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Most Multiple Myeloma Patients have Low Testosterone

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Hypogonadism is present in approximately a quarter of men older than 70 years [1,2] but age alone does not guarantee low testosterone [3]. The diagnosis is often based on two tests of serum testosterone (<300 ng/dL), ideally between 8–10 am, with severely low serum testosterone less than 200 ng/dL.

Multiple myeloma (MM) is a primarily a marrow-based plasma cell neoplasm, and patients are at high risk for secondary hypogonadism due to an average age of diagnosis 65–67 y.o. and the disease is characterized by inflammatory cytokines known to suppress the hypothalamic-gonadal axis. The diagnosis becomes more complicated as anti-neoplastic treatment with immune modulating drugs (IMiDs), proteasome inhibitors, sequential day dexamethasone exposure, and high dose melphalan can all cause fatigue, anemia, anhedonia, muscle cramping, and thyroid dysfunction - symptoms that overlap with those of hypogonadism. Gynecomastia in male patients after high dose melphalan[4] or other intense treatment[5] has been frequently reported. Obesity[6] and dexamethasone exposure both decrease sex hormone binding globulin (SHBG), thus decreasing serum total testosterone[7].

Cytogenetically high risk myeloma characterized in part by the amplification of 1q21 is associated with increased serum levels of soluble IL-6 receptor (sIL-6r)[8]. We proposed that secondary hypogonadism would be common amongst newly diagnosed myeloma patients, and additionally hypothesized that total testosterone levels would be associated with the presence of 1q21 amplification by CD138-selected fluorescent in-situ hybridization (FISH). Our primary objective was to correlate serum total testosterone with biochemical

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Declaration of interest statement

None of the authors have any relevant conflicts of interest to disclose.

prognostic information, e.g. International Stage (ISS), Revised International Stage (R-ISS), age, body mass index, and overall survival.

Overall, 561 patients who had a serum testosterone level measured within 6 months of diagnosis of a plasma cell dyscrasia were prospectively enrolled on our observational myeloma registry (NCT01408225) and study data was collected and managed using REDCap electronic data capture tools hosted at the Ohio State University[9]. Biochemical and myeloma related data were collected within 6 months of diagnosis but treatment exposure was not known at the time testosterone was drawn. FISH from diagnostic bone marrow was collected and high risk markers were defined to include t(4;14), t(14;16), del(17p). There were 426 multiple myeloma patients (305 M/121 F), 25 smoldering myeloma (SMM) patients (16 M/9 F), 55 MGUS patients (38 M/17 F), 47 AL Amyloidosis patients (34 M/13 F), and 8 plasmacytoma patients (7 M/1 F). We analyzed the total testosterone level between gender and disease subtype. The median testosterone levels (ng/dL) as shown in Figure 1A for the plasma cell dyscrasias were not statistically different between the diseases amongst males: MM 222.5, SMM 205.5, MGUS 212, and AL Amyloidosis 246 (see this distribution in females in supplementary figure 1).

We found 74% of our patients would be categorized as hypogonadal based on total testosterone using values obtained within 6 months of diagnosis. We expected a high proportion of low testosterone given the frequent reports of elevated circulating inflammatory cytokines[10]. We observed expected associations with BMI ($p=0.03$), opiate use ($p=0.005$), and a trend with serum albumin ($p=0.06$) [11]. We did not find a significant correlation between total testosterone levels and gender, age, β_2 microglobulin, creatinine, or modification of diet in renal disease (MDRD) calculated glomerular filtration rate (GFR), or the presence or absence of high risk DNA mutations by FISH. There was no association between total testosterone levels and high-risk genetic markers in males or females (supplementary figure 2). Patients with CKS1B (chromosome 1q) trisomies and tetrasomies had the lowest median testosterone level, contradicting our original hypothesis.

Delineating the relationship of testosterone levels and overall patient survival was achieved by first dividing the male multiple myeloma cohort into patients with testosterone levels above 325 ng/dL and below, and the female multiple myeloma patient levels 0–50 ng/dL and 50–100 ng/dL. Kaplan Meier analysis did not find a statistically significant difference in overall survival in either gender (Male: $p=0.45$; $n=305$; Female: $p=0.53$; $n=121$). We then compared patients with testosterone levels in the bottom 25% of the cohort against patients in the highest quartile of testosterone levels and show a statistically non-significant decrease in survival in male multiple myeloma patients with the lowest testosterone levels (supplementary figure 1c & d).

We compared our dataset to a national cohort - The National Health and Nutrition Examination Survey (NHANES), a program of studies designed to assess the health and nutritional status of adults and children in the United States. We compared our male MM patients against the national averages for male testosterone levels through an unadjusted T-test and found the data set from the NHANES to have a significantly higher mean (389

ng/dL, $P < 0.0001$). The NHANES dataset with accompanying testosterone levels is larger than ours with 1,625 male patients and 1,447 female patients.

We next compared the patients on our registry to the Vermeulen elderly cohort [12]. Comparing the specific age ranges to our data set using an unpaired T test, the mean total testosterone level was significantly higher in healthy males compared to patients with multiple myeloma in our study ($P < 0.0001$). The mean testosterone level for this healthy data set was 534 ng/dL, which is much higher than 260 ng/dL from our data set. All three data sets showed that testosterone levels were clinically significant from each other ($p < 0.0001$, figure 1c).

The most thorough review of serum testosterone in cancer patients was a cross-sectional study by Fleishman et al [13] finding the crude prevalence of hypogonadism (e.g. total testosterone < 300 ng/dL) was 48% and using free testosterone (< 52 pg/dL) was 78%. This study included 102 lymphoma and leukemia patients of which 46 (45%) were hypogonadal. This study did not answer whether cancer and/or anti-neoplastic therapy was a significant contributor to the higher prevalence of hypogonadism. Using an upper bound of 325 ng/dL, we found 74% of our patients would be categorized as hypogonadal based on total testosterone using values obtained within 6 months of diagnosis, but we cannot exclude that intervening treatment modified testosterone levels.

With myeloma bone disease present in the majority of patients, estrogens, androgens, testosterone and Vitamin D are important regulators of skeletal building and as a result, hypogonadism could significantly affect bone metabolism in MM patients [14]. Testosterone replacement for hypogonadism in myeloma patients is therefore attractive, but at least one early report suggests that vitamin D supplementation may be more effective than testosterone replacement [15].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1 **Figure 1.**

(A) This panel represents the distribution of serum testosterone levels in male plasma cell dyscrasia patients measured within 6 months of the patient's initial diagnosis. The number (N) of patients in each group are as indicated above each bar.

(B) For patients with multiple myeloma, a histogram is shown with the number of patients in each testosterone range.

(C) Comparison of mean testosterone levels of three different data sets: Ohio State Multiple Myeloma Registry, NHANES normal (<https://wwwn.cdc.gov/Nchs/Nhanes/Search/DataPage.aspx?Component=Laboratory&CycleBeginYear=2011>), and the Vermeulen elderly data sets. The number (N) of patients in each group are as indicated above each bar.

Table 1.
Correlation among Testosterone and other factors in Multiple Myeloma patients

Spearman rank correlation coefficients were used to assess strength of relationships between free testosterone levels and continuous variables. A Mann-Whitney assessed for a relationship between testosterone in those patients that used opiates and those that did not within 6 months of diagnosis. Lab values were obtained within a 6-month period from diagnosis date to match the time scale of testosterone values. The total number of male and female patients differ based on the availability of data in each row.

Variable	Male Patients			Female Patients		
	N	Spearman Correlation	P-value	N	Spearman Correlation	P-value
Age	305	0.103	0.07	121	0.013	0.89
BMI	278	-0.132	0.03	121	-0.02	0.83
Creatinine (mg/dL)	257	-0.06	0.33	99	0.008	0.94
MDRD GFR	257	0.066	0.30	99	-0.01	0.99
Albumin (g/dL)	297	0.11	0.06	115	-0.04	0.66
Beta-2 Microglobulin (mg/L)	272	0.09	0.17	106	-0.02	0.82
Opiate use	273	--	0.003	120	--	0.69