Adv Exp Med Biol - Advances in Microbiology, Infectious Diseases and Public Health (2022) 16: 17–32
https://doi.org/10.1007/5584_2021_629

Published online: 30 March 2021

Beyond Bone: Infectious Diseases and Immunity in Parathyroid Disorders

Valeria Hasenmajer, Giulia Puliani, Marianna Minnetti, Emilia Sbardella, Claudio M. Mastroianni, Gabriella D'Ettorre, Andrea M. Isidori, and Daniele Gianfrilli

Abstract

Parathyroid disorders are characterized by alterations in calcium and phosphate homeostasis due to inappropriately high or low levels of parathyroid hormone (PTH). Despite PTH receptor type 1 has been described in almost all immune lineages and calcium signalling has been confirmed as a crucial mediator for immune response, *in vitro* studies on the physiological interactions between PTH and immunity are conflicting and not representative of the clinical scenarios seen in patients with parathyroid disorders. Infectious diseases are among the main causes of increased morbidity and mortality in patients with secondary hyperparathyroidism and chronic kidney disease. More, immune alterations have been described in primary hyperparathyroidism. Recent studies have unveiled an increased risk of infections also in hypoparathyroidism, suggesting that not only calcium, but also physiological levels of PTH may be necessary for a proper immune response. Finally, calcium/phosphate imbalance could affect negatively the prognosis of infectious diseases. Our review aimed to collect available data on infectious disease prevalence in patients with parathyroid disorders and new evidence on the role of PTH and calcium in determining the increased risk of infections observed in these patients.

Keywords

Hyperparathyroidism · Hypoparathyroidism · Immune function · Infectious disease · PTH

Authors Hasenmajer Valeria and Puliani Giulia have equally contributed to this chapter.

V. Hasenmajer (✉), M. Minnetti, E. Sbardella, A. M. Isidori, and D. Gianfrilli
Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy
e-mail: valeria.hasenmajer@uniroma1.it; Marianna.minnetti@uniroma1.it; emi.sbardella@uniroma1.it; daniele.gianfrilli@uniroma1.it

G. Puliani
Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

Oncological Endocrinology Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy
e-mail: giulia.puliani@uniroma1.it

C. M. Mastroianni and G. D'Ettorre
Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy
e-mail: claudio.mastroianni@uniroma1.it; gabriella.dettorre@uniroma1.it

Abbreviations

cAMP	cyclic AMP
CKD	chronic kidney disease
PBMC	peripheral blood mononuclear cells
PHA	phytohemagglutinin

PMNL polymorphonuclear leukocytes
PTH parathyroid hormone
PTH1R type 1 PTH receptor

1 Introduction

Parathyroid disorders are characterized by alterations of parathyroid hormone (PTH) secretion, often leading to, or provoked by, an impairment in calcium and phosphate homeostasis. The hyperfunction of one or more parathyroid glands can be due to autonomous secretion of PTH (primary hyperparathyroidism) (Walker and Silverberg 2018), to a physiological response to hypocalcaemia, renal failure or vitamin D deficiency (secondary hyperparathyroidism) (Chandran and Wong 2019) or to autonomous PTH secretion after long-term secondary hyperparathyroidism (tertiary hyperparathyroidism) (Chandran and Wong 2019). Primary and tertiary hyperparathyroidism are characterized by increased calcium circulating levels and urinary excretion and decreased phosphate serum levels. Hypoparathyroidism, on the other hand, is characterized by undetectable or inappropriately low PTH secretion leading to hypocalcaemia and increased phosphate levels (Marcocci et al. 2015). Surgical lesion of one or more parathyroid gland is the main cause of hypoparathyroidism (Marcucci et al. 2018), but several other rarer aetiologies can affect PTH secretion (Mantovani and Elli 2019) and will be further discussed in the dedicated paragraph. Patients with parathyroid disorders are at an increased risk of comorbidities and concomitant diseases due to alterations of calcium homeostasis and bone and kidney disease.

Previous researches have highlighted the pivotal role of immune cells in mediating bone effects of PTH secretion. In animal models, T lymphocytes expressing CD40 ligand (CD40L) have been described as mediators of resorptive (Tawfeek et al. 2010) and anabolic (Robinson et al. 2015) effects of PTH. In fact, deletion of T Lymphocytes expressing CD40L, the PTH receptor (Tawfeek et al. 2010) or an impairment of antigen presentation (Bedi et al. 2010) blunted osteoclastogenic activity in experimental models of hyperparathyroidism (Gao et al. 2008). On the other side, T Lymphocytes also mediate the anabolic effects of intermittent PTH therapy (Terauchi et al. 2009), activating a sclerostin-independent pathway (Li et al. 2014). Regulatory T Lymphocytes are also expanded by intermittent PTH therapy (Yu et al. 2018), while Interleukin 17 producing T Lymphocytes increase its catabolic effects (Pacifici 2016).

More recently, a significant increase in infectious diseases and immune alterations in hyper- and hypoparathyroidism suggested a possible role for PTH-immune interactions beyond the osteoimmune niche in maintaining immune homeostasis and mediating systemic effects of alterations in PTH secretion.

PTH action is mediated by its receptors, PTHR1 and PTHR2. Both are group B canonical G protein-coupled receptors. PTHR1 binds both PTH and PTH related peptide (PTHrP), while PTHR2 is selective for PTH. For the scope of this review, we will focus on PTHR1 function given its role in calcium and bone homeostasis and the lack of data on PTHR2 and immunity. Conformational change of PTHR after ligand binding activates several intracellular pathways including primarily the Gs, cyclic AMP (cAMP) protein kinase A (PKA) cascade and the Gq, phospholipase C (PLC), Ca^{2+} and protein kinase C (PKC) signalling, even though activation of phospholipase D and mitogen-activated protein kinase (MAPK) signalling cascades have been described (Urena et al. 1993). While most studies have focused on the cAMP signalling pathway that mediates the osteoanabolic effects of PTHR1 binding, downstream signalling of PTHR1 activation directly modulates immune function, for example by increasing TNF secretion in T Cells (Tawfeek et al. 2010) or modulating the nuclear factor of activated T-cells (NFAT) family (Huang et al. 2010). Furthermore, PTH and Ca^{++} signalling are significantly intertwined.

Calcium levels are one of the main regulators of the immune response, due to the role of ionized calcium in intracellular signalling. Intracellular

calcium levels are tightly regulated by a variety of mechanisms, in which parathyroid hormone (PTH) plays a significant role. As extensively demonstrated in adrenal disorders (Isidori et al. 2018; Bancos et al. 2017) the immune system appears tightly correlated with the endocrine function as both react in a coordinated manner to face external challenges. The presence of the PTH receptor on immune cells suggests a physiological role in the immune response that extends beyond the regulation of bone remodelling.

Despite the increasing body of evidence on immune derangement in parathyroid disorders, results are often contradictory and data on the direct effect of PTH on immune homeostasis is scarce. In this context, the aim of this review was to summarise available evidence on prevalence, severity, predisposing factors and underlying mechanisms of infectious diseases in parathyroid disorders; to highlight contradictory conclusions and confounding factors possibly affecting the obtained results; and to provide more solid basis for further research on immunity in hyper and hypoparathyroidism.

2 Methods

We performed a research of published literature with no time constraints using the following keywords: "PTH", "parathyroid hormone", "hypoparathyroidism", "hyperparathyroidism", "primary hyperparathyroidism", "secondary hyperparathyroidism", "parathyroid disorders", "immune system", "immunity", "autoimmune diseases", "infectious diseases", "infections". Only English papers were included. Being out of the main topic of this review, papers on infections as a side effect of thyroid or parathyroid surgery were excluded, along with papers focusing on the aetiology and physiopathology of autoimmune hypoparathyroidism. The review has been conducted according to SANRA scale for the quality assessment of narrative review articles (Baethge et al. 2019).

3 PTH in the Healthy Immune System

Studies on the interactions between calcium homeostasis, PTH and the immune system were prompted in the late 1970s by the discovery of the players, subsequently identified as immune cells, mediating the interaction between PTH, bone resorption and osteoclasts, and the identification of PTH receptor on their surface (Perry et al. 1984; Yamamoto et al. 1983; Stock and Coderre 1982; Minkin et al. 1977). Early studies evaluated alterations of cyclic AMP (cAMP) concentrations or radionuclide binding as indirect indicators of PTH1R expression and activity. PTH1R binding in vitro targeted mononuclear leukocytes (Perry et al. 1984; Yamamoto et al. 1983; Stock and Coderre 1982; Minkin et al. 1977), while polymorphonucleates and red blood cells did not seem to express PTH1R (Yamamoto et al. 1983). Narrowing the analysis, studies on cAMP accumulation showed direct effects of PTH on monocytes, but not on lymphocytes (Stock and Coderre 1982), even though these results were conflicting with others identifying lymphocytes as a major target of PTH (Perry et al. 1984; Yamamoto et al. 1983). These contradictory findings are probably due to heterogeneity of methods used such as different concentrations of rat or bovine PTH, different duration of incubation, sampling lymphocytes from healthy donors or uremic patients or evaluating PTH binding via radionuclide analysis or other parameters such as rosette formation.

Functional studies on the effects of PTH on immune cells also showed conflicting results. A stimulatory effect was observed in mast cells, with increased release of mediators after antigen stimulation in cells pre-treated with 1-34 PTH (Simpson et al. 1991). 1-84 and 1-34 PTH stimulated T lymphocyte proliferation in vitro, with no effects on CD4/CD8 ratio, and increased cAMP production (Klinger et al. 1990). The authors speculated that, *in vitro*, acute administration of PTH elicits a different response when

compared to prolonged exposure to steadily high PTH, mimicking hyperparathyroidism (Klinger et al. 1990). In fact, *in vitro* studies with supra-physiological concentrations of PTH have shown a dose-dependent suppressive effect on lymphocytic function, and a decreased helper/suppressor ratio (Shasha et al. 1988). More recent studies have mostly focused on the interactions between PTH and immune cells in the osteoimmune niche, and an exhaustive description of these results is out of the scope of this review.

While the results on the *in vitro* effects of PTH on immune cells are insightful because free of clinical confounding factors, these experiments are far from resembling the complex scenarios of human parathyroid disorders, where an impairment in the immune system is now becoming a clearer data (Underbjerg et al. 2018).

4 Infectious Diseases and Immune Alterations in *Secondary Hyperparathyroidism* due to Chronic Kidney Failure

Secondary hyperparathyroidism is a frequent complication of chronic kidney disease (CKD), as a response to renal failure and the consequent imbalance in electrolyte excretion and resorption. In particular, hyperphosphatemia, due to impaired phosphate excretion, is the main driver of hyperparathyroidism in CDK, followed by the reduction of serum ionized calcium (Chandran and Wong 2019). Long-standing secondary hyperparathyroidism can lead to tertiary hyperparathyroidism, characterized by the autonomous activity of parathyroid gland(s) that cause hypercalcemia (Chandran and Wong 2019).

High levels of PTH and CKD are tightly intertwined, and many efforts have been paid during the last decades to unveil the possible relationship between hyperparathyroidism and the complications that characterized early and late stages of renal failure. Infectious diseases, together with cardiovascular diseases, are the main causes of morbidity and mortality in patients affected by CKD (Goldblum and Reed 1980). The annual mortality for sepsis is up to 300-fold higher in dialysis patients compared to the general population (Sarnak and Jaber 2000; Powe et al. 1999), and patients also showed poor vaccination responses (Girndt et al. 1995) and high incidence of infections (Goldblum and Reed 1980).

The risk of infections is higher also in earlier stages of CKD. In an observational cohort study on 9697 participants (aged 53–75 years), the decrease in glomerular filtration rate was associated with a progressive increase in the hazard ratio for both infections and infection-related deaths (Ishigami et al. 2017). Similar findings have been reported also for community-acquired infections, with an incidence of 74/1000 person-years in case of normal eGFR and 419/1000 person-years in case of glomerular filtration rate lower than 30 ml/min (Xu et al. 2017).

The underlying immune function impairment is caused by many different mechanisms as uremic toxins (including cytokines accumulation), pro-inflammatory status, complement activation, chronic inflammation, malnutrition (Syed-Ahmed and Narayanan 2019) and it is not possible to isolate the contribution of every single factor. Platinga et al., in a study on 1010 dialysis patients in the USA, demonstrated a higher incidence rate for all infections in patients with high phosphate levels at baseline, early after the start of dialysis, when compared to patients with normal phosphate levels, even after adjustment for PTH levels, dialysis dosage, and vitamin D supplements (Plantinga et al. 2008). In this study, increased phosphate seems an independent risk factor for infections. Considering infection type, sepsis and osteomyelitis were more frequent than in the case of normal phosphate levels. In CKD, the levels of FGF23, a hormone responsible for renal excretion of phosphate and vitamin D metabolism, are higher from the early phase of the disease (Wahl and Wolf 2012) and are associated to increase mortality. Recent evidence supports the detrimental role of FGF23 in innate immune function, and in particular in macrophage, blocking M2 polarization and reducing

recruitment of polymorphonuclear leukocytes (PMNL) (Fitzpatrick et al. 2018) and increasing pro-inflammatory chemokines (Wallquist et al. 2018). FGF23 acts also indirectly through a reduction in active vitamin D levels. Even if high phosphate levels are the main stimulator of FGF23 synthesis, also PTH is able to induce FGF23 transcription in bone cells (Lanske and Razzaque 2014).

In addition to the abovementioned factors, also chronic secondary hyperparathyroidism can play a role in immune dysregulation since high PTH levels have been associated with an impaired innate and acquired immune response (summarized in Table 1).

High levels of PTH in dialysis patients cause impaired phagocytosis of PMNL, through decreased ATP content, elevated basal levels of cytosolic calcium, and, consequently, a smaller rise in intracellular ionized calcium levels in response to antibody (Alexiewicz et al. 1991). Moreover, prolonged exposure to PTH significantly inhibited the random migration of PMNL (Doherty et al. 1988) and impaired the bactericidal activity of PMNL mediated by the generation of oxidizing radicals (Kiersztejn et al. 1992). To confirm that high PTH levels, and not only renal failure, were the cause of impaired phagocytosis, Chervu et al. compared rats affected by chronic renal failure subjected or not to parathyroidectomy or verapamil treatment. The study demonstrated that phagocytosis was impaired in animals with high PTH and intracellular calcium levels, which determine a reduction in ATP levels and an increase in cytosolic basal calcium levels, according to earlier observations. To investigate whether PTH binding or PTH-mediated increase in basal intracellular calcium levels caused the alterations in phagocytosis, the authors showed that parathyroidectomy and verapamil treatment restored normal phagocytosis (Chervu et al. 1992), demonstrating the interdependence of hyperparathyroidism and alterations of intracellular calcium balance. Studies on human subjects demonstrated the role of calcium antagonists in improving PMNL phagocytosis in the uremic state as well (Massry and Smogorzewski 2001). An interventional trial on CKD patients demonstrated that parathyroidectomy (and consequent normalization of PTH levels) can reduce, but not normalize, intracellular calcium levels in PMNL (Deicher et al. 2005).

Overall, animal studies seem to confirm the direct role of high PTH in causing PMNL impairment, while human studies suggest that high PTH is probably involved in altered PMNL phagocytosis even if it is not the only factor, as confirmed by the partial positive effect of parathyroidectomy.

Not only innate but also acquired immunity may be altered in secondary hyperparathyroidism due to CKD. In dialysis patients, T cell function is impaired. T cells are less responsive to IL-2 and mitogens stimulation (Alexiewicz et al. 1990a), and serum from uremic patients inhibited T cell response *in vitro*, but this inhibition decreased significantly when samples were collected from the same patients after parathyroidectomy (Giacchino et al. 1985), suggesting a direct contribution of high PTH levels on altered T cell response. As observed in PMNL, the main reason for the detrimental action of PTH on T cells is the high resting levels of intracellular ionized calcium (Alexiewicz et al. 1990a; Ori et al. 1999), which alter calcium homeostasis and dampen intracellular calcium variations. Calcium signalling is essential for cell proliferation and cytokine activation, through the action of the calcium-dependent ATPase (Ori et al. 1999). In addition, the total number of T lymphocytes is reduced in haemodialysis patients, and these results have been indirectly associated with osteoprotegerin, which is increased in renal failure and may contribute to immune response downregulation (Eleftheriadis et al. 2013).

Subset redistribution has also been described in patients with secondary hyperparathyroidism. Considering T cells subpopulation analysed by flow cytometry in haemodialysis patients with normal (16 patients) or high (18 patients) PTH levels, Griveas et al. demonstrated an increase of CD2, CD3, CD3/CD8, CD3/CD4 and CD4/CD8 ratio in the group with high PTH (Griveas et al. 2005). Conversely, Angelini et al. demonstrated a decrease in CD4 subpopulation and an increase in CD8 subpopulation, that only occurred in patients

Table 1 Effects of high levels of PTH on immune cells in secondary hyperparathyroidism due to chronic kidney disease (CDK)

Main PTH-related immune function alterations in CKD patients		
Cells	Alterations	References
T cells	Reduced response to mitogens and IL-2 Reduced proliferation Reduced T cells count Decrease of CD4/increase of CD8 Th17 cells are increased whereas Treg cells are decreased	Alexiewicz et al. (1990a) Ori et al. (1999) Eleftheriadis et al. (2013) Ozdemir et al. (2002), Angelini et al. (1993) Lang et al. (2014)
PMN	Impaired phagocytosis Inhibited the random migration Impaired the bactericidal activity	Alexiewicz et al. (1991), Chervu et al. (1992) Doherty et al. (1988) Kiersztejn et al. (1992)
B lymphocytes	Reduced response to mitogens Reduced proliferation Reduced immunoglobulin production	Alexiewicz et al. (1990b), Gaciong et al. (1991) Raskova et al. (1987), Smogorzewski and Massry (2001) Raskova et al. (1987), Gaciong et al. (1991)

with hyperparathyroidism and not in patients with normal PTH levels (Angelini et al. 1993). A reduction of $CD4^+/CD8^+$ lymphocyte ratio in patients with hyperparathyroidism was also confirmed by Ozdemir et al. (Ozdemir et al. 2002). In haemodialysis patients Th17 cells are increased whereas Treg cells are decreased, with, respectively, a positive and negative correlation with phosphate levels (Lang et al. 2014). These findings could be important in clinical practice since Th17 cells are involved in the pathogenesis of autoimmune disease while Treg reduces T cell response; an imbalance between Th17 and Treg function could facilitate the inflammatory process typical of CKD (Lang et al. 2014).

Not all studies demonstrated a reduction in T cell response in CKD patients, but the heterogeneity of results could be due to different stimuli utilized in experimental settings. A study using not phytohemagglutinin (PHA), which can stimulate T response through T cell receptor, but staphylococcal enterotoxin B, which links also class 2 MHC complex, failed to demonstrate a difference between haemodialysis patients with high o normal PTH levels (Eleftheriadis et al. 2007). Furthermore, results from clinical studies on CKD patients could provide different results compared to in vitro analyses of PTH effects on lymphocytes from healthy donors. In fact, this possible discrepancy with the T cells alteration observed in CKD could be explained by the prolonged exposure to PTH which is typical of dialysis patients (Klinger et al. 1990; Shurtz-Swirski et al. 1995).

The function of B lymphocytes is also impaired in CKD. The proliferation of B cells, both dependent and independent from T-cells, is reduced in patients affected by CKD (Raskova et al. 1987). This reduction cannot be completely attributed to PTH excess even if it has been demonstrated that PTH is able to reduce significantly B cell proliferation (Smogorzewski and Massry 2001). Moreover, functional studies have shown that PTH can reduce B cell proliferation and function through an increase in cAMP (Alexiewicz et al. 1990b). As in T cells, the resting levels of intracellular ionized calcium are higher in B cells in CKD patients (Smogorzewski and Massry 2001) and nifedipine is able to restore intracellular calcium levels in B cells (Alexiewicz et al. 1997). Different studies demonstrated a reduction in immunoglobulin production in CKD patients in response to mitogen (Raskova et al. 1987) or various vaccines including hepatitis B (Kohler et al. 1984) and influenza (Cappel et al. 1983). Immunoglobulin production in response to Staphylococcus aureus Cowan I or with pokeweed mitogen was also lower in haemodialysis patients than controls and the treatment with PTH, at the initiation of B-cells culture, reduced IgG, IgM and IgA production by B lymphocytes (Gaciong et al. 1991).

Tsanno-Martins et al. analysed the effect of parathyroidectomy on T- and B-cell function of haemodialysis patients affected by severe secondary hyperparathyroidism, demonstrating an increase of the lymphoproliferative response to PHA and pokeweed mitogen after surgery (Tzanno-Martins et al. 2000), suggesting a direct role of lowering of PTH levels in obtaining normal T- and B-cell function.

A possible role for vitamin D has also been proposed in modulating immune function in patients with secondary hyperparathyroidism. Martinez et al. evaluated the presence of 1,25OH vitamin D receptor in PBMC: compared to healthy controls, the number and the maximal binding capacity of the receptors was lower in patients affected by secondary hyperparathyroidism and increased in case of primary hyperparathyroidism. After parathyroidectomy for primary hyperparathyroidism or kidney transplant for secondary hyperparathyroidism, the number of receptors normalized (Martinez et al. 1994).

In conclusion, even if the role of uremic toxins, malnutrition, vitamin deficiency, and drug therapy cannot be ignored (Smogorzewski and Massry 2001), the secondary hyperparathyroidism contributes to the immune system derangement in patients with CKD, and clinicians should, therefore, pay special attention to prophylaxis, patient education and prompt therapeutic measures due to the high risk of infections in these patients.

5 Infectious Diseases and Immune Alterations in *Primary Hyperparathyroidism*

Primary hyperparathyroidism is a common endocrine disease, characterized by hypercalcemia and elevated or inappropriately normal levels of parathyroid hormone (Walker and Silverberg 2018). In most cases, it is caused by a solitary parathyroid adenoma, while diffuse hyperplasia, multiple adenoma, and parathyroid carcinoma are less frequent (Marcocci and Cetani 2011). The classical clinical presentation of primary hyperparathyroidism includes skeletal, renal, gastrointestinal, neurological, and psychiatric manifestations (Cope 1966), even if more than 80% of patients in Europe and the USA are diagnosed incidentally, during biochemical examinations (Walker and Silverberg 2018).

An increased risk of infections has been described in patients affected by primary hyperparathyroidism and this disease could be used as a model for evaluating the role of PTH itself in immune function impairment because it is not burdened by the other systemic alterations that characterize CKD (Shasha et al. 1989). Nevertheless, only a few studies have focused on immune function in primary hyperparathyroidism.

In a study on 3 patients and 3 controls, Shasha et al. demonstrated a reduction in T cells count in patients (−40%), with an impaired response to the stimulation with PHA, that was restored after parathyroidectomy (Shasha et al. 1989). Patients also showed a decrease in $CD4^+$ and an increase in $CD8^+$ lymphocytes, while after surgery CD4/CD8 ratio increased (Shasha et al. 1989). A subsequent study on 12 patients and 9 controls confirmed that response to PHA was reduced in patients and that the observed alterations were restored after parathyroidectomy; however, this study did not confirm a reduction in peripheral blood mononuclear cells (PBMC) subpopulations in patients compared to controls, except for an increase in CD4 and a decrease in CD8 before parathyroidectomy, also associated with a reduced response to activation markers as IL-2 and transferrin receptor (Kotzmann et al. 1998). In primary hyperparathyroidism, neutrophil leukocyte chemotaxis was altered compared to the control group and was restored after parathyroidectomy (Nordenstrom et al. 1989). Differently from secondary hyperparathyroidism, Elias et al. demonstrated that serum from patients affected by hyperparathyroidism was able to promote both patients' and controls' lymphocyte proliferation after stimulations with mitogen (Elias et al. 1982); these findings are consistent with the concept that not only PTH *per se* but also the length of exposure plays a role in immune function derangement. All in all, while studies are concordant in describing a decreased response to mitotic stimuli from adaptive immunity,

published literature does not provide a consistent immune profiling or model for immune derangement under continuously increased PTH secretion, and the small size of available studies do not support causal speculation on the underlying mechanisms.

On the other hand, hyperparathyroidism has been associated also with autoimmune and haematological diseases related to B cell hyperactivations, as reported in case reports, in which parathyroidectomy reversed the condition (summarized in (Canas et al. 2013)). The authors hypothesized that PTH may stimulate B lymphocyte activity and differentiation into plasma cells with the subsequent non-physiological production of antibodies (Canas et al. 2013). Moreover, hyperparathyroidism is associated with low chronic inflammation, and this could also explain the increased cardiovascular risk of these patients (Christensen et al. 2012). This twofold effect on the immune system is common to many other immune-modulatory hormones. Hypercortisolism is an excellent paradigm of this concept: while at therapeutic dosages glucocorticoids usually act as powerful anti-inflammatory agents, chronic exposure to supra-physiological and anti-circadian cortisol levels can lead to low-grade inflammation, increased metabolic and cardiovascular risk (Sbardella et al. 2018) and immune derangement (Hasenmajer et al. 2020).

In conclusion, primary hyperparathyroidism seems associated to immune system rearrangement, with on one hand an increased risk of infections, which seems to be reduced by parathyroidectomy, and on the other hand, an increase in low chronic inflammation that, in some cases, can lead to the development of autoimmune and haematological diseases.

6 Infectious Diseases in *Hypoparathyroidism*

Hypoparathyroidism is a chronic and relatively rare disease characterized by inappropriately low levels of PTH. Hypoparathyroidism is characterized by impaired calcium resorption and reduced phosphate excretion leading to hypocalcaemia and hyperphosphoremia (Mannstadt et al. 2017). To maintain physiological levels of circulating calcium, patients with hypoparathyroidism require replacement therapy with active vitamin D metabolites and calcium supplements. More recently, synthetic and recombinant PTH replacement has been proposed for hypoparathyroidism, allowing patients to lower and even discontinue the "conventional" regimen (Mannstadt et al. 2013).

However, most studies on hypoparathyroidism have been focusing on its aetiology and biochemical control of the disease, while data on comorbidities, mortality, and concomitant diseases were scanty or from preclinical studies. To investigate these overlooked aspects, retrospective studies on nation-wide cohorts have been recently conducted, unveiling some unexpected results.

Due to previous studies reporting a protective effect of vitamin D against infections (Holick 2007), in a retrospective study on a Danish Nationwide cohort the authors investigated the risk of infections in patients with hypoparathyroidism, showing an unexpected increased risk of infectious diseases (Underbjerg et al. 2014).

Since hypoparathyroidism can be due or associated with autoimmune diseases or conditions characterized by an impaired immune response such as Di George syndrome, to avoid confounding factors, only patients with post-surgical hypoparathyroidism due to non-malignant causes were included in the study.

Patients with hypoparathyroidism showed an increased risk of hospitalization due to infectious diseases, with a Hazard Ratio of 1.42. Since patients with hypoparathyroidism are at increased risk of renal disease, nephrocalcinosis, and hypercalciuria due to the impairment of calcium resorption in the renal tubule, the authors also performed a risk evaluation excluding urinary tract infections, with a persistently increased overall risk. Furthermore, to rule out opportunistic or health-care-related infections, episodes within 90 months from hospital discharge for any cause were excluded, without altering the

previously observed increased risk. Interestingly, patients with hypoparathyroidism also had shown a tendency towards a lower risk for malignancies, even though the results did not achieve statistical significance (Underbjerg et al. 2014).

Undjerberg et al. also evaluated patients with non-surgical hypoparathyroidism from the Danish registries (Underbjerg et al. 2015). According to the results from the post-surgical population, patients with non-surgical hypoparathyroidism were at an increased risk for hospitalization due to infectious diseases as well, with a higher prevalence of upper airway and urinary tract infections compared to controls. The total number of infections, with or without including urinary tract infections, was also increased (Underbjerg et al. 2015). As for malignancies, patients with non-surgical hypoparathyroidism showed a significantly lower risk of developing any malignancy and gastrointestinal cancer (Underbjerg et al. 2015).

To correlate the observed increased risk for long-term comorbidities with biochemical parameters mirroring disease control and therapy efficacy, data from all patients with hypoparathyroidism were included in a case-control study estimating the risk of complication according to biochemical findings (Underbjerg et al. 2018). For what concerns infectious diseases, results from the study showed a significant correlation between infections and higher time-weighted average serum phosphate concentration, along with hypercalcaemic episodes. High plasma phosphate and higher calcium-phosphate product were also associated with mortality in hypoparathyroidism patients, highlighting the importance of phosphate homeostasis in hypoparathyroidism (Underbjerg et al. 2018). Increased phosphate levels are also present in secondary hyperparathyroidism associated to CKD, however data on immune effects of phosphate are lacking. Examining only the hypoparathyroidism cohort, patients assuming relatively high doses of activated vitamin D showed a reduced number of infectious diseases compared to their counterparts (Underbjerg et al. 2018), suggesting a protective role for higher vitamin D dosages against microbial agents. However, most patients with secondary hyperparathyroidism assume relatively high doses of active vitamin D metabolites and infection rate and severity is significantly increased in this population, suggesting that the protective action of vitamin D can only slightly reduce the infective risk when other factors such as electrolyte imbalance or severe alterations of PTH secretion are involved.

Data on the higher prevalence of infections in hypoparathyroidism have been recently confirmed from a study on a Scottish cohort (Vadiveloo et al. 2019), showing an increased adjusted Hazard Ratio for infectious diseases in hypoparathyroidism compared to controls. When stratification for aetiologies was performed, though, the risk was increased only in the hypoparathyroidism due to non-surgical causes and hypomagnesemia groups (Vadiveloo et al. 2019). According to the Danish cohort, mean serum calcium concentration did not associate with infections, while a significant association with mortality and renal failure was unveiled (Vadiveloo et al. 2019).

A very recent study (Puliani et al. 2021) has analysed immune profiling in patients with chronic post-surgical hypoparathyroidism under conventional replacement compared to matched healthy controls. Study results have shown significant alterations in hypoparathyroidism patients with reduced circulating monocytes (nearly halved compared to controls). Patients also showed decreased $CD4^+$ T lymphocytes, $CD4^+$ T regulatory lymphocytes and $CD4^+$ Naïve T Lymphocytes compared to controls and increased NK cells. All the altered immune parameters were directly correlated with ionized and total calcium and PTH levels and inversely correlated with phosphate levels, while only NK cells number was directly correlated with Vitamin D levels. Moreover, patients showed decreased expression of inflammatory cytokines such as TNF and granulocyte monocytes colony stimulating factor (GM-CSF). In this study, patients with hypoparathyroidism reported increased number of urinary

tract infections and longer duration of respiratory tract infections compared to controls. The authors also evaluated PTHr1 expression in patients and controls, confirming the presence of PTHr1 on all immune lineages in peripheral blood mononucleated cells. The number of cells expressing PTHr1 was lower in hypoparathyroidism, but the intensity of expression was increased. Immunofluorescence analysis showed surface and cytosol binding for PTHr1 (Puliani et al. 2021).

In conclusion, data from retrospective studies have recently demonstrated an increase in infectious diseases, pointing towards a physiological role of adequate PTH levels in maintaining a healthy immune response. However, in these epidemiological studies, analysis of biochemical parameters only showed a significant correlation with phosphate and calcium-phosphate product, while no correlations with calcium levels or other parameters were unveiled. Insights from a recent study demonstrated significant alterations in immune profiling in patients affected by hypoparathyroidism under conventional replacement therapy, suggesting possible underlying mechanisms for the observed increase in infectious diseases but further confirmation studies are needed (immune alterations in hypo- and hyperparathyroidism are summarized in Fig. 1).

7 PTH Disorders in the Context of Other Syndromes

PTH alterations may be isolated or part of other genetic syndromes or autoimmune poliendocrinopathy. 22q11.2 deletion syndrome (22q11.2DS) is a complex of immune imbalance, endocrine disease, congenital heart disease, palatal abnormalities, cognitive deficits and neuropsychiatric illnesses and immune alteration due to 22q11.2 microdeletion (McDonald-McGinn et al. 2015). Actually, the term Di George Syndrome is reserved to patients with the same clinical presentation, without harbouring 22q11.2 deletion (McDonald-McGinn et al. 2015). 22q11.2DS occurs in approximately 1:4000 births (McDonald-McGinn and Sullivan 2011). During childhood, immunodeficiency present in about 75% of patients, and it is caused by thymic hypoplasia and impaired T cell production. Patients show a reduced number of CD3+ T cells and IgA deficiency can also be present (Smith et al. 1998). The infectious rate of affected patients is significantly higher, and recurrent sinusitis or otitis media involve at least one third of patients; recurrent lower airway infections are also increased (Jawad AF, 11713452) while opportunistic infections are rare (Ryan et al. 1997). On the other hand, allergic disease (Staple et al. 2005) and all kind of autoimmune disorders are common in these patients. The latter present in about 10% of patients (McDonald-McGinn and Sullivan 2011). In case of complete thymic aplasia, T cells can be absent. Clearly, these patients can necessitate thymus transplant or a fully matched T-cell transplant (McDonald-McGinn and Sullivan 2011). No data on the possible collaboration of hypoparathyroidism in causing immune derangement in 22q11.2 DS/Di George syndrome are available, although pathogenesis of these alterations has been described and does not involve PTH imbalances.

Hypoparathyroidism can also be part of Autoimmune Polyglandular Syndrome type 1 (APS-1), which is characterized by the concomitant presence of at least two of three of the following chronic mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency (Guo et al. 2018). Other autoimmune diseases may be present, such as type 1 diabetes mellitus, autoimmune hepatitis, hypothyroidism and hypergonadotropic hypogonadism (Perheentupa 2006). The syndrome is caused by a mutation in autoimmune regulator (AIRE) gene (Rizzi et al. 2006), which encodes for a transcription factor implicated central tolerance. In fact, AIRE protein promotes negative selection of T cells, particularly in the thymus (Anderson and Su 2016). The impact of APS-1 on immune regulation is dual: on one hand, affected patients develop autoantibodies against tissue-specific antigens; on the other hand, patients can present candidiasis and other infections of oral mucosa, nails and esophagus, which usually required specific treatment and can lead to severe complication (Guo et al. 2018;

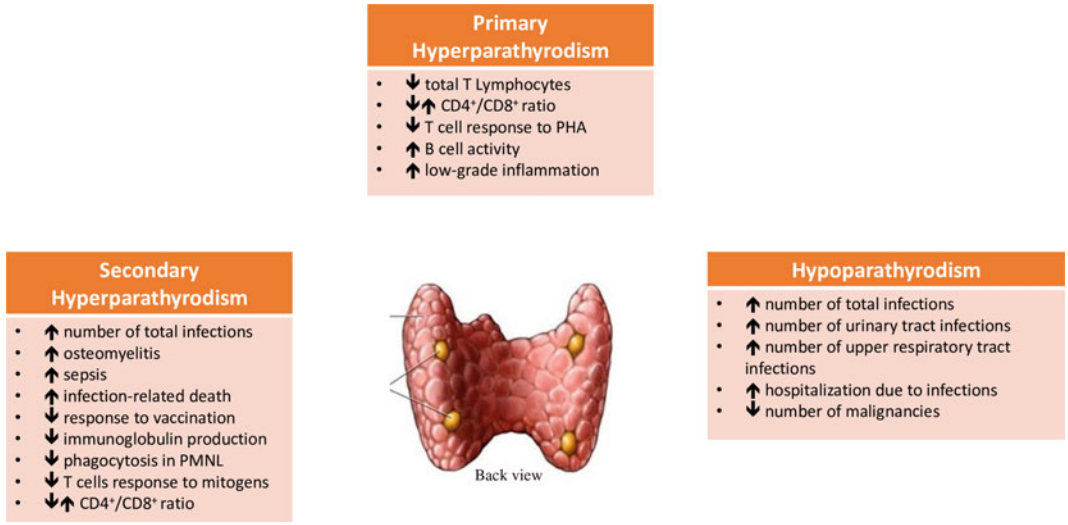

Fig. 1 Infection and immune-related complications in parathyroid disorders

Matheson and Mazza 2017). Potential contribution of hypoparathyroidism in candidiasis and infections in APS-1 patients is unknown.

Severe infections have been linked also to Hypoparathyroidism-Retardation-Dysmorphism (HRD) Syndrome. This is an autosomal recessive disorder caused by mutation in TBCE gene, that encodes one of the chaperone proteins necessary formation of α–β-tubulin heterodimers (Parvari et al. 2002). Affected patients can present susceptibility to recurrent bacterial infections, especially pneumococcal infections, sepsis, or relevant skeletal involvement (Hershkovitz et al. 2004). Immunological alterations found in patients with HRD are impairment of chemotactic migration and phagocytosis of PMN (Hershkovitz et al. 2007).

It is noteworthy that infections, in case of glandular involvement, can also cause PTH alterations. In this sense the link between infections and PTH dysfunction is a two-way path. In particular, it has been described that infection by M. tuberculosis can present as hyperparathyroidism (Mayo-Yanez et al. 2020; Kar et al. 2001; Singh et al. 2016). In a study describing 102 autopsy cases of patients affected by HIV, parathyroid hyperplasia was the most common histological alteration, with an higher frequency than controls (Cherqaoui et al. 2014). Beyond these histological examinations, another clinical study has demonstrated that HIV-affected patients showed lower levels of PTH than controls (Hellman et al. 1994), and both basal and EDTA stimulated PTH secretion is altered in HIV infected patients (Jaeger et al. 1994). On the contrary, parathyroid infection can also lead to glandular hypofunction. Interestingly, new onset hypoparathyroidism has been described also in a patient infected by Sars-Cov2 (Elkattawy et al. 2020).

8 Conclusions and Future Directions

Parathyroid disorders are characterized by alterations of calcium metabolism and non-physiological levels of PTH. Patients with hyper- and hypoparathyroidism are exposed to a higher risk of infectious diseases, increasing morbidity, and mortality. Throughout the last decades, many attempts in unveiling the pathophysiology of PTH and calcium metabolism disorders have been made, with conflicting results, and data from randomized trials are lacking. From our review emerged that hyperparathyroidism is associated to imbalances both in innate and in acquired immune response.

However, published studies have many limitations: most are on patients affected by hyperparathyroidism secondary to CKD, in which factors other than PTH can affect immune response, while other are *in vitro* studies or on animal models, and most of them were conducted with very heterogenous methods, compromising the reliability of results.

Therefore, trials on primary hyperparathyroidism and on the difference between patients who undergo surgical intervention (which is able to normalize PTH) compared to patients who receive medical therapy (which is able usually only to normalize calcium levels without normalizing PTH) might provide further explanation for the underlying mechanisms and long-term prognosis. Moreover, studies on normocalcemic hyperparathyroidism could highlight the potential detrimental role of high levels of PTH, independently from hypercalcemia.

In hypoparathyroidism, we have strong epidemiological data that show an increased risk of infections in hypoparathyroidism. mechanisms underling this condition are understudied, but a recent trial showed significant alterations in monocytes and $CD4^+$ lymphocytes. As in hyperparathyroidism, though, available studies are not powered enough to distinguish between the effects of PTH and those of concomitant biochemical alterations. Trials comparing conventional replacement therapy (calcium and calcitriol) and replacement therapy with PTH (PTH 1-84 or PTH 1-34) should therefore also include immunological evaluations in order to analyse the potential benefits of PTH replacement on infectious diseases and immune alterations. Finally, the evidence acquired so far is strong enough to suggest a major role for PTH in immune homeostasis and to prompt further translational studies.

In the era of precision medicine and tailored therapeutic approaches, the role of immune system as a biomarker of health and disease is increasing. Exploring the role of PTH on immune cells will help understanding the observed alterations in parathyroid disorders, evaluate the role of PTH replacement in preserving immune function in hypoparathyroidism and ultimately improve the quality of life and long-term longevity of patients with parathyroid disorders.

References

Alexiewicz JM et al (1990a) Evidence of impaired T cell function in hemodialysis patients: potential role for secondary hyperparathyroidism. Am J Nephrol 10 (6):495–501. https://doi.org/10.1159/000168175

Alexiewicz JM et al (1990b) Parathyroid hormone inhibits B cell proliferation: implications in chronic renal failure. J Am Soc Nephrol 1(3):236–244

Alexiewicz JM et al (1991) Impaired phagocytosis in dialysis patients: studies on mechanisms. Am J Nephrol 11(2):102–111. https://doi.org/10.1159/000168284

Alexiewicz JM et al (1997) A longitudinal study on the effect of nifedipine therapy and its discontinuation on [Ca2+]i and proliferation of B lymphocytes of dialysis patients. Am J Kidney Dis 29(2):233–238. https://doi.org/10.1016/s0272-6386(97)90035-4

Anderson MS, Su MA (2016) AIRE expands: new roles in immune tolerance and beyond. Nat Rev Immunol 16 (4):247–258. https://doi.org/10.1038/nri.2016.9

Angelini D et al (1993) Parathyroid hormone and T-cellular immunity in uremic patients in replacement dialytic therapy. Artif Organs 17(2):73–75. https://doi.org/10.1111/j.1525-1594.1993.tb00415.x

Baethge C et al (2019) SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev 4:5. https://doi.org/10.1186/s41073-019-0064-8

Bancos I et al (2017) Primary adrenal insufficiency is associated with impaired natural killer cell function: a potential link to increased mortality. Eur J Endocrinol 176(4):471–480. https://doi.org/10.1530/EJE-16-0969

Bedi B et al (2010) Inhibition of antigen presentation and T cell costimulation blocks PTH-induced bone loss. Ann N Y Acad Sci 1192:215–221. https://doi.org/10.1111/j.1749-6632.2009.05216.x

Canas CA et al (2013) Is primary hyperparathyroidism a pathogenic factor in some conditions mediated by B lymphocytes hyperactivity? Med Hypotheses 81 (1):111–113. https://doi.org/10.1016/j.mehy.2013.03.044

Cappel R et al (1983) Impaired humoral and cell-mediated immune responses in dialyzed patients after influenza vaccination. Nephron 33(1):21–25. https://doi.org/10.1159/000182898

Chandran M, Wong J (2019) Secondary and tertiary hyperparathyroidism in chronic kidney disease: an endocrine and renal perspective. Indian J Endocrinol Metab 23(4):391–399. https://doi.org/10.4103/ijem.IJEM_292_19

Cherqaoui R et al (2014) Histopathological changes of the thyroid and parathyroid glands in HIV-infected

patients. J Thyroid Res 2014:364146. https://doi.org/10.1155/2014/364146
Chervu I et al (1992) Impaired phagocytosis in chronic renal failure is mediated by secondary hyperparathyroidism. Kidney Int 41(6):1501–1505. https://doi.org/10.1038/ki.1992.219
Christensen MH et al (2012) Vitamin B6 status and interferon-gamma-mediated immune activation in primary hyperparathyroidism. J Intern Med 272 (6):583–591. https://doi.org/10.1111/j.1365-2796.2012.02570.x
Cope O (1966) The study of hyperparathyroidism at the Massachusetts General Hospital. N Engl J Med 274 (21):1174–1182. https://doi.org/10.1056/NEJM196605262742105
Deicher R et al (2005) Impact of parathyroidectomy on neutrophil cytosolic calcium in chronic kidney disease patients: a prospective parallel group trial. J Intern Med 258(1):67–76. https://doi.org/10.1111/j.1365-2796.2005.01508.x
Doherty CC et al (1988) Effect of parathyroid hormone on random migration of human polymorphonuclear leukocytes. Am J Nephrol 8(3):212–219. https://doi.org/10.1159/000167585
Eleftheriadis T et al (2007) No effect of serum parathyroid hormone level on antigen presenting cell-dependent T-cell reactivity in hemodialysis patients. Int Urol Nephrol 39(2):595–597. https://doi.org/10.1007/s11255-006-9100-y
Eleftheriadis T et al (2013) Serum osteoprotegerin is markedly increased and may contribute to decreased blood T cell count in hemodialysis patients. Int Urol Nephrol 45(6):1671–1677. https://doi.org/10.1007/s11255-012-0371-1
Elias AN et al (1982) Immunological aberration in primary hyperparathyroidism. Acta Endocrinol 101(1):47–50. https://doi.org/10.1530/acta.0.1010047
Elkattawy S et al (2020) A novel case of hypoparathyroidism secondary to SARS-CoV-2 infection. Cureus 12 (8):e10097. https://doi.org/10.7759/cureus.10097
Fitzpatrick EA et al (2018) Role of fibroblast growth Factor-23 in innate immune responses. Front Endocrinol (Lausanne) 9:320. https://doi.org/10.3389/fendo.2018.00320
Gaciong Z et al (1991) Inhibition of immunoglobulin production by parathyroid hormone. Implications in chronic renal failure. Kidney Int 40(1):96–106. https://doi.org/10.1038/ki.1991.186
Gao Y et al (2008) T cells potentiate PTH-induced cortical bone loss through CD40L signaling. Cell Metab 8 (2):132–145. https://doi.org/10.1016/j.cmet.2008.07.001
Giacchino F et al (1985) Parathyroid hormone as a uremic toxin: its influence on T lymphocyte receptors. Clin Nephrol 23(2):105–106
Girndt M et al (1995) Tetanus immunization and its association to hepatitis B vaccination in patients with chronic renal failure. Am J Kidney Dis 26 (3):454–460. https://doi.org/10.1016/0272-6386(95)90491-3
Goldblum SE, Reed WP (1980) Host defenses and immunologic alterations associated with chronic hemodialysis. Ann Intern Med 93(4):597–613. https://doi.org/10.7326/0003-4819-93-4-597
Griveas I et al (2005) Cellular immunity and levels of parathyroid hormone in uremic patients receiving hemodialysis. Ren Fail 27(3):275–278
Guo CJ et al (2018) The immunobiology and clinical features of type 1 autoimmune polyglandular syndrome (APS-1). Autoimmun Rev 17(1):78–85. https://doi.org/10.1016/j.autrev.2017.11.012
Hasenmajer V et al (2020) The immune system in Cushing's syndrome. Trends Endocrinol Metab. https://doi.org/10.1016/j.tem.2020.04.004
Hellman P et al (1994) Impaired parathyroid hormone release in human immunodeficiency virus infection. AIDS Res Hum Retrovir 10(4):391–394. https://doi.org/10.1089/aid.1994.10.391
Hershkovitz E et al (2004) Hypoparathyroidism-retardation-Dysmorphism (HRD) syndrome–a review. J Pediatr Endocrinol Metab 17(12):1583–1590. https://doi.org/10.1515/jpem.2004.17.12.1583
Hershkovitz E et al (2007) Hypoparathyroidism, retardation, and dysmorphism syndrome: impaired early growth and increased susceptibility to severe infections due to hyposplenism and impaired polymorphonuclear cell functions. Pediatr Res 62(4):505–509. https://doi.org/10.1203/PDR.0b013e31813cbf2d
Holick MF (2007) Vitamin D deficiency. N Engl J Med 357(3):266–281. https://doi.org/10.1056/NEJMra070553
Huang H et al (2010) Parathyroid hormone induction of cyclooxygenase-2 in murine osteoblasts: role of the calcium-calcineurin-NFAT pathway. J Bone Miner Res 25(4):819–829. https://doi.org/10.1359/jbmr.091019
Ishigami J et al (2017) CKD and risk for hospitalization with infection: the Atherosclerosis Risk in Communities (ARIC) study. Am J Kidney Dis 69 (6):752–761. https://doi.org/10.1053/j.ajkd.2016.09.018
Isidori AM et al (2018) Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. Lancet Diabetes Endocrinol 6(3):173–185. https://doi.org/10.1016/S2213-8587(17)30398-4
Jaeger P et al (1994) Altered parathyroid gland function in severely immunocompromised patients infected with human immunodeficiency virus. J Clin Endocrinol Metab 79(6):1701–1705. https://doi.org/10.1210/jcem.79.6.7989478
Kar DK et al (2001) Tuberculous granulomatous inflammation associated with adenoma of parathyroid gland manifesting as primary hyperparathyroidism. Endocr

Pathol 12(3):355–359. https://doi.org/10.1385/ep:12:3:355
Kiersztejn M et al (1992) Decreased O2 consumption by PMNL from humans and rats with CRF: role of secondary hyperparathyroidism. Kidney Int 42 (3):602–609. https://doi.org/10.1038/ki.1992.324
Klinger M et al (1990) Effect of parathyroid hormone on human T cell activation. Kidney Int 37(6):1543–1551. https://doi.org/10.1038/ki.1990.147
Kohler H et al (1984) Active hepatitis B vaccination of dialysis patients and medical staff. Kidney Int 25 (1):124–128. https://doi.org/10.1038/ki.1984.18
Kotzmann H et al (1998) Effects of parathyroid hormone and serum calcium on the phenotype and function of mononuclear cells in patients with primary hyperparathyroidism. Eur J Clin Investig 28(5):353–358. https://doi.org/10.1046/j.1365-2362.1998.00283.x
Lang CL et al (2014) Correlation of interleukin-17-producing effector memory T cells and CD4+CD25 +Foxp3 regulatory T cells with the phosphate levels in chronic hemodialysis patients. ScientificWorldJournal 593170:2014. https://doi.org/10.1155/2014/593170
Lanske B, Razzaque MS (2014) Molecular interactions of FGF23 and PTH in phosphate regulation. Kidney Int 86(6):1072–1074. https://doi.org/10.1038/ki.2014.316
Li JY et al (2014) The sclerostin-independent bone anabolic activity of intermittent PTH treatment is mediated by T-cell-produced Wnt10b. J Bone Miner Res 29 (1):43–54. https://doi.org/10.1002/jbmr.2044
Mannstadt M et al (2013) Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes Endocrinol 1(4):275–283. https://doi.org/10.1016/S2213-8587(13)70106-2
Mannstadt M et al (2017) Hypoparathyroidism. Nat Rev Dis Primers 3:17055. https://doi.org/10.1038/nrdp.2017.55
Mantovani G, Elli FM (2019) Inactivating PTH/PTHrP signaling disorders. Front Horm Res 51:147–159. https://doi.org/10.1159/000491045
Marcocci C, Cetani F (2011) Clinical practice. Primary hyperparathyroidism. N Engl J Med 365 (25):2389–2397. https://doi.org/10.1056/NEJMcp1106636
Marcocci C et al (2015) Italian Society of Endocrinology Consensus Statement: definition, evaluation and management of patients with mild primary hyperparathyroidism. J Endocrinol Investig 38(5):577–593. https://doi.org/10.1007/s40618-015-0261-3
Marcucci G et al (2018) HypoparaNet: a database of chronic hypoparathyroidism based on expert medical-surgical centers in Italy. Calcif Tissue Int 103 (2):151–163. https://doi.org/10.1007/s00223-018-0411-7
Martinez J et al (1994) 1,25-Dihydroxyvitamin D3 receptors in peripheral blood mononuclear cells from patients with primary and secondary hyperparathyroidism. Bone Miner 27(1):25–32. https://doi.org/10.1016/s0169-6009(08)80183-3
Massry S, Smogorzewski M (2001) Dysfunction of polymorphonuclear leukocytes in uremia: role of parathyroid hormone. Kidney Int Suppl 78:S195–S196. https://doi.org/10.1046/j.1523-1755.2001.59780195.x
Matheson A, Mazza D (2017) Recurrent vulvovaginal candidiasis: a review of guideline recommendations. Aust N Z J Obstet Gynaecol 57(2):139–145. https://doi.org/10.1111/ajo.12592
Mayo-Yanez M et al (2020) Parathyroid gland hyperplasia associated with tuberculous granulomatous inflammation manifesting as primary hyperparathyroidism. Med Mal Infect 50(8):738–741. https://doi.org/10.1016/j.medmal.2020.07.002
McDonald-McGinn DM, Sullivan KE (2011) Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Medicine (Baltimore) 90(1):1–18. https://doi.org/10.1097/MD.0b013e3182060469
McDonald-McGinn DM et al (2015) 22q11.2 deletion syndrome. Nat Rev Dis Primers 1:15071. https://doi.org/10.1038/nrdp.2015.71
Minkin C et al (1977) Effects of parathyroid hormone and calcitonin on adenylate cyclase in murine mononuclear phagocytes. Biochem Biophys Res Commun 76 (3):875–881. https://doi.org/10.1016/0006-291x(77)91582-0
Nordenstrom J et al (1989) Neutrophil leucocyte function in primary hyperparathyroidism. J Clin Lab Immunol 29(2):91–94
Ori Y et al (1999) Impaired lymphocyte calcium metabolism in end-stage renal disease: enhanced influx, decreased efflux, and reduced response to mitogen. J Lab Clin Med 133(4):391–400. https://doi.org/10.1016/s0022-2143(99)90071-9
Ozdemir FN et al (2002) Role of parathormone levels on T-cell response in hemodialysis patients. Transplant Proc 34(6):2044–2045. https://doi.org/10.1016/s0041-1345(02)02846-4
Pacifici R (2016) The role of IL-17 and TH17 cells in the bone catabolic activity of PTH. Front Immunol 7:57. https://doi.org/10.3389/fimmu.2016.00057
Parvari R et al (2002) Mutation of TBCE causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. Nat Genet 32(3):448–452. https://doi.org/10.1038/ng1012
Perheentupa J (2006) Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. J Clin Endocrinol Metab 91(8):2843–2850. https://doi.org/10.1210/jc.2005-2611
Perry HM 3rd et al (1984) Parathyroid hormone receptors in circulating human mononuclear leukocytes. J Biol Chem 259(9):5531–5535
Plantinga LC et al (2008) Serum phosphate levels and risk of infection in incident dialysis patients. Clin J Am Soc Nephrol 3(5):1398–1406. https://doi.org/10.2215/CJN.00420108

Powe NR et al (1999) Septicemia in dialysis patients: incidence, risk factors, and prognosis. Kidney Int 55 (3):1081–1090. https://doi.org/10.1046/j.1523-1755.1999.0550031081.x

Puliani G, Hasenmajer V, Sciarra F, Barbagallo F, Sbardella E, Pofi R, Gianfrilli D, Romagnoli E, Venneri MA, Isidori AM. Impaired Immune Function in Patients with Chronic Postsurgical Hypoparathyroidism: Results of the EMPATHY Study. J Clin Endocrinol Metab. 2021 Jan 23: dgab038. https://doi.org/10.1210/clinem/dgab038. Online ahead of print. PMID: 33484559

Raskova J et al (1987) B-cell activation and immunoregulation in end-stage renal disease patients receiving hemodialysis. Arch Intern Med 147(1):89–93

Rizzi M et al (2006) Disruption of immunological tolerance: role of AIRE gene in autoimmunity. Autoimmun Rev 5(2):145–147. https://doi.org/10.1016/j.autrev.2005.09.001

Robinson JW et al (2015) T cell-expressed CD40L potentiates the bone anabolic activity of intermittent PTH treatment. J Bone Miner Res 30(4):695–705. https://doi.org/10.1002/jbmr.2394

Ryan AK et al (1997) Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet 34(10):798–804. https://doi.org/10.1136/jmg.34.10.798

Sarnak MJ, Jaber BL (2000) Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int 58(4):1758–1764. https://doi.org/10.1111/j.1523-1755.2000.00337.x

Sbardella E et al (2018) Cardiovascular features of possible autonomous cortisol secretion in patients with adrenal incidentalomas. Eur J Endocrinol 178(5):501–511. https://doi.org/10.1530/EJE-17-0986

Shasha SM et al (1988) In vitro effect of PTH on normal T cell functions. Nephron 50(3):212–216. https://doi.org/10.1159/000185160

Shasha SM et al (1989) Effect of parathyroidectomy on T cell functions in patients with primary hyperparathyroidism. Am J Nephrol 9(1):25–29. https://doi.org/10.1159/000167930

Shurtz-Swirski R et al (1995) Parathyroid hormone and the cellular immune system. Nephron 70(1):21–24. https://doi.org/10.1159/000188538

Silva BC, Bilezikian JP (2015) Parathyroid hormone: anabolic and catabolic actions on the skeleton. Curr Opin Pharmacol 22:41–50. https://doi.org/10.1016/j.coph.2015.03.005

Simpson KM et al (1991) Potentiation of antigen-induced mast cell activation by 1-34 bovine parathyroid hormone. Proc Soc Exp Biol Med 197(1):44–48. https://doi.org/10.3181/00379727-197-43222

Singh HP et al (2016) Parathyroid adenoma associated with granulomatous inflammation: a curious cause of Hypercalcaemia. J Clin Diagn Res 10(4):ED21–ED22. https://doi.org/10.7860/JCDR/2016/18600.7623

Smith CA et al (1998) Increased prevalence of immunoglobulin A deficiency in patients with the chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Clin Diagn Lab Immunol 5(3):415–417

Smogorzewski M, Massry SG (2001) Defects in B-cell function and metabolism in uremia: role of parathyroid hormone. Kidney Int Suppl 78:S186–S189. https://doi.org/10.1046/j.1523-1755.2001.59780186.x

Staple L et al (2005) Allergies in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) and patients with chronic granulomatous disease. Pediatr Allergy Immunol 16(3):226–230. https://doi.org/10.1111/j.1399-3038.2005.00259.x

Stock JL, Coderre JA (1982) Calcitonin and parathyroid hormone inhibit accumulation of cyclic AMP in stimulated human mononuclear cells. Biochem Biophys Res Commun 109(3):935–942. https://doi.org/10.1016/0006-291x(82)92030-7

Syed-Ahmed M, Narayanan M (2019) Immune dysfunction and risk of infection in chronic kidney disease. Adv Chronic Kidney Dis 26(1):8–15. https://doi.org/10.1053/j.ackd.2019.01.004

Tawfeek H et al (2010) Disruption of PTH receptor 1 in T cells protects against PTH-induced bone loss. PLoS One 5(8):e12290. https://doi.org/10.1371/journal.pone.0012290

Terauchi M et al (2009) T lymphocytes amplify the anabolic activity of parathyroid hormone through Wnt10b signaling. Cell Metab 10(3):229–240. https://doi.org/10.1016/j.cmet.2009.07.010

Tzanno-Martins C et al (2000) Restoration of impaired T-cell proliferation after parathyroidectomy in hemodialysis patients. Nephron 84(3):224–227. https://doi.org/10.1159/000045581

Underbjerg L et al (2014) Postsurgical hypoparathyroidism--risk of fractures, psychiatric diseases, cancer, cataract, and infections. J Bone Miner Res 29 (11):2504–2510. https://doi.org/10.1002/jbmr.2273

Underbjerg L et al (2015) The epidemiology of nonsurgical hypoparathyroidism in Denmark: a Nationwide Case Finding Study. J Bone Miner Res 30 (9):1738–1744. https://doi.org/10.1002/jbmr.2501

Underbjerg L et al (2018) Long-term complications in patients with hypoparathyroidism evaluated by biochemical findings: a case-control study. J Bone Miner Res 33(5):822–831. https://doi.org/10.1002/jbmr.3368

Urena P et al (1993) Parathyroid hormone (PTH)/PTH-related peptide receptor messenger ribonucleic acids are widely distributed in rat tissues. Endocrinology 133(2):617–623. https://doi.org/10.1210/endo.133.2.8393771

Vadiveloo T et al (2019) Increased mortality and morbidity in patients with chronic hypoparathyroidism: a population-based study. Clin Endocrinol 90 (2):285–292. https://doi.org/10.1111/cen.13895

Wahl P, Wolf M (2012) FGF23 in chronic kidney disease. Adv Exp Med Biol 728:107–125. https://doi.org/10.1007/978-1-4614-0887-1_8

Walker MD, Silverberg SJ (2018) Primary hyperparathyroidism. Nat Rev Endocrinol 14(2):115–125. https://doi.org/10.1038/nrendo.2017.104

Wallquist C et al (2018) Associations of fibroblast growth factor 23 with markers of inflammation and leukocyte transmigration in chronic kidney disease. Nephron 138 (4):287–295. https://doi.org/10.1159/000485472

Xu H et al (2017) eGFR and the risk of community-acquired infections. Clin J Am Soc Nephrol 12 (9):1399–1408. https://doi.org/10.2215/CJN.00250117

Yamamoto I et al (1983) Circulating bovine lymphocytes contain receptors for parathyroid hormone. J Clin Invest 71(2):404–407. https://doi.org/10.1172/jci110784

Yu M et al (2018) Regulatory T cells are expanded by Teriparatide treatment in humans and mediate intermittent PTH-induced bone anabolism in mice. EMBO Rep 19(1):156–171. https://doi.org/10.15252/embr.201744421