

The Relation of Body Mass Index to Biochemical Parameters and Profile of Heart Failure

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The bidirectional relation between body mass index (BMI) and heart failure (HF) is complex and not fully understood. The obesity paradox phenomena is controversial and related to patient selection, parameters used for defining abnormal weight, characteristics of HF. Our study sustain the importance of controlling risk factors, in particular plasma glucose, lipid levels, as well as hypertension in patients with HF and BMI over 25 kg/m². Also, in contrast to the randomized control studies our results can only partially support data related to obesity paradox phenomena.

Keywords: characteristics of heart failure, body mass index, biochemical parameters, obesity paradox

Obesity and HF are among the most prevalent diseases and leading causes of morbidity and mortality worldwide. The relation between obesity and HF is complex and not fully understood. Beyond the hemodynamic and neuro-humoral mechanisms involved in HF, obesity itself is a risk factor for developing HF [1]. For example, Zona Franca Cohort Study [2] or the prospective analysis from Framingham Study data [cit. by 3] sustain that obesity, quantified by BMI, is an independent risk factor for developing HF. Kenchaiah et al. also demonstrate that the risk of developing HF is twice in obese patients compared to normal weight population [4]. The risk is similar in males and females, including pregnancy, which is also related to HF through specific mechanisms and determine the cardio-metabolic health in the offspring [5, 6]. On the other hand, the phenomena of *obesity paradox* makes the relationship between obesity and HF more intriguing, by supporting the advantage of survival for overweight, class I and class II obesity population versus normal weight or underweight patients [3, 7]. The mechanisms involved in obese patients with HF are complex and include activation of renin-angiotensin-aldosterone and sympathetic nervous systems, but also specific pathways such as insulin resistance, inflammation, lipotoxicity, adipokines. All of these mechanisms contribute to left ventricular (LV) hypertrophy, heart rhythm disorders, hyperdynamic circulation or overt LV dysfunction [8-11]. The relationship between obesity and other cardiovascular and metabolic risk factors and diseases such as hypertension, dyslipidemia, diabetes, endocrine disorders, chronic liver/pulmonary diseases, as well as genetic paths common to obesity and cardiovascular disease, also mediate the developing and progression of HF [12-18].

Experimental part

Material and methods

We conducted an observational retrospective study including 577 subjects who were admitted for HF in the Department of Cardiology. All the data between 2013 and

2014 were collected from Department of Cardiology archive with permission of St. Spiridon Hospital staff. We used World Health Organization classification of obesity based on BMI: underweight < 18.5 kg/m², normal weight = 18.5-24.9 kg/m², overweight = 25.0-29.9 kg/m², obesity ≥ 30 kg/m² [19]. Venous blood samples were collected after 12 hours fasting for the assessment of biochemical and hematological parameters. Fasting plasma glucose, total cholesterol and triglycerides were determined applying enzymatic colorimetric method, while HDL-cholesterol was measured using immunoturbidimetry. LDL-cholesterol levels were calculated by Friedewald equation as described elsewhere [20]. Serum urea, creatinine, uric acid, sodium (Na⁺), potassium (K⁺) levels were determined using reference methods for testing renal function. The CKD-EPI Creatinine Equation for Glomerular Filtration Rate (GFR) was used to estimate GFR. So, $eGFR = 141 \times \min(\text{SCr}/k, 1)^{\hat{a}} \times \max(\hat{a}\text{Cr}/k, 1)^{-1.209} \times 0.993^{\text{age}} \times [1.018 \text{ if female}]$, where SCr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, \hat{a} is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1. Liver blood tests (ALT, AST, total bilirubin), a complete blood cell count using an automated analyzer and thyroid function (TSH) were measured. According to the ESC guidelines [21], the algorithm for the assessment of HF probability was based on the clinical history (hypertension, diabetes, ischemic coronary disease - ICD, chemotherapy/radiation exposure; different grades of dyspnea according to the New York Heart Association (NYHA) functional classification; previously documented or treated HF), physical exam (rales, heart murmurs, gallop heart sound, bilateral lower limb edema, jugular vein turgescence), any ECG abnormalities. If more than one element was present, B type natriuretic peptide (BNP) was measured and transthoracic echocardiography (TTE) was performed for determining the structure and function of the heart. LV diastolic diameter (LVEDD), interventricular septum (IVS) and LV posterior wall (LVPW) were measured. LV mass

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was derived using Devereux formula usually stated as $0.8\{1.04[(LVEDD + IVSd + PWD)^3 - LVEDD^3]\} + 0.6 [19]$ and indexed to the body surface area ($BSA = 0.007184 \times G^{0.425} \times H^{0.725}$) ($LVMI - g/m^2$). The modified biplane Simpson's rule was used for assessing ejection fraction (EF) and the segmental wall motion abnormalities were also evaluated. Based on all these available data and other imaging and stress tests, which were needed in selected patients, the etiology of HF was established.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics Version 20.0. The variables were described using mean values \pm standard deviation (SD). Pearson coefficient and Chi-square test were used to analyze the linear correlation between BMI and other studied variables. One-way analysis of variance (ANOVA) was used to compare means of the samples. A two-sided p value < 0.05 was considered significant for all data analyses.

Results and discussions

We studied 577 patients divided in four BMI categories – underweight, normal weight, overweight and obese. Based on this BMI distribution, in our study were 282 subjects with $BMI \geq 25 \text{ Kg/m}^2$ (48.87%) including 23.6% overweight- and 25.2% obese patients, and 295 subjects with $BMI < 25 \text{ Kg/m}^2$ (51.12%) including 49% normal weight- and 2.12% underweight patients. The mean age was 68.94 ± 11.8 years old, the males represented 69.2% of the whole group.

An important biochemical parameter, also used as a biomarker for ruling-out HF is BNP. A particular issue for

our discussion is the literature mentioning about BNP levels which are disproportionally low in obese patients [21, 22, 23]. Our results confirm that the lowest mean values of BNP levels are in obese patients (633.20 pg/mL) compared to overweight-, normal weight- and underweight patients (801.53 pg/mL, 1118.46 pg/mL, 633.20 pg/mL, respectively). As described in table 1, it can be observed that the mean values are much over the cut-off level used for chronic or acute settings. However, BNP values were not significant different between BMI categories ($p = 0.143$) in contrast to other reports [9, 22-24], possibly related to the characteristics of patients with HF. Regarding the other biochemical and hematological parameters, we found a significant correlation with BMI categories for plasma levels of fasting glucose ($p = 0.05$), HDL-cholesterol ($p = 0.0001$), triglycerides ($p = 0.0001$) and sodium ($p = 0.01$) as also described in table 1. In our study, plasma fasting glucose had abnormal mean levels regardless of the BMI category, but without documenting diabetes. We also observed progressively increasing values with BMI increase. The results sustain the continuous interplay between plasma glucose, insulin resistance and HF developing. Our study also highlights the importance of plasma glucose control in patients with HF, knowing that the role of hyperglycemia on HF risk and progression is independent of other cardiovascular risk factors [25-28]. Lipid profile was also related to BMI categories as other studies demonstrate [9, 28, 29]. HDL-cholesterol levels had an inverse correlation with BMI categories, which is an important issue considering that higher baseline values are reported to be associated with better outcome in HF, particularly in ischemic etiology [30]. Interestingly,

Parameter	BMI kg/m ²				p value
	< 18.5	18.5-24.9	25.0-29.9	> 30	
BNP (pg/mL)	790.56	1118.46	801.53	633.20	0.143
Plasma fasting glucose (mg/dL)	118.33	117.87	131.49	136.350	0.005
Cholesterol (mg/dL)	177.63	175.11	172.93	174.85	0.97
LDL-cholesterol (mg/dL)	110.16	106.78	107.58	104.61	0.92
HDL-cholesterol (mg/dL)	54.18	47.2	41.39	42.06	0.0001
Triglycerides (mg/dL)	172.63	103.82	118.95	133.49	0.0001
Urea (mg/dL)	57.5	49.51	46.95	48.46	0.507
Creatinine (mg/dL)	0.99	1.06	1.26	1.12	0.38
Uric acid (mg/dL)	6.8	6.33	7.48	9.13	0.085
Na ⁺ (mEq/L)	136.08	139.43	139.45	140.04	0.01
K ⁺ (mEq/L)	4.64	4.5	4.42	4.55	0.24
eGFR (ml/min/1.73 m ²)	64.51	60.97	57.66	60.92	0.26
AST (U/L)	29.35	17.21	32.76	38.51	0.33
ALT (U/L)	19.34	18.22	27.45	35.23	0.41
Total bilirubin (mg/dL)	1.101	1.112	0.84	1.05	0.2
TSH (μ IU/mL)	1.34	1.76	2.24	1.98	0.72
Hb (g/dL)	13.05	13.28	13.95	13.45	0.41
Leucocyte (/mm ³)	8937	8801	9042	8493	0.74

Table 1
RELATION OF BIOCHEMICAL
AND HEMATOLOGICAL
PARAMETERS TO BMI
CATEGORIES

		NYHA class				Total
		I	II	III	IV	
BMI	underweight	0	6 (50%)	6 (50%)	0	12 (100%)
	normal weight	3 (1.06%)	154 (54.41%)	113 (39.92%)	13 (4.59%)	283 (100%)
	overweight	1 (0.75%)	74 (54.41%)	55 (40.44%)	6 (4.41%)	136 (100%)
	obese	1 (0.68%)	100 (68.49%)	41 (28.08%)	4 (2.73%)	146 (100%)
Total		5	334	215	23	577

Table 2
BMI * NYHA CLASSES CROSS
TABULATION

Parameter			Pearson Correlation	p value
Etiology	Hypertension	43.4%	0.182	0.000
	ICD	32.4%	0.100	0.002
	Alcohol	14.23%	-0.026	0.53
	Valvular heart disease	4.33%	0.098	0.019
	Others	5.57%	0.032	0.40
Risk factors/modifiers	Hypertension	26.12%	0.198	0.000
	Dyslipidemia	26.48%	0.138	0.001
	Diabetes	9.44%	0.292	0.000
	Smoking	17.92%	0.101	0.015
	Others (including alcohol)	20.04%	0.001	0.8

Table 3
RELATION OF BMI TO HF
ETIOLOGY AND RISK
FACTORS/MODIFIERS

triglycerides levels had the highest values in the lowest BMI category, an aspect that might be relevant to outcomes in HF. In our study, plasma sodium mean levels were normal, but a slight, significantly increase with BMI category was observed unlike other studies [31]. This aspect may have a favorable impact on outcomes, as hyponatremia is known to be a predictor of mortality in HF. On the other hand, the results may be interpreted according not only to BMI category, but also to other variables such as severity of HF, comorbidities, dietary intake or intensive diuretic treatment [32]. All other studied biochemical and hematological parameters were not related to BMI as other studies report [25, 26].

When we analyzed the distribution of NYHA classes for BMI categories, we observed that more obese patients belonged to NYHA II class compared to normal- and underweight subjects. Also, the ratio between obese and normal weight patients favors the first category for NYHA III and NYHA IV classes (table 2). These results are concordant to the lowest mean values of BNP in obese patients. From this point of view, our data support previous reports regarding the obesity paradox and prevalence of HF [9, 24, 33].

In terms of HF etiology, hypertension was the most frequent entity (43.4%), followed by ICD (32.4%), alcohol consumption (14.23%), valvular heart disease (4.33%) and other cumulative etiologies (5.57%). However, only ICD had a uniform distribution (Asymp. Sig. > 0.01). A positive and significant correlation was found between BMI categories (< 25 Kg/m² and over 25 Kg/m²) and hypertension, ICD, valvular heart disease (p < 0.05) (Table 3).

Our data are different from other reports where ICD is the most frequent etiology [34-36], probably related to the study design. For example, Pecini et al. selected the patients with pure ischemic, hypertensive, valvular heart disease etc. etiology, while in our cohort the etiology could be mixed. Similar to Schwartzberg's study [28] our obese patients had a lower prevalence of ICD compared to normal- and overweight patients. The distribution of etiology in relation to BMI categories is represented in figure 1A.

For traditional cardiovascular risk factors or risk modifiers, dyslipidemia was the most frequent (26.48%) followed by hypertension (26.12%), smoking (17.92%) and diabetes (9.44%). None of these factors had a uniform distribution (Asymp. Sig. < 0.01), but all of them had a significant positive correlation with BMI (p < 0.05). It is worth mentioning that other risk modifiers including alcohol consumption, chronic obstructive pulmonary disease or renal dysfunction accounted for 20.4% of cases. When the same risk factors were analyzed in relation to BMI categories, an increased frequency of hypertension, dyslipidemia was found in overweight and obese patients (FIG. 1B). Although diabetes is reported as more frequent in BMI > 25 kg/m² [33, 34], in our study it had the lowest

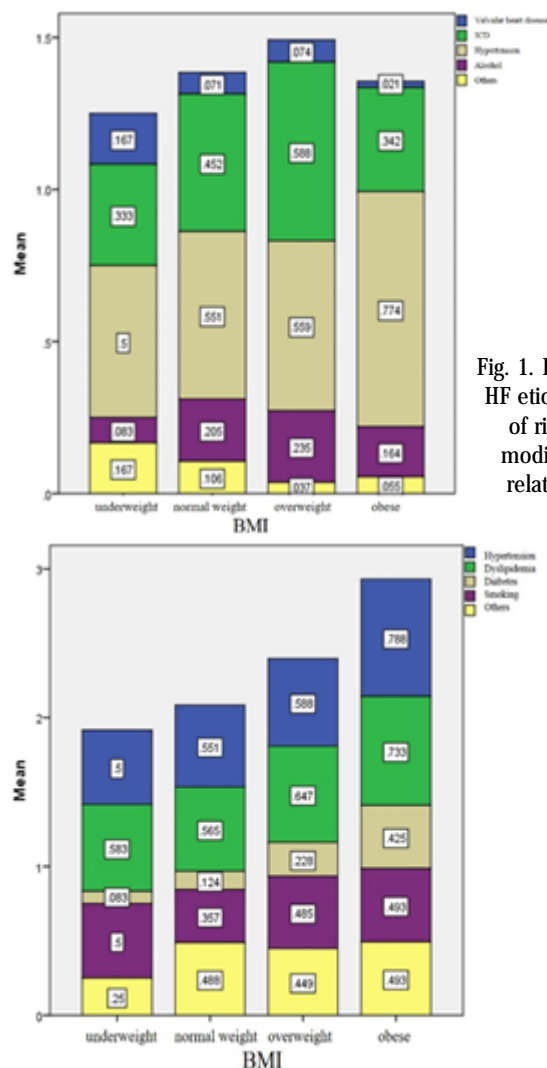


Fig. 1. Distribution of HF etiology (A) and of risk factors/modifiers (B) in relation to BMI

frequency among risk factors. This aspect could have a favorable influence on mortality as diabetets is known to be of particular importance on the survival of obese patients [24].

As expected, the analysis of LVMI revealed higher values in overweight and obese patients compared to normal weight and underweight subjects (279.76 g/m² and 275.90 g/m² versus 252.51 g/m² and 234.92 g/m²) with a significant variation between BMI categories (p = 0.02) (table 4). Our results are primarily explained by the increased incidence of hypertension with increasing BMI. The increasing incidence of clustering cardiovascular risk factors with increased BMI additively contributes to LV hypertrophy in our cohort, as also reported elsewhere [37]. According to the definition of HF based on EF [21], underweight patients belonged to HF with preserved EF (mean EF 52.25%) in contrast to all other patients who belonged to HF with

Parameter	BMI kg/m ²				p value
	< 18.5	18.5-24.9	25.0-29.9	> 30	
LVMi (g/m ²)	234.92	252.51	279.76	275.90	0.02
EF (%)	52.25	46.2	43.7	46.88	0.13
Rate of interventional revascularization (%)	0.0	4.1	8.1	6.2	0.21
Rate of coronary artery by-pass (%)	0.0	2.8	5.1	4.1	0.32
Rate of in-hospital patient death (%)	8.3	2.5	0.7	1.4	0.167

Table 4
RELATION OF HF
PROFILE TO BMI
CATEGORIES

midrange EF (mean EF between 40-49%) as described in table 4. Despite this profile of HF, there was no significant difference between BMI categories ($p = 0.13$).

Our study doesn't support other reports regarding preserved EF in obese patients [38, 39]. One explanation could be the higher incidence of hypertension and ICD, as well as cumulative cardiovascular risk factors influence in our overweight and obese patients. This particular distribution of etiology and risk factors may also explain the higher need for revascularization procedures with increasing BMI (table 4). Also, we can't support the recent findings that correlate higher mortality risk to midrange EF [40]. Although there was no significant difference between the rates of inpatient hospital related to BMI categories, underweight patients had a rate of 8.3%, the highest among the whole cohort (table 4), despite the preserved EF.

Conclusions

Taken together, our results sustain the importance of controlling risk factors, in particular plasma fasting glucose, lipid levels as well as hypertension in patients with HF and BMI over 25 kg/m². Although our study is retrospective, it reflects a real world cohort of patients with different characteristics of HF. So, in contrast to the randomized control studies our results can only partially support data related to the obesity paradox phenomena.

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