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Review

Evidence-based nutritional and pharmacological interventions targeting chronic low-grade inflammation in middle-age and older adults: A systematic review and meta-analysis

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ABSTRACT

Growing evidence suggests chronic low-grade inflammation (LGI) as a possible mechanism underlying the aging process. Some biological and pharmaceutical compounds may reduce systemic inflammation and potentially avert functional decline occurring with aging. The aim of the present meta-analysis was to examine the association of pre-selected interventions on two established biomarkers of inflammation, interleukin-6 (IL-6), and C-reactive protein (CRP) in middle-age and older adults with chronic LGI.

We reviewed the literature on potential anti-inflammatory compounds, selecting them based on safety, tolerability, acceptability, innovation, affordability, and evidence from randomized controlled trials. Six compounds met all five inclusion criteria for our systematic review and meta-analysis: angiotensin II receptor blockers (ARBs), metformin, omega-3, probiotics, resveratrol and vitamin D. We searched in MEDLINE, PubMed and EMBASE database until January 2017. A total of 49 articles fulfilled the selection criteria. Effect size of each study and pooled effect size for each compound were measured by the standardized mean difference. I^2 was computed to measure heterogeneity of effects across studies.

The following compounds showed a significant small to large effect in reducing IL-6 levels: probiotics (−0.68 pg/ml), ARBs (−0.37 pg/ml) and omega-3 (−0.19 pg/ml). For CRP, a significant small to medium effect was observed with probiotics (−0.43 mg/L), ARBs (−0.2 mg/L), omega-3 (−0.17 mg/L) and metformin (−0.16 mg/L). Resveratrol and vitamin D were not associated with any significant reductions in either biomarker.

These results suggest that nutritional and pharmaceutical compounds can significantly reduce established biomarkers of systemic inflammation in middle-age and older adults. The findings should be interpreted with caution, however, due to the evidence of heterogeneity across the studies.

1. Introduction

Older age is often associated with a higher burden of comorbidities that lead to declines in physical and cognitive function and ultimately, disability and death (Marengoni et al., 2009). In recent years inflammation has been shown to contribute to most if not all chronic diseases typical of old age (Stepanova et al., 2015). Moreover, aging itself could result in immune system dysregulation leading to chronic

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low-grade inflammation (LGI) (Ferrucci et al., 2005). Growing evidence suggests chronic low level elevation of proinflammatory cytokines and chemokines, a process also defined as "inflammaging" specifically contributes to age-related decline in function and increases risk of morbidity and mortality (Franceschi and Campisi, 2014).

The origin of inflammaging currently remains unclear (Baylis et al., 2013; Fougere et al., 2017; Franceschi et al., 2000; Fulop et al., 2014). Although there is likely a genetic predisposition (Capurso et al., 2007), many other factors can contribute to the inflammatory process. Some identified exogenous triggers include smoking (Behnia et al., 2016), air pollution (Fougere et al., 2015), persistent infections (Derhovanessian et al., 2011; Oppermann et al., 2012) and overweight or obesity (Giugliano et al., 2006). Several endogenous factors also play a relevant role, including: overproduction of reactive oxygen species (ROS) (Zhang et al., 2016) and advanced glycation end-products (AGEs) (Yamagishi and Matsui, 2016), mitochondrial dysfunction (Lopez-Lluch et al., 2015), renin-angiotensin system (RAS) deregulation (Duprez, 2006), hormonal changes (Epel and Lithgow, 2014; Gubbels Bupp, 2015), visceral adiposity (Palmer and Kirkland, 2016), changes in the gut microbiota (Biagi et al., 2010) and accumulation of cell debris due to a defective autophagy (Franceschi et al., 2017).

In humans, two of the most well accepted markers of systemic inflammation are interleukin-6 (IL-6) and C-reactive protein (CRP) (Michaud et al., 2013). The levels of both biomarkers typically increase with aging (Singh and Newman, 2011; Wyczalkowska-Tomasik et al., 2016), which leads to an increased risk of morbidity and mortality in older adults (Alley et al., 2007; Ferrucci et al., 1999; Harris et al., 1999). Higher IL-6 levels have been associated with indicators of physical frailty such as slower walking speed, impaired muscle strength, and lower extremity performance (Cesari et al., 2004; Taaffe et al., 2000), and sarcopenia (Haddad et al., 2005) which are predictive of future disability in nondisabled older adults (Ferrucci et al., 1999). Moreover, in the Longitudinal Aging Study of Amsterdam, moderately elevated CRP levels (3–10 mg/L) were associated with 3-year incident frailty (Puts et al., 2005). Elevated levels of both IL-6 and CRP have also been related to a decline in cognitive function (Schram et al., 2007) and Alzheimer's disease (AD) (Akiyama et al., 2000).

The rise of IL-6 and CRP levels are mechanistically linked to the activation of pro-inflammatory transcription factors, including nuclear factor kappa B (NF-κB) (Maggio et al., 2006). A consistent body of evidence suggests NF-κB is an attractive target for anti-inflammatory therapies (Gupta et al., 2010). Thus, the inhibitors, at various levels, of NF-κB pathway could lead to a reduction of inflammatory biomarkers (such as IL-6 and CRP) and potentially avert or slow the functional decline that occurs with aging.

A recent review by Gupta et al. (2010), based on *in vitro* data, provided a comprehensive overview on potential compounds that can inhibit the NF-κB pathway, including natural and synthetic products, proteins, and peptides. Although there is a growing body of evidence to suggest many of these compounds can reduce established inflammatory biomarkers, to date, the findings have not been systematically examined in middle-age and older adults with chronic LGI. Thus, the goal of this review was to examine the state of evidence from relevant randomized controlled trials (RCTs) to identify the most promising biological and pharmacological compounds that reduce inflammation in middle-age and older adults with elevated circulating levels of IL-6 and/or CRP.

2. Methods

2.1. Search strategy and study selection

This systematic literature review and meta-analysis followed the requirements of the PRISMA statement (Moher et al., 2009). The review was registered in PROSPERO, the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42017059820)

Three study authors (C.C., R.T.M. and S.A.L.) independently conducted a systematic search of the databases MEDLINE, PubMed, and EMBASE (all years to January 31st 2017).

To initially identify the potential compounds, we considered the molecules listed in a recent review by Gupta et al. (2010), since this review provided, on a molecular base, a comprehensive overview of targets of NF-κB. Furthermore, to maximize the public health impact of our meta-analysis, we selected compounds based on four criteria: safety, tolerability and acceptability, innovation, and affordability. First, we evaluated compounds in terms of their safety record in the general population, risk of adverse events, and potential interactions with other drugs. Next, we took into account tolerability and acceptability, considering side effects that may reduce quality of life and adherence to the treatment. For our innovation criterion, we prioritized compounds that did not already have an indication for anti-inflammatory therapy (e.g., non-steroidal anti-inflammatory drugs, corticosteroids and interleukin (IL)-1 beta inhibitor were excluded). Next, we considered costs of specific compounds and the potential for individuals to take specific compounds on a regular basis. To be included in the present meta-analysis, compounds had to meet all four criteria listed above.

Once we identified potential compounds, we applied the fifth criterion which was to select compounds that had sufficient evidence from four or more RCTs conducted in middle-age and older adults with chronic LGI (indicated by either elevated IL-6 or CRP levels). After a preliminary search in the above-mentioned databases, we excluded compounds that had less than four eligible studies. Several compounds that met our initial criteria (e.g. curcumin, vitamin-B6, −C, −E, β-carotene, melatonin) were subsequently excluded due to lack of sufficient evidence from clinical trials in middle-age and older adults with chronic LGI. Table 1 reports the results of the selection process.

Six compounds met all five inclusion criteria and were included in our systematic review and meta-analysis: angiotensin II receptor blockers (ARBs), metformin, omega-3, probiotics, resveratrol, and vitamin D. Search terms included combinations of the following keywords: ("losartan" OR "candesartan" OR "valsartan" OR "irbesartan" OR "telmisartan" OR "olmesartan" OR "eprosartan" OR "azilsartan" OR "fimasartan" OR "metformin" OR "omega-3 fatty acids" OR "n-3 polyunsaturated fatty acid" OR "n-3 pufa" OR "probiotic" OR "resveratrol" OR "vitamin D" OR "cholecalciferol" OR "ergocalciferol") AND ("inflammation" OR "interleukin-6" OR "c-reactive protein").

To be included in this review, studies were limited to RCTs (including both parallel and cross-over study designs) to ensure the effects of interventions on outcomes were compared to placebo or control group receiving no treatment. Studies were required to meet the following inclusion criteria: (1) conducted in humans aged 45 years or older; (2) included at least one specific nutritional or pharmacological intervention arm; (3) assessed the effect of treatment on an outcome of interest (IL-6 or CRP); (4) conducted in adults with baseline levels of IL-6 between 2.5 and 30 pg/ml and/or baseline levels of CRP between 2 and 10 mg/L, according to the most well accepted cut-off levels indicating chronic LGI (Ferrucci et al., 1999; Ockene et al., 2001; Ridker et al., 2008; Ridker et al., 2001; Sabatine et al., 2007; Steinmetz et al., 1995); (5) carried out for four weeks or longer; (6) with a sample size of at least 15 per group; and (7) written in the English language. In addition, studies with the following characteristics were excluded: (1) involving patients with infections, acute inflammatory diseases, acute coronary syndrome, chronic kidney disease, chronic liver and lung diseases, inflammatory bowel diseases, autoimmune disorders, cancers, or participants undergoing surgical procedures; (2) with another intervention co-occurring; and (3) with intravenous administration of treatment.

Articles were initially screened based on title and abstract by three study authors (C.C., R.T.M. and S.A.L.), with the full text sought if the abstract did not provide sufficient information to draw a conclusion