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Original Article

Thyroid dysfunction and takotsubo cardiomyopathy: a narrative review

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Abstract

Objectives: Takotsubo cardiomyopathy (TCM) is a transient left ventricular wall motion abnormality commonly following physical and emotional stress that can be resolved entirely. Recent case reports and some case-control studies have suggested a likely close association between thyrotoxicosis and TCM. It was shown that resolving thyroid functional status led to resolving TCM symptoms leading to normal cardiac function without a significant sequela, emphasizing a triggering role of thyrotoxicosis for flaring TCM. Here, the literature on the association between thyroid dysfunction and the likelihood of TCM is reviewed to describe the likely pathophysiology of TCM associated with thyroid dysfunction.

Keywords: Takotsubo cardiomyopathy, Thyroid, dysfunction

Introduction

Transient left ventricular (LV) apical ballooning syndrome, Takotsubo cardiomyopathy, Takotsubo syndrome (TTS), broken heart syndrome, ampulla cardiomyopathy, or stress-induced cardiomyopathy are interchangeable terms and have all been applied to define a syndrome characterized by transient left ventricular systolic and diastolic dysfunction (1).

Takotsubo cardiomyopathy (TCM) is defined as a transient left ventricular wall motion abnormality commonly following both physical and emotional stress that can be resolved entirely (2). It presents on histopathologic examination with predominant neutrophilic inflammation, contractile necrosis, and fibrosis, in contrast to ischemia-related cardiac dysfunction (3).

Although TCM is a new concept in the cardiovascular field, its outbreak has been reported worldwide. For the first time in 2006, TCM was classified as a subtype of acquired cardiomyopathies (2). From an epidemiological aspect, TCM was rarely noticed before the last two decades. However, the present literature reports more than one thousand cases affected by TCM. According to the literature, TCM is the final diagnosis in about 2% of all patients with a primary suspicion of ischemic heart disease (4).

Interestingly, this phenomenon has been reported significantly in postmenopausal women (5), with a greater tendency in older adults; However, some cases of illness among the younger generation have also been reported (6). This tendency has also been shown to be higher in those with a history of stress as well as those with a history of coronary artery disease, and therefore TCM appears to be triggered by these triggering factors (7). Despite the increasing incidence of TCM, the definitive etiology and diagnosis of TCM remain controversial. Some researchers have described the main criteria for defining and diagnosing TCM. Accordingly, TCM is mainly defined as a syndrome with nonspecific manifestations which cause acute balloon-like dilation of the left

ventricular apex in the absence of coronary artery disease without recognized etiology (8).

Patients initially complain of dyspnea and atypical chest pain, and rarely palpitations, nausea, syncope, or even cardiogenic shock, mimicking symptoms of progressive heart failure. However, it should be pointed out that the manifestation usually emerges from physical or psychological stressful events. A nonspecific pattern is predominant in electrocardiographic assessment. However, ST-segment elevation in precordial leads and ST-segment depression, and T inversion in the inferior wall leads may appear in half of the patients. This misdiagnosis can be made worse when some patients have a mild increase in cardiac enzyme levels (9); hence close survey by coronary angiography and Echocardiography is strongly recommended. Meanwhile, the presence of balloon-like left ventricular dilatation can be confidently diagnosed by echocardiography. Recent reports have emphasized the use of cardiac magnetic resonance imaging (MRI) to establish TCM diagnosis because it has high accuracy in detecting wall motion abnormalities, quantifying cardiac function, and detecting cardiac fibrosis or other inflammatory changes. Moreover, the precise differentiation of TCM of myocardial ischemic or infarction can be achieved by cardiac MRI (10).

One of the main features of the disease is that ventricular dysfunction is reversible, which has been confirmed in most previous studies. This functional reversibility and recovery occur mainly within one to four weeks after disease onset; thus, continuous or progressive ventricular dysfunction would suggest other differential diagnoses. TC disease has a good prognosis, with improvement reported in more than 95% of patients.

Recent studies have reported that factors such as male gender, acute physiological or psychological stress, severe left ventricular dysfunction (LVEF <45%), acute neuropathology, and very high troponin are associated with poor nosocomial outcomes (11).

For a poor long-term prognosis, factors such as older age, decreased ventricular ejection fraction (LVEF <45%), the presence of heart shock, the presence of atrial fibrillation, or neuropathology have been reported (3).

From a pathophysiological aspect, the fundamental pathogenesis of TCM remains uncertain. But, some hypotheses have been proposed to explain the background of TCM, such as catecholamine-induced cardiotoxicity, microvascular dysfunction, reperfusion injury, transient coronary artery spasm, micro-infarctions, and abnormalities in cardiac fatty acids metabolism. A high level of serum catecholamine following stress in patients diagnosed with TCM, suggests the critical role of catecholamine-induced cardiotoxicity (12). Also, microvasculature dysfunction associated with excessive vasoconstriction and myocardial perfusion abnormality has been reported as another element of TCM.(13). The central role of inflammatory cascades and their impact on cardiomyocyte cell lines and vasculature should not be ignored (14). The subsequent evidence has been colligated by increasing the level of white blood cell counts, C-reactive protein in affected patients, and some cytokines such as interleukin-6 and tumor necrosis factor-α (15).

In addition to some of the probabilities of TCM pathogenesis mentioned above, some potential risk factors for the disease have also been characterized. The most recognized risk factors are as follows: 1) lack of estrogen: this probably risk profile can explain the high rate of TCM among postmenopausal women. It has also been shown that sexual hormone replacement therapy might potentially affect TCM (16), 2) stressful events: the evidence has shown a high rate of mood disorders and antidepressant intake among patients with TCM. Accordingly, it appears that following stress, parasympathetic tension is reduced and response to adrenal medullary hormones is increased, which may be relevant to the causation of TCM (17), 3) genetic factors: Recently, various gene polymorphisms have been identified that might be associated with the increased risk of TCM. Some of the mutations of α- and β-adrenergic receptors, such as L41Q polymorphism of G protein-coupled receptor kinase (GRK5), are related to the likelihood of stunned neurogenic myocardium associated with RCM (18). Some other studies linked the risk for TCM with estrogen receptors polymorphisms such as rs2234693 locus of the ESR1 gene and rs1271572 locus of the ESR2 gene. This evidence emphasizes the probability of familial and genetic features of TCM (19).

In addition, there are some reports of endocrine disruption associated with TCM, for example, thyroidectomy stimulates the vagus and reduces blood pressure and bradycardia. Sympathetic and parasympathetic activity may have caused Takotsubo cardiomyopathy(20).

In response to a large number of catecholamines,

the heart responds transiently to the transient stunning of the heart. The reaction to over-sympathetic stimulation also appears to cause the myocardium to dilate. On the other hand, sensitivity to catecholamines also increases, which may be a possible mechanism of TCM (3).

The association of TCM with paraganglioma is suggested in 7.5-25% of cases, which is essential for screening, especially in patients without sediment and in the presence of hyperadrenergic symptoms (3).

Pheochromocytoma and paraganglioma directly increase TC secondary to increase in aminergic catechol, while other endocrine abnormalities increase aminergic catechol response through different mechanisms (3).

Additionally, the association between TCM and postmenopausal estrogen deficiency, hypothyroidism or hyperthyroidism, and primary or secondary adrenal insufficiency has been reported in numerous reports (21).

According to these reports, endocrine disorders appear to increase myocardial sensitivity to catecholamines. Possibly, treatment of adrenal insufficiency with a replacement dose of steroids may in some cases worsen systolic heart failure (3).

Materials and Methods

Search Strategy

A search was carried out using the major electronic databases such as PubMed, Web of Science, Google Scholar, and Scopus. The search was confined to English literature published between 2001 and 2021. All articles and reports related to Thyroid function and Takotsubo cardiomyopathy were reviewed. A total of 39 related articles have been reviewed to finally illustrate our topic addressed.

The keywords of the review were specified as:

Takotsubo
Thyroid dysfunction
Cardiomyopathy
LV dysfunction
Post stress cardiomyopathy
Precipitating factors
Thyroidectomy
Endocrine causes of heart failure
Endocrinological abnormalities

TCM and thyroid function

Recent research has found a strong relationship between thyroid function and thyroid function-related medications and risk of TCM. Some recent case reports have reveals the close association between TCM and hyperthyroidism. As reported by Irigaray Echarri et al. (22) a case report revealed hyperthyroidism caused by Graves' disease as a provocation for TCM, which initially manifested itself as chest pain and electrical ECG changes as well as severe ventricular dysfunction, but without lesions in the coronary tree. Rueda et al. (23) in another recent case report discussed the potential role of thyrotoxicosis in the pathophysiology of TCM; so that hyperthyroidism caused by Graves' disease was suggested as a cause of TCM after the distressing incident; however, both events, including TCM and thyrotoxicosis, resolved spontaneously with a favorable outcome. In another case report, Murdoch et al. (24) described a case of TCM and thyrotoxicosis as a consequence of a toxic multinodular goiter and finally concluded that autoimmunity is regarded as a trigger for thyrotoxicosis but could also be a trigger for TCM. In some other reports, relapse of thyrotoxicosis has been associated with a recurrence of TCM. Patel et al. (25) reported that a case with recurrent TCM in the presence of recurrent hyperthyroidism is associated with Grave's disease; in that case, resolving TCM was revealed following normalization of thyroid function. In a case report by Wu et al. (26), a case of type-2 diabetes mellitus and thyroid storm was described in which diagnosis of TCM was confirmed after assessing the patient by echocardiogram and coronary angiography. However, the patient expired due to the progression of diabetic-related complications and thyrotoxicosis along with the deterioration of cardiac dysfunction. In another report by Perkins

et al. (27), a case of Graves' hyperthyroidism was complicated by severe biventricular Takotsubo cardiomyopathy detected on cardiac catheterization. After appropriate pharmacological treatment of her hyperthyroidism, her cardiomyopathy completely disappeared . Eliades et al. (28) reported a case with symptoms of heart failure. Acute coronary syndrome was initially considered, but the diagnosis of TCM associated with thyroid storm was eventually made on the basis of cardiac catheterization and laboratory testing. Also, Sarullo et al. (29) described a case with the presentation of sinus tachycardia with ST-elevation in leads D1, aVL, and V1-V4 in the electrocardiogram, and akinesis of the left ventricular apex with overall severely impaired left ventricular systolic function and an ejection fraction of 28% on echocardiography. However, coronary angiography showed no significant coronary artery disease. Laboratory analysis revealed a transient increase in serum free triiodothyronine, free thyroxine, thyroid globulin antibodies and thyroid peroxidase antibodies. More interestingly, complete resolving thyroid functional status was accompanied by complete resolution of the left ventricular dysfunction. Kwon et al. (30) also reported a case that presented with chest pain and cardiac arrest and was eventually diagnosed as Takotsubo cardiomyopathy caused by iatrogenic thyrotoxicosis. Radhakrishnan et al. (31) reported another case in which the diagnosis of thyroid storm was made by the presence of fever, lethargy, tachycardia, heart failure and abnormal thyroid function tests. Echocardiographic assessment revealed severe left ventricular dysfunction with apical dilatation with the normal condition of the coronary tree on coronary arteriography. Treatment of thyrotoxicosis with corticosteroids resulted in complete resolution of LV dysfunction and cavity dilatation a few days after treatment of thyroid dysfunction. Most published studies on the association between thyroid dysfunction and TCM have focused on describing rare cases, but in a case-control study by Lee et al. (32) three groups of people, including patients with TCM, patients without TCM and healthy subjects were assessed with regard to thyroid function. Briefly, the patient, control I, and control II groups were as follows: the control I group, underlying disease (-) and stress CMP (-); the control group II, underlying disease (+) and stress CMP (-); the patient group, underlying disease (+) and exercise CMP (+).Compared to healthy controls, the TCM patient group had decreases in left ventricular ejection fraction (LVEF) and systolic blood pressure (BP), but increases in troponin-I, CK-MB, and B-type natriuretic peptide (BNP) level along with reduced T3 levels as well as increases in -thyroid peroxidase antibody (anti-TPO-Ab) positivity, C-reactive protein (CRP) and cortisol levels. Some evidence has also been found in the relationship between thyroid-related medications and the likelihood of TCM. As recently shown by Chae et al.(1), a case of posterior reversible encephalopathy syndrome with concomitant Takotsubo cardiomyopathy was reported that was eventually found to be associated with lenvatinib therapy for thyroid cancer. This association was explained by the side effects associated with drugs used, such as tyrosine kinase inhibitors. In another experiment, Balsa et al. (33) reported a case with iatrogenic hyperthyroidism on levothyroxine replacement therapy. Also Capel et al. (34) reported a case of TCM with no history of emotional trauma or other potential precipitating factors who was diagnosed with amiodarone-induced hyperthyroidism. Unfortunately, most published articles have focused on case reports, and rare case-control studies have examined such a relationship. Demonstrating causality between hyperthyroidism or related medications as precipitating factors for TCM requires cohort or case-control studies, or even clinical trials if humane-ethical approvals are achieved.

In a 2020 multicenter observational study, A. Aweimer and colleagues(35) analyzed sequential thyroid hormone profiles of patients during the acute phase of TCM or acute coronary syndrome (ACS) compared to age- and sex-matched controls. Among patients with TCM, FT4 concentrations were significantly higher when compared to controls or ACS. 25% suffered from subclinical or overt thyrotoxicosis. In 25%, FT4 levels were elevated despite non-suppressed TSH levels, representing an elevated predicted set point of thyroid homeostasis. Other patients developed subclinical or overt thyrotoxicosis during their hospital stay. The thyroid hormone profile was normal in only 38% of patients presenting with TCM Figuer 1.

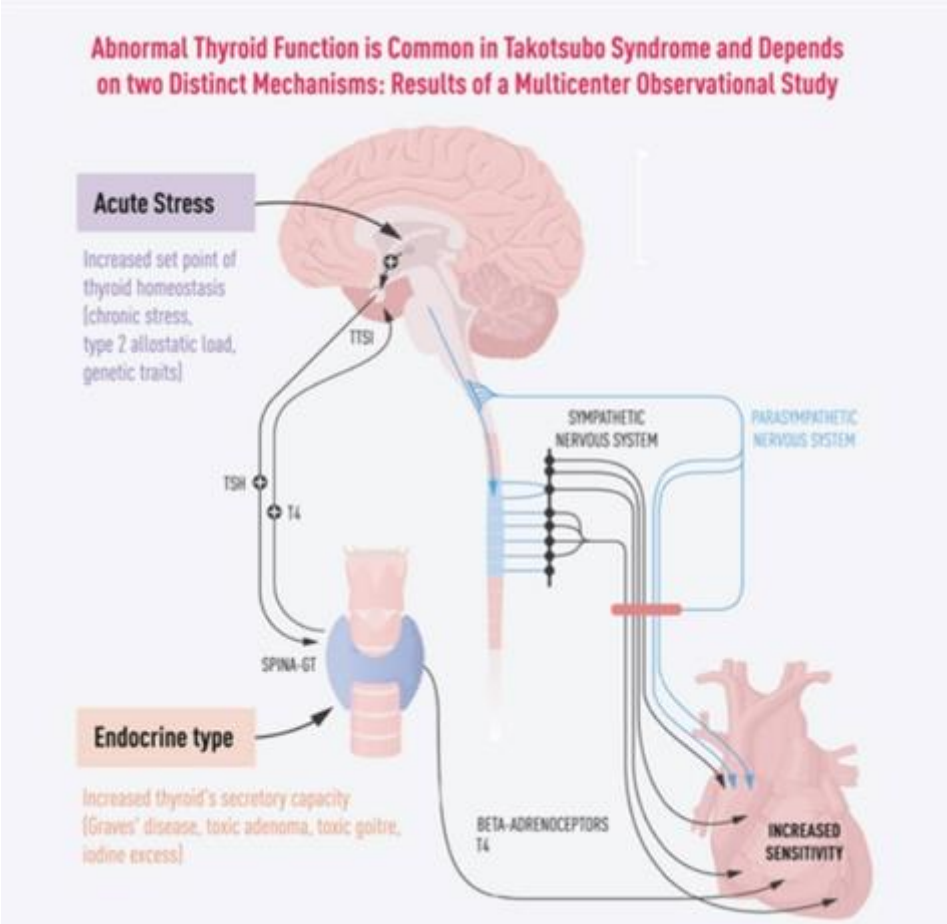

Figure 1. Abnormal Thyroid Function in Takotaubo Syndrome

The mechanism related to TCM following thyroid dysfunction

The pathophysiology of Takotsubo cardiomyopathy is complex, with multiple mechanisms being proposed. The neuroendocrine axis is probably contributed, with catecholamine-mediated myocardial damage through either direct toxicity, microvascular dysfunction, as well as sensitization of the myocardial tissue to sympathetic hormones by thyroid hormones exacerbating the catecholaminergic-mediated myocardial tissue damage through synergism Other possible mechanisms include elevation of circulating catecholamine levels, but this continues to be a controversial theory (35).

Tri-iodothyronine and thyroxine affect the expression of genes encoding structural and functional proteins in the myocardium that finally affect cardiac contractility and architecture (36). It has been demonstrated that a lower level of thyroid hormones leads to reduced myocardial contractility and cardiac atrophy along with loss of cardiac arteriole, chamber dilation, and transient reduction of myocardial blood flow (37). A close association between serum level of T3, and cardiac index left ventricular ejection fraction and myocardial peak oxygen consumption has also been shown, especially in heart failure conditions (38, 39).

These findings display the interaction between thyroid hormone and cardiac functional status, especially the effect of thyroid hormones on cardiac contractility; which may explain the relationship between TCM and thyroid dysfunction. As another explanation, adrenergic flaring associated with thyrotoxicosis may be related to microvascular spasms and epicardial coronary spasms without evidence of ischemic coronary diseases (40). Summarizing the pointed evidence may explain that thyroid dysfunction can be considered a major triggering factor for TCM; however, further experimental, molecular, and clinical studies are required to demonstrate such causality.

Conclusion

Overall, the optimal management of Takotsubo cardiomyopathy has not been determined. Yet, the mainstay of therapy focused on managing complications and heart failure therapy, which is commonly based on renin-angiotensin-aldosterone system blockage in companion with cardio selective beta-adrenergic receptor blockers in hemodynamically stable patients.

Since the sympathetic-adrenergic system plays a central role in the pathogenesis of this cardiomyopathy, thyroid dysfunction is often found in patients with TCM. But the causal association has yet to be fully established. Although the exact mechanisms by which thyrotoxicosis can induce TCM remains unclear, primary hyperthyroidism and an elevated set point of thyroid homeostasis are commonly encountered in TCM, suggesting a stress-dependent endocrine response may be a pivotal contributor to the pathophysiology of this condition. Therefore, thyroid function may be a worthwhile target in treating or preventing TTS.

References

1. Chae YK, Chiec L, Adney SK, et al. Posterior reversible encephalopathy syndrome and takotsubo cardiomyopathy associated with lenvatinib therapy for thyroid cancer: a case report and review. *Oncotarget*. 2018;9(46):28281-28289.
2. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. *Circulation*. 2006;113(14):1807-16.
3. Khatiwada S, Boro H, Farooqui FA, et al. Endocrine causes of heart failure: A clinical primer for Cardiologists. *Indian Heart J*. 2021;73(1):14-21.
4. Eshtehardi P, Koestner SC, Adorjan P, et al. Transient apical ballooning syndrome—clinical characteristics, ballooning pattern, and long-term follow-up in a Swiss population. *Int J Cardiol*. 2009;135(3):370-5.
5. Strunk B, Shaw RE, Bull S, et al. High incidence of focal left ventricular wall motion abnormalities and normal coronary arteries in patients with myocardial infarctions presenting to a community hospital. *J Invasive Cardiol*. 2006;18(8):376-81.
6. Maruyama S, Nomura Y, Fukushige T, et al. Suspected takotsubo cardiomyopathy caused by withdrawal of bupirenorphine in a child. *Circ J*. 2006;70(4):509-11.
7. Kurisu S, Inoue I, Kawagoe T, et al. Presentation of Tako-tsubo cardiomyopathy in men and women. *Clin Cardiol*. 2010;33(1):42-5.
8. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J*. 2008;155(3):408-17.
9. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352(6): 539-48.
10. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA*. 2011;306(3):277-86.
11. Maas AH, Rosano G, Cifkova R, et al. Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. *Eur Heart J*. 2021;42(10):967-984.
12. Abraham J, Mudd JO, Kapur N, et al. Stress cardiomyopathy after intravenous administration of catecholamines and beta-receptor agonists. *J Am Coll Cardiol*. 2009;53(15):1320-5.
13. Martin EA, Prasad A, Rihal CS, et al. Endothelial function and vascular response to mental stress are impaired in patients with apical ballooning syndrome. *J Am Coll Cardiol*. 2010;56(22):1840-6.
14. Nef HM, Möllmann H, Kostin S, et al. Tako-Tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery. *Eur Heart J*. 2007;28(20):2456-64.
15. Morel O, Sauer F, Imperiale A, et al. Importance of inflammation and neurohumoral activation in Takotsubo cardiomyopathy. *J Card Fail*. 2009;15(3):206-13.
16. Kuo BT, Choubey R, Novaro GM. Reduced estrogen in menopause may predispose women to takotsubo cardiomyopathy. *Gend Med*. 2010;7(1):71-7.
17. Choudhry NK, Brennan T, Toscano M, et al. Rationale and design of the Post-MI FREEE trial: A randomized evaluation of first-dollar drug coverage for post–myocardial infarction secondary preventive therapies. *Am Heart J*. 2008;156(1):31-6.
18. Zaroff JG, Pawlikowska L, Miss JC, et al. Adrenoceptor polymorphisms and the risk of cardiac injury and dysfunction after subarachnoid hemorrhage. *Stroke*. 2006;37(7):1680-5.
19. Pizzino G, Bitto A, Crea P, et al. Takotsubo syndrome and estrogen receptor genes: partners in crime? *J Cardiovasc Med (Hagerstown)*. 2017;

18(4):268-276.
20.Vujovic KS, Stefanovic BS, Matic D, et al. Takotsubo Cardiomyopathy Precipitated By Thyroidectomy-A Case Report. Ser J Exp Clin Res. 22(2): 181-5.
21.Gupta S, Goyal P, Idrees S, et al. Association of endocrine conditions with takotsubo cardiomyopathy: a comprehensive review. *J Am Heart Assoc*. 2018;7(19):e009003.
22.Irigaray Echarri A, Ernaga Lorea A, Esparza Eguilaz N, et al. Takotsubo Syndrome and hyperthyroidism: a case report. *An Sist Sanit Navar*. 2019;42(2):215-220.
23.Rueda D, Aguirre R, Contardo D, et al. Takotsubo myocardiopathy and hyperthyroidism: a case report and literature Review. *Am J Case Rep*. 2017;18:865-870.
24.Murdoch D, O'callaghan W, Reda E, et al. Takotsubo cardiomyopathy associated with primary hyperthyroidism secondary to toxic multinodular goiter. *Int J Angiol*. 2016;25(5):e121-e122.
25.Patel K, Griffing GT, Hauptman PJ, et al. Recurrent takotsubo cardiomyopathy related to recurrent Thyrotoxicosis. *Tex Heart Inst J*. 2016;43(2):152-5.
26.Wu W-T, Hsu P-C, Huang H-L, et al. A case of Takotsubo cardiomyopathy precipitated by thyroid storm and diabetic ketoacidosis with poor prognosis. *Acta Cardiol Sin*. 2014;30(6):574-7.
27.Perkins MJ, Schachter DT. Biventricular Takotsubo cardiomyopathy in Graves hyperthyroidism. *J Invasive Cardiol*. 2014;26(3):E35-6.
28.Eliades M, El-Maouche D, Choudhary C, et al. Takotsubo cardiomyopathy associated with thyrotoxicosis: a case report and review of the literature. *Thyroid*. 2014;24(2):383-9.
29.Sarullo FM, Americo L, Accardo S, et al. Tako-tsubo cardiomyopathy observed in a patient with sepsis and transient hyperthyroidism. *Monaldi Arch Chest Dis*. 2009;72(1):33-6.
30.Kwon S-A, Yang JH, Kim M-K, et al. A case of Takotsubo cardiomyopathy in a patient with iatrogenic thyrotoxicosis. *Int J Cardiol*. 2010;145(3):e111-3.
31.Radhakrishnan A, Granato JE. An association between Takotsubo cardiomyopathy and thyroid storm. *Postgrad Med*. 2009;121(3):126-30.
32.Lee SJ, Kang JG, Ryu OH, et al. The relationship of thyroid hormone status with myocardial function in stress cardiomyopathy. *Eur J Endocrino*. 2009;160(5):799-806.
33.Balsa AM, Ferreira AR, Alves M, et al. Takotsubo cardiomyopathy associated with levothyroxine over-replacement. *Eur Endocrinol*. 2017;13(1):30-32.
34.Capel I, Tasa-Vinyals E, Cano-Palomares A, et al. Takotsubo cardiomyopathy in amiodarone-induced hyperthyroidism. *Endocrinol Diabetes Metab Case Rep*. 2017;2017:16-0116.
35.Aweimer A, El-Battrawy I, Akin I, et al. Abnormal thyroid function is common in takotsubo syndrome and depends on two distinct mechanisms: results of a multicentre observational study. *J Intern Med*. 2021;289(5):675-687.
36.Trivieri MG, Oudit GY, Sah R, et al. Cardiac-specific elevations in thyroid hormone enhance contractility and prevent pressure overload-induced cardiac dysfunction. *Proc Natl Acad Sci U S A*. 2006;103(15):6043-8.
37.Tang Y-D, Kuzman JA, Said S, et al. Low thyroid function leads to cardiac atrophy with chamber dilatation, impaired myocardial blood flow, loss of arterioles, and severe systolic dysfunction. *Circulation*. 2005;112(20):3122-30.
38.Pantos C, Dritsas A, Mourouzis I, et al. Thyroid hormone is a critical determinant of myocardial performance in patients with heart failure: potential therapeutic implications. *Eur J Endocrinol*. 2007;157(4):515-20.
39.Pingitore A, Iervasi G, Barison A, et al. Early activation of an altered thyroid hormone profile in asymptomatic or mildly symptomatic idiopathic left ventricular dysfunction. *J Card Fail*. 2006;12(7):520-6.
40.Pingitore A, Galli E, Barison A, et al. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2008;93(4):1351-8.