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An Investigation Into The Effect Of Testosterone On Plasma Triglyceride And Cholesterol Levels

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ASTRACT

Studies have shown that in the male, tissue fat storage increases with age and the accompanying decrease in testosterone level. It is also widely accepted that elevated plasma levels of triglycerides and cholesterol are important risk factors for the development of cardiovascular diseases. The present work was therefore designed to study the effect of testosterone on plasma triglyceride and cholesterol levels.

Experiments were carried out on 30 intact adult male rats weighing 200-300gm. The rats were divided randomly into six groups that received different treatments of testosterone, adrenaline, and propranolol. Blood samples were obtained from all the rats by cardiac puncture and plasma samples were assayed for triglyceride and cholesterol.

Results of the study showed that testosterone caused a significant elevation of plasma triglyceride, and also enhanced an adrenaline-induced increase in plasma triglyceride. Propranolol treatment inhibited the increase in plasma triglyceride induced by testosterone. Plasma cholesterol level did not change with testosterone treatment although a combined treatment of testosterone and adrenaline caused a significant increase in cholesterol level, suggesting a synergistic action.

INTRODUCTION

Sex steroid hormones are known to affect fat metabolism but the mechanisms by which they do so are not completely understood. Testosterone is known to increase lipolysis in fat cells and has also been reported to increase beta-adrenergic lipolytic action of catecholamines.

Testosterone has been implicated in the pathophysiology of obesity in male[1], and studies have shown that abdominal fat in males increases with age and a decrease in teloriterone level[2]. Other studies reported an increase in lipolysis after treating rats with testosterone, while some workers observed that testosterone inhibits lipid uptake in adipocytes and stimulates lipolysis by increasing the number of beta-adrenergic receptors[3,4].

Plasma triglyceride are transported in the form of chylomicrons and other lipoproteins, and most are hydrolysed by lipoprotein lipase to fatty acids and glycerol. The unhydrolysed triglycerides circulate as chylomicron remnants. Plasma cholesterol also circulates in lipoprotein complexes. It is possible that the high cardiovascular risk associated with the use of testosterone as an anabolic steroid[5] is related to the effects of high doses of the hormone on fat metabolism. While some previous workers observed no change in total plasma triglyceride level after testosterone administration other reported an increase in plasma triglyceride[6,7,8].

There have also been varying observations on the effect of testosterone on plasma cholesterol. Some workers have reported a decrease in plasma cholesterol[9], but some other reported an increase[6,8]. The present study further investigates the effect of high testosterone treatment on fat metabolism and possible adrenergic interaction, using the parameters of serum triglyceride and serum cholesterol.

Animals

30 adult male Sprague-Dawley rats weighing 200-300gm were used for the experiments. (The rats were obtained from the experiments). The rats were obtained from the animal house of the College of Medicine, University of Lagos.

Methodology

Rats were randomly divided into 6 groups, A,B,C,D,E and F with 5 rats in each group. They were given the following treatments-

Group A rats (control) received no treatment.
Group B rats were injected with testosterone (20gm/kg b.w) for 4 days.
Group C RATS were injected with adrenaline (0.5ug/kg b.w)
Group D rats received both the testosterone and adrenaline injections
Group E rats were injected with propranolol (1mg/kg) and
Group F rats received a combined injection of propranolol and testosterone

All injections were given subcutaneously.

Rats were anaesthetized with urethane (25%) and blood was collected with heparinised needles and syringes through a cardiac puncture. The blood was centrifuged at 3000r.p.m. for 5 minutes to obtain plasma. Plasma samples were then assayed for cholesterol and triglyceride using enzymatic methods [10,11]

Statistical Analysis

Results are expressed as the means s.e. (standard error of mean)

The significance of differences were calculated with the analysis of variance (ANOVA) followed by a post-hoc

Newman-Keuls test. Ap value of 0.05 was taken as statistically significant.

RESULTS

Testosterone treatment caused a significant increase in plasma triglyceride from control levels (fig. 1) and further increased the adrenaline-induced elevation of plasma triglyceride. With adrenaline treatment plasma triglyceride significantly increased from control levels of 26.0±0.67mg/dl to 53.0±2.3 mg/dl, and with a combined treatment of testosterone and adrenaline plasma triglyceride significantly increased to 70.4±1.46mg/dl (fig.1).

Propranolol treatment (beta-adrenergic inhibition) inhibited both the testosterone-induced increase in plasma triglyceride, and that caused by the combined treatment of testosterone and adrenaline (fig.2)

Neither Testosterone nor adrenaline treatment caused any significant change in plasma cholesterol level. However it was observed that testosterone and adrenaline appeared to work additively to increase plasma cholesterol level (fig.3)

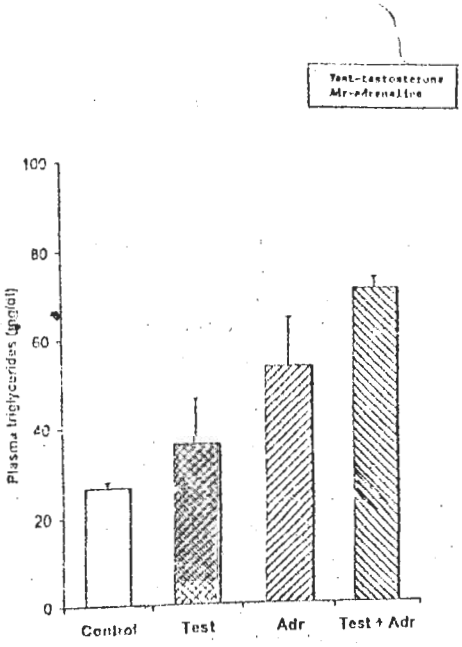

Fig. 1. Plasma triglyceride level after testosterone and adrenaline treatment

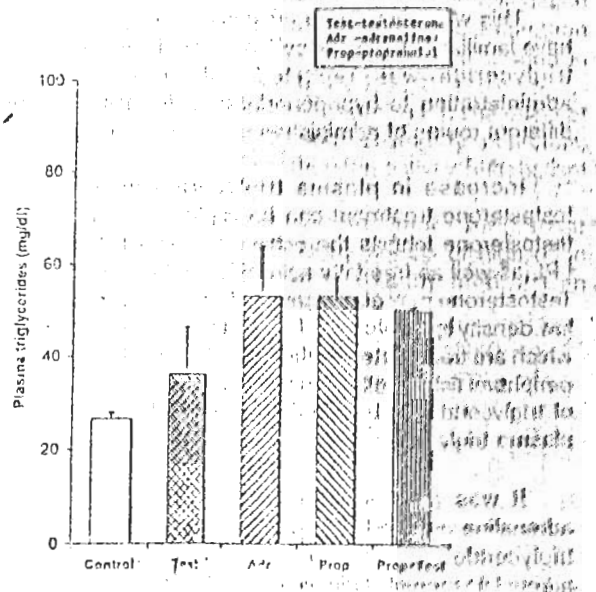

Fig. 2. Plasma triglyceride level after propranolol treatment (beta-adrenergic inhibition).

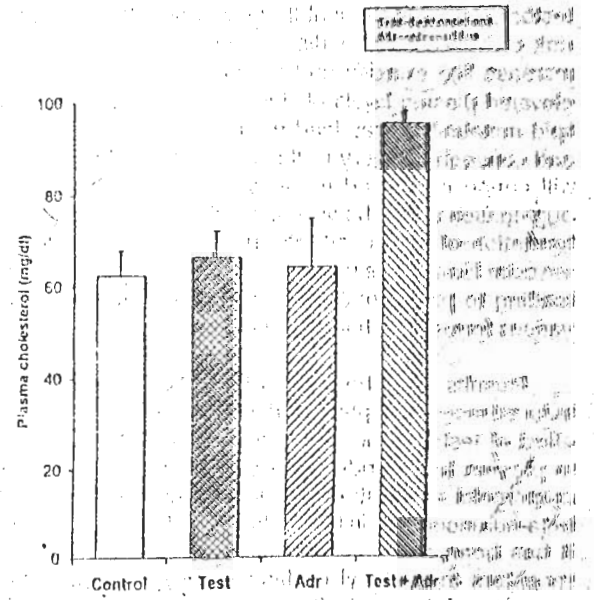

Fig. 3. Plasma cholesterol levels after testosterone and adrenaline treatment

DISCUSSION

Results of the present study show that testosterone elevates plasma level of triglyceride, an indication that testosterone effect on fat metabolism may include a depression of chylomicron clearance in the blood via an inhibition of plasma lipoprotein lipase (LPL.) Chylomicrons being very rich in triglycerides, an accumulation will result in an increase in total plasma triglyceride.

This was shown in a previous study on patients who have familial LPL deficiency[12]. A similar increase in plasma triglyceride was reported following testosterone administration to hypogonadal men for 190 days using different routes of administration[8]

Increase in plasma triglyceride in response to testosterone treatment can be explained by the fact that testosterone inhibits the activity of adipose tissue bound LPL as well as free fatty acid (FFA) uptake in adipocytes[1]. Testosterone may also stimulate hepatic production of very low density lipoprotein (VLDL) and endogenous triglyceride which are transported by the VLDL through the blood to the peripheral tissue cells. This action furthers the accumulation of triglycerides in blood with a resultant increase in total plasma triglyceride.

It was also observed in the present study that adrenaline administration caused an increase in plasma triglyceride. This increase may be due to the fact that adrenaline promotes biosynthesis of triglycerides in the liver which are transported in blood and stimulates glucose uptake into adipocytes, activities which prevent the breakdown of lipid in tissues, especially adipose tissue, and which promote synthesis and accumulation of triglyceride-rich chylomicrons and VLDL in blood[13]. Testosterone administration was found to enhance this adrenaline-induced elevation of plasma triglyceride. This suggests a synergistic or additive metabolic action between testosterone and adrenaline. The synergistic action of testosterone and adrenaline may predispose patients on testosterone replacement therapy or athletes to increased risk of cardiovascular disease in periods of adrenaline increase like exercise and anxiety because the resultant elevated plasma levels of triglyceride and perhaps other lipid metabolites may lead to an increase in plasma LPL and consequent injury to the vascular endothelium which will cause increased monocyte adhesion and platelet aggregation within the vascular wall[14]. All these lead to the formation of atherosclerotic plaques which narrow the vascular lumen. This promotes the formation of thrombosis leading to partial or total occlusion by emboli, causing various forms of ischaemic diseases.

Results from the present study also show that the induced increase in plasma triglyceride and the stimulatory effect of testosterone on the adrenaline-induced increase in plasma triglyceride were significantly reduced after propranolol administration, suggesting an involvement of beta-adrenoceptors in this metabolic action of testosterone. It has been suggested that testosterone through beta-receptors and adenyl cyclase activity in adipose cells, promotes fat metabolism by enhancing adrenaline activities[15]. Therefore testosterone may, through beta-adrenoceptor involvement influence the balance between the rate of fat metabolism in the tissue cells and fat metabolism in blood circulation.

Testosterone appears to have no effect on plasma cholesterol from the results of the present study. This suggests that although testoterone may influence various stages of fat metabolism both in the circulation and at tissue level, the net effect is a zero change in total plasma cholesterol. A similar result was reported in a study on monkeys treated with testosterone orally and intramuscularly for 120 days[16].

Plasma cholesterol level may not change in the presence of factors which trigger its negative feedback control mechanisms. Testosterone has been shown to reduce the plasma level of HDL which normally transports cholesterol from outside the liver back to the liver[17,18]. Thus a decrease in HDL by testosterone will cause an accumulation of cholesterol which negatively feeds back to inhibit endogenous synthesis of cholesterol by the tissue, and probably promote (its uptake) its uptake and utilization by the cells. This will lead to a fall in the elevated cholesterol level and ultimately a fairly constant plasma cholesterol level.

It was also observed from the present study that although adrenaline treatment did not induce any elevation of plasma cholesterol, simultaneous administration of testoterone and adrenaline did cause a significant increase in plasma cholesterol level further indicating a synergistic action between testosterone and adrenaline in fat metabolism.

From the results of the present study it is concluded that the ways in which testosterone affects fat metabolism include an increase in plasma triglyceride level the mechanism of which may involve beta-adrenoceptor activity.

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