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Editorial Open Access

Thyroid Hormone: A Therapy for Diabetic Vascular Complications?

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Editorial

Vascular complications are the leading cause of death in diabetic patients worldwide. Adverse micro- and macrovascular changes, which may occur early in diabetes mellitus (DM), are a major problem faced by these patients. This includes accelerated incidence of atherosclerosis, stroke, peripheral artery disease, retinopathy, nephropathy and coronary disease leading to myocardial infarction (MI) [1]. In recent years, progress in diabetes research has resulted in development of a series of anti-hyperglycemic drugs that successfully control glucose levels in most DM patients. However, these new treatments may not avert the onset of vascular complications. Alternative therapeutic strategies are clearly needed.

Thyroid hormones (TH) are crucial regulators of vascular function. It is well-documented in the literature that TH causes vascular relaxation. However, the mechanisms involved are not well understood. We have demonstrated TH-induced rapid nitric oxide (NO) production in vascular smooth muscle (VSMC) via PI3K/Akt signaling, suggesting involvement of this pathway in TH mediated vascular relaxation [2]. Cai et al. also observed that TH rapidly promotes vasorelaxation, with VSMC being a primary target of this hormone [3]. Inadequate TH production (hypothyroidism) is linked to impaired vascular reactivity and endothelial dysfunction [4]. As a consequence of these alterations, hypothyroid patients develop reduced renal perfusion, impaired coronary blood flow, increased arterial stiffness, and accelerated development of atherosclerosis [5-8]. Subclinical hypothyroidism has also been linked to impaired coronary blood flow in non-cardiac patients and is reversible with treatment [9,10]. A recent human study demonstrated that hypothyroid patients also exhibit high levels of vascular injury markers, closely associated with increased intima-media thickness in the common carotid artery [11,12].

TH also regulates vascular remodeling. Our group has found that hypothyroid rats treated with a low dose of TH for a short period restored impaired coronary arteriolar density. This work suggests that, aside from the effects on vasoreactivity, THs also play a significant role in remodeling of small vessels, [13]. These above-mentioned studies demonstrated that VSMCs are one of the principal targets of TH actions. VSMCs express deiodinases, enzymes responsible for converting T4 to active (T3) or inactive forms (rT3), which in turn regulates bioavailability for TH-regulated vascular signaling.

There is evidence indicating that the onset of vascular complications occurs in the early stages of hypothyroidism [14,15]. Importantly, TH therapy largely restores vascular performance, including improvement of endothelial dysfunction and restoration of coronary blood flow while delaying the progression of atherosclerosis [11,16]. Data from our group suggests that hypothyroidism leads to impaired coronary blood flow which is associated with microvascular remodeling of small arterioles, likely due to phenotypic switching of vascular smooth muscle cells. But, we have also noted atrophy of large elastic vessels. So, this condition could involve global atrophy on the arteriolar side. More work in this area could provide further insight to the mechanism.

An under appreciated problem is the high likelihood of hypothyroidism co-existing with another disease which also leads to vascular pathology, such as DM. Studies have found a high incidence of hypothyroidism in patients with DM. Importantly, both pathological conditions compromise vascular function in a similar manner.

Patients with diabetes have an increased incidence of overt and borderline hypothyroidism, microvascular impairment, and myocardial infarction (MI). Importantly, recent animal data suggest that heart diseases, such as DM, hypertension, and MI, trigger low TH function at the cardiac tissue level [16]. Low level of TH in the heart can eventually cause heart failure (HF), associated with impaired coronary blood flow and adverse remodeling of cardiac myocytes and blood vessels. While some diabetic patients may present a normal serum TH profile, this does not necessary mean that low tissue TH levels are not contributing to vascular complications. More concerning is that borderline low TH conditions largely go untreated in diabetic patients who may derive considerable vascular benefits from treatment.

While more than 30% of diabetic patients have diagnosable TH dysfunction, most commonly overt or subclinical hypothyroidism, serum analyzes likely underestimate the extent of tissue hypothyroidism. Recently our laboratory/group showed that diabetic rats may exhibit low levels of THs in cardiac tissue despite having normal serum TH levels. Moreover, we demonstrated that early administration of a small dose of triiodothyronine (T3) prevented development of the diabetic cardiomyopathy, including the reduction in arteriolar resistance vessel density in a rat model. Additionally, T3 supplementation also restored cardiac tissue T3 levels [17]. The small dose of T3 utilized in this study provided feedback inhibition of TSH but did not lead to a significant increase in serum T3 levels. We are observing a similar restoration of depressed cardiac T3 levels in other animal models of heart disease with this safe treatment approach. This is a protocol that could be safely used to restore TH function in cardiac patients.

Recently, an intriguing finding from our group is the presence of low cardiac T3 levels in the background of normal serum TH levels in animal models of heart disease. This result leads to speculation that other tissues, such as vascular tissues, may also exhibit reduced TH levels currently going undetected. Moreover, low dose TH supplementation may be beneficial not only to treat patients diagnosed with hypothyroidism but also those with cardiovascular complications due to low local/tissue TH levels. More work is required to clarify the extent of vascular TH dysfunction in DM. In particular, we need a

better understanding of mechanisms that affect TH bioavailability (e.g. TH nuclear receptors, deiodinases, TH membrane transporters, cytoplasmic TH binding proteins, etc.) in diabetic patients since changes in these important regulators have now been observed in animal models of DM.

To summarize: (1) low TH function has been linked to vascular dysfunction and HF; (2) patients with DM have a high incidence of serum detectible low TH function; (3) the extent of low T3 in heart and vascular tissues is likely underestimated in heart diseases when assessed by serum analyses; (4) patients with DM have an accelerated incidence of atherosclerosis and MI; (4) many animal and clinical studies have demonstrated improvement in atherosclerosis, DM, hypertension, MI, and idiopathic dilated cardiomyopathy with TH treatment; and (5) we have now demonstrated a safe, low dose T3 treatment/monitoring protocol that restores tissue T3 levels while showing dramatic improvements in function/remodeling of heart and blood vessels. We believe it is time to translate this information to cardiac patients, especially those with DM who are at high risk for cardiovascular complications despite glycemic control.

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