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Review article

Inflammation and sarcopenia: A systematic review and *meta*-analysis

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ABSTRACT

Inflammatory cytokines have been shown to prompt muscle wasting, ultimately stimulating protein catabolism and suppressing muscle synthesis. However, the possible association between inflammatory parameters and sarcopenia is poorly understood. We therefore aimed to summarize the current evidence about this topic with a *meta*-analysis of studies reporting serum inflammatory parameters in patients with sarcopenia vs. people without sarcopenia (controls). An electronic PubMed and Scopus search through to 09/01/2016 and *meta*-analysis of cross-sectional studies comparing serum levels of inflammatory cytokines between patients with sarcopenia and controls was made, calculating random-effects standardized mean differences (SMDs) ±95% confidence intervals (CIs) as the effect size. Out of 1370 initial hits, 17 studies with a total of 11249 participants (3072 with sarcopenia and 8177 without) were *meta*-analyzed. Sarcopenic participants had significantly higher levels of CRP (SMD = 0.51; 95%CI 0.26, 0.77; $p < 0.0001$; $I^2 = 96\%$) than controls. Conversely, serum IL6 levels were not significantly different (SMD = 0.35; 95%CI: −0.19, 0.89; $p = 0.21$; $I^2 = 97\%$) in people with sarcopenia versus controls. Sarcopenic people did not have higher levels of TNF-α than controls (SMD = 0.28; 95%CI −0.26, 0.83; $p = 0.31$; $I^2 = 97\%$). In conclusion, sarcopenia seems to be associated with elevated serum CRP levels; future longitudinal studies are needed to clarify this relationship.

Contents

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1. Introduction

Inflammation is an adaptive response of the immune system triggered by a homeostatic imbalance, to restore functionality. Whereas the acute inflammatory process induced by infection or tissue injury is clear, considerably less is known about the deleterious effects of chronic low-grade inflammation. The oxidative stress-induced redox imbalance and the sustained upregulation of pro inflammatory mediators are believed to act as the pathophysiological basis underpinning inflammatory disorders including cardiovascular diseases, cancer, diabetes, dementia and also sarcopenia [1].

According to the recent definitions of several working groups, sarcopenia is described as a syndrome characterized by a loss of muscle mass and strength with functional impairment and adverse outcomes [2,3]. The age related muscle loss coincides with a micro and macro architecture disorganization of the entire muscle mass. For instance, the conversion of type II (fast) fibers to type I (slow) fibers and subsequent lipid infiltration, which translate into impairment of muscle power and a greatly increased risk of falls [4]. Several studies have shown that sarcopenic individuals are either three times more likely to fall or have an higher risk of death relative to non sarcopenic individuals [5,6]. Moreover, sarcopenia itself is associated with disability and hospitalization [7].

A substantial body of literature has demonstrated that inflammatory cytokines activate many of the molecular pathways involved in skeletal muscle wasting leading to an imbalance between protein synthesis and catabolism [8,9]. High levels of inflammatory cytokines have been demonstrated to be negatively related to muscle strength and mass [10,11]. However, the research considering whether their serum cytokine levels could represent a biological marker of sarcopenia is equivocal [12].

Therefore, we conducted a systematic review and *meta*-analysis of observational studies exploring the association between serum inflammatory parameters and sarcopenia. We hypothesized that participants with sarcopenia have higher inflammatory parameters levels than normal controls.

2. Methods

This systematic review was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for the quality assessment of included studies [13] and the indications of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. [14]

2.1. Search strategy

Two investigators (MS, CL) independently conducted an electronic literature search using PubMed and Scopus, without language restriction, from database inception until 09/01/2016. In PubMed, controlled vocabulary terms and the following keywords were used: ("sarcopenia"[All Fields]) AND (("inflammation"[MeSH Terms] OR "inflammation"[All Fields]) OR inflammatory[All Fields] OR IFN[All Fields] OR ("interferons"[MeSH Terms] OR "interferons"[All Fields] OR "interferon"[All Fields]) OR TNF[All Fields] OR "tumor necrosis factor"[All Fields] OR IL[All Fields] OR "interleukin"[All Fields] OR "TGF"[All Fields] OR ("apoptosis"[MeSH Terms] OR "apoptosis"[All Fields]) OR apoptotic[All Fields] OR anti-apoptotic[All Fields] OR CRP[All Fields] OR "C-reactive protein"[All fields] OR ("cytokines"[MeSH Terms] OR "cytokines"[All Fields] OR "cytokine"[All Fields])). A similar search strategy was run in Scopus. Conference abstracts were also considered and at least 4 attempts were made to contact study authors for additional information. Reference lists of included articles and those relevant to the topic were hand-searched for identification of additional; potentially relevant articles.

2.2. Study selection

Included were studies that (1) compared data on inflammatory parameters between participants with sarcopenia vs. those without, (2) reported on serum levels of inflammatory cytokines, and (3) reported data about muscular mass assessed with Dual-energy X-ray Absorptiometry (DXA), Magnetic Resonance Imaging (MRI) or bioimpendenziometry (BIA) and not only with body composition estimates (e.g. calf circumference). Studies were excluded if they (1) did not use clear diagnostic criteria for sarcopenia, (2) measured only in vitro parameters or used animal models, or (3) did not measure or did not report quantitative cytokine levels in both sarcopenic and no sarcopenic subjects.

We also contacted authors asking for further information when: 1) data could not be *meta*-analyzed (i.e., no mean and standard deviation (SD) or equivalent for inflammatory parameters), 2) other relevant information was missing, 3) data about muscular mass were reported, but sarcopenia diagnosis no. At least 4 attempts were made with these Authors.

Study data consisting of cytokine levels with SDs larger than three times the mean were excluded from the analyses, as we considered these to be overly skewed and unreliable. [15]

2.3. Data extraction

Two authors (CT, SC) independently extracted data from the selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus. The following information were extracted: i) study population characteristics (e.g., sample size, demographics); ii) clinical setting in which the study was performed; iii) parameters related to sarcopenia and inflammation (age, gender, body mass index) in sarcopenic and no sarcopenic subjects, iv) diagnostic criteria for sarcopenia, and v) method of evaluation of inflammatory cytokines.

2.4. Assessment of study quality

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria [13] were used for the quality assessment of included studies. One Author made the assessment of quality (MS) and any discrepancies were addressed by a joint