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The Biochemical Features, Physiological Actions, And Clinical Importance of Procalcitonin: A Review

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Abstract

Procalcitonin (PCT), a peptide precursor of calcitonin, has emerged as an important biomarker (biomarker) clinically that can be used for diagnosis and subsequent management of bacterial infection. This review summarizes the biosynthesis, biochemical characteristics, physiological functions and clinical relevance of procalcitonin. PCT is produced by thyroid C cells under physiological conditions, and almost immediately converted to calcitonin giving rise to extremely low levels in circulation. In contrast, during systemic bacterial infections it is produced in relatively high states in various tissues with a corresponding increase in serum concentrations. From a biochemical perspective, PCT is representative of a "hormokine," bridging the immune and endocrine responses. On a physiological level, it helps to regulate inflammation and immune responses. Clinically, PCT has been used as a sensitive and specific biomarker for bacterial infections and sepsis, making it a valuable tool in differentiating disease causing by viral infection from that of bacterial origin. Moreover, antibiotic therapy based on PCT reduces unnecessary antibiotic therapy and improves treatment outcome. Procalcitonin is an important supporting diagnostic and prognostic biomarker, which undoubtedly has limitations but supports appropriate clinical decision-making and patient care in different medical contexts.

Keywords: Prohormone, Procalcitonin, C–cells, Parathyroid

Introduction

Procalcitonin (PCT) is one of the most widely studied circulating biomarkers in clinical medicine over the last 30 years, establishing an innovative territory at the intersection between

endocrinology, immunology and infectious disease. PCT was first characterized as the prohormone of calcitonin with 116-amino-acids secreted from the parafollicular C–cells of thyroid gland in 1984 and it was initially considered to a biologically inactive precursor, which has minimal levels in sera from healthy individuals (Vijayan et al., 2017). It was a perception that underwent radical change when Assicot et al showed that serum PCT levels were much higher in patients with systemic bacterial infection, thus turning an enigmatic prohormone into a clinically useful test (Cleland & Eranki, 2024). PCT is now included in standard diagnostic pathways for sepsis, lower respiratory tract infections, and antimicrobial stewardship programs worldwide; therefore an updated evaluation of its biochemical, physiological, and clinical aspects is timely and warranted.

Biochemically, PCT is encoded by the CALC-1 gene on chromosome 11p15. 2–15. No. 1, also forms calcitonin and katacalcin from post-translational cleavage by prohormone convertases endopeptidases (Vijayan et al., 2017). At physiological conditions, however, extra-thyroidal transcription of CALC-1 is inhibited and levels of plasma PCT are maintained below 0.05 ng/mL. In contrast, during systemic bacterial infection microbial toxins (especially lipopolysaccharide [LPS]) and pro-inflammatory interleukins, including interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α particularly stimulate the ubiquitous CALC-1 expression of parenchymal tissues throughout the organism leading to 1000–10000 fold raised serum PCT levels in 6–12 h (Sankar & Webster, 2013; Vijayan et al., 2017). PCT has kinetic properties of at least an order of magnitude better than that of C-reactive protein, giving it both early ability to detect bacterial disease and real-time monitor treatment response due to its biological half-life (BHL) in human plasma of 22–35 hours with relative stability (Sankar & Webster, 2013).

The physiological dissociation between the elevation of procalcitonin and its release as a calcitonin despite strong PCT surges during infection is remarkable: no significant alteration of serum calcium homeostasis occurs, suggesting that this prohormone behaves like a hormokine with similar effects on neutrophil migration, vascular tone, and host inflammatory cascade (Dahaba & Metzler, 2009). Significantly, viral infections, localized inflammation and most autoimmune processes generally do not stimulate comparable PCT release thus validating its use as a relatively specific marker of systemic bacterial infection (Paudel et al., 2025). However, recent studies have shown an increased PCT can be secondary to the same noninfectious stimuli such as medullary thyroid carcinoma, severe trauma or major surgery, cardiogenic shock, heat stroke and some autoimmune flares which requires ability of differentiating it according to context (Paudel et al., 2025).

In the post-pandemic around PCT, its clinical significance was extended remarkably. Recent meta-analyses have reported that PCT provides moderate to high diagnostic accuracy for sepsis in emergency department populations, with pooled sensitivity and specificity near 80% and 75%, respectively (Zaki et al., 2024). Studies confirm that, without compromise on clinical outcomes, PCT-guided algorithms reduce exposure to antibiotics (Kyriazopoulou & Giamarellos-Bourboulis, 2023), shorten treatment duration and lessen the incidence of antimicrobial-associated adverse events in successively wider domains from respiratory tract infections (Donnelly et al., 2023) to elective surgery recovery and then critical care settings (O'Driscoll & Tsoyi, 2023). PCT was especially useful during the COVID-19 pandemic setting as it aided to differentiate pure viral illness from secondary bacterial co-infection which influenced antibiotic stewardship (He et al., 2024). Furthermore, responses from ongoing studies are further improving threshold cut-off values for certain patient populations—neonates, immunocompromised hosts and individuals with renal dysfunction—as well as identifying new roles of PCT in prognosis, risk assessment and possibly precision medicine (He et al., 2024).

Yet, despite this abundance of evidence, controversies remain around ideal decision thresholds; performance in different clinical settings; and compound paths with novel multi-omic biomarkers—highlighting the indefinite need for common synthesis. Thus, this current review seeks to objectively appraise the available evidence for PCT by: (i) exploring the biochemical nature, gene regulation and post-translational processing of PCT; (ii)characterizing the physiological effects and kinetic release profile during infection and inflammation; (iii) summarising current knowledge on its utility with regards to diagnosis, prognosis and stewardship in important clinical contexts including sepsis, pneumonia and COVID-19; iv addressing key controversies, limitations and future research directions thus providing a practical guide for clinicians/researchers that describes rational approaches to modern-day PCT use.

Biosynthesis and Biochemistry of Procalcitonin

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin that belongs to the superfamily of calcitonin gene-related peptides (CGRP). It is structurally a 116–amino acid polypeptide with a molecular weight of ~13-15 kDa encoded by the CALC-1 gene on chromosome 11 (Davies, 2015; Mućka et al., 2025). Since this gene is transcripted and translated into preprocalcitonin which is the first pro-peptide with a signal

peptide that targets it to the endoplealasmic reticulum (ER). Biosynthesis of PCT is tightly regulated under physiological conditions and results from a cascade of molecular events, including several co-translational and post-translational modifications that dictate its biological fate.

CALC-1 mRNA is first translated into preprocalcitonin, the larger precursor peptide in the biosynthetic pathway. The N-terminal signal sequence of this molecule is rapidly cleaved in the rough endoplasmic reticulum to produce procalcitonin (PCT) which can be subsequently measured (Becker et al 2004; Matwiyoff et al, 2012). Then, PCT is transported to the Golgi apparatus, and undergoes enzymatic cleavage into smaller biologically active peptides. This includes calcitonin, a 32–amino acid hormone; katacalcin; and an N-terminal fragment of procalcitonin (N-PCT). The sequential cleavage is mediated by endopeptidases and is required for the synthesis of the mature form of the hormone that regulates calcium homeostasis (Meisner, 2014).

In a healthy state, procalcitonin is mainly synthesized in the parafollicular C cells of the thyroid gland, and most is transformed to calcitonin prior to its release into circulation. Consequently, intact PCT levels in the circulation of healthy subjects are extremely low or even undetectable (normally <0.05 ng/mL) (Müller et al., 2001). This efficient processing within the cell prevents an excessive PCT concentration in the bloodstream under non-pathological conditions. This physiologic process is regulated by serum calcium levels, hormone signals, and neuroendocrine activity (Davies, 2015).

Procalcitonin consists of three different regions: an N-terminal peptide, the central calcitonin sequence, and a C-terminal region (katacalcin). Its tripartite structure is representative of a prohormone that is cleaved proteolytically to yield biologic active and inactive fragments (Becker et al., 2004). Furthermore, initial biochemical studies revealed that procalcitonin is a glycoprotein and it undergoes synthesis-dependent glycosylation affects. This process would happen within the ER and Golgi apparatus which are cellular organelles involved in glycosylation and folding leading to maturation of this peptide (Jacobs et al. 1981).

We also present a novel model in which the biosynthesis of procalcitonin diverges substantially from normal physiological conditions, particularly during systemic bacterial infections and sepsis. It is upregulated in various non-thyroid tissues including liver, lungs, kidneys, adipose tissue and leukocytes in such cases. This phenomenon gives rise to the overall high levels of procalcitonin in systemic circulation, as opposed to its localized production in thyroid C cells (Müller et al., 2001). Significantly, the enzymatic machinery to convert PCT into calcitonin is missing or incomplete in these extra-thyroidal tissues. Therefore, procalcitonin is released directly into the circulation leading to extremelyhigh serum levels (Meisner, 2014).

Procalcitonin differentiation during the infiltration of infection is dependent on direct and indirect actions. Direct stimulation occurs through bacterial endotoxins (e.g., lipopolysaccharides [LPS]) that trigger activation of immune cells and gene expression. Pro-inflammatory cytokines affect CALC-1 gene transcription (indirectly), whereby more PCT is produced, being aggregated by, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and interleukin–1β (IL-1β). On the other hand, viral infections down-regulates PCT production by boosting interferon-gamma and inhibits цитокин-індукцій@ pathways. The clinical utility of PCT arose from this differential regulation, it serves as a biomarker to distinguish bacterial infections from other viral infections (Matwiyoff et al., 2012).

Biochemically, procalcitonin has both hormone precursor and inflammatory mediator characteristics, classifying it as a “hormokine.” In contrast to classical hormones, the catabolic peptide PCT can be synthesized systemically in response to inflammation and thus has a tissue distribution well beyond its original endocrine gland. Its half-life ranges approximately 20–24 hours which maintains stability in circulation and increases its diagnostic value. The slow-degrading properties allow for recurrent measurement of disease progression or response to treatment (Linscheid et al., 2003).

The theory of procalcitonin as a precursor molecule dates back to the 1970s when several studies showed the existence of a larger molecular weight precursor to calcitonin during biosynthesis experiments. Further studies confirmed that calcitonin originated from procalcitonin by means of proteolytic processing thus establishing the basic biochemical pathway, which is now widely accepted. Since then, various advancements in molecular biology have elucidated the gene structure and transcriptional regulation of PCT along with further discovery work on post-translational modifications involved (Moya et al., 1975).

Conclusion: The biosynthesis and biochemistry of procalcitonin is a multi-step, tightly-regulated process that starts with CALC-1 gene expression and follows through to the production of calcitonin under physiological conditions. However, this pathway is modified during systemic inflammation, particularly bacterial infections, when extensive production and secretion of intact PCT into the circulation takes place. The special biochemical features of hf DNA (such as structure, processing and inducibility) make

it an important clinically relevant biomarker in contemporary medicine.

Physiological activity of procalcitonin

C Procalcitonin (PCT), initially recognized as prohormone precursors of calcitonin, has undergone a progression from being viewed as a biochemically inactive intermediate to now being classified as a peptide with unique physiological and pathophysiological effects. PCT is synthesised mainly in the thyroid parafollicular C cells where under normal physiological conditions it is rapidly cleaved into calcitonin with a well-established role in calcium and bone metabolism. As a result, circulating concentrations of intact PCT are extremely low in healthy humans and rather seem to have an only limited direct physiological role under basal conditions (; Müller et al, 2001). However, during systemic inflammatory states, most notably bacterial infections, PCT is ubiquitously synthesized by several tissues and has also been shown to have biological effects that may go beyond its classical endocrine effect (Becker et al, 2004).

PCT possesses a unique physiological feature that characterizes it as a "hormokine," which is defined as molecules with bioactivity pertaining to both hormones and cytokines. This duality is most clearly revealed during systemic infections where widely disseminated PCT to the circulation in response to microbial toxins and pro-inflammatory mediators 7. Under these conditions, PCT mirrors the host immune response by regulating inflammatory signaling pathways. Using in vitro and in vivo experimental studies, PCT was found to stimulate the production of TNF-α by peripheral blood mononuclear cells (PBMCs), as well as IL-6 and IL-1β indicating a role for PCT to amplify the inflammatory cascade (Matwiyoff et al., 2012).

Beyond Cytokine Modulation: Role of PCT in Regulating Immune Cell Activity Its action is thought to occur through interactions with monocytes, macrophages, and neutrophils promoting their reactivity in response to bacterial infection. Such a potential interaction could in turn lead to the recruitment and activation of immune cells around sites of infection, clearing the pathogen. Nonetheless, constant or prolonged elevation of PCT might lead to inappropriate inflammation which could worsen tissue damage during severe حالات like sepsis (Becker et al., 2004).

Another important physiological facet of PCT is its interplay with the neuroendocrine system. Under the situation of systemic stress or infection then normal endocrine processing of procalcitonin fails, intact PCT are released to the circulation. This process demonstrates a transition from a highly regulated hormonal pathway to one that is more broadly orchestrated systemically. The ubiquitous expression of CALC-1 found in non-thyroid tissues under inflammatory conditions, indicates that PCT may function as a global DEFENSE system, providing a link between the endocrine and immune systems (Müller et al., 2001).

It also has vascular and metabolic effects. Increased concentrations of PCT have been linked to changes in vascular tone and endothelial screening, both key processes underlying the systemic synaptic response. In fact, some studies indicate that PCT has a possible role in vasodilation and increased vascular permeability, which are features of sepsis and systemic inflammation (Meisner, 2014).

On the metabolic side, PCT seems to play a role in mediating energy expenditure during infection. Acute states of inflammation are commonly accompanied by metabolic alterations, including increased energy expenditure and changes in glucose metabolism. Although the pancreatic C-terminal fragment of proinsulin (PCT) function in these processes has not been fully elaborated yet, its association with inflammatory severity indicates that it could represent a mediator of immune activation leading to metabolic reconditioning (Linscheid et al., 2003).

More interestingly, PCT shows some degree of specificity in its physiological response to different types of infections. Production of PCT is strongly induced in the case of bacterial infections and rarely increases or only slightly during viral infections. This difference is mainly due to the impact in PCT synthesis by interferon-gamma during a viral infection. Such selective regulation not only improves the utility of PCT as diagnostic but also indicate a possible role for PCT in modulating and individualizing the immune response to the type of pathogen (Matwiyoff et al., 2012).

In addition, its physiological and clinical significance is related to both the stability and kinetics of PCT. PCT has a half-life of around 20–24 hours, which is relatively long and enables elastin accumulation in the blood during continuous inflammatory stimuli. It increases levels within 4–6 hours after bacterial infection and reaches its peak level around 12–24 hours, indicating a rapid and persistent response to inflammatory stimuli. The aforementioned kinetic profile suggests that PCT may act in a manner similar to a signaling molecule, acting both at the periphery to integrate and extend inflammatory responses, thus bolstering ongoing immune-defense (Meisner, 2014).

However, the precise physiological function of PCT in healthy individuals is still poorly understood. Under the usual physiological condition, however, PCT exerts little or no inherent

biological activity due to its rapid conversion into calcitonin. Yet, under pathologic conditions, especially systemic infections, PCT becomes a novel player in immune and inflammatory pathways. The ZZZ peptide is a multifaceted peptide in terms of its ability to modulate cytokine secretion, its impact on immune cell activity, and its interaction with the vascular and metabolic systems.

Clinical significance of procalcitonin

Procalcitonin (PCT) is one of the most useful biomarkers in modern clinical practice as it has the ability to help in diagnosis, prognostication, and monitoring of infectious and inflammatory diseases. However, its clinical relevance is mainly due to the fact that it has a high specificity for bacterial infections, rapid kinetics with its peak concentrations at 1–8 hours after infection and it correlates well with disease severity. In comparison to traditional inflammatory markers like C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), however, it offers more detailed information about infection type and evolution, which is why PCT could be a cornerstone of evidence-based medicine (Mućka et al., 2025).

PCT is one of the main applications within clinical use for early diagnosis in case of bacterial infections and sepsis. Serum levels of PCT increase quickly (in the range of 4–6 hours) after a bactericidal kind of exposure (such as to bacterial endotoxins, etc.), reaching its zenith after 12–24 hours, hence making it an early and sensitive prognosticator for systemic contamination. Furthermore, PCT concentrations are low during viral infections and non-infectious inflammatory diseases because of the inhibitory effects of interferon-gamma. The differential response contributes to its diagnostic accuracy, providing clinically relevant data of great importance in differentiating between bacterial and viral etiology: a key factor for accurate therapeutic decision making (Müller et al., 2001; Matwiyoff et al., 2012).

PCT has shown a great sensitivity and specificity as diagnostic and prognostic marker in the context of sepsis. Higher levels of PCT are associated with the severity of infection, degree of systemic inflammation and potentially adverse outcomes. Previously published studies indicated that the unchanging or elevated PCT level is correlated with high mortality and that a PCT decrease indicates treatment response. Thus, serial measurement of procalcitonin is utilized as an indicator to monitor disease progress and assist decision making in critically ill patients (Schuetz et al., 2017).

One of the other major clinical applications of PCT is antibiotic stewardship Antibiotic overuse and misuse are pressing global health issues, with implications for the emergence of antimicrobial resistance. PCT-guided treatment also led to reduced unnecessary use of antibiotics without adversely affecting patient safety. Clinical protocols driven by PCT thresholds guide clinicians on when to start, continue or stop antibiotic therapy. An example of this is the low concentration of PCT, which indicates a very small risk of bacterial infection and can therefore prevent excessive antibiotic prescription. In contrast, high levels indicate the necessity of antimicrobial therapy. Such an approach has been shown to be valid in several RCTs and thus integrated into clinical pathways of many health systems [Schuetz et al., 2017, Bouadma et al., 2010].

Procalcitonin levels are of practical use in diagnosing and providing clinical guidance for respiratory tract infections as well, including pneumonia or acute exacerbations of chronic obstructive pulmonary disease (COPD). Under such conditions, PCT levels assists in identifying bacterial infections as opposed to viral or non-infectious aetiologies and can guide appropriate antibiotic therapy. Research has shown that PCT-based management in respiratory infections is associated with lower antibiotic exposure, shorter treatment duration and better clinical results (Christ-Crain et al., 2004).

Apart from the infectious diseases, clinical utility of PCT has been documented in many non-infectious inflammatory conditions [6]. PCT has been observed to be increased in major trauma, surgical procedures, burns and some malignancies. Nonetheless, the degree of PCT elevation is usually markedly lower than that which may accompany a severe bacterial infection and clinicians can take their interpretation in context. This highlights the merit of considering patient history and clinical findings alongside PCT as a diagnostic biomarker (Meisner, 2014).

PCT is especially relevant in the diagnosis of early neonatal sepsis and also amongst children. Recent studies have shown that 30% of neonatal herpes virus is diagnosed on post-mortem examination, as neonates generally present with very nonspecific symptoms, making it challenging to catch an infection early. PCT has proven to be an accurate biomarker in this setting, showing higher sensitivity and specificity than standard marker. The use of it in neonatal intensive care units has been associated with enhanced diagnostic accuracy and more specific antibiotic treatment (Becker et al., 2004).

Furthermore, PCT has been investigated in many different clinical contexts as a prognostic marker. Ultra-high procalcitonin level is a predictor of organ dys-function and death in the critically ill patients. PCT trends during follow up may inform

and complement treatment response to anti-infective therapy and disease trajectory. In intensive care settings, where clinical decisions must be made quickly, the evaluation was also dynamic (Schuetz et al., 2017).

Conclusion

As a novel biomarker characterized by an endocrine-immune interrelationship that combines its activity as a prohormone and inflammatory mediator, procalcitonin (PCT) is generated in the body under different biomedical conditions. The biosynthesis of IL-6 is highly regulated in the steady state, but its production is broadly activated during systemic bacterial infections to reach elevated concentrations in the circulation. In addition, the biochemical characteristics of PCT such as stability and rapid induction give strength to its reliability for clinical use. For instance, from a physiological perspective, PCT affects immune modulation and inflammatory signaling particularly associated with infection and sepsis. Ideal for early diagnosis, risk stratification and monitoring of bacterial infections, it has shown its utility clinically. In this regard, its capacity to direct antibiotic treatment has greatly facilitated the enhancement of antimicrobial stewardship and decrease in unnecessary antibiotic use. The PCT, though not without limitations, continues to surpass many other traditional markers because of its high specificity and dynamic response.

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