



BIOCHEMISTRY & PATHOPHYSIOLOGY OF C-REACTIVE PROTEIN [CRP]: A SIGNAL TO LIFE FROM THREAT

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Abstract: C-reactive protein (CRP) was discovered by Tillett and Francis in 1930. The name CRP arose because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the "c" carbohydrate antigen of the capsule of pneumococcus. CRP is a pentameric protein synthesized by the liver, whose level rises in response to inflammation. CRP is an acute-phase reactant protein that is primarily induced by the IL-6 action on the gene responsible for the transcription of CRP during the acute phase of an inflammatory/infectious process. There is some question about whether deregulation of the role of CRP in the clearance of apoptotic cells and cellular debris plays a role in the pathogenesis of systemic lupus erythematosus (SLE), but this has not been definitively demonstrated. It has been demonstrated to have some protective properties in animal studies on lung tissue in alveolitis by reducing neutrophil-mediated damage to the alveoli and protein leakage into the lung. CRP has both proinflammatory and anti-inflammatory properties. It plays a role in the recognition and clearance of foreign pathogens and damaged cells by binding to phosphocholine, phospholipids, histone, chromatin, and fibronectin. It can activate the classic complement pathway and also activate phagocytic cells via Fc receptors to expedite the removal of cellular debris and damaged or apoptotic cells and foreign pathogens. This can become pathologic, however, when it is activated by autoantibodies displaying the phosphocholine arm in auto-immune processes, such as idiopathic thrombocytopenic purpura (ITP). It can also worsen tissue damage in certain cases by activation of the complement system and thus inflammatory cytokines. As compared to the erythrocyte sedimentation rate, which is an indirect test for inflammation, the levels of CRP rise and fall rapidly with the onset and removal of the inflammatory stimulus, respectively. Persistently elevated CRP levels can be seen in chronic inflammatory conditions such as chronic infections or inflammatory arthritides such as rheumatoid arthritis. There are numerous causes of an elevated C-reactive protein. These include acute and chronic conditions, and these can be infectious or non-infectious in etiology. However, markedly elevated levels of CRP are most often associated with an infectious cause (an example of pathogen-associated molecular pattern recognition). Trauma can also cause elevations in CRP (alarming response). More modest elevations tend to be associated with a broader spectrum of etiologies, ranging from sleep disturbances to periodontal disease.

Keywords: Interleukin, Inflammation, Arthritis, Systemic Lupus Erythematosus, Apoptotic cell, Phospholipids, Macrophage, Adipocytes, Polysaccharide

Overview: C-reactive protein (CRP) is an annular (ring-shaped) pentameric protein found in blood plasma, whose circulating concentrations rise in response to inflammation. It is an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate

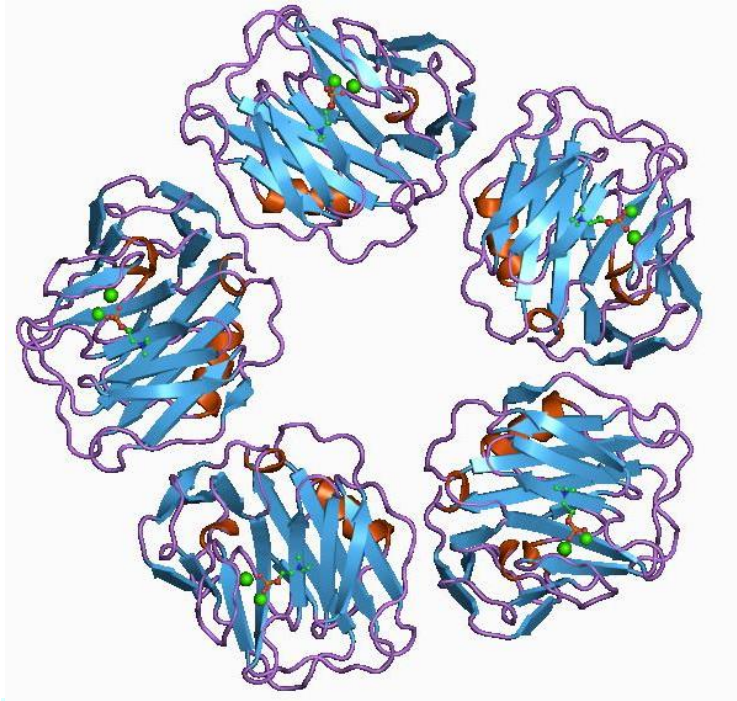


Figure-1: CRP protein

Biochemistry: CRP is synthesized by the liver in response to factors released by macrophages and fat cells (adipocytes). It is a member of the pentraxin family of proteins. Pentraxins (PTX), also known as pentaxins, are an evolutionary conserved family of proteins characterized by containing a pentraxin protein domain. Proteins of the pentraxin family are involved in acute immunological responses. They are a class of pattern recognition receptors (PRRs). They are a superfamily of multifunctional conserved proteins, some of which are components of the humoral arm of innate immunity and behave as functional ancestors of antibodies (Abs). They are known as classical acute phase proteins (APP), known for over a century. It is not related to C-peptide (insulin) or protein C (blood coagulation). C-reactive protein was the first pattern recognition receptor (PRR) to be identified.

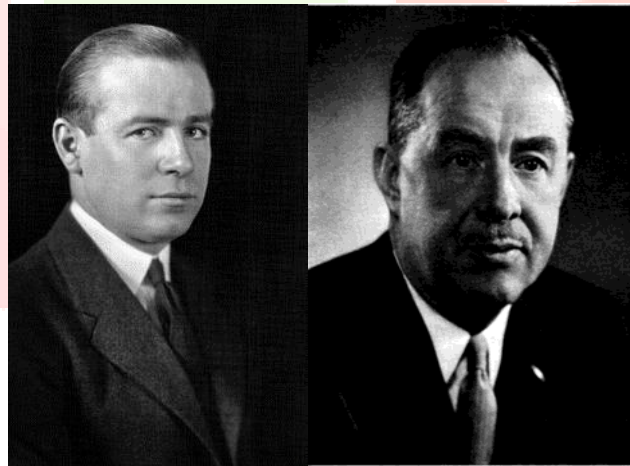
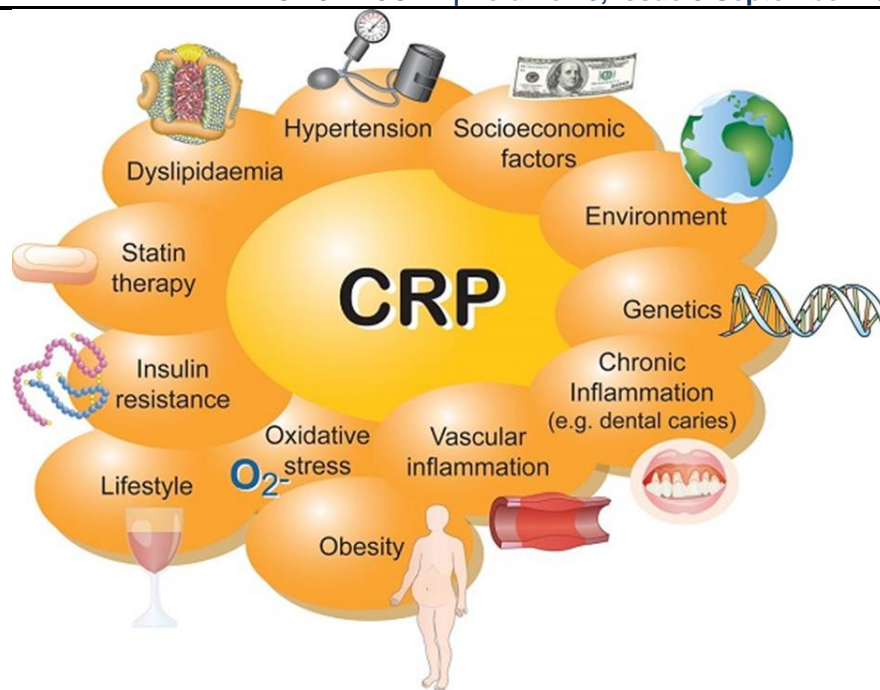


Figure-2: William Smith Tillett & Kary Banks Francis

Discovered by Tillett and Francis in 1930, it was initially thought that CRP might be a pathogenic secretion since it was elevated in a variety of illnesses, including cancer. The later discovery of hepatic synthesis (made in the liver) demonstrated that it is a native protein. Initially, CRP was measured using the quelling reaction which gave a positive or a negative result. More precise methods nowadays use dynamic light scattering after reaction with CRP-specific antibodies. William Smith Tillett (July 10, 1892 in Charlotte, North Carolina – April 4, 1974) was an American internist and microbiologist. He is best known for the discovery of C-reactive protein and the streptokinase. He was also a professor of medicine at the New York University School of Medicine. Kary Banks Francis (December 28, 1917 – August 7, 1990) was an American biochemist. In recognition of his role in the invention of the polymerase chain reaction (PCR) technique and discovery of CRP. CRP was so named because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the cell wall polysaccharide (C-polysaccharide) of pneumococcus.^[2]



C-Reactive protein (CRP) test

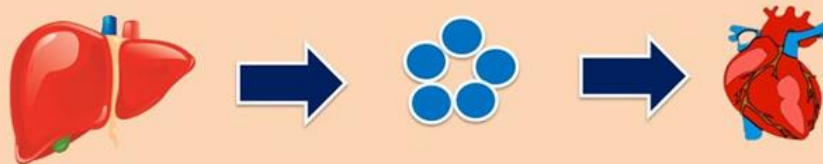


Figure-3: CRP testing

Genetics and structure: The CRP gene is located on chromosome 1 (1q23.). It is a member of the small pentraxins family. The monomer has 224 amino acids and molecular mass of 25,106 Da. The complete protein, composed of five monomers, has a total mass of approximately 120,000 Da. In serum, it assembles into stable pentameric structure with a discoid shape.

Function: CRP binds to the phosphocholine expressed on the surface of bacterial cells such as pneumococcus bacteria. This activates the complement system, promoting phagocytosis by macrophages, which clears necrotic and apoptotic cells and bacteria. This so-called acute phase response occurs as a result of increasing concentrations of IL-6, which is produced by macrophages as well as adipocytes in response to a wide range of acute and chronic inflammatory conditions such as bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury and necrosis. These conditions cause release of interleukin-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver. CRP binds to phosphocholine on micro-organisms. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages (opsonin-mediated phagocytosis), which express a receptor for CRP. It plays a role in innate immunity as an early defense system against infections.

Serum levels:

Measurement methods: Traditional CRP measurement only detected CRP in the range of 10 to 1,000 mg/L, whereas high sensitivity CRP (hs-CRP) detects CRP in the range of 0.5 to 10 mg/L. hs-CRP can detect cardiovascular disease risk when in excess of 3 mg/L, whereas below 1 mg/L would be low risk. Traditional CRP measurement is faster and

less costly than hs-CRP, and can be adequate for some applications, such as monitoring hemodialysis patients.

Normal: In healthy adults, the normal concentrations of CRP varies between 0.8 mg/L and 3.0 mg/L. However, some healthy adults show elevated CRP at 10 mg/L. CRP concentrations also increase with age, possibly due to subclinical conditions. There is also no seasonal variations of CRP concentrations. Gene polymorphism of interleukin-1 family, interleukin 6, and polymorphic GT repeat of the CRP gene do affect the usual CRP concentrations when a person does not have any medical illnesses. The plasma half-life of CRP is 19 hours, and is constant in all medical conditions.^[3]

Acute inflammation: When there is a stimulus, the CRP level can increase 10,000-fold from less than 50 µg/L to more than 500 mg/L. Its concentration can increase to 5 mg/L by 6 hours and peak at 48 hours. Therefore, the only factor that affects the blood CRP concentration is its production rate, which increases with inflammation, infection, trauma, necrosis, malignancy, and allergic reactions. Other inflammatory mediators that can increase CRP are TGF beta 1, and tumor necrosis factor alpha. In acute inflammation, CRP can increase as much as 50 to 100 mg/L within 4 to 6 hours in mild to moderate inflammation or an insult such as skin infection, cystitis, or bronchitis. It can double every 8 hours and reaches its peak at 36 to 50 hours following injury or inflammation. CRP between 100 and 500 mg/L is considered highly predictive of inflammation due to bacterial infection. Once inflammation subsides, CRP level falls quickly because of its relatively short half-life.

Chronic inflammation: CRP concentrations between 2 and 10 mg/L are considered as metabolic inflammation: metabolic pathways that cause arteriosclerosis and type II diabetes mellitus.

Clinical significance: Diagnostic use: CRP is used mainly as an inflammation marker. Apart from liver failure, there are few known factors that interfere with CRP production. Interferon alpha inhibits CRP production from liver cells which may explain the relatively low levels of CRP found during viral infections compared to bacterial infections. Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments. ELISA, immunoturbidimetry, nephelometry, radial immunodiffusion. Normal levels increase with aging. Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns (>200 mg/L). CRP cut-off levels indicating bacterial from non-bacterial illness can vary due to co-morbidities such as malaria, HIV and malnutrition and the stage of disease presentation. CRP is a more sensitive and accurate reflection of the acute phase response than the ESR (erythrocyte sedimentation rate). ESR may be normal while CRP is elevated. CRP returns to normal more quickly than ESR in response to therapy.

Cardiovascular disease: Recent research suggests that patients with elevated basal levels of CRP are at an increased risk of diabetes, hypertension and cardiovascular disease. A study of over 700 nurses showed that those in the highest quartile of trans fat consumption had blood levels of CRP that were 73% higher than those in the lowest quartile. Although one group of researchers indicated that CRP may be only a moderate risk factor for cardiovascular disease, this study (known as the Reykjavik Study) was found to have some problems for this type of analysis related to the characteristics of the population studied, and there was an extremely long follow-up time, which may have attenuated the association between CRP and future outcomes. Others have shown that CRP can exacerbate ischemic necrosis in a complement-dependent fashion and that CRP inhibition can be a safe and effective therapy for myocardial and cerebral infarcts; so far, this has been demonstrated in animal models only. It has been hypothesized that patients with high CRP levels might benefit from use of statins. This is based on the JUPITER trial that found that elevated CRP levels without hyperlipidemia benefited. Statins were selected because they have been proven to reduce levels of CRP. Studies comparing effect of various statins in hs-CRP revealed similar effects of different statins. A subsequent trial however failed to find that CRP was useful for determining statin benefit. In a meta-analysis of 20 studies involving 1,466 patients with coronary artery disease, CRP levels were found to be reduced after exercise interventions. Among those studies, higher CRP concentrations or poorer lipid profiles before beginning exercise were associated with greater reductions in CRP. To clarify whether CRP is a bystander or active participant in atherogenesis, a 2008 study compared people with various genetic CRP variants. Those with a high CRP due to genetic variation had no increased risk of cardiovascular disease compared to those with a normal or low CRP. A study published in 2011 shows that CRP is associated with lipid responses to low-fat and high-polyunsaturated fat diets.^[4]

Parameters	CRP	ESR
Normal level	<1.0 mg/L	Men = 0 to 5 women = 5 to 15 mm/Hour
Sensitivity of the test	More sensitive	Less sensitive
Pathophysiology (Etiology)	Dead and dying tissue release chemical factors, which stimulate the liver to produce CRP (IL1 and IL6)	Fibrinogen level goes up in the serum, which causes RBCs to clump
Rise of the test	Earlier increase	Late increase
Influence of other physiological factors	Not affect	Affected
Relation to antibody titer	Increase before antibodies	No relation to antibody
In acute inflammation	Early increase	Late increase
In recovery stage	Becomes normal early	Becomes normal late
AMI	Best indicator	No relation
Anginal attack	Normal	No relation
After the surgery	Good relation with recovery	No relation
Bacterial meningitis	The normal level excludes meningitis	No relation

Table-1: Comparison between CRP & ER

Coronary heart disease risk: Arterial damage results from white blood cell invasion and inflammation within the wall. CRP is a general marker for inflammation and infection, so it can be used as a very rough proxy for heart disease risk. Since many things can cause elevated CRP, this is not a very specific prognostic indicator. Nevertheless, a level above 2.4 mg/L has been associated with a doubled risk of a coronary event compared to levels below 1 mg/L; however, the study group in this case consisted of patients who had been diagnosed with unstable angina pectoris; whether elevated CRP has any predictive value of acute coronary events in the general population of all age ranges remains unclear. Currently, C-reactive protein is not recommended as a cardiovascular disease screening test for average-risk adults without symptoms. The American Heart Association and U.S. Centers for Disease Control and Prevention have defined risk groups as follows:

- Low Risk: less than 1.0 mg/L
- Average risk: 1.0 to 3.0 mg/L
- High risk: above 3.0 mg/L

But hs-CRP [high sensitivity-CRP] is not to be used alone and should be combined with elevated levels of cholesterol, LDL-C, triglycerides, and glucose level. Smoking, hypertension and diabetes also increase the risk level of cardiovascular disease.

Fibrosis and inflammation: Scleroderma, polymyositis, and dermatomyositis elicit little or no CRP response. CRP levels also tend not to be elevated in SLE unless serositis or synovitis is present. Elevations of CRP in the absence of clinically significant inflammation can occur in kidney failure. CRP level is an independent risk factor for atherosclerotic disease. Patients with high CRP concentrations are more likely to develop stroke, myocardial infarction, and severe peripheral vascular disease. Elevated level of CRP can also be observed in inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis. High levels of CRP has been associated to point mutation Cys130Arg in the APOE gene, coding for apolipoprotein E, establishing a link between lipid values and inflammatory markers modulation.

Cancer: The role of inflammation in cancer is not well understood. Some organs of the body show greater risk of cancer when they are chronically inflamed. While there is an association between increased levels of C-reactive protein and risk of developing cancer, there is no association between genetic polymorphisms influencing circulating levels of CRP and cancer risk. In a 2004 prospective cohort study on colon cancer risk associated with CRP levels, people with colon cancer had higher average CRP concentrations than people without colon cancer. It can be noted that the average CRP levels in both groups were well within the range of CRP levels usually found in healthy people. However, these findings may suggest that low inflammation level can be associated with a lower risk of colon cancer, concurring with previous studies that indicate anti-inflammatory drugs could lower colon cancer risk.

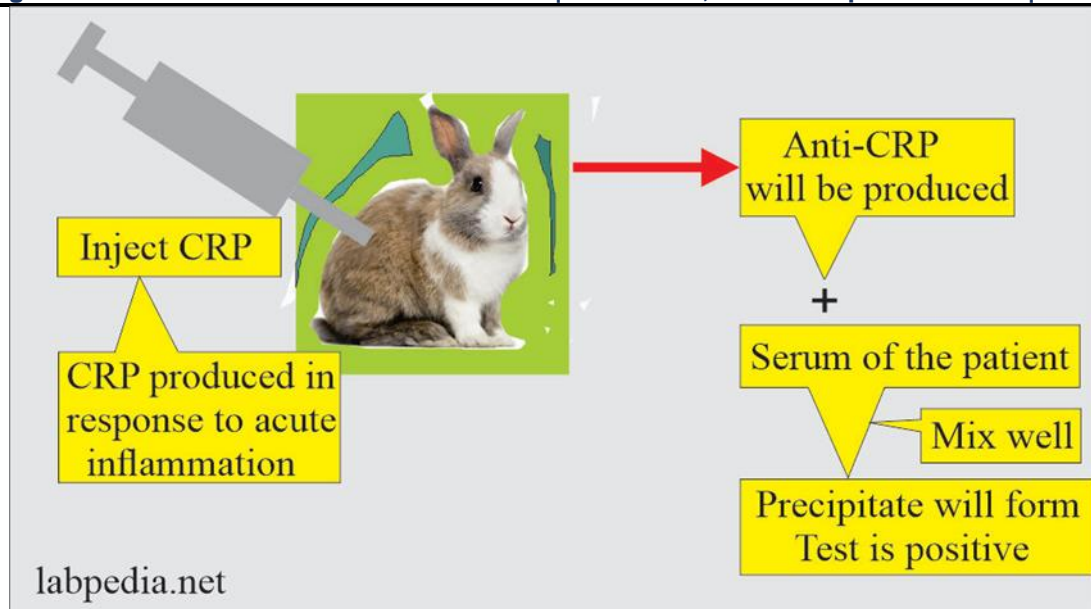


Figure-4: CRP reaction principle

Obstructive sleep apnea: C-reactive protein (CRP), a marker of systemic inflammation, is also increased in obstructive sleep apnea (OSA). CRP and interleukin-6 (IL-6) levels were significantly higher in patients with OSA compared to obese control subjects. Patients with OSA have higher plasma CRP concentrations that increased corresponding to the severity of their apnea-hypopnea index score. Treatment of OSA with CPAP (continuous positive airway pressure) significantly alleviated the effect of OSA on CRP and IL-6 levels.^[5]

C - reactive protein (CRP):

Sample

1. The venous blood of the patient is needed to prepare the serum.
2. A fasting sample is preferred.
3. A random sample can be taken.
4. Analyze the fresh sample.

Storage

1. Or can store at 4 °C for <72 hours.
2. At -20 °C for six months.

Indications for C - reactive protein (CRP)

1. Advised in bacterial infection.
2. It is advised in rheumatic fever.
3. It is advised in rheumatoid arthritis.
4. It may be advised after the surgery.
5. This is done in inflammatory diseases like acute rheumatic fever, rheumatoid arthritis, and bacterial infection.
6. It will help in the diagnosis of coronary artery disease.
7. This test can be done to diagnose bacterial endocarditis.
8. To diagnose appendicitis.
9. To diagnose active collagen vascular diseases.

Precautions for C - reactive protein (CRP)

1. This may be raised in cigarette smoking.
2. Avoid haemolysed and lipemic samples.
3. Raised values are seen in hypertension, diabetes mellitus, metabolic syndrome, gingivitis, and bronchitis.
4. Decreased values have seen weight loss, moderate consumption of alcohol, and exercise.
5. Estrogens and progesterone increase the C - reactive protein (CRP).
6. Niacin, statin, and fibrates decrease the C - reactive protein (CRP).

Keep in mind that:

1. Cigarette smoking may increase the level.
2. Estrogen and progesterone may increase the level.
3. Niacin and statin may decrease the value.
4. There may be an increased level of CRP in hypertension, diabetes mellitus, and metabolic syndrome.

7. Avoid lipemic or haemolysed samples.

Pathophysiology of C - reactive protein (CRP)

Definition of C - reactive protein (CRP):

1. CRP is produced in the liver, and its name is derived from its reaction with streptococcal capsular polysaccharides.
2. CRP level supporting the diagnosis of bacterial endocarditis, appendicitis, and active collagen diseases was $>10 \text{ mg/L}$.^[6]

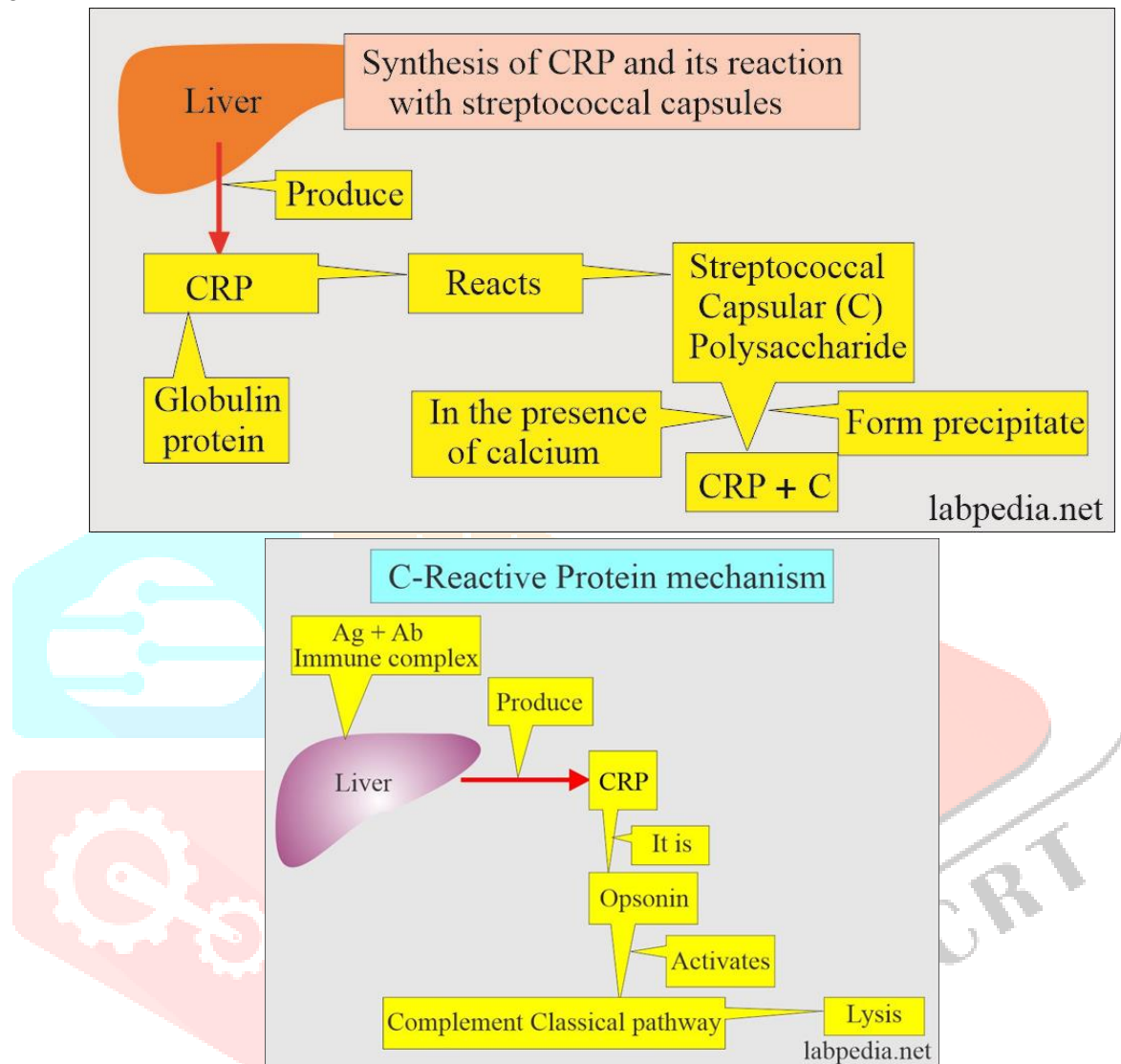


Figure-5: CRP synthesis and its reaction with streptococcal pneumoniae capsule & CRP mechanism injury
CRP synthesis and its reaction with streptococcal pneumonia capsule

3. There are changes in the plasma protein in response to:
 1. Acute illness.
 2. Trauma.
 3. Necrosis.
 4. Infarction.
 5. Burns.
 6. Chemical injury.
 7. Malignant tumors.
4. The acute reaction proteins pattern is also called:
 1. Acute inflammatory response pattern.
 2. Acute stress pattern.
 3. Acute-phase protein pattern.

CRP (C-reactive protein)**1. History of CRP:**

1. In 1930 Tillet and Francis found substance in the sera of acutely ill patients.
2. CRP was given its name in 1941 because it is a protein.
3. This substance binds the C-polysaccharides cell wall of *Streptococcus pneumoniae*.
4. This leads to the agglutination of the bacteria.
5. In 1940, this substance was shown to be a protein called C-reactive protein (CRP).
6. Its detection limit for infection and autoimmune diseases was 3 to 8 mg/L.
1. CRP molecular weight is ~115 kDa.
2. It is synthesized in the liver and has little or no carbohydrates.

2. Mechanism of action:

1. It binds the C-polysaccharide of *Streptococcus pneumoniae* and agglutinates the bacteria.
2. This complex CRP is a potent opsonin for monocytes, leading to phagocytosis and activating the complement system.
3. It activates the classical complement pathway.
4. It binds to polysaccharides present in many bacteria, fungi, protozoal parasites, and histones.
5. Its production is under the control of IL1 and IL-6.

CRP mechanism of injury

3. The C-reactive protein name is derived from its reaction with streptococcal capsular (C) polysaccharides.
1. CRP is the fastest responding acute-phase protein, as it increases 100 folds time with infection.
2. So this is the most sensitive indicator.
3. This increases in many diseases, so this has no specificity.
4. This is a nonspecific acute-phase protein with gamma mobility and is very helpful in monitoring inflammation.
1. C-reactive protein on serum electrophoresis is found in the gamma region.
2. CRP is synthesized in the liver, and its synthesis is initiated by antigen complexes.
3. Its production is controlled by interleukin-6.
3. CRP forms complex on the surface of bacteria (*E.coli*, *S.pneumoniae*), fungi, and other microorganisms.
1. CRP binds to polysaccharides present in many bacteria, fungi, protozoal parasites, and histones.
4. It is found in the Gamma-region band on serum electrophoresis.

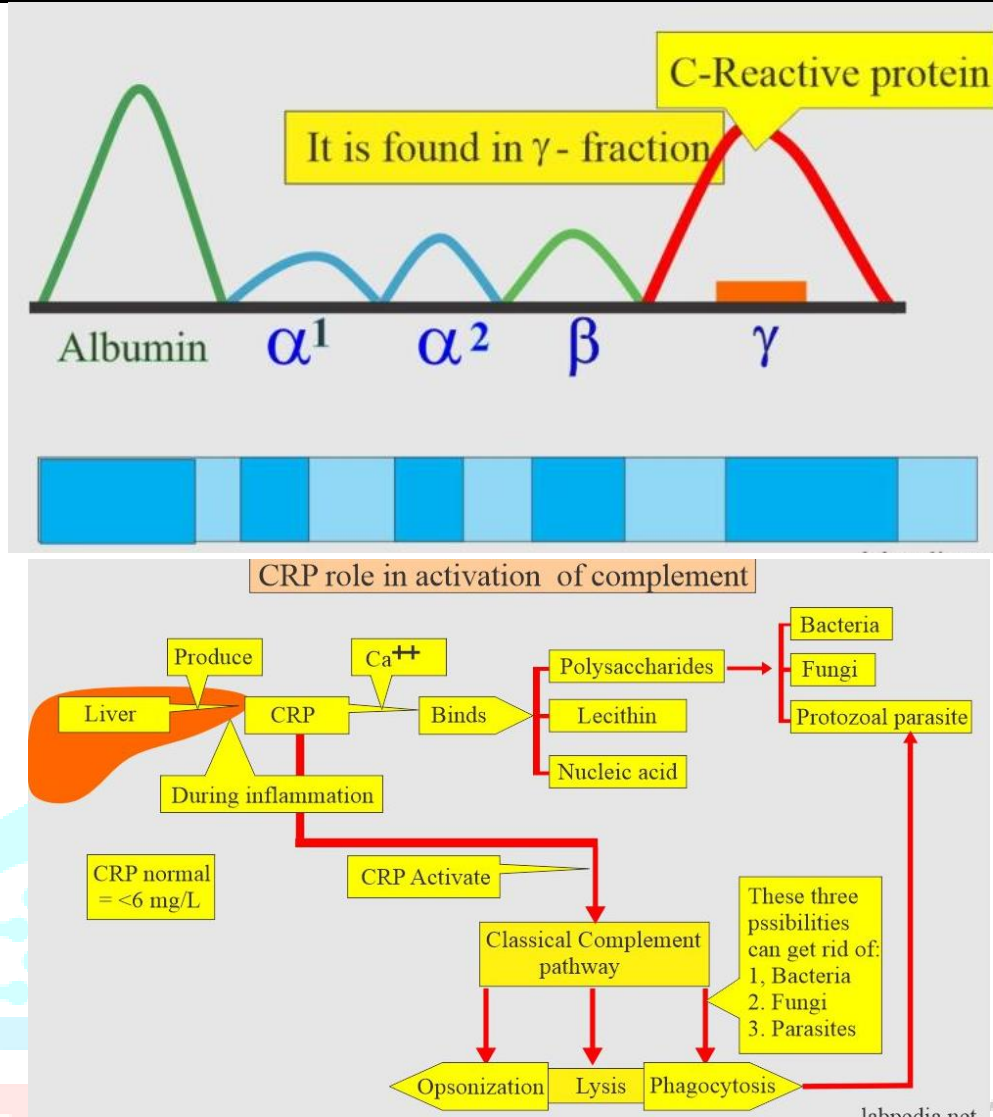


Figure-6: C - reactive protein (CRP): CRP on electrophoresis & CRP role in Complement activation

5. C-Reactive Protein (CRP): CRP on electrophoresis
6. CRP is absent from a healthy person.
7. CRP increased after any injury (trauma, bacterial infection, surgery, neoplasm, and inflammation) to 100 times.
 1. This is a nonspecific acute-phase protein.
 2. CRP starts rising after 4 to 6 hours of the infection, while other proteins rise after 12 to 36 hours of the initiating cause.
 3. CRP is functionally analogous to IgG, except it is not antigen-specific.
 4. This protein is synthesized in the liver and released into blood circulation after tissue injury in a few hours.
 1. The synthesis of the CRP is initiated by:
 2. Antigen immune complexes.
 3. Bacterial infection.
 4. Fungal infection.
 5. Trauma or tissue injury.

High-sensitivity CRP (hs-CRP):

1. hs-CRP is produced in the liver and is an acute phase reactant.
 1. It is induced by the release of interleukin 1 and 6; these interleukins reflect systemic inflammation activation.
 2. It detects the lower level of CRP, which is important to finding the risk of cardiac events.
 3. The sensitivity is 0.01 mg/dL.
 4. In the case of raised hs-CRP, follow-up serial measurements are needed.
 5. hs-CRP is useful for the risk of developing acute myocardial infarction with a history of acute coronary syndrome.

6. Value ≥ 1.0 mg/L indicates subclinical infection/inflammation; the test must be repeated in 3 to 4 weeks.

7. **Coronary risk grades:**

hs-CRP level	Degree of risk for cardiovascular diseases
<1.0 mg/L	Low risk
1.0 to 3.0 mg/L	Average risk
>3.0 mg/L	1. High risk 2. Risk also increases for peripheral vascular disease. 3. Risk increases for stroke

8. It is the first acute phase protein raised in inflammatory diseases, and its level increases tremendously.

1. It is raised in acute and chronic inflammation.

9. This promotes the binding of Complements and helps in phagocytosis.^[7]

CRP role in Complement activation

10. Its formation is initiated by the antigen-antibody immune complex.

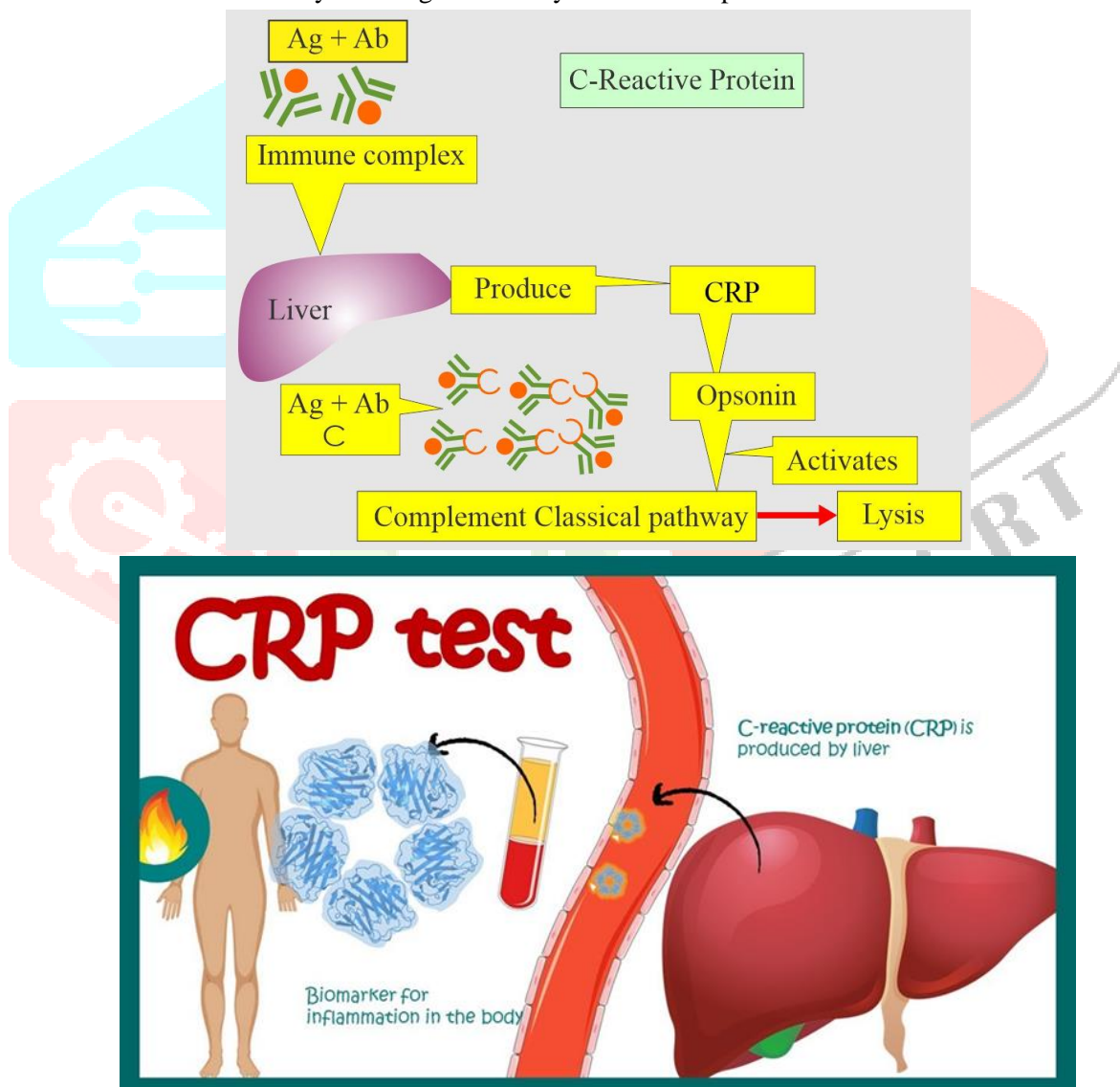


Figure-7: C - reactive protein (CRP): CRP and complement activation

C - reactive protein (CRP): CRP and complement activation

11. This can induce the production of cytokines.

12. This can cause inhibition of chemotaxis and modulation of the WBC function.

13. The normal CRP level is <2 to 3 mg/L.

1. The markedly raised level of >10 mg/L indicates an active inflammatory condition like collagen disease and infection.

2. Its level does not rise consistently in the virus infection.

CRP vs. ESR:

1. More sensitive and rapidly responding than the ESR.
 2. Other physiologic factors influence ESR, but CRP does not.
 3. CRP tends to increase before the increase in ESR and the rise in antibodies titer.
 4. CRP shows an earlier and more rapid increase in the acute inflammatory process than ESR.
 5. In recovery, it becomes normal before the ESR.
 6. It disappears when the disease is treated with cortisone or salicylates.
1. This is useful for assessing the risk of myocardial infarction in patients with acute coronary signs and symptoms.

C - reactive protein role in various diseases:

CRP may be an indicator of various diseases like:

1. Tissue injury or necrosis of the tissues.
2. Various infections.
3. Monitoring course and effect of therapy.

In myocardial infarction (AMI):

1. CRP is raised, and it correlates with CK-MB isoenzyme in AMI.
 2. Its peak level occurs 1 to 3 days later than CK-MB.
 3. hs-CRP values >10 mg/L within 6 to 24 hours after the symptom onset indicates an increased risk for a recurrent cardiac event within 30 days to 1 year.
 4. In unstable angina, hs-CRP values >10 mg/L will predict a higher chance of myocardial infarction/death compared to the group of patients with hs-CRP <10 mg/L.
 5. CRP may remain increased in AMI for at least three months.
 6. If the level persists, being raised indicates ongoing damage to myocardial tissue.
 7. The baseline level is a good marker for future cardiovascular disease.
1. CRP is a strong predictor of cardiovascular diseases than the low-density-lipoprotein (LDL) and cholesterol.
 2. CRP is a good marker for assessing the likelihood of recurrent myocardial infarction, restenosis, or death in patients with stable coronary disease.
 3. Its raised level is also reported as a risk factor for the development of hypertension.
 8. Its level is normal in the case of angina.

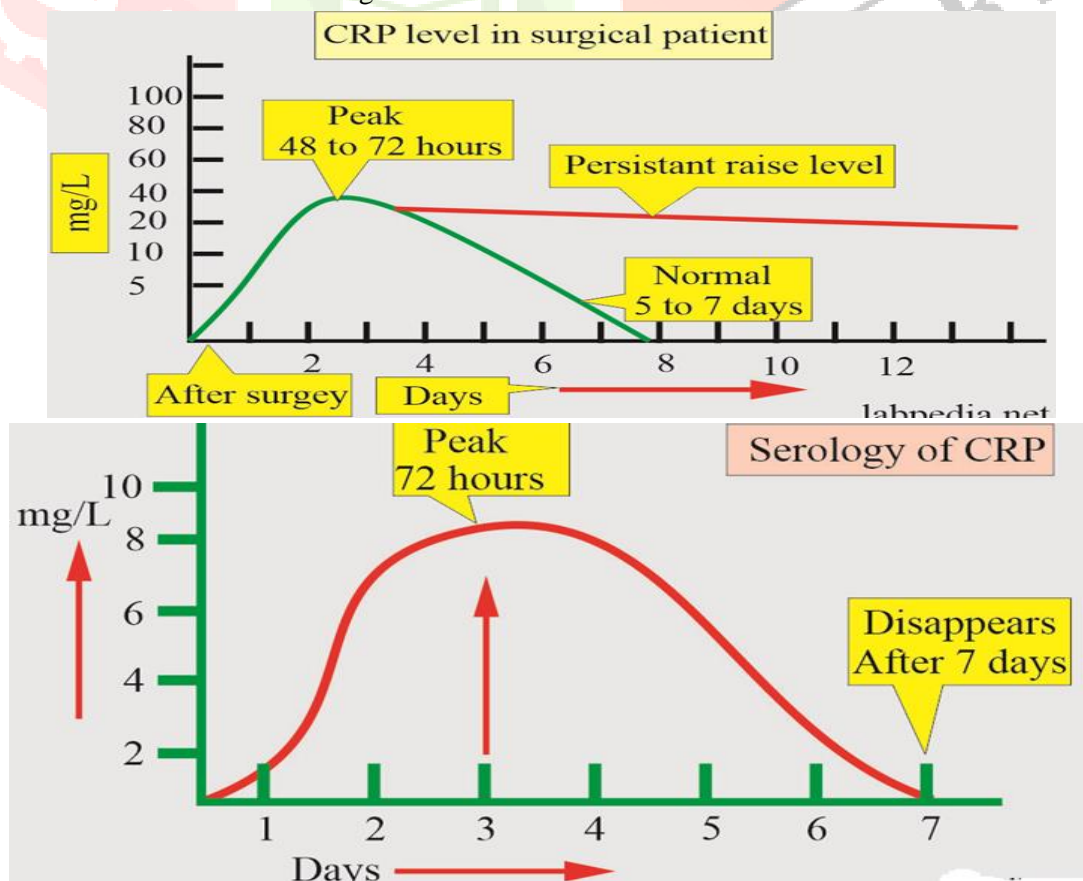


Figure-8: CRP level after surgery & CRP serology diagrammatic presentation

In Pancreatitis:

1. A level of 150 mg/L distinguishes mild from severe acute pancreatitis.

Rejection phenomenon:

1. It helps rejection of kidney or bone marrow transplants but is not helpful in heart transplants.^[8]

Malignant tumors:

1. In 1/3 of the cases, CRP is >10 mg/L in malignant tumors of the breast, lungs, and GI tract.

After surgery:

1. It may be advised **after the surgery** when its level increases in 4 to 6 hours.
2. The peak level reaches 48 to 72 hours.
3. It starts going down after a 3rd postoperative day.
4. It returns to normal in 5 to 7 days.
5. Failure to return to a normal level raised level which indicates a complication of infection or pulmonary infarction.

1. In that cases, advise CBC, ESR, temperature check, and pulse rate.

CRP level after surgery

Meningitis:

1. It helps in the differential diagnosis of bacterial or viral meningitis.
2. In viral meningitis, it will not be raised.
3. The normal value excludes bacterial meningitis.

In burns:

1. The level may exceed 1000 mg/L.

CRP level is useful in:

1. Clinical evaluation of SLE, Leukaemia, Blast crisis, and ulcerative colitis.
2. There is a good correlation with ESR, but CRP appears and disappears earlier than changes in ESR.
3. The level of CRP increases dramatically than other Acute-phase proteins. So CRP is more useful as acute-phase proteins.
4. The quantitative test is more useful than a qualitative test.

Jones criteria for the diagnosis of Rheumatic fever:

Manifestations	Signs and symptoms
Major	Polyarthritis, carditis, subcutaneous nodule, chorea, Erythema marinata
Minor	Fever and arthralgia
Minor	Raised CRP, raised ESR, evidence of group A streptococcal infection, and prolonged PR interval on ECG

Table-2: Rheumatic fever Sign

Serology of CRP:

1. CRP appears 24 to 48 hours after the onset of infection.
2. The peak level reaches 72 hours.
3. It disappears from circulation after seven days.

CRP serology diagrammatic presentation

4. Based on CRP level, there are the following categories:
 1. Normal level = <3 mg/L.
 2. High level CRP = >10 mg/L (active inflammation).
 3. Low level CRP = 3 to 10 mg/L. (Cellular stress).

Normal C - reactive protein (CRP)

- <1.0 mg/dL
- Source 2
 - <1.0 mg/dL or <10.0 mg/L
 - Cardiac disease risk:
 - Low = <1.0 mg/dL
 - Average = 1.0 to 3.0 mg/dL
 - High = >3.0 mg/dL
- Source 4

- CRP = <0.8 mg/dL (<8.0 mg/L) (by nephelometry)
- CRP reportable value = 0.3 to 20 mg/dL
- hs-CRP = 0.020 to 0.800 mg/dL (0.2 to 8.0 mg/L) (by immunoassay)
- Value ≥ 1.0 mg/L represents subclinical infection/inflammation and should be repeated in 3 to 4 weeks.^[9]

The raised level is seen in:

1. Soft tissue Trauma.
2. Infection.
3. Tissue necrosis.
4. Patients with Rheumatoid arthritis.
5. In Rheumatic fever.
6. Patients with systemic *lupus erythematosus*.
7. Patient with pneumonia.
8. Patient with malignancies.
9. In pregnant ladies.
10. Pulmonary tuberculosis.
11. Urinary tract infection.
12. Myocardial infarction.
13. Vasculitis syndrome.
14. Bacterial meningitis.

Decreased CRP level is seen in:

1. This may be seen in the moderate use of alcohol.
2. In weight loss.
3. Strenuous exercise.
4. Medicine like Niacin, and a statin.
5. Pregnancy.
6. Angina.
7. Seizures.
8. Asthma.
9. Common cold.
10. Rejection of heart transplant.
11. Autoimmune diseases like SLE, scleroderma, dermatomyositis, and mixed connective tissue disease.

The panic value of hs-CRP

- >3.5 mg/L
- In acute inflammation = >10.0 mg/L

Rheumatoid arthritis: In the context of RA, CRP is one of the acute phase reactants, whose assessment is defined as part of the joint 2010 ACR/EULAR classification criteria for RA with abnormal levels accounting for a single point within the criteria. Higher levels of CRP are associated with more severe disease and a higher likelihood of radiographic progression. Rheumatoid arthritis associated antibodies together with 14-3-3 η YWHAH have been reported to complement CRP in predicting clinical and radiographic outcomes in patients with recent onset inflammatory polyarthritis. Elevated levels of CRP appear to be associated with common comorbidities including cardiovascular disease, metabolic syndrome, diabetes and interstitial lung (pulmonary) disease. Mechanistically, CRP also appears to influence osteoclast activity leading to bone resorption and also stimulates RANKL expression in peripheral blood monocytes. It has previously been speculated that single-nucleotide polymorphisms in the CRP gene may affect clinical decision-making based on CRP in rheumatoid arthritis, e.g. DAS28 (Disease Activity Score 28 joints). A recent study showed that CRP genotype and haplotype were only marginally associated with serum CRP levels and without any association to the DAS28 score. Thus, that DAS28, which is the core parameter for inflammatory activity in RA, can be used for clinical decision-making without adjustment for CRP gene variants.^[10]

Viral infections: Increased blood CRP levels were higher in people with avian flu H7N9 compared to those with H1N1 (more common) influenza, with a review reporting that severe H1N1 influenza had elevated CRP. In 2020, people infected with COVID-19 in Wuhan, China had elevated CRP.

Conclusion: C-reactive protein (CRP) was discovered by Tillet and Francis in 1930. The name CRP arose because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the "c" carbohydrate antigen of the capsule of pneumococcus. CRP is measured in milligrams per liter (mg/L). Results for a standard CRP test are usually given as follows: Normal: Less than 10 mg/L. High: Equal to or greater than 10 mg/L. High-sensitivity C-reactive protein is produced by the body when blood-vessel walls are inflamed. The higher your levels of hs-CRP, the higher your levels of inflammation tend to be. But before we go any further, it's important to distinguish between acute inflammation and chronic inflammation. Bacterial infections, such as sepsis, a severe and sometimes life-threatening condition. A fungal infection and inflammatory bowel disease, a disorder that causes swelling and bleeding in the intestines. An autoimmune disorder such as lupus or rheumatoid arthritis. Very high levels of CRP, greater than 50 mg/dL, are associated with bacterial infections about 90% of the time. In multiple studies, CRP has been used as a prognostic factor in acute and chronic infections, including hepatitis C, dengue, and malaria. C-reactive protein activates macrophages to secrete tissue factor, a powerful procoagulant, which may lead to disseminated intravascular coagulation and thrombosis during inflammatory states. C-reactive protein increases the uptake of LDL into macrophages and enhances the ability of macrophages to form foam cells. Angiotensin receptor blockers (ARBs) (valsartan, irbesartan, olmesartan, telmisartan) markedly reduce serum levels of CRP. The findings with other ARBs (losartan and candesartan) were inconsistent. Antidiabetic agents (rosiglitazone and pioglitazone) reduce CRP levels, while insulin is ineffective. On the other hand viral infection without bacterial involvement is very improbable if CRP is > 40 mg/l. The results suggest that high CRP values rule out viral infection as a sole etiology of infection; bacterial infection and antibiotic treatment should be considered in these cases. CRP is a protein made by your liver. It's sent into your bloodstream in response to inflammation. Inflammation is your body's way of protecting your tissues if you've been injured or have an infection. It can cause pain, redness, and swelling in the injured or affected area. A high CRP test result is a sign of acute inflammation. It may be due to serious infection, injury or chronic disease. Your doctor will recommend other tests to determine the cause. Results for an hs-CRP test are usually given as follows: Lower risk of heart disease: hs-CRP level less than 2.0 mg/L. A wide variety of inflammatory conditions can cause elevated CRP levels, including: autoimmune conditions, including rheumatoid arthritis (RA), lupus, and certain types of inflammatory bowel disease (IBD), such as Crohn's disease and ulcerative colitis. Pericarditis, which is inflammation of the lining of the heart. The C-reactive protein (CRP) test is used to find inflammation in your body. Inflammation could be caused by different types of conditions, such as an infection or autoimmune disorders like rheumatoid arthritis or inflammatory bowel disease. This test measures the amount of CRP in your blood. Generally, CRP reading greater than 10 mg/L is considered dangerous. Statins are the usual course of treatment for high CRP levels. However, diet and exercise may also lower your levels. Anti-inflammatory foods such as salmon, tuna, and plant-based proteins are useful to lower CRP. In general, the normal CRP level is less than 0.9 milligrams per deciliter (mg/dL). The sensitivity and positive predictive value of CRP level greater than 35 mg/l for diagnosis of pneumonia was 100%. On serial monitoring a fall in CRP concentration also provided the earliest clue to therapeutic response, much before a fall in temperature, respiratory rate or ESR. In a community sample, higher plasma CRP concentration predicted higher fatigue level five years later independently of a series of risk factors such as BMI [Body Mass Index], depressive symptoms, sleep quality, pain, and physical activity. After the bacterial trigger for inflammation is eliminated, CRP levels decrease quickly, with a half-life of about 19 hours. There's no doubt that the very best way to lower CRP is through exercise, weight loss, and dietary control; of course, those are all proven already to lower vascular risk. There is a paper that came out in February comparing the Atkins diet, the Zone diet, the Weight Watchers diet, and the Ornish diet. High CRP levels of more than 350 milligrams per litre (mg/L) are considered dangerous. The dangerous CRP level is a sign of a serious underlying medical condition and means a higher risk of heart attack, cardiovascular diseases, or stroke. For example, ultra-processed foods like fast food, frozen meals, and processed meats have been associated with higher blood levels of inflammatory markers like CRP. Cherries. Cherries and other berries contain substances called antioxidants that help to calm inflammation. When people in one study ate 45 Bing cherries every day for about a month, their levels of CRP fell by 20%. Indeed, serial CRP levels in trauma patients aid in the discrimination of bacterial sepsis from noninfectious systemic inflammatory response syndrome. A cutoff value of 17 mg/dL or more for CRP gives a sensitivity of 74% and a specificity of 75% in predicting the presence of infection. Higher levels of CRP were associated with higher pain sensitivity ratings at pain threshold ($p = 0.02$) and tolerance ($p = 0.03$) after adjusting for age, body mass index, time to reach pain threshold or tolerance, and clinical pain status. This CRP indicates on going infection or inflammation in body, but it is not specific to any disease. Repeating the CRP after 4days shows whether the infection as come down. A high level of CRP in the blood can be a marker of inflammation. A wide variety of conditions can cause it, from an infection to cancer. High CRP levels can also indicate that there's inflammation in the arteries of the heart, which can mean a higher risk of heart attack. CRP—

C-reactive protein. Of the inflammatory conditions (n = 45), most were due to pericarditis (20 cases, CRP range 114.0 to 277.0 mg/L) or inflammatory bowel disease (21 cases, CRP range 100.6 to 203.2 mg/L). A few cases were due to pancreatitis (CRP range 124.0 to 296.0 mg/L). A steady intake of water decreases the concentration of hs-CRP. After the bacterial trigger for inflammation is eliminated, CRP levels decrease quickly, with a half-life of about 19 hours.

Cherries. Cherries and other berries contain substances called antioxidants that help to calm inflammation. When people in one study ate 45 Bing cherries every day for about a month, their levels of CRP fell by 20%. Maintain of CRP is regulated by: Exercise, Weight Loss, Balanced Diet, Alcohol in Moderation, Yoga, Tai Chi, Qigong, and Meditation, Sexual Activity and Optimism. On the other hand viral infection without bacterial involvement is very improbable if CRP is > 40 mg/l. Results suggest that high CRP values rule out viral infection as a sole etiology of infection; bacterial infection and antibiotic treatment should be considered in these cases. A significant relationship was reported between daily milk consumption and reduction in the inflammatory marker of CRP as well as decreased prevalence of metabolic syndrome and cardiovascular diseases. In this study, it has been we found that among healthy, community-dwelling individuals, egg feeding was associated with significant increases in CRP and SAA levels in LIS subjects. In addition, egg feeding was associated with a significant increase in non-HDL cholesterol in the same subjects. CRP levels of 1 mg per liter or lower are considered low risk for cardiovascular disease. CRP levels of 1-3 mg per liter are considered moderate risk for cardiovascular disease. CRP levels greater than 3 mg per liter are considered high risk for cardiovascular disease. Bananas are versatile fruits with anti-inflammatory, antimicrobial, and antioxidant properties that can help counteract inflammation and support the body's immune system. People may benefit from an anti-inflammatory diet and avoiding pro-inflammatory foods. Curcumin is a powerful anti-inflammatory nutrient that helps to reduce inflammation in arthritis, diabetes, and even depression. It significantly reduces CRP – inflammatory marker when you consume turmeric with black paper. Coffee may help reduce inflammation in most people. CRP is elevated in chronic stress and may be the link between stress and low-grade inflammation-related diseases. Scientists found that both psychological and social stress significantly impacts CRP. Here are five research-backed drinks that can help fight inflammation in your body. Baking soda + water. A recent study in the Journal of Immunology found drinking a tonic of baking soda and water may help reduce inflammation, Parsley + ginger green juice, Lemon + turmeric tonic, Bone broth, Functional food smoothie. “Yogurt is associated with decreased inflammation, decreased insulin resistance and it may prevent type 2 diabetes. Eggs are a source of vitamin D, which has anti-inflammatory effects. They're also a good source of protein and B vitamins. This meta-analysis suggests that ginger administration significantly reduced CRP level and improved glycaemia index [Hb1Ac] and lipid profile. Health experts recommend that a diet rich in anti-oxidants as well as staying hydrated with enough water are great ways to reduce inflammation in the body. Water is specifically recommended because it can flush toxins and other irritants out of the body. Higher levels of CRP were associated with higher pain sensitivity ratings at pain threshold (p = 0.02) and tolerance (p = 0.03) after adjusting for age, body mass index, time to reach pain threshold or tolerance, and clinical pain status. It may be hard to resist desserts, pastries, chocolate bars, sodas, even fruit juices. However, the American Journal of Clinical Nutrition warns that processed sugars trigger the release of inflammatory messengers called cytokines. Oat and its compounds have been found to have anti-inflammatory effects. A high level of CRP in the blood can be a marker of inflammation. A wide variety of conditions can cause it, from an infection to cancer. High CRP levels can also indicate that there's inflammation in the arteries of the heart, which can mean a higher risk of heart attack. Berries, Strawberries and blackberries to cranberries and blueberries, these gemlike fruits are particularly potent in antioxidant and anti-inflammatory activity, Apples, Stone fruits, Grapes, Citrus and Pomegranates. For most people, dairy does not cause inflammation, and there is no need to avoid it. Many dairy-containing foods may be eaten as part of a healthy diet. High intake of chicken and pork proteins aggravates high-fat-diet-induced inflammation and disorder of hippocampal glutamatergic system. Eggplants, peppers, tomatoes and potatoes are all members of the nightshade family. These vegetables contain the chemical solanine, which some people claim aggravates arthritis pain and inflammation. Wheat bread made with 100 % whole wheat is not inflammatory for most individuals who do not have a gluten allergy or intolerance. However, white wheat bread is made with refined carbohydrates which are highly inflammatory and harmful to overall health when consumed on a regular basis. Carrots with Beta-carotene is one of the main reasons carrots made this list of anti-inflammatory foods. A powerful antioxidant, beta-carotene is converted to vitamin A in the body. This vitamin is essential for your health. Eat plenty of fruits, vegetables, nuts. Eat these in moderation: fish (no farmed fish), poultry (chicken, turkey, etc.), eggs, lean red meat (preferably grass fed beef, lamb or bison), and dairy. Generally, a CRP reading greater than 10 mg/L is considered dangerous. It is likely caused by a severe bacterial infection and indicates acute inflammation that requires further tests to determine the cause of the inflammation. A high level of hs-CRP in the blood has been linked to an increased risk of heart attacks. Also, people with a high level of hs-CRP who have had a heart attack are more likely to have another one

compared with those with a normal hs-CRP level. An hs-CRP test isn't recommended for everyone.

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