

# Correlation between hand/wrist and panoramic radiographs in severe secondary hyperparathyroidism

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## Abstract

**Objectives** Hand/wrist and dental radiographs are important for osteoporosis analysis in secondary hyperparathyroidism (SHPT). This study evaluated whether a correlation exists between the effects of the disease on the hands and jaws, and investigated the association between osteoporosis progression in the hands and parathyroid hormone (PTH) levels in chronic kidney disease (CKD) patients.

**Materials and methods** Four panoramic radiographic parameters (mental index, mandibular cortical index, trabecular bone pattern, and calcification/resorption) and four corresponding hand/wrist radiographic parameters (metacarpal cortical thickness, phalangeal cortical index, trabecular bone pattern, and calcification/resorption) were applied to investigate possible

correlation between the effects of SHPT on the jaws and hands/wrists, by Spearman's correlation coefficient. PTH levels and the hand/wrist radiographic parameters were also tested by Spearman's correlation coefficient ( $p < 0.05$ ). The presence of brown tumors, vascular calcifications, and acroosteolysis on the hands was also evaluated.

**Results** Mandibular cortical index was strongly correlated with the phalangeal cortical index ( $p = 0.000$ ). Phalangeal cortical index and trabecular bone pattern of hand/wrist correlated with PTH levels (0.002 and 0.000, respectively). Brown tumors occurred in four CKD patients, while both vascular calcifications and acroosteolysis were observed in 19 patients.

**Conclusion** There is a significant correlation between the morphological changes caused by secondary hyperparathyroidism in hand and jaw bones. The morphological status can be assessed using the mandibular cortical index, besides the phalangeal cortical index. The latter correlates well with parathyroid hormone levels of advanced chronic kidney disease.

**Clinical relevance** Panoramic images reveal morphological changes in the jaw bone, indicating likewise changes in the hand/wrist in severe secondary hyperparathyroidism. The severity of the bone changes may be a reflection of the parathyroid hormone levels in advanced chronic kidney disease.

**Keywords** Secondary hyperparathyroidism · Carpal bones · Hand · Panoramic radiography · Parathyroid hormone · Kidney diseases

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## Introduction

Mineral and bone disorders in chronic kidney disease (CKD) are characterized by a complex array of biochemical

and hormonal alterations that cause diverse calcifications in the organism as well as skeletal changes, a condition called renal osteodystrophy [1, 2]. Secondary hyperparathyroidism (SHPT) is a consequence of these disorders and is seen in most patients with CKD undergoing hemodialysis. The physiopathology of this disease is related to a decline in phosphor excretion during the course of renal failure and a subsequent decrease in calcitriol secretion (active form of vitamin D). The resulting hypocalcemia causes an increase in the production of parathyroid hormone (PTH) by the parathyroid glands [3, 4]. In SHPT, vascular calcifications caused by cardiovascular diseases, and brown tumors, the most severe manifestation of renal osteodystrophy, are more prevalent among the elderly, patients undergoing hemodialysis for more than 3 years, patients with stage 5 CKD (glomerular filtration rate  $<15$  ml/min/1.73 m<sup>2</sup>) and with PTH  $>500$  pg/ml [5, 6].

PTH is the most important marker for the evaluation of the severity of SHPT and an increase in the levels of this hormone indicate generalized osteoporosis in the skeletal system [3]. During this process, the middle phalanges of the index and long fingers of the hand are the first sites of bone resorption [7, 8]. In this respect, metacarpal radiogrammetry, a technique that measures metacarpal cortical thickness in the index, long, and ring fingers, has been shown to be a good peripheral predictor of osteoporosis [9–11]. In addition, collar bones and the mandible are another sites commonly affected by osteoporosis in SHPT. Cortical bone resorption, loss of lamina dura around the teeth, and trabecular bone alterations are the most frequent radiologic manifestations [12, 13]. Within this context, the mental index and mandibular cortical index are the best parameters to evaluate basal cortical bone resorption in the mandible [14, 15]. In addition, the classification proposed by Lindh et al. [16, 17] is an adequate method to determine the effects of osteoporosis on the trabecular bone pattern in the mandible.

Since hand and wrist radiographs, together with dental radiography, are important imaging exams for the identification of the effects of osteoporosis in SHPT [18], the objective of the present study was twofold: (1) to determine whether a correlation exists between the effects of the disease on the hands and jaws using specific parameters, and (2) to investigate the association between osteoporosis progression in the hands and serum PTH levels in patients with CKD.

## Material and methods

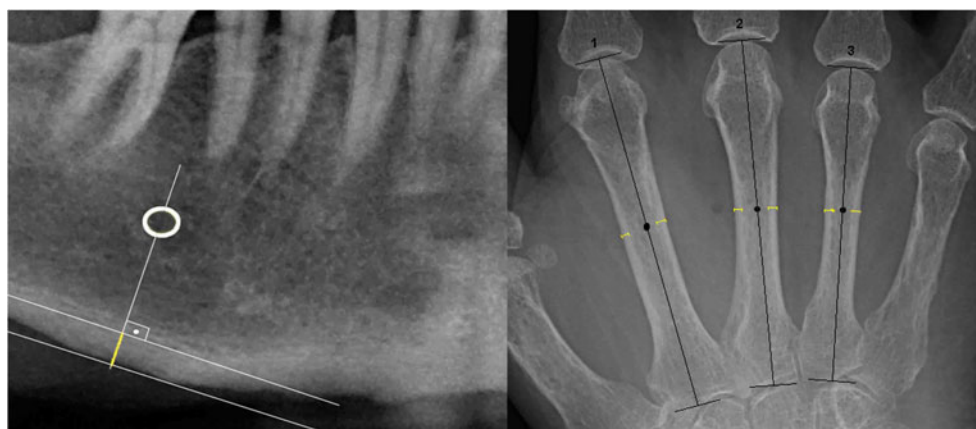
Thirty patients with CKD undergoing hemodialysis at a kidney therapy center were selected by application of the following inclusion and exclusion criteria: hemodialysis treatment for at least 3 years; stage 5 CKD (glomerular

filtration rate  $<15$  ml/min/1.73 m<sup>2</sup>); associated diagnosis of SHPT, with serum PTH levels  $\geq 500$  pg/ml; male patients; and a minimum age of 45 years. The study was approved by the Ethics Committee of our institution (protocol 068/2009) and all 30 volunteers signed a free informed consent form.

## Image acquisition

The same radiologist performed all radiographic exams. Three radiographs, including one panoramic radiograph and two hand/wrist radiographs (right and left hand), were obtained from each volunteer using the ORTHOPHOS XG 5 digital radiography system (Sirona Dental Systems, Charlotte, NC, USA) and saved in TIFF format. Four panoramic radiographic parameters and four hand/wrist radiographic parameters were applied to investigate signs of SHPT and to evaluate the possible correlation between the effects of the disease on the jaws and hands/wrists: (I) panoramic radiograph: Mental Index, a quantitative parameter that measures the mean cortical width of the mandible (millimeters) [19]; hand/wrist radiograph: Metacarpal Cortical Thickness, a quantitative parameter in which the mean cortical width (millimeters) of the middle metacarpals of the index, long, and ring fingers of the two hands is measured by radiogrammetry [11] (Fig. 1). (II) Panoramic radiograph: Mandibular Cortical Index, a qualitative parameter used to classify cortical morphology as normal (C1), moderately resorbed (C2), and severely resorbed (C3) [20]; hand/wrist radiograph: Phalangeal Cortical Index, a qualitative parameter used to classify cortical bone in the middle phalanges of the index, long, and ring fingers as normal (P1), moderately eroded (P2), and severely eroded (P3; Fig. 2). (III) Panoramic radiograph: Trabecular Bone Pattern of the mandible, a qualitative parameter used to classify the mandibular trabecular bone pattern as dense, heterogenous and sparse based on the classification of Lindh [17]. Specifically in the case of SHPT, the category “sparse with ground glass appearance” was added. Hand–wrist radiograph: Trabecular Bone Pattern of the hand/wrist, a qualitative parameter used to classify the trabecular bone quality in the middle phalanges of the index, long, and ring fingers using the same classification as described above (Fig. 3). (IV) Calcification/Resorption: a parameter that quantifies the number of resorption and calcification foci on panoramic and hand/wrist radiographs (Fig. 4). All parameters were analyzed using the Radioceph Studio 2 software (Radiomemory, Belo Horizonte, Brazil). For hand/wrist calcification/resorption, the presence of brown tumors, vascular calcifications, and acroosteolysis (severe bone resorption in the distal phalanges) [8] was also evaluated. As a benefit, the panoramic radiographs taken from the patients were used for dental treatment and the hand/wrist radiographs, to aid the nephrologists in the secondary hyperparathyroidism treatment.

**Fig. 1** Mental index and metacarpal cortical thickness (cortical width in the index, long and ring fingers of the two hands considering a final mean



#### Data collection and statistical analysis

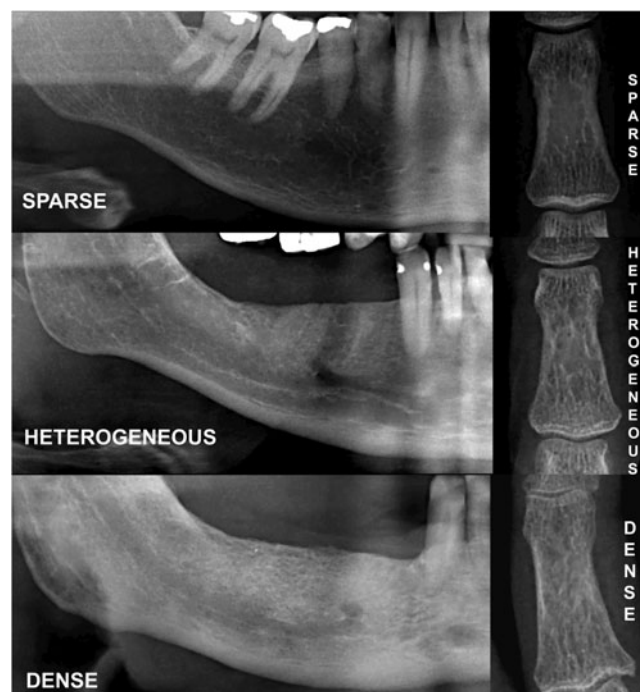
Three observers were trained for 1 week by applying the parameters to 10 panoramic and 10 hand/wrist radiographs. Divergent findings were discussed to increase reliability of the results. Next, in a double-blind study the three observers collected all data on two occasions, with an interval of 30 days between the first and second assessment.

For the evaluation of intra- and interobserver agreement, the intraclass correlation coefficient was used for quantitative parameters (mental index, metacarpal cortical thickness, and calcification/resorption) and the kappa index for qualitative parameters (mandibular cortical index, phalangeal cortical index, and mandibular and hand/wrist trabecular

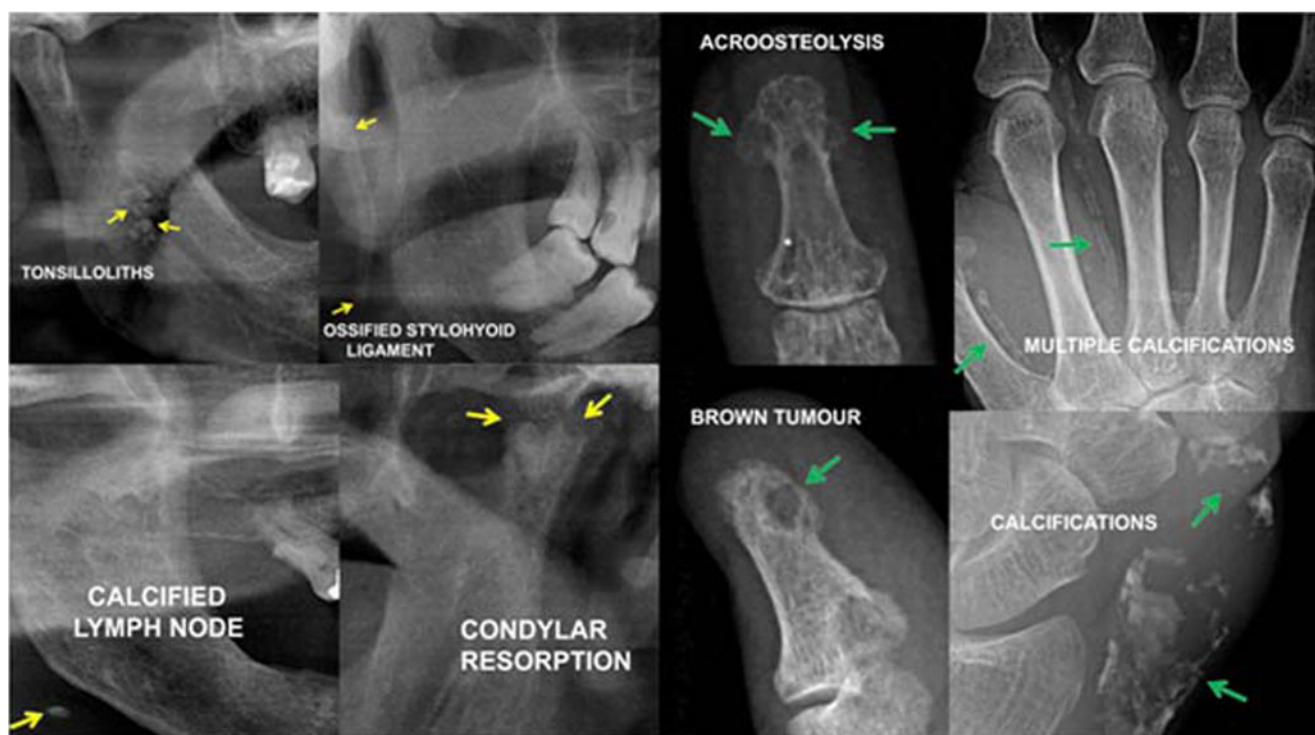
bone pattern). Spearman's correlation coefficient was applied to compare the panoramic parameters (mental index, mandibular cortical index, mandibular trabecular bone pattern, and calcification/resorption) with the corresponding hand/wrist radiographic parameters (metacarpal cortical thickness, phalangeal cortical index, hand/wrist trabecular bone pattern, and calcification/resorption). A level of significance of 5 % ( $p < 0.05$ ) was adopted. Spearman's correlation coefficient ( $p < 0.05$ ) was also used to evaluate the correlation between serum PTH levels of patients with CKD (PTH ranging from 500 to 2,103 pg/ml) and the hand/wrist radiographic parameters. The correlation between PTH levels and panoramic radiographic parameters has been reported previously.



**Fig. 2** Mandibular cortical index and the corresponding phalangeal cortical index



**Fig. 3** Trabecular bone pattern in the mandible and hands/ wrists



**Fig. 4** Foci of calcification/resorption on panoramic (yellow arrows) and hand/wrist (green arrows) radiographs

## Results

### Intraobserver and interobserver agreement

For the mental index and metacarpal cortical thickness, the intraclass correlation coefficient indicated excellent intraobserver agreement (0.81–0.91) and good interobserver agreement (0.61–0.73). Excellent intraobserver (0.95–0.99) and interobserver agreement (0.82–0.86) was observed for calcification/resorption foci on panoramic radiographs. And for hand/wrist calcification/resorption, intraobserver agreement was good (0.62–0.67) and interobserver agreement was moderate (0.57–0.61).

The kappa index indicated excellent intraobserver agreement (0.83–0.90) and good interobserver agreement (0.62–0.79) for the mandibular cortical index and

mandibular trabecular bone pattern. The phalangeal cortical index presented excellent intraobserver (0.87–1.00) and interobserver agreement (0.88–0.94). Finally, the trabecular bone pattern in the hands and wrists indicated good intraobserver (0.72–0.77) and interobserver agreement (0.70–0.78).

### Panoramic parameters versus hand/wrist indices

Table 1 shows the Spearman correlation coefficients and respective *p* values obtained for the correlation between panoramic and hand/wrist radiographic parameters.

The mandibular cortical index was positively correlated with the phalangeal cortical index ( $p=0.000$ ). With respect to the phalangeal cortical and mandibular cortical indices, most patients with CKD presented moderately eroded cortical

**Table 1** Panoramic radiographic parameters versus hand/wrist parameters

	Mental index × metacarpal cortical thickness	Mandibular cortical index × phalangeal cortical index	Mandibular trabecular bone pattern × hand/ wrist trabecular bone pattern	Panoramic calcification/ resorption × hand/wrist calcification/resorption
Spearman correlation ( <i>r</i> )	0.192	0.616	−0.122	0.257
<i>p</i> value	0.307	0.000	0.520	0.169

**Table 2** Distribution of the frequency of patients with chronic kidney disease according to phalangeal and mandibular cortical index

	P1/C1	P2/C2	P3/C3
Phalangeal cortical index (P1, P2, P3)	2	22	6
Mandibular cortical index (C1, C2, C3)	1	18	11

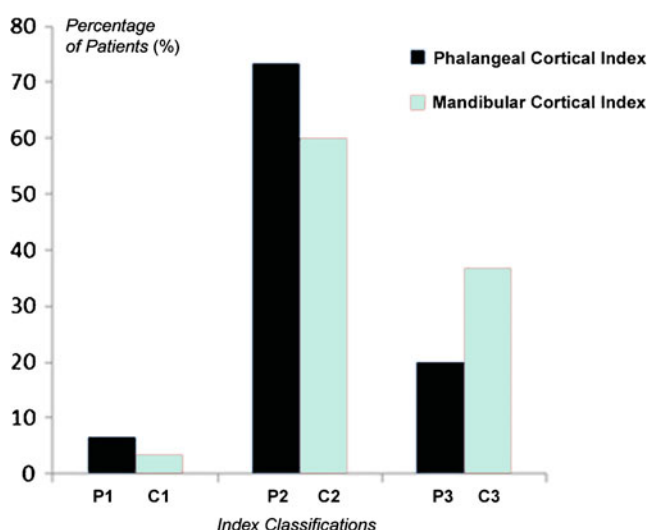
bone (P2/C2), followed by those with severe erosion (P3/C3), and only a minority had normal cortical bone (P1/C1; Table 2 and Fig. 5).

No correlation was observed between the other panoramic radiographic parameters and the corresponding hand/wrist indices ( $p>0.05$ ).

#### Parathyroid hormone levels versus hand–wrist parameters

Table 3 shows the Spearman correlation coefficients and respective  $p$  values obtained for the correlation between PTH levels and hand–wrist radiographic parameters.

A correlation was observed between PTH levels and the phalangeal cortical index ( $p=0.002$ ), i.e., cortical bone erosion tended to be more severe (P3) with increasing PTH levels. The negative correlation was observed between trabecular bone pattern in the hands and wrists and PTH levels ( $p=0.0007$ ), i.e., the trabecular bone pattern tended to become more dense with increasing PTH levels. Most CKD patients (57 %,  $n=17$ ) presented a dense trabecular bone pattern. The heterogenous pattern was observed in 33 % ( $n=10$ ) of the patients and the sparse pattern in only 10 % ( $n=3$ ). The category “sparse with ground glass appearance” was not observed.

**Fig. 5** Most patients with CKD presented moderately eroded cortical bone (P2/C2), followed by those with severe erosion (P3/C3), and only a minority had normal cortical bone (P1/C1)**Table 3** Parathyroid hormone levels versus hand–wrist radiographic parameters

	Metacarpal cortical thickness	Phalangeal cortical index	Trabecular bone pattern	Calcification/resorption
Spearman correlation ( $r$ )	−0.118	0.540	−0.585	−0.154
$p$ value	0.531	0.002	0.000	0.414

No correlation was observed between PTH levels and the other parameters studied (metacarpal cortical thickness and hand/wrist calcification/resorption).

Brown tumors occurred in four CKD patients, while both vascular calcifications and acroosteolysis were observed in 19 patients.

#### Discussion

The progressive decline of calcium levels in SHPT sensitizes calcium receptors of the parathyroid glands which, in turn, stimulate the increased production of PTH and trigger osteoporosis manifestations in the skeletal system, characterizing renal osteodystrophy [21]. The hands and wrists are the first sites of bone loss in SHPT. In this respect, carpal radiographs in combination with dental radiography are important for the early diagnosis of osteoporosis due to renal failure [12, 18]. In the present study, subjects with advanced stage CKD ( $\geq 3$  years of hemodialysis, stage 5, PTH  $> 500$  pg/ml,  $> 45$  years) were selected. In addition, only male patients were included in the study to prevent the influence of menopause-related hormonal alterations on osteoporosis due to SHPT.

In addition to its use as a predictor of osteoporosis [22, 23], the mandibular cortical index showed a positive correlation with serum PTH levels in patients with CKD. Marked differences in the classification of mandibular cortical bone were observed when compared to a control group of healthy subjects included in a previous study from our group. Like the mandibular cortical index, the phalangeal cortical index proposed in this study showed a good correlation with PTH levels. The middle phalanges of the hands were chosen for the definition of this index since these bone sites are the first to undergo resorption in SHPT [7, 8]. The present results suggest the use of the phalangeal cortical index as a complementary parameter to evaluate the severity of SHPT in patients with advanced stage CKD, since the exam is simple and requires only minimal radiation.

The classification of Lindh et al. [17] is a useful tool for the identification of women who are at risk of osteoporosis based on visual analysis of the trabecular pattern in mandibular bone. In a previous study from our group,

the mandibular trabecular bone pattern (based on the classification of Lindh and including the category “sparse with ground glass appearance”) was positively correlated with PTH levels and differed significantly from that of the control group. Although we found no correlation between the quality of mandibular trabecular bone and the corresponding hand index, there was an inverse correlation with PTH levels, i.e., the dense pattern was more prevalent among patients with higher PTH levels and the heterogenous and sparse patterns were more frequent among those with lower levels of the hormone. Although no control hand–wrist radiographs of healthy subjects matched for age were available in the present study, a predominance of the sparse pattern could be identified in 15 hand–wrist radiographs obtained from healthy subjects in the fourth decade of life, suggesting that the sparse pattern indicates normal trabecular bone, whereas the dense pattern is a sign of progression of renal osteodystrophy in the middle phalanges of the hands in patients with CKD as demonstrated in the present study.

The mental index is used for the investigation of osteoporosis, with a mandibular cortical thickness of about 3.0 mm indicating the presence of this condition [24, 25]. PTH levels were correlated with the mental index, in agreement with studies showing progressive cortical thinning with the progression of SHPT [12, 26, 27]. In the present investigation, metacarpal cortical thickness was a parameter designed to evaluate the effects of osteoporosis on the metacarpal cortical bones of the index, long, and ring fingers using radiogrammetry. This technique was an excellent tool for peripheral bone densitometry and has also been indicated for diseases that directly affect cortical bone, such as hyperparathyroidism [11]. Metacarpal cortical thickness was not correlated with the mental index or PTH levels. The use of manual radiogrammetry instead of the digital X-ray radiogrammetry employed in other studies [9, 10] may have compromised the efficacy of this technique in the present investigation. With respect to the presence of calcification/resorption on hand/wrist radiographs, no correlation was observed with PTH levels or calcification/resorption seen on panoramic radiographs. These results support the hypothesis that particular calcifications are extremely complex events that not only depend on PTH levels, but also on other biochemical markers such as serum calcium and phosphorus levels, alkaline phosphatase activity, hemodialysis duration, age, etc. [6, 28]. In this study, a high proportion of patients with CKD presented vascular calcifications ( $n=19$ ), acroosteolysis was observed in most distal phalanges of 19 patients, and brown tumors were identified on four hand–wrist radiographs, characterizing the severity of stage 5 CKD.

## Conclusion

There is a significant correlation between the morphological changes caused by secondary hyperparathyroidism in hand and jaw bones. The morphological status can be measured by the phalangeal cortical index, besides the mandibular cortical index. Furthermore, the phalangeal cortical index is significantly correlation with parathyroid hormone levels, and can therefore be applied to evaluate the severity of secondary hyperparathyroidism in patients with stage 5 CKD. There is a negative correlation between the hand–wrist trabecular bone pattern and parathyroid hormone levels, since differently from the mandible, in the hands the dense trabecular pattern was more prevalent among patients with higher PTH levels. In addition, a high prevalence of vascular calcifications and acroosteolysis is observed in the hands and wrists of most patients with advanced CKD.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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