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Does Thiazolidinedione therapy exacerbate fluid retention in congestive heart failure?

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ABSTRACT

The ever-growing global burden of congestive heart failure (CHF) and type 2 diabetes mellitus (T2DM) as well as their co-existence necessitate that anti-diabetic pharmacotherapy will modulate the cardiovascular risk inherent to T2DM while complying with the accompanying restrictions imposed by CHF. The thiazolidinedione (TZD) family of peroxisome proliferator-activated receptor γ (PPARγ) agonists initially provided a promising therapeutic option in T2DM owing to anti-diabetic efficacy combined with pleiotropic beneficial cardiovascular effects. However, the utility of TZDs in T2DM has declined in the past decade, largely due to concomitant adverse effects of fluid retention and edema formation attributed to salt-retaining effects of PPARγ activation on the nephron. Presumably, the latter effects are potentially deleterious in the context of pre-existing fluid retention in CHF. However, despite a considerable body of evidence on mechanisms responsible for TZD-induced fluid retention suggesting that this class of drugs is rightfully prohibited from use in CHF patients, there is a paucity of experimental and clinical studies that investigate the effects of TZDs on salt and water homeostasis in the CHF setting. In an attempt to elucidate whether TZDs actually exacerbate the pre-existing fluid retention in CHF, our review summarizes the pathophysiology of fluid retention in CHF. Moreover, we thoroughly review the available data on TZD-induced fluid retention and proposed mechanisms in animals and patients. Finally, we will present recent studies challenging the common notion that TZDs worsen renal salt and water retention in CHF.

Contents

Abbreviations: ADH, anti-diuretic hormone; AngII, angiotensin II; ANP, atrial natriuretic peptide; BNP, brain/B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; CHF, congestive heart failure; ECFV, extracellular fluid volume; ENaC, epithelial sodium channel; ET-1, endothelin 1; eNOS, endothelial nitric oxide synthase; FE_{Na}, fraction excretion of sodium; GFR, glomerular filtration rate; LV, left ventricular-; Na–K–ATPase, sodium-potassium ATP-hydrolyzing pump; NaPi2, sodium-phosphate cotransporter 2; NCC, sodium-chloride cotransporter; NHE3, sodium-hydrogen exchanger 3; NKCC2, sodium-potassium-2 chloride cotransporter; NO, nitric oxide; PGZ, pioglitazone; PPAR(α/β/γ), peroxisome proliferator-activated receptor type α/β/γ; RAAS, renin-angiotensin-aldosterone system; RBF, renal blood flow; RGZ, rosiglitazone; SGK1, serum- and glucocorticoid-regulated kinase 1; T2DM, type 2 diabetes mellitus; TZDs, thiazolidinediones; TBW, total body water; $U_{Na}V$, urinary sodium excretion.

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1. Introduction

In the modern western world, two of the leading causes of death are congestive heart failure (CHF) and type 2 diabetes mellitus (T2DM), each of which reaching epidemic proportions with regards to morbidity and mortality. Specifically, there are currently more than 5 million CHF patients in the United States, with anticipated 8.5 million patients until 2030. More than 650,000 new CHF cases are diagnosed yearly and it is a major cause of overall hospitalizations and hospital readmissions (mainly due to exacerbations). Additionally, despite advances in the understanding the pathophysiology and application of appropriate treatments in recent decades, CHF still imposes a dire prognosis, as about half of the patients are expected to die within 5 years of diagnosis. Furthermore, the economic burden associated with CHF hospitalizations and treatment is vast (Braunwald, 2013; Roger, 2013).

In addition, in the last decade the global dimensions of T2DM have reached extremely widespread proportions and continue to rise, concurrently with the social and economic burden associated with diabetic macro- and microvascular complications, including heart failure (Colagiuri & Davies, 2009). In particular, T2DM patients have a double risk of developing CHF than non-diabetic patients, due to both a higher prevalence of comorbidities that predispose to CHF and a multitude of metabolic abnormalities that accompany diabetes and are causative in cardiac dysfunction (Masoudi & Inzucchi, 2007).

Therefore, due to the great global burden of CHF and T2DM and their deadly combination, pharmacotherapy of diabetes dually faces the challenges of successfully managing of the disease considering the accompanying restrictions imposed by CHF and of modulating the cardiovascular risk inherent to T2DM (Masoudi & Inzucchi, 2007). The controversy regarding the thiazolidinedione (TZD) class of drugs for T2DM exemplifies the difficulty in implementing the use of an antidiabetic drug with fluid-retaining and edema-forming properties, perceived to exacerbate the course of CHF. Hence, we hereby provide a critical review of the evidence supporting this notion along with additional studies that argue against it.

1.1. Congestive heart failure (CHF)

1.1.1. Definition and principal features

Heart failure is a complex syndrome defined by the inability of the cardiac pump to adequately fill with blood or eject it due to a structural or functional impairment, thus failing to supply the body's basic circulatory and respiratory demands. The cardinal manifestations of heart failure are dyspnea and fatigue, that limit exercise tolerance and fluid retention, which may result in various combinations of pulmonary congestion, splanchnic congestion and peripheral edema (McMurray & Pfeffer, 2005; Yancy et al., 2013). Due to these 'congestive' features which are characteristic of a progressive stage and/or inadequately treated cases, the syndrome of heart failure is often termed congestive heart failure (CHF). CHF characteristically has a chronic and progressive disease course with intermittent exacerbations or decompensations. From an etiological perspective, CHF is a multifactorial disease with many attributable risk factors that injure or overload the heart. Among these, the leading ones in the western world are coronary heart disease, hypertension, diabetes mellitus, obesity, smoking and valvular disease (Roger, 2013).

1.1.2. Pathophysiology

1.1.2.1. Cardiac hypertrophy and remodeling. The pathogenesis of CHF involves complex structural alterations of myocardial tissue in response to various forms of stress which are gradually manifested by functional deteriorations, up to the point of symptom emergence. Cardiac hypertrophy is the process of cardiomyocyte enlargement in response to increased workloads or injury in order to reduce the myocardial wall stress and therefore the energetic demands. The process of cellular, histological and functional changes, which enable the heart to compensate functionally to overload or injury, regardless of the initial cause of stress, is collectively referred to as cardiac remodeling (Takimoto & Kass, 2007; Kehat & Molkentin, 2010).

Cardiac hypertrophy can be classified as physiological or pathological, depending on whether the inciting cause of overload is physiological (such as regular exercise, pregnancy) or pathological, and whether it is accompanied by tissue or organ damage. Pathological hypertrophy is associated with pressure overload (e.g., in hypertension and valvular stenoses), volume overload (e.g., in anemia, valvular regurgitations, cardiac septal defects and systemic arteriovenous fistula), myocardial injury (e.g., infarction, inflammation) or any combination of the above (Kehat & Molkentin, 2010; Abassi et al., 2011). Although various causes of cardiac remodeling share several molecular, biochemical and mechanical features, different stimuli induce diverse ventricular remodeling patterns (Bernardo et al., 2010; Kehat & Molkentin, 2010). In addition, different stimuli of pathological hypertrophy and subsequent remodeling induce distinct molecular pathways and histopathological patterns (Calderone et al., 1995; Kehat & Molkentin, 2010; Melenovsky, 2012).

Although cardiac remodeling is initially a beneficial and adaptive process, progressive functional changes eventually result in maladaptive, irreversible alterations, especially if the stressing stimulus persists. For example, in response to chronic stressors, concentric hypertrophy may progress to eccentric hypertrophy, in which case remodeling consists of initial cardiomyocyte hypertrophy, followed by apoptosis, fibrosis and extracellular matrix digestion. These lead eventually to overt dilation with reduced cardiac systolic function, which precedes and underlies the decompensation in cardiac function and the transition from being asymptomatic to clinical manifestations of CHF (Takimoto & Kass, 2007; Kehat & Molkentin, 2010). Alternatively, symptomatic CHF may result from diastolic dysfunction when remodeling consists primarily of fibrosis and ventricular stiffening (Udelson, 2011).

1.1.2.2. Fluid retention. A major hallmark of CHF which exacerbates its course and causes the most serious debilitating symptoms of the disease is fluid retention that occurs despite expanding extracellular fluid volume (ECFV) (Chaney & Shaw, 2010). Both low cardiac output and high-output states (characterized by reduced peripheral resistance and volume expansion localized to the venous compartment and interstitial space) are associated with reduced renal perfusion pressure and renal tubular sodium delivery. Thus, the 'effective' circulating volume, a term denoting the interaction between cardiac output and the peripheral vascular resistance in determining the 'sensed' arterial filling of circulating blood volume, is in fact reduced even in high-output cardiac failure states in which the absolute blood volume is expanded (Schrier, 1988a, 1988b). Hence, according to the arterial underfilling hypothesis (Schrier, 1988a, 1988b), compensatory neurohormonal and local renal effectors are then triggered to preserve the effective circulating volume and maintain perfusion to vital organs (Chaney & Shaw, 2010). This triggered response which utilizes various neurohormonal effectors, consists of a rapid hemodynamic component of systemic and renal vasoconstriction induced by baroreceptors, and a slower renal component of increased renal salt and water reabsorption. However, these compensatory mechanisms in CHF do not succeed in reversing the reduced cardiac function and peripheral vasodilation that caused them, and the disease course progresses gradually (Schrier & Howard, 1991). Eventually, the balance between the regulatory neurohormonal systems which act in a concerted manner under physiological conditions to maintain constant fluid balance becomes perturbed and leans towards chronic fluid retention (Schrier, 1988a, 1988b; Abassi et al., 2001, 2004; Chaney & Shaw, 2010).

Fluid retention alone does not necessarily account for congestive symptoms, with pregnancy being such an example. The symptoms of congestion in CHF are the combined result of fluid retention and edema formation, defined as leakage of fluid from the intravascular