MUSCULOSKELETAL MANIFESTATIONS IN PATIENTS WITH MALIGNANT DISEASE

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Abstract

Objectives: To describe and detect the incidence of musculoskeletal manifestations in different malignant diseases as well as their relation to the treatment received whether by chemotherapy or radiation therapy. **Methods:** 60 patients with different malignant diseases were included in this study, 45 with solid tumors and 15 patients with hematological malignancy. The mean age was 46.55±11.04 years and the mean disease duration was 2±0.75 years. The patients were fully examined for any rheumatologic involvement, laboratory investigations were performed as well as DXA study for bone densitometry. Treatment strategies were assessed including the chemotherapeutics, radiation therapy and/or surgery. **Results:** Myalgias and arthralgias were the most present followed by flexor tenosynovitis, frozen shoulder and fibromyalgia syndrome. Hypertrophic osteoarthropathy was seen in 5 patients, cutaneous vasculitis in two patients as well as arthritis. Osteonecrosis was present in one of the lunate carpal bones of a patient with NHL (1.67 %) and receiving high dose steroids. Rheumatoid factor was positive in 4 patients, three of which had HCV positivity and cryoglobulins. ANCA was negative in all the studied patients. The bone mineral density was significantly reduced in the patients with malignancy compared to the control. Mild to moderate osteoporosis was present being more evident in the spine and forearm. The bone loss was higher in those with solid tumors and even more obvious in those receiving aromatase inhibitors. **Conclusion:** Musculoskeletal manifestations occurring during malignancies and following the treatment represent a significant percentage of symptoms and signs which may raise a clue to differential diagnosis.

Introduction: Certain rheumatological diseases are associated with an increased risk of malignancy. Included in this group are dermatomyositis, polymyositis, rheumatoid arthritis (RA), systemic lupus erythematosus, Sjögren syndrome and systemic sclerosis **(1,2)**. On the other hand, some malignancies have rheumatological symptoms and may present with joint, muscle and soft tissue manifestations **(1,3).** The malignancies which have the most frequent musculoskeletal findings are leukemias and lymphomas, but paraneoplastic syndromes also occur with solid tumors.

In some cases the rheumatic symptoms are the presenting feature of the disease. In one series of patients admitted to a general hospital ward with a previously unclarified rheumatic disease, 23 percent had an occult malignancy **(4).** Remission of the tumor was associated with improvement in rheumatic symptoms. Symmetric polyarthritis affecting the wrists and small joints of the hands, mimicking RA, is a relatively rare presentation of paraneoplastic arthritis **(5).**

Joint involvement is unusual in lymphoma and is primarily seen with T-cell types **(6).** Articular symptoms in patients with lymphoma may result from secondary gout, a reaction to adjacent lymphomatous involvement or lymphomatous infiltration of the synovium **(7).** Synovial fluid may show atypical lymphocytes and synovial biopsies may demonstrate infiltration by lymphoma cells **(8).** In rare cases arthritis is a presenting feature of the disease **(9).**

Lymphoma may also have clinical features that can cause diagnostic confusion with systemic, or connective tissue disorders including those characterized by vascular and granulomatous inflammation. Patients with T-cell lymphoma may have arthritis, Coombs positive hemolytic anemia, skin rash, fever, and weight loss that are suggestive of SLE, systemic onset JRA and vasculitis. Angiocentric and angioinvasive lesions of various organs in large B-cell lymphomas, tissue infiltrates, extensive necrosis and inflammation may be confused with Wegener's granulomatosus. Up to 15% of patients with Hodgkin lymphoma have radiographic evidence of bone involvement, which is represented by bone pains, worse at night, involving mostly the vertebrae **(10).**

Chronic lymphoproliferative disease related to clonal or nonclonal reactive expansion of large granular lymphocytes is characterized by mild to moderate lymphocytes, bone marrow infiltrates, splenomegaly, granulocytopenia and anemias. Up to one third of patients with LGL syndrome have RA **(11)** and may fulfill the clinical criteria of Felty syndrome.

Leukemia can present with symmetric or migratory polyarthritis, arthralgias as well as bone pain and tenderness **(1, 12,13).** The frequency of articular manifestations in acute leukemia is approximately 4% in adults and 14% in children **(12).** The predominant leukemia causing arthritis in children is acute lymphocytic leukemia and polyarthritis can be the presenting complaint, in comparison, acute and chronic lymphocytic and myeloid leukemia can cause arthritis in adults. A variety of phenomena of suspected acute immune pathogenesis have been reported in association with myelodysplastic syndromes, such as monoarticular arthritis, relapsing polychondritis, Raynaud's phenomenon, Sjögren syndrome and vasculitis **(14).**

Various musculoskeletal or other connective tissue disorders may arise as the result of treatment of malignant disease. Arthralgia or arthritis may follow, or less often occur during, adjuvant chemotherapy. These phenomena are referred to as post chemotherapy rheumatism or chemotherapy-related arthropathy respectively **(15,16).**

Treatment of cancer by chemotherapeutic measures plays an important role as an etiology of musculoskeletal manifestation. A proposed mechanism for Aromatase inhibitors (AI) used in the treatment of breast cancer is the marked suppression of plasma estrogen levels by inhibiting or inactivating aromatase, the enzyme responsible for synthesizing estrogens from androgenic substrates **(17, 18).** Although the benefit of anastrazole was initially reported, this was not confirmed **(19).** Compared to tamoxifen, the incidence of ischemic cerebrovascular disease, endometrial cancer, venous thromboembolic events, hot flashes and vaginal bleeding were all less with anastrozole as well as letrozole **(20).**

However, bone fractures and musculoskeletal pain were more frequent. The impact of using letrozole on BMD was studied, followed up, and after 24 months the patients had a marked decrease in BMD at the hip (-3.6 versus -0.71%) and lumbar spine (-5.35 versus -0.7%), and more women become osteoporotic **(21).** In contrast to tamoxifen, which has estrogenic (i.e. protective) effects on the bones of postmenopausal women, all AIs cause bone loss by lowering endogenous estrogen levels **(21,22, 23, 24).**

The prevalence of musculoskeletal complaints in patients receiving AIs is unclear. Published data trials and patient surveys suggest that up to 44 to 47% of women experience joint pain or stiffness and may be responsible for treatment discontinuation **(25,26,27).** Some studies have been unable to define specific risk factors **(27).** Other risk factors for joint symptoms are prior hormone replacement therapy, hormone receptor positivity, obesity and prior chemotherapy **(18).**

In a prospective study of *Morales et al.,* **(28),** half of the women who developed short-term arthralgias after treatment with AIs had pre-existing musculoskeletal disorder (degenerative joint disease, morning stiffness) and their worsening was associated with articular and tenosynovial MRI changes in the hands.

Fracture rates were significantly higher with anastrazole compared to tamoxifen (22.6 versus 15.6 per 1000 women-years, hazard ratio 1.4) **(22).** The best way to prevent bone loss associated with AIs is unclear, but it is advisable to do exercises, receive calcium, vitamin D and bisphosphonate especially in post-menopausal women with T-score less than -2.0 regardless of the risk factor for fractures **(29).**

The aim of this study was to detect the different musculoskeletal manifestations of some malignant diseases as well as the effects of the treatment received.

Subjects and methods: Sixty patients with different types of malignancies have been collected from the oncology department, Cairo and Fayoum University Hospitals during the period of Jan 2006 to Jan 2009. Patients with bony pains more than two weeks duration and not responding to NSAIDs, or persistent in spite of normal bone scan and alkaline phosphatase level, and with out local tenderness or associated with non malignant biopsy proven skin lesion or arthralgias and/or arthritis not immediately following chemotherapy were selected and referred for Rheumatologic assessment. Patients were divided into solid tumors and hematological cancer.

The patients were subjected to full history taking and clinical examination. General constitutional symptoms such as fever, weight loss, jaundice and lower limb edema were considered and history of any splenectomy was taken. General examination included pulse, temperature and blood pressure. Local examination for the skin included purpura, nodules, livedo reticularis, ulcerations, edema, Raynaud's phenomenon, digital ischemia and bullae. Examination of the musculoskeletal system for detection of arthralgia and arthritis; whether mono or polyarthritis, myalgias, fibromyalgia syndrome and tendonitis. System examination was performed to detect sinusitis, deafness, peripheral neuropathy, muscle weakness or involvement of the kidneys, lungs, gastrointestinal tract and heart.

Laboratory investigations were performed including ESR, CBC with differential counts, Liver and kidney function tests, hepatitis markers cryoglobulins, serum uric acid and calcium. Autoimmune profile was done including Antinuclear antibody (ANA), Rheumatoid factor (RF) and AntiNeutrophil Cytoplasmic Antibody (ANCA). Bone mineral density (BMD) as assessed by DXA was performed to all patients and control. Plain x-ray of the affected joints was performed.

The medications received by the patients especially the chemotherapeutics (anastrazol and letrozole) and corticosteroids as well as the radiotherapy and surgery performed were taken into consideration. Post operative complications such as lymphedema were also considered.

Statistical analysis, Statistical Package for Social Science (SPSS) program version 15 was used for analysis of data. Data was presented as number (percent) and mean ± SD. Mann-Whitney test was used for analysis of 2 quantitative data. ANOVA was performed for analysis of three groups. Spearman correlation was used for detection of the relation between 2 variables. P-value was considered significant if < 0.05.

Results: The mean follow-up duration was 3 years, the female: male ratio was (4 to 1) having 48 females and 12 males. The age of the patients included in the present study ranged from 24 to 69 years with a mean of 46.55±11.04 years. The mean age of the control subjects was 49.3±9.62 years. The disease duration ranged from 1.4 to 9 years with a mean of 2.84±1.22 years. The frequency of solid tumors was 75% of the studied patients while it was 25% for those with hematological malignancies (table 1).

The musculoskeletal manifestations and laboratory parameters of the studied patients are shown in tables (2 and 3). Small vessel cutaneous vasculitis is shown in figure (1). The patients in the present study received treatment in the form of surgery in 41 patients (68.3%), Radiotherapy and chemotherapy in 37 and 58 patients respectively (61.7% and 96.7% respectively). Patients with breast cancer (27 patients) were receiving anastrazol as a chemo therapeutic agent in a dose of 1mg/day and letrozole in a dose of 2.5mg/day during the disease and the musculoskeletal symptoms related to therapy was detected. Patients with cancer colon (3 patients) were receiving xaliplatin, 4 patients with cancer stomach were using 5-flourouracil, 2 patients with cancer ovary used cyclophosphamide and one bladder cancer patient received carboplatin. Patients with non-Hodgkin's lymphoma (4 patients) were receiving high dose steroids up to 60 mg/day for a short duration as a part of their chemotherapy protocol. None of the patients used bone marrow growth factors during chemotherapy. Radiation therapy was given also using a single beam radiation at a dose of 5000 cg over 5 weeks. Ten patients performed surgery for their breast cancer.

Renal insufficiency was present in 1 patient, GIT manifestations in 3 and lymphedema in 6 patients (1.67%, 5 % and 10 % respectively) of all the patients with tumors. Osteonecrosis of one of the lunate carpal bones (Kienbock's disease: Lunatomalacia) was present on plain x-ray of the hand and wrist of one patient with NHL (1.67 %) and receiving high dose steroids as shown in figure (2).

Patients receiving aromatase inhibitors (anastrazole and lestrazole) (27 cases) had arthralgias in 14 cases (51.99 %) and one had polyarthritis. Those receiving radiotherapy (37 cases) had arthralgias in 19 cases (51.35 %), polyarthritis in two cases (one with avascular necrosis of the lunate carpal bone) and monoarthritis in another.

Anemia was present in 12 patents (20 %), leucopenia in 3 patients (5 %) and thrombocytopenia in 3 patients (5 %). Hepatitis C markers were positive in 3 patients (5 %) whose RF and cryoglobulins were positive.

Bone mineral densitometry was assessed by the DXA t score and results are shown in table (4). BMD was significantly lower in patients with Solid tumors and especially those receiving aromatase inhibitors (AI) as found in table (5). The BMD t score of the spine of all the patients with malignancy significantly negatively correlated with the kidney functions (creatinine and urea) at p value (0.03 and 0.035 respectively). The BMD t score of the radius significantly negatively correlated with the ESR (p 0.017).

Discussion: Several musculoskeletal manifestations were detected in the patients with malignancy in the present study. In agreement with the present results is the statement of *Kiltz et. al., (2007)* that the association between musculoskeletal features and lymphoproliferative disorders is well known and that rheumatologists may experience several problems with the various rheumatologic manifestations **(30)**. Additionally, *Fam,* **(31)** reported that malignant neoplasms are associated with a wide variety of rheumatological syndromes**.**

The mechanisms whereby the neoplasm leads to rheumatic symptoms are: direct invasion of the musculoskeletal system, synovial reaction of justa-articular bony or

capsular carcinomatous, secondary gout and paraneoplastic manifestations. Neoplasms constitute an important admission cause in internal medicine wards and rheumatic manifestations are common causes of internal medicine and rheumatology appointments **(32).**

In the present study, arthritis was found in 3 patients (5 %) and hypertrophic osteoarthropathy (HOA) in 5 patients (8.33 %). In accordance with these results are the findings of *Fam,* **(31)** and *Dabrowska-Zimoń and Brzosko* **(33)** that among the most frequently recognized rheumatological syndromes associated with malignancy are HOA, carcinoma polyarthritis and vasculitis. *Brooks* **(34)** stated that Leukemias sometimes present as synovitis and *Oztürkcan et. al.,* **(35)** reported that HOA occurred in 2.27 % of patients with lung cancer. Other authors reported HOA cases with malignancy **(36,37,38,39)**.

In this study, frozen shoulder was present in 9 cancer patients (15 %). *Massarotti et. al., (2008),* **(40)** described that a painful 'frozen shoulder' with disability may be seen after painful conditions as tumors. Moreover, frozen shoulder following breast cancer surgery is addressed **(41).**

In the present study, flexor tenosynovitis was found in 10 patients (16.67 %). However, in the study of *Sheehy et. al.,* **(42)** they announced that although rare, palmar fasciitis and polyarthritis syndrome are important paraneoplastic syndromes for rheumatologists to be aware of.

Fibromyalgia was present in 7 of the studied patients with malignancy (11.67 %). Similar results was present in a study on 122 hospitalized cancer patients as thirteen (10.7 %) had fibromyalgia syndrome **(43).**

In the present study, cutaneous vasculitis occurred in two patients (3.33 %) with hematological malignancy (Myelodysplastic syndrome) over the course of the disease, This is in agreement with the study of *Fain, et. al.,* **(44)** who state that in some patients, vasculitis occurs during the course of or prior to malignancies, most often hematologic rather than solid tumors in 2.3 – 8 % of these patients. MDS can be associated with

vasculitis, with a predilection for leukocytoclastic and , more rarely, polyarteritis nodosa. However, in the study of *Brooks* **(34)** it was reported that rheumatic manifestations, including cutaneous vasculitis and lupuslike syndromes, are seen in up to 10% of patients with myelodysplastic syndromes.

Osteonecrosis of one of the carpal bones was present on plain x-ray of the hand and wrist of one patient with NHL (1.67 %) who received high dose steroids. In accordance of the present results was the study of *Harper et. al.,* (**45)** who stated that avascular necrosis of bone is sometimes a complication of cancer chemotherapy that includes corticosteroids and generally occurs at a single site. Reports of simultaneous carpal avascular necrosis in more than 1 bone are rare **(46).** Following steroid therapy, osteonecrosis was reported in the capitate **(47)** and lunate **(48)** carpal bones.

In the present study, 14 patients (51.99%) receiving AIs had arthralgias. In agreement with the present work is the study of *Winters et. al.,(2007),***(49)** who informed that musculoskeletal pain was experienced in 25-30% of patients receiving AIs. They further stated that although quality-of-life studies demonstrate that AIs are well tolerated overall, some women discontinue this treatment because of musculoskeletal pain and little is known about how to predict, measure, or manage the musculoskeletal pain it causes. *Nemitz et. al., (2008)* **(50)** pointed to the intensification of a diffuse chronic pain syndrome and arthralgias by the introduction of an AI. Besides, *Coleman et. al.,* **(51)** *and Burstein,* **(52)** reported that the actual incidence of AI-associated arthralgias or musculoskeletal symptoms is not known, though such symptoms are quite prevalent and can be a reason for discontinuation of AI treatment. Arthralgia and arthritis have seldom been rigorously differentiated in clinical studies of AIs and the possible mechanisms of AI-associated arthralgia are unclear.

In the current work, hepatitis C markers were positive in 3 patients (5 %) whose RF and cryoglobulins were positive. In the study of *Saadoun et. al.,* **(53)** they referred to that the overall risk of NHL in patients with HCV-mixed cryoglobulinemia is estimated to be 35 times higher than that in the general population even though HCV infection is the second most common chronic viral infection in the world with a global

prevalence of about 2%. Mixed cryoglobulinemia reflects the expansion of B cells producing a pathogenic IgM with rheumatoid factor activity.

In the present study, the ANCA was negative in all the patients with malignancy including the two with cutaneous vasculitis . This is in agreement with several studies that supported that ANCA was repeatedly negative even in patients with tumors and associated vasculitis **(54,55,56).**

The study of ***Hamidou et. al.,*** **(57)** found that the global prevalence of ANCA in patients with malignancy associated vasculitis was 3%, which is similar to that found in the general population and that ANCA were not helpful for the diagnosis of vasculitis. In the study of *Wong et. al., (2008)* **(58)** cutaneous vasculitis was induced in breast cancer treated with aromatase inhibitors and only some patients with drug-induced cutaneous vasculitis have ANCA.

In the present work, the bone mineral density DXA t score was significantly reduced in the patients with malignancy compared to the age and sex matched control. Mild to moderate osteoporosis was present being more evident in the spine and forearm. The bone loss was higher in those with solid tumors and even more obvious in those receiving aromatase inhibitors. In harmony is the study of *Muslimani et. al., (2009)* **(59)** who found that patients on AIs who develop osteoporosis are at increased risk of musculoskeletal symptoms and bone fracture. Comedication with Ca/Bis reduces the likelihood for osteoporosis and musculoskeletal symptoms.

In conclusion, musculoskeletal manifestations occurring during malignancies and following the treatment represent a significant percentage of symptoms and signs which may raise a clue to differential diagnosis.

Disclosures:

The authors have no conflict of interest.

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2- Yasser Ezzat, None
3- Safaa Sayed, None
4- Ghada El-Mardenly, None
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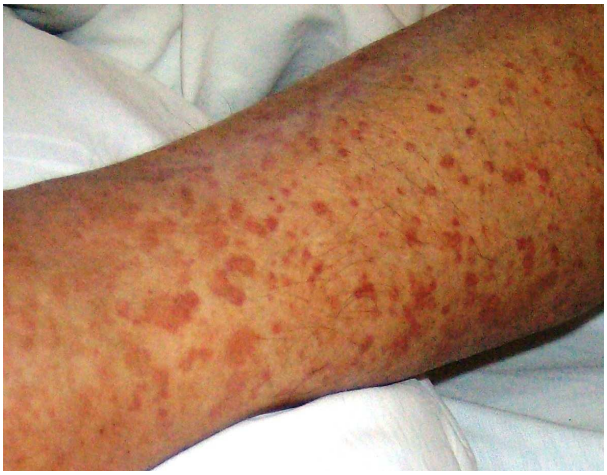

Figure (1): Small vessel cutaneous vasculitis in the form of papules over the leg in a patient with myelodysplastic syndrome (MDS).

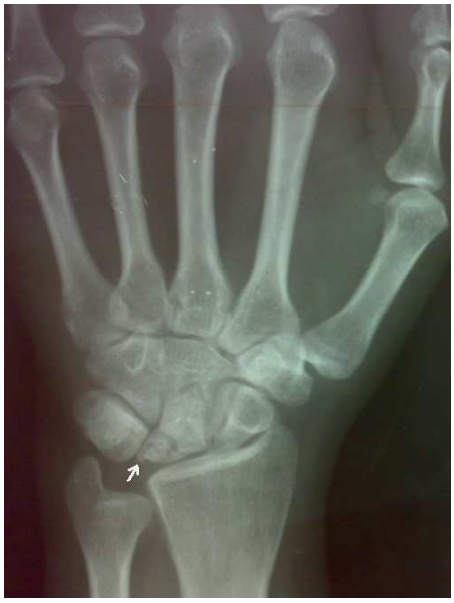

Figure (2): Plain x-ray of the hand and wrist showing Kienbock's disease of the lunate bone of a patient with NHL receiving high dose steroids and radiotherapy. The arrow points to the lunate bone which shows fragmentation and collapse.

Table (1): The types of solid and hematological tumors in the studied patients.

Type	Number	Percent
Solid tumors (N=45)		
Lung	4	8.88%
Breast	27	60%
Colon	4	8.88%
Hepatic	3	6.66%
Bladder	1	2.22%
Ovarian	2	4.44%
Endometrial	1	2.22%
Stomach	3	6.66%
Hematological tumors (N=15)		
Myelodysplastic	4	26.67%
Non Hodgkin lymphoma	4	26.67%
Hodgkin	4	26.67%
Chronic lymphatic leukemia	3	20%

Table (2): Musculoskeletal manifestations in patients with solid tumors and hematological malignancies.

Musculoskeletal manifestations Number (percent)	**All patients** 60 (100)	**Solid** 45 (75)	**Hematological** 15 (25)
Myalgia	14 (23.33)	12 (26.67)	2 (13.33)
Arthralgia	17 (28.33)	14 (31.11)	3 (20)
Polyarthritis	2 (3.33)	2 (4.44)	0 (0)
Monoarthritis	1 (1.67)	0 (0)	1 (6.67)
Peripheral neuropathy	1 (1.67)	0 (0)	1 (6.67)
FTS	10 (16.67)	9 (20)	1 (6.67)
FMS	7 (11.67)	7 (15.56)	0 (0)
Frozen shoulder	9 (15)	8 (17.78)	1 (6.67)
Cutaneous vasculitis	2 (3.33)	0 (0)	2 (13.33)
HOA	5 (8.33)	2 (4.44)	3 (20)

FTS: flexor tenosynovitis, FMS: fibromyalgia syndrome, HOA: hypertrophic osteoarthropathy

Table (3): Laboratory parameters of the patients with Solid and hematological tumors.

Laboratory Parameter Mean±SD	**All patients**	**Solid**	**Hematological**	**P**
ESR 1st hour (mm/Hg)	48.05±15.16	47.48±10.91	49.73±17.55	0.67
CRP (mg/L)	4.748±4.66	4.2±3.07	6.39±7.62	0.6
RBC (millions/mm^3)	4.19±0.55	4.19±0.56	4.17±0.55	0.71
Hemoglobin (g %)	10.62±0.82	10.62±0.83	10.65±0.82	0.97
WBC ($x10^3/mm^3$)	6.85±2.04	7.07±1.96	6.2±2.2	0.068
Platelets ($x10^3/mm^3$)	175.02±53.84	176.5±53.89	170.53±55.31	0.42
AST (U/L)	30.93±8.56	30.8±8.16	31.33±9.95	0.99
ALT (U/L)	28.75±7.59	28.8±8.13	28.6±5.91	0.92
Uric Acid (mg/dl)	3.92±0.81	3.84±0.77	4.15±0.94	0.19
Creatinine (mg/dl)	0.98±0.33	1.02±0.35	0.88±0.21	0.08
Urea (mg/dl)	34.13±7.12	34.18±7.16	34±7.28	0.89
Calcium (mg/dl)	9.35±0.68	9.42±0.62	9.11±0.81	0.19
Immunological profile Number (percent)				
Rheumatoid factor (RF)	4 (6.67)	4 (8.89)	0 (0)	
Anti-nuclear antibody	5 (8.33)	4 (8.89)	1 (6.67)	
ANCA	0 (0)	0 (0)	0 (0)	
Cryoglobulins	3 (5)	0 (0)	3 (20)	

Table (4): Bone mineral density (BMD) of the patients with Solid and hematological tumors.

DXA (t score) Mean±SD	**All patients**	**Solid tumors**	**Hematological tumors**	**Control**	**P value**
Spine	-1.51±0.99	-1.68±1.02	-1.01±0.74	-1.06±0.8	0.006
Hip	-1.32±0.98	-1.42±0.99	-1.01±0.9	-1.2±0.8	0.56
Radius	-1.06±0.85	-1.19±0.87	-0.65±0.64	-0.91±0.95	0.1

Table (5): Bone mineral density (BMD) of the patients according to aromatase inhibitors (AI) intake and control.

DXA (t score) Mean±SD	**Patients according to Aromatase inhibitors (AI) intake**		**Control**	**P value**
	On AI	**Not on AI**		
Spine	-1.86±1.01	-1.22±0.9	-1.06±0.8	0.003
Hip	-1.54±1.09	-1.14±0.84	-1.2±0.8	0.35
Radius	-1.34±1.02	-0.82±0.6	-0.91±0.95	0.036