ORIGINAL ARTICLE

Pervasiveness And Connotation of 1,25-OH Cholecalciferol Dearth in Patients With Multiple Myeloma

ZULFIQAR ALI[1], AFSHEEN AKBAR[2], MUHAMMAD FAISAL KHAN[3], *IMRAN ALI[4]*

ABSTRACT

Background: A lytic bone lesion in Multiple Myeloma (MM) is one of the dominant characteristic. There are multiple causes of lytic bone lesions in MM, but vitamin D3 deficiency is most frequently present in our society, and it is more evident in advance age and in such debilitating disease. Previously there is no any relevant research about this particulate issue. Existing research is to conclude pervasiveness and connotation of vitamin D3 dearth in MM.

Methods: The current research meant to establish the pervasiveness of vitamin D3 deficiency in 253 subjects who were diagnosed as MM, seen at several cancer hospitals in Pakistan. These subjects were measured at diagnosis before treatment, and 6 months after diagnosis (treatment is in carry-over phase with bisphosphonate, vitamin D3 and calcium supplements) for serum Calcium (Ca+), vitamin D3, serum paratharmone (PTH), bone-specific alkaline phosphatase (bALP), movement of markers through bone [serum C-terminal cross-linking telopeptide of collagen type-I (CTX) and urinary N-terminal cross-linking telopeptide of collagen type-I (NTX)] these both markers associate through the extent of lytic bone lesions.

Results: Within 253 diagnosed MM patients, 52% have severe deficiency, 39% have mild to moderate deficiency and merely 09% considered to have adequate levels of vitamin D3.

Keywords: Multiple Myeloma (MM), parathormone (PTH), macrophage inflammatory protein 1α (MIP1α), dikkopf-1(DKK1), and osteoprotegrin.

INTRODUCTION

MM is most important plasma cell neoplasm, typically presents as apprehensive throngs scattered throughout the musculo-skeletal system. Plasma cell myeloma is illustrated by myelomatous bone destruction, osteodynia, abnormally high concentration of calcium in circulating blood (calcaemia), myeloma kidney disease, and acquired immune abnormalities.[1]

In the marrow, malignant plasma cells glue to aggregates of polypeptide chains and bone marrow connective tissue cells all the way with the chain of matrix molecules which bind well to specific molecules e.g. the beta-1integrin members (integrin α-4, integrin α-5, integrin α-6), CD54, CD106 and C-X-C motif chemokine 12 (CXCL-12) that fastens CD184 on the cell membrane of malignant plasma cells, stir up equally movement of malignant myeloma cells to chemical concentration gradient and up ruling of cell membrane molecules which bind well to specific molecules i.e. integrin α-4. Myelomatous anchoring of malignant myeloma cells is possibly more assisted with additional adhesion molecules uttered with themselves, i.e. ADP-ribosyl cyclase-1, L-slectin ligand, syndecan-1 and VCAM-1.[2] Malignant plasma cells in the bone marrow microenvironment provokes the transcription and emission of cytokines, e.g. cachectin, interferon beta-2 (INFβ2), somatomedin C, inerleukin-21 (IL-21), CXCL-12 and vascular permeability factor (VPF), through equally affecting malignant myeloma cells and the bone marrow connective tissue cells; these factors activates signaling pathways e.g., MEK (RAF/MEK/MAPK), PI3K/AKT and Tyrosine kinase family that encourage cell proliferation and avert programmed cell death (apoptosis) of malignant cells. The reciprocal action among malignant myeloma cells and the bone substance micro-environment increase tumor expansion and arouse additional cytokine surge that liable for dissolution of bone tissue, which can leads to osteodynia, high concentration of calcium in circulating blood (calcaemia) and compression neuropathy by compression fractures.[1] Bone destruction is arbitrated due to inequity among bone resorption bustle and bone destruction bustle, i.e. bone resorption bustle augmented and bone destruction bustle reduced. Sticking together of malignant myeloma cells to connective tissue cells provokes the release of bone destruction-augmenting factors i.e. cachectin, INFB2, hematopoietin-1, catabolin, type IV collaginaeses, scatter factor, osteostatin, TNF superfamily member 11, vascular permeability factor, somatomedin C and C-C motif chemokine ligand 3. Two of the more significant are TNF superfamily member 11, and MIP-1α. TNF superfamily member 11 is a trans-membrane molecule, and is also called TRANCE or osteoprotegerin ligand. TNF superfamily member 11 attaches with efficient receptor CD254 on bone resorption cells, fuel in the genesis of now more osteoclasts and it leads to increasing bone damaging effect by osteoclasts. This movement can be barren with TNF superfamily member 11b, a receptor for CD265, which takes action while a distraction receptor used for TNF superfamily member 11. Consequently osteoclastic bustle is synchronized with an insubstantial equilibrium among TNF superfamily member 11, along with TNF superfamily member 11b. Physiologically the altitude of OPG is considerable elevated than RANK-L. Distinguishing with patients having MM this equilibrium is interrupted by rising level of RANK-L and declining level of OPG. MIP-1α is a fuel for osteoclast growth with a double mechanism:

1- MIP-1α augments the utility of RANK-L and;
2- MIP-1α straight forwardly arouses osteoclast forerunners undergo through course of development and achieve ripe osteoclast.

[1]Department of Pathology Avicenna Medical College Lahore
[2]Department of Physiology Avicenna Medical College Lahore
[3]Department of Biochemistry Multan Medical and Dental College Multan
[4]Punjab Social Security Health Management Company Hospital Manga Mandi Lahore
Correspondence to Dr. Zulfiqar Ali Email: dr.zulfiqarali53@gmail.com cell: 0300-4197929

C-C motif chemokine ligand 3 gene formulation is unusually standardized in plasma cell myeloma because of disturbed formulation of runt related transcription favtor-1 and acute myeloid leukaemia-1B (AML-1B) transcription factors. This inequity provokes MCGF that arouses the formation of cells that function in breakdown of bone tissues. IL-3 ultimately holds back osteoblast development.[3] The Wnt signaling pathway is decisive for bone forming cell development. Definitely, the multipotent adult somatic cell involves Wnt signaling on the way to develop into full-grown bone represent cell. Malignant plasma cells also release antagonist dikkopf-1(DKK1) of Wnt signaling pathway and SARP-2 are potent repressive of bone forming cell development. Additional important elements concerned in bone forming cells commotion are runt related transcription factor 2 and MCGF. The runt related transcription factor 2 differentiate multipotent adult somatic cell into bone forming cells. Myeloma patients with myelomatous bone disease have a considerable decline of runt related transcription factor 2; this is the consequence of Wnt signaling hang-up with dikkopf-1. MCGF has dual action i.e.; increase formation of osteoclast and hang-up of osteoblast differentiation. Malignant plasma cells display elevated IL-3 levels, consequently blocked osteoblast development. The resultant outcome is striking augment bone resorption, which show the ways to hypercalcemia, osteopenia and pathologic fractures[1].

Patients with MM, due myelomatous osteolytic lesion are at jeopardy of brutal hypercalcemia that can initiate nausea, vomiting, dehydration, hypertension, acute renal failure, pancreatitis, cardiac arrhythmia, coma, and death. The dehydration with hypercalcemia can be treated by enthusiastic intra-venous and oral hydration followed by an anti-osteo resorptive agent such as intravenous bisphosphonate. Serum calcium (Ca+) levels frequently turn down quickly, attaining the standard range within 2 to 3 days in >80% of cases. It sporadically set off underneath standard range at the lowest point. Corticosteroid therapy can also lessen serum calcium levels in 60% of patients with hypercalcemia[4].

Vitamin D normalizes Ca+ equilibrium by physiological processes. Deficiency of vitamin D3 show the way to excessive secretion of parathormone, kindles a bone distrusting cell arbitrated bone destruction and circuitously involves tumor necrosis factor ligand superfamily 11a and necrosis factor ligand superfamily 11b, unenthusiastically influence natural process of bone formation.[5]

Bisphosphonates have been proved pharmacologic treatment of myelomatous osteolytic ailment that can restrain osteoclast arbitrated bone resorption and avert a patient with plasma cell myeloma from hypercalcemia, osteopenia and pathologic fractures. Periodical intravenous infusions of pamidronate have been revealed to diminish the possibility of a myelomatous osteolytic disease in about half of patients having plasma cell myeloma. Pharmacologic mechanism of bisphosphonates is to hamper destruction of the hydroxyl-apatite crystals and decrease the biologic function of osteoclast. The nitrogen-containing bisphosphonates meddle with the biosynthetic mevalonate alleyway by holding farnesyl diphosphonate synthase, with the consequential functional failure of osteoclasts to produce the disheveled margins of their cell membrane required to set in motion osteo-resorption. Inhibition of osteoclast function decrease bone-lysis and modifying and that bisphosphonates thwart liberate of bone markers that encourage bone configuration.[2]

MATERIALS AND METHODS

We achieve multivariate analysis of variance (manova) useful for evaluation of two sets of lab results. The Spearman or Pearson correlation coefficients calculate approximately the divisions of inconstant data. Every statistical analysis was two-pronged, shows 0.05 level of significance. Laboratory analysis for serum Ca+, vitamin D3, PTH, bALP, CTX and NTX were performed in the chemical pathology laboratory at Sheikh Zayed Hospital Lahore. Serum Ca+, vitamin D3, PTH, bALP, CTX and NTX were performed with calcium colorimetric assay abcam USA[6], 1,25(OH) vitamin D3 ELISA abcam USA,[7] PTH electrochemiluminescence assay Roche USA,[8] bALP colorimetric assay abcam,[9] Human CTX enzyme linked immune-sorbent assay MyBioSource USA,[10] Human NTX enzyme linked immune-sorbent assay MyBioSource USA[11] respectively. Each test was performed and evaluated subsequent commendations in literature of company for each assay.

RESULTS

Table 01 details vitamin D levels in healthy peoples, mild to moderate deficiency and severe deficiency groups. based on this criterion we have compare Ca+, bALP, PTH, CTX and NTX in two groups, one group before treatment of lytic bone lesions, another group whose treatment is in carry-over phase with bisphosphonate, vitamin D3 and calcium supplements.

Table 2 Give information of statistic features and bone lesion indicator in patients with good health otherwise having MM, mild to moderate deficiency, and severe deficiency groups. Patients in the mild to moderate deficiency group, and severe deficiency groups had higher serum Ca+, bALP, PTH, CTX and NTX levels than those in the healthy group, otherwise having MM.

Table 3 details comparable evaluation of patient's parameters after six months of diagnosis, treatment is in carry-over phase with bisphosphonate, vitamin D3 and hydration for hypercalciuma. Vitamin D3 levels were correlated with patient demographic data and lab studies i.e; serum Ca+, PTH, bALP, CTX and NTX.

Table1: Vitamin D3 deficiency recognized according to international criterion

Parameters	Healthy peoples	Mild to moderate deficiency	Severe deficiency
Vitamin D3 Levels	17.1-25ng/mL	15-17ng/mL	<15ng/mL

Table 2: Evaluation of patient's parameters at diagnosis. Vitamin D3 levels were correlated with patient demographic data and lab studies

Characteristics	1,25 HO Cholicalciferol Vitamin D3 Level			
	17.1-25ng/mL	15-17ng/mL	<15ng/mL	P-Value
No of Patients (Total: 253)	22.77 (9%)	98.67 (39%)	131.56 (52%)	0.005
Bone Lesions %	63%	97%	100%	0.07
Mean Calcium (Reference Range: 8.5-10.5mg/dl)	10.6	12.3	13.7	0.05
Mean bALP (Reference Range: 6.5-20.1µg/L)	21.1	27.5	36.8	0.05
Mean PTH (Reference Range: 10-65ng/L)	56.3	71.2	88.2	0.03
Mean CTX (Reference Range: 35-836pg/ml)	803	934	1123	0.05
Mean NTX (Reference Range: 21-66nmol)	61	87.2	97.5	0.04

Table 3: Evaluation of patient's parameters after six months of diagnosis.

Characteristics	1,25 HO Cholicalciferol Vitamin D3 Level			
	17.1-25ng/mL	15-17ng/mL	<15ng/mL	P-Value
No of Patients (Total: 251)	65.26 (26%)	102.91 (41%)	82.83 (33%)	0.005
Bone Lesions %	51%	89%	100%	0.07
Mean Calcium (Reference Range: 8.5-10.5mg/dl)	10.4	12.5	14.1	0.05
Mean bALP (Reference Range: 6.5-20.1µg/L)	20.1	27.8	35.8	0.05
Mean PTH (Reference Range: 10-65ng/L)	59.3	76.3	89.5	0.03
Mean CTX (Reference Range: 35-836pg/ml)	810	941	1152	0.05
Mean NTX (Reference Range: 21-66nmol)	62.2	89.1	96.7	0.04

DISCUSION

Within 253 diagnosed MM patients, 52% have severe deficiency characterized by serum 1,25-OH D3 levels of <15ng/mL, 39% have mild to moderate deficiency characterized by serum 1,25-OH D3 levels of 15-17ng/mL and merely 09% considered to have adequate levels characterized by serum 1,25-OH D3 levels of 17.1-25ng/mL. Two patients were expired due to disease crises after 3 and 5 month of diagnosis respectively. Remaining 251 patients whose treatment is in carry-over phase with bisphosphonate, vitamin D3 and calcium supplements, 33% have severe deficiency characterized by serum 1, 25-OH D3 levels of <15ng/mL, 41% have mild to moderate deficiency characterized by serum 1,25-OH D3 levels of 15-17ng/mL 26% considered to have adequate levels characterized by serum 1,25-OH D3 levels of 17.1-25ng/mL. 20% patients having plasma cell myeloma shows hypercalcaemia at first visit. Frequent impediment created by increase serum calcium concentration is kidney disease due to inability of kidney to filter waste and extra fluid. Hypercalcemia managed with intravenous fluids that can repletion of volume and intravenous Bisphosphonates (Zoledronic acid). Recommended dose of zoledronic acid is 4 mg via 15 to 20 minutes infusion monthly. Patients with deranged kidney function, the prescribed amount of drug be obliged to as low as of 3 mg. Patients have vitamin D levels 15-17ng/mL, managed with replacement therapy i.e. Injection of activated ergosterol Vitamin D2 50,000 IU two times in a week for one and half month, whereas individuals have vitamin D level <15 ng/mL received 75,000IU once in week for one and half month. Vitamin D reconfirmed two months afterward and activated ergosterol Vitamin D2 surrogate management carry out again if individual have vitamin D levels become ≤17ng/mL. As levels become 25ng/mL, patients advised to be continue treatment existing of 1000IU vitamin D3 on a daily basis otherwise 50,000IU vitamin D2 every second week consecutively to facilitate innovative prime management to be successful. Levels of serum Ca+, PTH, bALP, CTX and NTX be carry out again after six months. Retaliation was constructive within good number patients, through boosts in activated ergosterol Vitamin D2 therapy as well as reduces in Parathormone levels, nevertheless within kidney impairment patients. It was observed in subsequent visits of patients that most of clinical features of 1,25-OH cholecalciferol insufficiency determined following activated ergosterol Vitamin D2 therapy, inclusive of myasthenia, tiredness and chronic osteodynia improved.

CONCLUSION

The current research work reveals increase pervasiveness of 1,25-OH cholecalciferol dearth in MM patients. The advised daily 1000IU of vitamin D should be regular maintenance dose, following improvement of the dearth, conducted through serum vitamin D3 level. MM related variations of bone turnover markers are also influenced by myeloma kidney, bone lytic lesions and 1,25-OH cholecalciferol dearth. Serum parathormone levels and bone turnover markers be elevated during 1,25-OH cholecalciferol dearth.

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