

REVIEW

## SECONDARY HYPERPARATHYROIDISM ASSOCIATED WITH CHRONIC KIDNEY DISEASE. UPDATED REVIEW ON THERAPEUTICAL MANAGEMENT

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### Abstract

*While a full and complete understanding of the pathogeny of secondary hyperparathyroidism in chronic kidney disease is not acknowledged yet, it is important that this condition has a high impact on the mortality and morbidity of dialysis patients. The intention of this review is to take us on a short journey to understand a bit more about this associated conditions and to explore how a treatment may be assembled to the best possibility at this point in time. From the basis of physiopathology we can state that in chronic kidney disease the hyperparathyroidism appears as a result of low renal function and its alteration of phosphor-calcemic homeostasis. The discussion between the borderline of medical therapy and a surgical approach is crucial. The correct administration of treatment following strictly the therapeutical scheme is absolutely mandatory. Furthermore, in the advanced cases the experience of the surgeon may be a barrier between the life and death of the patient.*

**Keywords:** *secondary hyperparathyroidism, chronic renal disease, therapy*

### Introduction

Secondary hyperparathyroidism refers to the excessive production of parathyroid hormone (PTH) by the parathyroid glands in response to low blood calcium levels, indifferent of its cause. In chronic kidney disease (CKD), the hyperparathyroidism appears as a direct result of the decreased renal function and the alteration of the phospho-calcium homeostasis. While a full and complete understanding of the pathogeny of secondary hyperthyroidism in chronic kidney disease is not acknowledged yet, it is important that this condition has a high impact on the mortality and morbidity of dialysis patients. The hypocalcemia, due to reduced synthesis of

calcitriol, the active vitamin D metabolite and the hyperphosphatemia provides persistent stimuli [1], leading to the enlargement of parathyroid glands and high parathyroid hormone secretion. What is of a great importance at this stage is the early diagnosis of secondary hyperparathyroidism, especially in chronic kidney disease [2], even though at this point in time the treatment and cure for this condition remains a challenge for the patient and the medical doctor. From the basis of the pharmacology we can state that a correct treatment protocol should include a combination of phosphate binders, dietary phosphorus restriction, Vitamin D analogues and calcimimetics [3]. In some cases treatment may reach as far as the association with the surgical

removal of the affected parathyroid glands. This short and concise article takes us on a short journey to explore both the physiopathological and the pathogenic mechanisms behind chronic kidney failure associated with secondary hyperparathyroidism, but also provides us with an updated therapeutical approach for the current management of this condition.

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## Materials and methods

This review aim is to provide an update on the therapeutical options for secondary hyperparathyroidism as a result of chronic kidney disease. Using a wide range of books from the medical literature applying for this domain and a variety of the new updated articles on treatment options we can conceive such a review.

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## Discussions and Results

Chronic Kidney Disease in a simple medical definition is stated as being structural and/or functional renal abnormalities persisting for more than 3 months with a decreased glomerular filtration rate and albuminuria. This condition is of a high medical importance for health care services, having a prevalence of 8-17% [4]. From the medical literature, we can understand the latest classification of chronic kidney disease. This classification is based on the presence of a decreased glomerular filtration rate regardless of its parenchymal damage for stages III or higher only [5]. However, the presence of parenchymal damage is taken into account for stages I and II [6]. The most common stage of chronic kidney disease is stage III, for which only 30% of patients reach an age of 70 years or more [7].

Having this basic medical knowledge about the chronic kidney disease we can now deepen our understanding on how the secondary hyperparathyroidism together with other complications arise from this renal disease.

Taking a closer look into the pathophysiological mechanism we can identify that when the glomerular filtration rate decreases, the phosphorus clearance decreases significantly, leading to phosphorus retention.

This hyperphosphatemia is thought to be one of the principal cause of secondary hyperparathyroidism.[8] At this level we can describe 3 mechanisms by which phosphorus induces PTH release [9]:

1. Direct stimulatory effect on the parathyroid glands.
2. Induction of mild hypocalcemia by precipitating with calcium as  $\text{CaHPO}_4$ .
3. The actual stimulation on Fibroblast Growth Factor (FGF-23) induces a severe inhibition of the of  $1-\alpha$  hydroxylase and decreased level of 1,25 dihydroxyvitamin D, more commonly known as calcitriol [10]. This points to a downregulation of the receptors found on the parathyroid glands for vitamin D which would lead eventually to a vitamin D resistance [11]. In short we can say that, the combination of decreased levels of calcitriol and the loss of its negative feedback on the parathyroid glands results in an elevated PTH level.

In other words, the fall of glomerular filtration rate  $< 60 \text{ ml/min/1,73m}$  and the decrease of renal mass leads to 3 main modifications:

- a. Decrease of Calcitriol
- b. Hypocalcemia
- c. Hyperphosphatemia

As a result of these modifications PTH hypersecretion and parathyroid glands hyperplasia develops.

Moreover, one of today's leading causes of bone disease and renal osteodystrophy is considered to be secondary hyperparathyroidism [12]. Some initial and common signs and symptoms include the bone deformation and fractures together with the frequent bone and joint pain. Two classical conditions are described at this stage: Osteitis Fibrosa Cystica and Adynamic Bone Disease [13]. Taking a deeper look on these two conditions we have on the one hand, Osteitis Fibrosa Cystica that is mainly caused by a by a high bone turnover due to elevated levels of circulating PTH. While on the other hand, we have Adynamic Bone Disease that appears as a result of low bone turnover due to prolonged PTH suppression. In fact, in most recent medical literature we find a description known as skeletal resistance that is a natural mechanism of the bone to defend itself against elevated levels of PTH, this is associated

with the last stages of CKD when the number of receptors for PTH in the skeleton is downregulated [14]. That said, we can understand how a clinical sign bone disease and bone symptoms are actually the result of a hidden secondary hyperparathyroidism of the chronic kidney disease diagnosis.

Taking the discussion into the management and treatment of the secondary hyperparathyroidism: the management of this condition is a complex approach that ideally requires a multidisciplinary communication between the nephrologist, endocrinologist, cardiologist, dietician, and the patient.

The medical therapy of the secondary hyperparathyroidism consists of a low phosphorus diet, phosphate binders, vitamin D derivatives and calcimimetics- Cinacalcet. Therefore, a logical scheme for the treatment can be classified into 2 simple phases [15].

1. Phase 1: has a goal to optimize the level of serum calcium and phosphate [16], their levels being controlled according to CKD stage and to prevent the parathyroid enlargement and hypersecretion. This is mainly achieved by dietary restrictions and phosphate binders and administration of calcitriol [17,18].

2. Phase 2: has as goal to control the PTH and vitamin D levels by further association of calcimimetics., especially in the cases when calcium and phosphorus levels are close to the upper limit of normal [19,20].

If, despite the adequate medical treatment, the PTH value remains increased, with the possibility of developing a tertiary hyperparathyroidism form, and the alteration of the phospho-calcium homeostasis still persists, the only possible solution would be a surgical treatment. The surgical excision of the abnormal parathyroid tissue is potentially the definitive therapy of this disease [21].

Looking at a deeper level to the surgical procedure we can describe the following aspects:

- First of all the surgical procedure takes place only if the as mentioned before, if despite the correct treatment the PTH value remains significantly elevated.

- During this surgical procedure general anesthesia is preferred due to the comfort in the operating theatre. It provides better security conditions allowing a permanent monitorisation

of the vital signs, especially in the case of changes of rhythm in patients with cardiovascular conditions and hyperkalemia. Also, it gives the surgeon more time to evaluate all parathyroid glands (even ectopically located ones) and promoting a vigorous hemostasis throughout.

- The incision is done transversely at the cervical level of neck, anteriorly.

- By this means we surgically expose the thyroid gland with each thyroidian lobe.

- The surgeon continues to explore the parathyroid region both superiorly and inferiorly, bilaterally. The tumoral parathyroid glands have to be detected both visually and manually.

- We can describe the 4 affected parathyroid glands to each have a diameter of 0.5 - 3 cm and most importantly with a firm and tough consistency. The consistency is a significant differential aspect between the primary and secondary hyperparathyroidism, since usually in the case of primary condition the tumor has a typical elastic texture.

- One of the most important aspects of the surgical procedure is the dissection of the recurrent laryngeal nerve bilaterally. If this is not done, the voice box of the patient will be affected permanently in the best case scenario.

- The surgeon removes 3 parathyroid glands and half of the last affected gland. The remaining half is kept together with its parathyroid artery, and they are installed with colored wire or metallic clip in the pre-thyroid muscle. In the case of a future surgical intervention this remaining half of the 4th parathyroid gland is easily found.

Usually the minimally invasive parathyroidectomy is not used in the case of these patients since each of the 4 parathyroid gland would need to be locally exposed resulting into 4 procedures one after the other. Moreover, a significant disadvantage for this type of procedure in the case of secondary hyperparathyroidism is the poor hemostasis outcome [22].

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## Conclusions

In conclusion, we must state that any patient diagnosed with chronic kidney disease

must be closely monitored for all possible complications including secondary hyperparathyroidism. This is a complex situation that needs an interdisciplinary approach. Also of great importance is to correctly administer the phases of the treatment scheme, especially the doses of the vitamin D in order to prevent or delay the secondary hyperparathyroidism. As stated before, in advanced cases the experience of the surgeon is crucial during the medical intervention. Research on developing more advanced therapeutical approaches still continues.

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