Chapter 3

C-reactive protein after major abdominal surgery: biochemical and clinical aspects

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Published: AMSj 2015; 2:e1-4
C-reactive protein (CRP) is an established marker for non-specific acute phase response to most forms of inflammation, which may be caused by infection or tissue damage, such as occurs in surgery. CRP is produced in the liver. In surgical patients, tissue damage is the main stimulus for CRP synthesis, and levels are independent of diurnal rhythm, diet or medication. These properties underscore the suitability of CRP as a marker for postoperative inflammation. CRP is non-specific to location of tissue damage or cause, indicating additional examinations are necessary in patients with elevated CRP levels in the postoperative phase. The aim of this study was to review the literature concerning biochemical and clinical aspects of CRP in relation to major abdominal surgery.
INTRODUCTION

Major elevations in C-reactive protein (CRP) levels have been observed in bacterial, viral and fungal infections, auto-inflammatory diseases, myocardial infarction, trauma, tissue damage and neoplastic disease 1.

In 1930, Tillet and Francis discovered CRP upon analysis of sera obtained from patients with severe pneumonia, and described it as the first acute phase protein 2. The protein was named after the capacity to precipitate the C-polysaccharide of streptococcus pneumoniae and is now considered a sensitive systemic marker of inflammation 3. Literature has focused on the use of CRP as a marker of inflammation 4. Here we review available literature concerning CRP in relation to major abdominal surgery.

PHYSIOLOGY

CRP is gathered among other acute phase proteins, which include proteinase inhibitors, coagulation, complement and transport proteins. CRP, however, shows the fastest response and sensitivity, together with serum amyloid A protein, a less commonly used acute phase response marker in clinical practice 3.

When the immune system is exposed to a pathogen, the innate immune system responds to pathogen associated molecular patterns (PAMPs) predominately via Toll-like receptor 2 (TLR-2) and TLR-4. Binding of PAMPs induces expression of nuclear transcription factors, which leads to subsequent local production of tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), IL-6, IL-8 and IL-12 5. IL-6 enters the bloodstream and activates hepatic transcription factors with subsequent production of CRP. A peak is seen 48 hours after initiation of an inflammatory stimulus, and plasma half-life of CRP is 19 hours 6.

Circulating CRP has a high affinity for phosphocholine residues, a breakdown product of cell membranes from damaged and apoptotic cells 7. Furthermore, CRP also binds lipids and lipoproteins 8. Upon aggregation of CRP or binding of CRP with a ligand, the complex is recognized by complement factor C1q. Further potentiation of the complement cascade occurs via C3 adhesion molecules and the membrane-attack complex (C5-9). Moreover, CRP is recognized by certain Fcγ receptors, which allows for direct opsonization and degradation. Based on these mechanisms, CRP is considered to not just be a biomarker of inflammatory activity, but also to contribute to metabolic, scavenging and host-defense functions 9.

Circulating CRP further stimulates the production of tissue-factor, and is therefore proposed to have a pro-coagulant effect. This is in line with the finding that higher baseline levels of CRP are observed in patients with coronary artery disease and myo-
It is proposed CRP may contribute to pathogenesis and progression of thrombo-occlusive complications 10.

When CRP is measured randomly in a general population, the average CRP levels tend to increase with age, possibly reflecting increased subclinical pathologies 11. Obese people have, within what is clinically still considered the normal range, a threefold higher baseline CRP than normal-weight patients 12. This increase is attributed to the increased number of adipocytes, which secrete IL-6 13. Although baseline levels may differ between different patient groups, research has shown that the stimulus of surgical trauma and inflammation surpasses the effect of patient factors, such as gender, age and BMI 14.

**CRP AND SURGICAL TRAUMA**

CRP levels increase after surgery. In uncomplicated patients a peak is seen 48-72 hours after surgery, to decrease thereafter in uncomplicated cases 15. Surgical tissue damage causes a shift in the balance between the T-helper 1 (Th1) and Th2 cells in favour of Th2 cells and predominant production of Th2 cytokines 16. Th1 cells secrete interferon-γ, activating inflammatory pathways via macrophage activation with upregulation of cytokines (TNF, IL-1, IL-6 and IL-8), resulting in a systemic inflammatory response. Th2 cells secrete cytokines, (i.e. IL-4 and IL-5) which aid in the upregulation of antibody formation via B-cells and mast cells 17. Th2 cells mainly produce anti-inflammatory cytokines (IL-4, IL-10 and IL-13), which promote myeloid derived suppressor cells (MDSC) to produce catabolising enzymes for arginine 18.

Arginine is a conditionally essential amino acid and a precursor for nitric oxide. Thus, postoperative arginine deficiency and Th2 shift results in suppression of T-lymphocyte dependent immune function and suppression of pro-inflammatory cytokines. Thus, arginine deficiency is a plausible cause of postoperative impaired immune function 19. After 24 hours, recovery commences and pro-inflammatory cytokines, such as TNF, IL-1 and IL-6 rise. The rise in IL-6 causes production of CRP with a peak seen 48-72 hours after surgery 20.

**POSTOPERATIVE MONITORING OF INFLAMMATORY RESPONSE**

As stated before, levels of CRP are determined only by their rate of synthesis. When the inflammatory stimulus subsides, CRP levels will decrease 6. In clinical practice, CRP levels decrease in patients with an uncomplicated postoperative course after 48-72 hours. In
patients with postoperative complications, on the other hand, CRP levels may remain high, or even increase further 20.

Differences in CRP levels between patients with an uncomplicated postoperative course are observed from as early as the second postoperative day. On the third postoperative day average CRP levels are reported to be 169 mg/L in uncomplicated cases, 193 mg/L in patients with minor complications and 256 mg/l in patients with major complications, requiring invasive treatment such as percutaneous drainage, reoperation or intensive care management 4.

Several studies have aimed to assess the optimal cut-off for CRP as a marker for complications. Established cut-offs range from 140 mg/L to 190 mg/L on postoperative day 3 21-23 and from 123 mg/L to 145 mg/L on POD 4 15, 24, 25. The majority of studies described a cut-off for CRP levels as a marker for complications after colorectal surgery, but similar cut-offs also hold for hepatopancreatobiliary surgery and upper gastrointestinal surgery 21, 26. The studies described above further support the use of CRP in early diagnosis of postoperative complications. Additional imaging may be necessary if CRP levels exceed the predetermined cut-off, and alternative explanations, such as wound infection or pneumonia, are absent. Differences in the established cut-offs for CRP can be explained by differences in the included populations and variability in the definitions for complications 27. Future research should aim to assess the optimal use of CRP as a marker for postoperative complications, and determine it’s value in early diagnosis of complications and consequent morbidity and mortality.

**DAILY PRACTICE**

Literature supports the use of CRP as an important marker in the risk assessment of patients following major abdominal surgery. An optimal cut-off is not yet implemented due to differences in populations, type of surgery and definitions of complications. A model for the prediction of major complications as a function of continuous CRP levels would allow for assessment of separate CRP values. High negative predictive values further emphasize CRP may be used as a safe discharge criterion in Fast Track protocols 4. A prospective study is underway in order to assess the role of routine measurement of CRP followed by additional imaging if levels are too high.

In the early postoperative phase CRP values are elevated following surgical trauma and are nonspecific for complications, and routine measurement is not recommended. On the third or fourth postoperative day routine measurements of CRP may be implemented, with elevated levels identifying patients who need additional assessment. Low CRP levels can be implemented as a safe discharge criterion. Different optimal cut-off levels for CRP as a marker for complications following major complication are proposed.
in literature. Based on a prediction model for complications, which is anticipated soon, the optimal cut-off can be determined at the discretion of the surgeon and the surgical team.

CONCLUSION

C-reactive protein (CRP) is an important inflammatory marker, synthesized in the liver, under stimulation of interleukin 6 (IL-6) and tumour necrosis factor α (TNF-α) in inflammatory processes, which enhances phagocytosis by macrophages. CRP levels rise in response to inflammation and tissue injury and hence, also after surgery. A peak in postoperative CRP levels is observed 48-72 hours after surgery. In uneventful cases, the levels decrease after this peak, in complicated cases they stay increased or even rise. Based on these characteristics, CRP is considered as a valuable marker for the grade of inflammation related to postoperative complications. Further research is necessary to determine the role of routine CRP measurements and additional examinations in a step-up postoperative protocol.
REFERENCES


