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The effect of medical castration on lipid levels in black South African men with Prostate cancer

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Full Title:	The effect of medical castration on lipid levels in black South African men with Prostate cancer
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Abstract:	ABSTRACT Background In South Africa, androgen deprivation therapy (ADT) is commonly given as primary therapy for prostate cancer (PCa) due to many patients presenting with advanced disease. The metabolic adverse effects of ADT on lipid profile and weight gain have been reported mainly in Caucasian populations but few studies have been performed in African populations. Men of African descent generally have favorable lipid profiles compared to other populations and our study looked to analyze the effect of medical castration on lipid levels in black South African men with PCa. Methods The aim of this study is to describe the changes in blood total cholesterol, triglycerides, LDL and HDL at 6 months and at 1 year in men with prostate cancer newly initiated on ADT. Changes to BMI, waist circumference and HbA1c were also measured after 1 year of ADT. Our study was conducted at Chris Hani Baragwanath Academic Hospital which is a teaching hospital affiliated with the University of the Witwatersrand. It is located in Soweto, South of Johannesburg and serves the 1.3 million local residents who are predominantly black and of the lower income bracket. This study enrolled 38 black South African men who were starting to receive ADT for PCa. Subjects were evaluated at baseline and at 6 and 12 months. Lipid profiles and HbA1C levels were measured using blood samples and body composition was measured using BMI and waist circumference. Results In this prospective single center study we found that ADT resulted in a significant rise in triglyceride levels and weight gain in black South African men reaching mean levels of obesity using ethnic specific definitions. High density lipoproteins levels decreased significantly particularly in the first 6 months of treatment and thereafter began to rise. ADT also resulted in an increased HbA1C level which is a marker for insulin resistance. Conclusions Androgen deprivation therapy unfavorably changed the body habitus and lipid profile of men with PCa. It was demonstrated that even black South Africans who generally have favorable lipid profiles compared to their counterparts are at risk of developing metabolic syndrome while being treated with ADT.
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Response to Reviewers:	Thank you both for your valuable comments. I have made the in text corrections that you have suggested, and I will be replying in a point by point format to your comments below as well as uploading a corrected document on the journals website Reviewer reports: Reviewer #3: A good and commendable effort My observations are: 1. Rather small sample size; more so in a facility with such large patient load as described in the methods. 2. Too many missing data for a supposed prospective study, with as much as 15-28% missing data for some variables. With a background small sample, this further compromises the reliability of data. REPLY There was in fact missing data from Table 2 - most importantly the dyslipidemia info (which was part of our study inclusion criteria) somehow got omitted. It has since been pulled from our original spreadsheet and corrected in the text. The other missing data (alcohol intake for example) does not form an important part of the study analysis and was unavailable from the onset. In terms of the sample size, we would have hoped for a larger sample especially given our large patient load but we had a limited time to complete the study as this was for degree purposes. For that reason once we had reached statistical significance we stopped accruing patients and began the write up. In addition we were hoping this study would serve as a pilot study for similar larger studies like this in the future. 3. The discrepancies in the number of patients (sample) still persist (see page 10 lines 6-7 and page 11 lines 43-44) 4. Few arithmetic errors on table 4 - see the uploaded edited manuscript. 5. Spelling error on page 9 line 44 REPLY All Corrected in text 6. On figure 2, the plotted graph is at gross variance with your results in table 5: (a) the percentage change in LDL at 6 month was negative (a decrease) and less than 5%, UNLIKE what your plot indicate; (b) the change in HDL at 12 months was still negative (a decrease) and NOT a positive as your plot indicate. REPLY We want to thank the reviewer for pointing out the error in this graph. We have corrected the graph 7. The discussion section could be much more lucid about the observed peculiarities of the findings in the study. REPLY Discussion section has been edited to demonstrate this 8. Comparing the result of this study with the study in Nigeria (as done on page 17) may be inappropriate as the study designs are different. REPLY This has been indicated in the text (see section from page 17 below) In terms of study design, the Nigerian study compared men on ADT to different treatment naive men and only looked at the 12 month period while we looked at the changes that occur in the very same men at baseline, and then again at 6 and 12 months of treatment with ADT. The Tanzanian study which did look at early changes (3 and 6 months) differed in the form of ADT with over 80% of their study participants

	having undergone surgical castration, something which was excluded in our study. This may limit the ability of direct comparisons between. In place of fasting glucose, a common parameter tested in other studies, we tracked Hba1c levels which although notably increased did not reach statistical significance likely due to our small sample size. 9. The conclusion section is rather lengthy with some repetitions and some unnecessary sections on treatment of dyslipideamia and diabetes/insulin resistance. REPLY Corrected as recommended. Conclusion is now shorter and more succinct Reviewer #4: Good data. Information on type of ADT used and whether a comparison on the type made any difference would be appreciated if available REPLY On page 8 this is covered. We mentioned that all patients had the same agents given as ADT (bicalutamide followed by Goserelin) and we excluded patients who had a surgical orchidectomy to remove that variable. See text from paper below Black men of African descent attending the CHBAH urology outpatient department from the nearby Soweto community. All men had a histologically confirmed diagnosis of PCa and were recently started on ADT due to their advanced disease status. Specifically, patients receiving 3 monthly depots of a GnRH agonist (Goserelin). This includes a prior 2 week course of an antiandrogen (Bicalutamide) given to prevent a flare phenomenon. Convenience sampling was applied to the above population.Patients excluded from the study were as follows: Patients who did not have a baseline lipogram prior to initiation of ADT Patients who failed to (or were unable to) consent to participate in the study. Patients already on lipid lowering agents Patients who are Human Immunodeficiency Virus (HIV) positive, both treated and newly diagnosed Patients previously or currently on androgen deprivation or testosterone therapy Patients who underwent a surgical orchidectomy "Part 5- Conclusions" is a bit long as some of these references should be put in "Discussion" REPLY Corrected as recommended. Conclusion is now shorter and more succinct Once again thank you for your interest in my paper. I hope you will find the above changes now meet your expectations
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human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.</i>	

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TITLE PAGE

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Title:

The effect of medical castration on lipid levels in black South African men with Prostate cancer

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DECLARATIONS:

Ethics approval and consent to participate

Our study falls under the MADCaP research group which is an international consortium that stands for Men of African descent and Carcinoma of the Prostate which aims to study the genetic and epidemiological risk factors of Prostate cancer among men of African ancestry. The original MADCaP study was approved in ethics clearance certificate M150934 dated 6th March 2017, which includes blood sampling and clinical data usage. The patient information sheet and informed consent document are available on request. A new substudy application for our specific study was approved by the Human Research Ethics Council in clearance certificate M2011141 dated 12 Nov 2020.

Consent for publication

The MADCaP research group has been given consent to carry out and publish their research work by all study participants. Consent forms can be made available on request

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All articles referenced in the text have been included in the reference section below.

Competing interests

The authors have no competing interests to declare.

Funding

No external funding was received for the completion of this study.

Authors' contributions

S.M. and M.J. conceived the idea for this study and were involved in planning and implementation of the research.M.H. reviewed the study design and oversaw the research drafting. S.M. and O.A. processed the experimental data and O.A. performed the statistical analysis. S.M. drafted the manuscript and designed the figures in partial fulfillment of the requirements for the degree of Master of Medicine. All authors discussed the results and commented on the manuscript.

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COVER LETTER

Prostate cancer is the leading cause of cancer death among men in Southern Africa. Aside from men of African descent having more aggressive forms of the disease, many men in Southern Africa present late due to limited access to health care. As a result many men are treated with androgen deprivation therapy (ADT), the mainstay of treatment in advanced prostate cancer.

ADT uses either bilateral orchidectomy or gonadotropin releasing hormone (GnRH) agents (agonists or antagonists) to inhibit the proliferation of hormone sensitive prostate cancer cells by blocking the downstream production of testosterone and inducing hypogonadism. The resulting low levels of testosterone controls disease and alleviates symptoms but can lead to worrisome metabolic side effects that have recently come into focus. ADT leads to altered lipid, glucose, muscle and bone metabolism that can cause, or worsen diabetes, sarcopenia, dyslipidemia and central obesity, potentially leading to cardiovascular disease.

Men of African descent generally have favorable lipid profiles compared to their caucasion counterparts and our study looked to analyze the effect of medical castration on lipid levels in black South African men with prostate cancer to determine if the dyslipidemia that results from ADT is similar to the changes found in other populations on ADT. This should help us better understand a disease and a treatment modality that is common in black South African men but is poorly studied and reported.

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ABSTRACT

Background

In South Africa, androgen deprivation therapy (ADT) is commonly given as primary therapy for prostate cancer (PCa) due to many patients presenting with advanced disease. The metabolic adverse effects of ADT on lipid profile and weight gain have been reported mainly in Caucasian populations but few studies have been performed in African populations. Men of African descent generally have favorable lipid profiles compared to other populations and our study looked to analyze the effect of medical castration on lipid levels in black South African men with PCa.

Methods

The aim of this study is to describe the changes in blood total cholesterol, triglycerides, LDL and HDL at 6 months and at 1 year in men with prostate cancer newly initiated on ADT. Changes to BMI, waist circumference and HbA1c were also measured after 1 year of ADT.

Our study was conducted at Chris Hani Baragwanath Academic Hospital which is a teaching hospital affiliated with the University of the Witwatersrand. It is located in Soweto, South of Johannesburg and serves the 1.3 million local residents who are predominantly black and of the lower income bracket. This study enrolled 38 black South African men who were starting to receive ADT for PCa. Subjects were evaluated at baseline and at 6 and 12 months. Lipid profiles and HbA1C levels were measured using blood samples and body composition was measured using BMI and waist circumference.

Results

In this prospective single center study we found that ADT resulted in a significant rise in triglyceride levels and weight gain in black South African men reaching mean levels of obesity using ethnic specific definitions. High density lipoproteins levels decreased significantly particularly in the first 6 months of treatment and thereafter began to rise. ADT also resulted in an increased HbA1C level which is a marker for insulin resistance.

Conclusions

Androgen deprivation therapy unfavorably changed the body habitus and lipid profile of men with PCa. It was demonstrated that even black South Africans who generally have favorable lipid profiles compared to their counterparts are at risk of developing metabolic syndrome while being treated with ADT.

KEYWORDS

Androgen deprivation therapy, Black African men, Metabolic syndrome, Dyslipidemia

CHAPTER 1: BACKGROUND

1.1 Prostate cancer in South Africa

Prostate cancer (PCa) is a leading cancer among aging men worldwide but its impact varies across different races, ethnicities and geographic locations. Global statistics show Pca to be the second commonest cancer among men but only the sixth in cancer related deaths. However in countries with predominant black populations it is not only the most common male cancer but also number one in cancer related deaths (Sung *et al.*, 2021).

Within the black population itself there is a five times increased mortality rate in men from the Caribbean and Sub Saharan Africa versus African Americans in the United States. (Rebbeck *et al.*, 2013). These differences are believed to be a combination of genetic and environmental factors leading to more aggressive tumor biology as well as health care system constraints such as poor screening and limited access across many regions of sub Saharan Africa. This results in many men already having advanced disease on presentation. (Chornokur *et al.*, 2011)

1.2 Androgen deprivation therapy

Androgen deprivation therapy (ADT) forms the cornerstone of treatment in advanced PCa and is based on the hormonal dependence of PCa, first described by Huggins & Hodges in their landmark paper in 1941 (Huggins and Hodges, 1941).

This discovery, which was the first known drug treatment of any cancer, won them the Nobel Prize in 1966 and nowadays is used to alleviate symptoms in metastatic disease as an adjunct to surgery or radiotherapy in high risk or locally advanced disease (Gunner, Gulamhusein and Rosario, 2016).

The aim of ADT is to generate castrate levels of testosterone, conventionally defined as <1.7mmol/L but ideally to below 0.7mmol/L (Gomella, 2009). This can be achieved through surgical castration (bilateral orchiectomy) or medical castration using centrally acting gonadotropin releasing hormone (GnRH) agents and or anti androgens, both of which block downstream production / utilization of testosterone. Long term ADT and the resultant testosterone deficiency, can have many physical and psychological adverse side effects.

1.3 Metabolic effects of ADT

The general side effects of ADT are most bothersome to patients and they include loss of libido and erectile dysfunction along with hot flushes, gynaecomastia, mood swings, depression and fatigue. The metabolic effects of ADT however, are more subtle, sometimes overlooked and possibly more dangerous in the long run. ADT leads to altered lipid, glucose, muscle and bone metabolism that can precipitate or exacerbate dyslipidemia and central obesity, insulin

resistance and diabetes, sarcopenia and osteoporosis potentially leading to cardiovascular disease, fractures and falls. (Mitsuzuka and Arai, 2018)

1.4 Weight gain & body composition

Prostate cancer generally affects men over the age of 50 who are prone to age-related changes in body fat accumulation, particularly central fat stores. These changes might be offset by tumor related cachexia, specifically in men selected for primary ADT who often have advanced disease at presentation. A consistent finding in men started on ADT is significant weight gain with some studies showing increases as high as 4% total body weight. (Nowicki, Bryc and Kokot, 2001) The level of weight gain depends mainly on the duration of treatment rather than the ADT agent used and seems to more severely affect men below the age of 65. (Seible *et al.*, 2014) The fat deposition is predominantly seen in subcutaneous stores rather than in visceral fat stores with the latter being the usual finding in classic metabolic syndrome (Smith *et al.*, 2002) (Cheung *et al.*, 2016). Prolonged ADT results in a sarcopenic type of obesity which affects the ratio and distribution of fat to muscle stores throughout the body. Reduction in lean muscle mass (often measured with cross sectional imaging of thigh muscles) has shown rates of loss as high as 15-20% (Chang *et al.*, 2014). ADT also results in a decrease of bone mineral density in the first year of treatment with loss rates higher than postmenopausal women (roughly 5% versus 2.5%). Unlike weight gain, these changes do not stabilize with time and after 10 years of ADT the rate of osteoporosis has been found to be as high as 80% versus 35% in hormone naive men. (Morote *et al.*, 2007). These muscle and bone changes increase the risk for frailty falls and fractures as evidenced by the nearly double rate of falls and fractures in men on ADT versus non ADT users (Winters-Stone *et al.*, 2017)**.**

1.5 Lipid metabolism

Lipid levels are affected by age, gender, diet and obesity. The landmark Framingham heart study highlighted the differences in lipid profiles between men and women. (Abbott *et al.*, 1983). Overall the female lipid profile is less atherogenic with greater high density lipoprotein (HDL) concentrations and lower low density lipoprotein (LDL) and triglyceride (TG) concentrations than age matched men. This benefit is mainly seen in premenopausal women partly due to the ability of estrogens to regulate lipid metabolism through estrogen receptors (α & □) located on on adipose and liver cells.

Population studies in men show that LDL levels gradually increase with age until the age of 60 to 65 and thereafter start to decline (Downer *et al.*, 2014). HDL levels are also noted to increase in elderly men likely as a result of age related hypogonadism. TG levels rise with age due to reduced activity by lipoprotein lipase, the enzyme responsible for plasma triglyceride clearance.

Obese patients classically have elevated TG levels and low HDL levels. Excess adipose tissue, particularly visceral stores, cause an increase in the level of circulating free fatty acids, many of which get converted into triglyceride rich lipoproteins by the liver. This affects the balance of other cholesterol rich lipoproteins, specifically HDL, in a reciprocal fashion so that elevated TG levels cause a drop in HDL levels. The inverse relationship and ratio of TG:HDL is clinically relevant and is often used as a surrogate marker for insulin resistance, which is also related to central adiposity. (Murguía-Romero *et al.*, 2013).

Testosterone plays an important role in regulation of lipid metabolism. Testosterone allows for upregulation of hepatic LDL receptors which are necessary in lowering serum LDL levels. Hypogonadism results in excess circulating LDL which can then be oxidized in sub endothelial tissues leading to atheroma plaque formation. (Cai *et al.*, 2015) Testosterone (both endogenous and exogenous) suppresses atheroprotective HDL levels (Bagatell and Bremner, 1995) while suppression of testosterone with androgen deprivation therapy results in elevated HDL levels, at least in the early phases of treatment. (Smith *et al.*, 2002)

1.6 Lipids and cancer

Lipids may play a role in carcinogenesis (Long *et al.*, 2018) and there have been multiple studies trying to establish elevated cholesterol as a risk factor for development of PCa. (Shafique *et al.*, 2012) (Kok *et al.*, 2011) (Allott *et al.*, 2014) (Mondul *et al.*, 2010). Their findings are somewhat contradictory and in a recent meta-analysis of 14 prospective studies, dyslipidemia was not found to be associated with the risk of either overall prostate cancer. (YuPeng *et al.*, 2015).

Testosterone, which itself arises from a lipid precursor - cholesterol, is mainly linked with progression of established prostate cancer but is not a risk factor for development of prostate cancer. This is not surprising as prostate cancer is generally a disease of older men rather than in young men who are at their peak with regards to testosterone levels. (Endogenous Hormones and Prostate Cancer Collaborative Group *et al.*, 2008)

Obesity however, usually defined as a body mass index (BMI) ≥ 30 kg/m2, has been linked to PCa mortality and aggressiveness in many populations (Zhang *et al.*, 2015) (Freedland *et al.*, 2009) (Bassett *et al.*, 2012) (Kachhawa *et al.*, 2018) and recently linked to intermediate risk disease in African men. (Agalliu *et al.*, 2021). Possible mechanisms leading to this association relate to hormonal and metabolic pathways. Hormonally, obese men tend to have lower levels of adiponectin as well as higher levels of insulin and insulin-like growth factor which have been associated with an increased risk of PCa. (Lavalette *et al.*, 2018) Likewise excess adipose tissue leads to elevated free fatty acids which are necessary for cell growth and turnover, cell membrane formation and oncogenic cell signaling pathways. These pathways have been found to be highly upregulated in PCa cells.(Rossi *et al.*, 2003)

In addition, activation of the androgen receptor increases expression of lipogenic enzymes such as Phosphatase and tensin homolog (PTEN), an enzyme that once deleted is linked to 40% of primary Pca and over 70% of metastatic Pca cases. Even after castrate resistance has developed, prostate cancer cells continue to produce de novo androgens which in turn signal increased fatty acid synthesis and tumor progression (Suburu and Chen, 2012). This has led to increased interest in the role of cholesterol-lowering agents such as statins in management of prostate cancer both in preventing progression of disease and by reducing the dyslipidaemic changes caused by ADT (Tan *et al.*, 2020).

1.7 Lipids in African men

Dyslipidemia has a high prevalence worldwide and is an independent risk factor for atherosclerotic cardiovascular disease. (Nelson, 2013). The reference values for lipid levels are tabulated below.

Table 1. Reference values for definition of dyslipidemia in men

Total cholesterol (TC)	>5.0 mmol/L
LDL	>3.0 mmol/L
HDL	<0.9mmol/L
TG	>1.7 mmol/L.

Data from National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) 3 (2001)

Importantly, nearly half of all ischaemic heart attacks and more than one quarter of all ischemic strokes are due to abnormal cholesterol levels (Klug *et al.*, 2018).

A recent South African population study of over 4000 participants aged 40 years and older showed that over two thirds (67%) met criteria for dyslipidemia yet only 1% were aware of their condition and even less on treatment (Reiger *et al.*, 2017)**.**

When studying the inter ethnic differences in lipid profiles it has been found that men of African descent had significantly lower TC, LDL and TG levels than other ethnic populations within Africa. These differences were seen even after adjusting for age, gender and BMI. Compared to Europeans and Indians, men of African descent have the lowest mortality attributable to 'sub-optimal' lipid levels (defined as TC ≥ 3.8 mmol/l). This was seen in the Soweto population as well as in other studies across Africa.

However, in terms of underlying cardiovascular risk, South African men as a whole are at a higher risk than other black Africans with among the highest prevalence of obesity, undiagnosed diabetes mellitus, smoking and high cholesterol in all of Africa (Klug *et al.*, 2018). This is most notable in black South Africans living in rapidly urbanizing areas, such as Soweto

where our study was conducted, which have increasing rates of cardiovascular (CVS) disease and morbidity. (Vorster, 2002)

1.8 Cardiovascular risk of ADT

Testosterone has a host of cardio-protective metabolic effects and hypogonadism is known to be an independent risk factor for cardiovascular disease. (Simon *et al.*, 1997) These effects are related to the direct vasodilatory effect of testosterone and by its ability to indirectly modify CVS risk factors such as insulin resistance, central adiposity, and exercise tolerance. (Bagatell *et al.*, 1994)

The exact level of CVS risk depends on the type of androgen deprivation used. Historically, hormone manipulation in prostate cancer was achieved by surgical castration (bilateral orchiectomy) or by medical castration using diethylstilbestrol (DES), an oral tablet containing synthetic estrogen.

Estrogen therapy, although cost effective and bone protective, was eventually discontinued in the 1980s when adverse cardiovascular events (CVE) were reported, particularly in the first year of DES therapy (Byar, 1973). Estrogen was replaced with oral anti androgens which, despite a favorable safety profile (and even preserved erectile function in the non steroidal group), failed to achieve survival outcomes similar to surgical castration when used as monotherapy (Iversen, Tveter and Varenhorst, 1996).

Surgical castration has a more favorable CVS risk profile than estrogen but is often underutilized due to its irreversible nature and psychological impact on masculinity. It does remain an important option in resource constrained environments such as Africa as it is a once off, simple and cost effective procedure that can even be done under local anesthetic.

The landscape of ADT changed with the development of long acting GnRH agents (initially only agonists) such as leuprolide or goserelin, which appeared safe and had similar survival outcomes when compared to surgical castration.These agents work as analogues to the naturally occurring gonadotropin hormone produced in the hypothalamus which is normally only cyclically released in response to low circulating testosterone levels. GnRH agonists cause continuous stimulation and eventual downregulation of luteinizing hormone (LH) and testosterone production. When starting these agents one must co-administer a short course of antiandrogens to prevent the testosterone flare from the agonistic effect which can initially worsen symptoms. These effects can be avoided if using a GnRH antagonist such as degarelix, which came on to the market in 2008 (Klotz *et al.*, 2008).

However, the CVS safety profile of these agents was brought into question in 2006 when Keating and colleagues identified an increased risk of CVS disease and incident diabetes mellitus in patients treated with GnRH analogues. This raised concern that more men might die from treatment of the disease rather than from the disease itself, something which had been

demonstrated in previous studies (Riihimäki *et al.*, 2011). These concerns were validated by other large observational studies which demonstrated an association between ADT and CVS disease (Zhang *et al.*, 2015). Despite causation being difficult to prove based on heterogeneity of population study designs, there was enough concern for the US Food and Drug Administration (FDA) in 2010 to issue safety warnings on GnRH agonists labels pertaining to the increased risk of diabetes, heart attack, sudden cardiac death, and stroke. Similar advisory statements were published by the American Heart Association, American Cancer Society, and American Urological Association (Levine *et al.*, 2010). The highest level of adverse CVE was seen in men with pre-existing CVS disease particularly in the early phases of treatment when treated with agonists vs antagonists (Bosco *et al.*, 2015).

Different theories have been proposed to explain how ADT can lead to acute CVE (when one would expect slow metabolic changes leading to increased risk) and they center around atheromatous plaque destabilization. The one theory relates to T cells which when stimulated by GnRH agonists (T cells have GnRH receptors) can cause intra-plaque T cell expansion, leading to fibrotic cap disruption and plaque destabilization (Albertsen *et al.*, 2014). This fits well with the current understanding that atherosclerosis is largely an inflammatory driven process with adaptive T cell immunity playing an important role (Robertson and Hansson, 2006).

Another theory relates to follicle stimulating hormone (FSH) which mediates lipid storage and also plays a role in endothelial function and is higher in men treated with GnRH agonists. Unlike GnRH antagonists which suppress both LH and FSH, GnRH agonists primarily suppress LH but not FSH. Likewise treatment with GnRH agonists may cause microsurges of FSH and testosterone between dosing intervals (Crawford *et al.*, 2017). FSH surges of up to 300% have also been documented after surgical castration (Koutsilieris and Tolis, 1985). The FSH theory helps explain why surgical castration and GnRH agonists had a higher rate of cardiovascular thrombotic events when compared to GnRH antagonists (Teoh *et al.*, 2015).

There has yet to be a head to head study between GnRH agonists and antagonists with a primary outcome of CVEs but many authors and clinicians already recommend GnRH antagonists rather than GnRH agonists for ADT in patients with pre-existing CVS disease. (Greiman and Keane, 2017).

1.9 Rationale for the study

Given the prevalence of advanced prostate cancer and the unique lipid profile in men of African descent in this study we undertake to investigate the dyslipidemia induced by ADT, something which has been studied elsewhere but never in South Africa.

CHAPTER 2: METHODS

2.1 Study aims and objectives

The primary objectives of this study are to:
Determine the incidence of dyslipidemia in the study population during the first year of androgen deprivation therapy. Specifically we aim to describe the changes in blood TC, TG, LDL and HDL in the study population at 6 months and at 1 year following initiation of ADT.
The secondary objectives of this study are to:
Determine the change in Body Mass Index (BMI), waist circumference (WC) and HbA1C in the study population after 1 year of ADT.

2.2.1 Study design

Prospective descriptive observational study

2.2.2 Setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is a teaching hospital affiliated with the University of the Witwatersrand medical school. It is located in Soweto, South of Johannesburg and serves the 1.3 million local residents who are predominantly black and of the lower income bracket. It is the third largest hospital in the world and its Urology outpatient department treats roughly 2200 patients a month.

Recently CHBAH was selected as a research site by an international consortium known as MADCaP (Men of African descent and Carcinoma of the Prostate) which aims to study the genetic and epidemiological risk factors of PCa among men of African ancestry. There are six other hospital sites across West and Southern Africa (Ghana, Senegal, Nigeria, Capetown & Stellenbosch) paired with four twinning universities in the United States (Albert Einstein & Columbia in New York, Dana Farber in Boston and Stanford in California). Of the 4185 patients recruited for the overall study, 1732 came from CHBAH (41%).

2.2.3 Study population

Black men of African descent attending the CHBAH urology outpatient department from the nearby Soweto community. All men had a histologically confirmed diagnosis of PCa and were recently started on ADT due to their advanced disease status. Specifically, patients receiving 3 monthly depots of a GnRH agonist (Goserelin). This includes a prior 2 week course of an antiandrogen (Bicalutamide) given to prevent a flare phenomenon.

Convenience sampling was applied to the above population.Patients excluded from the study were as follows:

1. Patients who did not have a baseline lipogram prior to initiation of ADT
2. Patients who failed to (or were unable to) consent to participate in the study.
3. Patients already on lipid lowering agents
4. Patients who are Human Immunodeficiency Virus (HIV) positive, both treated and newly diagnosed
5. Patients previously or currently on androgen deprivation or testosterone therapy
6. Patients who underwent a surgical orchidectomy

2.2.4 Patient selection

All men diagnosed with PCa between the period of Nov 2019 and March 2020 that met inclusion criteria and were planned for ADT were pulled from our clinic database. In total 38 patients were followed up prospectively between the period of April 2020 until March 2021.

2.2.5 Data collection

Blood samples drawn and sent to National Health Laboratory services (NHLS)
A baseline lipogram will be performed before initiation of ADT. As per recent South Africa Lipid guidelines a non fasting lipogram is sufficient for screening, diagnosis and monitoring of treatment effects (Klug *et al.*, 2018). A repeat non fasting lipogram was done at 6 months and then repeated at 12 months. Variables such as body mass index (BMI) and waist circumference were documented at baseline and at 12 months of ADT treatment. Other variables that have been recorded are age, medical comorbidities, highest education level, socioeconomic status and physical activity which all affect the development of dyslipidemia in the study population. Patients were also divided into metastatic vs non metastatic disease to help explain BMI changes in light of expected tumor related cachexia.

2.2.6 Data analysis

A Microsoft Excel® spreadsheet was used to capture all survey data and imported into Stata software for formal analysis. Descriptive statistics was performed reporting proportion and percentages for categorical variables, mean and standard deviation for continuous variables with normal distribution and median and interquartile range for skewed distributions. Lipid level and other parameters were compared with baseline at 6 months and 12 month using paired t-test for continuous variables and McNemar's test for categorical variables. A two sided p-value of 0.05 was considered significant throughout.

CHAPTER 3: RESULTS

In the period between Nov 2019 and March 2020, 50 men with histologically confirmed prostate cancer were started on ADT. Of those 50 men, 6 were excluded from the study and a further 6 patients were lost to follow up or died leaving a total of 38 men in the study.

Figure 1: Study flow diagram for patients selected

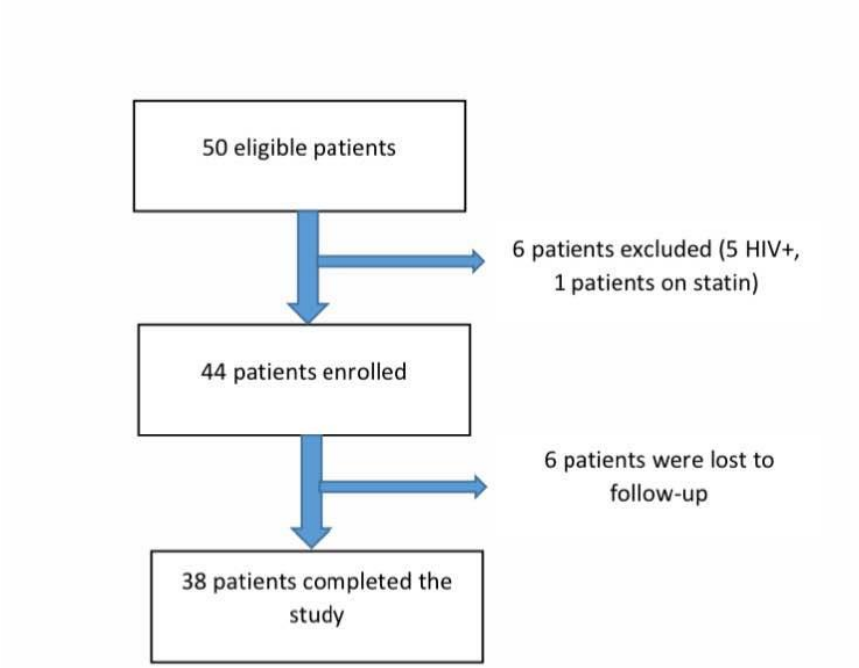


Table 2 shows the demographic characteristics of the 38 men included in the study and Table 3 shows the tumor factors in the same group. The mean age of study group was 68.5 years (61-71) with nearly two thirds (62%) of the men already overweight or obese at diagnosis with self reported rates of physical inactivity as high as 95%. Of note also is the fact that nearly half 45% of the men had dyslipidemia at baseline but were not on any lipid lowering agents. Alcohol use was high (71%) and income levels were low with a monthly household income of R1850 or less in 73% of the patients (roughly 120 USD).

The selected patients were all classified as D'amico high risk disease based on PSA levels (D'Amico *et al.,* 1997) with a mean prostate specific antigen (PSA) in the group of 67 ug/L (26-207) and an ISUP score of 4 or higher (corresponding to a Gleason grade group score of 8) in 50% of men selected. Of the 38 men nearly a third (31%) were already metastatic at time of diagnosis. ADT was initiated for all men while awaiting local treatment in the form of external beam radiation for the non metastatic group. None of the patients selected had received any curative therapy prior to ADT.

Table 2. Demographic characteristics of patients

Characteristics	**N=38**	**%**
Age in years		
<60	7	18.4

60-69	15	39.5
70-79	14	36.8
80+	2	5.3
Age in years, median (IQR*)	68.5 (61-71)	
Education		
Primary school and below	2	5.2
Secondary school	9	23.7
Post secondary school	24	63.2
Unknown	3	7.9
Income (per month)		
< R1850	29	76.3
R1851-R5000	1	2.6
Chose not to answer	8	21
Physical activity**		
No	36	94.8
Yes	1	2.6
Missing	1	2.6
BMI (Kg/m^2)		
<18.5 (underweight)	0	0
18.5-24.9 (normal)	14	37.8
25-29.9 (overweight)	13	35.1
≥ 30 (obese)	10	27
Missing	1	2.6

Dyslipidemia at baseline* **		
No	21	55
Yes	17	45
Hypertension		
No	11	29
Yes	26	68.4
Missing	1	2.6
Diabetes		
No	30	79
Yes	7	18.4
Missing	1	2.6
Smoker		
Non smoker	11	29.0
Ex smoker	16	42.1
Current smoker	10	26.3
Missing	1	2.6
Alcohol use		
Non drinker	1	2.6
Ex drinker	1	2.6
Current drinker	27	71
Missing	9	23.7

*IQR = Interquartile range

**Defined as any moderate-intensity sports, fitness or recreational activities that cause a small increase in breathing or heart rate (like brisk walking, cycling, swimming, volleyball) for at least 10 minutes continuously

*** Defined as one or more of the following:
TC >5.0 mmol/L, LDL >3.0 mmol/L, HDL <0.9 mmol/L, Triglycerides >1.7 mmol/L

Table 3. Tumor factors of prostate cancer cases

Characteristics	**N=38**	**%**
Metastases		
No	17	44.7
Yes	12	31.6
Missing	9	23.7
ISUP		
1-2	6	15.7
3	13	34.2
4-5	19	50
PSA, median (IQR) ug/L		67 (26-207)

ISUP (International Society of Urological Pathology), PSA (Prostate specific antigen)

In the 12 month period since initiation of ADT, there was a statistically significant rise in mean weight (4.6 kg) and in mean waist circumference (5.6cm) to levels classified as obese (>94cm) using ethnic specific definitions (Zimmet *et al.*, 2005). There was also an appreciable rise in the Hba1c levels of 0.36 %. This is a surrogate marker for insulin resistance which is yet another criteria for metabolic syndrome. Table 4 summarizes these changes below.

Table 4. Anthropometric variables for prostate cancer cases

Measurements	**Baseline (N=30) Mean ± SD**	**12 months (N=30) Mean ± SD**	**Mean percentage increase (%)**	**P value**
Weight (kg)	75.5 ± 15.4	80.1 ± 15.3	6.1	0.01
Waist Circumference (cm)	92.3 ± 12.6	97.9 ± 12.2	5.8	0.01

BMI	27.1 ± 5.0	28.2 ± 4.5	4.0	0.05
Hba1c (%)	6.36 ± 1.5	6.72 ± 1.7	5.6	0.03

SD (Standard deviation), Hba1c - Glycated hemoglobin

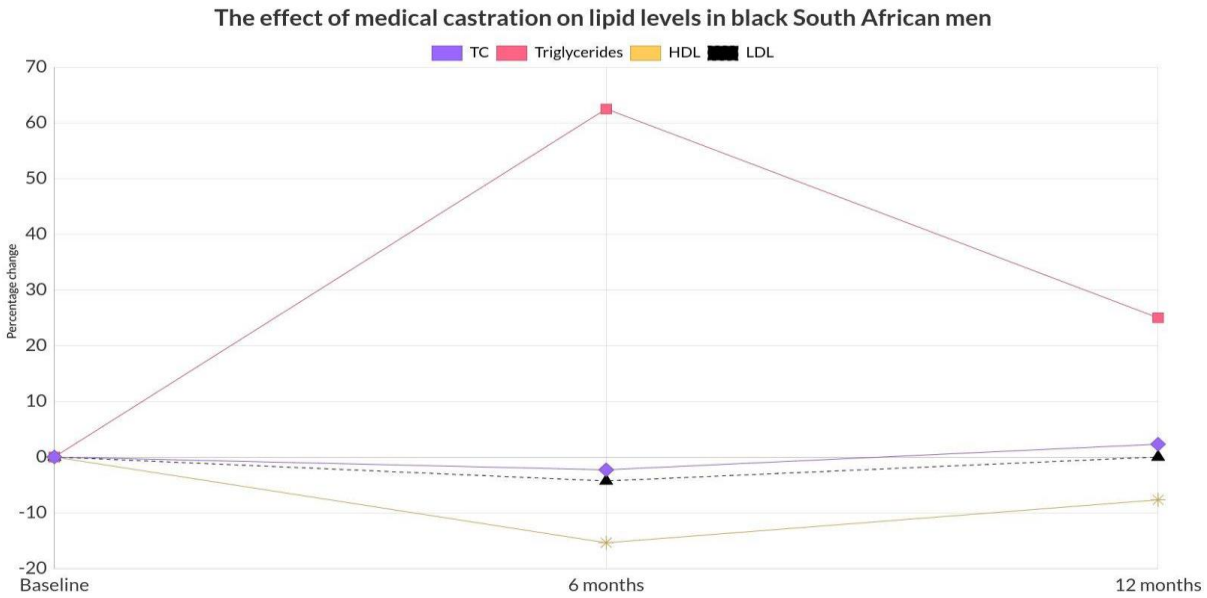
Table 5 shows the changes to the serum lipid levels during the study period. The first 6 months were marked by a significant rise in TG and a drop in HDL levels. After 12 months those effects were less pronounced but still deranged. Both TC and LDL were largely unchanged. These changes have been plotted on Figure 2 below.

Table 5. Changes to serum lipids during study period

	Baseline (N=38), (mean + SD)	**6 months (N=27), Mean ± SD**	**P value**	**12 months (N=31), Mean ± SD**	**[a] P value**
Total cholesterol (mmol/L)	4.3 ± 0.8	4.2 ± 1.6	0.80	4.4 ± 0.9	0.9
Triglycerides (mmol/L)	1.6 ± 0.9	2.6 ± 1.4	<0.01	2.0 ± 1.5	0.08
HDL (mmol/L)	1.3 ± 0.3	1.1 ± 0.3	<0.01	1.2 ± 0.4	0.08
LDL (mmol/L) *	2.3 ± 0.8	2.2 ± 0.9	0.90	2.3 ± 0.8	0.82

* N=29 at 12 months (LDL results of 2 patients not given due to excessive triglyceride level)
[a] P value for differences between baseline and 12 months.

Figure 2



CHAPTER 4: DISCUSSION

In this prospective single center study we found that ADT resulted in a significant rise in triglyceride levels and weight gain in black South African men reaching mean levels of dyslipidemia and obesity that meet criteria for metabolic syndrome. ADT also resulted in an increased HbA1C which is a marker for insulin resistance. HDL levels decreased significantly particularly in the first 6 months of treatment but by 12 months had started rising again. An important negative from this study was LDL which did not significantly change throughout the 12 month study period. The sum total of these changes reflect a picture similar to that of the classic metabolic syndrome.

What is unique is the changes to HDL levels and the location of central fat deposition. On ADT HDL levels are usually elevated, something which is not seen in the classic metabolic syndrome. (Braga-Basaria *et al.*, 2006) HDL is generally considered to be atheroprotective and elevated levels generally reduce overall cardiac risk, whether this holds true for ADT induced elevated HDL is a subject that remains to be seen and will require more research. Another notable difference is the body fat redistribution which on ADT occurs mainly in subcutaneous stores vs classic metabolic syndrome which is viscerally located. The overall differences are tabulated below:

Table 6. Differences between the classic metabolic syndrome and ADT induced metabolic syndrome

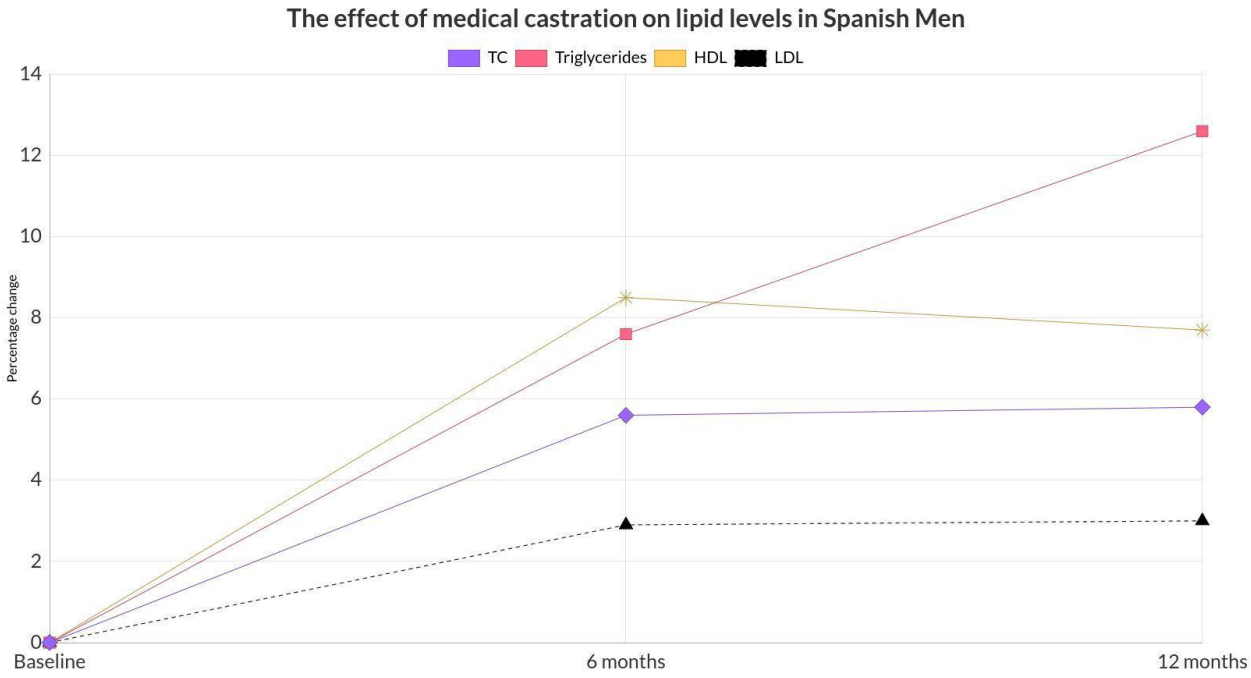
	Classic metabolic syndrome	ADT induced metabolic syndrome

Abdominal obesity	Increased	Increased
Fat deposition	**Visceral**	**Subcutaneous**
Insulin resistance	Increased	Increased
Triglycerides	Increased	Increased
LDL	Increased	Unchanged/increased
HDL	**Decreased**	**Unchanged/increased**

4.1 ADTs effect on lipids in other populations

The changes to lipid levels while on ADT have been studied in other populations yielding different results. In a similar study to ours out of Spain, all lipid parameters were significantly increased at both 6 months and 12 months with TG levels showing the greatest percentage change (Morote *et al.*, 2015). Their results have been shown in figure 3 below.

Figure 3



When looking at African populations we found two studies that investigated the metabolic changes induced by ADT one done in Nigeria, West Africa and one done in Tanzania, East Africa.

The Nigerian study showed that men on ADT for 1 year or more had significantly higher TC and LDL levels when compared with treatment naive patients (Essien et al. 2017). Unlike our study their men did not have significant changes to their TG and HDL levels. One possible reason for this may be that HDL, (a cholesterol rich lipoprotein) and triglycerides (which is a marker for TG rich lipoproteins such as VLDL) are inversely related and are most subject to change within the first few months of ADT when castration levels are being reached. Over time and especially after one year HDL levels start to drop as obesity and body habitus changes become more apparent. Therefore a study that doesn't include a 6 month HDL is likely not to demonstrate these acute changes. This theory holds true when looking at the Tanzanian study which tracked changes after 3 and 6 months and found significant elevations in all parameters, TC, LDL, HDL and TG (Nabunwa *et al.*, 2014).

Although our current study is not the first of its kind in Africa it does hold significance in terms of its findings. Our study looked at sub-Saharan African men which ancestrally differ from West and East African men. Obesity rates also differ between regions. In 2016, the World Health Organization (WHO) reported that the prevalence of general obesity ranged from 2.5% to 6.6% in East & West African men, but was almost 31% in black South Africans. (Cois and Day, 2015). This may be due to westernized diets and lifestyle which are becoming increasingly prevalent in communities like Soweto.

In terms of study design, the Nigerian study compared men on ADT to *different* treatment naive men and only looked at the 12 month period while we looked at the changes that occur in the very same men at baseline, and then again at 6 and 12 months of treatment with ADT. The Tanzanian study which did look at early changes (3 and 6 months) differed in the form of ADT with over 80% of their study participants having undergone surgical castration, something which was excluded in our study. This may limit the ability of direct comparisons between. In place of fasting glucose, a common parameter tested in other studies, we tracked Hba1c levels which although notably increased did not reach statistical significance likely due to our small sample size.

Our study had certain strengths. We assessed lipid levels at 6 months and 12 months to account for both short term and longer term changes. We also limited confounding factors by only following men given GNRH agonist monotherapy while excluding confounding factors like HIV and statin use. We did however have some weaknesses. Due to the small sample size (n=38) we were only able to do descriptive rather than full regression analysis. In addition, a pre ADT testosterone level was not captured which might have revealed a baseline hypogonadism which can be as 30% common in men between the ages of 40 and 70. (Mulligan *et al.*, 2006) Our mean participant age was 68.5 years.

A consistent finding between all studies, African and elsewhere, were changes to body habitus. Both waist circumference and BMI showed progressive increases throughout all study periods.

These changes, along with the relative insulin resistance of central adipose tissue is responsible for the metabolic-like syndrome seen to develop in men on ADT.

Borrowing from other authors (Grossmann and Zajac, 2011) a management plan of men starting ADT should include careful counseling on the risk benefits of ADT treatment followed by a metabolic risk assessment looking at BMI, WC, blood pressure, blood glucose levels and a baseline lipogram. A useful memory aid for cardiac prevention in Pca is the ABCDE mnemonic: A for awareness and aspirin; B for blood pressure control; C for cholesterol and cigarettes; D for diabetes mellitus and diet; and E for exercise (Hu *et al.*, 2020). These assessments should be repeated at 6 and 12 month intervals with appropriate referrals to dieticians and physicians as indicated.

When initiating ADT in patients with multiple CVS factors or a history of CVE one should consider referral to cardiology before treatment and if available, a GnRH antagonist should be used as the ideal ADT agent.

Specific treatment of dyslipidemia induced by ADT may include a statin which aside from lowering LDL levels may also slow prostate cancer cell growth by competitively inhibiting uptake of dehydroepiandrosterone sulfate (DHEAS) a testosterone precursor, into tumor cells. (Harshman *et al.*, 2015) This is in addition to the anti-inflammatory and antioxidant properties of statin therapy which may inhibit carcinogenesis. (Kim *et al.*, 2019) The decision if and when to start a statin should be according to baseline LDL levels, overall CVS risk profile and target LDL levels. We refer the reader to the 2018 SA dyslipidemia guidelines to help guide these treatment goals (Klug *et al.*, 2018). All patients that develop obesity would benefit from a weight loss programme which will decrease serum triglyceride and LDL levels and increase HDL levels proportional to the degree of weight loss and in relation to the dietary constituents of different weight loss programmes. (Feingold, 2020)

Insulin resistance and diabetes is often treated with metformin which may improve survival not only by improving insulin resistance, but also by directly inhibiting PCa cell growth. Insulin has been shown to promote de-novo androgen synthesis in PCa cells and therefore metformin, an oral biguanide which reduces circulating insulin levels has been shown to increase overall survival and prostate cancer specific survival in men with metabolic syndrome on long term ADT and may delay time to castrate resistance (Xiao *et al.*, 2017).

CHAPTER 5: CONCLUSIONS

In conclusion, despite the relative atheroprotective lipid profile of black African men, ADT significantly raised triglyceride levels and lowered HDL levels particularly in the first 6 months of treatment. After one full year on ADT, mean waist circumference increased to levels consistent with metabolic syndrome. These changes increase the risk of future cardiovascular events to a population that is already at risk due to westernization of diet and lifestyle. This is particularly

important against the background knowledge that ischemic heart disease is the most common cause of noncancer death in patients with prostate cancer on ADT. (Epstein *et al.*, 2012)

As such lifestyle, diet and possibly lipid lowering agents should be offered to such men to balance the risks of the ADT induced dyslipidemia and metabolic syndrome. Further studies should be done looking at men of African descent and the cardiovascular outcomes of ADT as a follow on from studies like ours.

LIST OF ABBREVIATIONS

PCa	Prostate Cancer
ADT	Androgen deprivation therapy
TC	Total cholesterol
LDL	Low density lipoprotein
HDL	High density lipoprotein
TG	Triglycerides
TRT	Testosterone replacement therapy
GnRH	Gonadotropin releasing hormone
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
BMI	Body mass index
WC	Waist circumference
CHBAH	Chris Hani Baragwanath Academic Hospital
MADCaP	Men of African descent and Carcinoma of the Prostate
HIV	Human Immunodeficiency Virus
NHLS	National health laboratory services
VLDL	Very low density lipoproteins
PTEN	Phosphatase and tensin homolog
MAD	Men of African descent

DHT	Dihydrotestosterone
HPA	Hypothalamic pituitary axis
RCT	Randomized control trials
CVS	Cardiovascular
CVE	Cardiovascular events
FDA	Food and drug administration
DHEAS	Dehydroepiandrosterone sulfate

CHAPTER 6: REFERENCES

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