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# Short term effects of spironolactone on blood lipid profile: a 3-month study on a cohort of young women with hirsutism

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Spironolactone is known to have antiandrogenic features and agonist activity at progesterone receptors, which are responsible for several of its hormonal side-effects.
- The potential unfavourable influences of this medication on serum lipoproteins have long been a concern but literature lacks sufficient data on this issue.

## WHAT THIS STUDY ADDS

- Spironolactone can adversely affect serum lipids by decreasing high-density lipoprotein and increasing low-density lipoprotein in women treated for hirsutism on a short-term basis.

## AIMS

To investigate the effects of spironolactone on serum lipids in women with hirsutism over a 3-month period.

## METHODS

In a prospective setting, 27 hirsute women (20 with polycystic ovary syndrome and seven with idiopathic hirsutism) with a mean age of 23.0 ± 5.1 years were studied at baseline and 3 months after receiving a daily dose of 100 mg of spironolactone. Patients did not receive any other medications and did not go through a specific diet during the study. Lipid profile, fasting blood glucose, testosterone, dehydroepiandrosterone sulphate (DHEAS) and prolactin (PRL) were measured at baseline and 3 months after therapy.

## RESULTS

Mean body mass index of patients was 26.1 ± 5.1 kg $m^{-2}$ before treatment and 25.9 ± 5.7 kg $m^{-2}$ after treatment (NS). The therapy was associated with a significant decline of mean high-density lipoprotein (HDL), 39.5 mg $dl^{-1}$ [95% confidence interval (CI) 35.6, 43.4] *vs.* 32.2 mg $dl^{-1}$ (95% CI 29.2, 35.2), and a significant increase in mean low-density lipoprotein (LDL), 133.1 mg $dl^{-1}$ (95% CI 120.2, 146) *vs.* 150.8 mg $dl^{-1}$ (95% CI 139.1, 162.5), and cholesterol/HDL ratio, 5 (95% CI 4.4, 5.6) *vs.* 6.4 (95% CI 5.7, 7.1) ($P < 0.05$). No significant change was noted in total cholesterol, triglyceride or fasting blood glucose levels. Serum values of testosterone, DHEAS and PRL decreased significantly after 3 months of therapy ($P < 0.05$).

## CONCLUSIONS

Spironolactone might have adverse effects on serum lipoprotein levels by increasing LDL and decreasing HDL over a short course of treatment. While treating hirsutism with spironolactone, special care should be given to women with metabolic disorders such as dyslipidaemia.

## Introduction

Initially developed as an aldosterone-blocking diuretic, spironolactone is now frequently used for the treatment of hirsutism. Several adverse effects have been reported with this 21-carbon steroidal compound, namely, hyperkalaemia, gynaecomastia, impotence, gastritis, and menstrual irregularity. The hormonal side-effects of spironolactone have been attributed to its antiandrogenic features and its affinity for the progesterone receptor [1].

Theoretically, the agonist activity of spironolactone at progesterone receptors can result in progestin-like effects on blood lipids, decreasing high-density lipoprotein (HDL) and increasing low-density lipoprotein (LDL). In our experience, we have noted that a dosage of 100 mg $day^{-1}$ of spironolactone may adversely affect the lipid profile of women with hirsutism. In this prospective study, we examined changes in serum lipid levels after 3 months' treatment with spironolactone.

## Methods

Fifty-three women were recruited from subjects referred to the Endocrine Clinic of Vali-Asr Hospital (a university referral centre, Tehran, Iran) for the treatment of hirsutism during 2006. We did not include subjects with primary hypothyroidism, nephrotic syndrome, Type 1/2 diabetes mellitus, or chronic liver disease, those receiving hormone replacement therapy or lipid-lowering drugs, or nursing mothers. Twenty-six women were lost to follow-up due to frequent menorrhagia, drug allergy, planning for pregnancy, and reluctance to continue follow-up owing to non-medical reasons such as difficulty in commuting to the hospital. Thus, 27 women were enrolled and studied for 3 months. Twenty subjects had polycystic ovary syndrome (PCOS) and seven had idiopathic hirsutism. Each patient received an average daily dose of 100 mg spironolactone for at least 3 months. Subjects did not receive any other medications and were not advised to go through any special diet during the study. Also, studied patients did not become pregnant during the study and they agreed to use only barrier methods of contraception.

The diagnosis of PCOS was based on the physical features of hyperandrogenism, disturbed menstrual cycles, elevated serum luteinizing hormone (LH) or LH/follicle stimulating hormone ratio, increased levels of serum testosterone and/or androstenedione and no evidence of ovarian or adrenal neoplasm or Cushing's syndrome [2]. Idiopathic hirsutism was considered in patients with regular ovulatory cycles (luteal phase progesterone levels > 12 nmol $l^{-1}$), normal androgen levels, and without any known underlying disease.

Two fasting blood samples were obtained from each patient after an overnight fast of 12 h: before initializing treatment and 3 months after therapy. The following biochemical parameters were determined: fasting blood sugar (FBS), triglyceride, total cholesterol (TC), LDL, HDL, testosterone, prolactin (PRL) and dehydroepiandrosterone sulphate (DHEAS). Enzyme colorimetric method (Pars Azmoon, Tehran, Iran) was used to determine lipid levels, glucose oxidase-peroxidase method (Nicholas-Piramal India Ltd, Mumbai, India) to measure FBS, commercial radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA, USA) to determine testosterone and DHEAS levels, and PRL was measured through immunoradiometric assay (Medicorp Inc., Montreal, Canada). Sensitivity, specificity, interassay and intra-assay coefficients of variation were within the prescribed limits given in the manufacturer's protocol.

The study protocol was approved by the Ethics Committee of Vali-Asr Hospital and written informed consent was obtained from each participant. SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) was applied to perform statistical analyses. Student's *t*-test for paired data was used to compare means. $P < 0.05$ was considered to indicate statistical significance.

## Results

Mean age of patients was 23.0 ± 5.1 years (range 10–39 years) and they had had hirsutism for an average of 3.3 ± 2.2 years (range 1–10 years). No significant change was noted in mean body mass index of patients before and after treatment (26.1 ± 5.1 and 25.9 ± 5.7 kg $m^{-2}$, respectively; NS). There was a significant decline in mean HDL [39.5 ± 10.3 mg $dl^{-1}$, 95% confidence interval (CI) 35.6, 43.4 *vs.* 32.2 ± 7.9 mg $dl^{-1}$, 95% CI 29.2, 35.2] and a significant increase in mean LDL (133.1 ± 34.2 mg $dl^{-1}$, 95% CI 120.2, 146 *vs.* 150.8 ± 31.0 mg $dl^{-1}$, 95% CI 139.1, 162.5) and cholesterol/HDL ratio (5 ± 1.5, 95% CI 4.4, 5.6 *vs.* 6.4 ± 1.9, 95% CI 5.7, 7.1) before and after treatment, respectively ($P < 0.05$). Table 1 displays pre- and post-therapeutic levels of biochemical parameters.

### Table 1

Comparison of biochemical parameters before and after treatment with spironolactone in 27 women with hirsutism

| Parameter† | Normal range | Before treatment | After treatment |
|---|---|---|---|
| **FBS (mg $dl^{-1}$)** | 76–109 mg $dl^{-1}$ | 86.5 ± 19.9 | 79.1 ± 9.1 |
| **TG** | <150 mg $dl^{-1}$ | 81.8 ± 31.6 | 83.8 ± 38.5 |
| **TC** | <200 mg $dl^{-1}$ | 188.9 ± 38.3 | 199.8 ± 33.7 |
| **HDL (mg $dl^{-1}$)*** | >35 mg $dl^{-1}$ | 39.5 ± 10.3 | 32.2 ± 7.9 |
| **LDL (mg $dl^{-1}$)*** | <130 mg $dl^{-1}$ | 133.1 ± 34.2 | 150.8 ± 31.0 |
| **TC/HDL*** | <5 | 5.0 ± 1.5 | 6.4 ± 1.9 |
| **Testosterone*** | 0.2–0.9 ng $ml^{-1}$ | 0.87 ± 0.5 | 0.70 ± 0.4 |
| **DHEAS*** | 65–380 µg $dl^{-1}$ | 327.1 ± 145.5 | 238.5 ± 143.6 |
| **PRL*** | <400 mU $l^{-1}$ | 349.6 ± 166.3 | 267.0 ± 172.8 |

*Significant difference ($P < 0.05$) before and after treatment. †Values are expressed as mean ± SD. FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRL, prolactin; TC, total cholesterol; TG, triglyceride; DHEAS, dehydroepiandrosterone sulphate.

**Table 2**

Findings of some recent studies regarding the effect of spironolactone on serum lipids

| Study | Dose/treatment duration (months) | Number of patients and their condition | Effect(s) of spironolactone |
|---|---|---|---|
| **Scherstén *et al.* (1980) [10]** | 50–200 mg/2 | 45 with HTN | Increased TG |
| **Falch and Schreiner (1983) [5]** | 100 mg/12 | 15 with HTN | No effect on TC and LDL; decreased TG and HDL |
| **Ames and Peacock (1984) [11]** | 2–4 | 11 with HTN | Decreased TG and TC |
| **Jeunemaitre *et al.* (1987) [6]** | ~100 mg/23 | 182 with HTN | Increased TG. No effect on TC |
| **Wild *et al.* (1991) [12]** | 200 mg/9 | 51 with hirsutism | No effect on serum lipids |
| **Garcá Puig *et al.* (1991) [13]** | 144 mg/12 | 22 with HTN | No effect on serum lipids |
| **Gökmen *et al.* (1996) [14]** | 100–200 mg | 12 with hirsutism | Increased HDL |
| **Zulian *et al.* (2005) [7]** | 100 mg/12 | 25 with PCOS | TG declined in overweight subjects and HDL increased in the lean |

HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; PCOS, polycystic ovary syndrome; TC, total cholesterol; TG, triglyceride.

## Discussion

The utility of spironolactone in the treatment of hirsutism depends on its capacity to compete with dihydrotestosterone for binding to the androgen receptor and its minor inhibitory effect on 5α-reductase. Besides, spironolactone inhibits cytochrome P450 enzymes involved in ovarian and adrenal steroidogenesis, resulting in decreased levels of testosterone and androstenedione [3]. As expected, the present study showed a decrease in the levels of total serum testosterone and DHEAS. Regarding the decline in PRL, our finding is also supported by previous authors [4]. Concerning FBS levels, we did not detect any significant change after therapy, which is supported by several previous studies [5–7].

Spironolactone has been shown to increase blood levels of oestradiol by increasing peripheral conversion of testosterone into oestradiol [8]. Considering the known favourable effects of oestrogens on lipid profile, it is interesting that the alterations of serum lipoproteins in our patients are in accordance with the effect of progesterone on HDL and LDL [9]. Therefore, it is tempting to attribute such changes in serum lipids to the progestagenic activity of spironolactone.

In medical literature, there is little evidence of the possible unfavourable effects of spironolactone on lipid profile in hirsute women. Besides, results of the few available studies are not consistent, probably due to variability in sample sizes, dose and duration of treatments, and different combination therapies (Table 2). It is worth emphasizing that our patients received merely spironolactone and did not experience any significant change in weight during the study. Therefore, the changes in serum lipids cannot be related to any other factor except spironolactone. Nonetheless, this study is rather limited in terms of being noncontrolled (no placebo group) and nonrandomized, its high drop-out rate and relatively small sample size and short duration.

Regarding the significant increase in TC/HDL ratio in our patients, whether this unfavourable finding has any clinical relevance respecting atherosclerosis cannot be answered by our short-term study. In the RALES trial on severe heart failure patients, Pitt *et al.* showed that 25 mg of spironolactone could significantly improve symptoms of cardiac failure and survival [15]. Considering dose and duration of therapy and nature of patients, it is obvious that one cannot compare results of our study with the RALES trial. As regards to practical implications of our study, changes noted in LDL and HDL might be transient and be encountered only in the short term and, thus, this study is not an argument against the use of spironolactone in young hirsute women.

In conclusion, a daily dose of 100 mg of spironolactone may have adverse effects on the lipid profile of women with hirsutism via decreasing HDL and increasing LDL. Treatment strategies with spironolactone need to consider its metabolic consequences, particularly in subjects with baseline metabolic disorders and dyslipidaemia.

## Competing interests

None to declare.

## REFERENCES


1 Garthwaite SM, McMahon EG. The evolution of aldosterone antagonists. Mol Cell Endocrinol 2004; 217: 27–31.

2 Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Polycystic Ovary Syndrome, eds Dunaif A, Givens JR, Haseltine F. Boston, MA: Blackwell Scientific, 1992; 377–84.

3 Searafini P, Lobo RA. The effects of spironolactone on adrenal steroidogenesis in hirsute women. Fertil Steril 1985; 44: 595–9.

4 Milewicz A, Silber D, Kirschner M. Therapeutic effects of spironolactone in polycystic ovary syndrome. Obstet Gynecol 1983; 61: 429–32.

**5** Falch DK, Schreiner A. The effect of spironolactone on lipid, glucose and uric acid levels in blood during long-term administration to hypertensives. Acta Med Scand 1983; 213: 27–30.

**6** Jeunemaitre X, Chatellier G, Kreft-Jais C, Charru A, DeVries C, Plouin PF, Corvol P, Menard J. Efficacy and tolerance of spironolactone in essential hypertension. Am J Cardiol 1987; 60: 820–5.

**7** Zulian E, Sartorato P, Benedini S, Baro G, Armanini D, Mantero F, Scaroni C. Spironolactone in the treatment of polycystic ovary syndrome: effects on clinical features, insulin sensitivity and lipid profile. J Endocrinol Invest 2005; 28: 49–53.

**8** Satoh T, Itoh S, Seki T, Itoh S, Nomura N, Yoshizawa I. On the inhibitory action of 29 drugs having side effect gynecomastia on estrogen production. J Steroid Biochem Mol Biol 2002; 82: 209–16.

**9** Fernandes CE, Pompei LM, Machado RB, Ferreira JA, Melo NR, Peixoto S. Effects of estradiol and norethisterone on lipids, insulin resistance and carotid flow. Maturitas 2008; 59: 249–58.

**10** Scherstén B, Thulin T, Kuylenstierna J, Engström M, Karlberg BE, Tolagen K, Nordlander S, Nilsson G. Clinical and biochemical effects of spironolactone administered once daily in primary hypertension. Multicenter Sweden study. Hypertension 1980; 2: 672–9.

**11** Ames RP, Peacock PB. Serum cholesterol during treatment of hypertension with diuretic drugs. Arch Intern Med 1984; 144: 710–4.

**12** Wild RA, Demers LM, Applebaum-Bowden D, Lenker R. Hirsutism: metabolic effects of two commonly used oral contraceptives and spironolactone. Contraception 1991; 44: 113–24.

**13** Garcá Puig J, Miranda ME, Mateos F, Herrero E, Lavilla P, Gil A. Hydrochlorothiazide versus spironolactone: long-term metabolic modifications in patients with essential hypertension. J Clin Pharmacol 1991; 31: 455–61.

**14** Gökmen O, Senöz S, Gülekli B, Işik AZ. Comparison of four different treatment regimes in hirsutism related to polycystic ovary syndrome. Gynecol Endocrinol 1996; 10: 249–55.

**15** Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341: 709–17.