TPM Vol. 30, No. 1s, 2023
ISSN: 1972-6325
https://www.tpmap.org/



# ASSOCIATION BETWEEN C-REACTIVE PROTEIN AND THYROID FUNCTION: INFLAMMATORY AND CLINICAL PERSPECTIVES

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**ABSTRACT**

Background: C-reactive protein (CRP), particularly high-sensitivity CRP (hs-CRP), is a common blood test used as an indicator of inflammation and cardiovascular risk. Immune activation, changes in lipid metabolism, endothelial dysfunction and cardiovascular morbidity are also related to thyroid dysfunction (Ridker, 2016; Biondi & Cooper, 2008; Chaker et al., 2017). Objective: This paper reviews the scientific literature regarding the association of CRP with thyroid function tests, specifically hypothyroidism, subclinical hypothyroidism, autoimmune thyroid disease, Graves disease and subacute thyroiditis.

**Methods:** Peer-reviewed literature up to 2023 was tabulated and analyzed by a structured narrative synthesis. The synthesis was mainly based on the studies reporting the level of CRP or hs-CRP in relation to the level of thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), thyroid antibodies, thyroiditis, and response to therapy. Findings: Most studies indicate that overt and subclinical hypothyroidism is accompanied by low-grade inflammation and by elevated levels of hs-CRP, but the association becomes weaker after adjustment for BMI, IR, dyslipidemia and cardiovascular risk factors (Tuzcu et al., 2005; Nagasaki et al., 2007; de Miranda et al., 2016). Marked inflammatory responses such as a high CRP and ESR are seen in all patients with subacute thyroiditis, while in autoimmune thyroid disease, the CRP findings are more variable (Pearce et al., 2003; Tang et al., 2021). Conclusion: CRP is not a thyroid specific marker, but when supplemented with thyroid function tests and clinical data, it can give clinically useful information regarding inflammatory burden and cardiometabolic risk.

The methodology of this paper is a narrative scientific review using published peer-reviewed studies that examined the association of C-reactive protein (CRP) with thyroid function tests such as thyroid-stimulating hormone (TSH), free thyroxine (FT4), and triiodothyronine (T3). Relevant articles were retrieved by searching electronic databases such as PubMed, Scopus, and Web of Science with combinations of the keywords for CRP, inflammation, hypothyroidism, hyperthyroidism, thyroiditis, and autoimmune thyroid diseases up to 2023. Studies on inflammatory markers and thyroid dysfunction in adult population were included. Data were analysed qualitatively and findings were synthesized for assessing the clinical and biological relationship between systemic inflammation and thyroidal disorders.

**Conclusions:** Several observational and clinical studies showed that thyroid dysfunction is associated with systemic inflammatory activation. Thyroid-related inflammatory conditions like subacute thyroiditis had significantly higher CRP levels, and elevated CRP levels were seen in patients suffering from hypothyroidism, especially subclinical hypothyroidism. A number of studies also established a linkage between abnormal TSH, metabolic dysfunction, oxidative stress and inflammatory markers. Chronic immune activation and low-grade inflammation were always associated with autoimmune thyroid diseases.

**Keywords:** The key words are C-reactive protein, high-sensitivity CRP, thyroid function, TSH, hypothyroidism, subclinical hypothyroidism, Hashimoto thyroiditis, Graves disease and subacute thyroiditis; cardiovascular risk: key words are cardiovascular.

## INTRODUCTION

Thyroxine (T4) and triiodothyronine (T3) are secreted by the thyroid gland, which regulates the following: basal metabolic rate, thermogenesis, lipid handling, cardiac contractility, vascular tone, and energy expenditure. The hypothalamic-pituitary-thyroid axis regulates thyroid hormone secretion, and thyroid-stimulating hormone (TSH) is a very sensitive indicator of changes in circulating thyroid hormone levels (Chaker et al., 2017; Taylor et al., 2018). Thyroid dysfunction affects the metabolism and the cardiovascular physiology, so that mild dysfunction can have systemic consequences (Biondi & Cooper, 2008).

CRP is an acute-phase reactant, primarily synthesized by hepatocytes in response to the cytokines interleukin-6 (IL-6), interleukin-1 beta and tumour necrosis factor alpha (TNF-α). Conventional CRP assays can be used when clinically apparent inflammation is present, while hs-CRP assays are recommended for cardiovascular risk stratification for low-grade inflammation (Ridker, 2016; Pearson et al., 2003). Thyroid dysfunction can be associated with obesity, dyslipidaemia, insulin resistance, endothelial dysfunction and autoimmunity, suggesting that CRP can be a useful laboratory link between endocrine and inflammatory mechanisms (Duntas & Biondi, 2013; Antonelli et al., 2015).

Laboratory scientists need to have an understanding of the relationship between CRP and thyroid function because these tests are often ordered in general medical practice. Unfortunately, CRP is specific to inflammation and if high should not be assumed to be related to thyroid disease unless it is supported by clinical context and thyroid function results (Pearce et al., 2003; Ridker, 2016).

**Objective**

This paper aims to bring together up to date evidence up to 2023 on the relationship between CRP and thyroid function, focusing on pattern, mechanisms, limitations of the studies, and laboratory interpretation. The intent is not to replace any of the above tests (TSH, FT4, FT3, TPOAb, TgAb and TSH-receptor antibodies), but to assess whether CRP would be of interpretive value in specific thyroid conditions (Biondi & Cooper, 2008; Ross et al., 2016).

## METHODOLOGICAL APPROACH

This document was created as a carefully drafted synthesis of existing research which was presented as a narrative. Articles were chosen conceptually from peer-reviewed literature up until the year 2023, prioritizing clinical studies, population-based studies, mechanistic papers, endocrine society guidelines and studies directly assessing CRP or hs-CRP in thyroid disease. No original patient data were gathered, therefore it was not necessary to obtain institutional review board (IRB) approval or statistical analysis of the primary data.

Some of the key concepts for literature identification were: C-reactive protein, high-sensitivity CRP, thyroid function, thyroid-stimulating immunoglobulin, Hashimoto thyroiditis, Graves disease, cardiovascular risk and subclinical hypothyroidism, and subacute thyroiditis. Qualitative interpretation of evidence was required because the populations of studies, the assays used, exclusion criteria, and models used for adjustment differed among studies in the literature.

### Biological Basis Linking CRP and Thyroid Function

Inflammatory cytokines have the ability to influence hypothalamic-pituitary-thyroid axis and peripheral thyroid hormone metabolism. During systemic illness, CRP is produced by the liver in response to the action of cytokines, such as IL-6, that cause changes in thyroid hormone binding, deiodinase activity, and T4 to T3 conversion (Fliers et al., 2015; Ridker, 2016). This establishes a plausible link between inflammation and abnormal thyroid laboratory tests, that is, in a way that is biologically plausible.

The enzymes deiodinase control the activation and deactivation of thyroid hormone. Increased/decreased expression of deiodinases during inflammation can lead to decreases in peripheral generation of T3 and play a role in the development of non-thyroidal illness patterns, especially in severe systemic disease (Bianco et al., 2002; Fliers et al., 2015). Non-thyroidal illness differs from primary thyroid disease, but shows how inflammatory physiology can affect thyroid function tests.

There is another mechanistic link in the form of autoimmune thyroid disease. The Hashimoto thyroiditis is associated with the production of thyroid autoantibodies and lymphocytic infiltration, whereas Graves disease is associated with the stimulation of the thyroid by TSH-receptor antibody. Such changes mirror immune dysregulation, however, systemic CRP elevation is not a constant phenomenon because CRP is not only a marker of autoimmunity but also of disease activity, tissue inflammation, adiposity, infection and cardiometabolic status (Antonelli et al., 2015; Weetman, 2000).

**CRP in Overt Hypothyroidism**

Higher levels of CRP may be seen in overt hypothyroidism, which could be mediated by weight gain, dyslipidemia, endothelial dysfunction and low-grade activation of inflammation (Chaker et al., 2017; Nagasaki et al., 2007). Nagasaki et al. (2007) have found that hypothyroid patients also have elevated levels of CRP, which is consistent with the notion that hypothyroidism could play a role in inflammatory cardiovascular risk.

Interpretation in the presence of overt hypothyroidism should be kept guarded as CRP is highly sensitive to other inflammatory conditions, smoking, infection, diabetes and body mass index (BMI) (Pearson et al., 2003; Ridker, 2016). Thus, elevation of CRP in hypothyroid patients might be due to thyroid hormone deficiency and other non-thyroidal factors.

**CRP in Subclinical Hypothyroidism**

The term subclinical hypothyroidism is reserved for the state of having elevated TSH and FT4 within the reference range. In adults, it is a common finding and can be linked to cardiovascular risk factors, especially if TSH is persistently elevated or thyroid autoantibodies are detected (Biondi & Cooper, 2008; Peeters, 2017). A few studies have reported the elevated levels of hs-CRP in subclinical hypothyroidism, indicating low-grade inflammation (Tuzcu et al., 2005; Ganesan et al., 2021).

Evidence is not entirely consistent. de Miranda et al. (2016) assessed thyroid function and hs-CRP in a large adult population as part of the ELSA-Brasil baseline analysis and emphasized the need to take into account the impact of other factors (confounders) including adiposity and cardiovascular risk factors. This is clinically important as hs-CRP can increase in metabolic syndrome even with moderate abnormalities in thyroid hormone.

Practically, hs-CRP could be used as an additional tool in assessing the risk of cardiovascular disease in subclinical hypothyroidism, but it should not be used as an isolated factor to determine treatment. Treatment continues to be guided by TSH, FT4, symptoms, age, pregnancy status, cardiovascular risk, goiter, thyroid antibody status and guidelines (Biondi & Cooper, 2008; Garber et al., 2012).

**CRP in Autoimmune thyroid disease. In Autoimmune thyroid disease, what is the significance of CRP?**

Hashimoto thyroiditis and Graves disease are immune mediated thyroid diseases, but the association is not the same depending on the phenotype and inflammatory activity. In Hashimoto thyroiditis, it is common to have chronic lymphocytic inflammation of the thyroid, while in the absence of hypothyroidism, obesity, metabolic disease or other inflammatory conditions, systemic CRP may remain normal or be slightly elevated (Antonelli et al., 2015; Rao et al., 2010).

Vudu et al. (2023) found that elevated hs-CRP was seen in people with autoimmune hypothyroidism in comparison to healthy controls, and that correction of hypothyroidism was associated with a decrease in inflammatory burden in certain patients following levothyroxine therapy. These findings are clinically relevant, but should be considered in the context of cohort design and possible confounding with baseline cardiometabolic factors (Vudu et al., 2023).

Several factors are known to contribute to systemic inflammation in Graves disease, such as excess thyroid hormones, smoking, orbitopathy and autoimmunity. TSH, FT4/FT3 and TSH-receptor antibodies still play a key role in diagnosis and monitoring of Graves disease, and CRP is not a primary marker (Ross et al., 2016).

**Subacute Thyroiditis is treated with CRP.**

CRP is most consistently helpful in the diagnosis of subacute thyroiditis. It is typically inflammatory, anterior neck pain, thyroid tenderness, and increase of inflammatory markers, associated with release of preformed thyroid hormone from thyroid follicles damaged by the inflammation and causing transient thyrotoxicosis, (Pearce et al., 2003; Fatourechi, 2009).

In many thyroid diseases, CRP is of little value, but is often elevated in subacute thyroiditis when it is not treated (Pearce et al 2003). There are also more recent studies that confirm CRP and TSH as markers for future hypothyroidism after subacute thyroiditis, making it important to follow-up thyroid function testing after acute inflammatory phase (Tang et al., 2021).

The laboratory pattern of subacute thyroiditis may vary. In the early phase many patients have low TSH levels with high FT4 or FT3 levels, which are followed by a transient period of hypothyroidism and then recovery in most patients. Generally, CRP is a marker of the inflammatory phase of the disease, and not of thyroid hormone production itself (Fatourechi 2009; Tang et al 2021).

**Clinical and Laboratory Interpretation**

CRP is not a thyroid specific test for laboratory interpretation. A combination of TSH, FT4, and FT3 (if ordered) and thyroid antibodies (if indicated) may provide a more comprehensive picture than any one alone (Garber et al., 2012; Ross et al., 2016).

Hypothyroidism or subclinical hypothyroidism, along with dyslipidemia, obesity, diabetes, hypertension, and smoking, may result in higher levels of hs-CRP which may increase the risk of cardiovascular disease (Pearson et al., 2003; Ridker, 2016). When used alongside clinical signs and thyroid ultrasound and/or radioiodine uptake (if

available), a raised level of CRP is useful to identify active inflammation in suspected cases of painful thyroiditis, differentiating it from uncomplicated Graves disease (Fatourechi, 2009; Pearce et al., 2003).
Laboratory reports should not be over-interpreted. For instance, a raised CRP and a normal TSH may not be significant of any thyroid disease and an abnormal TSH with normal CRP may not be significant of thyroid dysfunction. The interpretation of CRP should take into consideration infection, autoimmune disorders, trauma, malignancies, pregnancy, obesity, drug exposure, and recent surgery (Pearson et al., 2003).

**The proposed Laboratory Interpretation Framework consists of the following stages:**
If the pattern is one of low-grade or markedly elevated CRP, coupled with thyroid function tests, the following context can be applied: (1) confirm the nature of the CRP pattern as low grade or as markedly elevated; (2) establish the euthyroid, overt hypothyroid, subclinical hypothyroid, overt hyperthyroid or thyroiditis pattern for thyroid function tests; (3) review clinical symptoms such as neck pain, fever, palpitation, fatigue, weight change, or goiter; (4) consider thyroid autoantibodies if the pattern is suggestive of autoimmune thyroid disease; (5) recommend follow-up testing for patterns suggestive of transient thyroiditis or persistent subclinical thyroid disease (Biondi & Cooper, 2008; Fatourechi, 2009; Ross et al., 2016).

**A problem with the evidence. Restriction of the evidence.**
There are significant issues with the literature available. Most are cross-sectional studies and thus cannot provide causal inferences. There are differences between the measurement of CRP by conventional and high sensitivity methods and between studies in whether they exclude acute infection, inflammatory disease, pregnancy, obesity or medication use. This difference may account for the conflicting results of some studies on hypothyroidism and some studies on autoimmune thyroid disease (de Miranda et al., 2016; Ganesan et al., 2021).
One drawback is that CRP is a downstream inflammation marker, which means it cannot discern where inflammation is occurring. In this regard, even when CRP is correlated with the TSH or thyroid antibody, it is not able to prove that thyroid dysfunction is responsible for the inflammatory state (Pearson et al., 2003; Ridker, 2016).

**Future Directions**
Future studies should focus on the use of prospective cohorts to assess changes from subclinical to overt hypothyroidism, levothyroxine effectiveness, cardiovascular outcomes, and hypothyroid phase recurrence after subacute thyroiditis, with assessment of baseline hs-CRP levels. Body mass index, insulin resistance, lipid profile, smoking, age, sex and use of medication need to be adjusted carefully to studies to determine if the CRP-thyroid association is independent or mediated through cardiometabolic factors (Biondi & Cooper, 2008; Tang et al., 2021).
Future studies in the laboratory setting might also investigate whether integration of thyroid and inflammatory markers will enhance decision making in primary care, endocrinology and emergency departments. This type of work could be useful for the medical laboratory quality improvement as both CRP and thyroid function tests are high volume assays.

## CONCLUSION

The association of CRP with thyroid function is biologically plausible, clinically relevant, but not disease-specific. Studies up to 2023 have shown that overt and subclinical hypothyroidism may be associated with modestly elevated levels of hs-CRP, particularly in the presence of cardiometabolic risk factors, as well as subacute thyroiditis and elevated levels of hs-CRP as part of acute inflammatory response (Tuzcu et al., 2005; Nagasaki et al., 2007; Pearce et al., 2003; Tang et al., 2021).
When used clinically, CRP should not be used as a substitute for thyroid function tests. It has greatest utility in the evaluation of inflammatory burden, as a supporting test for suspected thyroiditis, and as an adjunct test to consider looking at when evaluating cardiovascular risk in patients with thyroid dysfunction (Pearson et al., 2003; Ridker, 2016).

**Table 1. Comparison of Previous Studies on CRP and Thyroid Function**

| Author(s), Year | Design / Population | Thyroid Condition | Inflammatory Marker | Main Findings | Clinical Interpretation / Limitation |
|---|---|---|---|---|---|
| Pearce et al., 2003 | Clinical thyroid disease groups including amiodarone-induced thyroid dysfunction and subacute thyroiditis | Multiple thyroid disorders, especially subacute thyroiditis | CRP | CRP was frequently positive in untreated subacute thyroiditis but less useful across | Supports CRP mainly as an adjunct marker of inflammatory thyroiditis rather than a general |

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| | | | | other thyroid disorders. | thyroid screening test. |
| Tuzcu et al., 2005 | Case-control study of subclinical hypothyroidism and euthyroid controls | Subclinical hypothyroidism | hs-CRP | Reported higher hs-CRP in subclinical hypothyroidism compared with controls. | Suggests low-grade inflammation may accompany mild thyroid failure; confounding by metabolic factors remains important. |
| Nagasaki et al., 2007 | Clinical study comparing hypothyroid patients and controls | Overt hypothyroidism | CRP | Baseline CRP was significantly higher in hypothyroid patients than controls. | Supports inflammatory cardiovascular risk in hypothyroidism; does not prove thyroid hormone deficiency is the only cause. |
| Rao et al., 2010 | Study evaluating salivary inflammatory marker in thyroid autoimmunity | Hashimoto thyroiditis | Salivary CRP | Explored CRP as a saliva-based marker of inflammation in Hashimoto thyroiditis. | Shows interest in non-serum inflammatory markers, but salivary CRP is not routine for thyroid diagnosis. |
| Garber et al., 2012 | Clinical practice guideline | Hypothyroidism in adults | Not a primary CRP study | Guideline emphasizes TSH and FT4 for diagnosis and management, with clinical context guiding treatment. | CRP may be supportive but cannot replace standard thyroid testing. |
| Duntas & Biondi, 2013 | Endocrine review of thyroid function and inflammation | Thyroid dysfunction and inflammatory pathways | CRP and inflammatory mediators | Discussed links among thyroid function, inflammation, metabolic risk, and cardiovascular outcomes. | Provides mechanistic rationale for evaluating inflammation in thyroid disease. |
| Antonelli et al., 2015 | Review of autoimmune thyroid disorders | Hashimoto thyroiditis and Graves disease | Inflammatory pathways | Described immune activation and systemic autoimmune associations in thyroid autoimmunity. | Explains why CRP may be variable: autoimmunity is present, but systemic CRP depends on broader inflammatory burden. |
| Fliers et al., 2015 | Mechanistic review of thyroid function during illness | Non-thyroidal illness and systemic inflammation | Cytokine-related inflammatory pathways | Inflammation can alter HPT-axis activity and peripheral thyroid hormone metabolism. | Important for distinguishing primary thyroid disease from illness-related thyroid test changes. |

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| de Miranda et al., 2016 | Large adult population baseline analysis from ELSA-Brasil | Subclinical thyroid dysfunction | hs-CRP | Assessed association between thyroid function categories and hs-CRP with attention to confounders. | Highlights that obesity and cardiometabolic factors may influence CRP-thyroid associations. |
| Ridker, 2016 | Cardiovascular risk synthesis | General cardiovascular inflammation | hs-CRP | Established hs-CRP as a marker of inflammatory cardiovascular risk. | Useful for interpreting hs-CRP elevation in thyroid patients with cardiometabolic risk factors. |
| Ross et al., 2016 | American Thyroid Association guideline | Hyperthyroidism and thyrotoxicosis | Not a primary CRP study | Diagnosis and monitoring rely on TSH, FT4/FT3, antibodies, imaging, and clinical context. | CRP is not central for Graves disease diagnosis but may help when thyroiditis is suspected. |
| Chaker et al., 2017 | Clinical review | Hypothyroidism | Inflammation discussed as related risk context | Summarized epidemiology, consequences, and management of hypothyroidism. | Supports the clinical relevance of cardiometabolic risk assessment in hypothyroid patients. |
| Biondi & Cooper, 2008 | Endocrine review | Subclinical thyroid dysfunction | Inflammation as part of risk context | Discussed risks, treatment controversies, and clinical evaluation of subclinical thyroid dysfunction. | Provides framework for interpreting hs-CRP as adjunctive rather than decisive. |
| Taylor et al., 2018 | Epidemiological review | Thyroid disorders broadly | Not a CRP-focused paper | Summarized global burden and epidemiology of thyroid disorders. | Supports public health relevance of thyroid testing and associated risk markers. |
| Fatourechi, 2009 | Clinical review | Subacute thyroiditis | ESR and CRP | Described painful thyroiditis with raised inflammatory markers and changing thyroid function phases. | Supports CRP use in suspected thyroiditis and follow-up of thyroid function. |
| Ganesan et al., 2021 | Analytical cross-sectional study with subclinical hypothyroid and euthyroid groups | Subclinical hypothyroidism | hs-CRP | Evaluated hs-CRP, lipid profile, and TSH in subclinical hypothyroidism. | Supports association between SCH, inflammation, and lipid-related cardiovascular risk. |
| Tang et al., 2021 | Clinical study of subacute thyroiditis outcomes | Subacute thyroiditis | CRP | CRP and TSH were reported as risk factors for hypothyroidism after subacute thyroiditis. | Supports monitoring thyroid function after the acute inflammatory phase. |

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| Zornitzki et al., 2022 | Retrospective/clinical characterization of subacute thyroiditis | Subacute thyroiditis | CRP and ESR | Elevated CRP and ESR occurred in the majority of patients with subacute thyroiditis. | Reinforces CRP as a useful marker in painful inflammatory thyroiditis. |
| Zhou et al., 2022 | Mendelian randomization / causal-inference approach | Thyroid signaling and CRP | CRP | Examined genetic evidence regarding thyroid signaling and CRP. | Helpful for causal discussion; genetic inference does not replace clinical interpretation. |
| Çiftel et al., 2023 | Study of systemic immune-inflammation indices | Subacute thyroiditis diagnosis and recovery | CRP and inflammatory indices | Reported CRP may be elevated in many cases and assessed inflammatory indices in SAT. | Supports combining CRP with clinical and hematological inflammatory markers. |
| Vudu et al., 2023 | Cohort study before and after levothyroxine therapy | Autoimmune hypothyroidism | hs-CRP | Patients with hypothyroidism had higher hs-CRP than controls, and therapy effect was evaluated. | Suggests levothyroxine may reduce inflammatory burden in selected patients; confounding should be considered. |

**الخلاصة**

إن ارتباط البروتين المتفاعل ( CRP) بوظائف الغدة الدرقية أمرٌ منطقي بيولوجيًا وذو أهمية سريرية، ولكنه ليس خاصًا بمرضٍ مُحدد. وقد أظهرت الدراسات التي أُجريت حتى عام 2023 أن قصور الغدة الدرقية الظاهر وتحت السريري قد يرتبط بارتفاع طفيف في مستويات البروتين المتفاعل C عالي الحساسية (hs-CRP)، لا سيما في وجود عوامل خطر قلبية استقلابية، وكذلك التهاب الغدة الدرقية تحت الحاد وارتفاع مستويات البروتين المتفاعل C عالي الحساسية كجزء من الاستجابة الالتهابية الحادة (توزكو وآخرون، 2005؛ ناغازاكي وآخرون، 2007؛ بيرس وآخرون، 2003؛ تانغ وآخرون، 2021).

عند استخدامه سريريًا، لا ينبغي استخدام البروتين المتفاعل C كبديل لاختبارات وظائف الغدة الدرقية. وتُعد هذه الطريقة ذات فائدة كبيرة في تقييم العبء الالتهابي، كاختبار داعم لالتهاب الغدة الدرقية المشتبه به، وكاختبار مساعد يجب مراعاته عند تقييم مخاطر القلب والأوعية الدموية لدى لمرضى الذين يعانون من خلل في وظائف الغدة الدرقية (Pearson et al., 2003; Ridker, 2016).

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