Chapter

Introductory Chapter: A Brief Statement about Parathyroid Glands

Beyza Goncu and Robert Gensure

1. Introduction

1.1 Discovery

Almost two centuries have passed since the discovery of parathyroid glands. Many studies have been carried out on their function and effectiveness. Many known and reputable books and studies are already available by respected scientists worldwide, including information about its embryological, developmental, anatomical, functional, and clinical importance, diagnosis, related diseases, and treatment processes. During the discovery process, the naming of the parathyroid organ was determined entirely according to its location. Considering the given name, the importance of the function provided by the parathyroid gland seems relative to be less effective than the other endocrine organs. Furthermore, the public often exposes it to preliminary assumptions as an organ related to thyroid tissue. However, they have nothing in common except that they are two organs with very different functions.

Parathyroid glands release parathormone (PTH) to perform its function and regulate the metabolism of blood calcium, phosphorus, vitamin D, and magnesium in this way [1]. Common diseases of the parathyroid glands are defined as hyperparathyroidism when the organ overproduces PTH, and hypoparathyroidism, when the organ produces less PTH or lacks PTH [2]. In the absence of the organ or the case of insufficient blood supply, individuals become deprived of the PTH hormone and its regulation.

2. Related diseases

Hyperparathyroidism is observed in cases where the function of the parathyroid glands increases above the average level. Hyperparathyroidism can occur as a secondary disease as a result of another condition. The primary disease, in this case, is chronic renal failure that causes secondary hyperparathyroidism [3]. Primary disease treatment processes are the main reason for the development of hyperparathyroidism. As a palliative treatment approach, patients are advised to use calcimimetics to suppress the production of higher PTH. Individuals have to take dialysis in cases where chronic kidney disease treatment cannot be provided. Thus, years spent in dialysis lead to overproduced PTH and increased proliferating signals to the parathyroid glands [4]. Growing parathyroid glands will release more PTH and pressure the target organs, such as bones. The individuals are partially excised by surgical methods at a certain period of their lives. Partial surgery defines as subtotal parathyroidectomy, meaning three glands plus half of the fourth gland. Rarely there are supernumerary parathyroid glands in patients [5].

Nevertheless, the surgeon may control the decreased PTH level during surgery (subtotal parathyroidectomy) or, if observed by scintigraphy, then may remove the extra gland.

Further, among four parathyroid glands, hyperparathyroidism is also observed without primary reason and is called primary hyperparathyroidism. One or very rarely two of the glands may overproduce PTH. After the exact diagnosis, it is possible to treat by surgical intervention [6–8]. Another type of hyperparathyroidism is paraneoplastic hyperparathyroidism, which is very rare. Parathyroid hormone-related peptide (PTH-rp) production increases over average PTH levels due to hypercalcemia [9].

Hypoparathyroidism occurs for autoimmune or idiopathic or iatrogenic reasons. Autoimmune-related parathyroid gland diseases are observed due to genetic factors [10]. In addition, it should not be forgotten that genetic factors are considered "rare diseases" when looking at parathyroid-gland-related diseases. However, the most striking part here is that there is no known treatment option for parathyroid-gland-related genetic diseases, and developmental anomalies are observed in most diseases.

Moreover, idiopathic hypoparathyroidism refers to insufficient PTH secretion unrelated to secondary or acquired reasons. Idiopathic individuals constitute the relatively most unknown disease group for hypoparathyroidism. Iatrogenic hypoparathyroidism is observed when the surgeon unintentionally damages or removes the parathyroid gland in cases such as thyroid gland operations. Whether it is genetic, idiopathic, or iatrogenic reasons, one common problem occurs: the lack of parathyroid gland function [2, 11]. Besides, the majority of hypoparathyroidism patients are individuals who have the disease due to iatrogenic reasons. Considering the purpose and regulation mechanisms of parathyroid glands, it has a significant role in the human body. If a lack of function is observed, individuals must accept a complicated process that lasts their entire lives: permanent hypoparathyroidism [12, 13]. The regimens that should be used after that diagnosis are a part of palliative treatment that is far from improving the patient's quality of life. Much information has already been shared about the number of medicines only aimed at symptomatic treatment. Side effects and secondary diseases that may develop are becoming more severe as time passes. Individuals experiencing many side effects related to medications have been reported. In cases where symptomatic treatment is insufficient, studies about the decrease in the medication's efficiency, the time-dependent increase in the amount of medication, and the incidence of observed disorders such as anxiety and depression are rapidly taking place in the literature [14–16].

2.1 Concerns

Contemporary studies offered a specific disease-characteristic questionnaire to measure disease manifestations for hypoparathyroidism patients. In 2019, Wilde et al. used an analytical empirical approach based on retrospective analysis without involving non-disease-specific questionnaires. These testing revealed major complaints include pain and cramps, gastrointestinal symptoms, depression and anxiety, neurovegetative symptoms, and loss of vitality [17]. A recent study by Bilginer et al. performed a medication adherence questionnaire (MAQ) to hypoparathyroidism patients concerning motivation and knowledge about the palliative treatment option. Observed concerns mainly involved the side effects such as nephrotoxicity for using calcium, and kidney damage, polyuria for using active vitamin D supplementation [15]. Considering its psychological effects, hypoparathyroidism, which affects the quality of life, is evaluated from a broader perspective with current studies. In a pilot study, it was even shown that the cognitive functions of hypoparathyroidism patients were weakened

[18]. More studies are urgently needed to prevent hypoparathyroidism from the very beginning. The iatrogenic causes after thyroid surgery must be reduced.

Parathyroid imaging is essential for the location and diagnosis of hyperfunctioning glands correctly. In 2021, the European Association of Nuclear Medicine (EANM) proposed a guideline about the imaging of parathyroid glands. Several approaches and techniques were presented for nuclear medicine physicians who perform parathyroid scintigraphy, single-photon emission computed tomography/computed tomography (SPECT/CT), positron emission tomography/computed tomography (PET/CT), and positron emission tomography/magnetic resonance imaging (PET/MRI). Assessing the localization of hyperfunctioning parathyroid lesions will be more accessible by this guideline [19].

3. Treatment Options

Reckoning the diseases associated with the parathyroid tissue, the treatment options are somewhat more limited. In the development of biomedical technology, two promising treatment options come forward, particularly in the treatment of hypoparathyroidism patients: the first is hormone replacement therapy [20, 21], and the second is parathyroid transplantation [22].

3.1 Hormone replacement therapy

Hormone replacement therapy provides the chance to treat the disease in a targeted way, in this sense, Natpara®, whose Phase studies have continued success for many years [23]. However, the manufacturer has recently announced that it would not continue producing due to technical problems [24]. Transcon PTH™, a prodrug product developed for a new PTH hormone therapy, also announced that it has applied to the Food and Drug Administration (FDA) for a Phase 3 study this year [25].

3.2 Parathyroid transplantation

Parathyroid transplantation is another treatment option for hypoparathyroidism, which has a 110-year history. The first transplant belonged to Brown in 1911 [26]. In the process that started after this date in history, many researchers/physicians continued to contribute to the improvement and efficiency of parathyroid transplantation [27]. Parathyroid gland transplantation is a method still used in today's transplantation processes shared by the Cleveland Clinic [28]. Among all parathyroid transplantations, the most extensive clinical series in the literature belongs to the Warsaw group from the University of Warsaw in Poland [29]. In 2017, they reported the survival results of 316 allotransplantation data. Since the early 1990s, many research projects have been added to the literature about cell isolation, graft delivery location, and follow-up parameters from the same group [29–33]. During the last five years of the parathyroid transplantation, advanced immunological transplantation criteria, including pre-op and post-follow-up processes after parathyroid transplantation, were brought to the literature by the same group from Bezmialem Vakif University in Turkiye [22, 34–43]

Parathyroid transplantation is the most effective and targeted hypoparathyroidism treatment in the literature due to limited access to hormone replacement therapy and ongoing phase studies. Long-term studies on research and parathyroid

transplantation outcomes are carried out in the literature at specific intervals. Treatment options for hypoparathyroidism have certain boundaries with more specific approaches than hyperparathyroidism. On the subject of hyperparathyroidism disorders, primary hyperparathyroidism is treated with surgical intervention and is rarely seen recurrently. Secondary hyperparathyroidism is due to another primary disease, and calcimimetics are recommended to reduce the pressure on the parathyroid glands. Considering the complaints we received from patients regarding the side effects of calcimimetics, the need for more research about the formulation of pharmaceuticals reveals that necessity.

4. Conclusion

The existing literature on treatment options for parathyroid gland diseases provides promising results. Simultaneous cellular and molecular biology studies are undoubtedly necessary and have positive effects in providing diagnostic, therapeutic, and predictive options. The unique function of the parathyroid glands and the inability to adequately treat the cause of the disease illustrate the urgent need for large cohort studies to be established. Even though the collaboration between the researchers on this subject is a fading dream, the editors hope this book will inspire such cooperation among scientific circles.

Conflict of interest

The authors declare no conflict of interest.

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