

C-Reactive Protein, Chronic Low Back Pain and, Diet and Lifestyle

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Rec Date: Jul 26,14; Acc Date: Oct 29,14; Pub Date: Oct 31,14

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Abstract

C-reactive protein (CRP) is best known as an acute phase protein and is typically assessed in most general blood work. High sensitivity CRP (hsCRP) may be a useful clinical marker of chronic inflammatory states in musculoskeletal conditions. It appears that it is raised in inflammatory chronic low back pain (CLBP) and associated with reduced pain thresholds, weakness and reduced function. It is also possible CRP could contribute towards the development and maintenance of CLBP by activating the complement system which increases peripheral nociception. Diet and lifestyle factors can promote raised CRP. A hsCRP level of <1mg/l appears ideal and the higher the level the more emphasis should be placed on chronic inflammation as a contributor to symptoms. Diet and lifestyle can significantly reduce CRP levels and may be a useful adjunct in treating CLBP patients with elevated CRP. This might make CRP a useful clinical marker of inflammation in CLBP and a therapeutic target for diet and lifestyle interventions.

Keywords: C-reactive protein; High sensitivity CRP; clinical marker

Introduction

C-reactive Protein (CRP) is best known as an acute phase protein and is typically assessed in most general blood work. More recently high sensitivity C-reactive protein (hsCRP) has been used in cardiovascular research as a marker of chronic inflammation. As chronic low back pain (CLBP) can have an inflammatory component it would be useful to have a clinical marker to assess in practice. Furthermore it may help us understand a component of how diet and lifestyle can influence CLBP.

C-Reactive Protein and Chronic Low Back Pain

In the 1940s CRP was considered as a possible marker of chronic low level inflammation but the standard assay lacks the sensitivity to determine normal ranges. Since the advent of the hsCRP test large-scale epidemiological studies have identified that CRP is a strong independent risk factor of future myocardial infarction, stroke, peripheral arterial disease, and vascular death among individuals without known cardiovascular disease [1]. In cardiovascular disease hsCRP is a sensitive and specific measure across many populations. As these conditions are associated with inflammatory processes it is possible hsCRP may be a useful marker of chronic inflammation in musculoskeletal conditions such as chronic low back pain.

More recently CRP has received attention as a marker of chronic inflammation in musculoskeletal conditions. Chronic inflammation has been associated with arthritis [2], and chronic musculoskeletal injuries [3-5]. Repetitive tissue injury has been theorized to contribute to lower level rises in chronic inflammation [3]. Inflammation and pain are intimately interrelated and pain perception may be higher in those with raised CRP. In a study of 99 pairs of twins, higher levels of CRP were associated with lower pain thresholds and increased pain sensation [6]. Similarly, in cancer patients CRP is significantly

correlated with perceived pain [7]. Thus an hsCRP test could provide insight in to the inflammatory contribution chronic pain states.

CRP is also associated with poorer function in symptomatic individuals. Carp et al. [4] found asymptomatic subjects averaged 0.8 mg/l, whereas those scoring 50-74 on the upper body musculoskeletal analysis (UMBA) averaged 1.8 mg/l, and those scoring over 75 on the UMBA averaged 5.4 mg/l. Interestingly, CRP was more strongly correlated with symptom levels than IL-1 β , TNF- α and IL-6. Suggesting CRP may be the more clinically useful marker. These results are similar to that of Ravaglia et al. [8] who found CRP levels were related to functional impairment. Cesari et al. [9] found older adults with a CRP >6 mg/l had significant weakness and poorer physical function compared with those with a CRP <6 mg/l, conditions that may lead to chronic pain states. Carp et al. explain their results by suggesting that worse disability is caused by worse injury and thus a greater acute phase response. However, injury and disability are not necessarily strongly associated. For example data from the LAIDBACK study has shown that at 3 years there is not a strong correlation between lumbar spine magnetic resonance imaging findings and symptoms [10]. It may be that in some patients it is the systemic inflammatory level that may be influencing the disability.

The association between raised CRP and CLBP is controversial. Studies looking at inflammatory pathologies such as herniated discs [11,12], nerve root inflammation [11], sciatica [13], and Modic changes [14] have shown positive correlations. Whereas those with smaller sample sizes and inclusion of acute and chronic patients in one heterogenous group have failed to show associations [15,16]. Briggs et al. [17] conducted a population based study using 15 322 participants examining CRP levels, obesity and low back pain (LBP). They found that those with CRP levels of >30.0 mg/l had nearly twice the odds of reporting LBP. It should be noted they used standard CRP assessment and thus the figures are higher than for the hsCRP. Additionally, those with a body mass index >30 and elevated levels of CRP were 2 to 3 times as likely to report LBP. They found a significant association between LBP and elevated CRP, suggesting CRP could be a valuable marker of chronic inflammation in CLBP patients.

CRP is more than a useful marker and can contribute towards the development of chronic pain. Animal studies have suggested raised CRP plays a role in the chronic inflammation that leads to reduced tissue tolerance, and paves the way for chronic pain states [18,19]. Further, CRP may contribute to the initiation and continuation of joint pain [20]. In cancer patients elevated CRP can modulate pain [21] and contribute to the amplification and persistence of pain [22]. CRP can be viewed as both a marker for the underlying processes involved in increased pain sensation and a direct contributor to increased pain sensation. CRP activates the complement system, which in turn sensitises peripheral nociceptors [23]. Effectors of the complement cascade impact peripheral nociceptive sensitisation through the release of soluble factors and interacting directly with nociceptors. For example C5a and C3a injection can cause behavioural hyperalgesia in rats. In addition effectors of the complement cascade activate mast cells, which can sensitise nociceptors in multiple ways [23]. Thus CRP could feasibly contribute to the progression towards and maintenance of CLBP.

Diet and Lifestyle may Increase C-Reactive Protein Levels

As CRP may contribute to the underlying pathogenesis of CLBP it is prudent to consider some of the contributing factors in this process. Diet and lifestyle are powerful modulators of CRP levels and thus may contribute to the pathogenesis of CLBP through this mechanism. Smoking has been found to be associated with raised CRP [24]. Sleep disorders and poor sleep quality are associated with elevated CRP [25,26]. Psychological stress has been linked with raised CRP when perceived stress is increased [27], and during depression and loneliness [28]. Increased dietary saturated fat increases CRP whereas an equal increase in unsaturated fatty acids did not [29]. Higher carbohydrate intake was associated raised CRP levels in overweight and obese individuals [30]. Of the minerals magnesium has perhaps been most closely associated with CRP. Current recommendations for magnesium intake range from 310-420mg per day. King et al. [31] found those who consumed less than the RDI of magnesium were greater than 1.45 times more likely to have a CRP level over 3.0 mg/l. 68% of US adults consumed less than the recommended daily intake (RDI), with 19% consuming less half the RDI. Of the vitamins deficiencies in vitamins B6 and D have received some interest. B6 appears to be utilised as part of the inflammatory process and thus those with elevated CRP level have significantly lower levels [32]. The interest in vitamin D and CRP has come from cardiovascular research. Low plasma vitamin D status is inversely associated with CRP levels [33]. Exercise can have both a positive and negative effect on CRP levels. However, overtraining such as that caused by playing professional soccer has been found to cause elevation in CRP during the season [34]. These results fit with the theme that deviations from a "healthy" lifestyle are associated with elevations in CRP levels.

Clinical Use

Given that there is an association between CLBP and CRP levels it is suggested an hsCRP test may be a useful clinical marker for managing these patients. This needs to be considered within a broader framework of the multitude of bio-psycho-social factors that influence CLBP. The question of what level is significant is unclear. In the literature there is no consensus for its use in musculoskeletal conditions. Levels as low as >1 mg/l have used, whilst the highest used is >6.0 mg/l. Thus in practice the measure can be used non-diagnostically with an appreciation of the cardiovascular research. It

needs to be remembered that levels may be spiked during acute infection, trauma and post intense exercise. A level >1 mg/l is likely indicative of increased systemic inflammation, the higher this figure is the more significant a contributor it should be considered.

Pharmacological approaches have been considered for modifying CRP levels, with statins being potentially the most promising but diet and lifestyle changes can significantly improve CRP levels. An 8-week mindfulness programme reduced CRP levels from 2.98 to 2.09 [35]. Similarly, an 8-week programme of exercise decreased CRP levels by 38% and improved function in automotive workers with low back pain [36]. As visceral adipocytes produce CRP reducing body fat levels is another potential therapeutic target, and a carbohydrate restricted has been shown to reduce CRP levels [37]. More broadly going from 2 to 5 or 8 portions of fruit and vegetables per day significantly reduced CRP levels [38]. Furthermore, in a study of 1200 Puerto Rican adults aged 45-75 the variety of fruit and vegetable intake but not the quantity was inversely related with CRP levels [39]. Specifically, vitamin C intake from fruit and plasma vitamin C levels was inversely related to CRP levels in a cross-sectional study of 3258 British men aged 60-79 [40]. Other substances high in antioxidants have been found to favourably alter CRP levels including coffee [41], fruit juice [42,43] and dark chocolate [44]. Thus, diet and lifestyle modification of CRP levels may prove an effective component of CLBP treatment and may help reduce symptoms through other mechanisms as well.

Conclusion

CRP may be a useful clinical marker of chronic inflammation in chronic low back pain. It appears that it is elevated in inflammatory CLBP and associated with reduced tissue tolerance, reduced pain thresholds, weakness and reduced function. It may also contribute to peripheral sensitisation as part of the progression towards and maintenance of chronic pain. Diet and lifestyle factors can promote raised CRP. An hsCRP level of < 1mg/l appears ideal and the higher the level the more emphasis should be placed on chronic inflammation as a contributor to symptoms. Diet and lifestyle can significantly reduce CRP levels and may be a useful adjunct in treating CLBP patients with elevated CRP.

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