

Urinary excretion of insulin after estradiol treatment of postmenopausal women

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Summary

The influence of estradiol treatment on the urinary excretion of insulin was investigated in postmenopausal women. Thirteen women were treated with transdermal estradiol and 12 with oral estradiol for 4 weeks. With transdermal, but not with oral administration, a significant increase of urinary insulin excretion was registered.

Key words: Hormone replacement therapy; Postmenopausal women; Urinary insulin excretion.

Introduction

In previous studies we have measured the urinary excretion of vasoactive substances in estradiol-treated postmenopausal women in order to explore the mechanism of the cardioprotective effect of estradiol. Until now the substances influencing the cardiovascular system that we have investigated comprised prostacyclin and thromboxane [1], cGMP as indicator of NO production [2], serotonin [3], melatonin [4] as well as relaxin [5].

Since the urinary excretion of relaxin was increased after estradiol therapy, it seemed of interest to explore whether insulin, which shares a similar chemical structure with relaxin and also plays a role in cardiovascular processes, acts in a similar way to relaxin.

Material and Methods

Twenty-five postmenopausal women with climacteric symptoms were enrolled in this study. All women had ceased menstruating for at least 12 months. Levels of 17 β -estradiol in serum were below 70 pmol/l and FSH levels above 40 IU/ml.

Hormone replacement therapy (HRT) was started with unopposed estradiol, 13 women receiving it transdermally (Estraderm TTS, 0.05 mg/day) and 12 women orally (estradiol valerate, 2 mg/day) for 4 weeks. The study was open and random allocation not used.

Urine, excreted between 10 pm and 6 am, was collected during two consecutive nights before and then 14 and 28 days after estradiol treatment. Aliquoted specimens were frozen at -20°C pending measurement.

Insulin was determined by a commercial radioimmunoassay. Inter- and intraassay variation coefficients were 9.8% and 8.2%, respectively.

Total estrogens (estrone and estradiol) excreted into the urine were determined as described [6]. Briefly, an aliquot of the urine was incubated for 2 h at 37°C with an enzyme solution (β -glucuronidase/arylsulfatase, Boehringer Mannheim, Germany). The estrogens were then extracted with ether. The aqueous phase was frozen overnight and the organic phase was decanted and evaporated under nitrogen. The concentrations of the estrogens were measured by radioimmunoassay (IBL, Hamburg, Germany). Inter- and intraassay variations were 8.3%

and 5.5% for estradiol and 7.8% and 6.0% for estrone, respectively.

Absolute and relative values were compared to the pretreatment values by the Wilcoxon-Rank-test.

Results

Basic data, of age, height, weight and time since menopause, of both groups are illustrated in Table 1. No significant differences were observed between the groups. In each treatment group there were 6 cigarette smokers (~20 per day). There were 6 women in the transdermal and 4 in the oral estradiol group who consumed alcohol (~1 pint of beer per day). None of the patients had diabetes or took drugs which influenced the glucose metabolism. Clinical data were therefore considered comparable in both treatment groups.

In all examined patients insulin could be detected in the urine. In the transdermal group absolute values for the 8 hour excretions before treatment of 18.5 pmol/8h (SEM 1.4) and after 14 and 28 days of estradiol treatment increased to 25.0 pmol/8h (SEM 2.0) and 25.5 pmol/8h (SEM 2.5). In the oral group the pretreatment values of 28.7 pmol/8h (SEM 4.1) decreased to 23.0 pmol/8h (SEM 3.4) and to 23.8 pmol/8h (SEM 2.3) after 14 and 28 days of estradiol treatment, respectively.

A more meaningful analysis of the results, however, is provided by calculating individually the changes in percentages of the pretreatment values = 100%. The results, expressed in this way are shown graphically in Figure 1. In the transdermal group the insulin values were on average 26.9% (SEM 28.4) after 2 weeks and on average 71.9% (SEM 27.6) after 4 weeks treatment. This latter result was significantly different to the pretreatment value ($p < 0.01$).

The urinary insulin excretion in the oral group decreased on average 10.0% (SEM 12.7) after 2 weeks and increased 4.9% (SEM 11.4) after 4 weeks of treatment. In both instances no statistically significant difference to the pretreatment value was observed.

Results of total urinary estrogen excretion and correla-

Table 1. — Basic data of the estradiol treated patients. Group I received transdermal estradiol, group II oral estradiol (means \pm SD).

	Group I 13 patients	Group II 12 patients
Age (years)	50.1 \pm 7.2	53.8 \pm 12.1
Height (cm)	165.8 \pm 4.9	165.4 \pm 5.9
Weight (kg)	66.0 \pm 7.9	68.0 \pm 10.5
Time since Menopause (years)	4.1 \pm 5.5	5.2 \pm 4.2
Nicotine use	6 patients	6 patients
Alcohol use	6 patients	4 patients

Table 2. — Total estrogen excretion and insulin/estrogen ratio in the urine of postmenopausal women after transdermal (n=13) or oral (n=12) estradiol administration before and after 14 days and 28 days of treatment (means \pm SEM). Significant difference between transdermal and oral group results * p <0.01.

	Total Estrogens (μ mol/8h)		
	before treatment	14 days	28 days
Transdermal Group:	1.2 \pm 0.2	3.2 \pm 0.3	3.5 \pm 0.4
Oral Group:	1.2 \pm 0.2	138.8 \pm 15.0*	128.1 \pm 14.5*
	Insulin/Estrogen-Ratio		
	before treatment	14 days	28 days
Transdermal Group:	15.42 \pm 1.3	7.81 \pm 0.9	7.29 \pm 0.9
Oral Group:	23.92 \pm 1.9	0.17 \pm 0.02*	0.19 \pm 0.04*

tions to urinary insulin are given in Table 2. Total estrogen excretion was higher in the oral than in the transdermal group. The insulin/estrogen ratio conversely demonstrated higher values in the transdermal group than in the oral group.

Discussion

Previous studies have shown that urinary insulin values correlate with plasma insulin values [7]. In the healthy adult insulin is filtered by the glomerulus and is reabsorbed for about 99% by the proximal tubulus and subsequently metabolized at this place [8, 9].

However, current literature on urinary insulin is scarce and the knowledge of renal insulin excretion is still insufficient [10]. In addition relevant research regarding the influence of estrogens on insulin excretion is sparse. One recent study on the influence of estrogen therapy on glucose metabolism in postmenopausal women reported a slight reduction of glucose tolerance, increase of plasma insulin concentration and reduced insulin sensitivity with oral but not with transdermal estrogen administration [11].

The present results, however, do not confirm such an increase of insulin after oral administration, since urinary excretion significantly increased only after transdermal administration. It is worth noting that conjugated equine estrogens were used in the "glucose" metabolism study combined with intermittent addition of progestogens.

The comparison of insulin with relaxin seems to be of special interest due to their structural homology and also their possible involvement in hemodynamic processes.

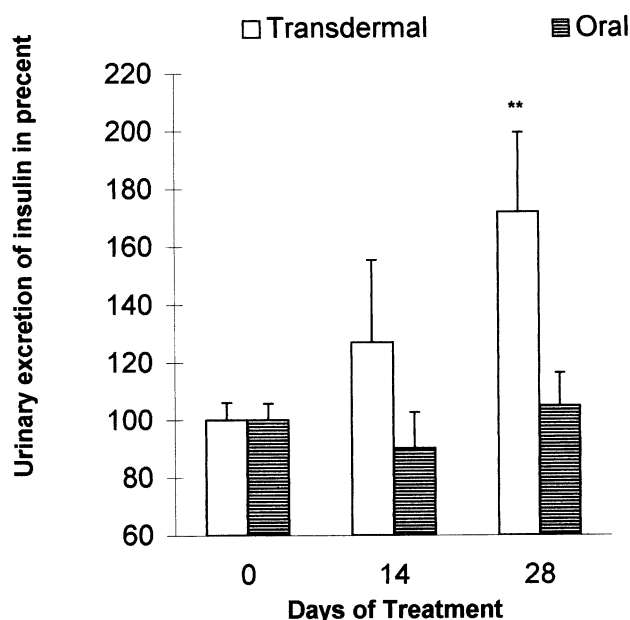


Figure 1. — Excretion of urinary insulin expressed as percent of pretreatment values after 14 days and 28 days treatment with transdermal (n=13) or oral (n=12) estradiol (means \pm SEM, ** p <0.01).

Ordinate: percentage of insulin excreted. Abscissa: days of estradiol treatment.

□ Transdermal estradiol treatment ▨ Oral estradiol treatment

The significance of insulin with respect to heart and circulation is well known. Of special interest are the direct vascular effects [12-14]. Relaxin has also been shown to exert actions on the cardiovascular system as, for instance, chronotropic and inotropic effects on the heart as well as lowering blood pressure [15-18]. Thus both substances can be considered as markers for cardiovascular actions. Surprisingly, urinary excretion of insulin is very similar to relaxin. The significantly increased excretion of both hormones only after transdermal administration, i.e. low dosage therapy reestablishing premenopausal hormone levels, indicates that both hormones were eliminated from the circulation via the kidney only under physiological conditions. Whether an increased production precedes this excretion could not be established in this study in the absence of blood level measurements.

The urinary excretion of total estrogens reflects the different pharmacokinetic profiles of the two estradiol administration routes. The insulin/estrogen ratio shows that after transdermal treatment low urinary estrogens is followed by higher insulin amounts compared to oral administration. Here again the insulin reaction is similar to the relaxin one. The significance of the estradiol effect on the insulin excretion by the kidney remains unclear.

Thus further studies are necessary to clarify whether the estradiol stimulated insulin excretion takes part in the cardioprotective action of estradiol in postmenopausal women.

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