THE IMPORTANCE OF “EXTRAGENITAL SYMPTOMS” DURING MENOPAUSE

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DEFINITION

Focusing more closely on the question of climacteric symptoms and by listing these symptoms in an order of occurrence, one finds that nearly 90% of the effects of sexual hormones are of an extragenital nature and that, therefore, the use of the expression “sexual” to describe these hormones is too much of a restriction in terms of a functional analysis (fig 1). The term “extragenital target organs” was chosen to account for the fact that it was only in the past 20 to 30 years that the whole variety of target organs became known and gave rise to a more specific discussion and understanding. It was our colleague, Dr Markus Metka, from the Gynecological Department of the Vienna General Hospital, who was one of the first to address this issue and to deal with it comprehensively [1]. The working group which he organised for that purpose drew the attention of specialists from the various disciplines to the interactions of sexual hormones and got them involved in further research.

One of the main tasks of this working group was to objectively discuss and study the “target organs” which had previously hardly attracted any interest. The variety of climacteric symptoms and the effects of long-term oestrogen substitution on the body, as mentioned above, requires a view of sexual steroids that reaches beyond the sexual sphere. It is from that perspective that...
The Importance of “Extragenital Symptoms” during Menopause

The concept of “extragenital target organs” have proven to be both helpful and easy to remember.

It is our opinion that, given the wealth of current knowledge and experience, the narrow-minded and one-sided opinion which is still common must be overcome. Such an endeavour must also include a detailed description of the large variety of symptoms and the numerous consequences of long-term estrogen deficiency. If the wide range of symptoms is known to the physicians, they will be able to better focus their patient information work and therapeutic approaches. What doctors need from their patients is a list of symptoms as detailed as possible. The questionnaire compiled by our group attempts to meet that need by providing an easily controllable basis of integration for doctors and patients (fig 2).

Especially when it comes to assessing less well-known climacteric symptoms, occurring alone or not, in association with general symptoms such as vasomotor disorders or incontinence, the problem of extragenital climacteric symptoms is often delegated to another discipline, like palpitations to internal medicine. Some isolated symptoms, which are less well-known or unknown may still be quite common, that can be seen from a survey conducted by the Menopause Outpatient Unit at the Gynecological Department of the Vienna General Hospital (see fig 1). According to that survey, palpitations are reported by 40% of women at the early stages of menopause. For some 15% of menopausal women, palpitations are in fact the only climacteric symptom, and it is a fact that most of these women not only undergo normal differential diagnosis in internal medicine, but are also often faced with one or more further examinations and even hospitalization. It thus not only appears to be important for the average physician to be informed about the wide spectrum of extragenital symptoms, but it also has to be our task to inform the public on the multitude of possible symptoms which may affect women during the period of hormonal change.
Some 80% of women consulted their doctor primarily because of hot flushes at the beginning of the menopausal debate – some 10 years ago – despite the large number of complaints that might have been inquired by the doctor or that were reported by the patients, the situation has considerably changed today as more and more women see their doctors for different extragenital symptoms, such as eye problems occurring at the onset of menopause.

Another important aspect that should not be overlooked in connection with extragenital target organs relates to the fact that knowledge about these symptoms has a highly beneficial effect on patient compliance. Only if the patient is fully informed on the origin of all her symptoms and if she feels an improvement in her condition as a result of therapy, she will be prepared to pursue a hormone replacement therapy as a long-term treatment option. It does, after all, make a difference whether a patient successfully follows a course of hormone substitution because of hot flushes alone or for a variety of climacteric symptoms.

**SEXUAL HORMONES AND EYE FUNCTION**

During the past few years, hormone replacement therapy has mainly focused on the typical menopausal disorders and their treatment. It is common knowledge today that steroid hormones are not only used for generally accepted endocrinological indications, but also for syndromes which until recently were the exclusive domain of other disciplines.

These disorders include ophthalmologic ailments such as keratoconjunctivitis sicca (dry eye syndrome) and glaucoma, which before were mostly treated with little success by ophthalmologists. That is why there is an ever greater need – not least due to pressure from our patients – to adopt an interdisciplinary approach in the treatment of certain disorders. One of the working groups at our department has therefore undertaken to objectively analyse these ophthalmologic symptoms on the basis of a large patient collective.

**Keratoconjunctivitis sicca**

In the medical literature, the dry-eye symptom is also referred to as the "sicca phenomenon". In a gynecological context, this sensation of dryness is not necessarily limited to the vaginal epithelium, but may also affect the eye. Thus, a dry conjunctiva is often the result of an oestrogen deficiency. It is amazing how many women suffer from this condition without associating it with a hormonal deficit. And even physicians are sometimes reluctant to trace the condition back to an oestrogen deficiency. It is a fact, though, that the problem often occurs during the time when the woman is still taking the pill and when the production of oestrogen by the body is stopped. Most of the complaints about a sensation of dryness of the eye come from women wearing contact lenses.

The clinical description of the symptom is invariably the same: The conjunctiva is sore and red, and the eye feels as though it has got sand in it. As a consequence, the pain becomes worse with every blink. Keratoconjunctivitis sicca is thus defined as a sensation of dryness and foreign body in the conjunctival region. If the dry-eye problem occurs simultaneously with the cessation of menstrual bleeding, a hormone deficiency may well be suspected. The
fact that keratoconjunctivitis sicca occurs with a high frequency in women during menopause while it is rather rare in men of the same age group suggests an endocrine cause of this eye problem that is so difficult to treat. It is therefore of an increasing clinical importance for the physician to consider the consequences of a steroid-withdrawal-related degeneration of the eye, in the same way as one would deal with an atrophy of the mucosa in the genital region.

Previous therapies mainly concentrated on cortison, vitamin A supplement and the use of tear fluid preparations. However, these therapeutic approaches are only meant as an attempt to treat the dry-eye symptom and do not offer any cause-related therapy. Therapeutic methods should be aimed at prevention and restitution of cell integrity in the conjunctival region, and less so on a mere substitution of tear fluid. Both the different cell types in the conjunctival region and the lacrimal gland itself are responsible for lacrimation. The tear film is thus hard to examine, given that numerous physical, chemical and biological mechanisms are involved, that the structure of the tear film is rather complex, and that the ocular surface is the most sensitive area of the entire human body. The tear film is composed of three major layers (fig 3):

- the watery phase: its function comprises nutrition, purification, transport, cooling and optimal refraction of the eye;
- the mucosal phase, which constitutes a bonding factor between hydrophilic watery phase and hydrophobic epithelium, but also has a lubricating and nutritional function; and
- the lipid phase, which protects the tears from evaporation and establishes chemical bonds. This is why sexual steroids have different points of attack on the tear film.

If the watery phase is reduced, an oestrogen deficiency is the predominant cause, whereas a reduction of the lipid phase is suggestive of an androgen deficiency in the patient concerned.

In order to examine the influence of 17β-oestradiol administered as eye drops in comparison to a traditional tear fluid substitute in postmenopausal women with keratoconjunctivitis sicca, a randomised, prospective study with 84 women was carried out at our department [2]. The women were randomly assigned to two groups of identical size, of which one was treated with a 17β-oestradiol drug while the other received a traditional tear fluid substitute preparation. A Schirmer test was performed at the beginning and after 4 months, with the subjective complaints being measured by means of a “visual analog scale”. The Schirmer test, which was used to examine the watery phase of the tears, constitutes a relatively rough measurement method although it is clinically quite useful as an indicator of tear secretion. A strip of filter paper, 30 mm long and 5 mm broad is folded 5 mm at one end. The folded
end is placed in the lower conjunctival sac. After 5 minutes, the length of the moistened strip is measured in millimetres from the fold and recorded. The normal value is between 10 mm and 30 mm (fig 4). The eye drops consisted either of an oestrogen solution (0.005 g 17β-oestradiol in 20 ml oleum sesami) or of a traditional tear substitute, and one drop of the corresponding eye fluid was dripped into each eye at 6-hour intervals for 4 months. A comparison between the two groups based on the visual analog scale after 4 months showed a significant difference in subjective eye complaints in favour of the group taking the oestradiol eye drops. The Schirmer test also revealed a significant difference when values before and after therapy were compared in the group receiving 17β-oestradiol eye drops (fig 5).

This study shows that topically applied 17β-oestradiol leads to a marked improvement of symptoms in post-menopausal women suffering from keratoconjunctivitis sicca. The normal function of the eye depends on blinking, secretion and composition of lacrimal fluid, and on the integrity of the surface cells of the conjunctiva. Further, a diffuse fibrosis and atrophy of lacrimal ducts during the menopause may also play a certain role. The positive influence of 17β-oestradiol may be explained by a stimulation of NO synthase, which may not only act on blood vessels but also on the lacrimal glands. One interesting phenomenon observed in the above study was the limited effect of the tear substitute on eye symptoms despite a course of systemic hormone replacement therapy. As against that, women taking oestrogen eye drops in addition to a systemic hormone replacement therapy reported an improvement or even a complete disappearance of symptoms. This finding suggests that there may be a blood-eye barrier which partly or wholly prevents an overflow of systemic 17β-oestradiol into the conjunctiva or lacrimal gland.

Not only oestrogens, but also androgens play an important role in lacrimation. As some researchers observed, the increased supply of androgens, eg, in polycystic ovaries, but also during gestation and lactation, prevents eyes from drying out. Androgen receptors were found in the epithelium of the lacrimal gland. In animal experiments, orchiectomy reduced the size of the lacrimal gland, while a supply of androgens resulted in a marked hyperactivity of that organ. The symptoms in patients suffering from Sjögren’s syndrome, which – like systemic lupus erythematoses and rheumatoid arthritis – is often associ-

![Figure 4. Schirmer test](image)

![Figure 5. Treatment of menopausal keratoconjunctivitis sicca with topical oestradiol](image)
ated with a clear decrease of serum testosterone, were improved by androgens. It thus appears that androgens are also effective in stimulating the lacrimal gland. However, these findings still need to be translated into a practically relevant form of therapy in the course of further clinical studies.

Changes in intraocular pressure

The increase in eye pressure – as in glaucoma – is a typical age-related phenomenon which may also be the result of an oestrogen deficiency. Glaucoma means that there is an increase in intraocular pressure (IOP) associated with a damaging effect on the optic nerve. The IOP (normal value 10–20 mmHg) is usually equilateral and, in conformity with the circadian rhythm, remains within rather narrow limits. The IOP tends to reach a peak in the early morning and to decrease during the day. The most common type of glaucoma is primary (open-angle) glaucoma, which occurs in approx. 4% aged over 50 years, with higher frequency in women than in men. As a diagnosis of glaucoma is usually only performed at the onset of presbyopia, i.e. at an age when the majority of menopausal symptoms also occur, a certain association between the condition and a decrease of C-18 and C-19 steroids may be suspected. A glaucoma is diagnosed by measuring IOP (using a Goldmann applanation tonometer) and, if necessary, by recording a daily pressure profile, by mirroring the papilla, and by examining the field of vision (fig 6).

There are numerous studies indicating a connection between an increase in IOP and the action of female steroid hormones, or rather a lack thereof. We were able to show, in a prospective clinical study, the impact of a hormone replacement therapy on patients with normal eye pressure and thus to provide a basis for further clinical studies to achieve a reduction of IOP in patients with glaucoma by means of a hormone replacement therapy [3, 4]. In this study, a significant decrease in intraocular pressure was achieved in postmenopausal women without an eye history, following a systemic hormone replacement therapy of only 12 weeks (fig 7).
Similar reductions of eye pressure were also observed in patients with primary glaucoma receiving a hormone replacement therapy. One explanation may be that the vasodilatory effect of 17β-oestradiol causes a release of outflow resistance in the iris-corneal angle. Both the ciliary muscle and the trabecular meshwork with Schlemm’s canal, which regulate the outflow pattern of aqueous humour, contain large amounts of type-3 NO synthase. The changes in ciliary muscle tone, which play an important role in eye pressure regulation, are also controlled by a cyclical AMP (cAMP)-independent, NO-induced mechanism. Overall, NO synthase may be of central importance in regulating outflow resistance.

SEXUAL HORMONES AND AUDITION

The ear is another of the so-called extragenital target organs under the influence of steroids. Recent findings suggest that hormonal changes during menopause may also impair auditory function. Hearing is associated with the generation of electric nerve signals in the inner ear and auditory path which may be conducted from the scalp by means of adhesive electrodes and then used for an objective auditory examination known as brain-stem audiometry. With this method, even the slightest change in auditory function can be measured. Using brain-stem audiometry, the physician may – in contrast to other auditory tests – objectively assess the patient’s hearing capacity because test persons, due to the method thus selected, are unable to influence the result. This test method provides for a recording of five different waves which originate in specific anatomic regions of the brainstem and which reflect the different sections of the route of an impulse from the inner ear to the acoustic centre in the brain.

In a prospective, interdisciplinary study conducted by the Departments of Gynecology and ENT at the Vienna University Hospital, an improvement of symptoms was observed in postmenopausal patients receiving a hormone replacement therapy assessed objectively by brain-stem audiometry [5]. The study showed that hormone replacement caused a shortening, i.e. an earlier onset, of brain-stem audiometric waves, which meant that electric impulses could be fed to the brain more swiftly. This result might be the starting point for new therapeutic options in the management of auditory dysfunctions during the menopause (Table 1).

Table 1. Brainstem audiometry in patients on placebo or tibolone, before and 12 weeks after treatment. Median values (SD) [5]

<table>
<thead>
<tr>
<th>Wave</th>
<th>Placebo before/after</th>
<th>Tibolone before/after</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (ms)</td>
<td>1.60 (0.24)/1.67 (0.21)</td>
<td>1.67 (0.10)/1.60 (0.13)</td>
</tr>
<tr>
<td>II (ms)</td>
<td>2.75 (0.20)/2.84 (0.20)</td>
<td>2.70 (0.15)/2.63 (0.14)</td>
</tr>
<tr>
<td>III (ms)</td>
<td>3.70 (0.25)/3.80 (0.24)</td>
<td>3.75 (0.21)/3.60 (0.18)</td>
</tr>
<tr>
<td>IV (ms)</td>
<td>4.93 (0.32)/5.03 (0.34)</td>
<td>4.95 (0.20)/4.85 (0.21)</td>
</tr>
<tr>
<td>V (ms)</td>
<td>5.66 (0.25)/5.81 (0.27)</td>
<td>5.73 (0.11)/5.58 (0.13)</td>
</tr>
</tbody>
</table>

P values for treatment factor in repeat measurement analysis of variances for difference before/after treatment. Difference between waves III and IV is significant for the five treatment comparisons after application of Bonferroni-Holm adjustment.
The connection between the endocrine system and bone density, which was already presumed by Albright [6] in 1941, has since been confirmed by experimental and clinical studies to the extent that the significance of a prophylactic application of sexual hormones in osteoporosis has been considerably advanced during the past decade. Due to this fact, it needs to be considered whether other tissues of the musculoskeletal system may be similarly regarded as target organs of sexual hormones as far as their aetiology and, possibly, also therapy are concerned.

**Historical overview**

Both osteoporosis and arthritis deformans are common disabling conditions which are known to increase considerably in frequency in women after the menopause. Arthrosis occurs in females during the menopause and is characterised by intermittent arthralgias and swollen fingers with a glossy skin. According to Fox, the prognosis is quite good. Already in 1908, Pineles referred to the endocrinological situation in the menopause as being the cause of the Heberden-Rosenbach node, which was first described by Heberden in 1802. In the German-speaking countries, it was the merit of Umber and, especially, Menge, to have published their clinical findings, thus having made them accessible to discussion. Umber referred to the disease of the smaller (finger) joints, affecting almost exclusively the female population, as “endocrine chronic peri-arthritis (destruens)”, noting that it was following a slowly progressing, afebrile course for years and decades and was closely associated with functional abnormalities of the gonads (menarche, menopause and sterilisation). He noted that climacteric arthropathies are starting before, during and after the menopause with tumefactions and pains, progressing for a year or two, and ultimately persisting, albeit often with the symptoms subsiding.

Menge stirred up a lot of commotion with his publication in 1924. He saw the syndrome of “arthropathia ovaripriva” in x-ray-castrated and, if somewhat less frequently, postmenopausal women with symptoms in the knee (usually in both knees) and sometimes in the shoulders and finger joints. The subjective complaints range from just a little to an order of magnitude that makes it impossible for the patient to walk or move her shoulders. In objective terms, he only found strong crepitations, noting that the symptoms were either likely to disappear spontaneously or to persist for several years. Zimmer noted that, as far as joint problems with a presumed ovarial origin are concerned, a distinction must be made between inflammatory and non-inflammatory arthropathies. Overviews on this complex matter were published by Cecil/Archer and Weil.

As in many other regards, the Second World War meant a rupture in the frequency of publications, with a marked

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**Table 2: List of authors on Arthropathia climacterica**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippokrates</td>
<td>1941</td>
<td>Silberberg</td>
</tr>
<tr>
<td>Celsus</td>
<td></td>
<td>Silberberg</td>
</tr>
<tr>
<td>Heberden</td>
<td>1802</td>
<td>Kellgren/Moore</td>
</tr>
<tr>
<td>Charcot</td>
<td>1889</td>
<td>Prill/Lauritzen</td>
</tr>
<tr>
<td>Fox</td>
<td>1895</td>
<td>Dequeker et al.</td>
</tr>
<tr>
<td>Pineles</td>
<td>1908</td>
<td>Rosner et al.</td>
</tr>
<tr>
<td>Umber</td>
<td>1914</td>
<td>Latman</td>
</tr>
<tr>
<td>Menge</td>
<td>1924</td>
<td>Linos et al.</td>
</tr>
<tr>
<td>Cecil/Archer</td>
<td>1925</td>
<td>Metka et al.</td>
</tr>
<tr>
<td>Weil</td>
<td>1929</td>
<td>Spector et al.</td>
</tr>
<tr>
<td>Zimmer</td>
<td>1930</td>
<td>Hannan et al.</td>
</tr>
<tr>
<td>Curschmann</td>
<td>1932</td>
<td></td>
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</table>
The Importance of “Exogenous Symptoms” during Menopause

143

drop in the number of papers appearing during that period. It is interesting, though, that there have overall been only a few publications until recently. Silberberg and Silberberg started a series of experimental studies in 1941, which were later followed up by Rosner (Table 2).

While the therapeutic use of sexual hormones for the prevention of osteoporosis is largely accepted today, its prophylactic and therapeutic application in the treatment of arthroses is still seen as an experiment. Hypotheses as to whether a given situation of the endocrine system (especially of sexual hormones) may, in general, be aetologically important for the pathogenesis of joint disorders have been around since the early days of medicine. These hypotheses were confirmed by a clinical finding that arthralgias may arise in a chronological connection with menopause or that their course may be influenced under the above mentioned circumstances.

In his book “On women’s diseases”, Hippocrates literally refers to a situation “of little menstrual bleeding causing pain to draw the limbs on the arms and legs and in the back”. He also notes that “a woman will feel pain in the region around the neck and the vertebral column and the loin”, adding that the pain is not always localised, but occurs “sometimes here, and sometimes there”. The symptoms “mostly affect women who are unmarried”. Celsus finds that “ailments in the joints of hands and feet are long-lasting and frequent. Only rarely are castrates affected, or other women than those whose menstruation is suppressed”. Later, there were also a few occasional references in the literature suggesting a connection between the menopause and the genesis of arthropathias. The French neurologist Charcot noted in several of his works that there was a relation between polyarthritis, on the one hand, and menopause, gravidity, partus and lactation, on the other. One of the first to describe the syndrome in great detail and to introduce the term “climacteric arthritis” was Fox in 1895.

**Definition (regarding concept of “Arthropathia climacterica”)**

Synonyms: “climacteric arthritis” (Fox), “arthritis of the menopause” (Cecil/Archer), “arthropathia ovaripriva” (Menge).

Arthropathia climacterica is a form of joint condition that is chronologically related to the menopause (pre-, peri- or postmenopausal). In clinical terms, the syndrome is characterised by pain and tumefaction in one or more symmetrically affected joints, especially of the proximal (PIP) and distal interphalangeal joints of the fingers, although the joints of the legs and large joints such as shoulders, knees or hips may also be affected. An involvement of the PIP joints may be regarded as a principal sign.

An x-ray follow-up of knee joints in the framework of the Framingham study [7] showed that the administration of hormone preparations (as a means of osteoporosis prevention) was associated with a rather low incidence of arthroses.

**SEXUAL HORMONES AND RHEUMATOID ARTHRITIS**

A far larger number of papers on epidemiological and aetiological questions in the context of joint symptoms and sexual hormones are dealing with the importance of these hormones in rheumatoid arthritis [8]. Effects on the activity of rheumatoid arthritis were observed not only during pregnancy, but also in dependency on the phase of the men-
The Importance of “Extragenital Symptoms” during Menopause

There have also been reports on arthroses of the mandibular joints (Art. temporo-mandibularis) in association with hormonal disorders. According to Ganshorn [11], there is a clear preference towards women as well as a chronological correlation between the onset of arthropathia and the production of estrogen during puberty. Other authors report a second peak of mandibular joint problems after the menopause [12, 13]. This means that the most conspicuous moments occur during the periods of hormonal transition. According to Loewit, this means that in around two-thirds of all cases women are affected by this condition. The authors only found a normal hormonal status in six patients, i.e. in roughly a quarter of the female study population, and therefore consider “endocrine influences to be important as intermediate prerequisites for the genesis of knee joint arthropathias”. On the basis of an overview of the available epidemiological information and the partly controversial experimental and clinical studies, an aetiological connection between arthritis deformans and sexual hormones may be considered. To verify this hypothesis, further studies will be required however. It will also be necessary to conduct broad-based prospective investigations in order to test the clinical efficacy as well as suitable animal studies to examine the effects of steroid hormones on various tissues of the joints (not only the cartilage).

**BIBLIOGRAPHY**

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