



## Low testosterone levels in male patients with hypertension

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**General Note**

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### ABSTRACT

Testosterone is the predominant sex hormone in men. Hypogonadism usually results in decreased libido, erectile dysfunction, decreased muscle mass and strength, obesity, depressed mood and diminished energy, osteoporosis and decreased sexual hair. However, low testosterone levels are also associated with a spectrum of serious complications. These include hypertension, diabetes mellitus, obesity, metabolic syndrome, dyslipidemia and chronic inflammation. Low testosterone levels have been shown to be an independent risk factor for cardiovascular and all-cause mortality. This study looks at the prevalence of low serum testosterone levels in hypertensive men and briefly reviews its impact on associated cardiovascular risk factors.

**Keywords:** hypertension, testosterone, cardiovascular disease, diabetes mellitus, dyslipidemia, inflammation, hypogonadism, obesity, metabolic syndrome.

**Abbreviations:** ASH: American Society of Hypertension; BMI: Body mass index; HIV: Human Immunodeficiency Virus Infection; HTN: Hypertension; JNC-7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

## 1. INTRODUCTION

It is estimated that up to 50 million people in the United States suffer from hypertension (Chobanian et al, 2003; Hajjar et al, 2003). It has also reached epidemic proportions worldwide. Approximately 20% of the world's adults are estimated to have hypertension (Hajjar et al, 2006). In 2001, almost 54% of all strokes and 47% of all ischemic heart disease related deaths worldwide were attributable to systolic hypertension (Lawes et al, 2004; Williams, 2009). Further, these deaths are expected to increase by over 60% by 2025, rising from 972 million to 1.56 billion (Kearbey et al, 2005). Hypertension is responsible for approximately one half of the health burden and costs worldwide (Abegunde et al, 2007). Hypertension and low testosterone levels often co-exist in men, and may be causally interlinked (Fogari et al, 2005; Fogari et al, 2002; Torkler et al, 2011). Both increase in prevalence with increasing age, regardless of race or ethnicity (Anderson et al, 1999). Testosterone deficiency has been associated with an increase in cardiovascular risk factors and major cardiovascular events, (Ohlsson et al, 2011) including a higher cardiovascular mortality in men (Khaw et al, 2007; Haring et al, 2012). Exogenous testosterone therapy is associated with an improvement in cardiac risk factors (Malkin et al, 2003). These data suggest that testosterone replacement therapy may be potentially cardio-protective in patients, (Saad, 2012) especially in those with hypertension (Charalambos et al, 2013). This study was done to evaluate the prevalence of hypo-testosteronaemia in a cohort of patients with hypertension.

## 2. METHODS

The charts of all patients seen over a period of one year were reviewed. We identified 214 male hypertensive patients who had their testosterone levels measured. Standard blood pressure measurement techniques were used with an appropriate-sized cuff at the level of the right atrium, with the patient rested for 5 minutes, and with the back supported. As part of the study, blood pressure was measured in both arms using the same sphygmomanometer during the same sitting. Systolic blood pressure was categorized as follows: Normal: less than 120/80 mmHg; Pre-HTN: 120 to 139/80 to 89 mmHg; HTN: 140/90 mmHg or greater: Stage 1: 140 to 159/90 to 99 mmHg, Stage 2: 160/100 mmHg or greater. All patients had been diagnosed with hypertension with at least 2 consecutive elevated BP measurements ( $\geq 140$  mm Hg systolic and/or 90 mm Hg diastolic or  $\geq 130/80$  mm Hg in the presence of diabetes mellitus or chronic kidney disease). All patients were on lifestyle changes recommendations and conventional anti-hypertensive patients, consistent with JNC 7 (Chobanian et al, 2003) and ASH guidelines (Gradman et al, 2010). Testosterone levels were measured by a commercial laboratory. Testosterone levels were classified as normal if they fell between 348 ng/dl to 1197 ng/dl, low if they were at or below 347 ng/dl and high if they were at or more than 1198 ng/dl.

## 3. RESULTS

Of the 214 male hypertensive patients, 63 (29.4%) patients had low testosterone levels (at or below 347 ng/dl) while 145 (67.8%) men had normal testosterone levels (between 348 ng/dl and 1197 ng/dl). 6 (2.8%) of the patients had testosterone levels more than 1197 ng/dl. Their ages ranged from 28 years to 88 years. None of them were on any hormonal treatment or had castration or radical prostatectomy.

## 4. DISCUSSION

Testosterone deficiency is common. (Mulligan et al, 2006) It is often unrecognized and untreated. One of the reasons for under diagnosis is the lack of specific signs and symptoms. These include reduced libido and reduced sexual activity, reduced muscle bulk and strength, erectile dysfunction, low energy and drive, depression and fatigue (Basaria et al, 2001). Its deficiency is associated with increased morbidity and mortality in the general population (Arnlov et al, 2006; Akishita et al, 2010; Ruige et al, 2011; Ohlsson et al, 2011; Laughlin et al, 2008; Tivesten et al, 2009) and those with medical disorders (Kyriazis et al, 2011). The most significant

association of low testosterone has been with cardiovascular risk factors, (Jones et al, 2009) including obesity, (Bajos et al, 2010; Larsen et al, 2007) metabolic syndrome, (Kupelian et al, 2006; Bal et al, 2007) insulin resistance, (Yeap et al, 2009) vascular inflammation, (Kupelian et al, 2010) arterial dysfunction, (Akishita et al, 2007; Yaron et al, 2009) hypertension (Torkler et al, 2011) and atherosclerosis (Muller et al, 2004). Testosterone deficiency has emerged as an important predictor of future cardiovascular events, including mortality (Ohlsson et al, 2011; Akishita et al, 2010).

#### 4.1. Hypertension

Testosterone levels are inversely associated with both systolic and diastolic blood pressure (Torkler et al, 2011). The mechanisms are multiple, including direct effects on the heart, vessels and the kidneys (Reckelhoff, 2001), and effects mediated via neuro-hormonal factors (Kienitz et al, 2008). Low plasma testosterone levels are associated with an increased risk of major cardiovascular events in hypertensive patients (Charalambos et al, 2013).

#### 4.2. Obesity

Low testosterone levels are associated with obesity (Allan et al, 2010). Serum testosterone also inversely correlates with BMI, waist-to-hip ratio and total body fat mass measurements in men (Sandeep et al, 2010). The negative impact of obesity on diabetes and cardiovascular disease has been well documented (Dhindsa et al, 2010). Testosterone replacement may help reduce obesity (Farid et al, 2012).

#### 4.3. Metabolic Syndrome

Epidemiological (Kupelian et al. 2006; Bal et al. 2007) and observational studies (Majon et al. 2005) have identified an inverse relationship between testosterone levels and risk of metabolic syndrome. Testosterone levels are significantly lower among men with metabolic syndrome (Laughlin et al, 2008; Brand et al, 2011).

#### 4.4. Diabetes Mellitus

Testosterone levels are low in men with type 2 diabetes than in non-diabetic men, (Sandeep et al, 2004) and predict the development of type 2 diabetes in men (Haffner et al, 1996; Stellato et al, 2000). Testosterone deficiency may contribute to the erectile dysfunction seen in these men (Malavige et al, 2009). The relationship is complex and is mainly due to an increase in insulin resistance (Nelly et al, 2005). Supplementation with testosterone has been shown to improve dysglycemia (Morales, 2010; Francisco et al, 2011).

#### 4.5. Hyperlipidemia

A negative association has been noted with total cholesterol, low-density lipoprotein cholesterol and triglycerides, and a positive correlation with high-density lipoprotein cholesterol and testosterone levels (Haffner et al, 1993). This abnormal lipid profile improves with testosterone replacement (Malkin et al, 2004).

#### 4.6. Inflammation

Testosterone levels are inversely associated with inflammatory cytokines (Maggio et al, 2006). An inverse association has also been found between testosterone and plasminogen activator inhibitor I, fibrinogen and factor VII (Hak et al, 2002). Testosterone replacement has a salutary effect on the inflammation (Malkin et al, 2004).

#### 4.7. Other co-morbidities

Low testosterone levels have also been associated with chronic obstructive lung disease, inflammatory arthritis, end stage renal disease, HIV-related weight loss and radical prostatectomy. Several drugs including alcohol, antiandrogen agents, antihypertensives, cytotoxic agents, digoxin, estrogens, ketoconazole, metoclopramide, certain antidepressants and tranquilizers and spironolactone have been linked with testosterone deficiency (Swerdlow et al, 2008). Statins have also been implicated (Stanworth et al, 2009). Alcohol, marijuana and opioid use is also associated with the development of testosterone deficiency in some men.

## 5. TREATMENT

Testosterone levels over 350 ng/dl (>12 nmol/L) do not require treatment. (Wang et al, 2009) International guidelines recommend that patients with testosterone levels less than 230 ng/dL (8 nmol/L) be given replacement while patients with borderline low levels (230-350 ng/dL (8-12 nmol/L)) be managed by repeating total testosterone levels with SHBG in order to calculate free testosterone.

The clinical picture may also be taken into consideration. Testosterone replacement should not be initiated if there is erythrocytosis, hyperviscosity, untreated obstructive sleep apnea, or uncontrolled severe heart failure. (Wang et al, 2009; Basaria et al, 2010; Bhasin et al, 2010) Therapy should be discontinued if the hematocrit cannot be maintained at <55%. (Wang et al, 2009) Other contraindications include severe untreated benign prostatic hypertrophy (Basaria et al, 2010).

## 6. CONCLUSION

This study shows a high prevalence of low testosterone levels in men with hypertension. Low testosterone levels are associated with an increased risk of cardiovascular disease, such as coronary artery disease, heart failure (Ruige et al, 2011) and stroke (Yeap et al, 2009). Studies have shown that men in the highest quartile of serum testosterone levels have around a 30% lower risk of cardiovascular events over five years compared with men in the lower three quartiles (Ohlsson et al, 2011). Hypertension is also a major contributory risk factor for these cardiovascular complications (Lawes et al, 2004; Williams, 2009). Studies show that testosterone deficiency is associated with a higher risk for major adverse cardiovascular events including mortality in hypertensive males without clinical atherosclerosis (Charalambos et al, 2013). Testosterone is known to augment vasodilatation, (Jones et al, 2004) and adequate levels may prevent the development or attenuate the progression of hypertension related complications. All men with hypertension should therefore be screened for hypo-testosteronaemia. Exogenous testosterone replacement is effective in raising serum testosterone levels in patients with hypogonadism. Supplemental testosterone has been shown to be beneficial in coronary artery disease (Mathur et al, 2009) and heart failure (Toma et al, 2012). Testosterone replacement therapy may therefore play a cardio-protective role in hypogonadic hypertensive men.

## DISCLOSURE STATEMENT

The author has no conflicts of interest to disclose.

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