GANZIMMUN DIAGNOSTICS AG

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DAkkS Deutsche Akkreditierungsstelle D-ML-13147-01-00

Laboratoryreport

Sample Material: urine

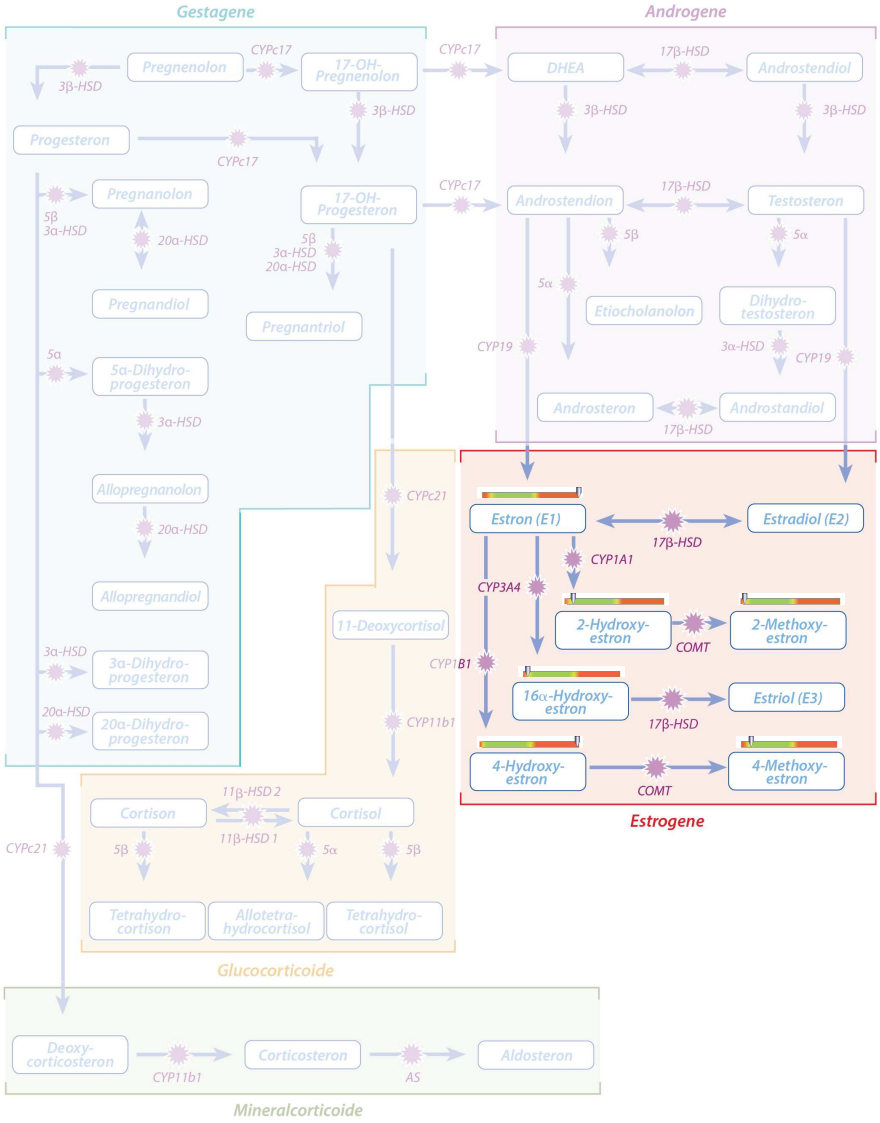
Test	Result	Unit	Initial Result	Norm
clinical chemistry				
Creatinine in urine (Jaffe)	1,24	g/l	2,37 Please mind the altered normal range.	0,25 - 2,00
endocrinology				
Estrone (E1)	72,55	µg/g creatinine		5,41 - 31,93
Metabolites with protective effects:				
2-hydroxy-estrone	4,94	µg/g creatinine		2,02 - 38,60
2-methoxy-estrone	0,25	µg/g creatinine		0,46 - 7,28
4-methoxy-estrone	0,31	µg/g creatinine		0,23 - 1,56
Metabolites with negative potential:				
16-hydroxy-estrone	0,82	µg/g creatinine		0,98 - 9,04
4-hydroxy-estrone	13,14	µg/g creatinine		< 6,67
Metabolite ratios:				
2-hydroxy-estrone/16-hydroxy-estrone ratio The 2-hydroxyoestrone/16-hydroxyoestrone ratio describes the relationship between the positive oestrone metabolite 2-hydroxyoestrone and the potentially negative oestrone metabolite 16-hydroxyoestrone. Please note that this ratio is not valid for 2OH- and 16OH oestrone results within the normal range.	6,02	Ratio		> 2,01
Methylation activity The methylation activity describes the ratio between 2- and 4-methoxyoestrone and 2- and 4-hydroxyoestrone.	0,04	Ratio		> 0,12

overview endocrinology:

endocrinology - interpretation of findings

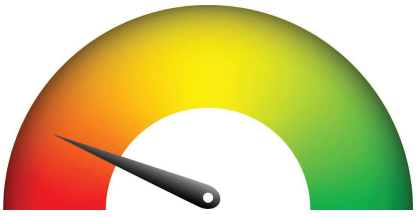
Eine Interpretation des Estronex-Profils in Bezug auf ein **Risiko östrogenabhängiger Tumorerkrankungen (insbes. Brustkrebsrisiko)** ist aufgrund nicht ausreichend gesicherter Literaturdaten **nur bei postmenopausalen Frauen möglich.**

(Eliassen et al.: Urinary estrogens and estrogen metabolites and subsequent risk of breast cancer among premenopausal women. Cancer Res. 2012 Feb 1; 72(3);696-706)



Legend

CYPc17	17α-hydroxylase
17β-HSD	17β-hydroxysteroid dehydrogenase
3β-HSD	3β-hydroxysteroid dehydrogenase
CYPc21	21-hydroxylase
5α	5α-reductase
5β	5β-reductase
CYP11b1	11β-hydroxylase
CYP19	Aromatase
11β-HSD	11β-hydroxysteroid dehydrogenase
CYP1A1	Cytochrome P450 1A1 (CYP1A1)
CYP3A4	Cytochrome P450 3A4 (CYP3A4)
CYP1B1	Cytochrome P450 1B1 (CYP1B1)
COMT	Catechol-O-methyltransferase
AS	Aldosterone synthase
3α-HSD	3α-hydroxysteroid dehydrogenase
20α-HSD	20α-hydroxysteroid dehydrogenase



The above diagram outlines the **risk of estrogen-dependent diseases**. The **methylation activity** serves as a guide value for the inactivation of carcinogenic estrogen metabolites, whereas the **2/16 ratio** represents the balance between "good" (2-hydroxy) and "bad" (16-hydroxy) estrogen metabolites. The higher the ratios, the lower the risk for estrogen-dependent diseases (green area).

Estrone (E1)

Estrone belongs to the group of natural estrogens. In the premenopause it is produced to about 70-80% by FSH secretion in the ovaries; postmenopausal estrone arises primarily from the conversion of androstenedione and DHEA by the enzyme aromatase. Postmenopausal estrone shows a less pronounced drop in comparison to those of estradiol.
Elevated estrone levels are found in overweight women and upon therapy with estradiol and estrone (conversion of estradiol to estrone). Higher estrone levels in the postmenopause are associated with a lower osteoporosis risk or atrophic symptoms of estrogen-dependent tissues. On the other hand, higher estrone levels increase the risk of endometrial degenerations. In the case of **elevated estrone levels, other estrogen metabolites are also likely to be increased**.
Furthermore, the increased reabsorption of intact estrogen molecules via the enterohepatic circulation can contribute to the increase of the estrone values. The microbial enzyme β-glucuronidase plays an important role in this process. The β-glucuronidase cleaves glucuronides so that hormones intended for excretion may re-enter the organism.

Indications for the **determination of estrone-levels** are:
- unclear bleedings
- clarification of estrogen effects in postmenopause
- review of hormone replacement therapy with estrone supplements

Metabolites with protective effects:

2-hydroxy-estrone

2-hydroxy-oestrone is produced by the hydroxylation of the A-ring from estrone. This reaction is catalized by the enzyme cytochrome P450 1A1. 2-hydroxy-oestrone has only a low binding affinity to the estrogen receptor and thus has **weakly pronounced estrogenic quality**. They act antiproliferative and protective by reducing the mitogenic activity of estradiol.

2-methoxy-estrone

Low 2-methoxy-estrone values indicate a **low methylation activity** and indirectly increase the risk of estrogen-dependent diseases (e.g., fibroids, endometriosis, or gynecological tumorous diseases).

Examination of the patient's supply with s-adenosyl methionine, vitamin B12, folic acid and vitamin B6 to ensure adequate COMT activity.

4-methoxy-estrone

4-methoxy-estrone is formed from 4-hydroxy-estrone by the catechol-O-methyltransferase (COMT). It is subsequently renally excreted after glucuronidation and sulfation.

Metabolites with negative potential:

16-hydroxy-estrone

Normal values of 16-alpha-hydroxyoestrone **reduce the individual risk** of e.g.,. **breast cancer or autoimmune diseases**. The biological action of 16-alpha-hydroxyoestrone is, however, affected by its relation to 2-hydroxyoestrone. Simultaneously decreased 2-hydroxyoestrone values may be indicative of reduced oestrogen production.

16-Hydroxy-estrone is obtained by the hydroxylation of **D-ring** from estrone. This reaction is mediated by the enzyme **cytochrome P450 3A4**. The metabolite has **strong estrogen-like effects.** The irreversible binding to estrogen receptors leads to a long-lasting DNA-stimulation with increases proliferation of oncogenic cells. 16-hydroxy-estrone has a **strong positive correlation with estrogen-dependent diseases (eg breast cancer)**.

4-hydroxy-estrone

High 4-hydroxy-estrone levels are associated with an **increasedrisk of breast cancer** due to its strong genotoxic and procarcinogens effect.

4-hydroxy-estrone is called **A-ring-metabolite** formed from estrone by the enzyme **Cytochrome P450 1B1**. Studies from Cavallieri and coworkers have shown that it can be metabolised to **quinones**, which might induce **DNA mutations** in tissue.
Frequent DNA mutations favor the development of malignant tumors. The enzyme CYP 1B1 also plays a crucial role in the activation of carcinogens. It has been shown in several studies that Chinese women with **CYP 1B1 polymorphism** have a higher risk of breast- ovarial- and endometrial- cancer than Caucasian women.
Although 4-hydroxy-estrone amount is only 1/6 from the 2-hydroxy-estrone, it has a **strong estrogenic, procarcinogens and genotoxic effect**.

The enzyme CYP 1B1 also plays a crucial role in the activation of carcinogens. It has been shown in several studies that chinese women with **CYP 1B1 polymorphism** have a higher risk of breast-, ovarial- and endometrial carcinoma than caucasian women; latter group, however, is associated with positive estrogen-receptor-status in breast cancer patients. In a Swedish study women who had CYP1B1 *3/*3 genotype and hormone replacement therapy achieved a 2-fold higher risk of developing breast cancer than women with HRT and without polymorphism.

Metabolite ratios:

2-hydroxy-estrone/16-hydroxy-estrone - ratio

The estrogen-metabolite ratio is used to show the balance between "good" (2-hydroxy) and "bad" (16-hydroxy) estrogens. Studies show that a high 2/16 ratio may indicate a reduced risk of developing breast cancer.

Methylation activity

Methylation activity is the ratio of 2- and 4-methoxy-estrone to 2- and 4-hydroxy-estrone. The phase II enzyme **catechol-O-methyltransferase (COMT)** catalyzes the methylation of estrogen metabolites, and thereby contributes to their inactivation and elimination.

Polymorphisms in the membrane-bound and cytosolic COMT forms result in different methylation activities. To ensure adequate COMT activity, the patients' intake of S-adenosylmethionine, vitamin B12, folic acid, homocysteine, and vitamin B6 should be checked.

medically validated by Frau Sabine Hein
Released by Dr. med. Patrik Zickgraf

All parameters marked with an * are tested at our accredited laboratory partners.
** study not accredited