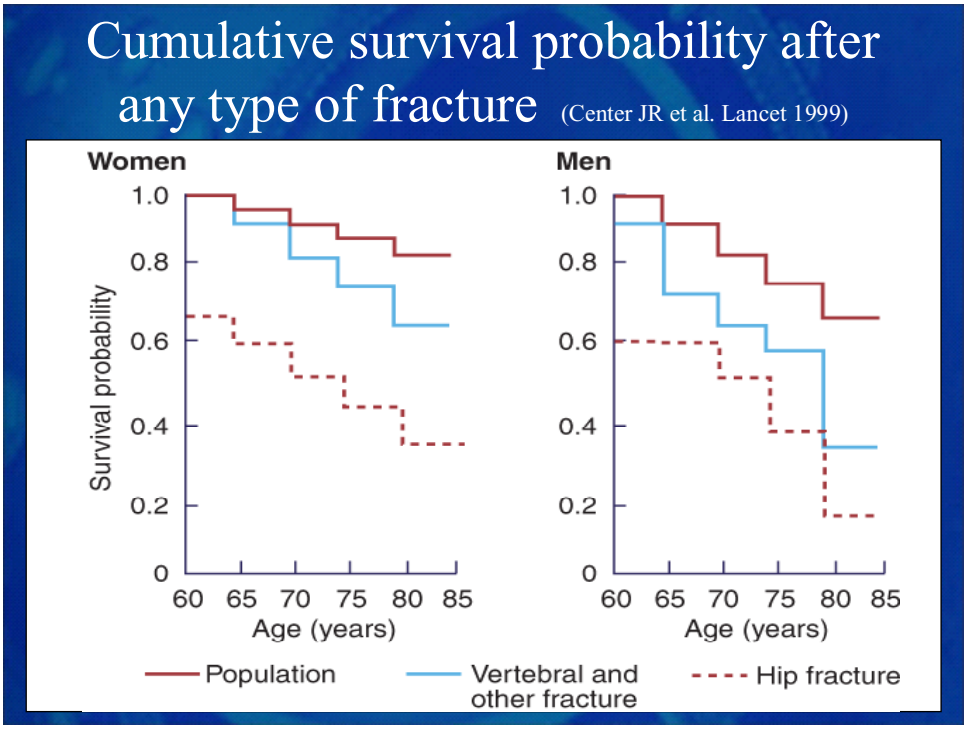
Pathogenetic correlation

Infectious Diseases Unit - S. Orsola Hospital

Marco Borderi
Infectious Diseases Unit - S. Orsola Hospital
Via Massarenti 9, 40138 Bologna, (BO) Italy
Tel.: +39 051 6363355 - E-mail: marco.borderi@aosp.bo.it

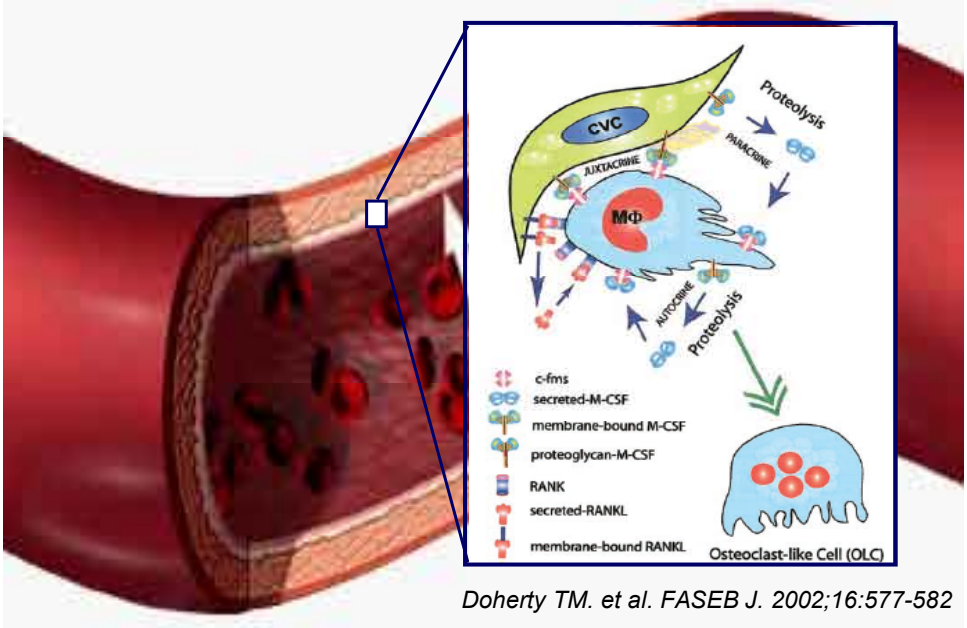
Reduced bone mineral density (BMD) is the most common bone lesion found in HIV-infected individuals. BMD is a parameter that predicts fracture risk, which in turn correlates with a shorter life expectancy. In the elderly, osteoporotic fractures and cardiovascular events are major causes of mortality and morbidity in the general population. In HIV-positive subjects, prevalence of these events is expected to rise in the next future, owing to the increasing longevity of our patients, so the need for early referral of high-risk subjects identified by different independent predictors of cardiovascular risk is also urged. Dao and colleagues compared total and fragility site fracture rates among 5826 HIV-infected adults participating in HOPS with rates among adults in the general US population. Fracture rates for the general population were estimated from National Hospital Discharge Survey data and National Hospital Ambulatory Medical Care Survey data. The results showed that overall fracture rates were higher among HOPS participants than the US general population aged 25-54 years. In addition to increased rate of fracture at fragility sites such as the wrist, vertebra, and femoral neck, both men and women in the HOPS cohort had a significantly higher rate of fractures at nonfragility sites compared with the general population ($P \leq .05$). Osteoporosis and related fractures are well-recognised public-health concerns, and increased mortality after fracture is accepted. Excess mortality varies after hip fracture, with 12-month rates ranging from 12% to 35%. Increased mortality is associated with all major osteoporotic fractures in women and men, but there is also an association between increased mortality and a collective group of other fractures, including pelvis, distal femur, proximal tibia, multiple rib, and proximal humerus. Most excess mortality occurs within the first 3–12 months after fracture, and increases with age. Fracture patients have a higher mortality than does the general population, especially those with hip fractures.



Low bone-mineral density has been associated with increased mortality independent of fracture. Many studies suggest that osteoporosis is a risk factor for cardiovascular events, suggesting an independent association between loss of BMD and vascular calcification, an index of atherosclerosis and cardiovascular risk.

The increased risk associated with osteoporosis is independent of traditional cardiovascular risk factors, is proportional to the severity of osteoporosis, and is not part of a general inclination to morbidities caused by frailty of osteoporotic subjects. Arterial calcification is the result of organized, regulated processes with many similarities to osteogenesis. Low BMD is associated with increases in the relative risk of cardiovascular events and related mortality, and we need to use BMD and vertebral fracture assessment, and investigate the relationship between severity of osteoporosis and risk of cardiovascular events, to answer if low BMD values and vertebral fractures are associated with an increased risk of cardiovascular events, and if the risk of cardiovascular events is proportional to the severity of osteoporosis. There is a significant age-independent association between the degree of aortic calcification and bone density and a strong inverse relation between gains in vascular calcification and bone loss. There is a graded association between the progression of vascular calcification and bone loss. After the mid-60s the prevalence of the metabolic syndrome, diabetes, and related cardiovascular complications show an increasing prevalence, so these patients are particularly suitable for assessing the use of bone assessment for the early prediction of the risk for cardiovascular events. Low bone mass is an even stronger predictor of cardiovascular disease than other well-known risk factors, such as serum cholesterol and smoking. Diagnosis of osteoporosis indicate an increase in risk for a cardiovascular event, even when adjusted for the potential confounding effects of age, prior cardiovascular disease, hypertension, hyperlipidemia, diabetes, smoking habits, or the clustering of these risk factors into a composite cardiovascular risk score, suggesting that the increased risk cannot be explained by common risk factors impacting on both organ systems. The increase in risk for cardiovascular events associated with prior fracture suggests that the association with increased hospitalization and mortality may be at least in part attributable to coronary and stroke events. The presence of at least one vertebral fracture is associated with an increased risk of cardiovascular events regardless of total hip BMD, and increasing number and severity of vertebral fracture are associated with a further increase in cardiovascular risk. Women with vertebral fractures have increased mortality, but clinically diagnosed vertebral fractures may represent only a third of all vertebral deformities. The vertebral fractures are generally only those coming to clinical attention. Since routine radiography is not performed, symptomless, prevalent, or incident vertebral fractures, which may represent up to two-thirds of all morphometric vertebral deformities, may have been undetected. The mechanism by which osteoporosis and cardiovascular disease may be linked is not fully understood, although age, diabetes, dyslipidemia, and hypertension are all established risk factors for cardiovascular disease that also have been associated with decreased BMD or increased fracture risk. Vascular and skeletal biology may share some common pathophysiological mechanisms, suggested by similarities between vascular calcification and active bone formation. Arterial tissue is calcified in an organized, regulated process by mechanisms similar to those involved in the mineralization of bone. The mineral deposit in the arterial wall, hydroxyapatite, is the same mineral found in bone, and it is structurally arranged with trabeculae and lacunae visible in the calcific deposit. Regulated osteogenesis may occur in some cells of the arterial wall. Indeed, cells with both osteoblastic and osteoclastic potential have been described in vascular tissues, and bone-related proteins have been identified in calcified arterial lesions. Monocyte and osteoclast precursors are both recruited by endothelial cells from circulating blood. Circulating monocytic and extraskeletal fibroblastic cells can be induced to differentiate into osteoclasts, and monocytes into OLCs, that show bone resorption activity. Osteoclasts are members of the monocyte/macrophage lineage originating from multiple cellular fusions of their precursors that proliferate and differentiate towards mature osteoclasts by means of macrophage colony-stimulating factor (M-CSF) and RANKL.

Mechanisms contributing to M-CSF- and RANKL-mediated maturation of macrophage to OLC in the arterial wall



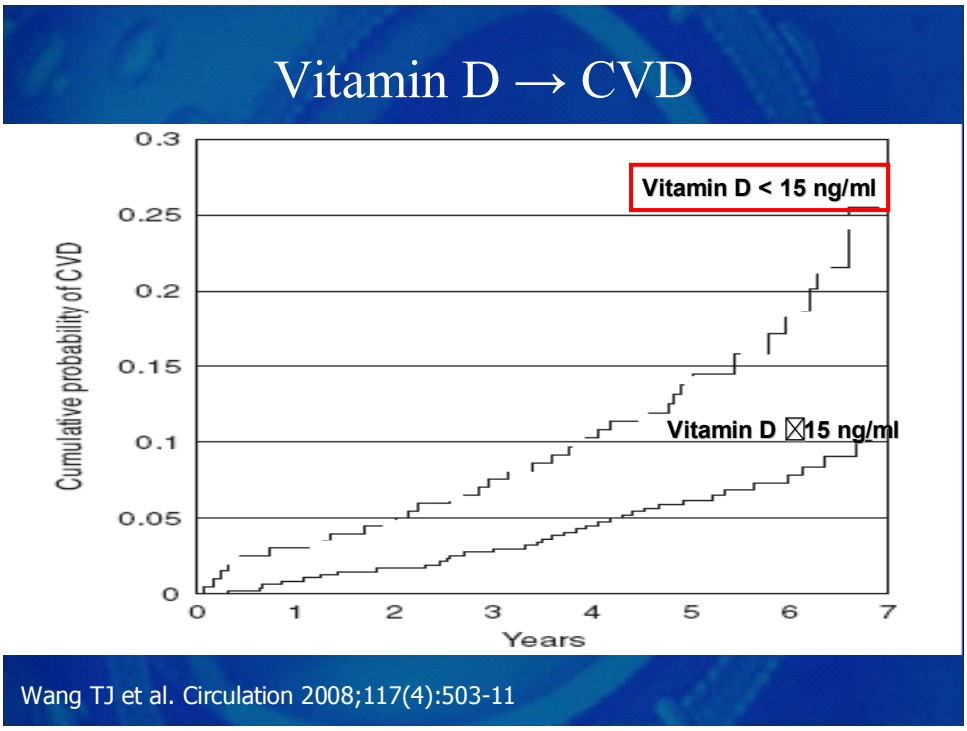
Doherty TM. et al. FASEB J. 2002;16:577-582

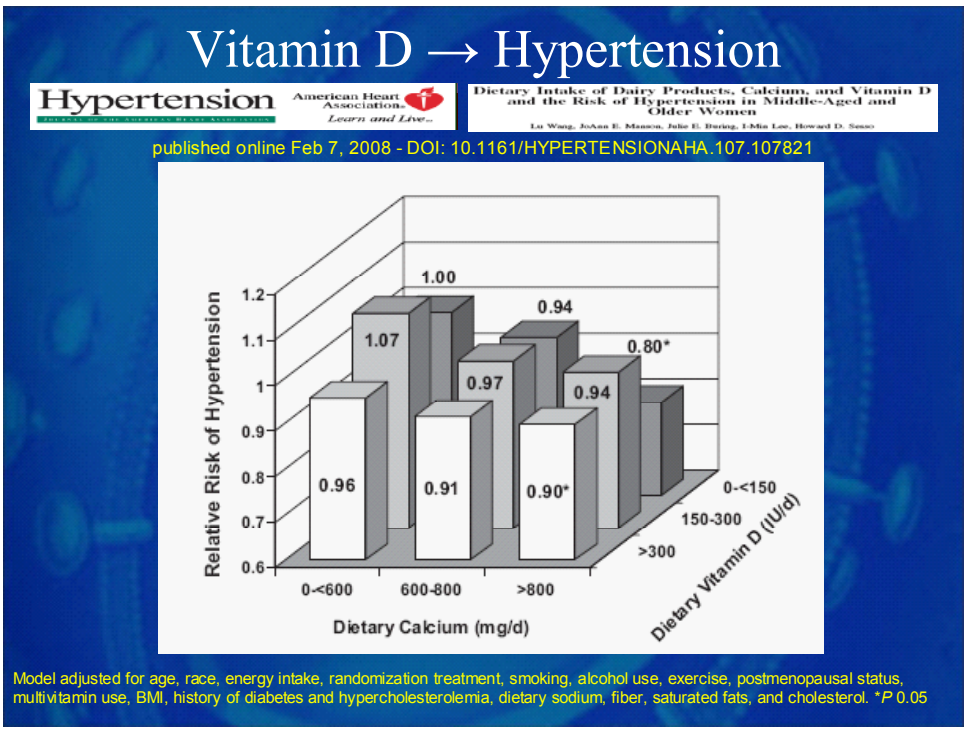
All cells of the vessel wall express M-CSF, and vascular endothelial cells express RANKL and OPG. RANKL

is expressed in small blood vessels of the skin, OPG is expressed in normal arteries, and OPG, RANK, and RANKL transcripts, normally expressed by osteoblastic stromal cells and osteoclast precursors, are found in cells associated with calcified arterial lesions of OPG-deficient mice. Regulators of bone turnover have all been identified in calcified atherosclerotic plaques in humans, and increased expression in these proteins has been associated with unstable carotid artery disease. The artery wall contains cells that retain the capacity to differentiate into osteoblastlike cells. The primary determinant of net mineral deposition in diseased arteries is inhibition of mineral resorption by OLCs rather than mineral deposition of osteoblast-like cells. Reduced mineral resorption might be secondary to decreased maturation, survival, and/or function of OLCs within developing calcified vascular lesion. Low levels of 25-hydroxyvitamin D (25-OH D) are present in as many as one third to one half of otherwise healthy middle-aged to elderly adults. Low levels of vitamin D may adversely affect the cardiovascular system.

Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle, endothelium, and cardiomyocytes. In vitro, 1,25-dihydroxyvitamin D (1,25-OH D) suppresses renin gene expression, regulates the growth and proliferation of vascular smooth muscle cells and cardiomyocytes, and inhibits cytokine release from lymphocytes. 1,25-OH D participates in the regulation of renin-angiotensin axis by directly suppressing renin gene expression. Putative vascular effects of vitamin D are wide-ranging and include modulation of smooth muscle cell proliferation, inflammation, and thrombosis. Vitamin D deficiency directly promotes the development of hypertension, which provides another potential mechanism linking vitamin D deficiency, hypertension, and cardiovascular risk. Many studies have reported cross-sectional associations between lower vitamin D levels and plasma renin activity, blood pressure, coronary artery calcification, and prevalent cardiovascular disease.

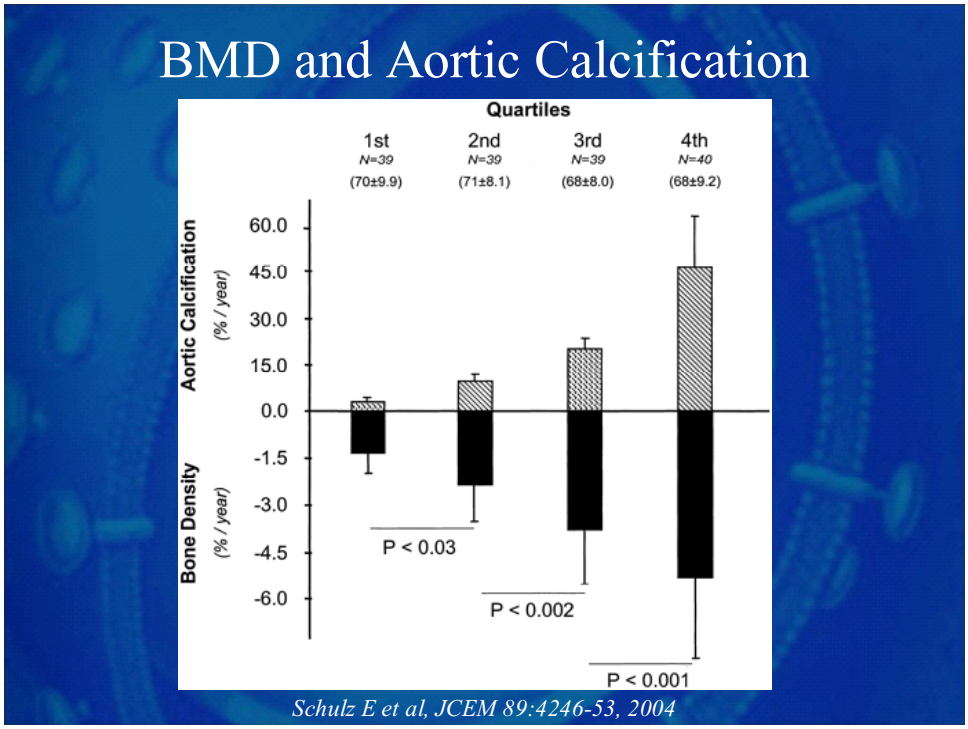
Other studies have reported higher rates of coronary heart disease and hypertension with increasing distance from the equator, a phenomenon that has been attributed to the higher prevalence of vitamin D deficiency in regions with less exposure to sunlight. Vitamin D deficiency is associated with increased cardiovascular risk, above and beyond established cardiovascular risk factors. Increased cardiovascu-





lar risk is present at 25-OH D levels (<15 ng/mL) compatible with at least moderate vitamin D deficiency. In many studies, lower 25-OH D levels have been observed in individuals with acute myocardial infarction, stroke, heart failure, and cardiovascular disease. In 2 studies, 25-OH D was assayed on presentation to the hospital with the cardiovascular event, which suggests that the low 25-OH D levels predated the cardiovascular event.

Vitamin D supplementation has promoted reductions in blood pressure, left ventricular hypertrophy, and inflammatory cytokines. Vitamin D did appear to reduce cardiovascular risk in obese individuals, and also in those with multiple coronary risk factors. In conclusions, there is an association between osteoporosis and risk of cardiovascular events that is independent of age and cardiovascular risk factors. Clinical management of patients with osteoporosis should include not only prevention of fractures but also prevention of cardiovascular disease. Moderate to severe vitamin D deficiency is a risk factor for developing cardiovascular disease. These findings may have potentially broad public health implications, given the high prevalence of vitamin D deficiency, the contribution of lifestyle and geography to vitamin D status, and the ease, safety, and low cost of treating vitamin D deficiency. Treatment of vitamin D deficiency, via supplementation or lifestyle measures, could reduce cardiovascular risk.



Schulz E et al, JCEM 89:4246-53, 2004

REFERENCES

1. Kartsogiannis, V., Zhou, H., Horwood, N. J., Thomas, R. J., Hards, D. K., Quinn, J. M., Niforas, P., Ng, K. W., Martin, T. J., and Gillespie, M. T. (1999) Localization of RANKL (receptor activator of NF-_B ligand) mRNA and protein in skeletal and extraskeletal tissues. Bone 25, 525–534
2. Simonet, W. S., Lacey, D. L., Dunstan, C. R., Kelley, M., Chang, M. S., Luthy, R., Nguyen, H. Q., Wooden, S., Bennett, L., Boone, T., Shimamoto, G., DeRose, M., Elliott, R., Colombero, A., Tan, H. L., Trail, G., Sullivan, J., Davy, E., Bucay, N., Renshaw-Gegg, L., Hughes, T. M., Hill, D., Pattison, W., Campbell, P., and Boyle, W. J. (1997) Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 89, 309–319
3. Lacey, D. L., Timms, E., Tan, H. L., Kelley, M. J., Dunstan, C. R., Burgess, T., Elliott, R., Colombero, A., Elliott, G., Scully, S., Hsu, H., Sullivan, J., Hawkins, N., Davy, E., Capparelli, C., Eli, A., Qian, Y. X., Kaufman, S., Sarosi, I., Shalhoub, V., Senaldi, G., Guo, J., Delaney, J., and Boyle, W. J. (1998) Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 93, 165–176
4. Hsu, H., Lacey, D. L., Dunstan, C. R., Solovyev, I., Colombero, A., Timms, E., Tan, H. L., Elliott, G., Kelley, M. J., Sarosi, I., Wang, L., Xia, X. Z., Elliott, R., Chiu, L., Black, T., Scully, S., Capparelli, C., Morony, S., Shimamoto, G., Bass, M. B., and Boyle, W. J. (1999) Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. Proc. Natl. Acad. Sci. USA. 96, 3540–3545
5. Rettenmier, C. W., Sacca, R., Furman, W. L., Roussel, M. F., Holt, J. T., Nienhuis, A. W., Stanley, E. R., and Sherr, C. J. (1986) Expression of the human c-fms proto-oncogene product (colony-stimulating factor-1 receptor) on peripheral blood mononuclear cells and choriocarcinoma cell lines. J. Clin. Invest. 77, 1740–1746
6. Sherr, C. J., Rettenmier, C. W., Sacca, R., Roussel, M. F., Look, A. T., and Stanley, E. R. (1985) The c-fms proto-oncogene product is related to the receptor for the mononuclear phagocyte growth factor M-CSF. Cell 41, 665–676
7. Sherr, C. J., Rettenmier, C. W., and Roussel, M. F. (1988) Macrophage-colony stimulating factor. M-CSF, and its protooncogene-encoded receptor. Cold Spring Harbor Symp. Q. Biol. 53, 521–530
8. Shalhoub, V., Elliott, G., Chiu, L., Manoukian, R., Kelley, M., Hawkins, N., Davy, E., Shimamoto, G., Beck, J., Kaufman, S.

A., Van, G., Scully, S., Qi, M., Grisanti, M., Dunstan, C., Boyle, W. J., and Lacey, D. L. (2000) Characterization of osteoclast precursors in human blood. Br. J. Haematol. 111, 501–512
9. Rajavashisth, T., Qiao, J. H., Tripathi, S., Tripathi, J., Mishra, N., Hua, M., Wang, X. P., Loussararian, A., Clinton, S., Libby, P., and Lusis, A. (1998) Heterozygous osteopetrotic (op) mutation reduces atherosclerosis in LDL receptor-deficient mice. J. Clin. Invest. 101, 2702–2710
10. Lusis, A. J. (2000) Atherosclerosis. Nature (London) 407, 233–241
11. Ross, R. (1999) Atherosclerosis-an inflammatory disease. N. Engl. J. Med. 340, 115–126
12. Roodman, G. R. (1996) Advances in bone biology: the osteoclast. Endocr. Rev. 17, 308–322
13. Suda, T., Udagawa, N., and Takahashi, N. (1996) Cells of bone: osteoclast generation. In Principles of Bone Biology (Bilezikian, J. P., Raisz, L. G., and Rodan, G. A., eds) pp. 87–102, Academic Press, San Diego
14. Han, C. I., Campbell, G. R., and Campbell, J. H. (2001) Circulating bone marrow cells can contribute to neointimal formation. J. Vasc. Res. 38, 113–119
15. McGowan, N. W., Walker, E. J., Macpherson, H., Ralston, S. H., and Helfrich, M. H. (2001) Cytokine-activated endothelium recruits osteoclast precursors. Endocrinology 142, 1678–1681
16. Neale, S. D., Smith, R., Wass, J. A., and Athanasou, N. A. (2000) Osteoclast differentiation from circulating mononuclear precursors in Paget's disease is hypersensitive to 1,25-dihydroxyvitamin D3 and RANKL. Bone 27, 409–416
17. Heinemann, D. E., Siggelkow, H., Ponce, L. M., Viereck, V., Wiese, K. G., and Peters, J. H. (2000) Alkaline phosphatase expression during monocyte differentiation. Overlapping markers as a link between monocytic cells, dendritic cells, osteoclasts and osteoblasts. Immunobiology 202, 68–81
18. Quinn, J. M., Horwood, N. J., Elliott, J., Gillespie, M. T., and Martin, T. J. (2000) Fibroblastic stromal cells express receptor activator of NF-kappa B ligand and support osteoclast differentiation. J. Bone Miner. Res. 15, 1459–1466
19. Miyamoto, N., Higuchi, Y., Tajima, M., Ito, M., Tsurudome, M., Nishio, M., Kawano, M., Sudo, A., Uchida, A., and Ito, Y. (2000) Spindle-shaped cells derived from giant-cell tumor of bone support differentiation of blood monocytes to osteoclast-like cells. J. Orthop. Res. 18, 647–654
20 Keene GS, Parker MJ, Pryor GA. Morbidity and mortality after hip fractures. BMJ 1993; 307: 12 48 – 50.
21 Jalovaara P, Virkkunen H. Quality of life after hemiarthroplasty for femoral neck fracture. Acta Orthop Scand 1991; 62: 208 – 17.
22 White BL, Fisher WD, Laurin CA. Rate of mortality for elderly patients after fracture of the hip in the 1980's. J Bone Joint Surg 1987; 69: 1335–40 .
23 Dahl E. Mortality and life expectancy after hip fractures. Acta Orthop Scand 1980; 163: 16 –70.
24 Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA. Race and sex differences in mortality following fracture of the hip. Am J Public Health 1992; 82: 1147–50 .
25 Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE. Survival experience of aged hip fracture patients. Am J Public Health 1989; 79: 274–78.
26 Lu-Yao GL, Baron JA, Barrett JA, Fisher ES. Treatment and survival among elderly Americans with hip fractures: a population-based study. Am J Public Health 1994; 84: 1287–91.
27 Poòr G, Atkinson EJ, Lewallen DG, O'Fallon WM, Melton LJ III. Age-related hip fractures in men: clinical spectrum and short-term outcomes. Osteoporosis Int 1995; 5: 419–26.
28 Schrøder HM, Erlandsen M. Age and sex as determinants of mortality after hip fracture: 3,898 patients followed for 2·5–18·5 years. J Orthop Trauma 1993; 7: 525–31.
29 Fisher ES, Baron JA, Malenka DJ, et al. Hip fracture incidence and mortality in New England. Epidemiology 1991; 2: 116–22.
30 Petitti DB, Sidney S. Hip fracture in women. Clin Orthop 1989; 245: 150–55 .
31 Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. Lancet 1991; 338: 355–58.
32 Aitken JM. Relationship between mortality after femoral neck fracture and osteoporosis. Denmark: International Symposium on Osteoporosis 1987: 45–48.
33 Boereboom FTJ, Raymakers JA, Duursma SA. Mortality and causes of death after hip fractures in The Netherlands. Netherlands J Med 1992 ; 41: 4–10 .
34 Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ III. Population-based study of survival after osteoporotic fractures. Am J Epidemiol 1993; 137: 1001–05 .
35 Holmberg S, Conradi P, Kalén R, Thorngren K. Mortality after cervical hip fracture. Acta Orthop Scand 1986; 57: 8–11.
36. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81:353–373.
37. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet. 1998;351:805– 806.
38. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int. 1997;7:439–443.
39. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Doughertly C, Gunter EW, Bowman BA. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr. 2002;76:187–192.
40. Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr. 2005;94: 483–492.
41. Merke J, Hofmann W, Goldschmidt D, Ritz E. Demonstration of 1,25(OH)2 vitamin D3 receptors and actions in vascular smooth muscle cells in vitro. Calcif Tissue Int. 1987;41:112–114.
42. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N. 25-Hydroxyvitamin D3-1_-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation. 2005;111:1666 –1671.
43. Merke J, Milde P, Lewicka S, Hugel U, Klaus G, Mangelsdorf DJ, Haussler MR, Rauterberg EW, Ritz E. Identification and

regulation of 1,25-dihydroxyvitamin D3 receptor activity and biosynthesis of 1,25-dihydroxyvitamin D3: studies in cultured bovine aortic endothelial cells and human dermal capillaries. J Clin Invest. 1989;83:1903–1915.
44. Sigmund CD, Okuyama K, Ingelfinger J, Jones CA, Mullins JJ, Kane C, Kim U, Wu CZ, Kenny L, Rustum Y. Isolation and characterization of renin-expressing cell lines from transgenic mice containing a reninpromoter viral oncogene fusion construct. J Biol Chem. 1990;265: 19916–19922.
45. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25- Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002;110:229 –238.
46. O'Connell TD, Berry JE, Jarvis AK, Somerman MJ, Simpson RU. 1,25- Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation and hypertrophy. Am J Physiol. 1997;272:H1751–H1758.
47. Rigby WF, Denome S, Fanger MW. Regulation of lymphokine production and human T lymphocyte activation by 1,25-dihydroxyvitamin D3: specific inhibition at the level of messenger RNA. J Clin Invest. 1987; 79:1659 –1664.
48. Wu J, Garami M, Cao L, Li Q, Gardner DG. 1,25(OH)2D3 suppresses expression and secretion of atrial natriuretic peptide from cardiac myocytes. Am J Physiol. 1995;268(pt 1):E1108–E1113.
49. Xiang W, Kong J, Chen S, Cao LP, Qiao G, Zheng W, Liu W, Li X, Gardner DG, Li YC. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. Am J Physiol Endocrinol Metab. 2005;288:E125–E132.
50. Resnick LM, Muller FB, Laragh JH. Calcium-regulating hormones in essential hypertension: relation to plasma renin activity and sodium metabolism. Ann Intern Med. 1986;105:649–654.
51. Kristal-Boneh E, Froom P, Harari G, Ribak J. Association of calcitriol and blood pressure in normotensive men. Hypertension. 1997;30: 1289–1294.
52. Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens. 1995;8:894 –901.
53. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation. 1997;96:1755–1760.
54. Doherty TM, Tang W, Dascalos S, Watson KE, Demer LL, Shavelle RM, Detrano RC. Ethnic origin and serum levels of 1_,25-dihydroxyvitamin D3 are independent predictors of coronary calcium mass measured by electron-beam computed tomography. Circulation. 1997;96:1477–1481.
55. Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. Int J Epidemiol. 1990;19:559 –563.
56. Poole KE, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, Warburton EA. Reduced vitamin D in acute stroke. Stroke. 2006;37:243–245.
57. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol. 2003;41:105–112.
58. Grimes DS, Hindle E, Dyer T. Sunlight, cholesterol and coronary heart disease. QJM. 1996;89:579 –589.
59. Voors AW, Johnson WD. Altitude and arteriosclerotic heart disease mortality in white residents of 99 of the 100 largest cities in the United States. J Chronic Dis. 1979;32:157–162.
60. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension. 1997;30:150 –156.
61. Fleck A. Latitude and ischaemic heart disease. Lancet. 1989;1:613.
62. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84:18 –28.
63. Cigolini M, Iagulli MP, Miconi V, Galiotto M, Lombardi S, Targher G. Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2006;29: 722–724.
64. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr, Tonelli M, Thadhani R. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007; 72:1004 –1013.
65. Zehnder D, Bland R, Chana RS, Wheeler DC, Howie AJ, Williams MC, Stewart PM, Hewison M. Synthesis of 1,25-dihydroxyvitamin D(3) by human endothelial cells is regulated by inflammatory cytokines: a novel autocrine determinant of vascular cell adhesion. J Am Soc Nephrol. 2002;13:621– 629.
66. Mitsuhashi T, Morris RC Jr, Ives HE. 1,25-Dihydroxyvitamin D3 modulates growth of vascular smooth muscle cells. J Clin Invest. 1991;87: 1889–1895.
67. Aihara K, Azuma H, Akaike M, Ikeda Y, Yamashita M, Sudo T, Hayashi H, Yamada Y, Endoh F, Fujimura M, Yoshida T, Yamaguchi H, Hashizume S, Kato M, Yoshimura K, Yamamoto Y, Kato S, Matsumoto T. Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. J Biol Chem. 2004;279:35798 –35802.
68. Kasuga H, Hosogane N, Matsuoka K, Mori I, Sakura Y, Shimakawa K, Shinki T, Suda T, Taketomi S. Characterization of transgenic rats constitutively expressing vitamin D-24-hydroxylase gene. Biochem Biophys Res Commun. 2002;297:1332–1338.
69. Schluter KD, Piper HM. Trophic effects of catecholamines and parathyroid hormone on adult ventricular cardiomyocytes. Am J Physiol. 1992;263:H1739–H1746.
70. Perkovic V, Hewitson TD, Kelynack KJ, Martic M, Tait MG, Becker GJ. Parathyroid hormone has a prosclerotic effect on vascular smooth muscle cells. Kidney Blood Press Res. 2003;26:27–33.
71. Amann K, Tornig J, Flechtenmacher C, Nabokov A, Mall G, Ritz E. Blood-pressure-independent wall thickening of intramyocardial arterioles in experimental uraemia: evidence for a permissive action of PTH. Nephrol Dial Transplant. 1995;10:2043–2048.
72. Martin-Ventura JL, Ortego M, Esbrit P, Hernandez-Presa MA, Ortega L, Egido J. Possible role of parathyroid hormone-related protein as a proinflammatory cytokine in atherosclerosis. Stroke. 2003;34:1783–1789.
73. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007;49:1063–1069.

74. Achinger SG, Ayus JC. The role of vitamin D in left ventricular hypertrophy and cardiac function. Kidney Int Suppl. 2005:S37–S42.
75. Lind L, Wengle B, Wide L, Ljunghall S. Reduction of blood pressure during long-term treatment with active vitamin D (alphacalcidol) is dependent on plasma renin activity and calcium status: a double-blind, placebo-controlled study. Am J Hypertens. 1989;2:20 –25.
76. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab. 2001;86:1633–1637.
77. Park CW, Oh YS, Shin YS, Kim CM, Kim YS, Kim SY, Choi EJ, Chang YS, Bang BK. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. Am J Kidney Dis. 1999;33:73– 81.
78. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006;83:754 –759.
79. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M. Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007;115: 846–854.
80. Borderi M et al. Metabolic bone disease in HIV infection AIDS. 2009 Jul 17;23(11):1297-310
81. Center JR et al. Mortality after all major types of osteoporotic fracture in men and women: an observational study Lancet 1999; 353:878–82
82. Doherty TM et al. Rationale for the role of osteoclast-like cells in arterial calcification 0892-6638/02/0016-0577 © FASEB
83. Schulz E et al. Aortic Calcification and the Risk of Osteoporosis and Fractures The Journal of Clinical Endocrinology & Metabolism 89(9):4246–4253
84. Tankò L et al. Relationship Between Osteoporosis and Cardiovascular Disease in Postmenopausal Women JBMR Volume 20, Number 11, 2005
85. Wang T et al. Vitamin D Deficiency and Risk of Cardiovascular Disease DOI: 10.1161/CIRCULATIONAHA.107.706127
86. Dao C, Young B, Buchacz K, Baker R, Brooks J, HIV Outpatient Study Investigators. Higher and increasing rates of fracture among HIV-infected persons in the HIV Outpatient Study compared to the general US population, 1994 to 2008. 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, California. Abstract 128.