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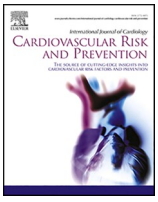

"Obesity paradox" and takotsubo syndrome

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ABSTRACT

Background: An "obesity paradox" has been reported in patients with hypertension and heart failure, in which obese patients fare better than patients with normal-weight. The purpose of this study was to determine whether there is an "obesity paradox" in patients with takotsubo syndrome (TTS).
Methods: The prevalence of obesity in databases/registries of patients with TTS was compared to the prevalence of obesity in world general populations. Obese patients with TTS were explored regarding the stress triggers precipitating the illness, hospital outcome, and post-discharge readmission. Finally, the literature on the "obesity paradox" was explored to understand how it could be applied to TTS.
Results: A prevalence of obesity of ~10–11% has been reported in large cohorts of patients with TTS, which represents 1/3 to ¼ of the prevalence reported in worldwide general populations, suggesting that, normal-weight than obese individuals, are more predisposed to develop TTS, with the latter nevertheless also suffering TTS, when triggered by enormous physical stresses. Obese patients with TTS are likely to have milder hospital outcomes, lower mortality, and lower rate of early readmission. A greater sympathetic nervous system (SNS) response in a number of hyperadrenergic states in normal-weight than obese patients, may explain findings in patients with TTS.
Conclusions: An "obesity paradox" has been identified in patients with TTS. Reporting on body mass index and other markers of obesity in patients with TTS, and implementing some recommendations on monitoring non-invasively the SNS in patients with TTS, may solidify that obesity has a preventive/ameliorating effect for TTS development and its clinical course.

1. Introduction

Obesity is an incident independent risk factor for dyslipidemia, type 2 diabetes mellitus (DM), metabolic syndrome (MetS), hypertension (HTN), sleep apnea disorders, cardiovascular disease (CVD), heart failure (HF), with reduced and preserved left ventricular ejection fraction (LVEF), arrhythmias, especially sudden cardiac death and atrial fibrillation, and chronic kidney disease (CKD) [1]. Overweight, defined as a body mass index (BMI) $\geq$25 and $<$ 30 kg/m^2 and obesity is encountered in 39%–49% of the world's population, with "the most recent nationally representative US estimates for obesity prevalence, based on the National Health and Nutrition Examination Survey reporting a crude prevalence of 39.8% in 2015–2016, which is an increase from the crude prevalence of 37.9% in 2013–2014" [1], and with women being more susceptible than men [2]. Although appropriately a war against obesity has been declared and waged by all concerned, an "obesity paradox" has been noted in association with HTN, resulting in a longer lifespan of obese than nonobese hypertensive patients [3]. Obesity in hypertensive patients has been associated with an underlying lower sympathetic nervous system (SNS) activity, than in nonobese hypertensive patients [3,4]. Consequently, and since TTS is pathophysiologically linked to a high blood-ridden catecholamine surge and/or an autonomic sympathetic nervous system (ASNS) seethe imparted locally to cardiomyocytes [5–8], one wonders whether a similar to the one noted in hypertension "obesity paradox" exists in TTS, exerting a protective effect for its emergence. As per this hypothesis, one would expect a lower prevalence of obesity in patients suffering TTS, than in the general population, suggesting that obese patients tend not to suffer TTS, as frequently as nonobese patients and only do so, when the odds are really overwhelming in terms of very high blood catecholamines and/or ASNS marked arousal, in the setting of intense physical or emotional stress. Also, the "obesity paradox" perhaps could be extended to the hospitalization and short- and long-term follow-up periods of patients admitted with TTS, imparting a lower rate of major adverse cardiac events (MACE) during hospitalization and lower rate of TTS recurrence. To this end, the literature linking obesity, or its absence, and TTS has been explored.

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Abbreviations and acronyms:

ARF	acute renal failure
ASNS	autonomic sympathetic nervous system
BMI	body mass index
BS	bariatric surgery
CAD	coronary artery disease
CKD	chronic kidney disease
CVD	cardiovascular disease
DM	diabetes mellitus
ECG	electrocardiogram
HF	heart failure
HTN	hypertension
LVEF	left ventricular ejection fraction
LOS	length of stay
MACE	major adverse cardiac events
MetS	metabolic syndrome
NE	epinephrine
SNS	sympathetic nervous system
TTS	takotsubo syndrome
US NIS	United States National Inpatient Sample

2. Methods

The PubMed was employed from its inception to 9/6/22 in response to MeHS "obesity and takotsubo" and 29 articles were accessed [2,3,9–35]; in addition, a recently published article with reference to morbid obesity [36] was included, for a total of 30 articles. A meta-analysis could not be performed, since many of the accessed articles (Table 1) did not comprise granular (individual patient-based) information on obesity. Obesity was defined as body mass index (BMI) $\geq$30 kg/m^2, although certain articles included patients characterized as being overweight (BMI $\geq$25.0 to $<$ 35 kg/m^2), or have class 1 (BMI $\geq$30 to $<$35 kg/m^2), class 2 (BMI $\geq$35 to $<$40 kg/m^2), and class 3 (BMI $\geq$40 kg/m^2) obesity, with obesity sometimes being categorized merely as "severe" or "morbid". It is conceivable that the accessed literature provides data on only a fraction of the obese patients who suffered TTS, since authors may have underreported obesity, or reported obesity only if it were excessive or morbid. Additional data on obesity and TTS were sought by exploring the established national or multinational database/registries of TTS about the prevalence of obesity, although such registries as a rule have not included obesity among the risk factors (HTN, DM, smoking, and hyperlipidemia), or other particulars which were systematically recorded as per study design. Information about HTN and DM was also sought and recorded, since HTN is thought of being prevalent in TTS [37], at rates similar to the one encountered in patients admitted to hospitals or in the general population, and DM is thought of having a low prevalence in patients with TTS [38–41], and thus the possibly detected lower prevalence of obesity in patients with TTS, in comparison with rates found in the general population or patients admitted to hospitals with various other pathologies (as per this study's hypothesis), might imply that in a representative reported TTS population, obesity exerts a protective effect for the emergence of TTS, as has been previously suggested for DM. An issue this author has struggled with was, whether there was justification to compare the published cases of patients with TTS with the world general populations, in reference to their corresponding prevalence of obesity. Such comparisons have previously been carried out in reference to the prevalence of DM [38–40]. Some of the databases/registries analyzed in Table 2, in which information on obesity prevalence in patients with TTS comprise of patients mainly from the USA or Europe, and comparisons of a prevalence of a risk factor in such cases could be either with corresponding general populations, or patients admitted to the hospital with other than TTS clinical pathologies.

Table 1
Papers about obesity and takotsubo syndrome accessed in PubMed (N = 30).

No.	Ref. #	Brief description of the essence of the paper
1.	[9]	A case report of a diabetic morbidly obese 68-year-old woman ("very elevated BMI"), with long-term use of methylprednisolone for the management of systemic lupus erythematosus, which had induced the morbid obesity, DM, associated obesity cardiomyopathy, and alveolitis with dyspnea, who suffered TTS, precipitated by physical and emotional stress, trying to get up after a fall.
2.	[10]	A case report of a 54-year woman with type 2 DM and obesity (BMI 30 kg/m^2), who suffered TTS in association with an anaphylactic shock caused by succinylcholine, during general anesthesia for laparoscopic promontofixation surgery; the patient also received epinephrine which could also be implicated in the emergence of TTS.
3.	[11]	A case report of a 61-year-old man with HTN and morbid obesity (BMI 46 kg/m^2), chronic obstructive pulmonary disease, and obstructive sleep apnea, who suffered TTS postoperatively after radical resection of a squamous cell carcinoma of the skin overlying the right zygoma and temporal area extending into the auricle, following engagement in an argument.
4.	[12]	A review of reversible cardiomyopathies, among which TTS and obesity cardiomyopathies are discussed; the latter responds favorably to BS.
5.	[13]	A previously healthy nonobese 30-year old man suffered TTS in the setting of playing online violent electronic games; excessive use of video games is linked to obesity.
6.	[14]	A case report of a 32-year old morbidly obese woman (BMI 46 kg/m^2) who suffered an inverse TTS after hemithyroidectomy, in the immediate post-operative period.
7.	[15]	A metanalysis of 19 studies of risk factors in 1109 patients with TTS revealed a 17% prevalence of obesity, which appears to be lower than expected.
8.	[16]	A French national study of nonacademic hospitals of 117 patients was associated with an 11.5% obesity (BMI $\geq$30 kg/m^2), which appears to be lower than expected.
9.	[17]	A review on women's CVD; obesity is mentioned as a risk factor for CVD and the importance of the obesity's management in the prevention and therapy is discussed; no refence is made on the association of obesity and TTS.
10.	[18]	A report of 40-year old woman with HTN and obesity (BMI of 43.28 kg/m^2) who suffered TTS 105 days after BS, and following laparoscopic surgery for a subphrenic abscess resulting from the BS, who also received dopamine and NE; also, a report of a 31-year old woman with HTN and obesity (BMI 38.28 kg/m^2) who developed TTS in the immediate postoperative period following BS.
11.	[19]	A meta-analysis of 30 case reports of CKD and TTS; obesity is mentioned as a risk factor for CKD, but no information on obesity of these 30 patients is provided.
12.	[20]	A report of a 72-year old woman with HTN, type 2 DM who suffered TTS in the setting of a strangulated internal hernia through pars flaccida defect, following laparoscopic fundoplication and right hemicolectomy for stage II cecal cancer 6 years previously; however, no mention of obesity is made.
13.	[21]	A study of readmission of 5997 patients with TTS, based on data from the US National Readmissions Database (2013–2014), revealed that obesity predicted a lower 1-month readmission rate.
14.	[22]	A study based on the USA NIS database (2010–2014) identified 612 obese TTS (weighted n = 3034) and 5696 nonobese TTS (weighted n = 28,186) patients, and revealed that obese TTS patients were more prone to develop cardiac complications than the nonobese TTS patients, although all cause in-hospital mortality and length of stay was similar in these 2 subgroups.
15.	[23]	A letter to the Editor regarding the interaction of obesity and DM in patients with TTS, referring to the article of reference #22 (vide supra), and pointing out that the rates of DM appeared to be lower than expected in both obese and nonobese patients with TTS.
16.	[24]	A response of the authors of the article of Ref. #22 to the letter to the Editor (Ref. #23) regarding the interaction of obesity and DM in patients with TTS; higher frequency of uncomplicated and complicated DM was found in the obese patients with TTS, although the propensity-matched analysis did show a lower frequency of uncomplicated and complicated DM in the obese patients with TTS (non- statistically significant differences, to establish any protective role of DM in the setting of obesity).
17.	[25]	

(*continued on next page*)

Table 1 (*continued*)

No.	Ref. #	Brief description of the essence of the paper
		A case report of a 66-year old woman with HTN and obesity (BMI 34 kg/m^2) who suffered TTS, triggered by excessive stress due to prolonged immobilization in her bathtub while taking a bath.
18.	[2]	A review on heart disease, particularly on primary prevention of HF in women; obesity is mentioned as a risk factor of HF.
19.	[26]	This study of 80 patients with TTS concluded that early prognosis for patients and low BMI is relatively favorable, whereas the 5-year follow-up is associated with extremely high mortality; overweight patients have the best prognosis in the long-term follow-up.
20.	[27]	A case report of an obese, asthmatic, and pre-diabetic 52-year old woman with TTS triggered by emotional distress at her mother's funeral; also, she had spontaneous coronary artery dissection during the index admission and a subsequent readmission.
21.	[28]	A case report of 3 patients with TTS following a COVID-19 infection, with one being of a 46-year old obese man with type 2DM, who succumbed to his illness.
22.	[29]	A case report of an obese (BMI 37 kg/m^2) 50-year-old man with TTS in the setting of a bilateral submassive pulmonary embolism.
23.	[30]	This US NIS (2016–2017) data-based study revealed a prevalence of obesity of 12.7%; the cluster of patients with HTN and DM had the lowest inpatient mortality, shortest LOS, and lowest incidence of ARF among the four clusters.
24.	[31]	A case report of a 62-year-old obese woman with HTN who suffered TTS in the setting of management (transurethral electroresection of tumor and chemotherapy) for a high-grade bladder cancer.
25.	[32]	This study explored in a pre-clinical murine TTS model the effect of suberanilohydroxamic acid, a cancer drug previously shown to improve cardiopulmonary function to reduce the isoproterenol-induced left ventricular myocardial injury and collagen deposition; no mention about obesity could be found in the article.
26.	[33]	This PubMed-based study (1/1/10–1/15/21) summarized data from Refs. #21 and #22); existing evidence suggests that obesity and chronic kidney disease are related to poor prognosis in TTS, while the relationship between DM and TTS prognosis is ambivalent.
27.	[34]	This US NIS (2016) data-based study showed that among patients with cancer, those with TTS were more likely to be obese, although this had no impact on in-hospital mortality.
28.	[3]	An "obesity paradox" in patients with essential hypertension due to lower ASNS activity than in nonobese hypertensive patients has been described, raising the issue whether this also applies to patients with TTS.
29.	[35]	Two nonobese women (75-year old and 90-year-old) with TTS are described, who were among 7 women who had concomitant Covid-19 infection and legionnaire's disease.
30.	[36]	A case report of a 54-year old morbidly obese woman with HTN, chronic obstructive pulmonary disease, tobacco dependence with a 30 pack-year history, and peptic ulcer disease, who suffered TTS due to diffuse epicardial coronary vasospasm.

Abbreviations: ARF = acute renal failure; ASNS = autonomic sympathetic nervous system; BMI = body mass index; BS = bariatric surgery; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; NE = norepinephrine; HF = heart failure; HTN = hypertension; LOS = length of stay; US NIS = United States National Inpatient Sample; TTS = takotsubo syndrome.

For example, patients with TTS are frequently compared to patients who have been admitted to the hospital with CAD or acute myocardial infarction/acute coronary syndromes. However, no matter with which group patients with TTS are being compared, they have a prevalence of obesity ~1/3 to ¼ of the corresponding metric of the USA, Europe, or world populations. Indeed, if patients with CAD or other pathologies are employed as comparators the difference in the prevalence of obesity would be even larger, considering the high rate of obesity in hospitalized patients.

3. Results

Table 1 provides information on the triggers precipitating TTS in obese patients. From all 30 papers outlined, patient-specific ("granular") data in reference to the precipitating stress particulars were available in 13 patients (item #s: 1,2,3,6,10 [2 patients], 12,17,20,21,22,24,30); in 12 patients the precipitating stress was of severe physical nature (surgery, anesthesia, catastrophic illness, grave extraneous circumstances), while in 1 patient the stress was strictly emotional, associated with the funeral of the patient's mother (item # 20). The balance of papers referring to the association of obesity and TTS, comprised meta-analyses or review articles on patients with obesity and TTS, lacking patient-specific data, pertaining to the precipitating TTS stress. Finally, there were a few papers tangentially related to obesity and TTS (referring to obesity as a risk factor, one (item #19) reporting on a patient with a low BMI, or including nonobese patients, or even patients who had not suffered TTS.

Table 2
Prevalence of obesity, hypertension and diabetes mellitus in patients with takotsubo syndrome from the world literature.

Ref.#	Number of patients	Obesity (%)	HTN (%)	DM (%)
[34]	568,239	5.0	64.7	15.3
[22]	6308	9.7	64.5	19.6
[21]	5997	10.7	65.9	20.2
[15]	1109	17.0	54.0	10.7
[30]	3141	12.7	49.0	19.5
[47]	4733	12.9	44.4	18.7
[16]	117	11.5	57.9	11.5
[37]	1750	Not reported	65.2	14.2
[42]	1071	Not reported	68.0	19.0
[43]	2898	Not reported	51.7	13.3
[40]	5642	Not reported	43.0	14.0
[45]	344	Not reported	57.0	17.0
[46]	1601	Not reported	66.9	20.0

Abbreviations: DM = diabetes mellitus; HTN = hypertension.

Table 2 depicts the prevalence of obesity in 7 large databases of patients with TTS [15,16,21,22,30,34,47]. Also, the prevalence of HTN and DM are depicted. Of interest is that 6 more of the most frequently quoted databases from national and multinational database/registries [37,40,42,43,45,46] did not provide data on obesity, while they provided information on the prevalence of HTN and DM. The prevalence of obesity appears to be between 10% and 11%, if one considers the prevalence of 5.0% in the largest database of 568,239 patients with TTS [34]. The exact prevalence is not offered herein, because its calculation was not feasible due to the overlap of some of these 6 out of 7 large databases, reporting on obesity, which have included partly the same patients, reported in different papers, with differing total numbers of patients. Indeed, 6 other databases/registries of TTS, among the most often quoted, have not reported data on obesity (Table 2).

The percent prevalence of HTN in most of these 12 large databases/registries is reported to be around 55%–65%, while the percent prevalence of DM is reported to be around 15% (Table 2). Again, the exact prevalence for HTN and DM cannot be calculated for the reasons explained above.

MACE, prognosis during hospitalization and at follow-up, readmissions, and recurrence of TTS, although they constitute data, and ordinarily should have been included in the "Results", are being dealt with in "Discussion" with appropriate reference to the literature sources.

4. Discussion

4.1. Epidemiology of obesity in TTS

The prevalence of obesity in patients admitted with TTS is <1/3 to ¼ of the one in the general population Table 2 [1,48–52], and this is further supported by considering that the prevalence of obesity in elderly women is even greater than in men [2 [, which is of importance, since ~90% of patients with TTS are women. The databases included in Table 2 are representative of the patients who have suffered TTS, and thus the detected low prevalence of obesity should be considered credible, when contrasted with the prevalence of HTN [21,22,33,34], and DM [38–41], which appear to be what has been previously reported in patients with TTS in the world literature. Prevalence of obesity of 5.04%

reported in the 1st study in Table 2 [34], should be seen in the context of the underlying population, which consisted of patients with active cancer and TTS, and thus these data are probably unsuitable for assessing the prevalence of obesity in TTS in general (vide infra). Underreporting of obesity is a possible underlying reason for the low prevalence of obesity in patients admitted with TTS, although it is very unlikely, since low prevalence of obesity was detected in all reported relevant databases (Table 2).

4.2. Outcomes of patients with obesity and TTS

In a retrospective cohort study of 6308 patients with TTS, employing an analysis of the Nationwide Inpatient Sample database, 2010–2014, the authors reported that the obese patients were more likely to have cardiac arrest, cardiogenic shock, respiratory failure, acute myocardial infarction, and mechanical hemodynamic support (Impella placement), although all-cause hospital mortality, arrhythmias, venous thromboembolism, hospitalization expenses, and length of stay (LOS) were similar between obese and nonobese patients with TTS, in the unmatched and propensity-matched cohorts [22].

In contrast, in another retrospective study of 5997 patients with TTS, employing the Healthcare Cost and Utilization Project's National Readmission Database of 2013 and 2014, sponsored by the Agency for Healthcare Research and Quality, obesity predicted a lower 1-month readmission rate, while it was associated with high rates of comorbidities (HTN, DM, chronic pulmonary disease, stroke/transient ischemic attack, peripheral vascular disease, iron-deficiency anemia, congestive HF, hypothyroidism, and renal failure at baseline [21]. This lower readmission rate early on after discharge [21] may be an expression of an extended "obesity paradox" associated with better short- term outcomes among obese patients with HF with both reduced and preserved LVEF, and other cardiovascular diseases (CVD), when compared with patients with normal BMI [53–55]. The above should be seen in the context of defining obesity only by the BMI, since there is debate as to whether this is sufficient (i.e., BMI may not be the best indicator of body-fat composition [53–56]. About 0.4% of the patients suffered recurrence of TTS within 6 months following the index TTS hospitalization, and >90% of TTC recurrences occurred within the first 3 weeks; however, no data on the recurrence of TTS in obese versus nonobese TTS patients were reported [21].

A study of 568,239 patients with TTS with active cancer, employing the 2016 United States National Inpatient Sample, were contrasted with 4,151,352 patients who had cancer but no TTS [34]; obesity was present in 5.04% of the patients with cancer and TTS, and these patients had a higher rate of HTN, HF, hyperlipidemia, reduced LVEF, obesity, cerebrovascular disease, anemia, and chronic obstructive pulmonary disease. The data contained in this article are not suitable to explore the impact of obesity on the clinical outcome of patients with TTS, since there is a confounding influence of cancer on the prevalence of obesity stemming from the presence of malignancy, stress of treatments such as surgery, chemotherapy, immunotherapy, and radiotherapy, in addition to the possible presence of various internal paraneoplastic syndromes [34].

In the COUNTS Study, which successfully merged 19 databases of previously published series of patients with TTS [15], a mean prevalence of obesity of 17% was detected, but the authors did not report outcomes of patients with TTS according to the presence or absence of obesity.

In a study employing the National Inpatient Sample database from 2016 to 2017 [30], the authors reported an overall prevalence of obesity of 12.7%, and provided details on outcomes for 4 clinical clusters (metabolic disease cluster, with patients with most prevalent HTN, DM, and hyperlipidemia; chronic obstructive pulmonary disease and smoking cluster, with most prevalent history of chronic obstructive lung disease and smoking; psychiatric disorders cluster, with patients having significant psychiatric disorders (anxiety and major depression disorders); and minimal risk factors cluster, with patients who had the fewest risk factors among the four clusters. Of interest is that the metabolic disease cluster had the lowest inpatient mortality, shortest LOS, and the lowest incidence of acute renal failure [ARF]), while the chronic obstructive pulmonary disease and smoking cluster had had the poorest overall outcomes with highest in-hospital mortality, the longest LOS, and the highest incidence of ARF. The authors did not include obesity in any of their clinical clusters, but if one considers that obesity is prevalent in patients with DM [53] and is a "part and parcel" of the MetS, who tend to have the obesity phenotype with excess body fat around the waist, obese patients probably were overrepresented in the clinical metabolic diseases cluster, the group with the best outcome, suggesting that obesity had an ameliorating effect in patients admitted with TTS. However, the authors did not specifically report on the association of obesity and clinical outcomes [30].

The authors of "The Observational French SyndromEs of TakoTsubo (OFSETT) study" reported on 117 patients with a prevalence of obesity of 11.5% [16], but did not address the in-hospital outcomes of their obese versus nonobese patients with TTS.

4.3. Postulated mechanism of obesity in TTS prevention or amelioration of clinical outcomes

Both obese and nonobese patients suffer TTS. Obese patients suffering TTS are shown to be exposed to enormous physical stresses (Table 1), which overwhelm the postulated herein obesity-derived preventive effect for the emergence of TTS. The detected low prevalence of obesity in large databases of patients with TTS (Table 2) suggests an underlying preventing effect for the TTS emergence, predisposing normal-weight individuals to TTS. Also, obese patients with TTS have been found to have a milder outcome profile than nonobese patients, and may be spared an early readmission after an index TTS admission (vide supra). In contrast, low BMI patients with TTS have a fatal 5-year prognosis [26], indirectly suggesting that obesity has a protective effect for the long-term outcome of patients who have suffered TTS.

An "obesity paradox" has been observed in patients with HTN [3,54,57], and in HF with both reduced and preserved LVEF [53,54,58]. Indeed, there is large literature on the beneficial effects and benign outcomes associated with overweight and obesity in a large array of diseases, although such outcomes are observed in relatively younger individuals and those without significant coronary artery disease (CAD) risk factor profiles. Consequently, it is not surprising that also patients with TTS, a form of partially or totally reversible acute HF condition, may manifest an "obesity paradox" [21,41,54,58].

But what could be the mechanism(s) of the preventive effects exerted by obesity in the emergence of TTS? In general obesity is viewed as one of the risk factors for CAD and other cardiac pathologies, and traditionally is seen as the phenotypic substrate for increased oxidative stress, which is one of the proposed etiopathogenetic mechanisms of TTS [22]. Obesity is a defining component of the MetS which is alarmingly increasing in frequency worldwide [1,2,17,59]. Obesity-generated MetS is associated with SNS overactivity, believed to cause the underlying HTN [59], while the SNS overactivity is linked to a complex array of factors (insulin resistance, arterial baroreceptor impairment, and dysregulation of leptin and adiponectin) [59]. Considering the derangement in this complex homeostatic apparatus present in obesity, our prevailing method of documenting obesity employing the BMI, appears wanting, and needs an upgrade in the clinical diagnosis of obesity [53,54,59]. It is conceivable that the "type of obesity" is of importance, since individuals with "central obesity" show increased SNS activity, in contrast to those with "subcutaneous form of obesity" [55,56,59], although both such groups of individuals will be characterized as obese, based on BMI. This is of importance since TTS is pathogenetically linked to an ASNS surge and/or marked rise of blood-ridden catecholamines [5–8]. Accordingly, one could speculate that groups of patients with TTS comprise individuals with "central obesity" characterized by high baseline ASNS activity, predisposing the emergence of TTS, and patients

with "subcutaneous form of obesity", who happened to have suffered TTS triggered by enormous physical stresses, experience the ameliorating effects of their underlying low baseline ASNS activity, on their in-hospital outcomes and subsequent follow-up clinical course. However, this remains to be shown by more sophisticated diagnosis of obesity in future studies of patients with TTS, although there is the potential of looking at this issue retrospectively in previously finalized or ongoing databases/registries of TTS [37,40,42–46], with more sophisticated characterization of obesity [55,56]. Current work refers to "obesities" instead of "obesity" [55,56], meaning that there exists a large array of obesity phenotypes, based on body fat composition and distribution (i.e, " central" vs. "diffuse", and presence of visceral adipose tissue and of ectopic fat) with associated varying metabolic derangement, and presence of other risk factors, in different combinations. Indeed, such phenotypes may have a different SNS response to various physical and emotional triggers, and thus may have a different degree of predilection to HTN, HF, and TTS. Thus, an expression of this great heterogenicity of obesity, emphasizing other obesity metrics than the BMI calculation, is the presence/absence of a predisposition to TTS, and different clinical outcomes in patients with DM, HTN, and HF and other pathologies [55].

The issue of "obesity paradox" in patients with HTN and other hyperadrenergic states have been systematically explored by employing in tandem assessment of the renal and cardiac SNS outflow, cardiac sympathetic nerve noradrenaline (NA) reuptake, and single fiber sympathetic firing discharges using invasive methodologies [3,4]. Specifically, the regional (renal or cardiac) SNS release of the sympathetic neurotransmitter, NA, has been measured by the isotope 20 dilution assessment of NA plasma kinetics methodology, while recording of single nerve fiber discharges in sympathetic nerves have been registered by subcutaneously-placed microelectrodes, employing the clinical microneurography technique [3,4]. These studies have provided evidence that "normal-weight patients with essential HTN have preferential activation of the cardiac sympathetic outflow, faulty neuronal NA reuptake, and a pattern of sympathetic nerve discharge where individual fibers commonly fire in multiple salvos of doublets and triplets within a single cardiac cycle" (Fig. 1) [4]. This SNS behavior is absent in obese patients with essential HTN [3,4], while these 2 different pathophysiologic SNS phenotypes in normal-weight and obese hypertension continue to elude an explanation. Such SNS expressions of the "obesity paradox" are seen in type 2 DM, HF, in addition to HTN [4]. The importance of these insights in the pathophysiology and management of a large host of conditions like HTN, HF, depressive disorders, panic disorders, postural tachycardia syndrome, genetic long QTc syndrome, and ageing is immense, as is their role in impacting vascular endothelium, in atherosclerosis and left ventricular hypertrophy cardiac arrhythmias, and thrombosis, leading to myocardial and cerebral infarctions [3,4].

Considering the noxious role of SNS enhanced activity in TTS and the modifying influence of obesity, it may be of importance, along with reporting BMI and other markers of obesity [55,56], to incorporate in the diagnostic and monitoring routine of patients with TTS noninvasive, rather than invasive [3,4] ways, of assessment of SNS activity and their impact in the blood circulation. Accordingly, starting again to measure catecholamines (adrenaline, NA, dopamine), as it were common early after the formal description of the TTS, would be a good starting point [8]. In addition, a commercially available noninvasive technique of simultaneous recording of skin sympathetic nerve activity and the electrocardiogram (ECG) employing conventional ECG electrodes may be of true value [60,61] This well studied method has been used to estimate the sympathetic tone, and has been evaluated in subjects with the cold water pressor test and the Valsalva maneuver, and patients with epilepsy, ventricular arrhythmias, including electrical storm, bilateral stellate ganglion blockade with lidocaine injection, and atrial fibrillation [60,61], and appears to be a suitable accompaniment to the blood measurements of catecholamines [8,61] in patients with TTS. The interplay of the status of body mass, and SNS activity [3,4] and the blood catecholamines [8] may be worth delving into, as we explore the pathophysiology of TTS.

4.4. Limitations

A possible underreporting of obesity in patients with TTS may have deprived us of accurate data on the prevalence of obesity [22], although this appears unlikely since low obesity prevalence was noted in all large databases of patients with TTS which were analyzed (Table 2). Before

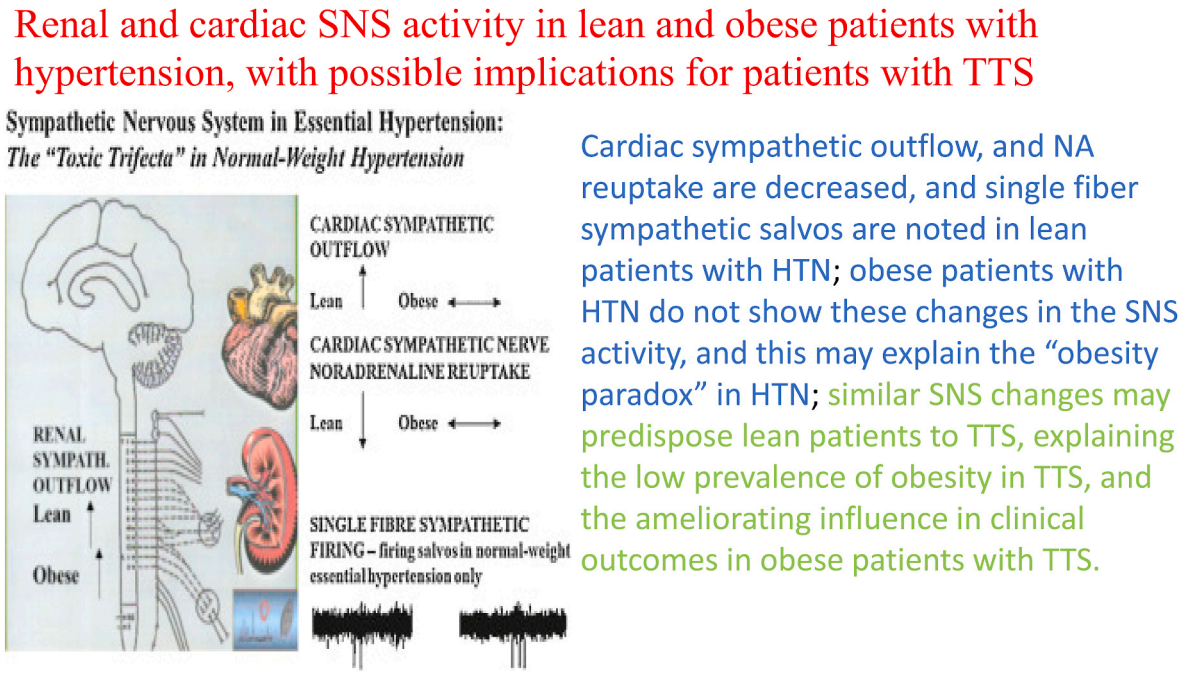

Fig. 1. NE = epinephrine; HTN: hypertension; SNS = sympathetic nervous system; TTS = takotsubo syndrome. The pictorial material in the composite above is reproduced in a modified form, with the permission of the publisher [4].

we engage further in the exploration of the mechanism(s) of the possible beneficial effects of obesity (or its particular phenotypes) in TTS, we should secure more evidence that, the prevalence of obesity (employing more sophisticated markers of obesity than the BMI) in patients admitted with TTS, is truly low. Until then the present work should be considered a hypothesis-generating study. Although the review was limited only to PubMed, the emphasis herein is not so much about patients with obesity (Table 1) which was based on PubMed, but about the prevalence of obesity in TTS (Table 2), for which all the frequently quoted databases/registries of patients with TTS, analyzed in this article, have been included).

4.5. Future studies

Future studies on the effects imparted by obesity in the emergence of TTS and the subsequent hospital and outpatient course of afflicted patients would be aided by including BMI and other obesity metrics and measurements in all literature reports on patients with TTS. This particularly applies to large national or multinational databases/registries, which collect data on patients with TTS in a more disciplined and uniform fashion, and are looked upon as the gold standard for informing the profession on the epidemiology, pathophysiology, diagnosis, management, and follow-up of patients with TTS.

5. Conclusions

Based on information from large databases/registries, the prevalence of obesity in patients with TTS is lower than the one in the general population, and this raises the possibility that obesity, or its particular phenotypes, exerts a preventive effect for the emergence of TTS, extents an ameliorating influence in the hospital course of afflicted patients, and reduces the rate of early readmissions. Such beneficial influences constitute the “obesity paradox”, already observed in patients with hypertension, HF, and a host of other medical conditions. The postulated mechanism exerted by obesity in patients with TTS, may further be elucidated, by reporting on the BMI of patients suffering TTS, and by monitoring of the SNS activity input to the heart in patients with TTS, employing existing noninvasive methodologies.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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