Relationship between heart failure with preserved ejection fraction and thyroid disorders: Review of the Literature

Abstract

Introduction: Heart failure with preserved ejection fraction may be combined with some other disease or as a result of dysfunction in their normal performance. Thyroid dysfunctions and abnormal thyroid hormone levels may be in close relation with heart problems, and may be indicators of future heart failure.

Methods: Scopus and PubMed were searched methodically using "thyroid disorders" and "heart failure with preserved ejection fraction" as search terms on April 2015 to find articles with English language in which the association between thyroid disorders and heart failure with preserved ejection fraction (HFPEF) had been evaluated. Full text of all relevant articles was comprehensively reviewed and used for data extraction.

Results: Of total 51 articles found in PubMed, 34 records found in Scopus and 3 articles found through reference list screening, only 13 papers fully met the inclusion criteria for further assessment. A total of 2135 patients participated in the included literatures, 1450 were male and 595 were female.

Discussion: Results of studies show that cardiac and thyroid functions are in close relationship, in which the level of thyroid hormone, predominantly T3 level can be considered as an independent prognostic factor in HFPEF. Moreover, findings suggested that thyroid hormones level can be considered as predictors for mortality due to HF.

Conclusion: Based on the results obtained in the included documents, there may be association between thyroid disorders and thyroid hormone levels with cardiac complications, particularly heart failure with preserved ejection fraction.

Keywords: Ejection fraction, Heart failure, Thyroid disorders

Introduction

Congestive heart failure (CHF) is a major problem in internal medicine. Many clinical studies have shown that in a large group of patients with CHF, the normal left ventricular systolic function is preserved. Clinical and paraclinical findings indicate the normal left ventricular ejection fraction (LVEF) in heart failure stages (1). Almost half of patients with heart failure have normal left ventricular ejection fraction that has been previously known as diastolic heart failure (2). In recent years, the incidence and prevalence of heart failure with normal ejection fraction (HFNEF) has increased (3).

Heart failure with normal left ventricular ejection fraction has three diagnostic criteria including the existence of signs and symptoms of heart failure, normal left ventricular ejection fraction and evidence of diastolic dysfunction (4). HFPEF is a disorder predominantly found in older patients, with more frequency among women, whereas only 4 to 6% of men are affected (1, 4, 5) . HFPEF already causes severe chronic symptoms and decreased exercise tolerance, and in case of hospitalization, it may cause mortality similar to heart failure with reduced ejection fraction (HFREF) (6). Heart failure with preserved ejection fraction (HFPEF) is defined as the existence of impaired diastolic functional parameters in echocardiography in the presence of ejection fraction equal to or greater than fifty percent. Also HFPEF is defined as symptomatic HF with an LV ejection fraction 50% (7, 8). Moreover, based on population studies it is now confirmed that more than 50% of patients with HF have HFPEF (9). Ejection fraction also shows the percentage of blood that is ejected out of the left ventricle (LV) with each contraction to the left ventricle end diastolic volume.

Nowadays, non-invasive imaging techniques are used to evaluate these parameters without the need to use other unpleasant methods. On the other hand, most patients have other co-morbid disorders related to this heart problem including hypertension, chronic kidney disease, diabetes mellitus, morbid obesity, coronary artery disease and anemia. Therefore, co-morbid disorders such as thyroid dysfunctions may have prognostic value for heart function, especially HFPEF. Since, few studies have been conducted on the underlying causes and clinical symptoms of HFPEF, in this study, various aspects of the disease and its association with thyroid disorders are systematically reviewed.

Methods

Search methods

PubMed and Scopus were searched systematically using the key terms "thyroid disorders" and "heart failure with preserved ejection fraction" in the title, abstract, and keywords to find all articles in which the relationship between heart failure with preserved ejection fraction and thyroid disorders had been investigated. For this purpose, following search strategy ((Heart failure with preserved ejection fraction OR Heart failure (HF) with preserved ejection fraction OR (HFPEF))) AND thyroid disorder was used to find relevant document in PubMed. But, different search strategy was used to find related documents in Scopus database. First, "thyroid disorders" was searched in Scopus, and then "heart failure with preserved ejection fraction" was searched within the results. Afterwards, the results were limited to those articles with English language. The databases search was completed on April 2015. Reference list of all relevant documents was also screened manually to include other potentially relevant articles.

Study selection and inclusion/exclusion criteria

No time limitation was defined for article selection, but we included only articles with English language to avoid errors and misinterpretation of data during the processes of data extraction. We also included different types of articles including case reports, cross-sectional, case-controls and prospective cohort studies for data extraction. But, conference papers, abstracts, letters, review articles and meta-analysis were excluded from further assessment. We also excluded articles that had been conducted on animals from further assessment. As well, by reviewing the title, keywords and abstract of papers, we excluded duplicated articles and papers with subject irrelevancy in the first step of article selection. Therefore, inclusion criteria for article selection in this literature review were all documents in which the association between heart failure with preserved ejection fraction and various thyroid disorders had been investigated.

Data synthesis

General available data including the date of publication, country of origin, study design, the name of first author and method of assessment were systematically extracted and categorized. Other existing data including demographic data of studied population and total number of patients were collected as possible as based on the previously defined inclusion and exclusion criteria. Data were categorized based on the results of studies reporting the association between cardiac disease and thyroid dysfunction. The data reporting possible positive or negative association between the thyroid endocrine system dysfunction and heart failure with preserved ejection fraction were extracted and used in further possesses of data analysis. Different methods including evaluation of oxygen consumption in patients with Low triiodothyronine, thyroid function test and echocardiographic assessment had been assisted in the included articles to evaluate variables such as thyroid hormone level, cardiac function and left ventricular improvement. All processes including data extraction and selection of articles were performed

with standard protocol according to the recommendation of PRISMA 2009 checklist by two independent reviewers (10). And, in cases of possible discrepancies, it was resolved between the investigators prior to further data synthesis.

Results

Study search results

A total of 51 related documents were found in PubMed and 34 in Scopus databases. By reviewing the abstract of articles, 48 documents were excluded in the first step due to subject and language irrelevancy. Considering the duplicated articles, only 27 publications seemed to meet all of the previously defined inclusion criteria, and also seemed to be related to the main subject of this study. After several steps of article selection, only 10 unique records seemed more relevant to the purpose of this study. Three additional unique publications were also included by manual reference list screening of the previously included articles. Finally, after comprehensive reviewing of the selected articles, only 13 relevant documents, which met the all defined inclusion criteria were selected, and the data were extracted. Figure 1 shows the step by step process of study selection and literature search.

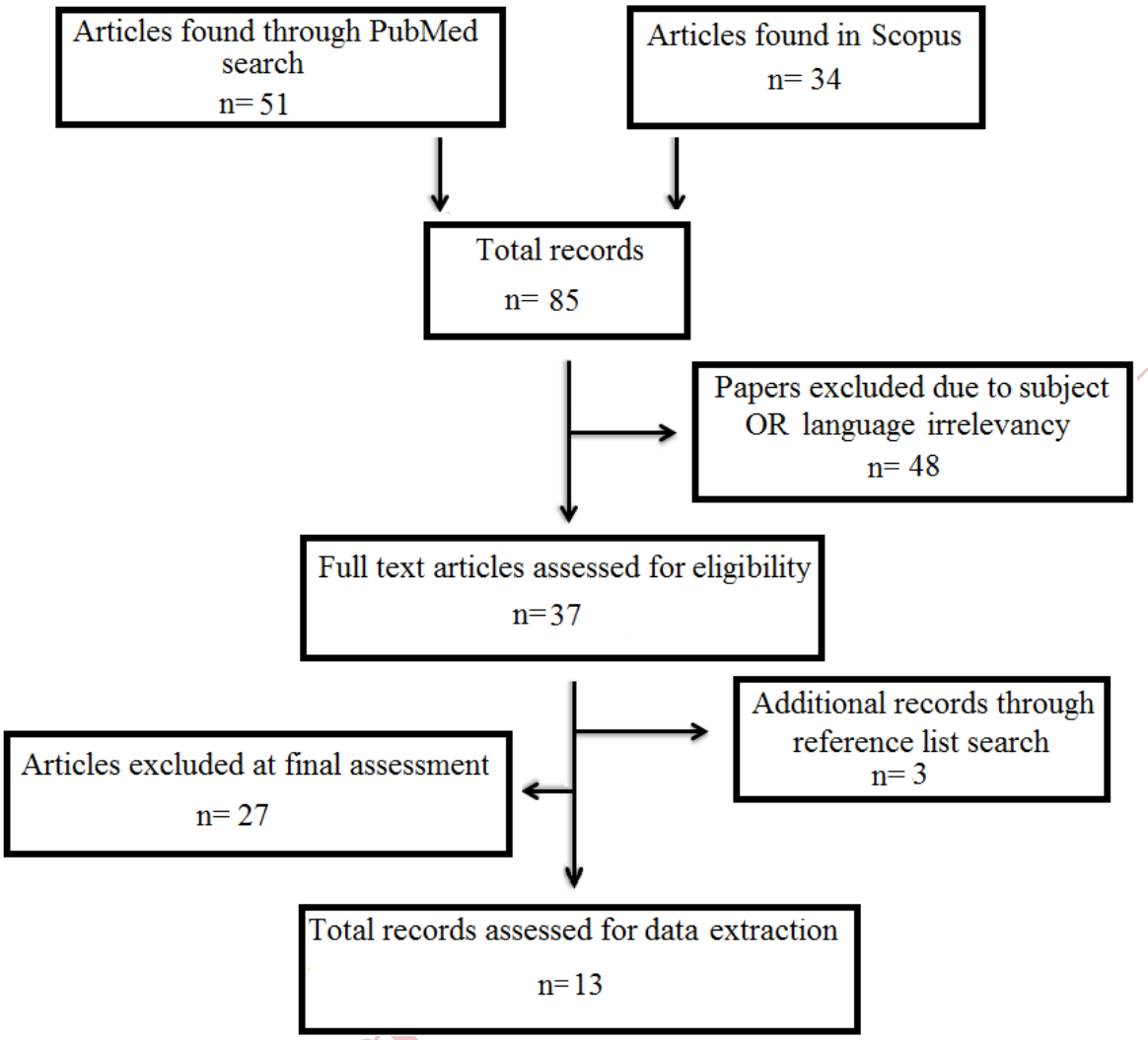

Figure 1. Flowchart of the literature search used in this study for selection of studies

General characteristics of the included articles

Total number of patients participated in the selected studies in which the association between heart failure with preserved ejection fraction and different types of thyroid disorders had been investigated were 2135 patients. The age of studied population in the selected literatures ranged from 15 year old children to 95 year old patient. Of these patients, 1450 were male and 595 were female. Follow-up duration of the studies varied from three weeks to 9 year among the included literatures. Patients with different grade of HFPEF or hyper- hypothyroidism had been studied in the selected articles. This review included 6 case report or case series, 4 prospective cohort, 1

case-control and 2 cross-sectional studies. The most recent and old publication included in this literature review were published in 2015 and 1995, respectively. As well, the number of patient varied from 1 in case reports to 758 in a cohort study. Of these populations, 92 patients had thyroid dysfunction and 2043 patients had different types of heart disease, particularly HFPEF. Because some informative data including the age, sex ratio and other demographic information had not been described in some included studies, the data could not be reported based on sex and age. The general characteristics of these studies are summarized in table 1 in chronological order of the published time (Table 1).

Table 1. General information of the included articles

No	First author	Year	Country	Study population *	Sex ratio	Study design ®	Number of patients
1	Anakwue RC (11)	2015	Nigeria	Thyrotoxicosis patients	NM *	CC	50
2	Frey A (12)	2013	Germany	Patient with HF	Male:538 Female: 220	PCS	758
3	Selvaraj S (8)	2012	USA	Patient with HF	Male: 28 Female: 61	PCS	89
4	Fontana M (13)	2012	Italy	Patient with HF	Male: 190 Female: 50	CSS	240
5	Pfister R (14)	2010	Germany	Patient with HF	Male: 356 Female: 148	PCS	504
6	Passino C (15)	2009	Italy	Patient with HF	Male: 332 Female: 110	PCS	442
7	Froeschl M (16)	2005	Canada	Patient with HF	Male: 1	CR	1
8	Ceviz N (17)	2004	Turkey	Patients with goiter	NM	CSS	40
9	Khandwala HM (18)	2004	Canada	Patients with CHF	Male: 1	CR	1
10	Boccalandro C (19)	2003	USA	Thyroid disorder	Female: 1	CR	1
11	Goldman LE (20)	1999	Canada	Patients with CHF	Female: 1	CR	1
12	Wilson BE (21)	1996	USA	Thyrotoxicosis patients	Male: 1	CR	1
13	Umpierrez GE (22)	1995	USA	Patients with CHF	Male: 3 Female: 4	CS	7

*** CHF: Congestive heart failure, HF: Heart failure**

® PCS: Prospective cohort study, CR: Case report, CS: Case series, CC: Case control study, CSS: Cross-sectional study

Study results

The results of studies included in this literature review showed that possible correlation may exist between thyroid endocrine system dysfunction and heart failure with preserved ejection fraction. As well, almost all studies confirmed that thyroid hormones may play important role in prognosis and also in the treatment of heart failure (HF), especially HF with preserved ejection fraction. Findings show that low level of triiodothyronine (T3) is more prevalent in patients with cardiovascular disease, especially those with preserved ejection fraction. Therefore, the results of this review suggest prognostic value of triiodothyronine in heart failure. Also, the results were indicative of close relationship between limitations in exercise capacity and functional impairment in neuro-hormonal regulatory system.

Echocardiographic evaluation of left ventricular function showed that heart failure with reduced ejection fraction may possibly exist in patients with thyrotoxicosis and other thyroid disorders. Moreover, the results showed that diastolic dysfunction, and higher pulse pressure/stroke volume ratio may also be associated with lower levels of T3; and therefore, T3 may be associated with the severity of heart failure with preserved ejection fraction. Table 2 shows the main clinical characteristics of included studies.

Table 2. Specific characteristics of the selected studies

NO	First author	Assessment methods *	Follow-up duration	Findings
1	Anakwue RC	TFT	1 year	Positive association between HFREF and thyrotoxicosis
2	Frey A	TFT	3 year	Thyroid function has prognostic value in heart failure
3	Selvaraj S	T3 level assay	-	T3 is associated with the severity of HFpEF
4	Fontana M	T3 level assay	3 year	Results confirm the association between neurohormonal activation and exercise intolerance

5	Pfister R	T3 level assay	3 year	low-T3 level were predictive for cardiovascular mortality
6	Passino C	T3 level assay	3 year	T3 was independent predictors of mortality and has additive prognostic value in HF
7	Froeschl M	TFT	1 month	Treatment of the improved cardiac function
8	Ceviz N	CFT and EC	-	Thyroid dysfunction does not affect left ventricular functions
9	Khandwala HM	TFT	2 years	Thyroid hormone treatment improved LV ejection fraction
10	Boccalandro C	Treatment for hyperthyroidism	19 months	LVEF improved after treating hyperthyroidism
11	Goldman LE	Treatment for hyperthyroidism	-	CHF and LVEF improved after treatment for hyperthyroidism
12	Wilson BE	Treatment for thyrotoxicosis	10 months	Treatment for thyrotoxicosis improved cardiac function
13	Umpierrez GE	Treatment for hyperthyroidism	5 months to 9 years	LVEF improved after treating hyperthyroidism

*** EC: Echocardiography, CFT: Cardiac function test, TFT: Thyroid function test**

Major limitations in this study were unreported demographic data such as sex ratio and age in some studies. Also, outcome data had not been categorized in some reports.

Discussion

It is now confirmed that cardiovascular health depends on several neuro-hormonal regulatory system and normal endocrine function. Various cardiovascular complications due to endocrine dysfunction are atherosclerosis, CHF and systolic hypertension as a result of growth hormone (GH) deficiency, adrenal gland irregularity and thyroid dysfunction, respectively (23). Disorders of the endocrine system, including hormone hyper and hypofunction have several damaging effects on the cardiovascular system. The results of several studies are suggestive of association between the endocrine hormone system and heart function (24, 25). The results also show that

treatment of the thyrotoxicosis leads to improvement of cardiac contractility, and heart function (16). Results of a single cohort study on 24 patients showed that hypothyroidism may have undesirable cardiovascular effects in patients with differentiated thyroid carcinoma (DTC) (26). According to our findings in the present review, cardiac and thyroid functions are in close relationship, in which the level of thyroid hormone, particularly T3 can be considered as an independent and additive prognostic factor in HF (15). Also, findings suggest potential role of synthetic T3 replacement as an effective and novel therapeutic approach to improve cardiac function in patients with HFPEF (27).

Study on animal model showed thyroid hormone can increase the expression of mRNAs coding sarcoplasmic reticulum Ca2+-ATPase; therefore, it can improve cardiac function and myocardial performance through improvement in left ventricular ejection fraction (28, 29). Results of studies on animals also suggested that thyroid hormone may regulate heart rate through the activation of hyperpolarization-activated cyclic nucleotide-gated channel (HCN2) gene expression (30).

Since cardiac, especially left ventricular function can be improved after thyroid hormone treatment, the level of thyroid hormones may have prognostic value in HF. Moreover, thyroid hormones level is considered as predictors for mortality due to HF. Therefore, the results of studies in this literature review showed association between thyroid function or thyroid hormone level and heart failure with preserved ejection fraction.

Conclusion

The results of this study showed that there may be close relationship between thyroid dysfunction including low T3 level and hypo- hyperthyroidism with cardiac functions, especially heart failure with preserved ejection fraction.

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