HEALTH RESORT TREATMENT IMPROVED THE NEUROSTEROID PROFILE IN THYROIDECTOMIZED WOMEN

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Objective: The aim was to study the effect of climatotherapy and spa treatment on selected neuro- and immunomodulatory steroids known to affect well-being, and homocysteine, in a homogenous group of thyroidectomized women under standard substitution regime.

Methods. Dehydroepiandrosterone, its precursors and metabolites, cortisol, major sex steroids, SHBG, and homocysteine were measured before and after three-weeks stay in a health resort Jeseník (Graefenberg) in Czech Republic. The studied group consisted of 21 women after total thyroidectomy which was performed at least 3 months before the admission to the spa resort. All patients received thyroid hormone substitution treatment which was not changed during their stay in that resort.

Results. Out of the steroids investigated, five, namely dehydroepiandrosterone, androstenedione, testosterone, 7β-hydroxy-dehydroepiandrosterone and cortisol were changed significantly after treatment. The most considerable was the decrease of cortisol and of homocysteine ($p < 0.000$ each).

Conclusion. Spa resort treatment of thyroidectomized women substituted with thyroid hormones resulted in significant, mostly beneficial effects on steroid spectrum. This effect was achieved without any use of psychopharmacs.

Key words: Balneotherapy – Neurosteroids – Thyroidectomy

It is generally accepted that regular spa regime including rational and controlled diet, sufficient sleep and as much as possible avoidance of stress situations may improve many clinical and biochemical parameters and well-being (STRAUSS-BLASCHE et al. 2000).

The past decades brought a number of evidence, but also discussions, on beneficial effects of dehydroepiandrosterone (DHEA) as a neuroprotective, cardioprotective, antidiabetic, antiobese, anticancerogenic agent, and on its overall positive influence on well-being; for recent reviews see e.g. (FRIESS et al. 2000; ALLOLIO and ARLT 2002; SCHUMACHER et al. 2003; TCHERNOF and LABRIE 2004). In many instances these effects are based on its immunomodulatory properties and its ability to counteract the excessive effects of glucocorticoids (KALIMI et al.1994; DILLON 2005; BAUER 2005). Recent reports demonstrate that some DHEA metabolites, namely its 7-hydroxylated products may be in some instances even more effective as immunoprotective and neuroprotective substances than DHEA itself (MORFIN 2002; TRINCAL et al. 2002).

Here we focused especially on the effect of climatotherapy and spa treatment on the above mentioned steroids, the major stress steroid hormone cortisol, and also on main sex steroid hormones. In addition the levels of homocysteine were measured, as an independent risk factor involved in pathogenesis of cardiovascular diseases (DE BREE et al. 2002).

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The study was performed in a group of thyroidectomized women substituted with thyroid hormones, who entered the spa resort (Priessnitz, Jeseník – Gräfenberg) at the earliest 3 months after operation, and underwent the three-weeks spa therapy for various psychical disorders. From the point of view of the homogeneity, such a group may represent a suitable model for investigation of the effect of balneotherapy on the above mentioned hormonal parameters.

Materials and Methods

Subjects. The investigated group consisted of 21 women aged 25-66 (mean 42.9) years after total thyroidectomy for Graves-Basedow thyreotoxicosis confirmed histologically. Among them, 19 were in fertile age and two were postmenopausal. All of them were 3-5.5 months (mean 3.6) after the operation. They all were on a standard substitution regime set up by the hospital physician, receiving substitution treatment by L-thyroxine either by Letrox (BerlinChemie, Berlin, FRG) or Euthyrox (Merck, Darmsatdt, FRG) which was not changed during their stay in the spa resort. None of them received any other medicaments including antipsychotic drugs. Exclusion criteria were: malignity within the last five years, chemotherapy or radiotherapy in personal history, corticoid treatment, cardiovascular diseases and bronchial asthma. Four women from originally 25 did not meet these criteria and were excluded from the study.

On the day of admission and during the stay in the spa resort they underwent a standard clinical examination by an internist, neurologist, psychiatrist (including a battery of psychological tests based on filling of various questionnaires), rehabilitation physician and kinesiotherapist, cardiology investigation and basic laboratory and hematology tests.

The study was approved by the Local Ethical Committee of the Priessnitz Spa Resort and the Local Ethical Committee of the Institute of Endocrinology. All women signed a written informed consent with including into the study, provided that their anonymity was guaranted.

Spa regime. All women were accepted to the spa resort (Priessnitz, Jeseník – Gräfenberg) on the same day and dismissed on the same 21st day. They all were accommodated in the same spa house of the same category and were given rational food (a full-value easily digestible diet with common representation of major components, i.e. 15 % proteins, 30 % fats, 55 % sacharides and sufficient amount of vitamines, 9500 kJ/day). They were motivated not to eat any additional food to prevent any undesired weight gain. They underwent the same basic treatment regime for indication status after thyroidectomy (characterized by neurasthenia, secondary depression or anxiety and vegetative imbalance), which included especially:

- three times a week a group light physical exercise in a gymnasium,
- twice a week a group hydro-kinesio therapy in a rehabilitation water pool,
- five times during the stay a complete herb bath,
- daily climatotherapy – a 2 h walk in terrain on marked foot-paths under gradual increase of load from 2 to 8 km with a physiotherapist,
- daily phototherapy with a polarized polychromatic light focused on the scar.

Hormone analyses. Blood for hormone analyses was collected from cubital vein between 8-9 a.m, on the day of entering the spa resort and then before its leaving. Serum was separated and stored frozen at –20 °C until analyzed.

Thyroid parameters: TSH, normal range 0.27-4.30 mIU/l, fT4, normal range 12.0-22.0 pmol/l) and fT3, normal range 2.8-7.10 pmol/l, were determined by electrochemiluminescent immunoassay (ECLIA) (Roche Diagnostics, Mannheim, Germany, using commercial Elecsys System 2010).

Steroid and other hormonal analyses: Androstenedione (Putz et al. 1982), 7ß-hydroxydehydroepiandrosterone Lapcik et al.1998), its 7α-hydroxyisomer (Lapcik et al. 1999), cortisol (Bicikova et al. 1988), pregnenolone sulfate (Hill et al. 2002), and testosterone (Hampl 1994) were determined by published radioimmunoassays (RIA) developed in the author´s laboratory. Dehydroepiandrosterone, its sulfate, estradiol, progesterone and 7α-hydroxyprogesterone were measured by commercial RIA kits from Immunotech (Czech Division, Marseille, France), lutropin (LH), folitropin (FSH) and sex hormone-binding globulin (SHBG) by IRMA kits from the same manufacturer. In all the latter instances the STRATEC analyzer from Immunotech was used. Free testosterone index (IFT) was calculated as the ratio of total testosterone * 10 and total SHBG.

Homocysteine (physiological levels up to 15 mmol/l) was determined by a gas chromatographic method according to Tallova et al. (1999)

Statistical evaluation. The differences in measured parameters before- and at the end of spa resort treat-

ment were evaluated by analysis of covariance (ANCOVA) using statistical software Statgraphics Plus version 7 (Manugistics Inc., Rockville, MA, USA). The effect of the treatment was evaluated by using a general linear model with repetition, considering the treatment effect and individual subjects as factor variables, and the effect of menstrual cycle (with values 1 and 2 for follicular and luteal phase, respectively) as covariates. In another word, the results represent comparison of the situations before and after treatment after adjustment to actual phase of a menstrual cycle.

Results

Hormonal changes of major sex-steroids, SHBG, DHEA its precursors and metabolites, cortisol, gonadotropins and homocysteine were evaluated in a group of 21 women after total thyroidectomy performed at least 3 months before admission to the spa resort. We have focused on immomodulatory and neuromodulatory steroids. In addition, the major thyroid parameters were followed. In the situation when thyroid hormone levels depended exclusively on the substitution regime, which was not changed during the spa resort treatment, the determination of thyroid hormone levels served only for control purposes. During the stay the average levels of TSH were maintained within the range from 4.11 to 5.05 mIU/l, while fT_4 and fT_3 varied from 19.27 to 19.7, and from 4.10 to 4.27 pmol/l, respectively, without any significant changes.

Among twelve steroids mentioned above, only five, namely DHEA, androstenedione, testosterone, 7β-OH-DHEA and cortisol were changed significantly after treatment, as shown in Figure 1. The most considerable was the decrease of cortisol and, out of non-steroidal parameters, the decrease of homocysteine (in each instance $p<0.0000$). The changes of levels of other steroids were insignificant (data are not given). Determination of LH and FSH served only for adjustment of the results to the phase of menstrual cycle. In addition, Fig. 1 shows also the changes of the ratios of DHEA and both its 7-hydroxylated metabolites to cortisol, and the decrease in free testosterone index.

Discussion

Total thyroidectomy and consequent deep hypothyroidism present a severe intervention into hormonal regulation affecting all hormonal systems. Hypothyroidism is also a risk factor for development of neuropsychic as well as for cardiovascular disorders (Boelaert and Franklyn 2005). A relevant independent marker for the latter is homocysteine. The lack of thyroid hormones, which must be substituted from exogenous sources for the rest of life, does not mean that regulatory mechanisms including thyroid axis itself would not persist.

In our study TSH levels corresponded to a mild subclinical hypothyroidism, but the substitution regime was intentionally not changed during stay in the resort. Thus, patients who were not influenced by endogenous thyroid production and supplied with known doses of thyroid hormones, represent from the point of view of homogeneity a suitable model for investigation of efficacy of treatment regimes on various hormonal and other parameters. The period from thyroidectomy to the beginning of the spa treatment was long enough in comparison to treatment duration. Therefore it could be anticipated that the effects on investigated steroid and homocysteine could be ascribed to the health resort treatment.

Other clinical and laboratory parameters, including a complex examinations by internist, neurologist, cardiologist and psychiatrist, along with basic clinical biochemistry data were followed, too, at admission, during- and at the end of the stay in the spa. The results have been published elsewhere (Jandova et al. 2006). Of interest may be the finding of an improvement of psychic markers (anxiety, phobia, obtrusive ideas etc.) in average by 41.7 % at the end of treatment.

In this paper, however, we confined to the effect of balneotherapy on selected hormonal parameters, first of all on those, known to be tightly associated with well-being as DHEA and some of its metabolites, possessing immunomodulatory and neuromodulatory properties. The major finding was the marked decrease of cortisol from supraphysiological to physiological levels after health resort treatment. It was accompanied by a less significant decrease of unconjugated DHEA, which, nevertheless remained within physiological range for the appropriate age category (Sulcova et al. 1997), and may be due rather to decrease of peripheral sulfatase activity. The more important objective marker of the protective function of immune system and overall well-being is the ratio of DHEA to cortisol, which increased (Purohit and Reed 2002). Of particular importance, however, was the highly significant increase of the ratio of 7-hydroxylated DHEA metabolites to cortisol after treatment (see Fig. 1), since 7-hydroxy-DHEA isomers are believed now not only to be locally

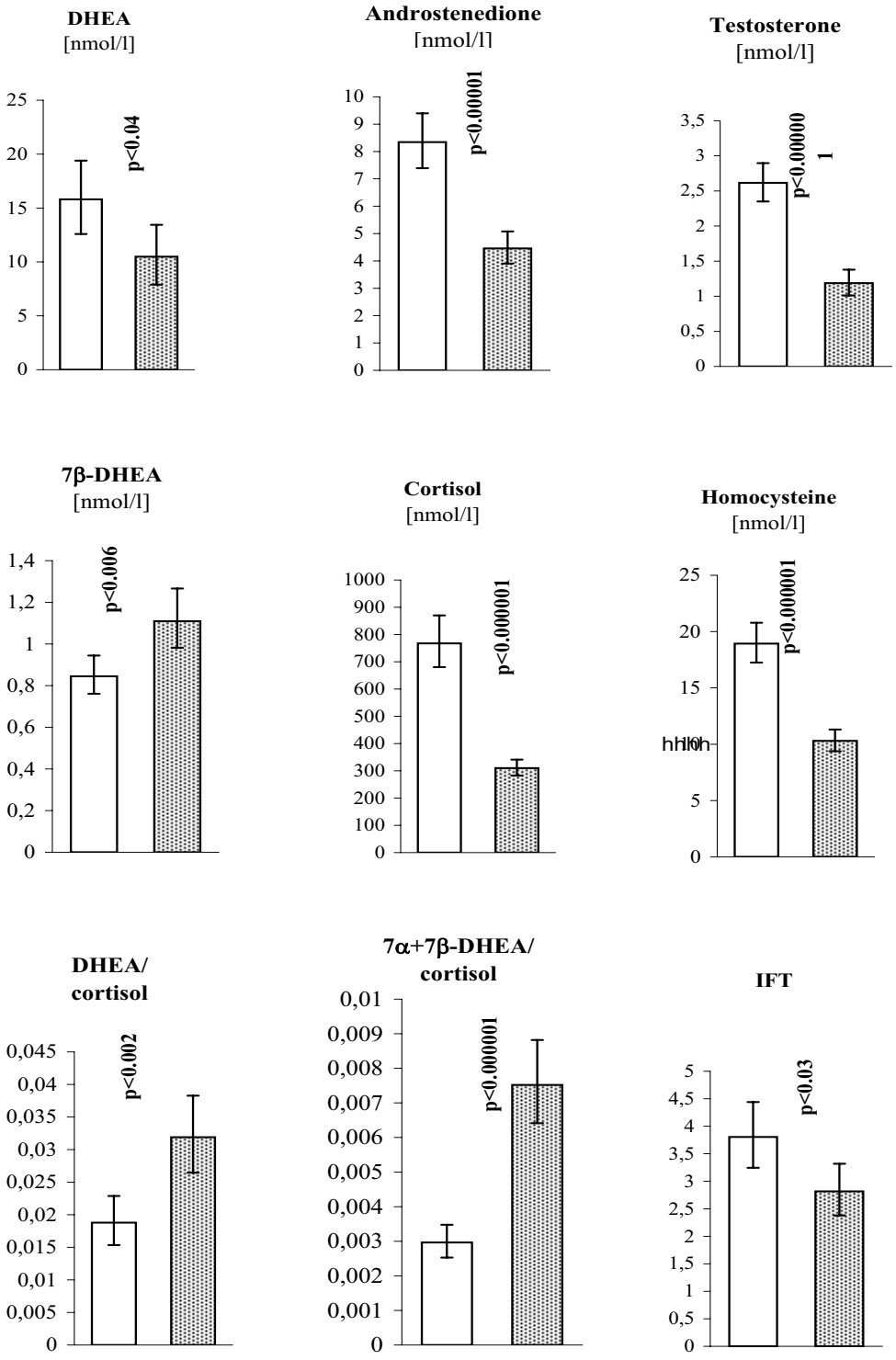

Fig. 1 Effect of 3 weeks spa resort treatment on the levels of dehydroepiandrosterone (DHEA), androstenedione, testosterone, 7β-hydroxy- dehydroepiandrosterone (7b-DHEA), cortisol and homocysteine, and on the ratio of DHEA- and its 7-hydroxylated metabolites to cortisol as well as on free testosterone index (FTI). In premenopausal women significance of the changes was evaluated by analysis of covariance (ANCOVA) after adjustment to the phase of menstrual cycle.
Empty columns: before treatment, full columns: after treatment.

active immunoprotective-, but also neuroprotective agents (Morfin and Starka 2002). All these findings may be interpreted as strengthening of the immunity. Of interest is also the decrease of total as well as free testosterone and especially its precursor, androstenedione, the increased levels of which are typical for hyperandrogenic states.

Finally, the treatment led to a dramatic decrease of homocysteine to physiological levels, in spite of a mild subclinical hypothyroidism of the subjects. Elevated levels of homocysteine are typical for hypothyroid states and this amino acid belongs to links explaining the increased risk of cardiovascular diseases in thyroid disorders (De Bree et al. 2002).

In conclusion, spa resort treatment of thyroidectomized women substituted with thyroid hormones resulted in significant, mostly beneficial effects on steroid spectrum. This effect was achieved without any use of psychopharmacs.

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