

incriminated as inducing hypersensitivity reaction leading to stent thrombosis.⁶ Bioresorbable poly (L-lactide) acid screws, used in orthopedics, have induced systemic hypersensitivity reactions proven by positive skin tests and necessitated to remove the screws.⁷ Bioresorbable poly (L-lactide) gel injections can induce also granulomatous reactions.⁸ The eluted everolimus substance from absorb bioresorbable stent has been already associated with the development of hypersensitivity pneumonitis, atopic dermatitis, exanthema, and generalized as well as lingual angioedema.⁹

Therefore, efforts to avoid and/or prevent locally induced acidity, local hypersensitivity inflammation, and foreign body reaction, together with technical and structural improvement seem to be of paramount importance for prevention of the so feared scaffold thrombosis.

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Prevalence of Diabetes Mellitus in Patients With Takotsubo Syndrome According to Age and Sex



The pathophysiology of takotsubo syndrome (TTS) remains elusive. A plausible pathomechanism, currently considered, is that TTS is mediated by an autonomic sympathetic nervous system (ASNS) surge and/or blood-borne catecholamines from adrenal oversecretion. Diabetes mellitus (DM) via its underlying ASNS neuropathy exerts a halting effect on both direct stimulation of the heart via norepinephrine, and the release of epinephrine by the adrenal glands.^{1,2} Consequently one should expect a lower prevalence of DM in cohorts of patients with TTS.^{1–3} Kato et al,⁴ in response to an inquiry,³ about the prevalence of DM in the InterTAK (International Takotsubo) Registry of 1,613 patients, contributed by the Registry participants from 8 European countries and the United States,⁵ have advanced the interesting concept of a differential in a plausible DM-mediated pathogenetic mechanism of TTS; they theorized⁴ that, while the prevalence of DM in patients ≥ 60 years old with TTS is lower than the one of general populations, both in Europe and the United States, and thus DM may be “cardioprotective” (due to the underlying autonomic peripheral neuropathy), patients < 60 years old with TTS in both continents have a higher prevalence of DM than the corresponding general populations (and thus DM predisposes them to develop TTS via an underlying microvascular impairment which they have, rather than ASNS

neuropathy, which they had not yet developed).

To investigate this hypothesis, all 4,106 reports, published in Pubmed from its inception to December 31, 2018, were accessed through the MeSH term “takotsubo,” and a meta-analysis was carried out on 2,667 suitable patients, who had individual patient-based data on age, sex, and history of DM. The original database of the world literature, without language restrictions, included 2,823 individually presented patients, but after the employment of “Google translate,” help sought by native speakers with medical background, except on rare occasions when this could not be accomplished, and repeated contacts through e-mails, with the corresponding authors of reports, 156 patient cases had to be excluded, when information about age, sex, and history of DM could not be securely documented. More details on methodology can be found elsewhere.^{1,2} Also very rarely there was information available about the particulars of DM, and that included that the patient had type 1 or 2 DM. In 2 patients the diagnosis of DM was made for first time in the setting of the patients’ admission with TTS, and in 4 patients the diagnosis of having and being treated for “hyperglycemia,” than DM, was provided. The assembled cohort of 2,667 patient cases was by an average age of ~ 6 years younger than the InterTAK Registry patients, with 39.6% being < 60 years old, and with 84.4% being women (Table 1). What is new in this Reader’s comment, compared with the previously published reports based on the same assembled database from the world literature,^{1,2} is that more patients are included in the present work, and a new analysis of prevalence of DM according to sex, and the dichotomized brackets of < 60 years and ≥ 60 years old of patients with TTS is provided herein, specifically for the purposes of an exploration of the hypothesis of Kato et al,⁴ of an alleged pathophysiologic differential of DM mediation in the emergence of TTS in patients younger versus older than 60 years old.

The prevalence of DM in all patients, women, and men for the ages < 60 and ≥ 60 years old, except for men ≥ 60 years old, was lower than in the general populations of Europe, the United States, and the world, as seen

Table 1

Prevalence of diabetes mellitus in patients with takotsubo syndrome from the world literature (all, N = 2,667; female, N = 2,251; male, N = 416)

Study cohorts	Patients <60 years old (N = 1,056)	Patients ≥60 years old (N = 1,611)
All patients	58 (5.5%)	191 (11.9%)
Female	48 (5.8%)	160 (11.3%)
Male	10 (4.4%)	31 (16.2%)

by comparisons with Fig. 1, and Ref. 3 of Kato's article,⁴ both based on data from the cited International Diabetes Federation, IDF Diabetes Atlas. Thus this analysis of data from the world literature did not disclose the theorized by Kato et al,⁴ higher prevalence of DM in patients with TTS <60 years old, and lower prevalence of DM in patients with TTS ≥60 years old, than expected in the corresponding world populations of subjects of the same ages; indeed the former, considering the subgroups of all the patients, females, and males, had a prevalence of DM of 5.5%, 5.8%, and 4.4%, correspondingly (Table 1). Consequently there is no difference in the prevalence of DM in patients with TTS <60 years old and ≥60 years old with TTS in the world literature, and in both the prevalence of DM is lower than expected in the corresponding subjects of the general world populations.

The prevalence of DM in male patients ≥60 years old from the world literature is similar to the reported prevalence of patients from the United States, and of the same age bracket, and may reflect the physical triggers for TTS in such patients.^{4,5} Although DM may exert in general a "protective effect" for the emergence of TTS, the

enormity of associated physical stresses, due to the associated serious comorbidities, anesthesia, surgery, sepsis, etc, could overwhelm the "cardioprotective" effect, mediated by DM.

The above should provide the impetus for authors of future contributions to the literature on TTS, to provide information about DM (type, duration of the illness, HbA1c, therapy, and complications, including peripheral and ASNS neuropathy of their reported patients. Also registries, like the InterTAK^{4,5} could benefit us all by "beefing-up" their databases with more information about DM, provided by the participants who have contributed patients to the registries. This could truly "open the next chapter of this topic,"⁴ and possibly contribute to the unraveling of the pathophysiology of TTS.

Disclosure

The author has no conflicts of interest to disclose.

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