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Original Article

Antiandrogenic therapy can cause coronary arterial disease

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Abstract

Aim: To study the change of lipid metabolism by antiandrogen therapy in patients with prostate cancer.

Materials and methods: We studied with a 2.5 years follow-up the changes in plasma cholesterols (C), triglycerides (TG), lipoproteins (LP), and apolipoproteins (Apo) B-100, A-I, and A-II profiles in 24 patients of mean age 60 years with low risk prostate cancer (stage: $T1cN_0M_0$, Gleason score: 2–5) during treatment with cyproterone acetate (CPA) without surgical management or radiation therapy.

Results: Significant decreases of HDL-C, Apo A-I and Apo A-II and an increase of triglyceride levels in VLDL were induced by CPA. After a period of 2.5 years on CPA treatment, four patients out of twenty-four were found to be affected by coronary heart disease.

Conclusions: Ischaemic coronary arteriosclerosis with an incidence rate of 16.6% as caused by prolonged CPA therapy is mediated through changes in HDL cholesterol, Apo A-I and Apo A-II profiles, other than the well-known hyperglyceridemic effect caused by estrogen.

Key words antiandrogen, CAD (coronary arterial disease), CPA (cyproterone acetate), hormonal therapy, prostate cancer.

Introduction

Cyproterone acetate (CPA), commercially named Androcur, is widely used as an antiandrogenic preparation in the treatment of prostate cancer. CPA inhibits competitively at androgen (such as dihydrotestosterone) receptor sites in the androgen-dependent target organs, that is, it shields the prostate from the effect of androgens originating from the gonads and/or the adrenal cortex. Immediate antiandrogen therapy controls tumor invasion and reduces the risk of recurrence in patients with node-positive prostate cancer after radical prostatectomy, and improves survival, yet cardiovascular complications are well recognized side-effects of hormonal therapy in men with prostate cancer.[1,2] While Wallentin and Varenhorst,[3] as the pioneers, studied the effect of CPA on plasma lipids and lipoproteins, this present paper further investigated the effect of the prolonged CPA treatment on the changes in plasma lipoprotein profiles and its related mechanism to induce cardiovascular disease.

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Materials and methods

Subjects

Volunteer patients aged 55–67 years (average age 60 years) were included in the study, which was

approved by the institutional committee for human studies. Thus 48 patients who refused to accept radical prostatectomy or radiation therapy were recruited consecutively from among men referred for treatment of low risk prostate cancer (The clinical stage was $T1cN_0M_0$, the Gleason scores were between 2 and 5, and the PSA level ranged 5.7–17.7 ng/mL). None of the patients had ever had liver or renal dysfunctions, diabetes mellitus, or hypertension (blood pressure <140/90 mmHg) before. More importantly, none of them had a cardiac infarct in the past. A majority of patients had maintained normal activity.

Study protocol

The 48 patients were pooled and unclassified for the plasma analysis from the start, since previous results indicated that the plasma lipids, lipoproteins, and apolipoproteins in patients stratified according to the extent of disease were not different.[4] They were not asked to change their diet. Twenty-four volunteers were assigned to Group 1 (the control group) and received placebo glucose in a total of 200 mg per day, while the remaining 24 patients (group 2) were given CPA (total 200 mg daily b.i.d. p.o., or two tablets [50 mg/tablet] twice daily = 200 mg) after meals. All the subjects were then followed consistently every 3 months, and the final analyses were performed with their blood sampled after 2.5 years of treatment. The plasma analyses were carried out to examine the plasma lipid, lipoprotein, phospholipids, triglyceride, and apolipoprotein (apo-) A-I, A-II, and B-100 profiles. In the second part of study, all patients were examined with an electrocardiogram (ECG) every 3 months to serve as the preconfirmatory examination. Those who had shown extraordinary hypertension with sudden vertigo and feelings of difficulty breathing, being suspected to have coronary artery disease (CAD) or atherosclerosis, were requested to receive further confimatory examinations.

Laboratory analytical methods

Analyses of plasma lipids and lipoproteins

Briefly, morning blood samples were taken after at least 12 h fasting immediately before the start of treatment. The two groups were followed up continuously every 3 months, and finally resampled after 2.5 years of treatment. Blood was collected from an antecubital vein into evacuated tubes with 1.2 mg/mL K_3-EDTA (for lipid and lipoprotein measurements) and heparin (for steroid analyses). The tubes were immediately cooled in ice water. Plasma was separated at 4°C and stored at this temperature until analyzed. All lipoprotein analyses were started within 4 days of obtaining the samples. Aliquots of plasma were stored at −70°C and thawed immediately before other analyses. The very low density (VLDL), low density (LDL), and high density lipoprotein (HDL) fractions were separated by ultracentrifugation at hydrated density 1.006 and heparin-manganese chloride precipitation in accordance with the Lipid Research Clinics Program.[5] Triglyceride (TG) concentrations in plasma, VLDL, and in the combined LDL and HDL fractions were determined by an enzymatic method.[6] Phospholipid (PL) concentrations were determined in plasma and in the LDL and HDL fractions by phosphorus quantification in lipid extracts.[7] Cholesterol (C) concentrations in plasma and the lipoprotein fractions were determined enzymatically.[8] Apolipoprotein B-100, A-I, and A-II levels were assayed using double antibody RIAs. Intraassay coefficients of variation were less than 7%. All samples from a particular study were analyzed in the same assay.

Preconfirmatory examination

Electrocardiogram

All patients were consistently and directly measured with ECG instrument every three months.

Confirmatory examinations

Two kinds of examinations were performed for confirmation of arteriosclerotic heart diseases, that is:

1 Brain Magnetic Resonance Imaging (MRI); and
2 The Stress/Redistribution Thallium Perfusion SPECT Study:

Following the intravenous injection of 9.25×10^7 Bq of ^{201}TlCl after intravenous administration of dipyridamole 0.56 mg/kg (Boehringer, Ingelheim, Germany), SPECT imaging of heart was perfumed using a Siemens Electron CAM gamma camera (Siemens, Hoffman Estates, IL). Single photon emission tomograms were reconstructed in horizontal and vertical long axis as well as short axis projections. Bullseye analysis was performed on the resultant sets.

Statistical analysis

The paired *t*-test was used to test the significance of differences among the various groups; $P \leq 0.05$ was taken to indicate significant unless stated otherwise.

Results

Plasma lipid analysis

Prolonged CPA administration significantly decreased the levels of HDL-C (from 44.7 ± 4.8 to 35.1 ±4.2 mg/dL), Apo A-I (from 92.3 ± 6.7 to 80.5 ± 4.0 mg/dL), and Apo A-II (from 41.2 ±2.7 to 33.7 ± 2.6 mg/dL), and in the same period, significantly increased level of VLDL-TG (from 76.8 ± 9.2 to 85.2 ±8.3 mg/dL); in contrast, increased levels yet without significance were found for LDL-C (from 148.6 ± 9.5 to 155.6 ± 4.4 mg/L) and LDL Apo B-100 (from 98.4 ± 7.0 to 103.7 ± 5.4 mg/dL). Phospholipid levels remained unchanged (Table 1). In the CPA-treated group, four patients were found to be afflicted with CAD after 2.5 years of treatment; significant ($P < 0.05$) changes in mean phospholipids profiles were noted which involved the increased triglycerides in VLDL (Fig. 1a), and the decreased Apo-A I, Apo-A II, and cholesterol in HDL (Fig. 1c). In contrast, values of cholesterol and Apo-B-100 remained almost unchanged (Fig. 1b).

Findings from ECG

The 12-lead resting ECG examination was applied every 3 months in each group. After a period of 2.5 years observation, all patients except four in Group 2 who showed abnormal localized T waves, showed

Table 1 Effects of prolonged antiandrogenic treatment on plasma lipoprotein-lipid and apolipoprotein (Apo) profiles in 24 men with prostate carcinoma*

	Group 1	Group 2	*P*
VLDL			
Cholesterol, mg/dL	17.6 ±2.0	16.0 ±2.2	NS
Triglyceride, mg/dL	76.8 ±9.2	85.2 ±8.3	<0.05
Apo B-100, mg/dL	19.2 ±1.8	20.5 ±4.1	NS
LDL			
Cholesterol, mg/dL	148.6 ±9.5	155.6 ±4.4	NS
Apo B-100, mg/dL	98.4 ±7.0	103.7 ±5.4	NS
HDL			
Cholesterol, mg/dL	44.7 ±4.8	35.1 ±4.2	<0.05
Phospholipids, mg/dL	94.2 ±4.3	96.5 ±3.9	NS
Apo A-I, mg/dL	92.3 ±6.7	80.5 ±4.0	<0.05
Apo A-II, mg/dL	41.2 ±2.7	33.7 ±2.6	<0.05

*Values are expressed as (mean ± SD) mg/dL.

Confidence level $P < 0.05$. NS, non-significant; Group 1: control ($n = 24$) with placebo glucose; Group 2: CPA (cyproterone acetate)-treated ($n = 24$), treatment period: 2.5 years for all patients without any combined surgery or radiation therapy.

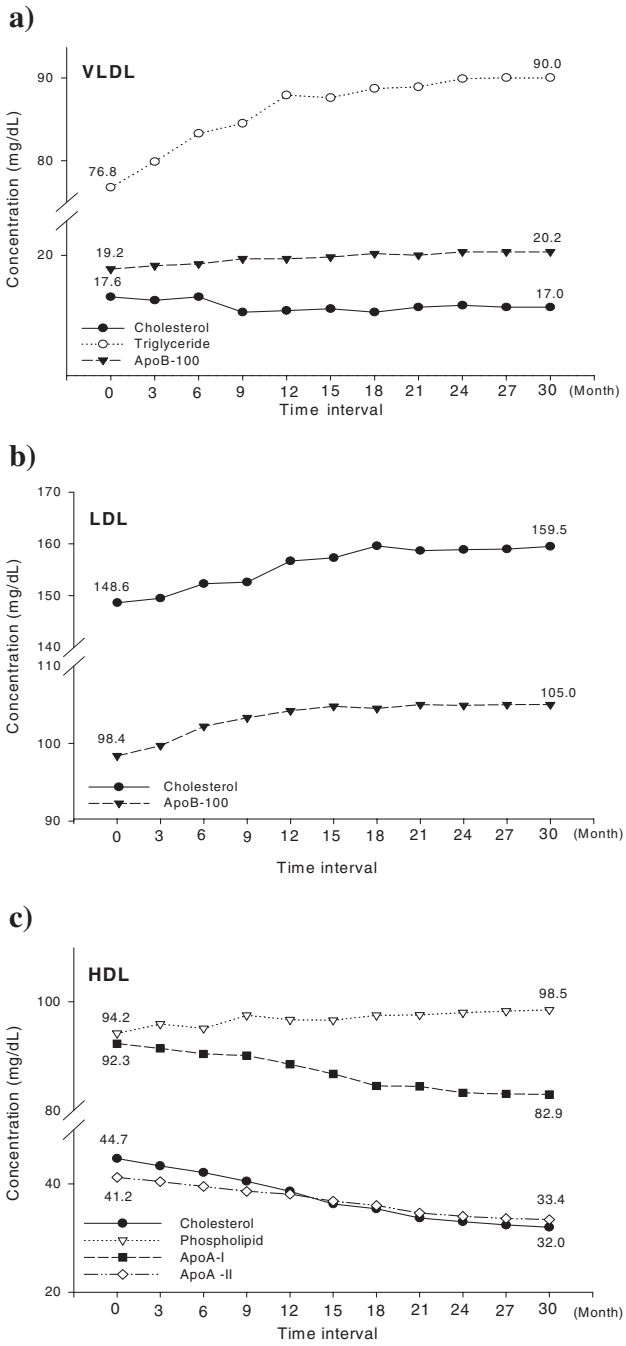

Fig. 1 The mean phospholipids profile change in the four patients with CAD post CPA treatment. (a) the profiles of triglycerides, ApoB-100, and cholesterol in VLDL. (b) the profiles of cholesterol and ApoB-100 in LDL. (c) the profiles of phospholipids, ApoA-I, ApoA- II, and cholesterol in HDL.

normal ECG patterns just like those before the CPA therapy (figures not shown here).

Findings from brain MRI

From every 3-monthly follow up, 4 out of 24 patients were suspected to have coronary heart diseases from the ECG diagnosis. After 2.5-year administration of CPA, two of them with the symptom of vertigo were shown to have the risks for atherosclerotic heart disease (ASHD): hypertension, hypercholesterolemia and dizziness, while the other two patients were found to have severe occasional heart attacks with sensation of shortness of breath. Hence the four patients immediately received MRI examinations. Results from the MRI scanning revealed that A292 cerebral artery occlusion had occurred with unspecified causes in the two patients (figures not shown here), suggestive of 'cerebral artery occlusion, unspecified', and afterwards, ASHD was confirmed to have occurred at 2.5 years post CPA treatment, the other two were specified to have a distinct coronary occlusion (figures not shown here).

The stress/redistribution thallium perfusion SPECT study

The stress images demonstrated in two patients, after having received CPA therapy for a period of 2.5 years, a state of moderate ischemia in the inferoapical wall, mild ischemia in the inferolateral and severe ischemia of infarct in the inferobasal wall (figure not shown here).

Discussion

Post CPA treatment, HDL-C, Apo A-1, and Apo A-II levels were all found to have significantly decreased. In contrast, no significant differences in phospholipid and LDL ApoB-100 levels were seen (Table 1), a result consistent with that of Moorjani *et al*.[9] that HDL-C level is known to be an important negative risk factor for coronary heart disease, in contrast with a weaker association with LDL cholesterol. Hypercholesterolemia, including HDL-C[9] (Table 1) plus LDL-C[9] (Table 1), and ApoB-100[9] together are well-known strong determinants for cardiovascular disease for both men and women, but actually, delicate variations of the individual plasma lipoproteins are proven to be related to the development of ischaemic cardiovascular disease and can be brought about by hormonal treatment.[3,10,11]

As revealed in Table 1, CPA still conserves some partial androgenic activity.[12] The variation of high VLDL-TG and low HDL-C levels (Table 1) was in good agreement with the well-known inverse relationship as indicated by Wallentin and Varenhorst.[3] These changes, if maintained for a prolonged period, would increase the risk of cardiovascular disease[1,2,10] as is evidenced in this study with an incidence rate of 16.6% (Fig. 1; the ECG and MRI scannings, and the Stress/Redistribution Thallium Perfusion SPECT Study). Contemporary basic research demonstrated that cardiovascular toxicity occurred in 10% to 30% of patients after hormonal treatment, with events including deep vein thrombosis, myocardial infarction, transient ischemic attack, edema and gynecomastia.[2] In terms of significant cardiovascular side-effects, there were significant differences among treatment groups administrating Diethylstilbestrol (DES; 3 mg/day, $n = 239$) compared with CPA and medroxyprogesterone acetate. The DES patients experienced a 9.6% rate of thrombolic events, 2.7% of which were lethal. The rate of thrombolic events in other research ($n = 226$) with treatment of either DES or estramustine phosphate was 17%, with 16% of those being lethal.[1,2] Similar studies by Schroder[13] indicated that DES at a dosage of 3 mg/day carries a significantly higher risk of overall cardiovascular toxicity than does CPA, but severe cardiovascular complications did not differ between the two groups. Long-term androgen deprivation therapy can also result in several changes, including hot flashes, gynecomastia, osteoporosis, anemia, psychiatric and cognitive problems, and fatigue and diminished quality of life.[14]

Within the liver, ovaries, testes, and adrenals, some components of HDL are removed by a process depending on binding of the accepting lipoprotein to the cell surface which is mediated by the class B, type I scavenger receptor (SRBI). SRBI is responsible for the hepatic removal of mature forms of HDL, and may have both pro- and anti-atherogenic effects that are a function of the level of expression, a fact indicating that pathways other than those involving HDL may be affected,[15] suggesting that any anti-atherogenic therapies must be capable of up-regulating the pathway. Part of the anti-atherogenic effect of SRBI may occur through the removal of atherogenic lipids that have accumulated in HDL by direct transfer from the arterial wall via the ATP-binding cassette transporter A1 (ABCA1) or by transfer from the apo-B-containing lipoproteins.[15] Hence cyproterone acetate is expected to enhance the down-regulation of this pathway.

CPA is as effective as estrogen therapy and has a better side-effect profile, although cardiovascular and hepatic side-effects are still of concern. Compared with flutamide, in a recently completed EORTC study, side-effects such as gynecomastia, diarrhea, nausea, and liver

function deterioration occurred less often, and thrombotic effects more often, in the CPA group.[16] The latter effect has been confirmed in this study. Elsewhere a report demonstrated that CPA may be used to suppress the hot flushes associated with orchiectomy or LHRH agonist therapy;[17] however in our study, during the whole investigation, no patient was noted with flushes. Actually, the adverse effects associated with CPA are mostly those related to hormone withdrawal, among which cardiovascular complications were found in approximately 10% of treated men,[18] further strong evidence for our observation. Smith[19] and later a review by Higano[20] reported in 32 evaluable subjects with body weight increasing by 2.4 ± 0.8%, fat body mass increasing by 9.4 ± 1.7%, and lean body mass decreasing by 2.7 ± 0.05%. In addition, total cholesterol concentrations increased by 9.0 ± 2.1%, with serum triglycerides increased by 26.5 ± 10%.[19] These changes were associated with increases in insulin levels and an increase in central arterial pressure, suggesting large artery stiffening and increased risk of developing cardiovascular disease.[21] Our study with the CPA-treated group showed increases of body mass index (BMI) by 2.6 ± 0.7%, fat mass by 8.6 ± 2.1% (data not shown), which were consistent with that previously reported.

We confess that there should have been a more cautious survey on the pathological examination on a larger population, in order to assure a thorough and complete dataset. However, at the outpatient department (OPD), some patients were rather difficult to follow up and only those who had relatively severe symptoms came to OPD. By referring the data from the biochemical examinations, we could only roughly concluded four cases in Group 2 subjects being suspective of CAD. We really did not know whether this rate should be increasing or decreasing.

In conclusion, prolonged cyproterone acetate administration can lead to the risk of cardiovascular complications. In treatment of prostate cancer, a compromise between the use and the non-use of antiandrogens and, in addition, whether to prescribe other adjuvant therapy is a very difficult decision for the physician to make.

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