J Clin Periodontol 2007; 34: 1039–1045 doi: 10.1111/j.1600-051X.2007.01153.x

Journal of Clinical Periodontology

Alveolar bone loss in liver transplantation patients: relationship with prolonged steroid treatment and parathyroid hormone levels

Orit Oettinger-Barak[1,2], Elena Segal[3], Eli E. Machtei[1,2], Shlomi Barak[2], Yaacov Baruch[2,4] and Sofia Ish-Shalom[2,3]

[1]Periodontal Unit, Department of Oral & Dental Medicine, Rambam Health Care Campus, Haifa, Israel; [2]Technion–Ruth and Bruce Rappaport Faculty of Medicine, Haifa, Israel; [3]Metabolic Bone Diseases Unit, Rambam Health Care Campus, Haifa, Israel; [4]Liver Unit, Rambam Health Care Campus, Haifa, Israel

Oettinger-Barak O, Segal E, Machtei EE, Barak S, Baruch Y, Ish-Shalom S. Alveolar bone loss in liver transplantation patients: relationship with prolonged steroid treatment and parathyroid hormone levels. J Clin Periodontol 2007; 34: 1039–1045. doi: 10.1111/j.1600-051X.2007.01153.x.

Abstract

Aim: To evaluate the relationship among alveolar bone loss (ABL), bone status and calcium-regulating hormones in liver transplantees.

Patients and Methods: Twenty-one liver transplantees underwent a full oral examination. The correlations among bone densitometry, bone metabolic status and drug treatment were examined.

Results: Twelve patients had osteopenia, and six were osteoporotic. ABL was 4.33 ± 2.32 mm (range 0.67–9.92). Parathyroid hormone (PTH) levels ranged from 14 to 106 (mean 55.2 ± 26.4). The mean $25(OH)D_3$ was 11.68 ± 4.7, range 3.5–21.1 ng/ml. Nine patients were vitamin D deficient (<10 ng/ml); none of the patients had $25(OH)D_3$ levels $\geqslant 30$ ng/ml. No correlation was found between ABL and current or total glucocorticoids dose, although there was an inverse relation with the duration of treatment ($r = -0.474$, $p = 0.03$). A positive correlation was found between ABL, PTH ($r = 0.419$, $p = 0.059$) and hip bone mineral density (BMD) ($r = 0.482$, $p = 0.027$). ABL correlated closely with age, PTH, glucocorticoid treatment (duration) and hip BMD ($r = 0.810$, $p = 0.004$).

Conclusions: The majority of liver transplant patients had insufficient $25(OH)D_3$ serum levels. Changes in calcium-regulating hormones and hip BMD were correlated with ABL. Therefore, therapeutic intervention aimed at treating vitamin D deficiency and secondary hyperparathyroidism should be considered in these patients. The benefits of vitamin D treatment in the management of secondary hyperparathyroidism and possible decrease in ABL deserve further evaluation in controlled trials.

Key words: alveolar bone loss; bone mass; glucocorticoids; liver transplantation; periodontal disease

Accepted for publication 26 August 2007

In the last two decades, orthotropic liver transplantation has become an accepted treatment for a range of acquired and congenital liver disorders that result in irreversible hepatic failure. One of the known sequelae of liver transplantation is the loss of bone mass (Katz & Epstein 1992). Regardless of the pre-operative bone density, most liver transplantees will suffer bone loss, mostly during the first months after transplantation (McDonald et al. 1991, Meys et al. 1994, Rodino & Shane 1998). This bone loss is attributed to the effect of the transplantation process itself, but the associated glucocorticoid therapy is also considered to be a significant contributory factor (McDonald et al. 1991, Rodino & Shane 1998). Marked trabecular bone loss has been observed during the early post-transplantation period. However, very few studies

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests.

have been performed to elucidate the long-term impact of liver transplantation on bone metabolism (Keogh et al. 1999), and the data on alveolar bone loss (ABL) after liver transplantation are even scarcer (Oettinger-Barak et al. 2002).

Bone loss may also be the result of the underlying pre-transplant liver disease. Cirrhotic patients demonstrate a significant decrease in bone mass, reduced bone formation and significant disorders of bone mineral metabolism (Diamond et al. 1989, Rodino & Shane 1998).

The pathogenesis of post-transplantation bone disease is only partially understood. Increased serum intact parathyroid hormone (PTH) and decreased serum $25(OH)D_3$ levels are among previously proposed mechanisms (Compston et al. 1996).

It has long been postulated that alveolar bone density may be affected in a manner similar to bone mineral density (BMD) at other sites, as manifested by decreased BMD and quality (for a review, see von Wowern 2001).

Data regarding alveolar bone condition in patients after liver transplantation are scarce. In our previous publications, we showed greater ABL in liver transplantees compared with matched healthy controls with similar plaque and gingival indices (Oettinger-Barak et al. 2002). Furthermore, these patients also demonstrated greater pocketing and attachment loss (Oettinger-Barak et al. 2001). Hence, we decided to explore metabolic factors and their potential effect on the periodontal disease, as reflected in the ABL.

The aim of the present study was to evaluate bone metabolic status and levels of calcium-regulating hormones in liver transplant recipients and to correlate them with alveolar bone measurements.

Patients and Methods

Twenty-one liver transplant patients, 10 men and 11 women, who were followed up in the Liver Diseases Unit of Rambam Health Care Campus, were enrolled into this study. A full periodontal examination was performed in the periodontal unit, including both panoramic radiographs and clinical measurements (for detailed description and results see Oettinger-Barak et al. 2001, 2002). All the patients in the present study exhibited moderate-severe chronic periodontitis. A detailed description of the clinical findings in this patients' group was published previously (Oettinger-Barak et al. 2001, 2002). Bone densitometry data and the results of the bone metabolic status evaluation were obtained during an observational study that was also conducted in our centre (Segal et al. 2003). The data were collected during the post-transplantation period.

The mean age was 52.8 ± 12 years (range 32–73 years). The post-liver transplantation period was 2.5–14.5 years, mean 7.7 ± 4 years. Six of the patients were post-menopausal. None of the women were on hormone therapy.

The group was heterogeneous with regard to the underlying pre-transplant liver disease.

Drug therapy

Information regarding previous and present treatment was retrieved from detailed patient charts at the liver transplant clinic. All the patients were receiving immunosuppressive treatment with cyclosporine A or tacrolimus, 10 of them combined with prednisone. The duration of prednisone treatment ranged from 1.5 to 12 years (mean 6.47 ± 3.6). In 11 patients, prednisone treatment had been stopped 1.5–4.5 years before our examinations (mean 2.0 years). Calcium and vitamin D supplementation had been routinely initiated in all patients in the Liver Diseases Unit after the bone status evaluation described in our previous work (Segal et al. 2003). Compliance with calcium and vitamin D supplements was not longitudinally assessed, due to the cross-sectional character of the study.

Laboratory evaluation

Bone formation was assessed by measuring serum bone-specific alkaline phosphatase (BAP) by an immunoradiometric assay (IRMA; Tandem-R-Ostase, Beckman Coulter, Fullerton, CA, USA); bone resorption was assessed using urinary excretion of deoxypyridinoline (DPD) crosslinks, by Pyrilinks-D ELISA (Metra Biosystems, Mountain View, CA, USA); $25(OH)D_3$ was determined by ^{125}I-radioimmunoassay (DiaSorin, Stillwater, MN, USA); and intact plasma PTH was assessed by IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Male gonadal status was assessed by measuring serum total testosterone concentration by an electrochemiluminescence immunoassay using a Roche Elecsys 2010 analyser (Mannheim, Germany). Liver enzymes, liver and kidney function tests were evaluated using the standard technique (Hitachi 747, Roche).

Bone densitometry

BMD measurements of the lumbar spine (LS) and femoral neck (FN) were performed using dual-energy X-ray absorptiometry (Lunar DPX scanner, Madison, WI, USA). The BMD results were expressed in comparison with young adults (*T* scores).

ABL measurement

The panoramic radiographs were all digitized and stored electronically. Next, using computer-based measurement software (X-View Inc., Jerusalem, Israel), the height of the alveolar bone crest was measured from a fixed reference point (the cemento-enamel junction) proximal to all available teeth, excluding third molars.

Statistical analysis

Pearson's correlation coefficient test was used to assess the correlation between ABL and all measured parameters

Table 1. Bone mineral density – WHO criteria

	Normal no. (%)	Osteopenia no. (%)	Osteoporosis no. (%)
Lumbar spine	11(52.4%)	5 (23.8%)	5 (23.8%)
Men	4 (19%)	3 (14.3%)	3 (14.3%)
Women	7 (33.3%)	2 (9.5%)	2 (9.5%)
Femoral neck	8 (38%)	10 (47.6%)	3 (14.3%)
Men	3 (14.3%)	5 (23.8%)	2 (9.5%)
Women	5 (23.8%)	5 (23.8%)	1 (4.7%)
Either lumbar spine or femoral neck	13 (61.9%)	12 (57.1%)	6 (28.6%)
Men	5 (23.8%)	6 (28.6%)	4 (19%)
Women	8 (38%)	6 (28.6%)	2 (9.5%)

Table 2. Calcium regulating hormones and bone turnover markers

	No.	Normal values	Mean ± SD	Range	Correlation with alveolar bone loss	
					r	*p*
25(OH)D_3	20	10–55 ng/ml	11.69 ± 4.8	3.5–21.1	0.105	0.65
Parathyroid hormone (PTH)	21	12–65 ng/l	55.23 ± 26.44	14–106	− 0.42	0.06
Urinary deoxypyridinoline crosslinks (DPD)	19	2.3–7.4 nmol/mmol Creat (F+M)	11.44 ± 6.47	3.7–28		NS
Bone-specific alkaline phosphatase (BAP)	8	Men 8–16.6 μg/l	18.79 ± 8.15	10.8–31.7		NS
	3	Women 5.8–11.6 μg/l	13.9 ± 3.54	10.9–17.8		
	6	Women – menopausal 8.5–17.9 μg/l	17.48 ± 5.7	136–25.7		

Table 3. 25(OH)D_3 serum concentration

Definition of vitamin D status	25(OH)D_3 range (ng/ml)	No. of patients	Alveolar bone loss (mean ± SD) (mm)
Deficiency	⩽10	9	3.80 ± 1.4
Insufficiency	10–14.9	7	5.16 ± 1.9
Inadequacy	15–29.9	5	4.12 ± 3.9
Normal	⩾30	0	
Total		21	4.33 ± 2.3

Table 4. Immunosuppressive treatment

	No.	Mean ± SD	Range	Correlation with alveolar bone loss	
				r	*p*
Duration of glucocorticoid treatment	21	6.48 ± 3.63	1.5–12	− 0.47	0.03
Cumulative cyclosporine A	18	$6 \times 10^5 \pm 5.2 \times 10^5$	1.9×10^4–1.5×10^6	− 0.38	0.11
Cumulative tacrolimus	11	$7.0 \times 10^3 \pm 1.1 \times 10^4$	720–36,741		NS

Table 5. Alveolar bone height measurements

	No.	Range (mm)	Mean (mm)	SD (mm)
Total	21	0.67–9.92	4.33	2.32
Maxilla	14	0.66–7.8	3.9	2.13
Mandible	17	1.67–6.23	3.52	1.16

Table 6. Multiple regression analysis for bone loss

	Coefficients	Standard error	Standard coefficients	*F* to remove	*p*
Intercept	1.803				0.605
Age	0.039	0.056	0.202	0.194	0.492
PTH	0.035	0.019	0.393	3.467	0.081
T score hip	− 0.6	0.538	− 0.331	1.243	0.281
Prednisone years	− 0.346	0.104	− 0.54	11.068	0.004

PTH, parathyroid hormone.

(BAP, DPD, 25(OH)D_3, plasma PTH, serum testosterone concentration, liver enzymes, creatinine, urinary creatinine, osteocalcin, prednisone years, cyclosporine years, tacrolimus years, cumulative prednisone, cumulative cyclosporine, cumulative tacrolimus, hip BMD, LS, etc.). Multiple regression analysis was used to determine the association between bone loss and the markers that were statistically significant in the univariate analysis. The markers were forced into the model. Age was also included, to control for it.

Results

Twelve of the patients had BMD parameters conforming to the definition of osteopenia; six were defined as osteoporotic (Table 1). Ten of them reported previous low-impact fractures and were defined as having severe osteoporosis.

Fractures included: lumbar vertebrae (four patients), ankle (three patients) and others (seven, mostly ribs). Six patients had a history of more than one fracture.

Bone turnover markers and calcium-regulating hormone evaluation results are presented in Table 2.

Nine patients were defined as being vitamin D deficient, having 25(OH)D_3 levels below 10 ng/ml. None of the patients had adequate 25(OH)D_3 levels above 30 ng/ml. Data of serum 25(OH)D_3 levels are presented in Table 3. Six patients had secondary hyperparathyroidism, and 13 had mild chronic renal failure. All the males had normal total serum testosterone levels.

The duration of glucocorticoid treatment was 1.5–12 years (mean 6.48 ± 3.63 SD) (Table 4).

The mean ABL was 4.33 ± 2.32 mm (range 0.67–9.92 mm) (Table 5).

No correlation was found between the ABL and the current or total dose of glucocorticoids. Likewise, we could not establish an association between age and ABL ($r = 0.368$, $p = 0.101$) (Fig. 1), while a negative correlation was found between the duration of glucocorticoid treatment and ABL: $r = -0.474$, $p = 0.03$ (Fig. 2). A positive correlation

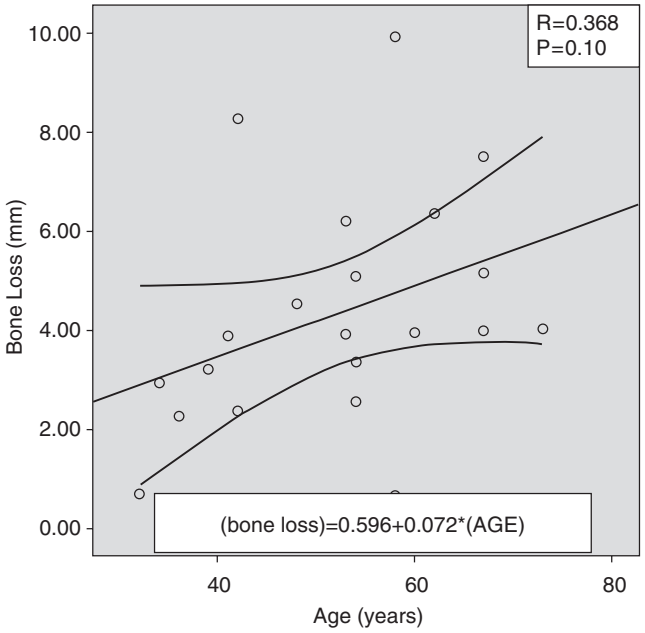

Fig. 1. Correlation between age and alveolar bone loss.

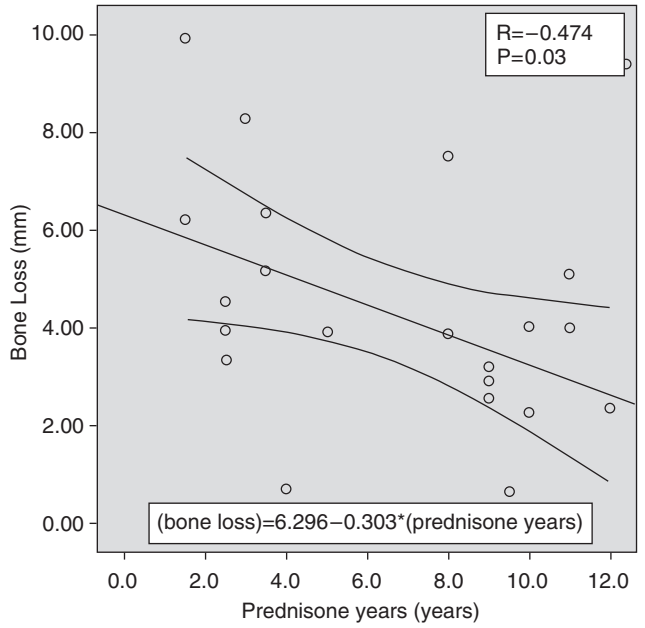

Fig. 2. Correlation between duration of glucocorticoid treatment and alveolar bone loss.

was observed between ABL and plasma PTH levels ($r = 0.419$, $p = 0.059$) (Fig. 3), as well as a decrease in hip BMD, expressed as *T* scores ($r = 0.482$, $p = 0.027$) (Fig. 4). Conversely, $25(OH)D_3$ did not show significant correlation with ABL (Fig. 5).

Multiple regression analysis including the above parameters revealed a strong correlation ($r = 0.810, p = 0.004$) between ABL and age, PTH, duration of glucocorticoid treatment (negative correlation) and hip BMD expressed as *T* score (Table 6).

Owing to the small sample size and changes in the drug therapy over time, we were not able to compare ABL among the patients currently treated with cyclosporine A or tacrolimus. However, no significant correlations were found between ABL and duration of either immunosuppressive medication.

Discussion

We found in this study a strong correlation between age, calcium-regulating hormones and ABL. In our previous publications, post-liver transplantation patients exhibited significantly greater ABL compared with healthy controls (Oettinger-Barak et al. 2002). The above parameters could explain 65% of this bone loss ($r^2 = 0.65$). Currently, there are scarce data on the relationship among radiographic ABL and liver disease, transplantation or immunosuppressive therapy. A decrease in osteoblastic activity in the alveolar bone was reported following experimental liver injury and mechanical stress in rats (Lassila & Virtanen 1984). Another possible mechanism for ABL is excessive resorption, stimulated by the increased levels of serum cytokines associated with liver cirrhosis (Van Dyke et al. 1993). Post-transplantation bone loss might reflect the accumulated bone loss over the years before the liver transplantation. In addition, further bone loss immediately following transplantation is a well-documented complication (Rodino & Shane 1998, Oettinger-Barak et al. 2002). Most studies evaluating the association between BMD and ABL show positive correlations (Kribbs 1990, Wactawski-Wende et al. 1996, 2005, Tezal et al. 2000, Hildebolt et al. 2002, Geurs et al. 2003, Mohammad et al. 2003, Yoshihara et al. 2004). The observation that intra-alveolar trabecular bone is affected by the same local and systemic influences as cortical bone might explain this correlation (Choel et al. 2003), although other studies found no evidence for such a correlation (Elders et al. 1992, Klemetti et al. 1993).

In the present study, the positive correlation found between ABL and FN bone loss supports the premise that both processes are influenced by common factors, and thus anti-osteoporotic treatment might be beneficial for ABL. Indeed, some studies found improvement in alveolar bone mass in post-menopausal women treated with bisphosphonates (El-Shinnawi & El-Tantawy 2003, Rocha et al. 2004) and hormone replacement therapy (Lopez-Marcos et al. 2005), and in an animal model using intermittent PTH injections (Barros et al. 2003).

Digitized panoramic radiographs were used in this study to measure ABL. Rohlin et al. (1989) compared

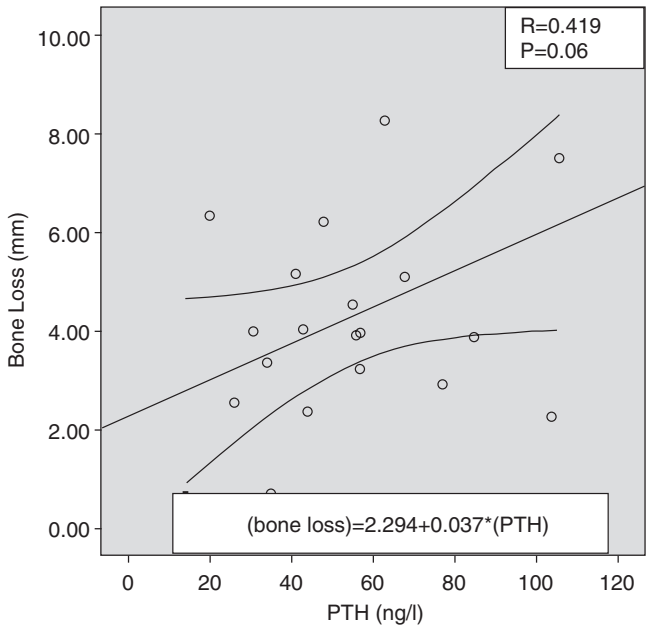

Fig. 3. Correlation between plasma parathyroid hormone (PTH) levels and alveolar bone loss.

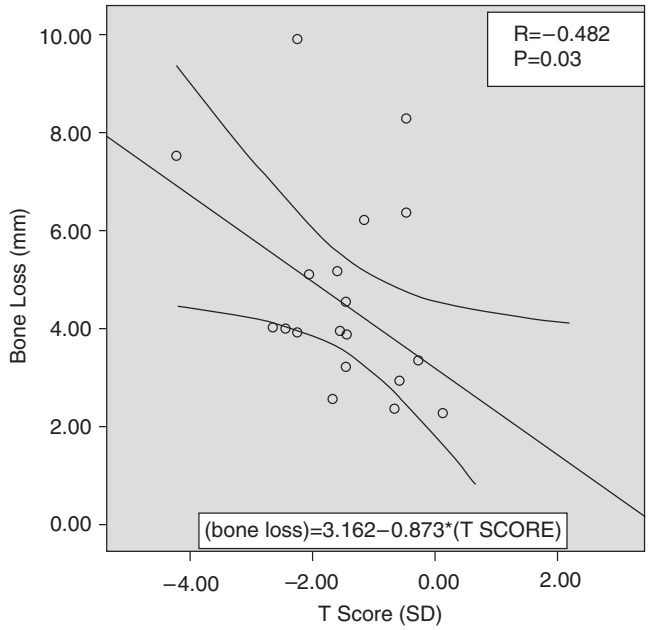

Fig. 4. Correlation between hip bone mineral density and alveolar bone loss.

panoramic and periapical radiographs in the diagnosis of periodontal bone loss, and found 66–74% concordant scores between the two methods for the maxillary and mandibular arches, respectively. Likewise, Akesson, using panoramic radiographs for the assessment of marginal bone loss, reported high concordance between panoramic and intra-oral radiographs (Akesson 1991). Similarly, Walsh et al. (1997) reported good a correlation between panoramic radiographs and clinical parameters for the assessment of periodontal disease.

As for BMD measurements, the regions that are usually measured on the proximal femur are neck, trochanteric, inter-trochanteric and Ward's triangle. The first three together form the ''total hip''. ''Ward's triangle'' is an unreliable square and is not used for analysis. The trochanteric region is less dense because it has more trabecular bone (similar to the LS). In general, the DEXA of the hip (either total hip or FN, where both provide the same fracture prediction) is the best predictor of both hip fractures and spine fractures; thus, it is the best parameter for the diagnosis of osteoporosis. Lunar densitometers, using older software that was available to us in this study, provided trochanter and FN measurements. Because trochanter BMD is not a separate predictor of osteoporosis, we used the universally accepted FN BMD (which represents a combination of cortical and trabecular bone) in the correlation analysis (Johnell et al. 2005, Abrahamsen et al. 2006, Kanis et al. 2006, Siris et al. 2007).

The striking finding was the negative correlation between the duration of prednisone therapy and ABL. One would expect that bone loss would increase with increased accumulated prednisone intake (Di Munno & Delle Sedie 2006, Dovio et al. 2006, Popp et al. 2006). In our previous publication, a significant inverse correlation was observed between the time interval following liver transplantation (the onset of immunosuppressive therapy) and the extent of ABL (Oettinger-Barak et al. 2002). It is therefore suggested that this phenomenon might be attributed to either the restoration of liver function and concomitant reduced cytokine levels (Kita et al. 1994), or the associated immunosuppressive medication, which has also been shown to affect bone metabolism via a reduction in IL-Iβ (Dawson et al. 1996, Myrillas et al. 1999), IL-6 (Myrillas et al. 1999) and TNF. Deficient or insufficient vitamin D levels (Lips 2006, Souberbielle et al. 2006) contribute to bone loss, and cause sustained elevation of PTH that may further increase bone loss.

Almost half of our patients (43%) had vitamin D deficiency ($25(OH)D_3$ serum levels below 10 ng/ml), and none of them had reached vitamin D adequacy. Although data on vitamin D and dental health outcomes are scarce, available evidence suggests that serum $25(OH)D_3$ concentrations between 36 and 40 ng/ml are desirable and the use of at least 800 IU of $25(OH)D_3$ is appropriate (Bischoff-Ferrari et al. 2006).

The supplement dose used was probably insufficient to achieve the desirable

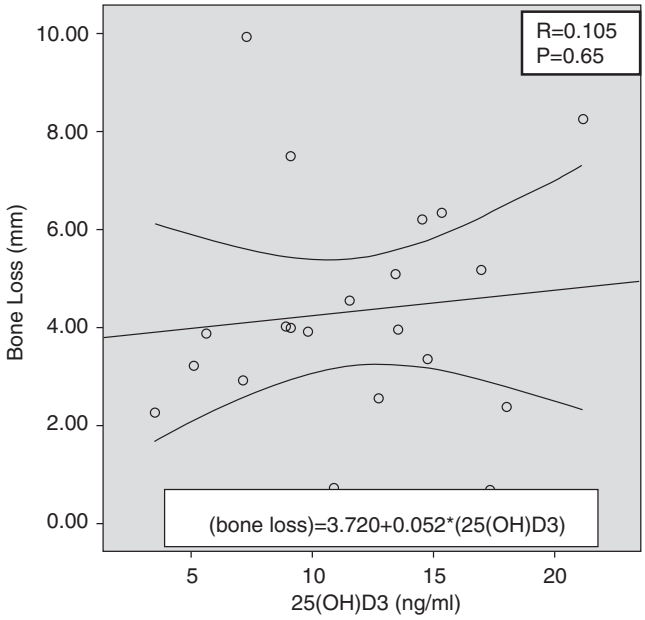

Fig. 5. Correlation between $25(OH)D_3$ and bone loss.

$25(OH)D_3$ concentration, because each 100 IU of vitamin D_3 supplementation usually leads to a 1 ng/ml increase in the $25(OH)D_3$ serum level (Vieth 2006); an individually adjusted dose of vitamin D_3 based on the severity of vitamin D deficiency is probably preferable to the 800 IU supplementation that was administered in this study.

In conclusion, liver transplant patients demonstrated substantial ABL. Elevated plasma PTH and low $25(OH)D_3$ serum levels could explain most of this loss and therefore could serve as risk indicators, or maybe even as risk factors for ABL (Bischoff-Ferrari et al. 2006). It is therefore suggested that full metabolic evaluation, including levels of calcium-regulating hormones, should be included in the assessment of post-transplantation patients examined for periodontal disease, as part of an overall evaluation of potential aetiological factors for periodontal disease. The benefits of vitamin D treatment in the management of secondary hyperparathyroidism and possible decrease in ABL deserve further evaluation in controlled trials.

References

Abrahamsen, B., Rejnmark, L., Nielsen, S. P., Rud, B., Nissen, N., Mosekilde, L., Barenholdt, O. & Jensen, J. E. (2006) Ten-year prediction of osteoporosis from baseline bone mineral density: development of prognostic thresholds in healthy postmenopausal women. The Danish Osteoporosis Prevention Study. *Osteoporosis International* **17**, 245–251.

Akesson, L. (1991) Panoramic radiography in the assessment of the marginal bone level. *Swedish Dental Journal* **78** (Suppl.), 1–129.

Barros, S. P., Silva, M. A., Somerman, M. J. & Nociti, F. H. Jr. (2003) Parathyroid hormone protects against periodontitis-associated bone loss. *Journal of Dental Research* **82**, 791–795.

Bischoff-Ferrari, H. A., Giovannucci, E., Willett, W. C., Dietrich, T. & Dawson-Hughes, B. (2006) Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *American Journal of Clinical Nutrition* **84**, 18–28.

Choel, L., Duboeuf, F., Bourgeois, D., Briguet, A. & Lissac, M. (2003) Related Trabecular alveolar bone in the human mandible: a dual-energy x-ray absorptiometry study. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics* **95**, 364–370.

Compston, J. E., Greer, S., Skingle, S. J., Stirling, D. M., Price, C., Friend, P. J. & Alexander, G. (1996) Early increase in plasma parathyroid hormone levels following liver transplantation. *Journal of Hepatology* **25**, 715–718.

Dawson, J., Hurtenbach, U. & MacKenzie, A. (1996) Cyclosporin A inhibits the in vivo production of interleukin-1beta and tumour necrosis factor alpha, but not interleukin-6, by a T-cell-independent mechanism. *Cytokine* **8**, 882–888.

Diamond, T. H., Stiel, D., Lunzer, M., McDowall, D., Eckstein, R. P. & Posen, S. (1989) Hepatic osteodystrophy: static and dynamic bone histomorphometry and serum bone glaprotein in 80 patients with chronic liver disease. *Gastroenterology* **96**, 213–221.

Di Munno, O. & Delle Sedie, A. (2006) Glucocorticoid-induced osteoporosis and rheumatic diseases. *Pathogenesis, Prevention and Treatment Reumatismo* **58**, 11–21.

Dovio, A., Perazzolo, L., Saba, L., Termine, A., Capobianco, M., Bertolotto, A. & Angeli, A. (2006) High-dose glucocorticoids increase serum levels of soluble IL-6 receptor alpha and its ratio to soluble gp130: an additional mechanism for early increased bone resorption. *European Journal of Endocrinology* **154**, 745–751.

Elders, P. J., Habets, L. L., Netelenbos, J. C., van der Linden, L. W. & van der Stelt, P. F. (1992) The relation between periodontitis and systemic bone mass in women between 46 and 55 years of age. *Journal of Clinical Periodontology* **19**, 492–496.

El-Shinnawi, U. M. & El-Tantawy, S. I. (2003) The effect of alendronate sodium on alveolar bone loss in periodontitis (clinical trial). *Journal of the International Academy of Periodontology* **5**, 5–10.

Geurs, N. C., Lewis, C. E. & Jeffcoat, M. K. (2003) Osteoporosis and periodontal disease progression. *Periodontology 2000* **32**, 105–110.

Hildebolt, C. F., Pilgram, T. K., Yokoyama-Crothers, N., Vannier, M. W., Dotson, M., Muckerman, J., Armamento-Villareal, R., Hauser, J., Cohen, S., Kardaris, E. E., Hanes, P., Shrout, M. K. & Civitelli, R. (2002) The pattern of alveolar crest height change in healthy postmenopausal women after 3 years of hormone/estrogen replacement therapy. *Journal of Periodontology* **73**, 1279–1284.

Johnell, O., Kanis, J. A., Oden, A., Johansson, H., De Laet, C., Delmas, P., Eisman, J. A., Fujiwara, S., Kroger, H., Mellstrom, D., Meunier, P. J., Melton, L. J. III, O'Neill, T., Pols, H., Reeve, J., Silman, A. & Tenenhouse, A. (2005) Predictive value of BMD for hip and other fractures. *Journal of Bone Mineral Research* **20**, 1185–1194.

Kanis, J. A., Johnell, O., Oden, A., Johansson, H., Eisman, J. A., Fujiwara, S., Kroger, H., Honkanen, R., Melton, L. J. III, O'Neill, T., Reeve, J., Silman, A. & Tenhouse, A. (2006) The use of multiple sites for the diagnosis of osteoporosis. *Osteoporosis International* **17**, 527–534.

Katz, I. A. & Epstein, S. (1992) Post transplantation bone disease. *Journal of Bone Mineral Research* **7**, 123–126.

Keogh, J. B., Tsalamandris, C., Sewell, R. B., Jones, R. M., Angus, P. W., Nyulasi, I. B. & Seeman, E. (1999) Bone loss at the proximal femur and reduced lean mass following liver transplantation: a longitudinal study. *Nutrition* **15**, 661–664.

Kita, Y., Iwaki, Y., Demetris, A. J. & Starzl, T. E. (1994) Evaluation of sequential serum interleukin-6 levels in liver allograft recipients. *Transplantation* **57**, 1037–1041.

Klemetti, E., Kolmakov, S., Heiskanen, P., Vainio, P. & Lassila, V. (1993) Panoramic mandibular index and bone mineral densities in postmenopausal women. *Oral Surgury, Oral Medicine and Oral Pathology* **75**, 774–779.

Kribbs, P. J. (1990) Comparison of mandibular bone in normal and osteoporotic women. *Journal of Prosthetic Dentistry* **63**, 218–222.

Lassila, V. & Virtanen, P. (1984) Influence of experimental liver injury on rat blood and alveolar bone under stress. *Acta Anatomica Basal* **118**, 116–121.

Lips, P. (2006) Vitamin D physiology. *Progress in Biophysics and Molecular Biology* **92**, 4–8.

Lopez-Marcos, J. F., Garcia-Valle, S. & Garcia-Iglesias, A. A. (2005) Periodontal aspects in menopausal women undergoing hormone replacement therapy. *Medicina Oral, Patologia Oral and Cirugia Bucal* **10**, 132–141.

McDonald, J. A., Dustan, C. R., Dilworth, P., Sherbon, K., Sheil, A. G. R., Evans, R.A & McCaughan, G. W. (1991) Bone loss after liver transplantation. *Hepatology* **14**, 613–614.

Meys, E., Fontanges, E., Furcade, N., Thomasson, A., Pouyet, M. & Delman, P. D. (1994) Bone loss after orthotopic liver transplantation. *American Journal of Medicine* **97**, 445–450.

Mohammad, A. R., Hooper, D. A., Vermilyea, S. G., Mariotti, A. & Preshaw, P. M. (2003) An investigation of the relationship between systemic bone density and clinical periodontal status in post-menopausal Asian-American women. *International Dental Journal* **53**, 121–125.

Myrillas, T. T., Linden, G. J., Marley, J. J. & Irwin, C. R. (1999) Cyclosporin A regulates interleukin-1beta and interleukin-6 expression in gingiva: implications for gingival overgrowth. *Journal of Periodontology* **70**, 294–300.

Oettinger-Barak, O., Barak, S., Machtei, E. E., Ardekian, L., Baruch, Y. & Peled, M. (2001) Periodontal changes in liver cirrhosis and post-transplantation patients. I: clinical findings. *Journal of Periodontology* **72**, 1236–1240.

Oettinger-Barak, O., Machtei, E. E., Barak, S., Baruch, Y., Ardekian, L. & Peled, M. (2002) Periodontal changes in liver cirrhosis and post liver transplantation patients. II: radiographic changes. *Journal of Periodontology* **73**, 313–316.

Popp, A. W., Isenegger, J., Buergi, E. M., Buergi, U. & Lippuner, K. (2006) Glucocorticosteroid-induced spinal osteoporosis: scientific update on pathophysiology and treatment. *European Spine Journal* **11**, 1–15.

Rocha, M. L., Malacara, J. M., Sanchez-Marin, F. J., Vazquez de la Torre, C. J. & Fajardo, M. E. (2004) Effect of alendronate on periodontal disease in postmenopausal women: a randomized placebo-controlled trial. *Journal of Periodontology* **75**, 1579–1585.

Rodino, M. A. & Shane, E. (1998) Osteoporosis after organ transplantation. *American Journal of Medicine* **104**, 445–450.

Rohlin, M., Akesson, L., Hakansson, J., Hakansson, H. & Nasstrom, K. (1989) Comparison between panoramic and periapical radiography in the diagnosis of periodontal bone loss. *Dentomaxillofacial Radiology* **18**, 72–76.

Segal, E., Baruch, Y., Kramsky, R., Raz, B. & Ish Shalom, S. (2003) Predominant factors associated with bone loss in liver transplant patients after prolonged post transplantation period. *Clinical Transplantation* **17**, 13–19.

Siris, E. S., Genant, H. K., Laster, A. J., Chen, P., Misurski, D. A. & Krege, J. H. (2007) Enhanced prediction of fracture risk combining vertebral fracture status and BMD. *Osteoporosis International* **18**, 761–770.

Souberbielle, J. C., Friedlander, G., Kahan, A. & Cormier, C. (2006) Evaluating vitamin D status. Implications for preventing and managing osteoporosis and other chronic diseases. *Joint Bone Spine* **73**, 249–253.

Tezal, M., Wactawski-Wende, J., Grossi, S. G., Ho, A. W., Dunford, R. & Genco, R. J. (2000) The relationship between bone mineral density and periodontitis in postmenopausal women. *Journal of Periodontology* **71**, 1492–1498.

Van Dyke, T. E., Lester, M. A. & Shapira, L. (1993) The role of host response in periodontal disease progression: implications for future treatment strategies. *Journal of Periodontology* **64**, 792–806.

Vieth, R. (2006) Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. *Journal of Nutrition* **136**, 1117–1122.

von Wowern, N. (2001) General and oral aspects of osteoporosis: a review. *Clinical Oral Investigation* **5**, 71–82.

Wactawski-Wende, J., Grossi, S. G., Trevisan, M., Genco, R. J., Tezal, M., Dunford, R. G., Ho, A. W., Hausmann, E. & Hreshchyshyn, M. M. (1996) The role of osteopenia in oral bone loss and periodontal disease. *Journal of Periodontology* **67**, 1076s–1084s.

Wactawski-Wende, J., Hausmann, E., Hovey, K., Trevisan, M., Grossi, S. & Genco, R. J. (2005) The association between osteoporosis and alveolar crestal height in postmenopausal women. *Journal of Periodontology* **76**, 2116–2124.

Walsh, T. F., al-Hokail, O. S. & Fosam, E. B. (1997) The relationship of bone loss observed on panoramic radiographs with clinical periodontal screening. *Journal of Clinical Periodontology* **24**, 153–157.

Yoshihara, A., Seida, Y., Hanada, N. & Miyazaki, H. (2004) A longitudinal study of the relationship between periodontal disease and bone mineral density in community-dwelling older adults. *Journal of Clinical Periodontology* **31**, 680–684.

Address:
Orit Oettinger-Barak
Periodontal Unit
Department of Oral and Dental Medicine
Rambam Health Care Campus 31096
PO Box 9602
Haifa
Israel
E-mail: o_o-barak@rambam.health.gov.il

Clinical Relevance

Principal findings: In the present study of liver transplant patients, calcium-regulating hormones and FN bone measurements were shown to correlate with ABL. Age, plasma PTH levels, duration of glucocorticoid treatment and hip BMD expressed as a *T* score could explain 65% of this bone loss. Impaired vitamin D status was observed in all patients.

Practical implications: The findings of our study suggest that routine assessment of these parameters should be made. Furthermore, future preventive strategies within the research or clinical set-up need to be encouraged. Finally, raising the awareness of periodontists to potentially correctable metabolic factors may improve patient care and decrease the severity of periodontal bone disease.