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Invited critical review

Markers of bone metabolism in congestive heart failure

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Abstract

Congestive heart failure (CHF) is a chronic disease, whose incidence is especially growing in the subpopulation of elderly people. CHF is characterized by dyspnea and fatigue at rest or with exertion, ankle swelling and pulmonary edema. Cardiac transplantation is the ultimate therapeutic measure in patients with end-stage CHF. Some risk factors associated with CHF such as low mobility, renal failure, and prescription of specific drugs may predispose patients to develop osteoporosis. This review article gives an overview about markers of bone metabolism in CHF patients as well as in heart transplant recipients. At first, the physiology of bone metabolism is summarized. Then, a short description of different bone formation and resorption markers is presented. They can be used to characterize actual bone metabolism and can be helpful to explain possible mechanisms of bone loss. Regarding pre-transplant CHF patients, available data indicate that the disturbances in bone metabolism are only subtle. Heart transplant recipients, however, are at increased risk for osteoporotic bone loss due to the use of immunosuppressive agents such as corticosteroids and calcineurin inhibitors. Preventive strategies are able to normalize bone metabolism and to attenuate the high bone loss during the first year after heart transplantation.

Keywords: Congestive heart failure; Bone formation; Bone resorption; Heart transplantation

Contents

1. Introduction

Congestive heart failure (CHF) is a frequent chronic disease in Western societies. Approximately 10 million European and 5 million American suffer from CHF [1,2].

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CHF is predominantly a disease of the elderly. The prevalence of CHF increases rapidly, as both the elderly population increases and survival from myocardial infarction improves as a result of novel treatments [3]. Congestive heart failure is the pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to supply adequate blood flow and therefore oxygen delivery to peripheral tissues and organs or to do so only from elevated filling pressures. The most common causes of heart failure are coronary artery disease and hypertension [4]. The pathophysiology of CHF involves changes in cardiac function, neurohumoral status, systemic vascular function, and blood volume. The progression of CHF is related to local and systemic neuroendocrine activation. On the level of the myocardium, neuroendocrine activation as well as mediators of inflammation and free oxygen radicals contributes to hypertrophy, dilatation and remodeling of the ventricles [5].

The clinical syndrome of CHF is characterized by dyspnea and fatigue at rest or with exertion, ankle swelling and pulmonary edema. The New York Heart Association classification (NYHA I–IV) is a commonly used way to classify the severity of heart failure and to gauge the progression of CHF in a particular patient (Table 1). This classification is used to determine how much CHF limits their lifestyle, and does not apply to a particular decompensated episode.

Medical treatment of CHF includes prescription of ACE-inhibitors, β-blockers, loop as well as thiazide diuretics, aldosterone antagonists, digitalis glycosides, and AT_1-receptor blockers. Moreover, a large percentage of CHF patients is on anticoagulation therapy with coumarin derivatives, since CHF patients are at an increased risk for atrial fibrillation or an ejection fraction < 20–25% which may both lead to thromboembolism.

Despite evidence-based advances in the treatment of CHF over the past 15 years [1], large observational studies have failed to show a substantial change in the prognosis of patients with heart failure. Survival is still only 35–50% 5 years after the first diagnosis of CHF [6,7]. Therefore, heart transplantation is the ultimate therapeutic measure in patients with end-stage CHF.

Bone diseases are also frequent in western societies. From the 18th century until the first two decades of the 20th century rickets, also named the English disease, was endemic in Europe and North America. Rickets could be largely prevented in Europe and North America by daily vitamin D supplements or by exposure to artificial ultraviolet B exposure. In adults, severe vitamin D deficiency results in demineralization of the skeleton leading to osteomalacia. Especially immobile subjects are at risk for severe vitamin D deficiency, which leads to suppression in intestinal calcium absorption and to an impairment of calcium balance. Less severe vitamin D deficiency, also called vitamin D insufficiency, contributes to the bone disease osteoporosis [8]. The pathogenesis of osteoporosis, however, is multi-factorial. Hypogonadism, older age, small and thin bones, Caucasian and Asian ethnicity, and a family history of fractures are all important risk factors for osteoporosis. Nowadays osteoporosis is the most common bone disease in western societies. In the United States, about 10 million people over age 50 have osteoporosis. Another 34 million American are at risk for low bone mass [9]. Solely in the United States, osteoporosis is responsible for more than 1.5 million fractures annually.

Table 1
NYHA classification

Class I:	No limitation in normal physical activity by symptoms
Class II:	Ordinary physical activity results in fatigue, dyspnea, or other symptoms
Class III:	Marked limitation in normal physical activity
Class IV:	Symptoms at rest or with any physical activity

CHF-associated symptoms such as low mobility and renal failure as well as the prescription of specific drugs may probably further increase the risk of osteoporosis. Since osteoporosis itself is a cause of morbidity and immobilization, risk factors for osteoporotic bone loss should be recognized and preventive strategies should be introduced, if necessary and possible. This review article gives an overview of available biomarkers that allow to study possible changes in bone formation and resorption. Moreover, the kind and extent of bone loss in CHF patients as well as in heart transplant recipients are summarized.

2. Physiology of bone metabolism

Bone is a living tissue that undergoes continuous turnover processes. Reconstruction comprises bone resorption and bone formation. In the adult skeleton, new bone formation is primarily the result of bone remodeling. In both trabecular and cortical bone, bone remodelling results from the coupled bone resorption/formation activity of bone remodelling units that substitute old bone by new bone. Bone remodelling is a life-long process in order to maintain the mechanical properties of the skeleton at its best. Usually, bone resorption and formation are coupled in the skeleton of young adults. Net bone resorption can however occur due to an uncoupling of the bone formation and resorption processes [10]. Skeletal integrity mainly depends on mechanical loading. Consequently, bone mass and strength are primarily influenced by mechanical forces. Except trauma, muscle forces cause the largest loads on bones and the largest bone strains. In order to measure the effect of mechanical forces on bone the unit microstrain (με) is used [11]. For example, a force of 1000 με results in a compression in bone length of approximately 0.1%. Bone loss occurs if the forces acting on bone do not exceed a threshold of approximately 800 με while bone accretion occurs above a threshold of approximately 1600 με.