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Thyroid Hormones in Dilated Cardiomyopathy: Is It a Promising Therapeutic Option?

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Dilated cardiomyopathy (DCM) is chronic heart muscle disease characterized by progressive ventricular enlargement and contractile dysfunction involving either left or both ventricles [1,2]. It is considered one of the leading causes of heart failure with reduced ejection fraction (HFrEF) worldwide. The reported prevalence of DCM in Europe and North America is ~36 cases per 100,000 population, which is clearly lower in Eastern Asia (i.e., 14 cases per 100,000 in Japan), and might be higher in Africa and Latin [3].

Heart failure in DCM is associated with serious consequences and carries a considerable mortality risk similar to, or higher than mortality attributed to other non-ischemic HF aetiologias (e.g., valvular or hypertensive) [4]. Despite different etiologies of DCM, there is common essential pathological features when HFrEF supervene. Observational data prior to guideline-directed medical therapy (GDMT) for the management of HF indicate that significant clinical improvement occurred in less than 20% of HF patients with DCM, while 77% died within 2 years of diagnosis, mostly due to progressive pump failure. Sudden cardiac death and systemic embolism, mainly attributable to atrial fibrillation, taken into consideration the rest of the cardiovascular mortality [5]. There is current notion that all HF syndromes are invariably progressive, and all patients will follow a trajectory and true recovery may not be achievable for a portion of patient population. However, a substantial functional improvement and reverse LV remodeling can occasionally be achieved, especially with the use of GDMT [5,6].

Although patients with DCM have been represented in clinical trials, distinct features of their therapeutic responses, relative to other aetiologias of HF, remain unknown. For HFrEF, standard therapy is indicated regardless of the underlying cause. In contrast, for the chosen cases, specific treatment options have been established, targeting a particular underlying pathophysiology (e.g., monoclonal antibodies, immunotherapy, and others), thereby increasing the approaches for better prognosis [7].

Over the last three decades, patient's outcomes have changed with advancement in pharmacotherapy for HFrEF patients. In a cohort of Japanese DCM patients enrolled between 1982 and 1989, the 5- and 10-year survival rates were 61% and 35%, respectively [7]. In patients assessed between 1990 and 2002, the 5- and 10-year survival rates had increased to 81% and 65%, respectively. A promising prognosis has been reported with GDMT, demonstrating transplant-free survival at 1, 2, and 4 years of follow-up in 94%, 92%, and 88% of patients, respectively [8]. Over the same time, survival free of HF hospitalization was 88%, 82%, and 78%, respectively. Implantable cardioverter defibrillator, cardiac resynchronization therapy, as well as heart transplantation in advanced HF have all provided further improvements in outcomes [9].

Hormone Treatment in HF

Neurohormonal systems play a crucial role in cardiovascular homeostasis, pathophysiology, and disease prognosis. Hormone therapy such as the lately invented dual acting drug valsartan/sacubitril are appropriate candidates for HFrEF, in addition to the conventional medications encompassing beta receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, sodium glucose transporter-2 inhibitors (SGLT2i) and mineralocorticoid receptor antagonists. In HF patients with volume overload the vasopressin antagonists can alleviate the symptoms better to loop diuretics. Moreover, a combination of selective glucocorticoid receptor agonist and mineralocorticoid receptor antagonist and SGLT2i can also be utilized in patients with diuretic resistance. Clinical trials also indicate that in HFrEF patients with low insulin-like

growth factor-1 or low thyroid hormone (TH) levels, supplemental treatment with growth hormone or thyroid hormone seems to be cardioprotective [10].

DCM and Thyroid Hormones

The two main thyroid hormones (TH) T4 and T3 are secreted by the thyroid gland in response to stimulation by thyroid stimulating hormone (TSH). Both T4 and T3 have biological actions but T3 is considered the active hormone. The metabolism of TH is regulated by enzymes called deiodinases. Type I (DIO1) and type II iodothyronine deiodinase (DIO2) lead to extrathyroidal T3 production from the precursor T4. DIO1, which is active in the liver and kidney, produces 15-20% of total circulating T3, whereas DIO2 activity located in the heart, pituitary, brain, and brown adipose tissue is responsible for the remaining two-thirds of T3 production whereas DIO3 catabolizes both TH and terminates their action [11,12].

The significance of TH of any given tissue is dependent on both circulating as well as intracellular TH levels, which are regulated by DIOs and TH transporters. Cardiac status is influenced by TH genomic and non-genomic actions. The direct genomic actions are exerted by T3 in the nucleus through binding to nuclear receptors leading to the regulation of the target gene expression to control transcription in the cardiomyocyte; whereas the extranuclear, nongenomic actions exerted through the ion channels located in the cell membrane, glucose, and amino acid transport, and several intracellular signaling pathways [13,14]. The two main TH receptors (TRs) are α, which is highly expressed in cardiomyocytes, and β. TRs can bind to TH response elements even in the absence of TH, leading to suppression of target genes transcription. Thus, gene regulation in the cardiomyocyte is dependent on the TH availability [13,14].

Thyroid hormones have a direct inotropic effect on the heart by positively regulating the gene expression of the β1-adrenergic receptor. It regulates myocardial contractility and systolic function through upregulation of the transcription of structural and functional proteins of the heart, namely by activation of genes encoding Na/K ATPase, myosin heavy chain (MHC) α, and sarcoplasmic/endoplasmic reticulum calcium ATPase 2, voltage-gated potassium channels, and atrial and brain natriuretic peptides resulting in a heightened velocity of contraction [12,13]. It is negatively regulating the transcription of MHC-β and phospholamban, Na/Ca exchanger, transcription-associated protein 1 (TRa1), and adenylyl cyclase type 5 and 6, boosting the velocity of diastolic relaxation [13-16].

Changes in TH levels are associated with changes in inotropic and chronotropic functions, myocardial oxygen consumption, cardiac output, blood pressure, and systemic vascular resistance. Myocardial dysfunction in hypothyroidism and hyperthyroidism is reported in the literature. Normal thyroid hormone levels play a role in the transition from the fetal heart to adult phenotype of heart [17,18].

Thyroid hormones can vary at a local level independently of the serum TH levels. LV function appears to be more closely related to TH cardiac levels than to thyroid hormone serum levels [19,20]. Even though the cardiac tissue locally converts T4 into T3, [18,19], the heart is vulnerable to reductions in the levels of serum T3. Moreover, when serum T3 levels drop, the heart may become hypothyroid to a moderate extent [18,19]. This may lead to local cardiac hypothyroidism in heart failure. Based on these findings and the role that TH play in cardiovascular regulation, they were proposed as a potential target for HF therapy [18,19]. However, the effect of thyroid hormone, especially T4, as therapeutic strategy in heart failure patients is still challenging.

Several experimental studies have shown beneficial effects of thyroid hormone as a supplement [19]. They demonstrated improvement of LV systolic function and tends to improve diastolic function in rats with myocardial infarction–induced HF treated with T3 [20]. Animal experiments in HF have indicated that low cardiac tissue T3 levels may be present even in the background of normal serum thyroid hormones [18,19]. The restoration of cardiac tissue T3 levels was associated with an improvement of LV function in rats [19,20].

There is growing evidence that impaired microvascular blood flow contributes to HFrEF and HFpEF. A study by Khalife et al. demonstrated that T3/T4 treatment of hamsters with DCM completely arrested progressive pathology including fibrosis and myocyte loss [21]. Importantly, TH treatment restored impaired coronary blood flow, suggesting impaired microvascular blood flow was related to low tissue T3. Clinical studies indicate impaired microvascular function in DCM [22], that may be due to low TH function [23].

A large body of evidence suggests an increase of cardiovascular events with borderline low thyroid hormones conditions such as subclinical hypothyroidism, which were better after thyroid hormone treatment. Previous studies in HFrEF patients have also shown an increased mortality with low thyroid function. However, this association is controversial, as one meta-analysis did not reveal a link [19], and two others reported a relation [20,21]. No studies have examined the effects of TH treatment on mortality in HF patients.

A recent study indicated that serum BNP may serve as a surrogate for low cardiac tissue T3 levels [24]. This could be a valuable tool to adjust TH levels in HF patients.

In dilated cardiomyopathy and subclinical hypothyroidism, thyroid hormones prevented progression of fibrosis, necrosis, loss of cardiac cells, dilation, and dysfunction of the left ventricle [22-24]. Previous investigation have shown that chronic hypertension is associated with impaired cardiac function and decreased levels of T3 both in serum and in cardiac tissue which leads to HF. Treatment with supplementation of thyroid hormones restored serum and cardiac T3 levels, improved cardiac function, and promoted remodeling benefits without causing any symptoms or signs of hyperthyroidism [22-24].

From practical standpoint, the emerging concept of adding thyroid hormones to the therapeutic armamentarium looks interesting, especially among patients deemed eligible without apparent contraindication or documented intolerance. A recent study indicated that serum BNP may serve as a surrogate for low cardiac tissue T3 levels. This could be a valuable tool to adjust TH levels in HF patients [24].

Another recently published study [1], oral treatment of DCM patients with T4 is associated with improvement of functional status and LV mechanics as assessed using speckle-tracking imaging. While thyroid hormone levels increased, they remained in the normal range. In this study T4 was well tolerated and not associated with adverse effects or altered hemodynamics. These encouraging findings are promising and indicate that there might be a role for the use of thyroid hormones in treating DCM. But it is unclear which specific patients should be treated and what is its long-term effect on morbidity and mortality? Large multicenter randomized trials of thyroid hormones and more definitive data for these hormones in primary DCM are necessary.

Conclusion

Despite substantial advances and innovations in both pharmacological therapy and medical devices, the prognosis of HFrEF remains poor. There is an unmet need to develop alternative or additional treatment modalities. Hormonal imbalance is a key finding and common feature in HFrEF, which translates into progression of the underlying disease, development of cardiovascular comorbidities, and increases in major adverse cardiovascular events. Hormonal modulation is therefore an important therapeutic approach for HF. The potential cardiovascular efficacy and safety of thyroid hormone therapies or supplementation are still not well investigated but seem to have a key role in DCM and need to be prudently evaluated in large-scale clinical studies.

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