Clinica Chimica Acta 436 (2014) 323–328

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Biomarkers for cardiac cachexia: Reality or utopia

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ARTICLE INFO

Article history:
Received 12 May 2014
Received in revised form 18 June 2014
Accepted 21 June 2014
Available online 28 June 2014

Keywords:
Chronic heart failure
Wasting
Hormonal markers
Inflammation
Multimarker strategy

ABSTRACT

Cardiac cachexia is a serious complication of chronic heart failure, characterized by significant weight loss and body wasting. Chronic heart failure-related muscle wasting results from a chronic imbalance in the activation of anabolic or catabolic pathways, caused by a series of immunological, metabolic, and neurohormonal processes. In spite of the high morbidity and mortality associated to this condition, there is no universally accepted definition or specific biomarkers for cardiac cachexia, which makes its diagnosis and treatment difficult. Several hormonal, inflammatory and oxidative stress molecules have been proposed as serological markers of prognosis in cardiac cachexia but with doubtful success. As individual biomarkers may have limited sensitivity and specificity, multimarker strategies involving mediators of the biological processes modulated by cardiac cachexia will strongly contribute for the diagnosis and management of the disease, as well as for the establishment of new therapeutic targets. An integrated analysis of the biomarkers proposed so far for cardiac cachexia is made in the present review, highlighting the biological processes to which they are related.

Contents

1. Introduction

Chronic heart failure (CHF) is a major public health issue and one of the most common causes of death in western countries [1–4]. At advanced states patients can develop cardiac cachexia (CC), a serious complication characterized by significant weight loss and body wasting [2,5–8]. Since there is no universally accepted definition of CC [4,7,9], this condition is rarely identified or diagnosed and rarely treated [9]. According to Anker and Coats [10], CC should be considered when a weight loss higher than 7.5% of the previous normal weight is observed in patients with CHF with at least six month duration and without signs of other primary cachectic states (like cancer, thyroid disease, or severe liver disease). A few years later, this definition was adjusted and CC is now considered as a weight loss higher than 6% over a period of at least six months [11].

The pathophysiology of CC is complex and multifactorial, the result of several factors interacting in a complex system with metabolic, immune and neurohormonal consequences, triggered to protect the

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http://dx.doi.org/10.1016/j.cca.2014.06.022
0009-8981/

heart and the circulation from damage [2,4,8]. CHF-related muscle wasting results from a chronic imbalance in the activation of anabolic or catabolic pathways. Tumor necrosis factor alpha (TNF-α) is one of the candidates that have been suggested as a common mediator in all forms of cachexia. Other cytokines such as interleukin 1 (IL-1) and interleukin 6 (IL-6) have also been implicated in the pathogenesis of CHF [2]. Furthermore, there are numerous hormone systems contributing to the wasting process by altering appetite and energy expenditure. The imbalance in these hormone systems, potentially triggered by pro-inflammatory cytokines, may be responsible for the development of satiety without adequate food intake [4]. Many of the hormones that are altered in wasting conditions have been implicated in the regulation of protein degradation at the cellular level [12].

Cachexia is not only related with poor outcomes, but also with an unfavorable response to drug treatment and poor quality of life [13]. Despite the high morbidity and mortality associated to CC [7,13–15], there are no known specific biomarkers for the diagnosis of this condition. But for early phase diagnosis and management of CC the evaluation of laboratory, clinical and functional parameters are required [16]. In the following sections a critical analysis of candidate biomarkers proposed for the diagnosis and management of CC is made.

2. Candidate biomarkers for CC

An ideal biomarker should be a prognostic indicator that assists in the early diagnosis of CC, and consistently reflects the therapeutic response [17]. Some of the defined criteria for the clinical usefulness of biomarkers are schematized in Fig. 1. Several hormonal, inflammatory and oxidative stress molecules have been proposed as markers for CC (Table 1). Some of these are not, at least apparently, direct effectors in the development of the wasting syndrome observed in CC, providing only information about the changes observed in these patients. However, it is also important to consider that their action can lead to the activation of other factors which may play important roles in the pathophysiology of the underlying disease. Up-regulated biomarkers are mainly molecules involved in the cardiovascular system homeostasis (e.g. natriuretic peptides and renin–angiotensin–aldosterone system (RAAS)) and catabolic factors (e.g. catecholamines, cortisol and TNF-α). Some anabolic hormones such as growth hormone (GH) and insulin are also up-regulated, whilst the remaining anabolic factors can be unaltered or down-regulated.

2.1. Biomarkers involved in blood pressure maintenance

Severe CHF is characterized by low cardiac output, decreased end-organ perfusion, and low blood pressure, leading to the activation of various interrelated neurohormonal systems [18]. The activation of these systems is, initially, an important compensatory mechanism, maintaining blood pressure and adequate tissue perfusion. However, their prolonged activation has deleterious effects on hemodynamics and on the heart itself [19].

The decreased blood pressure observed in CHF leads to the activation of various vasoactive neurohormonal systems that include sympathetic nervous system (SNS), natriuretic peptides (NP), renin–angiotensin–aldosterone system and arginine vasopressin system (AVP) [18,20]. Activation of the SNS, accompanied by a raise of norepinephrine and epinephrine levels, increases cardiac contractility, heart rate, and systemic vasoconstriction, which immediately increases blood pressure [18]. Both norepinephrine and epinephrine can cause a metabolic shift towards catabolism, leading to a graded increase in resting energy expenditure in patients with CC [21]. Catecholamines also have modulatory effects on fat cell function, stimulating lipid mobilization in adipose tissue [22]. The adipokine zinc α2-glycoprotein (ZAG) was recently suggested to be involved in sympathetic-mediated lipolysis [23]. The sustained sympathetic stimulation seen in CHF activates RAAS and other neurohormones (e.g. AVP), with subsequent salt and water retention, vasoconstriction, edema and increase in pre- and after-load [24].

Angiotensin II (Ang II) is the main effector molecule of the RAAS [25] and there is recent evidence that increased levels of this hormone may play an important role on CC [26]. In fact, patients with CC often have increased circulating Ang II levels [25,27,28]. Moreover, studies revealed that Ang II infusion induces marked diaphragmatic skeletal muscle atrophy [29], weight loss and decrease in circulating IGF-1 levels in rodents [30]. Ang II-induced weight loss is due to both anorexigenic and catabolic effects [25–27]. Ang II contribution to skeletal muscle wasting is mainly through an up-regulation of proteolysis via activation of forkhead box protein (FoxO) transcription factors, caspase-3, and the ubiquitin proteasome pathway (UPP). This hormone also

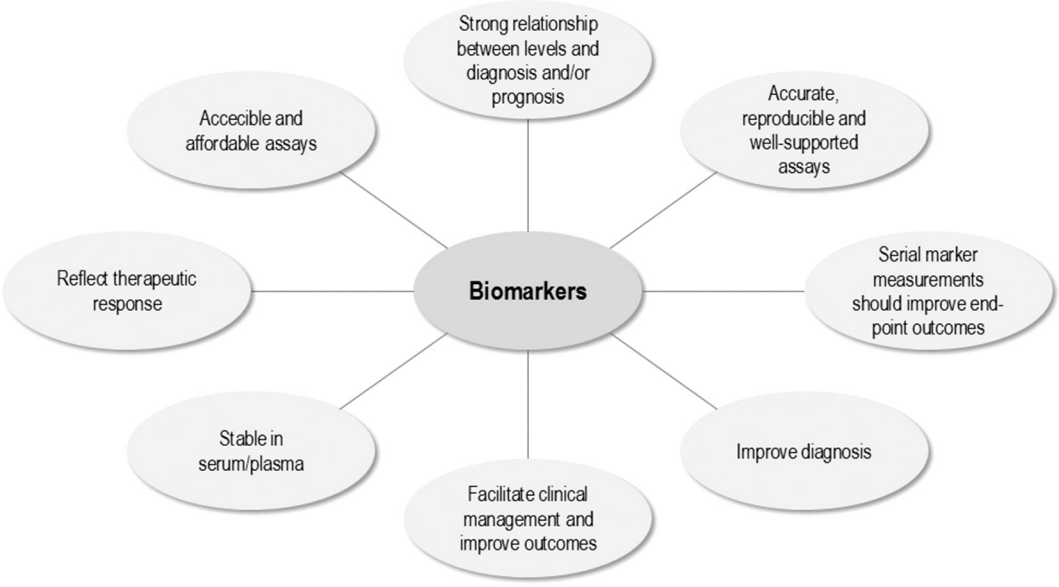

Fig. 1. Criteria for the clinical usefulness of biomarkers.