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Testosterone Therapy and the Heart

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1. Introduction

Testosterone (T) therapy has been offered to men who have low T levels, who are symptomatic with classical androgen deficiency syndromes, to induce and maintain secondary sex characteristics and to improve muscle mass and strength, bone mineral density, their sexual function, and sense of well-being. Hypogonadism is a clinical syndrome that is caused by inability of the testis to produce physiological levels of T in men. The age-related reduction in T levels is a result of defects in both hypothalamic-pituitary and testicular function. A diagnosis of androgen deficiency should be made only when low serum T and consistent symptoms and signs are encountered in men. It is not recommended to offer T therapy to all older men with low T level. A decision should be made on an individualized basis for older men with clinically significant symptoms of androgen deficiency and consistently low T level.
Hyperandrogenemia in women and hypoandrogenemia in men are associated with increased risk of coronary artery disease. In addition, these states are associated with insulin resistance, visceral obesity, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, low-densitylipoprotein (LDL) cholesterol and plasminogen activator inhibitor (PAI-1). These gender differences and confounders make the exact role of endogenous androgens in atherosclerosis unclear. In contrast, exogenous androgens exert both apparently beneficial and deleterious effects on cardiovascular risk factors by reducing serum levels of PAI-1 (apparently deleterious), HDL-C, insulin, leptin, lipoprotein(a), visceral fat mass (apparently beneficial), and fibrinogen in women as well as men. Androgen-induced reduction in circulating HDL-C levels should not reflexively be considered to be pro-atherogenic, because it may show increased reverse cholesterol transport instead. Short-term use of supraphysiological doses of exogenous T can decrease the severity and frequency of angina pectoris and reverse the electrocardiographic signs of myocardial ischaemia; yet long-term effects have not been determined. Nonetheless, the effects of pharmacological doses of androgens particularly on flow-mediated dilatation and arterial compliance must be interpreted with caution, since in addition at physiological concentrations detrimental effects, neutral, and beneficial effects on vascular reactivity can be observed. Testosterone induces an anti-atherogenic effect by facilitating efflux of cellular cholesterol to HDL and induces pro-atherogenic effects on macrophage function by increasing the uptake of modified lipoproteins.

2. Endogenous T and CAD morbidity\mortalitiy

In half of cross-sectional studies [Wu and Eckardstein 2003; Alexandersen et al 1996], serum levels of T were lower in patients with CAD than healthy controls. The other half of the

studies demontrated no difference in T levels when cases and controls are compared. In none of the studies, high levels of T were seen in patients with CAD. In all the studies, an inverse association was found between CAD and levels of free T [Wu and Eckardstein 2003; Alexandersen et al 1996]. None of six longitudinal studies revealed any significant association between the future risk of CAD events and serum levels of T in men [Wu and Eckardstein, 2003; Alexandersen et al., 1996].

European Prospective Investigation into Cancer in Norfolk Study demonstrated that serum levels of T at baseline were inversely associated with cardiovascular mortality and all-cause mortality in men aged 40-79 with no history of cancer or cardiovascular disease (Khaw et al., 2007). This risk association persisted after correction for traditional cardiovascular risk factors, indicating that the benefit may involve additional pathways. Also, other studies have showed the association between low testosterone and cardiovascular disease and increased mortality (English et al., 2000; Shores et al., 2006). Thus, increasing research on the clinical implications of physiological decline in androgens with aging has led to rekindled interest in the potentially cardioprotective role of T. Abuse of T is associated with increased risk of cardiovascular disease and sudden death, yet higher T serum levels within the physiological range have been associated with a more favourable cardio-metabolic risk profile. In contrast, low T serum levels have been associated with elevated triglyceride and low high-density-lipoprotein-cholesterol levels, glucose intolerance, diabetes, and central obesity (Kapoor et al., 2005; Tong et al., 2005; Wu and Eckardstein, 2003). This is in part because of the increased triglyceride and lipoprotein lipase uptake by adipocytes, causing central obesity and insulin resistance. The central obesity leads to increased peripheral conversion of T to estradiol by aromatase activity, further worsening this vicious cycle. Decreased serum levels of T are associated with a pro-inflammatory state with raised levels of inflammatory mediators like TNF-a and IL-1b, which can be improved with T substitution (Malkin et al., 2004).

Besides its pro-atherogenic effects by altered lipid profile and insulin resistance, T has also direct effects on the vasculature. T causes coronary vasodilation and improves chronic stable angina in men (English et al., 2000). Androgen receptors have been found in the myocardium and may exert some of the effects of T on the cardiac remodeling and renin-angiotensin-aldosterone system. T and other anabolic hormone deficiencies are associated with the severity of heart failure and increased mortality (Jankowska et al., 2006). T augments expression of heat shock protein 70 in cardiac myocytes, through which it may play an important role in preconditioning and protection against cardiac ischemia (Liu et al., 2006).

Studies that demonstrated an association between low serum T levels and raised cardiovascular mortality in general excluded patients at high risk for cardiovascular disease or those with established cardiovascular disease. This association whether applies to subjects with established cardiovascular disease has not been defined. In a study of 930 men with angiographically proven coronary disease that were followed up for a mean duration of 7 years, a high prevalence of low T at baseline ranging from 17 to 24% was seen. Decreased serum T levels as defined by baseline serum T levels of <2.6 nmol/l were an independent predictor of vascular and all-cause mortality (Malkin et al., 2010). In a recent study, Ruige et al. (Ruige et al., 2010) have reviewed the literature on serum T levels and overall mortality up to 2009. They demonstrated an excess mortality in elderly men (>70 years of age) who have a reduced T, which has been especially marked in studies since 2007.

It is important to consider the limitations of observational studies in showing the associations between coronary artery disease (CAD) and serum levels of endogenous androgens. These

studies have had extremely variable CAD endpoints (e.g., ultrasound- or postmortem- based diagnosis, unspecified cardiac events, morbid conditions such as myocardial infarction [MI] and angina, mortality, and the performance of angiography), heterogeneous study populations, and variable selection criteria. For instance, most CAD patients have been taking medications and have changed their lifestyle, factors which could affect them compared to controls. In some studies, allocation of poorly matched controls may be problematic in analysis. Among patients, the time interval from MI to sampling changed from 3 months to several years and has not been always standardized for diurnal rhythm of hormone levels. Also, in most of the studies, no adjustment has been made for confounding factors. For instance, the diagnoses of hyperandrogenemia in women and hypoandrogenemia in men were confounded by accompanying concurrent metabolic disorders, such as insulin resistance, obesity, impaired fibrinolysis, and dyslipidemia, which are frequently seen in chronic diseases, including CAD and lower serum levels of T (Eckardstein & Wu, 2003).

3. Exogenous T in cardiovascular disease

The long-term effects of exogenous T on incidence of coronary events have not been determined. However, few small studies demonstrated that therapeutic doses of T decreased the severity and frequency of angina pectoris and reversed electrocardiographic signs of myocardial ischemia. Webb et al. [Webb et al 1999] demonstrated that a single intravenous (IV) bolus of 2.3 mg T prolonged time to 1-mm ST segment depression by 66 seconds in 14 men with low plasma T levels and CAD. The plasma levels of T increased from 5.2 to 117 nmol/l, suggesting that this is a pharmacological action on the coronary vessels. These acute, direct pharmacological effects of T have been further investigated during coronary angiography. Administration of T over a 3-min period into the coronary arteries of 13 men with the diagnosis of CAD during coronary angiography at supra-physiological doses of 8 lmol/l, but not at the physiological doses of 8 nmol/l, cause coronary vessel diameter and blood flow to increase significantly at all four doses of T tested. These results have been also confirmed by a similar study of 14 men with CAD [Rosano ET 1999].

T has been employed at either pharmacological doses to exert selective effects on haematopoeitic marrow, muscle, bone, or other salutary effects in men with various chronic diseases (Handelsman, 2005; Liu, 2004) or at physiological doses as androgen replacement therapy for men with disorders of the hypothalamo-pituitary-testicular axis (Handelsman, 2005; Zitzmann & Nieschlag, 2000). Randomized placebo-controlled studies demonstrated that T employed to patients with chronic heart failure decreases systemic vascular resistance and improves both overall exercise capacity and cardiac output (Malkin et al., 2006; Pugh et al., 2003, 2004). Yet, effects on objective echocardiographic findings were little, suggesting that improvements could have been indirect through enhanced exercise endurance resulting from skeletal muscle or psychological effects. The effects of androgens on undamaged and damaged myocardium might be variable. One randomized placebo-controlled study demonstrated no deleterious effects on cardiac structure or function in 16 athletes after 8 weeks of 200 mg nandrolone decanoate injections (Hartgens et al., 2003). Likewise, the effects of testosterone have not been tested to determine whether androgen activation by aromatization to estradiol and/or amplification by 5 α reduction influences effects of androgens on cardiac function. Routine echocardiographic evaluation used in the above studies may not have sufficient sensitivity to determine subtle changes of myocardial function seen with drugs including androgens.

Androgens might exert cardiac effects through indirect mechanisms like in blood vessel disorders such as atherosclerosis, increased erythropoiesis, hyperviscosity, haematocrit, and hypertension. In addition, androgens might exert direct effects on cardiac muscle and its function by the androgen receptor expressed in cardiac muscle. In vitro studies of nonhuman cardiac myocytes demonstrated that T can decrease peak shortening times and action potential duration (hence altering repolarization) (Kimura et al., 1993). The direct effects of androgens on cardiac muscle have been less investigated (Sader et al., 2001). They are mostly based on case reports of cardiomyopathy in some androgen abusers on postmortem examinations (Sullivan et al., 1998). Some studies of anabolic steroid abuse indicate that androgen abuse in athletes may cause left ventricular hypertrophy, which may persist afterwards. Yet, several important limitations should be mentioned such as the lack of randomization, the confounding role of strength training, and self-selection. A study of testosterone and nandrolone (Chung et al., 2007) employed for 4 weeks demonstrated no adverse effects of androgens on non-invasive measures of cardiac function, which is consistent with a previous study using nandrolone for 8 weeks (Hartgens et al., 2003). Despite these promising findings during short-term use, longer studies would be necessary to show the maintenance of such a safety profile for long term. Retrospective data of over 2000 elite athletes from the East German national sports doping program, who were taking high dose synthetic androgens and were regularly monitored medically showed no cardiovascular complications. However, hepatic and other complications were frequently reported (Franke & Berendonk, 1997).

Previous work suggests that T may relieve symptoms in patients with angina pectoris and resolves post-exercise ST-segment depression in patients suffering from angina (Jaffe, 1977). Jaffe et al. (Jaffe, 1977) demonstrated that intramuscular T injection for 4 to 8 weeks in 50 men, who had ST-segment depression after exercise, improved post-exercise ST-segment depression, compared with placebo. This work did not study mechanisms by which T reduced ST-segment depression. Although early studies suggested beneficial effects of T in patients with angina, these studies were not placebo-controlled, were not randomized and the diagnosis of coronary artery disease was not angiographically established. Furthermore, the study by Jaffe (Jaffe, 1977) investigated the effect of T only on post-exercise ST-segment depression. It did not provide any information on hemodynamic parameters and the time course of ST-segment depression. Furthermore, not all previous studies in patients with angina pectoris have used pure T and therefore have not investigated the effect of T by itself on cardiovascular physiology. Yue et al. (Yue et al., 1995) demonstrated that T exerts endothelium independent dilatation of isolated rabbit aorta and coronary artery. The authors indicated that this may depend on an effect of T on potassium channels and potassium conductance but not on ATP-sensitive potassium channels, and they demonstrated that this effect is neither mediated by a classic hormonal receptor nor is sex-dependent (Yue et al., 1995). Experimental evidence indicates that T may have a potential beneficial effect on myocardial ischemia by playing a role in the regulation of coronary artery tone.

Mechanisms of action proposed for the effects of T were vasodilation of coronary arteries or their collaterals and an increase in hemoglobin levels which improves oxygen-carrying capacity of blood. Yet, the vasoactive properties of T have not been reported until recently.

The time elapsed to 1-mm ST-segment depression was reported to be prolonged after intravenous infusion of T. This indicates an acute anti-ischemic effect of T. The increase in heart rate- blood pressure product and heart rate shown either at 1-mm ST-segment depression or at peak exercise may suggest a direct vasodilator effect of T on coronary circulation. However, heart rate and blood pressure at rest were similar before and after T

employment. This suggests that a peripheral effect of T may not determine its anti-ischemic effect. The prolongation of time to 1-mm ST-segment depression observed is similar to that observed in women after acute employment of 17b estradiol, suggesting a similar effect of sex hormones in men and women (Rosano et al., 1993). Collins et al. (Collins et al., 1995) indeed demonstrated that intracoronary infusion of 17b-estradiol restores endothelium dependent vasodilatation in women but not in men, indicating a specific role of sex hormones on the cardiovascular system. The anti-ischemic effect of T reported might explain the cardio-protective effect of T substitution in men with hypotestosteronemia. In the present study, mostly the patients with lower testosterone benefited from testosterone employment (Rosano et al., 1999).

A recent study has shown that ventricular functions are normal in men with idiopathic hypogonadotropic hypogonadism (IHH) and substitutive therapy has no effects on ventricular functions, however it may increase peak pulmonary artery pressure (PAP) in small amounts (Yaylali et al., 2010). This finding is in line with previous studies demonstrating normal left ventricular functions in IHH men (Baysan et al., 2007; Celik et al., 2001; Hartgens et al., 2003). In addition, substitutive therapy had no effects on RV systolic or diastolic functions. This study found no evidence of clinically significant effects of the use of substitutive therapy on ventricular functions in the short term. However, substitutive therapy may increase PAP in small amounts which may be related to its vasoactive properties in the pulmonary vasculature. The younger normal even testosterone deplete heart is a totally different state than the diseased atherosclerotic or failing older heart. In this respect previous studies examined the effects of exogenous testosterone on the hearts of older men which were already affected by atherosclerosis or syndrome of heart failure. In contrast, this study investigated the ventricular functions in much younger hearts with no evidence of atherosclerosis or heart failure before and after substitutive therapy.

It has been shown that 12 weeks of treatment with T in men with CHF was well tolerated, safe, and led to significant improvements in symptoms and physical capacity. Larger clinical trials are needed to evaluate the mechanism of action of T, beneficial effect and confirmation of its safety in selected patients (Lellamo et al., 2010).

4. Effects of T on cardiovascular risk factors

Several cross-sectional population studies have demonstrated statistically significant correlations between various cardiovascular risk factors and plasma levels of T, however the correlations were opposite in women and men. The plasma T levels in men were frequently found to have positive correlations with serum levels of HDL –C and have inverse correlations with plasma levels of low-density lipoprotein cholesterol (LDL-C), triglycerides, fibrinogen, total cholesterol, and PAI-1 (Hergenc et al., 1999; Tchernof et al., 1996; Tsai et al., 2000). Yet, serum levels of T were found to have even stronger inverse correlations with BMI, waist-hip ratio (WHR), waist circumference, amount of visceral fat, insulin, serum levels of leptin, and free fatty acids. The correlations of T with the cardiovascular-disease risk factors except visceral fat and insulin lost their statistical significance after adjustment for obesity and insulin resistance (Hergenc et al., 1999; Tchernof et al., 1996; Tsai et al., 2000). These findings suggest that a low serum level of T is a component of the metabolic syndrome in eugonadal men, which is a cluster of cardiovascular risk factors such as obesity, hypertriglyceridemia, glucose intolerance or overt type 2 diabetes mellitus, low HDL-C, and arterial hypertension. Metabolic syndrome is considered a procoagulatory and an anti-fibrinolytic state. And insulin resistance plays an important role in its etiology. Thus,

the frequent association of high T levels with a more favorable cardiovascular risk factor profile in men perhaps does not reflect direct regulatory effects of T on lipoprotein metabolism and the hemostatic system. Some studies demonstrated the loss of these associations when serum levels of free T were used to correlate with lipids and other cardiovascular-disease risk factors instead of serum levels of total T were used. In agreement with these findings, a reduced number of CAG repeats in the androgen receptor, which facilitates its binding to T, was associated with decreased levels of leptin, HDL-C, BMI, and low body fat mass (Zitzmann et al., 2001, 2003). One reason for the discrepancy between the associations of endogenous T and the biological effects with various cardiovascular risk factors is the inhibitory effect of insulin on the production of SHBG so that insulin resistance results in low levels of SHBG and low levels of total T as a result.
The association between increased risk of coronary artery disease and plasma testosterone levels has been attributed in part to the unfavorable effect of T on fibrinolysis and HDL cholesterol (Glueck et al., 1993; Jones et al., 1989; Sorva et al., 1988). Plasma levels of HDL cholesterol are higher in women than in men, and some studies indicate that T substitution in men causes a decrease in plasma levels of HDL cholesterol (Jones et al., 1989; Sorva et al., 1988). Glueck et al. (Glueck et al., 1993) demonstrated that T correlates with tissue plasminogen activator, the major stimulator of fibrinolysis positively, and with fibrinogen and plasminogen activator inhibitor inversely. However, recent studies have demonstrated that 2-month therapy with testosterone undecanoate had a beneficial effect on lipoprotein profiles in older men (Uyanik et al., 1997). Although there might be an effect of plasma T levels on pro-thrombotic state, yet there is no epidemiological evidence showing an association between coronary artery disease and high testosterone levels (Uyanik et al., 1997).

5. Effects of androgens on vascular reactivity

T can exert vasodilatation or vasoconstriction via endothelium-independent or endothelium-dependent mechanisms and by genomic or non-genomic modes of action. The variation in these findings appears to be due to differences in concomitant disease, species, gender, and, most importantly, the dosage of T given. The significant reduction in nitrate-induced (and hence endothelium-independent) dilatation of the brachial arteries in female-to-male transsexuals taking high-dose androgens indicate these possible adverse effects associated with use of T (McCredie et al., 1998). In another study, castrated patients with prostate cancer had a greater flow-induced (i.e., endothelium-dependent) dilatation of brachial arteries compared to controls; however, the degree of nitroglycerin induced endothelium dependent vasodilatation did not differ between the two groups (Herman et al., 1997). In a study of 110 healthy men, a positive association between endothelium-dependent as well as endothelial-independent vasodilatation and the numbers of CAG repeats in exon 1 of the androgen receptor gene was observed. Therefore, the greater the sensitivity to T, the less brachial arteries dilate in response to either administration of nitrate or increased blood flow (Zitzmann et al., 2001). In contrast to these studies, IV administration of T in acute interventional studies to male patients with CAD showed apparently beneficial vasodilatory effects of T. Likewise, most in vitro studies with animal vessels and in vivo studies in monkeys and dogs of both sexes indicate that T induces beneficial effects on vascular reactivity. Intracoronary injections of acetylcholine caused a significant endothelium-dependent vasodilatation in ovariectomized female cynomolgus monkeys treated with T for 2 years compared to untreated animals. In contrast, endothelium-independent vasodilatation occurred in the two groups normally (Adams et

al., 1995). In dogs, T induced vasodilatation of coronary arteries by both endothelium-dependent and -independent mechanisms (Chou et al., 1996; Costarella et al., 1996). In addition, the results of studies with isolated aortas and/or rings of coronary arteries from pigs, rats, and rabbits showed that T administration improved both endothelium-independent and/or endothelium-dependent vascular responsiveness in both sexes (Chou et al., 1996; Costarella et al., 1996; Yue et al., 1995). Yet, it must be noted that all these studies used supra-physiological doses of T in the micro-molar range. Teoh et al. (Teoh et al., 2000) demonstrated a direct vasodilatory effect of T on porcine coronary artery rings when given at micro-molar concentrations. But no direct effect was observed when T given at nano-molar concentrations. In contrast, physiological doses of T reduced the vasodilatory effects of calcium ionophores and bradykinin. Likewise, T impaired endothelium-dependent relaxation of aortic rings from rabbits that were either exposed to tobacco smoke or that were either made hypercholesterolemic. In addition, T inhibited the adenosine-mediated vasodilatation of rat coronary arteries (Ceballos et al., 1999; Farhat et al., 1995; Hutchison et al., 1997). The molecular and cellular mechanisms by which E2 and T regulate vascular tone are not well known. Evidence for and against endothelium-dependent or endothelium-independent mechanisms has been found. Some studies indicate endothelial nitric oxide involvement (Chou et al., 1996; Costarella et al., 1996; Geary et al., 2000). The nitric oxide synthase inhibitor L-NMMA inhibited T-induced vasodilatation in the aortas of rats, the coronary arteries of dogs, and the cerebral arteries of rats. Yet, another study demonstrated no effect of L-NMMA on T-induced vasodilatation of rabbit coronary arteries and aortas (Yue et al., 1995). Likewise, Hishikawa et al. (Hishikawa et al., 1995) demonstrated that E2 but not T stimulated in vitro expression of nitric oxide synthase in human aortic endothelial cells. It has been observed that T increases the response of coronary arteries to prostaglandin F2a (Farhat et al., 1995). Also, dihydro-T increases the density of thromboxane receptors in rats and guinea pigs (Masuda et al., 1995). Yet, results of some in vitro and in vivo animal studies suggest that pretreatment with the prostaglandin synthesis inhibitor indomethacin induced no effect on T-induced vasodilatation. The role of eicosanoids in mediating the actions of T on the arterial wall still remains controversial. It is unknown whether T regulates vasoreactivity by either non-genomic or genomic effects or both. Androgen receptor expression has been determined in rat endothelial cells and aortic smooth muscle cells. In human arterial cells expression of the androgen receptors has not been directly demonstrated. However, the association of endothelium-independent and endothelium-dependent vasoreactivity with the CAG repeat polymorphism in the androgen receptor suggests some indirect evidence for the expression of the androgen receptor on vascular smooth muscle cells and endothelial cells, respectively (Zitzmann et al., 2003). Also, steroid hormones can regulate vascular tone by modulation of cell membrane channels (e.g., voltage-dependent, ATP-sensitive, and calcium-activated potassium channels) and by non-genomic mechanisms that involve plasma membrane steroid receptors. Several observations indicate that T, especially at supra-physiological doses, modulates vascular tone via its secondary metabolites (e.g., E2) and/or non-genomic modes of action. Flutamide or cyproterone acetate, the androgen receptor antagonists did not reduce the effects of T on pig or rabbit coronary arteries (Teoh et al., 2000). The expression of aromatase in vascular endothelial cells (Harada et al., 1999) increases the possibility that T can be converted to E2 and T induces its vasoactive effects through stimulation of the estrogen receptors. Yet, neither the estrogen-receptor antagonist ICI 182,780 nor the aromatase inhibitor aminogluthemide prevented the T-induced vasodilatation (Chou et al., 1996). Barium chloride decreased the T-induced

vasorelaxation of rabbit coronary arteries and aortas, indicating that T modulates the opening of potassium channels in vascular smooth muscle cells.

6. Conclusion

The clinical picture of male hypogonadism carries a significant morbidity. After a careful diagnostic evaluation to identify the underlying cause of hypogonadism, substitutive therapy may be instituted after examining benefit to risk ratio for an individual patient. The clinician has a choice among different T preparations, tailoring pharmacokinetics and route of employment to the patient. Long-term effects of substitutive therapy on the cardiovascular system still remain unclear. Published data mostly consists of small, observational studies with no clear definition of outcome. We still lack large randomized controlled studies investigating the relationship between substitutive therapy and cardiovascular risk, although androgen replacement therapy has been found to have beneficial effects on bone density, body composition, metabolism, and muscle strength in hypogonadal men. The effects of physiological doses of T on the lipid profile remain to be fully defined and the risk of not replacing T in the deficient men also remains unclear. Firstly, we might think that T and cardiovascular disease are clearly related, but the intricacies of the relationship are much more complex. As the role of androgens in cardiovascular system becomes clearer in the future, we may find out the mechanisms that play a role in the observed sex differences in the incidence of coronary artery disease in the middle-aged population.

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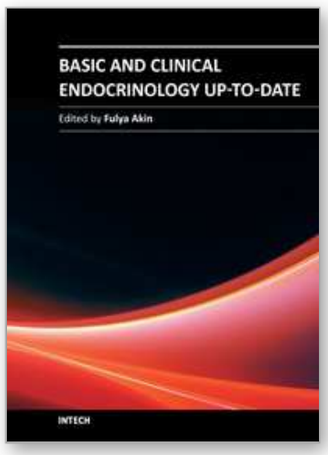
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This book provides the most up-to-date information on the basic and clinical aspects of endocrinology. It offers both researchers and clinicians experts, gold-standard analysis of endocrine research and translation into the treatment of diseases such as insulinoma, endocrine disease in pregnancy and steroid induced osteoporosis. Investigates both the endocrine functions of the kidneys and how the kidney acts as a target for hormones from other organ systems. Presents a uniquely comprehensive look at all aspects of endocrine changes in pregnancy and cardiovascular effects of androgens.

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