Assessment of total parathyroidectomy with and without autoimplantation in prevalent hemodialysis patients

Thesis

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List of abbreviations

25OHD	25-hydroxyvitamin D
ALP	Alkaline Phosphatase
BMP	bone morphogenetic protein
cAMP	Cyclic adenosine monophosphate
CaSR	Calcium sensing receptors
CKD	Chronic Kidney Disease
DCT	distal convoluted tubule
DM	Diabetes Mellitus
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FGF23	Fibroblast growth factor 23
FGFR	Fibroblast growth factor receptor
Hb	Hemoglobin
HPO_4	Phosphoric acid
iPTH	Intact parathyroid hormone
IQR	Interquartile Range
K/DOQI	Kidney diseases outcome quality initiative
KDIGO	Kidney Disease: Improving Global Outcomes
MBD	Mineral and Bone Disorder
NKF	National Kidney Foundation
PTH	parathyroid hormone
PTH2R	PTH2 receptor
PTHrP	PTH-related protein
PTX	Parathyroidectomy
RANK	the receptor activator of nuclear factor kappa B
RANKL	the receptor activator of nuclear factor kappa B ligand
s.Ca	Serum Calcium
SD	Standard deviation
sHPT	secondary hyperparathyroidism
TAL	thick ascending limb of the loop of Henle
tPTX	total parathyroidectomy
VDR	vitamin D receptor

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Introduction

Secondary hyperparathyroidism (sHPT) is a common complication of CKD that, before currently available medical and surgical therapies, resulted in considerable morbidity and mortality, including crippling bone disease. Recently, many observational studies have reported associations between levels of serum PTH, calcium and/or phosphorus and the relative risk of cardiovascular and all-cause mortality. Experimental and clinical data support the hypothesis that abnormalities of mineral metabolism constitute important 'nontraditional' cardiovascular risk factors **(KDIGO guidelines of CKD-MBD, 2009).**

In patients with End stage renal disease, sHPT induces osteitis fibrosa with skeletal deformity and progressive bone loss as well as cardiovascular complications, e.g. extraosseous vessel or tissue calcifications, associated with a high mortality risk. Despite advances in medical prophylaxis and treatment, in many patients sHPT is refractory to medical treatment,and surgical parathyroidectomy (PTX) is required **(Stracke et al., 2009).**

Over the past few years, recommended target ranges have been promoted for serum calcium, phosphorus, and PTH, and an increasing number of therapies are available that assist in achieving these targets. Traditionally, these have included calcium salts, calcitriol, and alfacalcidol. More recently, active vitamin D analogs, cinacalcet hydrochloride, and non-calcium- or aluminum-based phosphate binders have become available. Surgical parathyroidectomy remains a definitive therapy **(KDIGO guidelines of CKD-MBD, 2009).**

Calcimimetics are novel agents that increase the senstivity of calcium-sensing receptor in the parathyroid gland e.g Cinacalcet which has some limitation in its use as it is effective only in PTH level of 500-800 pg/ml **(Block et al., 2009).**

In a recent study,among patients treated with cinacalcet,only 63% of patients with a baseline PTH of 500-800 pg/ml achieved the targeted PTH of 150-300 pg/ml **(Messa et al., 2008).**

Data demonstrating the impact of cinacalcet on all cause mortality, bone histomorphometry fracture rate and cardiovascular events rate are missing **(Joy et al ., 2007).**

Surgical treatment is reserved for patients whose PTH values persist above 800 pg/ml with hyperphosphatemia and hypercalcemia despite medical treatment **(Eknoyang et al., 2003).**

Three surgical approaches for parathyroidectomy have been reported : subtotal parathyroidectomy , total parathyroidectomy with autoimplantation of parathyroid tissue into the forearm musculature and total parathyroidectomy without autoimplantation. Subtotal or total parathyroidectomy with autoimplantation is done but both are associated with a high recurrence rate, the third surgical strategy is total parathyroidectomy without autoimplantation **(CHAN et al., 2009).**

To minimize the risk for recurrence and severe relapse with calciphylaxis, total parathyroidectomy without autoimplantation was performed since 1993 **(Strackes et al., 2008).**

Although there is some fear of adynamic bone disease in case of hypoparathyroidism and some resistance to active vitamin D supplementation, postoperatively, total parathyroidectomy without autoimplantation has found more followers during last 5 years **(Lorenz et al., 2006).**

During the embryological development of the parathyroid glands it has been suggested that microscopic islands ‘‘rests’’ of parathyroid tissue can be deposited anywhere along the descent of the glands from the third and fourth branchial pouches. The proportion (24%) of patients with no detectable serum PTH postoperatively is similar to other smaller series of total parathyroidectomy without implantation (10%–22%) **(Saunders et al.,2005).**

The aim of the study

To assess the outcomes of total parathyroidectomy with and without autoimplantation in ESRD patients on regular hemodialysis.

Physiology of parathyroid

Emberyology:

The parathyroid glands arise from endodermal epithelial cells, in conjunction with the thymus. The superior parathyroid glands are derived from the fourth branchial pouch. These glands are closely associated with the lateral lobes of the thyroid and have a short line of embryologic descent.The inferior parathyroid glands are derived from the third branchial pouch. These glands are closely associated with the thymus and have a longer line of embryologic descent, which leads to more variability in their anatomic position. Inferior parathyroids can be found as high in the neck as the carotid sheath and can also be found in the anterior mediastinum or even the pericardium. However, the majority of inferior parathyroids are found near the inferior pole of the thyroid. The locations of ectopic parathyroid glands are related to the common origins of parathyroid, thyroid, and thymic tissue. The third branchial pouch contributes to thymus development as well as parathyroid and thyroid development. Both the third and fourth branchial pouches also contribute to thyroid development **(Bliss et al., 2000).**

Size and location:

Normal parathyroid glands are approximately the size of a grain of rice or a lentil. Normal glands are usually about 5 by 4 by 2 millimeters in size and weigh 35 to 50 milligrams. Enlarged parathyroid glands can be 50 milligrams to 20 grams in weight, most typically weighing about 1 gram and 1 centimeter in size **(Pelizzo et al., 1998).**

The appearance of parathyroid glands can vary considerably. The color varies from light yellow to reddish-brown. Most parathyroid glands

(83 percent) are oval, bean shaped or spherical, but can also be elongated (11 percent). Other variations such as teardrop, pancake, rod-like, sausage, and leaf shaped parathyroid glands have been described. Occasionally the glands are bi-lobated (5 percent) or multilobated **(Reeve and Delbridge ., 1998).**

Most (84 percent) patients have four parathyroid glands, two superior and two inferior glands. Additional glands are found in 13 percent of patients and only three glands in a very small number of patients (≤3 percent). The terms "superior" and "inferior" refer to a gland's embryologic origin, rather than the gland's location in the neck. During parathyroid exploration, deductive reasoning based on the embryologic origin of identified parathyroid glands helps the surgeon to identify themissing glands. The parathyroids are usually in close association with the thyroid. Although there is significant variability in the position of the glands, they are usually symmetric. The superior glands are symmetric in 80 percent of cases and inferior glands are symmetric 70 percent of the time **(Pelizzo et al., 1998).**

Introduction:

Parathyroid hormone (PTH) is one of the two major hormones modulating calcium and phosphate homeostasis, the other being calcitriol (1,25-dihydroxyvitamin D) **(Potts et al ., 1996).**

The minute-to-minute regulation of serum ionized calcium is exclusively regulated through PTH, maintaining the concentration of this cation within a narrow range, through stimulation of renal tubular calcium reabsorption and bone resorption **(Brown et al., 1983 and Diaz et al., 1999).**

On a more chronic basis, PTH also stimulates the conversion of calcidiol (25-hydroxyvitamin D) to calcitriol in renal tubular cells, thereby stimulating intestinal calcium absorptionPTH secretion is, in turn, regulated by serum ionized calcium acting via an exquisitely sensitive calcium-sensing receptor (CaSR) on the surface of parathyroid cells **(Brown, 1995).**

The receptor has a long amino terminus, seven transmembrane segments, and a shorter intracellular carboxyl terminus. When activated by a small increase in serum ionized calcium, the calcium-receptor complex acts via one or more guanine nucleotide-binding (G) protein through second messengers such as intracellular calcium and inositol phosphates to inhibit PTH secretion. Conversely, the effect of deactivation of the receptor by a small decrease in serum ionized calcium is to stimulate PTH secretion **(Habener et al., 1976).**

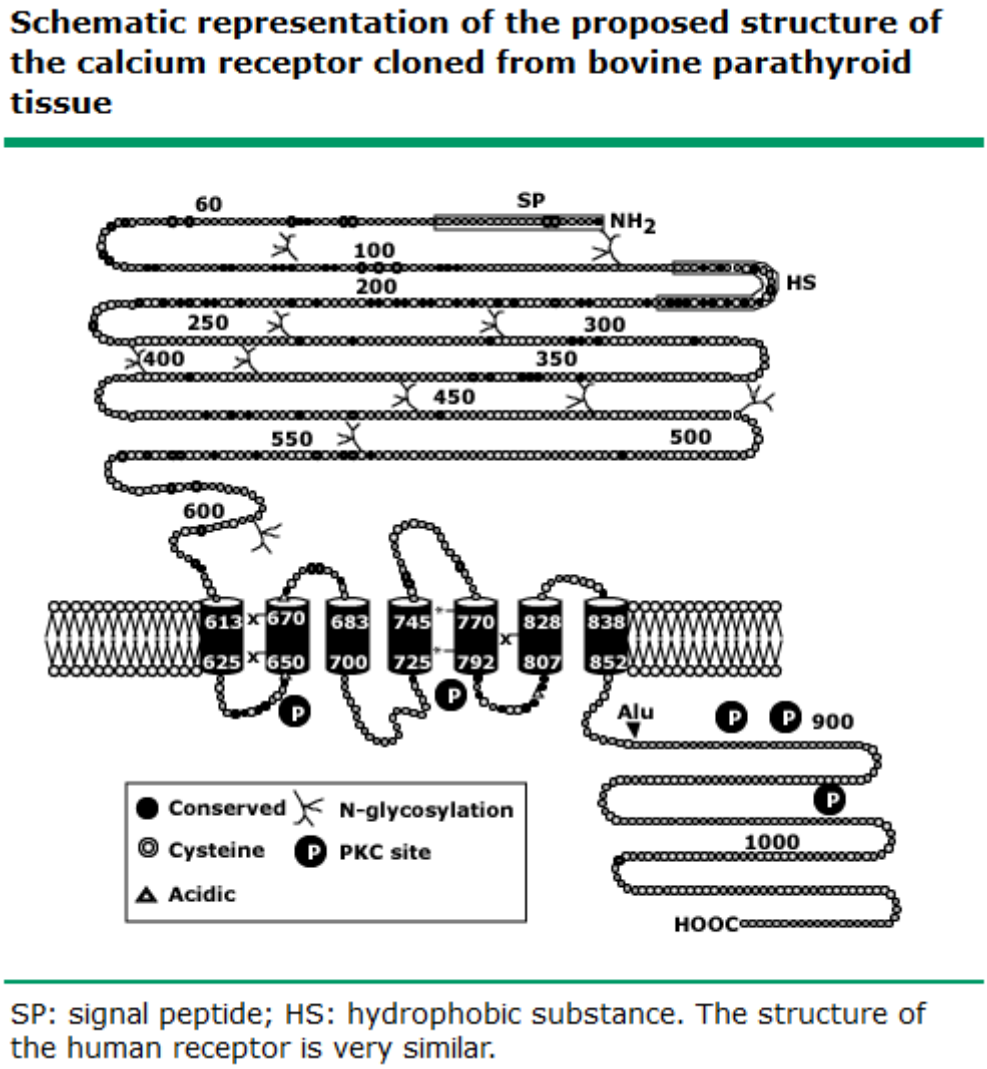

Figure (1): Structure of the calcium receptor from bovine parathyroid tissue (**Brown et al., 1993).**

Normal PTH secretion:

PTH synthesis and degradation : PTH is synthesized as a 115- amino acid polypeptide called pre-pro-PTH, which is cleaved within parathyroid cells at the N-terminal portion first to pro-PTH (90 amino acids) and then to PTH (84 amino acids). The latter is the major storage, secreted, and biologically active form of the hormone **(Murray et al., 2005).**

The biosynthetic process is estimated to take less than one hour. The N-terminal cleaved pre-sequence is rich in hydrophobic amino acids that

are necessary for transport into the endoplasmic reticulum, while the basic pro-peptide directs accurate cleavage of pro-PTH into the mature 1-84 molecule. The C-terminal portion of PTH is also essential for the PTH secretory process **(Murray et al., 2005).**

PTH 1-84 is secreted by exocytosis within seconds after induction of hypocalcemia. Calcium regulates not only the release but also the synthesis and degradation of PTH, in all its molecular forms as described below **(D'Amour et al., 2006).**

In addition to intact PTH, some inactive carboxyl-terminal fragments and small amounts of active amino-terminal fragments of PTH are present in the parathyroid glands. During hypocalcemia, intracellular degradation of PTH decreases, and mostly PTH 1-84 is secreted; in comparison, during hypercalcemia mostly biologically inactive carboxyl-terminal fragments of PTH are secreted. These carboxy-terminal fragments include long, amino-terminally cleaved species, such as PTH 7-84, which possesses some biological activity **(Potts et al., 1996 and Diaz et al., 1999).**

Under normocalcemic conditions, PTH 1-84 constitutes 20 percent of total circulating PTH molecules. This proportion increases to 33 percent under hypocalcemic conditions, and decreases to 4 percent in the presence of hypercalcemia. Once secreted; PTH is rapidly cleared from plasma through uptake principally by the liver and kidney, where PTH 1-84 is cleaved into amino- and carboxyl-terminal fragments that are then cleared by the kidney. Intact PTH has a plasma half-life of two to four minutes. In comparison, the C-terminal fragments, which are cleared principally by the kidney, have half-lives that are 5 to 10 times greater.