The effect of cyproterone acetate on serum lipids in normal men

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Abstract. In a male anti-fertility study 7 volunteers received the anti-androgen cyproterone acetate (5 or 10 mg daily) orally in a paired study. A significant reduction in serum-cholesterol and LDL-cholesterol, and a significant increase in the intravenous-fat-tolerance-test (IVFTT) was observed. Thus low doses of cyproterone acetate reduced the serum testosterone concentration and some of the atherosclerotic risk factors.

Cyproterone acetate, an anti-androgen and progestational compound is used in male fertility studies (5—10 mg per day), and in high doses (50—600 mg per day) in the treatment of hypersexual men. The basis for their applications is a decrease in spermatogenesis and a reduction in serum testosterone concentration (Føgh et al. 1979). However, androgens influence the concentration and metabolism of serum lipids and lipoproteins (Solyom 1971; Cohen et al. 1961; Eder 1959). An increase in serum cholesterol and serum LDL, and/or a decrease in serum HDL are considered to be risk factors in atherosclerotic diseases (Kannel et al. 1971). Consequently it is pertinent to determine whether anti-androgens such as cyproterone acetate have any effect on these parameters. An effect of cyproterone acetate on thromboembolic risk factors such as platelet aggregation has been observed recently (Føgh et al. 1980).

Materials and Methods

Seven healthy men (25—35 years old) were investigated in a male anti-fertility study (a WHO multicenter trial). The volunteers received one daily oral dose of 5 or 10 mg of the anti-androgen cyproterone acetate (1,2-methylene-6-chloro-4,6-pregnadien-17-ol-3,20-dion-17-acetate). Blood samples were obtained 3—6 months after the start of the treatment and after at least 4 months without treatment (Table 1). The samples were drawn from the volunteers at different months through the year to avoid seasonal variations in serum lipids. In all studies the blood samples were collected after at least 20 min in the supine position between 8 and 10 a.m. in the fasted state. Serum or plasma was separated by centrifugation (3000 r.p.m., 10 min) within 2 h, and kept at 0—4°C until analyses were performed. Plasma for analysis of post-heparin-lipolytic-activity (PHLA) was stored at −80°C and analysed within 12 months. Serum cholesterol was measured by a modification of the Libermann-Burchard method (Lykkelund & Damgaard-Petersen 1979). Triacylglycerides were extracted from serum with diisopropyl ether:ethanol (2:1, v/v). Phospholipids were removed by silicic acid adsorption. After saponification, glycerol was oxidized to formaldehyde, which was measured spectrofotometrically after the addition of acetyl acetone and ammonium salt.

HDL was measured as HDL-cholesterol concentration

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in serum after precipitation of LDL + VLDL cholesterol by heparin/manganese (Bachorik et al. 1976). LDL was calculated as LDL-cholesterol = serum cholesterol – (HDL-cholesterol + serum triglycerides/5) (Friedewald et al. 1972). Post-heparin-lipolytic-activity (PHLA) was measured in plasma exactly 10 min after iv injection of heparin (60 IU per kg body weight) (Færgeman & Damgaard-Petersen 1973). Post-heparin-lipolytic-activity includes at least the activities of two different triglyceride hydrolizing enzymes, namely a post-heparin-lipoprotein-lipase-activity (PLLA), which is believed to be the rate limiting enzyme in the initial removal of chylomicrons and very-low-density-lipoproteins (VLDL) from the bloodstream, and post-heparin-hepatic-triglyceride-lipase-activity (HTLA), which may be involved in the metabolism of chylomicron and VLDL remnants (Krauss et al. 1973). In post-heparin plasma the PLLA is inhibited almost completely by 1 m sodium chloride (Fielding 1974). Consequently the lipolytic activity measured in post-heparin plasma after addition of sodium chloride is equal to post-heparin HTLA and PLLA was calculated as the difference between PHLA and HTLA (PHLA = HTLA + PLLA). The intravenous-fat-tolerance-test (IVFTT) was performed as described by Carlson & Rössner (1972), whereby 10% intralipid (Vitrum, Stockholm, Sweden) (1 ml/kg) was injected iv as a bolus and the clearing of plasma was followed for 40 min by nephelometric measurements of plasma samples drawn every 5 min. The fractional removal rate constant (k2) was calculated. Blood samples for analyses of serum testosterone were drawn between 8 a.m. and 6 p.m. and at the same time of the day for each volunteer. Serum testosterone was analysed by a radioimmunoassay (Corker et al. 1978). Student's t-test and the non-parametric Wilcoxon rank serum test for paired observations were used for statistical evaluation of the results.

### Table 1.

Individual results from investigation of 7 men during and after treatment with cyproterone acetate (5 or 10 mg/day).

<table>
<thead>
<tr>
<th>Subject</th>
<th>S-TG</th>
<th>S-CHOL</th>
<th>HDL</th>
<th>LDL</th>
<th>PHLA (total)</th>
<th>PHLA (inhrib.)</th>
<th>PHLA (resist.)</th>
<th>IVFTT</th>
</tr>
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<tr>
<td>H.L.J.</td>
<td>-drug 0.71</td>
<td>5.74</td>
<td>1.37</td>
<td>4.05</td>
<td>277</td>
<td>209</td>
<td>68</td>
<td>0.083</td>
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<tr>
<td></td>
<td>+drug 0.37</td>
<td>5.62</td>
<td>1.48</td>
<td>3.97</td>
<td>298</td>
<td>200</td>
<td>98</td>
<td>0.090</td>
</tr>
<tr>
<td>L.D.</td>
<td>-drug 0.89</td>
<td>6.69</td>
<td>1.21</td>
<td>5.08</td>
<td>255</td>
<td>155</td>
<td>100</td>
<td>0.037</td>
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<tr>
<td></td>
<td>+drug 0.79</td>
<td>6.66</td>
<td>1.40</td>
<td>4.90</td>
<td>256</td>
<td>165</td>
<td>91</td>
<td>0.049</td>
</tr>
<tr>
<td>P.N.</td>
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<td>6.12</td>
<td>0.97</td>
<td>4.04</td>
<td>264</td>
<td>230</td>
<td>26</td>
<td>0.021</td>
</tr>
<tr>
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<td>4.89</td>
<td>0.96</td>
<td>3.38</td>
<td>321</td>
<td>288</td>
<td>35</td>
<td>0.040</td>
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<td>L.C.</td>
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<td>1.99</td>
<td>2.68</td>
<td>233</td>
<td>163</td>
<td>70</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
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<td>4.54</td>
<td>1.66</td>
<td>2.71</td>
<td>279</td>
<td>242</td>
<td>37</td>
<td>0.058</td>
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<tr>
<td>A.P.</td>
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<td>1.28</td>
<td>2.89</td>
<td>316</td>
<td>260</td>
<td>66</td>
<td>0.092</td>
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<tr>
<td></td>
<td>+drug 0.46</td>
<td>3.48</td>
<td>1.15</td>
<td>2.12</td>
<td>281</td>
<td>200</td>
<td>81</td>
<td>0.087</td>
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<td>C.P.T.</td>
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<td>1.63</td>
<td>3.18</td>
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<td>261</td>
<td>36</td>
<td>0.053</td>
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<td>297</td>
<td>267</td>
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<td>0.048</td>
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<tr>
<td>N.B.</td>
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<td>1.66</td>
<td>4.14</td>
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<td>14</td>
<td>0.071</td>
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<td>5.38</td>
<td>1.66</td>
<td>3.52</td>
<td>345</td>
<td>330</td>
<td>15</td>
<td>0.088</td>
</tr>
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</table>

S-TG: Serum triglyceride concentration.
S-CHOL: Serum cholesterol concentration.
HDL: High density lipoprotein cholesterol concentration.
LDL: Low density lipoprotein cholesterol concentration.
PHLA (inhrib.): Post-heparin-lipolytic-activity inhibited by sodium chloride (post-heparin-lipoprotein-lipase-activity).
PHLA (resist.): Post-heparin-lipolytic-activity resistant to sodium chloride (post-heparin-hepatic-triglyceride-lipase-activity).
IVFTT: Intravenous fat tolerance test (triglyceride fractionel removal rate constant).
Results

Treatment of 7 young male volunteers with cyproterone acetate shows a reduction in cholesterol ($P < 0.01$), in LDL ($P < 0.025$), and an increase in the intravenous-fat-tolerance-test ($P < 0.05$). Concerning triglycerides a decrease was seen in 6 cases but the changes were insignificant ($0.05 > P < 0.10$) (Table 1). When the non-parametric Wilcoxon rank sum test is used, only the reduction in serum cholesterol and LDL is significant. Serum testosterone during the cyproterone acetate treatment decreased approximately 50 per cent (Føgh et al. 1979).

Discussion

There are no reports of the effect of anti-androgens on blood lipids and lipoproteins, and most of the investigations concerning the relation between treatment with sexual hormones and the changes in serum lipids have not measured the serum testosterone concentration. We have shown in a paired study that an anti-androgen which reduces the serum testosterone concentration level by about 50 per cent of the normal level, also reduces serum cholesterol, LDL and increases the fractional triglyceride turnover (IVFTT).

Androgens have been shown to reduce the serum concentration of triglycerides, VLDL and HDL, and increase serum cholesterol and LDL (Solyom 1971; Eder 1959; Furman et al. 1958). Oxandroloiene, a syntetic, anabolic, androgenic steroid, has been demonstrated to decrease serum triglycerides and increase post-heparin-lipoprotein-lipase-activity, post-heparin-hepatic-triglyceride-lipase-activity and fractional triglyceride turnover (Glueck et al. 1976; Olsson et al. 1974; Enholm et al. 1975). Consequently, after a reduction in serum testosterone one might expect a decrease in serum cholesterol and LDL, which is confirmed by our study. One might also expect an increase in serum triglycerides and a reduction in the post-heparin-lipolytic-activities and the fractional triglyceride turnover. We found no increase in serum triglycerides, which may be explained by assuming that the anti-androgen cyproterone acetate in low doses acts as a partial agonist. In normal subjects post-heparin-lipoprotein-lipase-activity is accepted to be the rate limiting factor in the removal of triglycerides from blood, we did not observe an increase in post-heparin-lipoprotein-lipase-activity together with the measured decrease in triglycerides and increased fractional triglyceride turnover. However, changes in post-heparin-lipoprotein-lipase-activity has been shown to occur without any measurable changes in IVFTT and changes in IVFTT has been reported without changes in post-heparin-lipoprotein-lipase-activity (Rössner et al. 1971; Boberg et al. 1971). Another explanation could be that lipoprotein lipase activity in situ (at the capillary walls) is increased, but the release by heparin may be inhibited (Glad et al. 1978), but the IVFTT employ an artificial substrate, the clearance of which from plasma may differ from that of chylomicrons and very low density lipoproteins.

In a paper by Furman et al. (1958) it is mentioned as a personal communication that eunuchs manifest less extensive coronary atherosclerosis at autopsy than do non-castrated men. This could be explained by a low serum testosterone concentration resulting in a low serum cholesterol and LDL concentration as shown in our study, which means a reduction in the athero sclerotic risk factors.

In summary, our data indicate that cyproterone acetate (5–10 mg per day orally) which are pharmacological effective in the male volunteers in reducing serum testosterone and sperm count (Føgh et al. 1979), also reduce serum cholesterol and LDL, which are known as atherosclerotic risk factors.

Acknowledgments

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References


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