between the development of heart failure and increased BMI in almost 6000 patients belonging to the Framingham Heart Study. (6) The risk of heart failure increased 5% in men and 7% in women for each point of increased BMI.

The proposed mechanisms are manifold: on the one hand, the increased prevalence of cardiovascular risk factors (diabetes, hypertension, dyslipidemia); on the other hand, the increase in cardiac remodeling due to enhanced preload, neurohumoral activation and oxidative stress. Direct damage to the myocardium due to cardiac steatosis and lipoapoptosis has also been described (7).

In turn, obesity is related to obstructive sleep apnea, which is associated with the development of heart failure, although the mechanisms are not clear (8). Many studies refer to the development of concentric hypertrophy in obese patients with preserved ejection fraction. Recent studies report systolic function impairment when measured with more sensitive methods such as strain and tissue Doppler imaging. (9).

The role of BNP as a diagnostic and prognostic marker in heart failure is well known, as well as the fact that its blood levels are reduced in obese patients due to an alteration in the peptide clearance and its receptors.

Despite all these findings, in 2001 Horwich described the "obesity paradox" in a cohort of 1203 patients with advanced heart failure. Patients with BMI >27.8 kg/m^2 had a significantly longer transplant-free survival time than patients with a lower BMI. The



BMI Body Mass Index UW Underweight

Fig. 1. Survival during the first year according to BMI.

worst results were seen in patients with low BMI, followed by patients with normal BMI. (2) In 2015, the association between pre-morbid obesity and mortality after incidental heart failure was re-analyzed in a cohort of patients from the ARIC (Atherosclerosis Risk In Communities) registry, which included 15 792 persons aged 45 to 64 years from four communities in the United States. When analyzing this cohort of 1487 patients with incidental heart failure - newly diagnosed and hospitalized - the researchers found that 35% were already overweight and 47% were obese four years before diagnosis. After a 10-year follow-up, with a total mortality of 43%, it was observed that overweight and obesity were associated with 23% and 25% reduction in the risk of mortality at 10 years, respectively. (10)

We can then mention two ways of looking at the relationship between the heart and obesity. On the one hand, the most logical correlation for a cardiologist is as a cardiovascular risk factor that alters the heart structure. On the other hand, the anti-intuitive view: obesity as a "protective factor" in heart failure.

The special interest of this association, in addition to not being described in our region, is that the elderly population, which is the one with the highest prevalence of heart failure, also benefits from the "obesity paradox".

Although patients ≥65 years were included, the population in our study was characterized by having a median age over 80 years in all subgroups. As expected, obese patients were those with the highest prevalence of diabetes compared with the rest of the patients (p=0.006) with no other difference regarding other cardiovascular risk factors, or history of cardiovascular disease or previous ventricular function. (Table 1)

Nevertheless, overweight patients had a lower risk of mortality adjusted at one year than underweight patients (HR 0.51, 95% CI 0.29-0.90), the risk being even lower in obese patients (HR 0.36, 95% CI 0.19-0.67). (Table 2) These results, which show a "protective" relationship of increased BMI over normal or low BMI in the development and prognosis of heart failure, coincide with a meta-analysis of 9 observational studies of heart failure that included 28 209 patients demonstrating lower cardiovascular disease mortality (19% vs. 40%) in patients with higher BMI at 2.7 years (11) and with the data shown in the ADHERE Registry with 108 927 patients, which showed a 10% decrease in mortality for every 5-point increase in BMI. (12)

As can be seen in Figure 1, overweight patients have lower mortality at one year than normal weight and underweight patients. In addition, obese patients have lower mortality than overweight patients. That is, a gradient of benefit in mortality is observed as BMI increases, with statistical significance from a BMI >27kg/m^2. This gradient of benefit, which becomes significant in overweight, is similar to that evidenced in the cohort analysis of 1487 patients in the ARIC study, with a 10-year follow-up. (10) In this analysis, in the same way as in our study, the patients' BMI was taken in the months prior to hospitalization for heart failure.

The progression of heart failure is accompanied by an increased catabolic load. The cachexia observed in terminal stages of heart failure is associated with an abnormal increase in cytokines and neurohormone

Table 1. Characteristics of the models evaluated[¥]

	In-hospital Mortality	p	Mortality at 1-year post-discharge (crude)	p	Mortality at 1-year post-discharge (adjusted)*	p
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Underweight			**Reference**			
Normal weight	1.74 (0.22-14)	0.60	0.66 (0.41-1.05)	0.08	0.65 (0.40-1.05)	0.84
Overweight	1.16 (0.13-10)	0.89	0.49 (0.28-0.85)	0.01	0.51 (0.29-0.90)	0.02
Obesity	2.89 (0.35-23)	0.32	0.32 (0.17-0.59)	<0.001	0.36 (0.19-0.68)	0.001

• adjusted for age, gender, renal failure, initial presentation, and readmissions for heart failure during follow-up.

levels, conferring an increased risk of mortality. Patients with cardiac cachexia would have a worse prognosis compared with obese patients, and this could be considered a bias when analyzing the protective relationship of BMI with obesity; however, in our analysis, only 3 patients in the underweight group had BMI <18.5kg/m², and it is this small group of patients that we could consider with cachexia.

In relation to BMI and age, multiple studies have shown that the indicators of the adult population do not have to coincide with those of the elderly population, since BMI between 25 and 28 kg/m² is associated with lower mortality in the population ≥70 years (3,13). The consensus of the Spanish Society of Parenteral and Enteral Nutrition (SENPE) defines overweight as BMI >27 kg/m² in this group of patients. (14)

In the same line with what has been described, when analyzing the different subgroups of our study, the prognosis of patients with heart failure improves from a BMI of 27 kg/m² (Figure 1), the mortality reduction not being significant in subgroups below this value, which defines overweight in the elderly.

The mechanisms that explain the obesity paradox are not clear. Several hypotheses can be listed:

1- The increased presence of adipocytes provides reserves against catabolic changes associated with the development of cardiac cachexia, which worsens the prognosis of patients with heart failure.
2- Obese or overweight people have some factors that protect them from inflammation, such as lipoproteins that neutralize toxins released by certain intestinal bacteria, a greater number of receptors for tumor necrosis factor (TNF) inhibiting circulating TNF, and a decreased response of the neurohumoral system. Hence, they respond better to chronic diseases such as heart failure. (15-17)
3- Obese patients present greater functional impairment, so heart failure is manifested and/or diagnosed in earlier stages than in patients with normal or low BMI, leading to better results due to earlier establishment of the treatment.
4- Patients with higher BMI receive more medication, either for hypertension or diabetes, and these drugs improve the prognosis of heart failure.
5- Patients with higher BMI have lower amount of circulating natriuretic peptides: it is known that patients with obesity have lower BNP dosages despite heart failure. New drugs that inhibit the degradation of these peptides (sacubitril) have also been shown to improve the prognosis in patients with heart failure. (18)

The confirmation of these findings in our population is interesting, not in the sense of indicating a hypercaloric diet, nor of setting BMI targets in patients with heart failure, but as a starting point to try to understand the multiple mechanisms surrounding this paradox and focus on those that could condition the survival of the elderly with acute heart failure: reliable anthropometric measurements, adequate energy reserve, early functional impairment, optimal medication, and circulating peptide levels.

Limitations

This is a single-center study so the results and conclusions cannot be generalized to other populations with different characteristics.

The reliability of BMI as a representation of adiposity can be questioned, but for reasons of widespread acceptance and ease of use, BMI is used to estimate body composition and identify overweight and obese patients.

CONCLUSIONS

In the elderly population with AHFS, the subgroups with higher BMI have a better prognosis during the first year, fulfilling the "obesity paradox" regardless of cardiovascular history and ejection fraction. The BMI of 27 kg/m², from which overweight is considered in elderly patients, would be an adequate cut-off point to identify groups with different prognosis.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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