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Metabolic Syndrome in Patients on Androgen Deprivation Therapy for Prostate Cancer as seen at Kilimanjaro Christian Medical Center, Moshi, Tanzania.

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Background: ***Prostate cancer is a frequently diagnosed malignancy in elderly men worldwide. Previously displayed as rare in Africa, but now a common diagnosis and a cause of mortality.***
Androgen deprivation therapy (ADT) is the main stay of treatment in Africa due to men presenting with advanced or metastatic disease. Men on androgen deprivation therapy will either develop androgen resistant prostate cancer and die of it or die of other causes. Men with prostate cancer on ADT have been found to have increased non cancer mortality and most of the excess mortality have been attributed to treatment. This study was aimed at evaluating the metabolic risk factors in men undergoing short term androgen deprivation therapy at Kilimanjaro Christian Medical Center (KCMC), Tanzania.
Methods: ***This was a prospective cohort study, we evaluated 83 prostate cancer patients; 48 on surgical castration, 9 medical castration (zoladex) and 26 were followed up with no treatment. Data analysis was done using stat version 12. Student 2 sided t tests was used to compare mean of the various variables between ADT group and none ADT group.***
Results: ***The mean age at diagnosis was 75±6.7 (55-95). The group of patients on ADT compared to the group of patients not on ADT had a statistically significant increase in all the lipid fractions i.e. low density lipoprotein(LDL), high density lipoprotein (HDL), cholesterol (CHOL), triglyceride (TGA) P=≤0.001 at three and six month, fasting plasma glucose (P=<0.001) at three and six month, waist circumference P=0.02 and p=0.001 at three and six month respectively, compared to prostate cancer patients not on treatment. No patient in the six month had increments in serum and anthropometric parameter to meet the definition of a metabolic syndrome.***
Conclusion: ***Six month of androgen deprivation therapy is associated with a statistically significant increase in the fasting plasma glucose, lipid fractions, and waist circumference.***

Key words; Metabolic syndrome, Androgen Deprivation Therapy

Introduction

Prostate cancer (PCa) is a common malignancy in elderly men worldwide. In Africa PCa was previously displayed as rare, but now the world health organization approximates its prevalence at 4 % [1]. There is a feeling that this is an under estimation, for example in Uganda it accounts for 39.2 per 100,000 men and 300 per 100,000 men in Nigeria, which approaches that of African American and Jamaica [2, 3]. The greatest challenge for African urologists is an increase in the incidence of PCa, which is complicated by the fact that most patients present with advanced or metastatic disease. Therefore almost all our patients are palliated with androgen deprivation therapy (ADT).

Men treated for PCa have profound hypogonadism which has been found to be an independent factor for cardiovascular disease and metabolic syndrome (MS) due to adverse lipid profile and increased fasting plasma glucose [4]. Testosterone below normal range is associated withan increase cardiovascular risk factor. Diethylstilbestrol was the first to be used for medical ADT,

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but was later found to be associated with cardiovascular toxicity in 30% of patients [5-6]. Rosler and Witztum[7] performed a prospective trial of ADT on sexual offenders and found out a decrease in bone mineral density, increase in insulin resistance, diabetes and worsening dyslipidemia. Twelve month of ADT in men with PCa has been associated with increase in all the lipid fractions and these changes were apparent at 3 months of treatment and permanent while patients continued ADT [8].

Men with PCa on ADT have been found to have increased non cancer specific mortality and most of the excess mortality has been attributed to treatment [9]. Having a MS before starting ADT has been associated with poor outcome compared to those without e.g. median time to PSA progression is 11 months vs. 32 month respectively, median overall survival for those with a MS was 40 month and forthose without metabolic syndrome the median time for overall survival was not reached due to the short time of follow up [10].

Despite the dramatic clinical response to ADT, men undergoing ADT will either die of non cancer specific mortality approximated at 20% or will eventually develop castrate resistant PCa and die of the disease. There was a paucity of data on metabolic cardiovascular risks associated with ADT in our institution and very little data if any reported in the African setting. We evaluated metabolic cardiovascular risk factors in men undergoing short term ADT in our institution.

Patients and Methods.

This was prospective cohort study. It was conducted at KCMC consultation hospital, located in Moshi municipality in Tanzania, which serves an average of eleven million people. The study involved all patients newly diagnosed with PCa by histology, clinical stage III /IV who had been counseled and accepted ADT. The study protocol was approved by the Kilimanjaro Christian medical university ethics review committee. Excluded from the study were those patients who met the inclusion criteria but had cardiovascular and metabolic co-morbidity or factors that might affect serum lipid e.g. renal insufficiency (Cr> 120 Mmol/l) or hepatic disease, smoking and use of drugs such as thiazide diuretics. Patients who had serum lipid level of cholesterol>6.5mmol/l triglyceride (TGA)>1.7mmol/l low density lipoprotein (LDL)>5.44mm/l, fasting plasma glucose (FPG) >6.5mmol/l< blood pressure (BP)>135/85MmmHg, waist circumference102cm> and body mass index (BMI) >30kgm^2> were excluded from the study.

Patients were divided into two groups, the ADT group consisted of patients who met the inclusion criteria, with clinical signs and symptoms sufficient to warrant immediate ADT/ (metastasis on lumbosacral x-ray, recurrent lower urinary tract obstruction after TURP, bone pain,) and those who we reluctant to differ treatment. The Non ADT group consisted of patients who fitted the inclusion criteria, with no sufficient signs and symptom to warrant immediate ADT and accepted to differ treatment until metastatic progression. Minimum time of follow up was six calendar months and maximum time of follow up fifteen month. Patients were instructed to fast for 12 hours the day before the intended visit using telephone. Anthropometric measurement of height and weight were taken simultaneously using a health O meter. Waist Circumference (WC) was taken using measuring tape with patient in full expiration in standing position at the level of the umbilicus as the smallest girth between the coastal margins and iliac crest. BP was taken using sypygomomanometer while the patient was in sitting position for 5 minutes. The same equipments were used consistently in all patients for all the follow up's and patients were followed up every three month.

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Two fasting blood samples were collected from each consenting participant. The first 2 ml blood sample was collected in a tube containing sodium fluoride preservative for FPG estimation and second 4 ml blood sample was collected in a plain tube. All samples were transported in a cooler box from Urology ward to a Clinical laboratory for testing. Samples were centrifuged at 3000 rpm for 5 minutes. Serum separated was stored at -20°C until analysis. Samples were tested using Roche reagent kits for FPG, total CHOL, TGA'S, LDL and HDL on a COBAS Integra 400 plus auto-analyzer using enzymatic methods according to standard operating procedures. Calibration was done using Roche calibrators, and quality control sera from the manufacturer were tested alongside the test samples.

A metabolic syndrome in this study was defined according to the adult treatment panel III , which say that an adult male is considered to have a metabolic syndrome if he has any three or more of the following , FPG≥6.1Mmol/l, TGA>1.7Mmol/l, HDL< 1 Mmol/l , BP>135/85 and WC≥102 cm. Data was analyzed using stat version 12; data were presented as mean ± standard deviation frequencies or percentage. A student 2 sided t test was used to compare mean of the various variables between ADT group and non ADT group.

Results

The period between January to December 2012, 115 men were histologically diagnosed with PC only 83 were recruited in the study as they met the inclusion criteria: 57 (68.7%) in the ADT and 26 (31.3%) in the non-ADT group. Table 1 shows the demographic characteristics of the patients. The mean age at diagnosis was 75±6.7 (55-95). ADT consisted of surgical castration (bilateral orchiectomy) in 48 and medical castration (goserelin – Zoladex®) 3.5mg subcutaneous every month with 50mg of casodex for only 28 day at initiation of therapy in 9 patients. The mean follow-up was 6 months (range 6 to 15 months). Seven patients in the ADT group died during the follow-up. No patients in the non-ADT group required ADT during the study period. The mean of the values of the various parameters of the ADT and Non ADT group did not reach that required for the definition of the metabolic syndrome, and no individual patient in the two groups had three or more parameters which met the definition of a metabolic syndrome during the study period (Table 2). Comparing the ADT and non-ADT groups at 3 and 6 months, the mean change in waist circumference (WC) was significantly greater in the ADT group, but the blood pressure(BP), body mass index (BMI) and hemoglobin (Hb) did not differ significantly (Table 3).

Table 1 .Demographic Characteristics of Patients.

Characteristic	**ADT group n=57(69%)**	**Non ADT group n=26(31%)**
Age (years)		
Mean (SD)	74.9(7.6)	75.6(7.8)
Residence		
Rural	26	14
Urban	30	12
Family history of PCa		
+ve	1	1
-ve	53	25

Abbreviations: ADT -androgen deprivation therapy, SD-standard deviation
PCa-prostate cancer
Note -One patient data on address was not recorded.
-Three patient data on family history was not recorded.

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Table 2. Summary of patient parameters before division into ADT and non ADT group

Parameter	Mean at diagnosis
Age(Yrs.)	75±6.7 (55-95)
Systolic BP (MmHg)	130±12.8 (100-132)
LDL (Mmol/L)	2.6±0.84 (0.79-4.50)
HDL (Mmol/l)	1.33± 0.41(0.4-2.0)
Chol (Mmol/l)	4.0±0.94 (0.25-6.50)
TGA (Mmol/l)	0.95 ±0.39(0.07-1.02)
Hb (Mmol/l)	11.25 ±2.16(9-16)
BMI (kg/m2)	22.9 ± 3.84(16-30)
WC (cm)	82.0 ±13.77(27-100)
FPG (Mmol/L)	3.9 ±0.47(2.2-5.0)
Abbreviations: FPG-fasting plasma glucose, WC-Waist circumference,LDL- low density lipoprotein,HDL-high density lipoprotein,TGA-triglycerides,Hb-hemoglobin,BMI –body mass index BP-blood pressure, CHOL-cholesterol	

Table 3. Anthropometric and biochemical profile at 3 month of follow up.

	ADT group n=57(69%)	**nonADT group N=26(31%)**	
Characteristic	***Mean(SD)***	***Mean (SD)***	***p-value***
Systolic BP(MmHg)	133.35(13)	132.92(10.7)	0.88
WC(cm)	85.98(9.7)	78.08(19.81)	0.02
BMI (KgM2).	23.4(3.5)	23.83(3.4)	0.43
Hemoglobin(g/dl)	11.41(1.9)	12.16(1.8)	0.09
LDL(Mmol/l)	3.38(1.01)	2.53(0.8)	<0.001
HDL(Mmol/	1.52(0.5)	1.15(0.4)	0.001
TGA(Mmol/l)	1.5(0.6)	0.83(0.3)	<0.001
CHOL(Mmol/l)	5.01(1)	3.92(0.7)	<0.001
FPG(Mmol/l)	4.59(0.9)	3.87(0.5)	<0.001
Abbreviations: ADT-androgen deprivation therapy, BP-blood pressure, WC-waist circumference, LDL- low density lipoprotein, HDL -high density lipoprotein, TGA-triglycerides, CHOL-cholesterol, FPG-fasting plasma glucose, BMI -body mass index.			

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There was statistically significant increase in the mean change of all the serum lipid (LDL, DDL, CHOL and TGA) parameters between the two groups at three and six month P (≤0.001).The difference in the mean of the FPG between the two groups was statistically significant at three and six month (p <0.001) (Table 4).

Table 4. Anthropometric and biochemical profile at 6month of follow up.

	ADT group	**ADT group**	
	n=57(68%)	**N=26(32%)**	
Characteristic	***Mean(SD)***	***Mean (SD)***	***p-value***
Systolic BP(MmHg)	138.6(13)	132.9(12)	0.08
WC(cm)	87.24(10)	78.44(22)	0.01
BMI(KgM2)	24.07(3.7)	24.42(3.5)	0.69
Hemoglobin(g/dl)	11.91(2.1)	12.49(1.6)	0.23
LDL(Mmol/l)	3.99(0.8)	2.83(1.1)	<0.001
HDL(Mmol/	1.81(0.5)	1.23(0.4)	<0.001
TGA(Mmol/l	1.95(0.7)	0.92(0.4)	<0.001
CHOL(Mmol/l)	5.69(0.9)	3.94(0.7)	<0.001
FPG(Mmol/l)	4.89(0.7)	3.87(0.5)	<0.001
Abbreviations: ADT-androgen deprivation therapy, BP-blood pressure, WC-waist circumference, LDL- low density lipoprotein, HDL -high density lipoprotein, TGA-triglycerides, CHOL-cholesterol, FPG-fasting plasma glucose, BMI -body mass index			

Discussion

The mean age at diagnosis was 75±6.7; this was high compared to Mohamedali [11] who found that the average age at diagnosis was 68.9.This is mainly due to lack of screening in the Africa setting**.** Serum changes in the lipid fraction were statistically significant between the two groups at three and six month, this was similar to Braga (p <0.005) in a 12 month Crossectional study n=58 (20 ADT: 18 PCa after radiation therapy (XRP)/radical prostatectomy (RP): 20 normal elderly men).Though he obtained significant results his study was Crossectional and therefore difficult to ascertain temporal relationship, in homogeneous groups on XRT and RP which would have some influence on metabolism in some way [12]**.**

The current study had two homogenous groups in terms of serum and anthropometric parameters at inclusion, though we lacked a third group to cater for the effect of disease on metabolism. We were also able to demonstrate that these changes occur earlier than twelve month. Mohamedali [11] did not demonstrate significant results in his twelve month case control prospective cohort n=75 (38 ADT: 37 non ADT) , though he had increases in serum parameters, this was mainly due to having a small group in the analysis after excluding a large number on cholesterol lowering drugs and some who were diabetic.

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The increases in the lipid fractions in the current study are most likely due to ADT since similar results were not obtained in the non ADT group. There was a statistically significant increase in the FPG at three and six month of follow up in current study. Smith [8] was not able to demonstrate a statistically significant change in FPG in a twelve week prospective study of PCa patients on medical castration**.** This may not reflect the similar trend though this was a prospective study, is was somehow different from the current study since all of his patients were on medical castration and current study most of our patient were on surgical castration. He had a very small sample, a short time of follow up and lacked a comparison a group, might have affected his results. Despite of one patient developing diabetes within the twelve weeks, the change in glucose level was not statistically significant.

From the finding of our study, patients on surgical castration may experience an early onset of hyperglycemia compared to medical castration. However Basaria et al[13] were able to demonstrate a statistically significant increase in FPG level (p=0.002) in his cross sectional study of PCa patient on ADT for 12-101 month n=58 (18ADT:17XRT/RP: 18normal elderly)**.** Moreover he had a third group of normal elderly men to cater for the effect of disease on metabolism, the controls he used had under gone RP / XRT this might in some way have confound his results, because RP and XRT may have some effects on metabolism. Since it was a cross sectional study, may present some difficult in determining temporal relationship. The result of our study could also have been confounded in some way due to lack of a third group to cater for the effect of age on metabolism. The increase in the FPG in the current study is most likely due to ADT since similar results were not demonstrated in the non ADT group.

The mean change in waist circumference between the two groups was statistically significant at three and six month of follow up, similar finding was by Bragain his cross-sectional study involving PCa patient on ADT for 12 month compared with those on XRT and RP plus normal elderly men [12]**.** The pattern may be different as he had significant results in his study which was a crossectional study and also had inhomogeneous group. The XRT and RP group could be considered in the normal elderly men since they were give a curative therapy and therefore cured, for this reason prostate cancer played a minimal role in metabolism. The current study results could also have been confounded in some way due to lack of a third group to cater for the effect of age on metabolism.

Conclusion

Six month of ADT use is associated with a statistically significant increase in the fasting plasma glucose, lipid fraction and WC, though none of the increases reached clinically significant level to require medical intervention.

Recommendation

From the results of this study it is important for urologist starting patients on ADT to obtain a baseline lipid fraction, Fasting plasma glucose, and anthropometric parameters before initiating ADT. It is also reasonable to follow up these parameters 6 monthly in those who had normal baseline serum biochemical characteristics and normal anthropometric parameters before starting ADT. We also recommend another prospective study to try and find out if these parameters actually reach a clinically significant level, when and which risk factors are responsible for early metabolic derangement.

Study strength

Only ADT naïve patients with normal biochemical and anthropometric measurements were included in this study, therefore the study gave a clear picture of the gradual changes in the

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metabolic derangement during ADT. PCa patients on ADT were compared with PCa patients not on ADT to cancel out the effect of disease on metabolism, to allow only ADT play a role on metabolic changes. We included only black Africans in this study; therefore the effect of race did not affect the study result.

Study limitations

We were not able to measure testosterone during the study period; therefore study could not demonstrate castrate levels of testosterone in the study subjects.All our patients were on minimal androgen blockade this may have confounded the true picture in some way. Short follow up period in some way might have had affected on the study results.

We did not have a third comparative group to cancel out the effect of age on metabolism. The number of patients in the treatment arm did not balance exactly those in the non treatment arm; therefore the study may have overestimated some of the parameters**.** Patients were also randomly assign to the two groups.

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