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Hyperparathyroidism in Hemodialyzed Patients – Relation to Melatonin and Reproductive Hormones Before and After Parathyroidectomy

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1. Introduction

Currently there is considerable interest generated about the interaction of parathyroid glands, possible role of melatonin and reproductive hormones on bone metabolism. In hemodialyzed (HD) patients with hyperparathyroidism (HPT) the melatonin concentrations are affected, but still not well studied. It has been also pointed out that the removal of the pineal gland or administration of its extracts produces alterations in the morphology and hormone secretion of the parathyroid glands (Kiss et al., 1969; Shoumura et al., 1992). On the other hand, parathyroidectomy (PTX) leads to sleep disturbances (Chou et al., 2005).

Renal diseases and hemodialysis are accompanied by profound changes in the mineral metabolism (Block et al., 2004; Hutchison et al., 1993). These changes are often associated with large variation of HPT. It is also well known that secondary HPT is common in chronic kidney disease patients (Chan et al, 2010; Rudser et al., 2007; Tominaga et al., 2001). Changes in the levels of gonadal steroids also occur in elderly patients, particularly in HD ones. However, it is not fully elucidated if the replacement steroid therapy influences parathyroid hormone responsiveness to hypercalcemia.

In HD patients melatonin disturbances are known to occur (Kancheva et al., 2008; Koch et al., 2009a, 2009b). In addition, patients with end-stage renal disease suffer from a number of related disorders (Koch et al., 2010a; Lüdemann et al., 2001; Young et al., 2005) including endocrine abnormalities, psychiatric disorders and impairment of sleep parameters. It seems

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that there is a difference between conventional daytime HD and nocturnal HD patients. While in nocturnal HD patients nocturnal melatonin rise is noticed, in daytime and peritoneal dialysis patients such rise is absent (Koch et al., 2010b). Some data also suggest that melatonin (or pineal extract) is involved directly in the changes of the ultrastructure of the hamsters' parathyroid glands and in the amount of pro-secretory cell granules (Chan et al., 1991). Animal data indicated that the pineal melatonin is involved in the regulation of calcium and phosphate metabolism by stimulating the activity of the parathyroid glands and by inhibiting calcitonin release. Calcium decline is connected with parathyroid hormone secretion increase and *vice versa*.

There are reports of the direct effects of melatonin on calcium metabolism (Csaba & Baráth, 1974; Csaba & Bókay, 1977) and more recent findings of melatonin effects on the development of osteopenia associated with loss of gonadal function and senescence (Cardinali et al, 2003; Heaton & Morales, 2001; Ostrowska et al., 2010; Sandyk et al., 1922). Melatonin has an impact in the occurrence of the bone disorders and some authors have suggested that the hormone could be used as diagnostic and even therapeutic tool (Sánchez-Barceló et al., 2010). It should be mentioned that melatonin influences bone tissue metabolism and a possible mechanism might involve regulation of calciotropic and gonadal hormones (Heaton & Morales, 2001; Ladizesky et al., 2003). Long term melatonin administration is rather inhibitory on parathyroid function and bone metabolism.

The levels of parathyroid hormone and the gonadal hormones are affected by the so termed chronic kidney disease-mineral and bone disorders. (Doumouchtsis et al., 2008; Gal-Moscovici & Sprague, 2007; Gardham et al., 2010; Hamada & Fukagawa, 2009; Moe et al., 2007). Recent studies of androgens on bone physiology and mineral metabolism at cellular level in animal models and humans revealed that androgen steroids influence bone mass, age related bone loss and the occurrence of fractures, especially in elderly men (Ebeling, 1998, 2010.; Lindberg et al., 2005; Vanderschueren et al., 2004) Nevertheless, the specific role of androgens in bone metabolism and skeletal maintenance in men and women is still not fully understood.

The major circulating androgen in men is testosterone. In peripheral tissues it is converted by 5a-reductase to 5a-dihydrotestosterone (DHT). Androgens have anti-osteoporotic effect via direct interaction with androgen receptors, as well as effect mediated by estrogen receptors after aromatization to estradiol (Ashida et al., 2010). In the same time the pivot role of estrogens on bone formation recently has also been underlined (Leder et al., 2003; Riggs et al., 2002). The relative contribution of sex steroids on bone health and turnover remains still unclear, particularly in HD patients with HPT, because gonadal hormones concentrations are usually affected in chronic renal failure (Doumouchtsis et al., 2008, 2009). Cytochrome P450 enzyme aromatase system is a key component converting adrenal and testicular C19 steroids into C18 steroids. Experimental studies and some clinical observations have directly pointed out the importance of aromatization of androgens into estrogens (Gennari et al., 2004; Nuti et al., 2007). A priming estrogen effect on androgen acting on bone metabolism level is not excluded (Rochira et al., 2007; Zirilli et al., 2008).

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) are suspected to be negatively associated with bone mineral status (Doumouchtsis et al., 2008). In pregnant rats PTX decreases GnRH (gonadotropin releasing hormone)-stimulated release of LH and FSH

in their offspring (Fujii et al., 1986). Allan et al. (2010) demonstrated that FSH has dose-dependent anabolic effects on bone via an ovary-dependent mechanism, which is independent of LH activity, and does not involve direct FSH actions on bone cells. According to Kovács et al. (1994) after PTX in postmenopausal women the stimulated by GnRH secretion of FSH was significantly decreased while the decrease of LH secretion was not significant. The relative contribution and relationships among testosterone, LH, FSH and parathyroid hormone in HD patients with HPT are still not well known and deserve further elucidation.

2. Relationship between parathyroidectomy, calcium, phosphate and melatonin levels in hemodialyzed patients

In HD patients several disturbances are known to occur. Among them are the changes of melatonin secretion and its proposed effects on the levels of calcitonin and parathyroid hormone. Indeed, after pinealectomy functional changes in parathyroid glands take place. It could be expected that the elevated levels of calcium in HPT patients on HD and subsequently their decrease after PTX might influence the plasma concentrations of melatonin.

Nine HD patients with HPT participated in the study. Two profiles of nocturnal melatonin and parathyroid hormone were performed on each participant, i.e. before and 1-3 months after PTX. In addition, serum levels of calcium and phosphate were followed twice – before and after the operation. Melatonin concentrations were determined by the method of Fraser et al. (1983), intact parathyroid hormone – with a commercial kit from Nichols Institute, San Juan Capistrano, CA, USA and serum minerals by Merck Autoanalyzer.

Due to the non-Gaussian data distribution the variables of nocturnal profiles of melatonin and parathyroid hormone were treated by a power transformation to attain symmetric distribution and constant variance (Meloun et al, 2000, 2002).

Nocturnal profiles of melatonin in HD patients before and after PTX showed significant time dependence (F-ratio=3.14, $p<0.002$, ANOVA) which was much weaker when the effect of PTX was taken into account. The dependence is presented on Figure 1. It could be seen that the operation resulted in a significant increase in nocturnal melatonin concentrations (F-ratio=11.2, $p<0.002$, ANOVA).

As expected, the PTX was followed by radical parathyroid hormone decrease (F-ratio=682, $p<0.0001$, ANOVA), which showed no nocturnal variation both before and after the PTX – Figure 2.

Calcium and phosphate levels were measured before and after the PTX each time at the beginning of blood sampling. Individual mineral levels are presented on Figure 3. Calcium concentrations significantly decreased ($p<0.001$, Student's paired t- test) after the operation while phosphate levels increased ($p<0.05$, Wilcoxon's robust paired t-test).

The detail parameters of the investigated hormones and minerals before and after the operation and their differences are presented in Table 1.

Despite of the nocturnal melatonin increase in patients after parathyroidectomy Kancheva et al (2008) found that the patients return to more physiological way of melatonin secretion, i.e. with lower baseline levels and a relative higher further increase. It is difficult to speculate

about the possible reasons for the occurrence of the aforementioned described phenomenon as the number of participants in the study was limited.

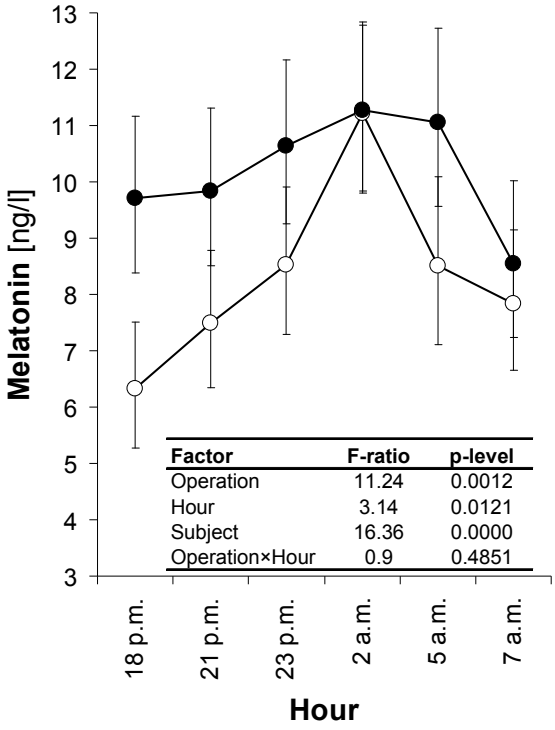

Fig. 1. Nocturnal profiles of melatonin in hemodialyzed patients before and after parathyroidectomy evaluated by repeated measures ANOVA consisting of Operation (before, after) and Hour within-subject factors, subject factor, and Operation × Hour interaction. The empty and full circles represent re-transformed mean melatonin levels with their 95% confidence intervals for individual hours of the trial before and after parathyroidectomy, respectively.

In patients with end-stage renal disease mineral metabolism disturbances are usual outcome of the disease (Lamb et al, 2007). Elevation in serum calcium levels was noticed before PTX, but phosphate levels were diminished at this time, which was not found in some other studies (Malberti, 2010; Martin & González, 2011; Molony & Stephens, 2011). There has been lack of consensus about augmented phosphate concentration in these patients. (Gal-Moscovici & Sprague, 2007). Gardham et al. (2010) found higher intraindividual variation of phosphate in HD patients than in healthy persons. Young et al (2005) also reported that serum phosphate below 3.5 mg/dL was found in patients with low serum albumin concentration, in older age, and whilst using dialysate with higher calcium. It should be mentioned that mineral metabolism in renal failure is deeply connected with many other disease processes, and phosphate concentration changes are only part of multifaceted

process of the chronic renal disease. That is why the effect of PTX on bone mineral density in HD patients with secondary HPT depends on pre- and postoperative determination of parathyroid hormone level for prediction of bone health and supplementation of minerals and active vitamin D metabolites after PTX (Cozzolino et al., 2004; Yano et al, 2003).

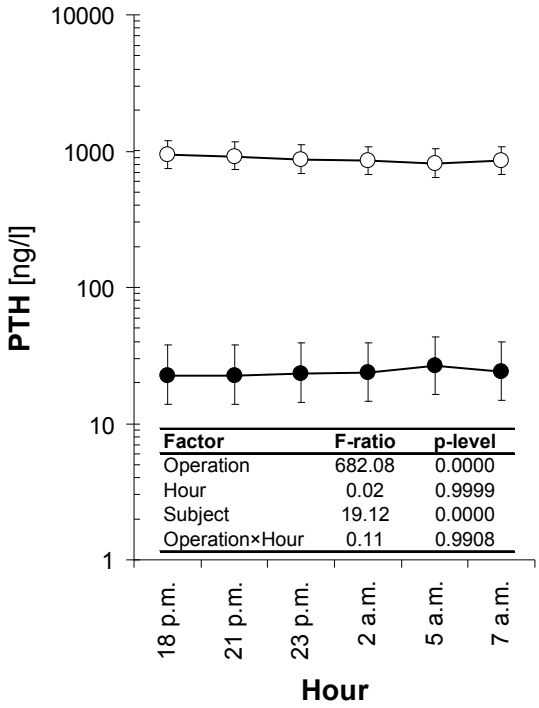

Fig. 2. Nocturnal profiles of parathyroid hormone (PTH) in hemodialyzed patients before and after parathyroidectomy. The drawings and symbols are the same as in Figure 1.

Calcium serum levels were significantly higher before PTX than 1 – 3 months after the operation (Table 1). In HD patients elevated calcium levels are usual (as the reported ones), but not in all cases as published by other authors (Miller et al., 2010). Moreover, abnormalities of both hypo- and hypercalcemia are frequent in patients receiving dialysis therapy, according to Morton et al. (2010). Calcium pull (Pirklbauer & Mayer, 2011) exists in three main forms in the body- the physiologically active free or ionized fraction, a protein bound fraction, and a fraction connected to other anions. Approximately 12% of the bound blood calcium is linked to various anions including phosphate (Ferrari et al., 2009). Ionized calcium is most commonly measured; moreover it is the only physiologically active form of calcium (Monfort et al., 2008). Very close correlation between total and ionized calcium was found ($r = 0.842$; $p < 0.001$) by Carney (1992) and a dialysis did not alter this relationship, despite the obvious significant increase in pH. During dialysis, the ionized calcium fraction decreased and the bound calcium increased along with blood pH. The results of Gosling et al. (1975) however, showed that the fall in

ionized calcium and rise in protein-bound calcium are higher and could not be explained only by the redistribution of calcium fractions due to the pH change. At present time, calcium concentration could easily be computed by correcting formulas, obtaining a value of calcium that might possess a significant difference in relation to total calcium. Thus, corrections should be abandoned and preferably ionized calcium should be measured in hemodialysis patients.

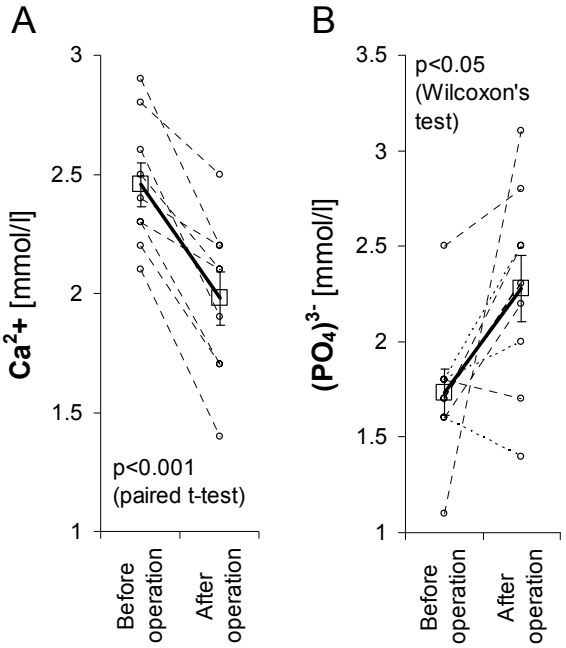

Fig. 3. Changes in serum levels of calcium (section A) and phosphate (section B) after parathyroidectomy. Circles represent experimental points while the squares with error bars represent means ± SEM.

Hypercalcemia, on the other hand, can be associated with increased extraosseous calcium. In general, secretion of parathyroid hormone increases when calcium concentration decreases and vice versa declines when calcium amount rises. Calcitonin also takes part in the regulation of the calcium homeostasis by restraining the bone resorptive effects of parathyroid hormone and also gonadal steroid hormones which enhance the renal and intestinal absorption of calcium. In HD patients with HPT, before PTX, as expected the levels of parathyroid hormone and calcium were high in our study. Parathyroid hormone takes a central role in bone metabolism and bone health. High and low parathyroid hormone levels are connected with high and low turnover bone disease, but high and low parathyroid hormone concentrations are also significantly dependant on age, gender, race, period of hemodialysis and other treatments as well as comorbid conditions (especially

Table 1. Values of the followed parameters before and after operation as well as their differences

Substance	Before operation						After operation							
	n	mean	SD	median	lower quartile	upper quartile	n	mean	SD	median	lower quartile	upper quartile	n	
PTH [ng/l]	9	1187	626	1373	1089	1683	9	33,73	28,75	38	10	52	9	-
Melatonin [ng/l]	9	29,17	27,33	24,8	10,6	34	9	53,19	40,71	37,2	25	78,5	9	2
Ca^{2+} [mmol/l]	9	2,456	0,27	2,4	2,3	2,6	9	1,978	0,335	2,1	1,7	2,2	9	-
PO_4^{2-} [mmol/l]	9	1,733	0,361	1,7	1,6	1,8	9	2,278	0,529	2,3	2	2,5	9	0

* Wilcoxon paired robust test

diabetes mellitus) (Sawaya et al., 2002; Young et al., 2005), although Cheng et al. (2011) recommend further investigations about the involvement of gender. Secondary and even tertiary HPT are common in chronic kidney disease. Total PTX is one of the treating options of those disorders. After the operation parathyroid hormone decreases precipitously and remains stable for certain time bellow the normal concentration. Hyperparathyroidism aggravates and complicates chronic kidney disease and the disturbances in mineral metabolism which include not only abnormal mineral metabolism, but also altered bone structure and dangerous extra skeletal calcifications.

It should be mentioned that melatonin influences bone metabolism and possible mechanism/s might involve regulation of parathyroid, calciotropic and gonadal hormones. Long term melatonin administration is rather inhibitory on parathyroid function and bone metabolism.

In spite of the fact that hormonal disturbances are known occurrences in patients with end-stage renal disease (Viljoen et al., 1992), investigation on the function of melatonin have not yielded much information about the relationships between this hormone and parathyroid hormone, bone and kidneys in health, and particularly, in disease. Little is known about melatonin levels in patients with chronic renal failure and HPT. During the diurnal light phase, melatonin levels are very low, i.e. approximately on the baseline level. Changes in usually high nocturnal melatonin concentrations are only with significant meaning. As mentioned above, the PTX in our study resulted in significant increase of nocturnal melatonin in all HD patients, which persisted one to three months after the operation-Figure 1.

Initially, the relation between pineal gland and parathyroid glands was proved by Au & Raisz (1965), Krstic (1966) and also by an application of isotopes (Kiss and al., 1969). It has been found that extirpation of the pineal gland or applying its extracts leads to changes in the morphology of parathyroid glands and in the processes being under their control. The influence of the pineal gland on the parathyroids is a positive one and pinealectomy is inhibitory to parathyroid function. Thus, the pineal gland must be assumed to have a role in the regulation of metabolism and of electrolyte equilibrium (Kiss et al., 1969). Chan et al. (1991) proved that serum calcium levels of hamsters treated with melatonin were significantly low than those in controls. On the other hand, Shoumura et al. (1992) incubated parathyroid glands with melatonin and described that the ultrastructure and secretory activity of the parathyroid glands were affected, but in opposite direction. A decrease was noticed in the functional activity of the glands 1 hour after the treatment. The parathyroid gland cells showed a few pro-secretory granules in the Golgi area, numerous lipid droplets, decrease of the Golgi complex and the cisternae of the rough endoplasmic reticulum. These changes were considered to be suppressive of the synthesis of parathyroid hormone as a result of melatonin action.

Regarding the studies performed in HD patients: Most of them are conducted during the daytime, and the results about melatonin concentration are conflicting. Luedemann et al. (2001) reported that melatonin levels not only before, but also after hemodialysis in HD patients were highly elevated, when compared with melatonin levels of control subjects. On the contrary, Karasek et al. (2002, 2005) discovered diminished melatonin levels in patients with chronic renal disease undergoing hemodialysis in comparison with the ones in healthy controls. One of the possible explanations, according to the authors, is that the decline in

melatonin levels is due to impairment in adrenergic function. A further factor which might influence melatonin concentration is the parathyroid hormone. Results concerning the effect of PTX and its impact on melatonin are also inconsistent. Abdel-Wanis et al. (2001) first described a case of coexisting neurofibromatosis, primary HPT due to parathyroid adenoma and osteomalacia. The authors also described a drop in melatonin levels after PTX. On the other hand, Chou et al. (2005) investigating the levels of melatonin after PTX in a patient found no changes in nocturnal melatonin concentration one week after PTX. The result of our study (Kancheva et al., 2008) established increased nocturnal levels in HD patients one to three months after PTX. The existing data also suggest that the pineal gland might be involved in the regulation of calcium metabolism (Carman et al., 1976; Csaba & Barath, 1974; Kiss et al., 1969). Pinealectomy results in decrease in parathyroid glands activity, but the changes are reversed after administration of melatonin.

The effect of melatonin on calcium metabolism might be mediated via parathyroid glands. To asses the effect of pinealectomy, melatonin administration and the influence of lighting conditions Ostrowska et al. (2001; 2003a, 2003b) traced the daily rhythm of selected bone markers in rats. The authors evaluated the levels of serum alkaline phosphatase, carboxyterminal propeptide of type I procollagen as well as cross-linked carboxyterminal telopeptide of type I collagen. Exposure to long days (23.5 h light, 0.5 h dark) was found to be inhibitory on these markers, while short days (23.5 h, dark, 0.5 h light) had a stimulatory effect, proving that lighting condition and melatonin influenced the bone metabolism in rats. Mammalian bone is remodeling continuously by resorption of old bone by osteoclasts and formation of new bone by osteoblasts. Not only melatonin but estradiol, growth factors and cytokines also promote bone formation and might have preventing effect on bone loss (Roth and al., 1999; Wolden-Hanson et al., 2000; Manolagas, 2000; Ladizesky et al., 2003). Osteoblasts also synthesize other proteins which are incorporated into the bone matrix, including osteocalcin and osteonectin. In the same time osteoclasts generate high levels of superoxide anions during bone resorption that take part in the degradative process (Fraser et al., 1996; Melhus et al., 1999; Berger et al., 1999). Melatonin is known as a powerful free-radical scavenger, antioxidant and with its ability to neutralize free radicals. The hormone could stimulate the activity of antioxidative enzymes like superoxide dismutase (Collin-Osdoby et al., 1998; Reiter et al., 2001, 2009).

According to Vaziri et al. (1993) serum melatonin in patients with HD decreases during dialysis with approximately 25%. It was suggested that hypercalcemia itself provokes the increase of melatonin. In volunteers Wikner et al. (1997) proved that indeed exogenous hypercalcaemia influenced melatonin, increased its secretion and serum level by 20% but left urinary melatonin excretion unaffected.

Melatonin is synthesized in bone marrow. Evidences for synthesis in mouse and human bone marrow cells were presented by Tan et al. (1999) and Conti et al (2000). These cells contain aryl-alkyl-N-acetyltransferase activity and express the mRNA encoding hydroxyindole-O-methyltransferase, proving their ability to synthesize melatonin *de novo*. High melatonin levels might have a protective role against oxidative damage in the proliferating hematopoietic cells or in taking part of bone development through osteoblast formation.

The early differentiation and higher expression of bone marker proteins and also the osteogenic differentiation on bone marrow stem cells are evoked by melatonin presence

(Zaminy et al., 2008). Ostrowska et al. (2003b) found a correlation between the higher melatonin levels and low levels of bone forming markers and increased ones of bone resorption markers after pinealectomy in rats. Activities of the osteoblasts and osteoclasts, cultured together with the presence of melatonin, were both diminished judging by specific bone markers of each cell type (Suzuki & Hattori, 2002). The physiological meaning of this fact should be studied considering eventual existing cell-to-cell communications.

The osteoclast activity is regulated by osteoblast produced factors. Some of the factors are matter of current interest and they are: osteoprotegerin (OPG), receptor activator of nuclear factor (NF) –κB (RANK) and RANK ligand (RANKL). It is known that RANKL polypeptide is a type II transmembrane protein and by its expression by osteobalsts it coordinates the bone remodeling by stimulation of bone resorption (which is done by the osteoclasts). Osteoprotegerin is also produced by the osteoblasts and the overexpression of OPG osteoclast production. In brief, the expression of RANKL and OPG decreases coordinates the bone resorption and density positively and negatively, respectively by controlling the activation state of RANK on osteoclasts (Boyle et al, 2003).

Regarding the effect of melatonin on the bone metabolism (Koyama et al., 2002) proved that melatonin at pharmacologic doses increases bone mass by suppressing resorption through down-regulation of RANKL-mediated osteoclast formation and activation.

Recent studies indicated that melatonin may influence bone directly acting on osteoclasts and osteoblasts and/or by down-regulating receptor activator of nuclear factor- κB ligand (RANKL) (Ostrowska et al, 2010).

3. Hyperparathyroidism, parathyroid hormone and steroids in mineral and bone metabolism

The contribution of sex steroids, mainly testosterone and estradiol to bone regulation implies that their dysfunction may be implicated in the emergence of renal osteodystrophy accompanied with HPT in HD men. In male HD patients, the testosterone concentration declined significantly with aging, whereas the esrogen values increased with longer duration of HD. It is generally accepted that estrogens play greater role in maintenance of bone's health than androgens. Testosterone has underlined anti-osteoporotic and beneficial effect on bone metabolism, bone mineral density and maintaining bone mass in men, via direct interaction with androgen receptors. Its influence in the same time is believed to be mediated by estrogen receptors after aromatization of testosterone to bioavailable estradiol.

In postmenopausal women parathyroid hormone suppression by exogenous calcium is reduced. It was suggested that actually estrogen replacement therapy stimulates the parathyroid glands and consequently augments basal parathyroid hormone secretion. To test whether this relationship might be caused by estrogen deficiency 9 postmenopausal women were given transdermal estradiol treatment for 3 months at a dose of 100 μg/day. Parathyroid hormone reactivity to intravenous administration of $CaCl_2$ (10 % solution, 0.2 mL/kg for 5 minutes) was determined before and at the end of the treatment period. Compliance to treatment was evaluated by determination of serum levels of estradiol and FSH. Estradiol was measured by means of an own radioimmunological method (Hampl et al., 1988) and FSH using commercial kit (Kosice, Slovak Republic). Comparing estradiol and FSH values and decremental area of parathyroid hormone and incremental area of calcium

before and after estrogen treatment, Student's paired t-test was used. Decremental area of parathyroid hormone and incremental area of calcium were defined as areas circumscribed by baseline and serum levels of these indicators. To see whether the decremental or incremental areas differed significantly from zero Student's one sample t-test was used. The results were then evaluated independently also by a substantially more robust non-statistical, so-called Gnostic method, suited for evaluation of small groups data samples (Baran, 1988; Kovanic, 1986).

Estrogen treatment raised the basal serum estradiol (Zofkova et al. 1993), reduced the corresponding FSH, but left serum calcium and parathyroid hormone levels unchanged as shown in Table 2 and Figure 4.

	Before E_2 treatment	At the end of E_2 treatment	Normal range: Follicular phase	Luteal phase	Midcycle phase	Postmenopausal phase
S-Estradiol (nmol/l)	0.1±0.02	0.46±0.10	0.099-0.95	0.2-1.5	-	0.015-0.150
		$p<0.01$				
S-FSH (U/l)	77.5±7.4	33.9±5.7	2-10	0.5-10	10-30	15-140
		$p<0.001$				
Ca_u mmol/12 h (08:00 - 20:00 h)	5.2±0.4	4.3±0.6	-	-	-	-
Ca_u mmol/12 h (20:00 - 08:00 h)	3.4±0.4	2.7±0.3	-	-	-	-
Ca/Cr index	0.15±0.03	0.10±0.01		normal range up to 0.2		

Results are expressed as mean±SE; n=9.

Table 2. Effect of Estraderm (E2) on serum levels of estradiol and FSH, and urinary excretion of calcium during two 12-h periods following immediately upon an iv calcium load.

Similar urinary calcium excretion values were recorded before and after estradiol treatment (Table 2). Intravenous infusion of $CaCl_2$ induced hypercalcemia as demonstrated in Figure 4.

From Figures 5 and 6 it is apparent that it might be possible to expect that estradiol increases the suppressability of parathyroid hormone (i.e. the ratio of the decremental area of parathyroid hormone after/before >1) in more than 75.8 % and reduces the serum calcium level achieved after a calcium load (i.e. the ratio of the incremental area of calcium after/before <1) in more than 82.1 % of the population of post-menopausal women.

From the results presented it is reasonable to assume that estrogen deficiency contributes to the impaired parathyroid hormone suppressibility. The effect of estradiol on basal hypercalcemia described by other authors (Boucher et al., 1989; Gallagher & Nordin, 1975) was not confirmed. Lower increment of calcemia after estrogen treatment attained by administration of the same calcium load as in the control test does not exclude the possibility that estrogen alters body distribution of calcium.

Renal osteodystrophy is a term used to describe secondary HPT, disorders of bone turnover, abnormalities of calcium and phosphate metabolism, and osteomalacia (Isaia et al., 2008). According to Danese et al. (2006) there are no associations between calcium and phosphate concentrations with the risk of fractures, there are weak with parathyroid hormone, and prospective studies are needed to determine whether therapies that maintain parathyroid

hormone concentrations within or near the reasonable range will result in complications of disordered mineral metabolism. Secondary HPT is one of the major abnormalities determining chronic kidney disease as parathyroid hyperplasia very frequently is a result of changed calcium and phosphate metabolism. Fukagawa et al. (2011) consider that mortality rate for patients on HD with secondary HPT is extremely high, many of them are on HD therapy for a longer time and this could increase the prevalence and degree of secondary HPT. In the same time the increase in serum calcium and phosphate that does accompany HPT play a more crucial role in the development of vascular calcification, than HPT itself (Goodman, 2002; Qunibi, 2007; Raggi et al., 2004).

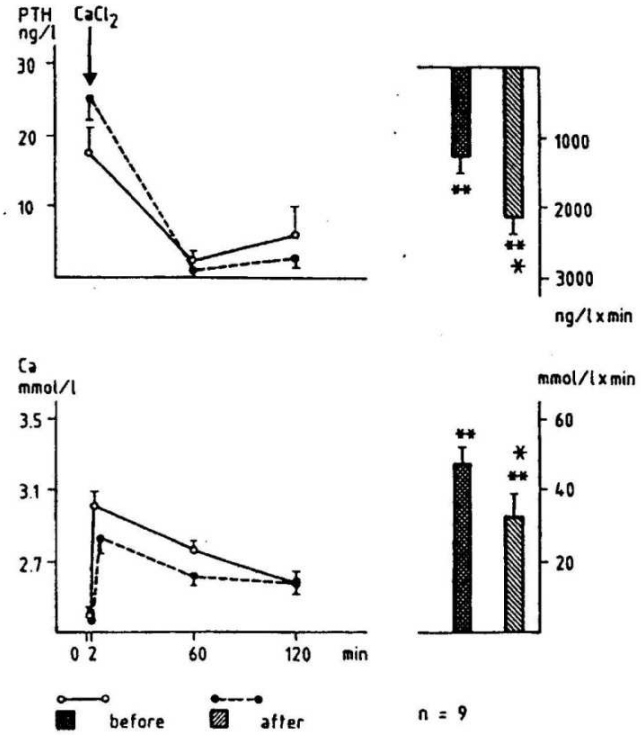

Fig. 4. Serum PTH and calcium responses to iv injection of calcium chloride in 9 postmenopausal women investigated before and after 3 months period of transdermal estradiol treatment. Values denoted are means ± SE (evaluated by paired t test). Normal basic ranges for the various parameters were as follows: serum PTH : 10 – 55 ng/L; total serum calcium: 2.24 – 2.60 nmol/L.

Estrogens could inhibit parathyroid hormone activated bone resorption both *in vitro* and *in vivo*. Estrogens could block parathyroid hormone activated osteoclast formation by abolishing parathyroid hormone responsive cyclic adenosine monophosphate (cAMP) pathway in mouse bone culture (Kaji et al., 1996; Kanatani et al., 1998). It was determined

that estrogen inhibits parathyroid hormone-stimulated osteoclast formation by directly acting on hemopoietic blast cells in mouse and rat, possibly through blocking the cAMP-dependent protein kinase pathway but not the calcium/protein kinase C pathway (Kanatani et al., 1998).

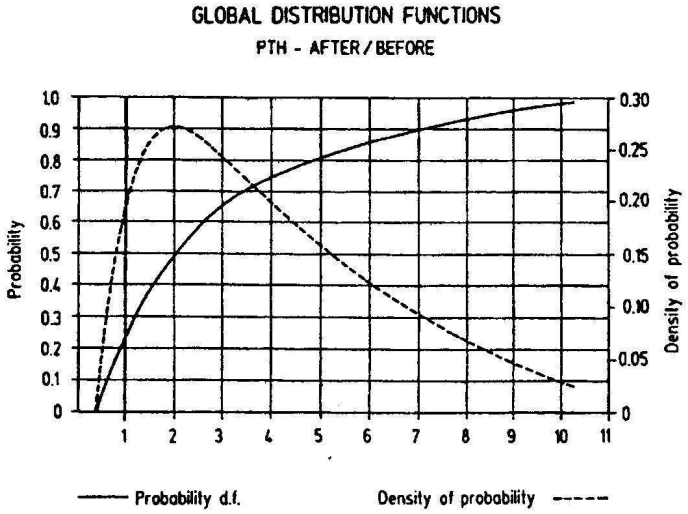

Fig. 5. Global distribution function and density of the decremental PTH area ratio after/before E2 (evaluated by gnostical method). It appears that the sample of ratio can be considered as homogenous. The probability of a ratio not to exceed 1 (the risk of negative result of the treatment) is estimated as 0.242 for the original data.

More recent findings related to the putative role of fibroblast growth factor 23 (FGF-23) on the estrogen receptors support the conception of indirect effects of estrogens on bone metabolism and on the regulation of parathyroid hormone by estrogens. It is likely that FGF-23 mediates its functions through FGF receptors (FGFR1) and the co-receptor Klotho. In addition, FGF23 has ability to reduce parathyroid hormone secretion (Jüppner et al., 2010; Nakai et al., 2010). However, during the early stages of chronic kidney disease, increased FGF-23 production enhances phosphate excretion, prevents the development of hyperphosphatemia, reduces the circulating levels of $1,25(OH)_2$ vitamin D_3, and subsequently contributes to the development of secondary HPT. In patients undergoing HD, FGF-23 levels are elevated in response to hyperphosphatemia and eventually to vitamin D therapy, but fail to suppress the secretion of parathyroid hormone. Experimental data suggests that the parathyroid resistance to FGF-23 may be caused by decreased expression of Klotho-FGFR1 complex in hyperplastic parathyroid glands (Komaba & Fukagawa, 2010).

Estrogens are supposed to have both direct and indirect effects on bone via the estrogen receptor α and estrogen receptor β. They exert estrogen-dependent parathyroid hormone suppression but the mechanisms by which estrogens modulate parathyroid hormone are controversial. Carrillo-López et al. (2009) investigated the levels of parathyroid hormone in a

combined rat model (i.e. rats with chronic kidney disease and ovariectomy). Estrogens were administered to the animals and the authors proved that the estrogen treatment significantly decreased both parathyroid hormone mRNA and serum levels as well, but did not find any estrogen receptor α or β mRNA or protein in the parathyroid glands. These results pointed out an indirect effect of estrogen action on parathyroid hormone regulation. In the same time estrogen treatment significantly decreased serum $1,25(OH)_2$ vitamin D_3 and phosphate concentrations. Fibroblast growth factor 23 mRNA levels were increased as a result of the estrogen treatment. Experiments *in vitro* shown that estrogens led to up-regulation of FGF23 in osteoblast-like cells in a time- and dose-dependent manner, suggesting that parathyroid hormone is regulated indirectly by estrogens, probably trough FGF-23.

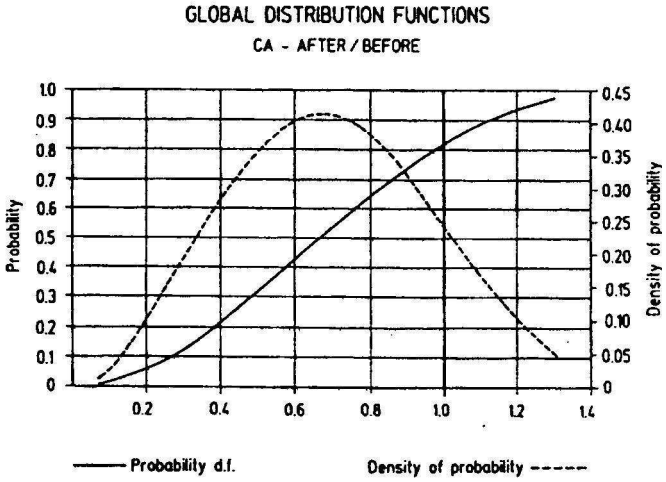

Fig. 6. Global distribution function and density of the incremental calcium area ratio after/before before E2 (evaluated by gnostical method). The probability of failing treatment (of a ratio exceeding 1) is 0.179 for the original data.

The recent experiments outline that estrogens suppress parathyroid hormone synthesis and secretion in concentration-dependent manner, probably mainly by an indirect mechanism. Additionally, the calcium-phosphate-vitamin D-parathyroid hormone axis can also be indirectly affected by estrogens (Cannata-Andía et al., 2010). In addition, fibroblast growth factor 23 also positively correlates with the concentration of estrogens.

Androgens are also supposed to regulate bone metabolism in mammals. Testosterone inhibits osteoclast formation by parathyroid hormone, but through an androgen receptor. Gonadal androgen steroids act also directly on osteoblasts by binding to androgen receptors. Chen et al. (2001) performed a study to investigate if testosterone and DHT would influence osteoclast formation stimulated by parathyroid hormone and $1,25(OH)_2$ vitamin D_3 in mouse bone cell culture. Induced osteoclast formation was inhibited in concentration-dependently manner by testosterone and even stronger by DHT, but the one activated by $1,25(OH)_2$ vitamin D_3 was not blocked. Applying in their experiment a specific

estrogen antagonist and an aromatase inhibitor the authors confirmed that testosterone inhibited osteoclast formation induced by parathyroid hormone through the androgen receptor, but not through the production of estrogen by aromatization of androgen.

In bone tissue both androgen and estrogen receptor are expressed. Wiren et al (2008) used transgenic mice population with overexpressed androgen receptors. The authors found that enhanced androgen signaling results in low bone turnover and inhibition of bone formation by differentiated osteoblasts and that androgen action on mature osteoblast is not anabolic.

Anabolic steroids have been applied to treat patients with osteoporosis. They might act directly on the bone tissue, but it has been also suggested that they have an indirect effect, exerted via changes in the secretion of calcitonin (Salamano et al., 1990). Moreover, a positive correlation between the levels of testosterone and calcitonin has recently been found (Liu et al., 2011). A direct relationship between parathyroid hormone and androgens is not elucidated. In order to test the effect of synthetic anabolic steroid (synthetic androgen) on calcium- induced suppressibility of parathyroid hormone in postmenopausal women stanazolol (Stromba®, Sterling products, UK) was orally given for 1 month in daily dose of 10 mg to postmenopausal women with osteoporosis. Each woman had two identical i.v. $CaCl_2$ tests (10 % CaCl2, at a dose of 0.2 mL/kg body weight for 5 minutes) – one before and the other at the end of the treatment period. Serum parathyroid hormone, LH, testosterone, and ionized calcium were determined in blood samples taken before, 5, 60 and 120 minutes after the calcium loading. Student's paired t-test was used when the decremental parathyroid hormone and the incremental calcium areas were compared before and after the stanazolol treatment. The same test was also used when comparing basal values for the various parameters before and after the treatment.

Exogenous hypercalcemia suppressed serum parathyroid hormone almost identically before and after stanazolol treatment, as reflected by the decremental areas of parathyroid hormone (Figure 7). The calcium induced hypercalcemia expressed as an incremental area of calcium was of a similar magnitude before and after the drug application (Figure 7).

Stanazolol reduced the serum LH from 38 ±4 to 30 ± 3 UI/L ($p < 0.01$) and testosterone from 0.77 ± 0.10 to 0.44 ± 0.08 nmol/L ($p < 0.05$), which confirmed that a good compliance was achieved by the treatment. In conclusion, the study does not support the hypothesis that the effect of stanazolol on bone is mediated by an alteration of parathyroid hormone secretion (Zofkova et al, 1994).

The androgen receptor mediates biological responses to androgens (Clarke & Khosia, 2009). Since androgens can be converted into estrogen, the specific role of the androgen receptors in mineral metabolism and homeostasis remains controversial. Kenny et al. (1998) found that in old age testosterone concentrations were below the normal range in 38 % of men, and parathyroid hormone levels were elevated in 23 of them, but there is no other data available about the direct relationship between these two hormones.

4. Hyperparathyroidism and gonadotropic hormones

Reproductive hormone concentrations are influenced in chronic renal failure. With the progression of the kidney disease (and with the introduction of systematic HD) sexual and gonadotropic hormone concentrations are affected. Decrease in plasma testosterone and

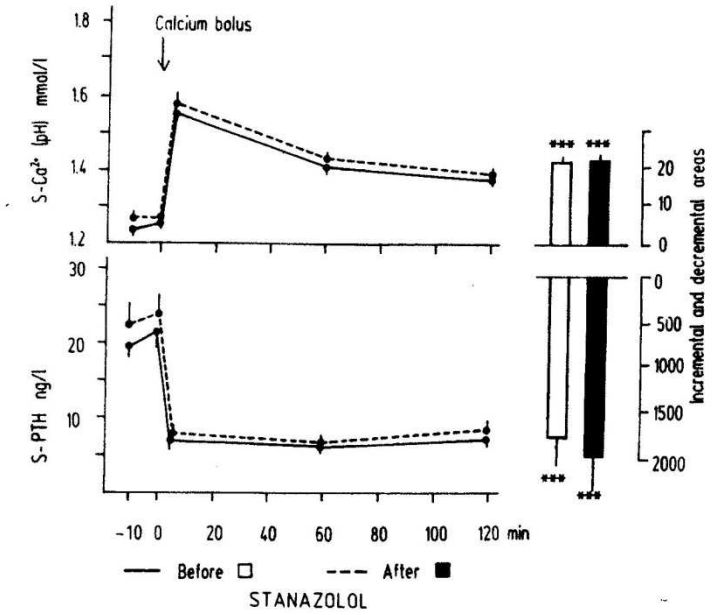

Fig. 7. Left panel. Serum ionized calcium (corrected by pH – Ca^{2+} /pH) and PTH response to iv calcium before after 1 month's treatment with stanazolol in 11 postmenopusal women. Values denoted are means ± SEM. Normal basal range for serum ionized calcium are 1.17 – 1.29 mmol/L and PTH 12 – 55 ng/L. Right panel. Corresponding incremental and decremental areas.

estradiol also affect bone metabolism and bone mineral density. Impotence and azoospermia are usual among male patients undergoing a chronic HD program. The current evidence suggests that androgens have direct beneficial effects on bone metabolism. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) are suspected to be negatively associated with bone mineral status. The relative contribution and relationships among testosterone, LH, FSH and parathyroid hormone in HD patients with HPT are still not well known and deserve elucidation.

The function of the adenohypophyseal-gonadal axis in HD male patients is modified: the serum testosterone concentration is low, and the gonadotropin levels are increased. The pathogenetic role of secondary HPT in this disorder seems not to be fully defined. The effect of secondary hyperparathyroidism upon hormones of the pituitary-testicular axis was studied by Bogićević & Stefanović (1988) in end-stage kidney disease male patients on maintenance HD. A significant positive correlation was found between the serum levels of PTH and LH (r = 0.405). Akmal et al. (1988) described an important role for the excess blood levels of PTH in uremia in the genesis of the hypotestosteronemia.

To test the effect of PTX on the secretion of LH, FSH, and testosterone seven HD men with advanced secondary HPT (in whom PTX was performed) were included in the study. Nine healthy men served as controls. Three identical gonadotropin releasing hormone (GnRH) tests (0.1 mg over a period of 30 seconds) were performed for each patient – before PTX, 3

and 6 months after the operation and one for the controls. Blood samples for the determination of serum LH, FSH, and testosterone were taken before (time 0) and 20, 40, 60, 80, and 100 minutes after the treatment with GnRH. Serum intact parathyroid hormone, 1,25(OH)$_2$ vitamin D$_3$, 25(OH) vitamin D$_3$, total calcium, phosphate, prolactin, hemoglobin, and hematocrit were estimated at time 0. Decremental areas under the curve (AUC) for LH, FSH, and testosterone were determined. The AUC is defined as an area circumscribed by the joint line of values measured at 0, 20, 40, 60, 80, and 100 minutes after the GnRH administration and the horizontal line provided by the values at time 0. Bonferroni test was used to compare the AUC values of LH, FSH, and testosterone as well as through the second period after the PTX.

Serum parathyroid hormone, calcium, and phosphate prior to PTX markedly exceeded the upper limit of reference values. These indices decreased in all of the investigated patients at the third month after the operation ($p<0.01$, $p<0.01$ and $p<0.1$, respectively, as compared with the mean values before the operation – Table 3).

	Normal range	Before PTX	After PTX	
			3rd month	6th month
Serum intact PTH, ng/l	10. 0 - 65	956. 1 ± 115.7	81.0 ± 34.0 [a]	138.1 ± 57.1 [a]
Total calcium, mmol/l	2. 20 - 2. 60	2.44 ± 0.04	2.11 ± 0.09 [a]	2.23 ± 0.13 [a]
Phosphates, mmol/l	0. 80 - 1.62	2.25 ± 0.09	1.55 ± 0.08 [a]	1.78 ± 0.12 [a]
1.25(OH)$_2$D$_3$, ng/l	18.0 - 62. 0	14.44 ± 4.41	37.81 ± 7.57 [b]	27. 6 ± 1. 17 [b]
25(OH)D$_3$, ng/ml	16.0 - 74. 0	11.72 ± 1. 35	18. 91 ± 2.47	18.91 ± 4. ±
Prolaktin, μg/l	3.0 - 17.7	43.23 ± 17.21	47. 79 ± 18.87	41.54 ± 15.92
Haemoglobin, g/l		81.2 ± 7.66	87. 2 ± 5.78	25. 8 ± 2.1
Haematocrit, %				

The Bonferroni test was calculated for n = 7.

[a] $p<0.01$ as compared with the values before PTX.

[b] $p<0.05$ as compared with the values before PTX. There were no differences between those values of the first and the second postoperative in any of the investigated parameters

Table 3. Serum intact PTH, total calcium, phosphates, 1,25 (OH)$_2$D$_3$, 25(OH) vitamin D$_3$, prolactin, haemoglobin, haematocrit in dialyzed men before and 3 and 6 months after PTX (mean ± SEM)

At the sixth month, the mean serum parathyroid hormone and phosphate levels were lower ($p<0.01$ and $p<0.05$ as compared with the same values before PTX) although an increasing tendency in both parameters was apparent. However, the changes of these concentrations were not significant when compared with the values at the third month (Table 3).

Serum 1,25(OH)$_2$ vitamin D$_3$ increased in all except one patients after three months ($p<0.01$, table 1), and sixth months after PTX ($p<0.01$ as compared with the concentration before PTX, Table 3). The response of serum 25(OH) vitamin D$_3$ to PTX was not as significant early after PTX as later (Table 3). In HD patients serum testosterone concentrations were lower as compared in healthy men, and the secretory response to GnRH was very flat. The peaks in testosterone secretion recorded in the healthy subjects at the 40th and 100th min after GnRH applications were not observed either before or after PTX. There were no differences between the mean concentrations of basal or GnRH-induced testosterone AUC levels either before PTX or during both periods after the operation (Figure 8). The basal serum LH

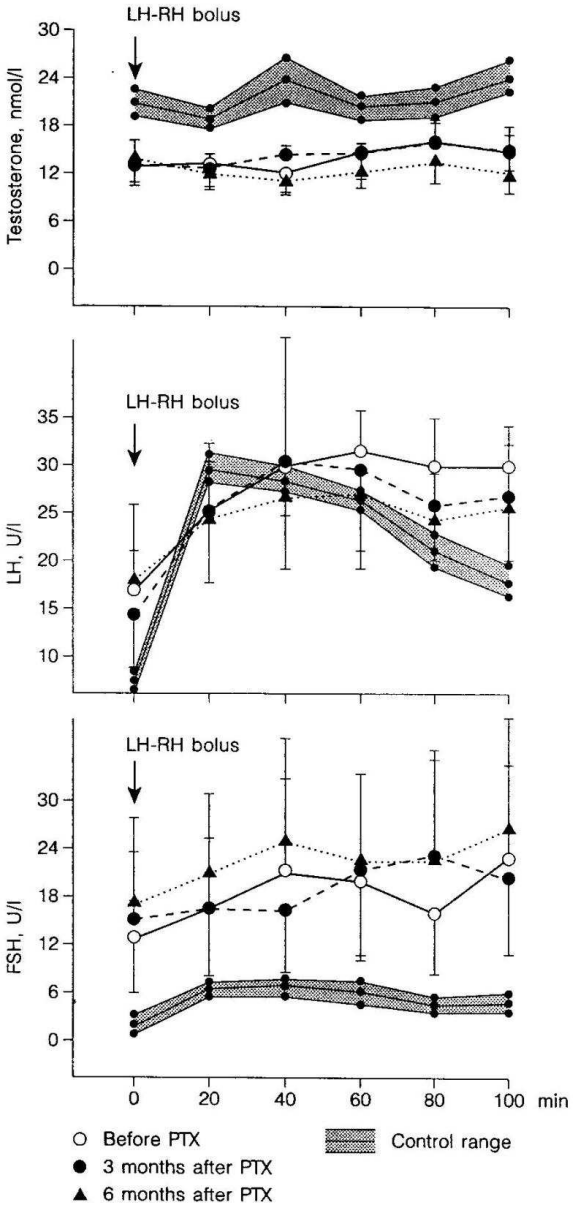

Fig. 8. Testosterone, LH and FSH responses to LH-RH before PTX (open circles and soild lines), at 3rd month after PTX (closed circules, and dashed lines), and at 6th month after PTH (triangles and dotted lines). The values are means ± SEM, evaluated by Bonferroni test for n = 7. The shaded area represents the mean values ± SEM of 9 healthy men (mean age 29.8, range 20 - 38 years) who did not take any form of medication.

concentrations exceeded the upper limit of the normal male range. The AUC was 1.110 ± 223 UI/L x min. The secretion kinetics of the gonadotropic hormone after GnRH administration was altered in the patients before and during the first and second periods after PTX, the increase being slower so that the peak is reached later as compared with healthy men (between the 40th and the 60th min after GnRH stimulation). Thereafter, a plateau followed instead of a decline as registered in the case of healthy men. No significant differences between LH AUC values before or after the PTX were observed.

The serum concentrations of FSH were higher in HD patients before and after PTH as compared with healthy subjects. The secretion kinetics of FSH before and after PTH was very similar. Serum prolactin exceeded the upper range of normal values and before and also after the PTX. No correlations were observed between parathyroid hormone, calcium, phosphate, $1,25(OH)_2$ vitamin D_3, or 25(OH) vitamin D_3 and AUC values of testosterone, LH, FSH, prolactin either before PTX or after the operation. Taken as a whole, the obtained data show that adenohypophyseal-gonadal dysfunction in HD men is not dependent on the activity of the parathyroid hormone-$1,25(OH)_2$ vitamin D_3 axis (Zofkova et al., 1996). Fujii et al. (1986) have found a long lasting alteration in the hypothalamo-pituitary- gonadal axis in the female offspring rats born to PTX mothers. The authors observed a decrease in GnRH-stimulated release of LH and FSH in the PTX first generation rats, more pronounced in females at 14 and 22 days of age. An association of increased parathyroid hormone and decreased vitamin D metabolite was detected in patients obesity by Panidis et al. (2005), but they did not report any existing relation between FSH, LH and parathyroid hormone. Inappropriately low concentrations of FSH and LH with respect to sex steroids were measured by Rochira et al. (2007) in a subject with osteopenia and aromatase deficiency, but also no other relations between the hormones were described. Castelo-Branco et al. (2008) evaluated the effect of FSH levels in the development of human osteoporosis and found that bone mineral density correlated positively with the FSH levels, but did not appear to have a major role in the development of bone loss in young women with primary amenorrhea. The authors also did not announce any relationships between parathyroid hormone concentrations and FSH.

5. Concluding remarks

In hemodialyzed patients with secondary hyperparathyroidism, parathyroidectomy significantly increased the nocturnal secretion of melatonin. The increased parathyroid hormone levels have been related to lower melatonin levels. Removal of the pineal gland or administration of its extracts produces alterations in the morphology and hormonal secretion of the parathyroid glands. Patients with end stage renal disease or on systematic HD suffer from related to melatonin disorders. The pineal gland and melatonin might be assumed as one of the regulating factors of the metabolism and electrolyte equilibrium. Despite some controversial results, data indicates that pineal melatonin is involved in the regulation of calcium and phosphate metabolism by stimulating the activity of the parathyroid glands and by inhibiting calcitonin release. It is supposed that hypercalcemia itself provokes an increase of melatonin and that exogenous hypercalcaemia has impact on melatonin levels, increasing its secretion and serum level by 20%. Osteoclasts generate high levels of superoxide anions during bone resorption that take part in the degradative process. Additionally, melatonin is known as a powerful free-radical scavenger, antioxidant and

with its ability to neutralize free radicals, and thus promotes bone formation and prevents bone resorption. Melatonin is synthesized in bone marrow cells. These cells contain aryl-alkyl-N-acetyltransferase activity and express the mRNA encoding hydroxyindole-O-methyltransferase, proving their ability to synthesize melatonin *de novo*, which might have protective role against oxidative damage in the proliferating hematopoietic cells or in taking part of bone development through osteoblast formation. It is suspected that melatonin might affect the bone directly acting on osteoclasts and osteoblasts and by suppressing resorption through down-regulation of RANKL-mediated osteoclast formation and activation.

The contribution of sex steroids to bone regulation implies that their dysfunction may be complicated by renal osteodystrophy accompanied with HPT in HD patients. Testosterone has pronounced anti-osteoporotic and beneficial effect on bone metabolism, bone mineral density and maintaining bone mass in men. Testosterone's effect (at least part of it) is believed to be mediated by estrogen receptors after aromatization of testosterone to bioavailable estradiol. From the results obtained it is possible to assume that estrogen deficiency contributes to the impaired parathyroid hormone suppressibility and alters body distribution of calcium. Increased serum calcium and phosphate along with HPT play more crucial role in the development of vascular calcification, than HPT itself.

Estrogens have direct and indirect effects on bone via the estrogen receptor α and estrogen receptor β. There are evidences that estrogen suppresses parathyroid hormone synthesis and secretion in concentration-dependent manner, probably mainly by an indirect mechanism. The concept of the indirect effect of estrogens on bone metabolism and on the parathyroid hormone regulation recently is supported by the putative role of fibroblast growth factor 23 (FGF-23) and the co-receptor Klotho on the estrogen receptors.

The direct relationship between parathyroid hormone and androgens is not elucidated. The effect of synthetic androgen stanazolol on calcium - induced suppressibility of parathyroid hormone in postmenopausal women does not support the hypothesis that the effect of stanazolol on bone is mediated by alteration of parathyroid hormone secretion.

In chronic renal disease, the levels of gonadal hormones are usually influenced. As kidney disease progresses and with the introduction of systematic HD the sexual and the adenohypophyseal gonadotropic hormones are commonly affected. Pituitary-gonadal axis in HD patients with HPT is also affected and modified, i.e. the serum testosterone concentration is low and gonadotropin levels are increased. No correlations have been found between the parathyroid hormone, LH, FSH, prolactin, calcium, phosphate, $1,25(OH)_2$ vitamin D_3 and 25(OH) vitamin D_3 values before or after the performed PTX in our already mentioned study. Probably, adenohypophyseal-gonadal dysfunction in men on HD does not dependent on the activity of the parathyroid hormone-$1,25(OH)_2$ vitamin D_3 axis.

6. Acknowledgements

Supported by a grant project NS/9831-4 of the Internal Grant Agency of the Czech Republic.

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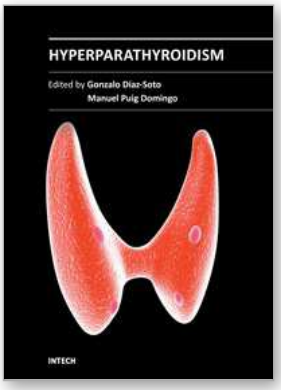

Hyperparathyroidism

Edited by Dr. Gonzalo Diaz Soto

ISBN 978-953-51-0478-0
Hard cover, 96 pages
Publisher InTech
Published online 04, April, 2012
Published in print edition April, 2012

This book is the result of the collaboration between worldwide authorities of different specialities in hyperparathyroidism. It aims to provide a general but deep view of primary/secondary and tertiary hyperparathyroidism, from a physiological basis to hyperparathyroidism in hemodialyzed patients, as well as new treatment approaches, techniques and surgical scenarios. We hope that the medical and paramedical researchers will find this book helpful and stimulating. We look forward to sharing knowledge of hyperparathyroidism with a wider audience.

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Radmila Kancheva, Ivana Zofkova, Martin Hill, Sylvie Dusilova-Sulkova, Ludmila Kancheva, Sven Rojdmark, Antonin Parizek, Michaela Duskova, Zoltan Paluch, Veronika Cirmanova and Luboslav Starka (2012). Hyperparathyroidism in Hemodialyzed Patients – Relation to Melatonin and Reproductive Hormones Before and After Parathyroidectomy, Hyperparathyroidism, Dr. Gonzalo Diaz Soto (Ed.), ISBN: 978-953-51-0478-0, InTech, Available from: http://www.intechopen.com/books/hyperparathyroidism/hyperparathyroidism-in-hemodialyzed-patients-relation-to-melatonin-and-reproductive-hormones-before-

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