Patients who are admitted to the Department of Internal Medicine with a very low C-reactive protein concentration

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Abstract

Introduction: C-reactive protein (CRP) is a marker commonly used in clinical practice as a reference for the inflammatory activity in vivo. Low levels are often associated with good health and lower risk for adverse outcomes.

Patients and methods: We examined medical records of the last 6 years, of all patients admitted for hospitalization in internal medicine wards who had the first CRP measurement below ≤ 0.03 mg/L (detection limit). Diagnosis criteria and 7 days’ survival were reviewed.

Results: Out of 61,590 total admissions to internal medicine wards, three hundred and thirteen patients had CRP equal to or lower than 0.03 mg/L (0.5%). Second CRP measurement revealed gradual increment up to 10.8 ± 35.4 mg/L. Four patients died within 7 days from admission.

Discussion: Presentation to the internal medicine department with a very low concentration of CRP is highly unusual, but it does not exclude the existence of significant acute morbidities. Clinicians should take additional CRP tests before any conclusion is considered regarding the presence or absence of an inflammatory response.

Keywords

very low C-reactive protein, inflammatory disease, C-reactive protein and etiology, C-reactive protein in general population, in-hospital mortality

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Introduction

C-reactive protein (CRP) is a commonly used biomarker for the detection of inflammation and for the assessment of its severity.1-4 As early as the 1970s, it was established as a marker for infections, inflammation, ischemic and traumatic tissue injury, and malignancy.

When presenting with a very low concentration of this biomarker, clinicians might conclude that these individuals do not harbor any significant disease that is generally associated with an inflammatory response.5-8

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In addition, there are no guidelines to suggest the necessity to repeat the test before any firm conclusion is taken regarding an eventual ongoing inflammatory response. Unlike the common practice to repeat troponin in patients with chest pain and an eventual evolution of an acute coronary syndrome and a first very low troponin, we are not aware that this is the routine in patients that are admitted to the hospital with a first very low CRP (vlCRP) test.

We have presently explored a cohort of patients that were admitted to the Department of Internal Medicine in a relatively large tertiary medical center in order to try and characterize this specific population.

To the best of our knowledge, this is the first study that explored this special clinically relevant issue. Inquiring if the existence of vlCRP concentrations does not exclude the presence of serious medical conditions including acute infections and in-hospital death.

**Patients and methods**

**Data extraction from the MDCClone system**

The MDCClone system is a data extraction system designed to ease query of large medical records. Its main feature is manufacturing synthetic data to test hypotheses before turning to original data if necessary. After obtaining approval of institutional “Helsinki” committee, the synthetic date could be declassified and original data obtained for publication.

**Patients group**

We have presently included all patients admitted to one of our nine departments of internal medicine between 1 October 2014 and 30 September 2020 and had a CRP test taken within 48 h of admission. Excluded were patients in whom a different diagnosis was recorded between admission and discharge record due to the possibility that another illness had emerged during the hospitalization period. Patients were categorized into one of the following groups: cardio-respiratory, dermatological, endocrine, hematological, infectious, inflammatory, neurological, oncological, nephrological, and miscellaneous medical conditions. For each patient, we extracted data regarding age, gender, length of hospitalization, diagnosis upon admission and discharge, up to five consecutive CRP concentrations following admission, and whether they were prescribed statins prior to admission or not.

**Control group**

A total of 17,322 persons attending the Tel Aviv Sourasky Medical Center for a routine health examination between September 2002 and December 2020 as part of periodic health check-ups were asked to participate in the Tel-Aviv Medical Center Inflammation Survey. For the purpose of the present study, we included participants with valid tests of wide-range CRP at a similar timeframe (1 October 2014 through 30 September 2020).

All investigations were conducted in accordance with the ethical standards of The Tel Aviv Sourasky Medical Center and the World Medical Association Declaration of Helsinki. The study was approved by the institutional review board of The Tel Aviv Sourasky Medical Center with approval number 2017-0491-TLV (patient group) and 2002-049-TLV (control group).

**Laboratory methods**

Wide-range C-reactive protein (wrCRP) was measured by ADVIA, Siemens Healthcare Diagnostics Inc., Tarrytown, NY 10591-15097 USA The ADVIA® Chemistry wrCRP method measures CRP in serum and plasma by a latex-enhanced immunoturbidimetric assay. The analytical range of wrCRP according to Siemens Inc. is 0.03 mg/L for ADVIA systems. The analytical performance of wrCRP was evaluated according to conventional protocol based on samples and controls to assess accuracy and repeatability of low-concentration CRP beyond the analytical range. The coefficient of variation (%CV) for 0.03 mg/L CRP was 14.63%
Results

During the time period between 1 October 2014 and 30 September 2020, sixty one thousand five hundred and ninety patients were admitted to the nine departments of internal medicine at the Tel Aviv Sourasky Medical Center, in whom up to five consecutive CRP tests could be retrieved. Out of this cohort, three hundred and thirteen patients (0.5%) had a CRP concentration of ≤ 0.03 mg/L. Out of this group of three hundred and thirteen patients, only 223 patients had the same diagnosis upon admission and discharge; we decided to exclude patients who were misdiagnosed or developed another condition while hospitalized (Figure 1).

There were 115 (51.3%) women and 108 (48.7%) men at a mean ± SD age of 50.6 ± 21.1 and 52.7 ± 23.4 years, respectively (Table 1). Out of all patients, 163 (72.8%) had a 2nd CRP measurement, 93 (41.5%) had a 3rd, 42 (18.7%) had a 4th and 19 (8.5%) had a 5th measurement. Results of CRP concentrations of the above-mentioned tests are shown in Figure 2, revealing a gradual increment up to a mean ± SD of 10.8 ± 35.4 mg/L.

Table 1. Patients’ demographics.

| Population characteristics | N = 223 |
|-----------------------------|---------|
| Sex                         | 115 (51.3%) female and 108 (48.7%) male |
| Age                         | Female (50.6 ± 21.1) and male (52.7 ± 23.4) |

Table 2. Etiologies of patients admitted with very low CRP.

| Etiology                                                                 | N =          |
|---------------------------------------------------------------------------|--------------|
| Neurological                                                              | 61 (27.3%)   |
| Cardiological                                                             | 59 (26.2%)   |
| Inflammatory and endocrinological                                         | 21 (9.3%)    |
| Hematological                                                             | 18 (8%)      |
| Infectious                                                                | 14 (6.3%)    |
| Musculoskeletal pain                                                      | 6 (2.6%)     |
| Suicide attempts, medication overdose, and abdominal pain                 | 5 (2.2%)     |
| Inflammatory bowel disease, elective admission, and vomiting             | 4 (1.8%)     |
| Nephrological                                                             | 3 (1.33%)    |
| Involuntary weight loss and anorexia nervosa                              | 2 (0.9%)     |
| Upper GI bleeding and drowning                                            | 1 (0.45%)    |
Presented in Table 2 are the various diagnostic categories included in the present study, the most prevalent ones being neurological, 61 patients (27.3%); cardiovascular, 59 patients (26.2%); inflammatory and endocrinology, each with 21 patients (9.3%); hematological, 18 patients (8%); as well as 14 patients with infectious conditions (6.3%). The other less common diagnostic conditions are reported in the table as well.

Of special interest is the group of 14 patients with infectious conditions, the details of which are reported in Table 3, and included individuals with both viral and bacterial infections.

Furthermore, four patients died within 7 days of admission (Table 4), two of them due to intracranial hemorrhages both spontaneous as well as traumatic injury during an acute alcoholic intoxication. An additional 80-year-old man with colon cancer died due to septic shock.

Table 3. Summary of 14 patients admitted with infectious etiologies and very low CRP.

| Patient ID | Age | Gender | Diagnosis | Duration of illness prior to admission | Symptoms and etiology | Admission duration | CRP 1 | CRP 2 | Chronic illnesses |
|------------|-----|--------|-----------|--------------------------------------|------------------------|------------------|-------|-------|------------------|
| 1          | 87  | F      | Gastroenteritis | Few days | Abdominal pain and diarrhea | 3 days | 0.02 | 0.01 | DMII, HTN, and IHD |
| 2          | 77  | F      | Urosepsis      | 4 to 5 hours | Abdominal pain | 1 day | 0.04 | 0.03 | Alzheimer’s, DMII, HTN, hyperthyroidism, and HTN |
| 3          | 76  | F      | Herpes zoster  | 4 days | Herpetiform rash with fever and dissemination | 2 days | 0.00 | ND | HTN and Hyperlipidemia |
| 4          | 75  | M      | Bronchitis     | Few weeks | Few weeks of productive cough | ≤ 1 day | 0.02 | ND | DMII, IHD, Asbestos exposure, and HTN |
| 5          | 73  | F      | Pneumonia with MSSA bacteremia | 3 days | Shortness of breath and productive cough | 4 days | 0.03 | 0.03 | Asthma, RA, and osteoporosis |
| 6          | 64  | M      | Viral meningitis | Few hours | Fever and headache | 10 days | 0.03 | 0.11 | GCA |
| 7          | 58  | F      | Aseptic meningitis after VZV infection | 6 days | Headache | 8 days | 0.03 | 0.14 | Hyperlipidemia and osteoporosis |
| 8          | 45  | M      | Secondary syphilis | 3 months | Syphilitic rash, Admitted for intravenous treatment | 13 days | 0.03 | 0.02 | HIV, ITP, and Torre–Muir syndrome |
| 9          | 38  | F      | FUO          | 2 months | HIV carrier, 2 months of fever and weight loss | 2 days | 0.01 | ND | HIV and HCV |
| 10         | 73  | F      | Herpes zoster | 2 days | Herpetiform rash 2 days prior to admission | 2 days | 0.02 | 4.48 | HTN and CP |
| 11         | 31  | M      | HIV with low CD4 count without AIDS-defining lesions | 2 months | Positive HIV screening before rehab | 4 days | 0.02 | 0.05 | HIV, HCV, and IVDU |
| 12         | 29  | M      | Cellulitis around PEG | Several days | Erythema around PEG | 6 days | 0.04 | 0.02 | Cerebral palsy, PEG, and S/P TB |
| 13         | 27  | M      | Latent TB     | Asymptomatic | CXR showed latent TB infection | 1 day | 0.01 | ND | None |
| 14         | 55  | F      | CDI diarrhea  | 3 weeks | CDI | 8 days | 0.02 | 0.04 | Schizophrenia thalassemia minor, and hyperlipidemia |

DM: diabetes mellitus; PUD: peptic ulcer disease; IHD: ischemic heart disease; HTN: hypertension; RA: rheumatic arthritis; CP: cerebral palsy; PEG: parenteral gastrostomy; ADEM: acute disseminated encephalomyelitis; TB: tuberculosis; WPW: Wolff–Parkinson–White; CDI: clostridium difficile infection; IBD: inflammatory bowel disease; IVDU: intra venous drug use; FUO: fever of unknown origin; GCA: giant-cell arteritis.
An additional patient with drug overuse succumbed to bilateral pneumonia. In both patients, an elevation in CRP concentration could be noted in following tests.

We have presently determined the prevalence of vlCRP in the apparently healthy control group. Out of a total of 4153 participants in the Tel-Aviv Medical Center Inflammation Survey, 45 (1.08%) had a wrCRP concentration of \( \leq 0.03 \text{ mg/L} \).

Finally, we present the results of wrCRP concentrations of various age groups in our control group of 4153 individuals, showing that a presentation to the hospital with a wrCRP concentration of \( \leq 0.03 \text{ mg/L} \) is unexpectedly low (Figure 3).

### Discussion

To the best of our knowledge, this is the first study that explored a unique clinical situation in which patients are admitted to the Department of Internal Medicine with a very low concentration of CRP. Although at first glance, the physician might conclude that these individuals do not harbor a significant inflammatory response, our study does show that this is not necessarily the case. In fact, it can be seen that at least some of these individuals had serious medical conditions, which in certain patients, even ended in death within a short period.

It is well established that most apparently healthy individuals harbor a sub-clinical low-grade inflammation. This low-grade occult inflammatory response increases with age and is associated with increased morbidity and mortality.\(^{21-26}\) However, individuals who present very low concentrations of this biomarker are generally very healthy.\(^{27}\) Therefore, it is highly unusual to detect very low concentrations of this protein in individuals who are hospitalized with serious medical conditions.

The reason that patients present to the hospital with very low concentrations of CRP is not entirely clear. One possibility can be that these individuals have a baseline vlCRP that, due to a short time from the initiation of the inflammatory stimulus, did not increase. An additional possibility is the presence of immune paresis that resulted in very low concentrations of this particular protein.\(^{28}\) In any case, our study clearly shows that if repeated several times, the

### Table 4. Summary of all cases with 7-day mortality after admission with extremely low CRP.

| Demographic | Chronic conditions | Chronic prescription medication | Diagnosis | Scenario summary | Length of hospitalization | Highest CRP |
|-------------|--------------------|---------------------------------|-----------|------------------|--------------------------|-------------|
| 79-year-old male | DMII, IHD, CVA, CRF, and HTN. | Allopurinol, clopidogrel, metformin, famotidine, acetylsalicylic acid, folic acid, atenolol, and simvastatin | Intracranial hemorrhage | Spontaneous intracranial hemorrhage | 1 day | 0.0 |
| 27-year-old male | – | – | Intracranial hemorrhage | Multiple contusions. Fractures of the base of the skull, ileum, and pneumothorax | 3 days | 0.0 |
| 31-year-old male | Crohn’s disease, alcoholism, and drug abuse | – | Aspiration pneumonia | Bilateral aspiration pneumonia | 6 days | 199 |
| 80-year-old male | IHD, carcinoma of rectum, and s/p left anterior resection with colostomy | Spironolactone, dutasteride, bisoprolol, escitalopram, furosemide, tamsulosin, clopidogrel, and ramipril | Septic shock | Small-bowel obstruction and Bacteroides fragilis bacteremia | 5 days | 15.0 |

DMII: diabetes mellitus type 2; IHD: ischemic heart disease; CVA: cerebro-vascular accident; CRF: chronic renal failure; HTN: hypertension; AF: atrial fibrillation.

![Figure 3. Control group distribution of C-reactive protein by age groups.](image-url)
concentration of this biomarker does increase suggesting that the presence of vlCRP is not a result of a genetically or biochemical inability to synthesize the protein.

A particular possibility of consumption blood CRP concentrations should be discussed as opposed to the expected age-related CRP concentrations in the general population (Figure 3); the CRP concentrations in our cohort were at least one order lower. We therefore raise the possibility that at the beginning of the insult, most circulation CRP precipitates in the affected organs. It cannot be excluded, therefore, that at the beginning of the event, the concentrations of this protein decrease from normal values and increase later due to the synthesis of additional protein following the release of the relevant cytokines.

It is concluded that presentation to the Department of Internal Medicine with a very low concentration of CRP is highly unusual given that the normal range of CRP in healthy population is tenfold.29 Presentation with vlCRP does not exclude the existence of significant acute morbidities, and clinicians should take additional CRP tests before any conclusion is considered regarding the presence or absence of an inflammatory response.

Conclusions

1. Admission vlCRP does not mean necessarily that the patient cannot synthesize the protein.
2. Early arrival could explain, in part, the presence of very low concentrations of the protein, and follow-up measurements are needed to detect the presence of an inflammatory response.
3. It cannot be excluded that the presence of admission vlCRP is due to consumption of the protein in the site of injury. Therefore, clinicians who admit patients with a vlCRP should not necessarily conclude that their patients harbor no inflammatory response or tissue destruction.
4. Repeated testing, preferably after several hours, should be conducted if suspicion is high for an underlying condition that is overlooked. And laboratory data and values should always be examined in the larger clinical picture.

Limitations

There are several limitations to the present study, the main one being its retrospective design. Another limitation is that part of our patients had no follow-up CRP measurements, so it is not known whether they really had no inflammation. Finally, we have no information regarding the baseline CRP concentrations for each of our patients.

Power analysis for sample size calculation was not done because statistical analysis between group was not relevant.

Declaration of conflicting interests

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Ethics approval

Ethical approval for this study was obtained from the institutional review board of The Tel Aviv Sourasky Medical Center with approval number 2017-0491-TLV (patient group) and 2002-049-TLV (control group).

Informed consent

All investigations were conducted in accordance with the ethical standards of the Tel Aviv Sourasky Medical Center and the World Medical Association Declaration of Helsinki. The study was approved by the institutional review board of the Tel Aviv Sourasky Medical Center with approval number 2017-0491-TLV (patient group) and 2002-049-TLV (control group). Informed consent was not necessary due to the anonymity of the data used and this study being a retrospective medical record analysis.

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