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REVIEW

What Does Minor Elevation of C-Reactive Protein Signify?

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ABSTRACT

Reports of the predictive value of minor elevation of serum C-reactive protein (CRP) levels (between 3 and 10 mg/L) for atherosclerotic events have generated considerable interest, as well as a degree of controversy and confusion. CRP concentrations in this range are found in about one third of the American population. To better understand the mechanisms underlying minor elevation of CRP, we have surveyed its reported associations with a variety of states and conditions. It has become clear that even minimal environmental irritants and inflammatory stimuli elicit a minor CRP response. Minor CRP elevation has been found associated with a number of genetic polymorphisms, with membership in different demographic and socioeconomic groups, with a variety of dietary patterns and with many medical conditions that are not apparently inflammatory. Finally, minor CRP elevation bears negative prognostic implications for many conditions, particularly age-related diseases, and predicts mortality in both diseased and apparently healthy individuals. In sum, minor CRP elevation is associated with a great many diverse conditions, some of which are, or may prove to be, causal. Many of these reported associations imply a mild degree of tissue stress or injury, suggesting the hypothesis that the presence of distressed cells, rather than a resulting inflammatory response, is commonly the stimulus for CRP production.

KEYWORDS: C-reactive protein; Inflammation; Tissue injury; Acute phase response

Population studies have shown that serum levels of the acute phase protein C-reactive protein (CRP) are broadly distributed and highly skewed to the right. Most samples are clustered in the lowest values determined, the remainder being distributed up to 10 mg/L or so in most studies (Figure 1). In about two thirds of Americans, the serum concentration is less than 3 mg/L, higher concentrations being found in the remaining third.[1-4] Strikingly, employment of a more stringent cutoff of 2 mg/L (suggested by some as the threshold of high cardiovascular risk), reveals that more than half of adults fall above this value.[5]

What underlies such minor elevation of CRP in such a high proportion of the population? Although elevation of CRP has generally been taken to denote the presence of inflammation, it is not at all clear that this is an accurate perception.[6] The evidence that minor CRP elevation bears negative prognostic implications for future major cardiovascular events[4,7] further underscores our need to elucidate the mechanisms underlying the CRP response.

To better understand the significance of minor CRP elevation, we have surveyed its reported associations and reports of its prognostic implications. Conditions reported in peer-reviewed journals were included if the author reported a statistical test that showed a significant association. Although many of these observations reflect single, unconfirmed reports, and many are uncorrected for possible confounders, their number, high prevalence and diversity make them worthy of note.[8] Although not all associations indicate causality, this broad overview strongly suggests that there are multiple possible underlying causes of minor CRP elevation, many sharing the underlying characteristic of a degree of tissue injury or stress.

CONDITIONS ASSOCIATED WITH MINOR CRP ELEVATION

Many individuals included in unselected general populations have minimal degrees of tissue injury (and consequent low-grade inflammation) now known to be associated with

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minor CRP elevation. A number of such examples, to be expected in a "normal population," are shown in Table 1. In addition, prevalent minor environmental irritants such as secondhand smoke exposure and air pollution cause tissue injury and minor CRP elevation.[9-15] CRP levels can also be increased by widely employed estrogen-containing preparations.[16-20] Although one might expect comparable CRP elevation in common minimally inflammatory states such as tennis elbow, bursitis, ingrown toenails, or severe sunburn, we are unaware of any systematic studies exploring this possibility.

Both family and twin studies indicate substantial heritability of CRP levels.[21-23] A large number of specific genetic polymorphisms have been reported to be associated with higher basal CRP levels[24] (Table 2). Although four of these polymorphisms are within the CRP gene, none alter the amino acid sequence of the protein. The others are at other loci, several of which are not clearly related to inflammatory processes. Demographic and socioeconomic factors may also explain minor CRP elevation in some individuals (Table 3). CRP levels have been found to increase minimally with age, and to differ in different ethnic groups and between males and females, although the latter finding has been questioned.[2-5]

CLINICAL IMPLICATIONS

- Minor elevation of C-reactive protein levels (3–10 mg/L), found in about a third of Americans, is associated with a variety of dietary patterns and apparently non-inflammatory medical conditions, many of which imply mild degrees of tissue injury.
- Minor C-reactive protein elevation bears many negative prognostic implications and predicts mortality in both diseased and healthy individuals.
- These findings suggest that the presence of distressed cells, rather than inflammation, is commonly the stimulus for C-reactive protein production.

Minor CRP elevation is associated with low socioeconomic status, noteworthy in view of the high prevalence of disease and premature death in such populations.[25] It is of interest that diabetics who do not attend religious services are more likely to have elevated CRP levels than do attenders.[26] Finally, a number of dietary patterns are reported to be associated with minor CRP elevation (Table 4), as is poor physical conditioning. Many of these are known to result in sub-optimal physical status and metabolic stress or are recognized risk factors for disease.

A large number of medical conditions, not apparently inflammatory by traditional criteria, are associated with minor CRP elevation (Tables 5 and 6). Many reflect sub-optimal tissue status. Examples include atrial fibrillation, hypertension, high pulse pressure, albuminuria, exhaustion, hypertriglyceridemia, and obstructive sleep apnea. Many of these conditions are now being regarded as inflammatory merely because they are associated with minor CRP elevation, reflecting a tendency to supplant the traditional criteria by which inflammation has been recognized—accumulation of phagocytic cells or increased capillary permeability for proteins and fluid—by molecular evidence only. For example, expression or activation of inflammation-associated cytokines and transcription factors is often taken as evidence of an inflammatory process. Such conclusions are treacherous, because these molecules are multi-functional, playing many other roles unrelated to inflammation.[27] Similarly, minor CRP elevation does not necessarily indicate inflammation. It is not yet time for us to discard our traditional criteria.

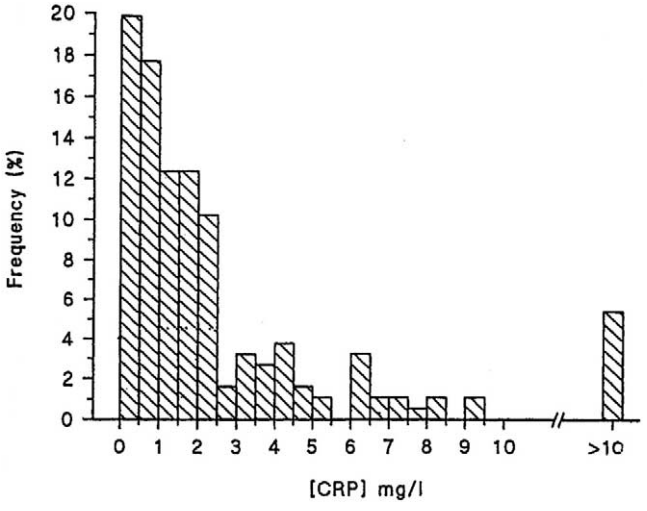

Figure 1 Circulating CRP levels in 186 healthy blood donors assayed using an ELISA. Reprinted with permission from: Whicher JT, Banks RE, Tompson D, Evans SW. The measurement of acute phase proteins as disease markers. In: Mackiewicz A, Kushner I, Baumann H, eds. *Acute Phase Proteins: Molecular Biology, Biochemistry, and Clinical Applications*. Ann Arbor, MI: CRC Press; 1993:633-650.

Table 1 Association of CRP with low-grade inflammatory processes

	Reference
Minor upper respiratory infections	48
Osteoarthritis	49-51
Periodontitis	52-56
Denture-related oral mucosal lesions	57
Superficial thrombophlebitis	58
Moderate chronic obstructive pulmonary disease	59
Ankylosing spondylitis before the development of significant clinical signs	60
Rheumatoid arthritis before onset of symptoms	61
Vestibular neuronitis	62

CRP = C-reactive protein.

Table 2 Association of CRP with genetic factors

	Reference
GT repeat lengths other than GT^{16} or GT^{21} in the CRP intron	63
TT homozygotes at position 1444 in the 3′ UTR of the CRP gene	64
GG homozygotes at position1059 in the CRP coding region (silent mutation)	65, 66
GG homozygotes at position 1846 or 2302 in the 3′ flanking/untranslated region of the CRP gene	66
GG homozygotes at position 252 in the LTA gene	67
TT homozygotes at position 3954 or T alleles at position 4845 in the IL-1β gene	68, 69
C alleles at position −174 or −572 in the IL-6 promoter	70-72
Missense mutation B299G in the toll-like receptor 4 coding region	73
Missense mutations R482Q or R482W in the Lamin A/C coding region	74
Homozygosity for a 7 bp insertion in intron 4 of the HP1 allele of the haptoglobin gene	75
C alleles at position 202 or T alleles at position 314 in the fucosyltransferase 3 coding region	76
AA homozygotes at position −25 in the Cathepsin S (CTSS) gene promoter (SNP at chromosome 1q21 near the CRP gene)	77
TT homozygotes at position 159 in the CD14 gene	78
Hereditability of baseline CRP values	23
Point mutations in the MEFV gene	79
Polymorphisms in glucocorticoid receptor (ER22/23EK noncarriers)	80
Polymorphism in cyclooxygenase 2 gene (−765G allele)	81

UTR = untranslated region; LTA = LT-α gene; MEFV = Mediterranean Fever gene.

The metabolic conditions associated with minor CRP elevation are of particular interest. CRP levels are positively associated with body mass index (BMI). CRP elevation is associated with insulin resistance, and the entire metabolic syndrome,[2,28] and seems to predict development of frank diabetes.[29-31] CRP levels increase continuously across the spectrum of fasting glucose levels, even in the normal range.[32] The possible participation of inflammatory mediators in the pathogenesis of these conditions is of intense current interest.[28,33,34]

A tangled web ensues when attempts are made to adjust for possible confounders, many of which are related to one another. Various authors have adjusted for age, sex, race, BMI, smoking status, use of nonsteroidal anti-inflammatory drugs, and prevalence of morbidity,[35] as well as ethnicity, diabetic status, hormone replacement therapy, systolic blood pressure, level of physical activity, waist circumference, blood pressure, and insulin levels.[36,37] It is possible that CRP is a proxy or a consequence of many of these. Many other adjustments would need to be made to thoroughly account for all reported associations. Stratifying individuals based on these clinically recognizable characteristics would merely be a partial solution, because we cannot readily adjust for the genetic factors associated with minor CRP elevation.

Table 3 Association of CRP with demographic and socioeconomic factors

	Reference
Increasing age	1, 2, 82, 83
Female sex	1, 17, 83, 84
Ethnicities	1, 77, 83, 85-88
Fewer years of school	89
Low socioeconomic status	90-92
Low birth weight	93

CRP ELEVATION BEARS GLOBALLY POOR PROGNOSTIC IMPLICATIONS

The ability of CRP to predict undesirable outcomes is not limited to cardiovascular events. In healthy populations, minor CRP elevation has now been reported to predict development of a number of other diseases (Table 7). In addition, minor CRP elevations predict undesired outcomes or complications in various medical conditions (Tables 8 and 9). Strikingly, minor elevation of CRP predicts a greater likelihood of dying in individuals with different diseases (Table 10). People with worse disease (attested by higher CRP levels) can be expected to have a poorer prognosis, of

Table 4 Association of CRP with dietary and behavioral factors

	Reference
Dietary glycemic load	94, 95
High protein diet	96
Low arginine intake	97
Low fiber consumption	98, 99
High saturated fat consumption	98
Diet enriched in trans fatty acids	100, 101
Low fruit and vegetable intake	102
Western dietary pattern	103
Moderate to high coffee consumption	104
Notably high or low alcohol intake	105-108
Poor physical fitness and/or low levels of physical activity	109-119
Living at high altitude	120

Table 5 Association of CRP with medical conditions (cardiovascular)

	Reference
Abdominal aortic aneurysm	121
Abnormal T axis on ECG	122
Acute left heart decompensation	123
Aortic arch atheromatosis	124
Aortic stenosis	125
Arterial stiffening	126
Atrial fibrillation	127, 128
Carotid intimal thickness and stenosis	129-133
Congestive heart failure	134
Degenerative aortic stenosis	125
Heart rate at rest and Q-T interval	135
High pulse pressure	136
Hypertension	137-140
Left ventricular hypertrophy	141
Offspring of people with myocardial infarction	142
Peripheral arterial disease	143
Prehypertension	89
Reduced heart rate variability	144
Rheumatic valve disease	145
Silent brain infarcts	146
Stress hyperglycemia during myocardial infarction	147

ECG = electrocardiograph.

course. More striking, however, are the observations that all-cause, as well as cardiovascular, mortality in apparently healthy elderly or middle-aged people is predicted by minor CRP elevation (Table 10).

One possible explanation for the globally poor prognostic implications of minor CRP elevation is that it is a surrogate, merely serving as an indicator of a wide variety of conditions that themselves represent risk factors.[38,39] For example, many risk factors for cardiovascular disease are associated with raised serum concentrations of CRP, including cigarette smoking, obesity, insulin resistance, diabetes, hypertension, poor physical conditioning, hypertriglyceridemia, depression, and being the offspring of patients with myocardial infarction. Recent evidence indicates that CRP determination adds little to the predictive value of traditional risk factors.[7]

CRP ELEVATION MAY REFLECT DISTRESSED OR INJURED CELLS RATHER THAN AN INFLAMMATORY RESPONSE

The classical definition of inflammation has been "the response to tissue injury."[27] Injury, resulting in distressed cells, is the trigger, and inflammation the consequence. The tissue injury that occurs when cells have been stressed by an insult of some kind often results in metabolic impairment and local expression of cytokines. Tissue injury does not necessarily imply cell death. There is a spectrum of responses to insult, ranging from sub-inflammatory, non-necrotic changes in response to mild stresses to full blown overt inflammation in response to major injury.

This spectrum is illustrated by an experiment of nature in 3 related conditions: active variant angina, unstable angina, and myocardial infarction. Active variant angina, in which severe myocardial ischemia is caused by occlusive coronary artery spasm, is an example of minor, non-necrotic tissue injury. CRP induction is not seen in this condition, although its experimental model, ischemia and reperfusion of the myocardium, results in release of oxygen-derived free radicals, neutrophil adherence, and production of cytokines.[40] More substantial tissue injury results from the more substantial insult seen in unstable angina, which often results in modest CRP elevation. Finally, frank infarction, with necrosis of cells (and a histologically evident marked inflam-

Table 6 Association of CRP with medical conditions (noncardiovascular)

	Reference
Age-related macular degeneration	148
Antibodies to *H. Pylori*	149
Previous uveitis	150
Albuminuria and microalbuminuria	151-155
Chronic fatigue	156
Exhaustion index	157
Dementias	158, 159
Depression	157, 160-166
Down's syndrome	167
Glucose levels (fasting)	32
Impaired cognition	168
Insulin levels (fasting)	169, 170
Insulin resistance	86, 171-177
Osteopenia and osteoporosis	178
Metabolic syndrome	86, 179, 180
Insulin-induced hypoglycemia	181
Diabetes mellitus	182-184
Diabetic ketoacidosis	185
Previous gestational diabetes	186
Diminished glomerular filtration	187
Obesity	171, 173, 177, 182, 188-191
Total abdominal adiposity	192
Large long-term weight fluctuations	193
Familial hypoalphalipoproteinemia	194
Healthy FMF carriers	195
Hypertrigliceridemia	196
Low free thyroxin levels	197, 198
Obstructive sleep apnea	199, 200
Penile vascular disease in men with erectile dysfunction	201
Polycystic ovary syndrome	202
Early pregnancy	203
Preterm delivery	204
Resting heart rate and heart-rate corrected QT interval	135
Restrictive lung disease	59
Lumbar disc herniation	205
Low hand grip strength	206

FMF = Familial Mediterranean Fever.

Table 7 Association of CRP with likelihood of developing diseases in healthy populations

	Reference
Atrial fibrillation	207
Cataracts in men	208
Colon cancer	209
Congestive heart failure in the elderly	210
Decreased likelihood of successful aging	211
Dementia and cognitive decline	158, 212, 213
Diabetes mellitus	29, 31, 214
Hypertension	215
Impaired cognition in elderly	216
Ischemic stroke in elderly	217, 218
Metabolic syndrome	219
Preeclampsia	220
Rheumatoid arthritis	61, 221
Sudden cardiac death in men	222
Type 2 diabetes	29, 223-225

matory response) invariably results in a major CRP response.[41]

Although it has generally been assumed that a CRP response indicates an underlying inflammatory process, it is equally likely that it reflects distressed or injured cells. In this scenario, minor CRP elevation identifies individuals who bear an increased burden of stressed, injured tissue resulting from a broad variety of causes, even when no overt inflammatory response is clinically apparent. Such incipient tissue injury bears the seeds of future development of overt disease and of a variety of poor outcomes. This explanation would account for many of the apparently noninflammatory conditions and poor prognostic implications associated with a minor CRP response.

Table 8 Association of CRP with development of complications or worse outcomes (cardiovascular)

	Reference
Carotid plaques in individuals with risk factors for cardiovascular disease	226
Cerebrovascular complications in patients undergoing CABG	227
Future clinical events in patients with troponin T-negative chest pain	228
Heart failure after acute myocardial infarction	229
Heart failure following myocardial infarction	230
Less procedural success following percutaneous balloon mitral valve commissurotomy	231
New vascular events following first TIA or ischemic stroke	232, 233
Nonfatal myocardial infarction and restenosis in patients undergoing coronary angioplasty	234-236
Readmission to hospital in patients with congestive heart failure	134
Repeat angina after percutaneous coronary intervention	237
Dense spontaneous echo contrast in subjects with atrial fibrillation	238

CABG = coronary artery bypass graft; TIA = transient ischemic attack.

Table 9 Association of CRP with development of complications or worse outcomes (noncardiovascular)

	Reference
Frailty in the elderly	239
Organ failure in individuals admitted to intensive care units	240
Progression to diabetes in individuals with impaired glucose tolerance	241
Poor glycemic control in diabetics	242
Deterioration of renal function in renal transplant recipients	243
Diabetic nephropathy in patients with type 1 diabetes mellitus	244
Gestational diabetes in pregnant women	245
Preeclampsia and growth restricted babies in pregnant women	246
Major embolic events in patients with infectious endocarditis	247
Chronic allograft nephropathy in renal transplant patients	248
Poorer recovery after surgery for lumbar disc herniation	205

PRACTICAL CONSIDERATIONS

The acute phase response is a continuum, not an all-or-none response, and daily life is full of minor degrees of tissue injury and commonplace environmental irritants. Consequently, drawing a precise boundary between "normal" and "abnormal" CRP levels is difficult. For practical purposes, however, it seems reasonable to conclude that CRP levels of

Table 10 Association of CRP with likelihood of dying

	Reference
In patients admitted to ICU	240
Following stroke	249
Following acute myocardial infarction	229, 230
In patients with coronary disease or undergoing coronary angioplasty or bypass grafts	227, 234, 250, 251
In patients with malignant lymphoma	252
In patients with multiple myeloma	253, 254
In patients with non-ST elevation acute coronary syndrome.	255
In women with HIV infection	256
In patients with esophageal carcinoma	257, 258
In patients undergoing renal transplant	259
In Japanese with type 2 diabetes mellitus	260
In patients with end stage renal disease on dialysis	261-265
Following surgery for colorectal cancer	266
In elderly or middle aged people	267-269

roughly 3 mg/L or less represent truly "normal," or innocuous, values,[42] and that CRP levels over 10 mg/L reflect clinically significant inflammatory states, "macro-inflammation," as long recognized.[43,44] Although intermediate values may indicate the presence of a broad array of minor inflammatory states, they may also reflect genetic factors, demographic variables, behavioral and dietary patterns, and a continually expanding list of physical conditions (Tables 2-5) which, although not overtly inflammatory, may represent minor degrees of tissue injury.

It has been proposed that CRP screening be employed to identify individuals at risk of coronary disease.[45,46] The argument for prognostic utility of such screening is based largely on empiric estimates of relative risk, statistically valid in large populations. It does not depend on an understanding of underlying mechanisms. Accordingly, the recognition that minor CRP elevation may reflect tissue injury or stress rather than inflammation does not alter its pragmatic utility.

This is not a formal systematic analysis. The associations reported here do not prove causality. As indicated above, many of them reflect unconfirmed reports, uncorrected for possible confounders, raising the possibility that some of these associations may not hold up with time. Nonetheless, their number, high prevalence and diversity suggest that there are many possible underlying causes of minor CRP elevation in a given individual. Existing data tell us little about the absolute risk of a mildly elevated CRP level for cardiovascular events,[47] nor what the likelihood of a false positive result is. CRP screening for risk stratification may be ill advised in view of the wide variety and nonspecificity of apparently unrelated phenomena associated with minor CRP elevation.

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