# DRY EYES DISEASE. A REVIEW

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*The author of the study declares that no conflict of interest exists in the compilation, theme and subsequent publication of this professional communication, and that it is not supported by any pharmaceuticals company. The author further declares that the study has not been submitted to any professional journal or printed elsewhere.*

Received: 6 May 2020
Accepted: 20 June 2020
Available online: 30 November 2020

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## SUMMARY
## DRY EYE DISEASE. A REVIEW

This article provides a comprehensive view of the issue of dry eye. It emphasizes provisions of the Tear Film and Ocular Surface Society, discusses the new classification and definition of dry eye based on its pathophysiology, and emphasizes the correct diagnostic and therapeutic approaches, which appears in the form of algorithms.

Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.

Dry eye disease is a dynamic and complex disease of the ocular surface and ocular adnexa with known risk factors. It is a disease with a cyclical character, in which the most important step is to find the etiological trigger, to restore homeostasis and break the vicious circle. The key elements in the diagnosis are increased osmolarity of the tear film and inflammation of the ocular surface, which are accompanied by ocular symptoms (discomfort, visual disturbance). Inflammation is not always associated with hyperemia and can be confirmed by several techniques and methods. However, in current clinical practice, there is still no "gold standard" and sufficient tests to diagnose inflammation of the ocular surface. The treatment of dry eye disease must be individualized, dynamic and optimized for each stage of the disease.

**Key words:** dry eye disease, TFOS, DEWS, DEWS II, vicious circle, ADDE, EDE, MGD

*Čes. a slov. Oftal., 77, 2021, No. 3, p. 107–119*

## INTRODUCTION

This review article deals comprehensively with the definition, epidemiology, pathophysiology, correct diagnosis, management and therapy of dry eye disease. The inspiration for the publication of this study was participation in the European meeting and workshop Ocular Surface Masterclass in February 2020 in Barcelona, Spain, which involved presentations of advances and innovations in the field by leading specialists in the issue of dry eye disease.

In order to aid a better understanding of dry eye disease, in March 2015 members of the Tear Film and Ocular Surface Society (TFOS), a non-profit organisation, held the Dry Eye Workshop II (DEWS II), which was attended by 150 clinical and scientific specialists representing 23 countries worldwide. The aim of the TFOS DEWS II was to establish a global consensus on the basis of current procedures from evidence-based medicine, and to redefine dry eye disease with reference to its multifactorial nature. The aim was to compile recommendations for diagnosis, management and therapy, and to propose recommendations for the clinical evaluations of new pharmaceuticals interventions for the treatment of dry eye disease. Members of TFOS DEWS II updated the generally comprehensible definition of dry eye disease and reviewed the classic schema for the purpose of facilitating treatment of dry eye disease on a pathophysiological and clinical basis. In July 2017, they published a report in the Ocular Surface journal. It was agreed at DEWS II that a unifying element in dry eye disease is the loss of homeostasis of the tear film, and that the main feature of DED is ocular symptoms, which include discomfort and/or disturbances of vision. Key etiological factors in the occurrence of DED include increased hyperosmolarity, inflammation and damage to the ocular surface. In the etiopathogenesis a role is also played by neurosensory abnormalities. The TFOS DEWS II report is a continuation of the original publication of TFOS DEWS from 2007. The modern classification and diagnosis of dry eye disease evaluates the epidemiology, etiology and pathophysiology of the disease [1,2].

Dry eye disease (DED) is a chronic disease, representing a worldwide problem. It affects hundreds of millions of people worldwide and is one of the most common causes for patients to visit ophthalmologists. This symptomatic

pathology is distinguished by a vicious circle of instability of the tear film and its hyperosmolarity, which leads to inflammation of the ocular surface, damage thereto, and to neurosensory abnormalities. Mild to severe dry eye disease is linked with pain, restriction of regular daily activities, reduced vitality and often with depression [2].

## DEFINITION OF DRY EYE DISEASE

"Dry eye is a multifactorial disease of the ocular surface, characterised by loss of homeostasis of the tear film and accompanied by ocular symptoms, in which an etiological role is played by instability and hyperosmolarity of the tear film, inflammation and damage to the ocular surface and neurosensory abnormalities" [2].

Development of definition: Dry eye was formally classified as a disease 30 years ago. The first formulation of the definition of dry eye disease, published in 1995 on the basis of a consensus of the working group National Eye Institute (NEI) in the Industry Working Group on Clinical Trials in Dry Eye was as follows: "Dry eye is a disorder of the tear film caused by insufficient tears or their excessive evaporation, which causes damage to the ocular surface in the region of the interpalpebral aperture, and is linked with symptoms of ocular discomfort." The definition identified the significance of the quality of the tear film and the quantity of tears as the causes of dry eye, and used the term "disorder" and not "disease". In 2006 the Delphi group proposed a new term for dry eye - "tear dysfunction syndrome" - reflecting the significance of the quality and quantity of tears. In 2007 the TFOS published the first definition of dry eye from the international Dry Eye workshop (DEWS), on the basis of a three-year process founded upon an international consensus, which is generally known as TFOS DEWS. The workshop was composed of 58 members from 11 countries and recorded significant progress in the field of dry eye. The definition was as follows: "Dry eye is a multifactorial disease of the tears and ocular surface, which results in symptoms of discomfort, disturbances of vision and instability of the tear film with potential damage to the ocular surface. It is accompanied by high osmolarity of the tear film and inflammation of the ocular surface." TFOS DEWS was the first to acknowledge that dry eye is a genuine disease with a multifactorial etiology. Symptoms of discomfort and transitional disturbances of vision were acknowledged as primary, while by contrast tear osmolarity and inflammation were described as occasional and in no way causal manifestations of the disease. The development then continued with the publication of the TFOS DEWS II report in 2017, which acknowledged a significant role of inflammation and osmolarity of the tear film, which are key elements contributing to the pathogenesis and the maintenance of the vicious circle. The DEWS II definition includes the expected result of the disease (clinically measurable disruption of homeostasis of the tear film), and also emphasises significant etiological triggers which are essential in the specification of the definition of DED and its differentiation from other diseases of the ocular surface [2,3].

## CLASSIFICATION SCHEMES OF DRY EYE DISEASE

The classification schemes serve as a guide to diagnosis and configuration of adequate treatment. The definitions and classifications of DED over the last more than 20 ye-

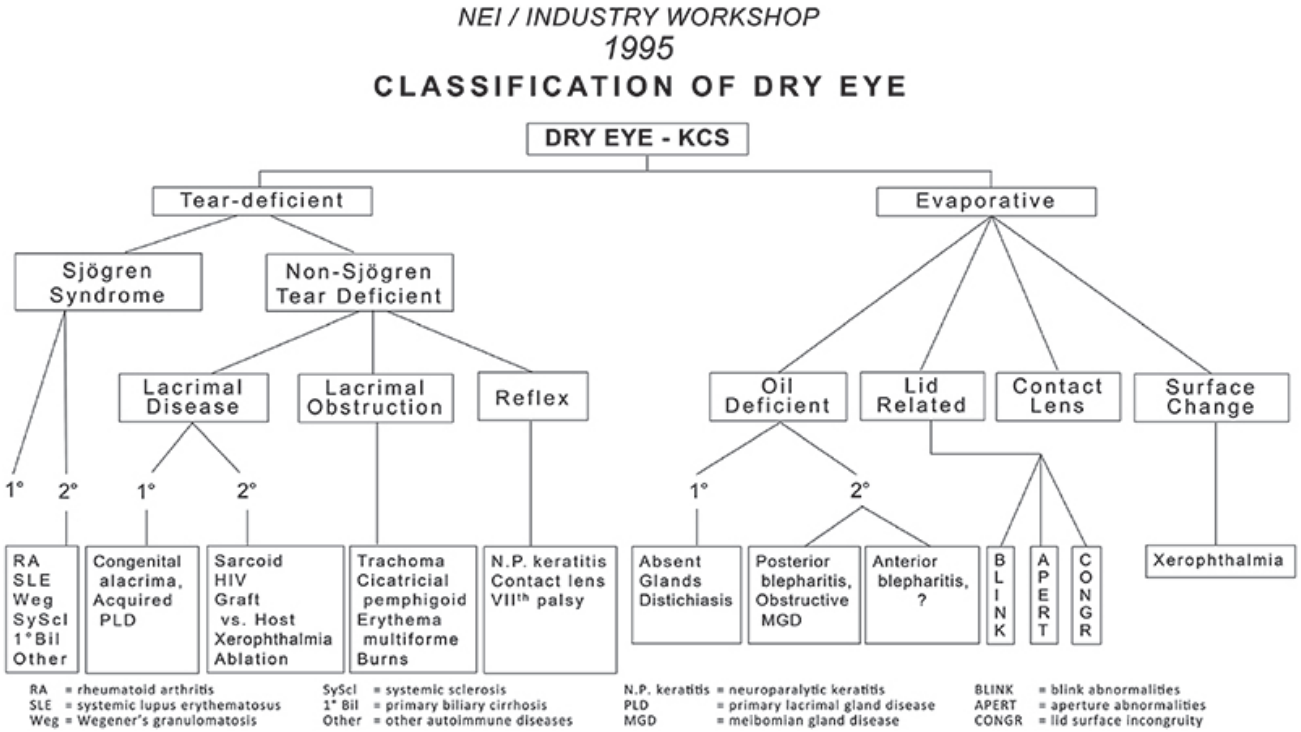


**Fig. 1.** Classification of NEI / Industry workshop 1995 [3]

ars have undergone a fundamental development thanks to a better understanding of the pathophysiology. The original NEI report determined two primary categories of dry eye: the category of aqueous-deficient and the category of evaporative. Within the framework of these two categories, it proposed a range of internal and external etiological factors, which it considered to contribute to the progression of DED (Fig. 1). The classification scheme in the TFOS DEWS report (Fig. 2) retained the two primary categories (aqueous-deficient and evaporative), and in the sub-classifications again stated the potential etiologies of the disease. TFOS DEWS II noted the problems with the interpretation of the original scheme. This primarily concerned a differentiation between the primary categories of DED and the specificity of its diagnosis. Another problem was the differentiation of DED from other diseases of the ocular surface. As soon as the patient enters the "vicious circle", regardless of the primary trigger, the subsequent instability of the tear film, hyperosmolarity and inflammation lead to further adverse changes, which often obscure the differences between the fundamental categories. For the purpose of illustration, Sjögren syndrome, which was classified in the reports form 1995 and 2007 exclusively as caused by a deficit of water, is ever increasingly acknowledged in connection with evaporation thanks to the associated dysfunction of the meibomian glands. The current classification of TFOS DEWS II presented in fig. 3 contains the clinically decisive algorithm, based on current knowledge of the pathophysiology. This classification scheme describes the whole range of possible sub-categories and mentions their predominant etiology (aqueous-deficient and evaporative). The purpose of classification is to improve the diagnostic methodology, treatment and future research [2,3].

## TERMINOLOGY OF DRY EYE DISEASE

The terminology used in the definition was important in establishing an internationally accepted definition suitable for translation into multiple languages. The DEWS report from 2007 acknowledged dry eye to be a multifactorial pathology, a **complex functional** disorder, which cannot be characterised by a single process, manifestation or symptom. DEWS also accepted dry eye to be a **disease**, signifying a disorder of structure or function, or a condition resulting in specific manifestations or symptoms. The term **ocular surface** covers the structure of the eye and the adnexa, including the cornea, conjunctiva, eyelids, eyelashes, lachrymal film, main and accessory lachrymal glands and meibomian glands. Homeostasis describes a condition of dynamic balance. Impaired homeostasis means various changes in the tear film and on the surface of the eye in reaction to the triggering etiology. **Disorder of homeostasis of the tear film** is considered to be a unifying characteristic, and describes the basic process in the development of DED. The definition from 1995 indicated discomfort as the main **symptom**

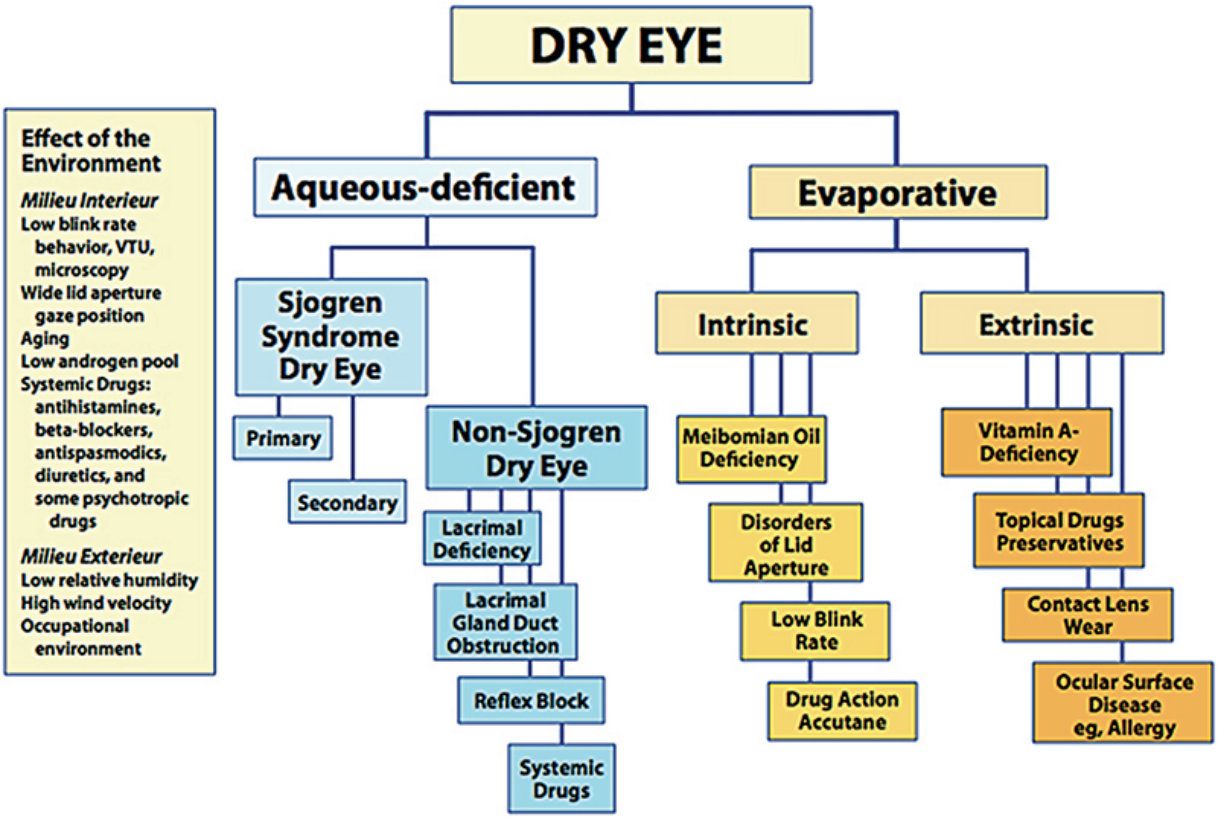


**Fig. 2.** Classification of DEWS Report from 2007 [3]

of DED, and the DEWS definition from 2007 then extended the symptoms with disturbances of vision. DEWS II in 2017 retained both discomfort and disturbances of vision as fundamental symptoms. In order to determine a diagnosis of dry eye disease it is necessary to identify symptomatic affliction and the presence of accompanying symptoms of damage to the ocular surface. The revised definition at the same time differentiates DED from other diseases of the ocular surface, which imitate or mask **dry eye disease**, or may occur concurrently with dry eye. DED is often considered a diagnosis of exclusion.

Fig. 3 presents the **decisive algorithm**, beginning with an evaluation of symptoms (symptomatic and asymptomatic patients) and manifestations of **diseases of the ocular surface**. The group of symptomatic patients without demonstrable clinical signs of damage to the ocular surface includes neuropathic pain (caused by either a lesion or disorder in the somatosensory system, in which subjective complaints disproportionately predominate over clinical manifestations) and the pre-clinical stage of dry eye disease (symptoms identical to DED upon an absence of clinical manifestations). The group of asymptomatic patients manifesting clinical signs of damage to the ocular surface is divided into patients with reduced corneal sensitivity (secondary neurotrophic damage to the corneal nerves upon a background of long duration of DED) and patients with prodromal manifestations and a predisposition to dry eye (changes of the ocular surface resulting in frequent illness, which could be a risk of manifestation of DED over time). The classification scheme of DEWS II based on pathophysiology places emphasis on the two predominant and mutually exclusive categories of DED: insufficient water (**aqueous-deficient dry eye – ADDE**) and evaporation (**evaporative dry eye – EDE**). Evaporative, to which the greater part is devoted, is more common than aqueous-deficient dry eye. Meibomian gland dysfunction (MGD) is considered the main cause of dry eye. ADDE describes conditions influencing the lachrymal gland, abnormalities of eyelid positioning and blinking, conditions with mucin deficiency, damage to the ocular surface by contact lenses or the influence of systemic drugs etc. [2,3].

## FACTORS OF INCIDENCE AND PREVALENCE OF DRY EYE DISEASE

A significant influence on the regulation of the ocular surface and ocular adnexa is exercised by differences between the sexes, and hormones, which play a role in the pathogenesis and prevalence of DED. The correlation with prevalence within the framework of sex is no surprise, a role is played by sex chromosomes, sex-specific autosomal factors and epigenetics (e.g. microRNA, DNA methylation and acetylation, histone modification). **Sex** influences not only the risk of

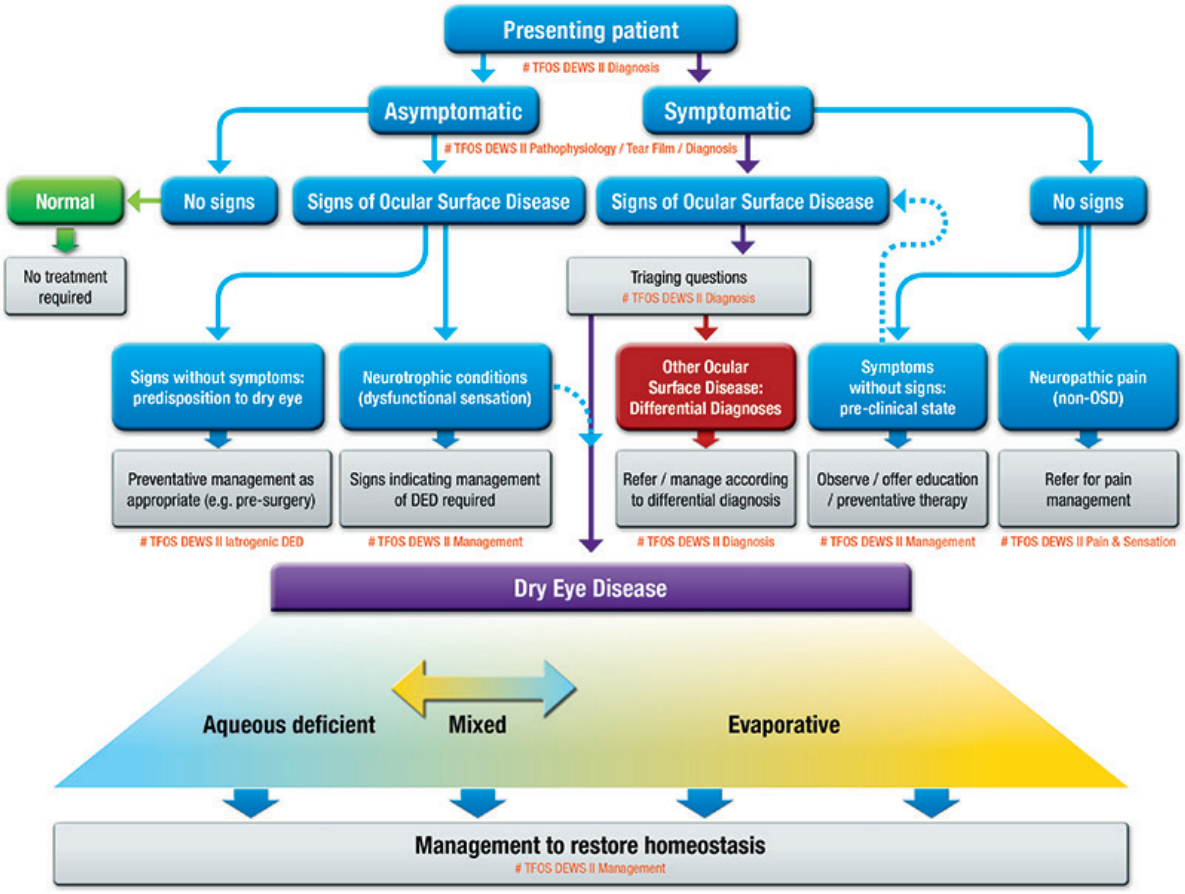


**Fig. 3.** DEWS II Report from 2017 – revised classification scheme [2]

incidence of DED, but also manifestations of the disease, immune response, perception of pain, behaviour, access to the system of healthcare and patient satisfaction with treatment. The sex genotype (XX, XY) determines the genetic and molecular basis of the differences in health and illness. If genetic and physiological differences between men and women are combined with environmental factors, they lead to behavioural and cognitive differences. Female sex is one of the most widely studied and carefully identified risk factors of DED. At the same time, a demonstrable risk factor is autoimmune disease in connection with DED (e.g. Sjögren syndrome). Comorbidities and associated factors with DED in women include depression, chronic pelvic pain, irritable bowel syndrome and chronic pain syndrome. In men these factors are medications for hypertension, benign prostatic hyperplasia and antidepressants. Other comorbidities are systemic lupus erythematosus, rosacea, anxiety, hay fever and xerostomia. Differences in connection with sex exist in the anatomy, physiology and pathophysiology of the ocular tissues and adnexa. For example, increased diffuse atrophy and periductal fibrosis in the lachrymal glands of older women may contribute to the prevalence of DED. Sex-specific changes of the cornea (changes in thickness, hydration, curvature and sensitivity, endothelial pigmentation, feeling of foreign body, tolerance of contact lenses and visual acuity) may appear in women during the menstrual cycle, pregnancy and menopause. Sex differences exist also in the survival of grafts (corneas from male donors may have a higher degree of survival than from women, whereas transplants in female recipients show a higher degree of survival than in men).

The female cornea has a pronouncedly higher gene expression for transglutaminase 1 (the enzyme catalysing the networking of proteins), and its level is usually increased in DED and keratinisation of the cornea. Sensitivity is higher in women than in men. Women have shorter and narrower lachrymal canaliculi than men, and in addition in women there is a sharp angle between the bone channel and the nasal floor, and these factors may contribute to chronic inflammation of the lachrymal drainage pathways, and thus explain the more frequent primary obstructions of the nasolachrymal duct. Sex differences also exist in the tear film. Men have a stronger lipid layer and higher tear osmolarity, whereas in women there is a shorter breakdown time, an increase of tear osmolarity during the ageing process and an earlier decrease of peroxidase activity. Specific differences in immune response include the fact that men have a larger percentage of inflammatory cytokines and women have lower natural killer cell activity. In women there is a preponderance towards extracellular response of auxiliary T-lymphocytes 2 (T-helper 2, Th2 response), whereas men have a larger cellular immune response mediated by T-lymphocytes 1 (T-helper 1, Th1 response). Women therefore produce a higher level of circulating antibodies than men, including higher levels of autoantibodies if they are afflicted by autoimmune diseases. Attention is also focused on the role of epigenetic regulation of microRNA (small double-chain non-coding RNA, which negatively regulate gene expression) in differences of immunity, of which there are approximately 800 in humans, approximately 10 % of which are found in chromosome X (X-bound miRNA). Another factor contributing to differences between the sexes is the microbiome, above all microbial settlement in the intestines, which plays a fundamental role in the development, maturing and modulation of the host's immune response. Immunity may also be influenced by non-biological factors (chemicals and metals) causing an occupational risk. Female sex and higher age are the main factors in connection with chronic pain (in DED neuropathic pain). Subjective complaints of patients are described by diverse expressions such as dryness, burning, stinging, itchiness, feeling of foreign body, hot flushes, discomfort, painful irritation, photophobia, feeling of watery eyes, pressure, pain or disturbances of vision. These complaints often do not correlate with the severity of DED, and it is difficult to evaluate the degree of pain reliably. A visual analogue scale (VAS) is used as a tool to evaluate pain. Within the framework of DED, subjective complaints questionnaires are used, most frequently the Ocular Surface Disease Index (OSDI), in which we obtain a sum of the symptoms rather than intensity of pain. The role of genotype in pain remains underestimated. Chronic pain (also within the framework of DED) causes depression, in which depression occurs more frequently in women than in men. In patients with DED there is a markedly higher incidence of sleep and mood disorders in relation to age and not to sex [2,4].

**Hormones**. The endocrine system plays a large role in the pathogenesis of DED and the differences between the sexes. The difference in connection with sex in the prevalence of DED is in large part attributed to the effects of sex steroids (androgens, oestrogens, progestins), hypothalamo-hypophyseal hormones, glucocorticoids, insulin, insulin-like growth factor 1 (IF-1) and thyroid gland hormones. Sex steroids act on a whole range of ocular tissues, and are linked with the treatment of several ocular conditions, including DED, meibomian gland dysfunction (MGD), healing of wounds, keratoconjunctivitis, rejection of corneal transplant and corneal pathology. The target organs for androgens are the lachrymal and meibomian glands. A deficit of androgens is a significant risk factor in the pathogenesis of dysfunction of the lachrymal glands and MGD, and at the same time is linked with the development of both categories of DED (ADDE and EDE). **Androgen** induced effects have a molecular biological base, and may support the proliferation of epithelial cells. Androgen deficiency is a risk factor for the development of inflammation of the lachrymal glands and DED in women with Sjögren syndrome, but it is not their cause.

Women with Sjögren syndrome have a deficit of androgens and raised levels of anti-inflammatory cytokines (IL-1, TNF-α and IL-6) in exocrine tissues. These cytokines may disrupt the normal activity of steroidogenic enzymes, which has the result of reducing testosterone levels, increasing oestrogen levels and deepening the inflammation. Androgens suppress the expression of anti-inflammatory cytokines and increase the level of the anti-inflammatory cytokine IL-10. The anti-inflammatory effect is locally specific: the androgens reduce the accumulation of lymphocytes in the lachrymal and salivary glands, but do not reduce the scope of the inflammation of the lymphatic tissues. Local or systemic appli-

cation of androgens significantly reduces manifestations of DED. Reduction of the levels of androgens in serum, which takes place during menopause, pregnancy, lactation or use of oral contraceptives containing oestrogen, may trigger the development of non-immune type DED – primary lachrymal gland deficiency. Androgens stimulate the immune system of the lachrymal gland and the transport of secretory immunoglobulins (IgA) into tears, which helps protect the integrity of the ocular surface against microbial infection and toxicity. Androgens stimulate the function of the meibomian glands, support lipogenesis, extend the breakdown time of the tear film, reduce evaporation, suppress keratinisation and modulate development and differentiation. During the ageing process there is a significant decrease in the quality of sebum, as well as changes in the lipid spectrum of secretion and an increase of metaplasia of the mouth of the meibomian gland. Androgens stimulate the proliferation and immune response of the cornea and conjunctiva. Androgen deficiency is linked with the development of epitheliopathy, whereas by contrast treatment with androgens stimulates mitosis, corrects defect and facilitates healing of wounds, suppresses angiogenesis and dystrophy in the cornea. Androgens also alter the progression of allergic conjunctivitis. Oestrogen had effects on the immune system, depending on the dose and concentration. In general, oestrogen increases the immune response supporting the production of B-cells and antibodies, subgroups of T-cells, dendritic cells, macrophages and regulatory cytokines. The effect of oestrogen on the lachrymal gland under certain conditions supports inflammation and autoimmune diseases. Intracellular synthesis of oestrogen depends on the circulating levels of precursors of steroid hormones and on testosterone. Testosterone has an important influence on the action of oestrogen by means of aromatisation to oestrogen in the target tissues, including the ocular surface. Higher levels of endogenous serum oestrogen are linked with increased osmolarity, reduced secretion of tears and MGD. It is necessary to correlate the effects of oestrogen on the ocular surface simultaneously in connection with the effects of progesterone and especially androgens. The higher prevalence of DED in women may be due rather to the reduction of the effect of androgens than to the increased action of oestrogen itself. **Progesterone** is primarily composed of cholesterol in the adrenal glands and in the ovaries, and its influence on the prevalence of DED is not known. **Glucocorticoids** are important endogenous regulators of inflammatory reaction. Synthetic derivatives of these hormones are used as anti-inflammatory substances. Local glucocorticoids are used as short-term therapy in the treatment of medium-severe and severe forms of DED. The long-term use of these hormones involves adverse side effects (infection, glaucoma, cataract). Two main glucocorticoids are produced in cells: cortisone and cortisol (active form). Under physiological conditions, autocrine synthesis of cortisol takes place through the corneal epithelium, which contributes to the immune protection of the ocular surface. Cortisol can be produced by the primary cultures of human corneal epithelial cells, fibroblasts and allogenic macrophages. The effect of glucocorticoids on the ocular surface and adnexal tissues depends on the concentration. The **hypothalamus-hypophysis axis** is the main regulator of the endocrine system.

The hypothalamus processes signals from the central nervous and peripheral endocrine system, and transmits these impulses to the anterior and posterior hypophysis. The hypophysis then releases hormones, which have a regulatory function and influence on the ocular surface and adnexa. Hypophyseal hormones modulate growth, differentiation, function of the lachrymal and meibomian glands and play a role in the support of sex dimorphism of tissues. The origin of prolactin in lachrymal glands is not only the hypophysis, but also the epithelial cells of acini of the lachrymal glands (tear synthesis). **Prolactin** is secreted by the lachrymal gland into tears, and with regard to its pro-inflammatory effects it may play a role in the pathogenesis of Sjögren syndrome and in supporting the generation of autoimmunity. By contrast, the capacity of testosterone to reduce the gene regulation of the prolactin receptor in the lachrymal glands may be one of the mechanisms by which androgens suppress inflammation in this tissue in the case of Sjögren syndrome. Women with seborrhoeic MGD have pronouncedly higher levels of prolactin in serum. It has been demonstrated that fragments of prolactin inhibit the angiogenesis of the cornea. Local application of α-melanocyte stimulating hormone (**α-MSH**) supports the volume and stability of tears, improves the integrity of the cornea and suppresses inflammation of the ocular surface. Adreoncorticotropic hormone (**ACTH**) may be synthesised or accumulated inside the myoepithelial cells in the lachrymal glands. Circulating levels of ACTH have been positively correlated with central corneal thickness. Receptors of thyroid stimulating hormone (**TSH**) have been identified in the lachrymal gland. These receptors are considered to be the target of autoantibodies in endocrine orbitopathy. Levels of TSH in serum of women but not of men are also raised in the case of seborrhoeic MGD. Thyroid gland hormones (T3, T4) support the synthesis of proteins, growth and differentiation of tissues, influence lipolysis and lipogenesis. Their deficiency causes hypercholesterolaemia and reduction of lipid secretion by the sebaceous glands. Reduction of levels of T3 and T4 indicates hypotrophy of the lachrymal glands and metaplasia of the cornea. The potential effects of other hypothalamic and hypophyseal hormones on the ocular surface have not yet been defined. Growth hormone (**GH, somatotropin**), insulin-like growth factor (**IGF-1, somatomedin**), as well as **insulin**, are anabolic promoters responsible for mitosis, growth, differentiation and repair. GH, IGF-1 and insulin contribute to the metabolism of glucose, amino acids, DNA, lipids and proteins. Receptors of GH, IGF-1 and insulin in the lachrymal glands and surface tissues of the eye have an influence on the development of tissues and on healing of wounds. A role in the modulation of GH, IGF-1 and insulin activities is played by sex hormones. DED is linked with ageing, and **ageing** is accompanied by reduced levels of sex hormones and increased resistance to insulin. Diabetes reduces the microvascular, nervous and metabolic integrity of the ocular surface, lachrymal and meibomian glands. Clinical manifestations of diabetes include lower corneal sensitivity, shorter breakdown time of the tear film, as well as Schirmer test, higher

tear osmolarity, epithelial metaplasia and changes of proteins in tears, worsening with the duration of the disease, and poor glycaemic control. GH may also play a role in healing of the cornea and regeneration of nerves. IGF-1 supports the proliferation and migration of epithelial cells and fibroblasts of the cornea, differentiation of limbal stem cells and proliferation of endothelial cells of the cornea in animal models. Treatment with IGF-1 accelerates healing of wounds and regeneration of corneal nerves, prevents surface keratopathy in diabetics following cataract surgery, and accelerates re-epithelialisation in patients with neurotrophic keratitis. Autologous serum containing insulin and growth factors is used for alleviation of symptoms of severe form of DED [2,4].

## EPIDEMIOLOGY OF DRY EYE DISEASE

Subjective patient complaints negatively influence their quality of life and labour productivity. DED has an impact on individuals by influencing visual functions and generating physical and psychological discomfort. In epidemiological studies, various questionnaires are used to evaluate DED. **Prevalence** is the proportion of patients with the disease in the population within a given period of time. Precise data about the prevalence of DED is not known due to a lack of uniform classification. Estimates of prevalence differ depending on the definition, classification, diagnostic criteria and characteristics of the population being studied. The prevalence of DED in studies is within the range of 5 % to 50 %. Studies in which the diagnosis is based on signs of the disease generally state a higher and more variable level of the disease, in certain populations as high as 75 %. The prevalence of DED increases with age and there is a higher prevalence in women. **Incidence** describes the number of newly diagnosed patients in a given period of time. The incidence of DED is presented only by a very limited number of studies, and data is imprecise. Future research should determine a better evaluation of the prevalence of DED of various severity, incidence in various populations, potential risk factors, and should clarify the impact of climate, environment and socio-economic factors [2,5].

## RISK FACTORS OF DRY EYE SYNDROME

Risk factors have been categorised as consistent (unchanging), probable and ambiguous (unconvincing). Each of these groups is then divided into modifiable and unmodifiable. **Consistent unmodifiable** risk factors include age, female sex, Asian race, MGD, disease of conjunctival tissue and Sjögren syndrome. **Consistent modifiable** risk factors include androgen deficiency, work at computer, wearing contact lenses, hormone replacement therapy by oestrogens, transplantation of haematogenous cells, environmental factors (pollution, low humidity, air conditioning) and use of pharmaceuticals (antihistamines, antidepressants, anxiolytics and isotretinoin). Diabetes, rosacea, viral infection, disorder of the thyroid gland, psychiatric and affective disorders (anxiety, depression) and pterygium have been identified as **probable unmodifiable** risk factors. **Probable modifiable** risk factors include low intake of fatty acids, refractive surgical procedure, allergic conjunctivitis and pharmaceuticals (anticholinergics, diuretics, beta-blockers). **Ambiguous unmodifiable** risks are Hispanic ethnicity, menopause, acne and sarcoidosis. **Ambiguous modifiable** risks are smoking, alcohol, pregnancy, demodex (Demodex folliculorum, a mite from the family of demodex, which is parasitical on the skin of the eyelids, often associated with MGD, forming cylindrical scales on the eyelash follicle), botulotoxin injection, multivitamins and oral contraception. Stress may be a trigger of DED, and there is a question of the role of genetic susceptibility. It is important to differentiate DED from other conditions such as allergic and infectious diseases, inflammatory states and other chronic pathologies of the ocular surface [2,5].

## PATHOPHYSIOLOGY OF DRY EYE DISEASE

TFOS DEWS II reviewed the mechanisms that contribute to the origin and maintenance of DED. A fundamental mechanism of DED is **hyperosmolarity** of tears, which is generated by excessive evaporation, and damages the ocular surface, leading to inflammations.

Hyperosmolarity causes loss (apoptosis) of the epithelial and goblet cells. It subsequently results in a reduction of the lubrication capacity of the ocular surface, with rapid breach of the tear film and a further increase in hyperosmolarity. The cycle of events, referred to as a **vicious circle**, is presented in the centre of fig. 4. In the case of **ADDE**, hyperosmolarity is manifested in a condition in which secretion of tears is reduced in the conditions of their normal evaporation from the eye. In **EDE**, hyperosmolarity is caused by excessive evaporation of the tear film within the conditions of a normally functioning lachrymal gland.

Hyperosmolarity is a function of tear evaporation in ADDE and EDE, and in this sense, all forms of DED are evaporative. Hyperosmolarity is considered a trigger of a cascade of events in the superficial epithelial cells, which leads to a release of inflammatory mediators and proteases. These mediators, together with hyperosmolarity, cause apoptosis of the corneal epithelial cells and conjunctiva and goblet cells of the conjunctiva, and damage the glycocalyx (protective layer of hydrophilic mucins bound to the surface of the epithelial cells, ensuring adhesion of the tear film, forming an interface between the hydrophobic epithelium and the hydrophilic layer of the tear film, and playing a role in the trituration of the tear film and moistening of the ocular surface). The result is characteristic punctate injury to the epithelium (**epitheliopathy**) and instability of the tear film. However, instability of the tear film may be characteristic also of other conditions influencing the ocular surface (xerophthalmia, ocular allergies, preservative substances, contact lenses). In DED associated with MGD, hyperosmolarity of tears is caused by a deficiency of the lipid layer of the tear film. ADDE has various different causes. It may be a consequence of a blockage of sensory impulses into the lachrymal gland, which are essential for maintaining homeostasis of the tear film. A block in the reflex arc may be caused by chronic abu-

se of local anaesthetics, damage to the trigeminal nerves or refractive surgery. Drainage of tears into the lachrymal sac may be restricted by an obstruction of the lachrymal drainage pathways, which occurs in all cicatricial pathologies such as trachoma, ocular cicatricial pemphigoid, erythema multiform, reaction of a graft against the host and chemical injury (burn, scorching). Another risk factor which may cause a reduction of tear secretion is systemically used pharmaceuticals (antihistamines, beta-blockers, diuretics and certain psychotropic drugs), as well as age. A frequent cause of ADDE is inflammatory infiltration of the lachrymal glands in connection with an autoimmune disease such as Sjögren syndrome (SSDE) or non-Sjögren syndrome (NSDE-KCS). A low level of androgens also predisposes the individual to inflammation of the lachrymal gland. Injury to the epithelium, defective gylcocalyx, loss of tears and goblet cells leads to increased damage by means of friction mechanism. Injury stimulates the nerve endings of the cornea, which leads to discomfort, more frequent blinking and a compensatory reflexive increase in tear secretion. This compensation of hypersecretion is more probable in EDE, in which the function of the lachrymal gland is normal. A schematic diagram representing the etiology and mechanism of MGD, which is the main cause of EDE, is presented in fig. 5. There are two forms of MGD: **non-cicatricial MGD** and **cicatricial MGD**. The schema illustrates the influence of age, hormones, skin diseases (e.g. treatment of acne vulgaris with cis-retinoic acid may generate atrophy of the meibomian glands), local pharmaceuticals (pilocarpine, timolol) and toxins (polychlorinated biphenyls). A key event in non-cicatricial form is hyperkeratinisation of the mouth of the meibomian glands, which leads to obstruction, dilation of the canaliculi and atrophy of the glands, and later to obliteration of the mouth of the meibomian glands. Obstruction may be worsened also by increased viscosity of the secretion thanks to changes in the lipid composition. Inflammatory mediators and lipids released into the tear film and onto the ocular surface then cause epitheliopathy. Symptoms of inflammation are common on the edge of the eyelid. In cicatricial form, submucosal scars are formed, as well as scars of the mouth of the meibomian glands and terminal channels beyond the posterior edge of the eyelid and on the tarsus. The low production of secretion of the meibomian glands and changes in the lipid composition lead to instability of the tear film, increased evaporation of tears and ultimately to EDE [2,6].

In patients with DED there are perceptible changes in the tear film, nevertheless our relatively limited understanding of the role of the tear film, its structure and biophysical aspects

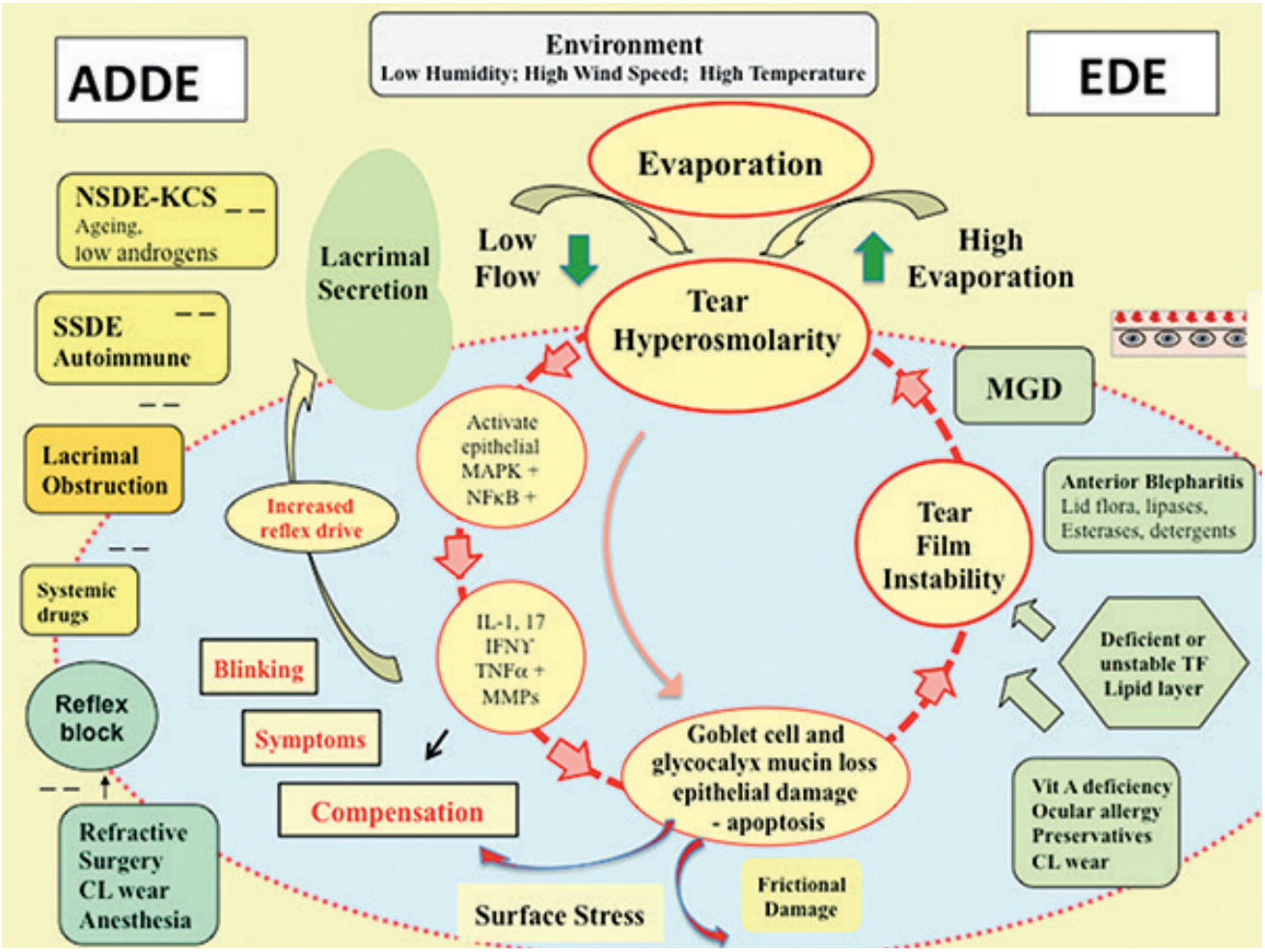


**Fig. 4.** Pathophysiology of DED – TFOS DEWS II REPORT [2]

prevents us from comprehending its precise significance in the pathophysiology of DED. Clinically DED is distinguished by a loss of volume of tears, more rapid breakdown of the tear film and increased evaporation of tears from the ocular surface. The subcommittee of TFOS DEWS II recommended a **two-phase model of tear film**. The lipid layer covers over the base muco-aqueous layer. The tear film is composed of several substances, including lipids, proteins, mucins and electrolytes. All of this contributes to the integrity of the tear film. In DED osmolarity increases, as well as changes of other components such as proteins and mucins, which can be used as biomarkers in DED. The thickness of the lipid layer need not influence the speed of evaporation unless it is very thin (less than 24 nm) or entirely absent. Increased expression of the secretion of the meibomian glands in normal eyes nevertheless correlates with reduced evaporation in both healthy individuals and in patients with DED. An abnormal lipid layer of the tear film is linked with increased evaporation (evaporation in a healthy eye is 0.14 ± 0.97 µL/min, in patients with MGD 0.26 ± 0.16 µL/min). However, the speed of evaporation differs markedly depending on external conditions, such as air flow and humidity. The secretion of the meibomian glands (meibum) has a complex structure and thermotropic behaviour, and its melting temperature (~30°C) is lower than the surface temperature of the eye (35°C), and as a result it is possible that meibum may be a locally effective barrier against evaporation. The suppression of evaporation is based on a certain organisation and composition of the lipid layer (polar lipids, branched lipids, polyunsaturated fatty acids in meibum). Collapse and evaporation on the ocular surface is prevented not only by the lipid layer, but also by interaction of the entire tear film and specific interactions of proteins or secretory mucins (or a combination thereof), including salts. The muco-aqueous layer covers the apical cells of the epithelium and their gylcocalyx, which is rich in carbohydrates. In the tears of patients with DED there are perceptible changes in the quantity of mucin or glycosylation of various components. The dense polymer network of mucins retains water, increases hydration and suppresses further evaporation of tears. Mucins, together with proteins and polar lipids, improve the distribution and structure of the lipid layer of the tear film. All the key components of the tear film thereby increase its resistance to evaporation. An endeavour to characterise the biochemistry of the tear film may lead to an identification of new markers, which can be used for the diagnosis, prognosis and treatment of DED. A holistic approach in understanding the structure and function of the tear film will undoubtedly lead to better treatment of patients with DED [2,7].

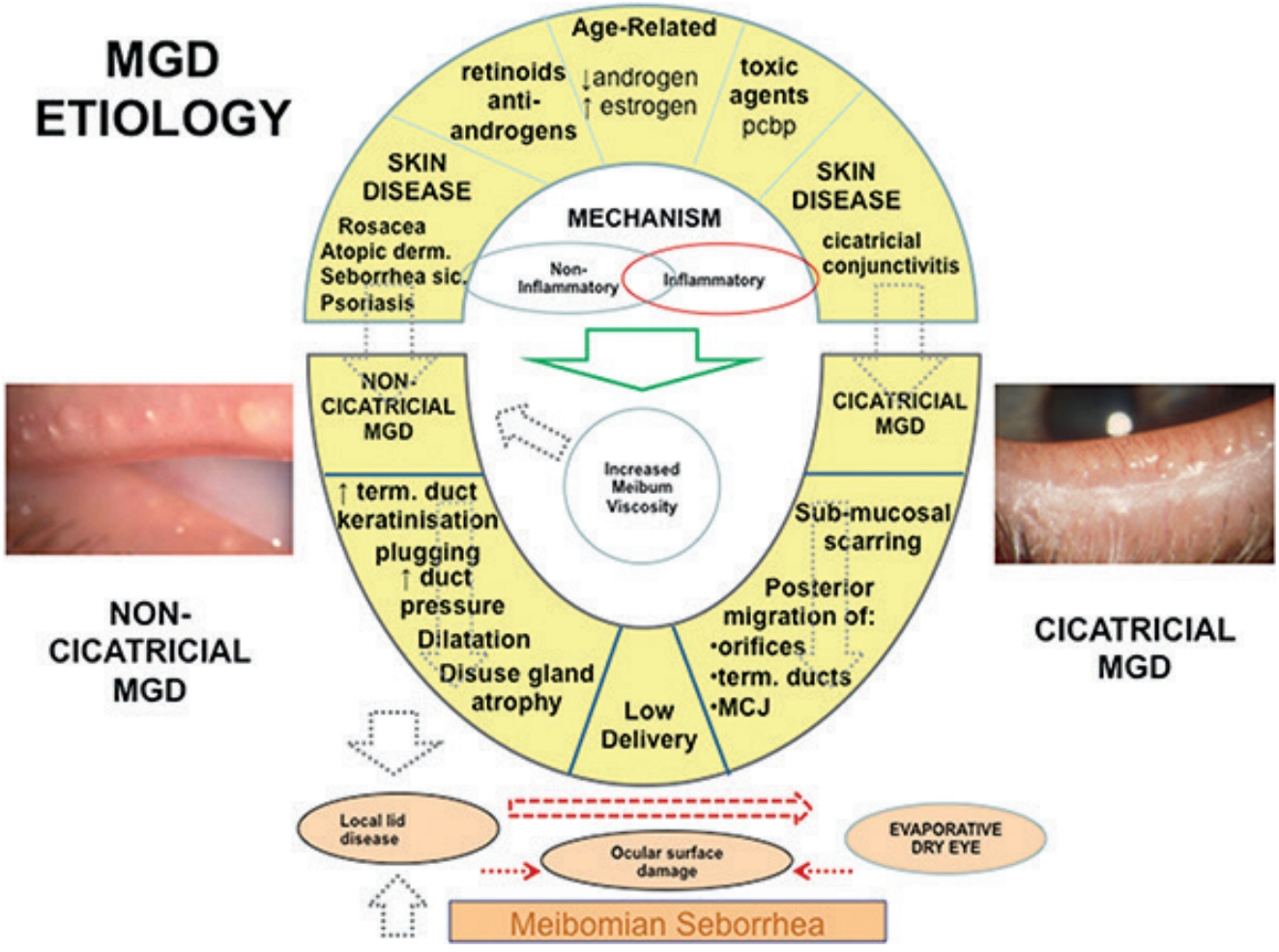


**Fig. 5.** Pathophysiology of MGD – TFOS DEWS II REPORT [2]

**Pain** in DED is caused by hyperosmolarity of tears, loss of lubrication capacity, flushing out of inflammatory mediators and neurosensory factors. We divide pain into nociceptive and neuropathic. Nociceptive pain occurs in reaction to tissue damage. Neuropathic pain occurs as a consequence of a lesion inside the somatosensory nervous system, and is indicated as pathological or pain without a biological value. Pain linked with mechanical, chemical and thermal stimulation of the ocular surface is mediated via the peripheral axons of the neurons of the trigeminal ganglion innervating the cornea and conjunctiva, whereas cold thermoreceptors detect moisture and reflexively maintain basal tear production and blink speed. In the corneal stroma, axons form the subepithelial nervous, the ascending branches of which bisect and terminally expand in the surface layers of the epithelium. The sensory nerves functionally pertain to the polymodal nociceptive neurons, pure mechano-nociceptor neurons and cold thermoreceptor neurons.

These neurons are projected into two regions of the nuclear complex of the trigeminal brain stem (one is activated by changes of moisture of the ocular surface, the second is mediated by sensory discriminatory aspects of ocular pain and reflexive blinking), and thus play a significant role in maintaining homeostasis of the ocular surface. Evaporation of tears causes discrete cooling of the ocular surface and increases tear osmolarity, by which the basal activity of the cold thermoreceptors is increased. Spontaneous blinking is maintained by a constant nervous impulse from the cold thermoreceptors of the ocular surface. Secretion activity of the main lachrymal gland is regulated primarily by the autonomous parasympathetic nerves, their reactivity is regulated by reflexive influences from the sensory neurons of the ocular surface. These generate secretion of the goblet cells by means of unidentified efferent fibres. Reduced tear secretion in the case of DED causes exposure of the corneal epithelium to adverse environmental impacts and often leads to inflammation and damage to the peripheral nerves. Damage causes sensitisation of the polymodal and mechano-nocireceptors, and simultaneously also suppresses the activity of the cold thermoreceptors, which evokes a feeling of dryness and causes pain. In DED the nerve damage is permanent, leading to an unusual increase of neuronal activity and morphological changes of innervation of the cornea. Damage to nerves and long-term inflammation alters the gene expression of the ion channels and receptors on the neurons of the trigeminal ganglion and brain stem, alters their excitability, connectivity and reaction. The maintenance of molecular, structural and functional defects in the sensory pathways ultimately leads to dysesthesias and neuropathic pains. The condition of the corneal nerves is evaluated with the aid of aesthesiometry and in vivo confocal microscopy. Subjective patient complaints and their symptoms ensue from the irregularity of the tear film and ocular surface. Increased frictional forces damage the ocular surface, which results in characteristic punctate epithelial keratitis, limbic keratoconjunctivitis, filamentary keratinitis and the formation of horizontal conjunctival folds parallel to the lower eyelid (lid parallel conjunctival folds - LIPCOF) [2,8].

## IATROGENIC DRY EYE DISEASE

Dry eye may be caused by a range of iatrogenic influences, which include use of pharmaceuticals, wearing contact lenses and surgical procedures. Locally used medications in ophthalmology (adrenergic agonists, anti-allergic drugs, antiviral drugs, beta-blockers, carboanhydrase inhibitors, cholinergic agonists, miotics, mydriatics/cyclоplegics, prostaglandins, topical anaesthetics and non-steroid anti-inflammatory drugs) can cause DED due to their allergic, toxic and immuno-inflammatory effects on the ocular surface. Preservative substances such as benzalkonium chloride (BAK) have been recognised as a risk factor. They are used due to their antibacterial effects, but may worsen DED due to their toxic and pro-inflammatory effect. A number of systemically used pharmaceuticals (vasodilators, anti-cholinergic drugs, anti-hypertensives, analgesics, sulfonylurea, anxiolytics/hypnotics, antidepressants, sedatives, antihistamines, anti-malaria drugs and drugs used in oncology) may trigger DED secondarily due to the reduction of tear production, altered reflexive secretion and inflammatory effects on the secretion glands. Drugs with an anti-cholinergic effect (anti-hypertensives, antidepressants) may reduce tear formation by binding to receptors of the lachrymal and meibomian glands. Some drugs used in oncology trigger punctate keratitis. Other factors causing DED include wearing contact lenses. The following biophysical changes appear in contact lens wearers: thinner, uneven lipid layer, instability of tear film, lower basal level of tear turnover and lowered tear meniscus.

Iatrogenic DED is most often caused by surgical procedures on the cornea such as refractive laser procedures (primarily LASIK) and keratoplasty. Here DED originates as a consequence of breach of the corneal nerves or postoperative application of local pharmaceuticals. Hyposensitivity of the cornea following a refractive laser procedures (PRK, LASIK) occurs due to direct damage to the corneal nerves or abnormal neuronal remodelling, and has been recognised as the main risk factor of postoperative DED. Advances in surgical procedures serve to minimise denervation of the cornea during surgical procedures and reduction of the incidence of postoperative DED. Damage to the corneal nerves occurs also following perforating keratoplasty, in which persistent defects of the corneal epithelium appear, which may lead to ulcers and potential failure of the graft. Studies indicate promising results for the renewal and regeneration of sensory nerves following keratoplasty after the application of various neurotrophic factors (substance P, IGF-1).

Other risk factors of the origin of postoperative DED include cataract surgery, glaucoma surgery, conjunctival surgery, oculoplastic procedures and aesthetic reconstructions. Surgical procedures generate dysfunction of the tear film as a consequence of reduced sensitivity of the cornea, loss of conjunctival cells, an increase of inflammatory mediators and the triggering of inflammation, and also as a consequence of the effects of eye drops

containing preservative substances and anaesthetics. Reconstructive procedures then generate morphological changes of the eyelids and meibomian glands. Another risk factor of the origin of DED is the application of botulotoxin and various cosmetic procedures (make-up, fillings, tattooing, piercing). However, the actual prevalence of iatrogenic DED is not known. In regular practice attention should be paid to early detection of dry eye disease before eye operations [2,9].

## DIAGNOSIS OF DRY EYE DISEASE

Members of TFOS DEWS II identified key tests and techniques used for the diagnosis and monitoring of DED and for the quantification of subjective symptoms. They proposed the most appropriate order of tests and the technique of their performance within a clinical environment in order to meet the definition of DED. Several tests were proposed for diagnosis, the sensitivity and specificity of which is highly dependent upon the inclusion criteria, the severity of DED and the examined population. The recommended tests for diagnosis of DED and assessment of its severity is presented in fig. 6. Before diagnosis it is important to ask classification questions for differential diagnostics and exclusion of conditions imitating DED. Afterwards screening of symptoms should be conducted by completing the DryEye Questionnaire-5 (DEQ-5) or Ocular Surface Disease Index (OSDI) questionnaire. A positive score of symptoms should then lead to a more detailed examination and performance of diagnostic tests. Among the key diagnostic tests are shortening of the non-invasive tear breakup time (NIBUT < 10 s), measurement of tear osmolarity (> 308 mOsm/L, or variability in time and variability between both eyes > 8mOsm/L, which increases with the severity of DED), and staining of the ocular surface with fluorescein and lissamine green (cornea, conjunctiva and edges of eyelids). Positivity of tests in any eye is considered a symptom of impaired homeostasis.

Diagnosis of DED is determined on the basis of a positive score of symptoms and one or more positive results of homeostasis markers. Further classification tests should subsequently be conducted, providing information about the etiology of DED, which include meibography (imaging of morphology and function of the meibomian glands following eversion of the eyelids), lipid interferometry (measurement of thickness and dynamics of lipids) and evaluation of tear volume in order to determine the sub-classification (ADDE or EDE) and severity of DED, with the aim of selecting the best treatment strategy. The diagnostic methodology is a certain guide for ophthalmologists, and defines the questions which patients must be asked in order to enable differentiation of DED from

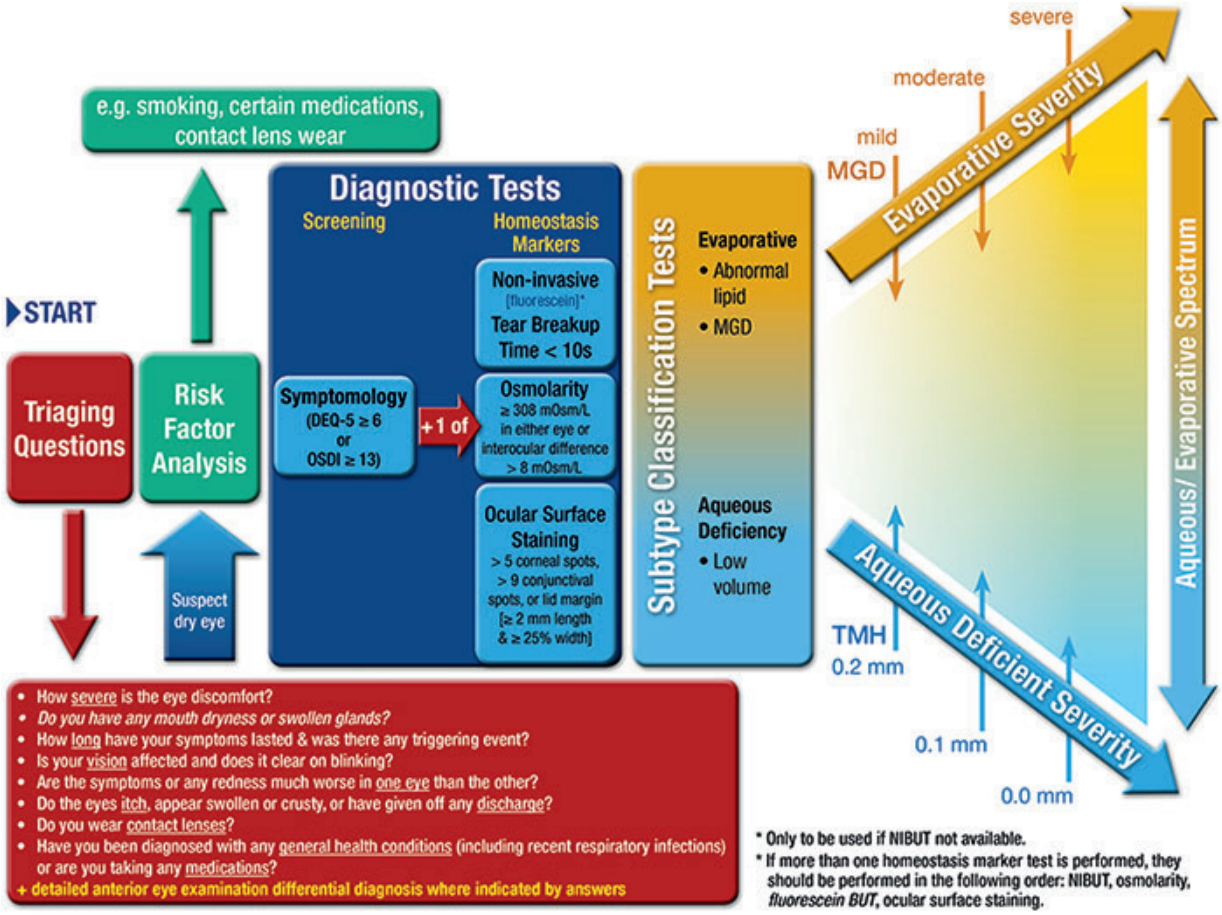


**Fig. 6.** Recommended diagnostic approach for DED [2]

other pathologies of the ocular surface, or from cases in which dry eye is secondary within the framework of the basic pathology. However, in regular clinical practice there is still no "gold standard" or a sufficient amount of tests for diagnosing inflammation of the ocular surface [2,10].

## MANAGEMENT AND TREATMENT OF DRY EYE DISEASE

Members of TFOS DEWS II conducted a review of the current options of evidence-based treatment. Management of DED is complicated due to its multifactorial etiology. With regard to all the available evidence, a management algorithm was proposed, which represents a gradational approach in the decision-making and treatment according to the severity of the disease. In selection of the most appropriate strategy, it is of decisive importance to distinguish between two subtypes of DED. The options for treatment that are currently available then depend on these subtypes. The main aim of management is to restore homeostasis of the ocular surface and tear film on the basis of breaking the cyclical character of DED. The task is to identify and treat the primary trigger of the pathology. Management is then implemented progressively. The proposed algorithm is not strictly prescribed, but represents an aid which may help when commencing treatment in the majority of patients. It is not identical for all stages of DED due to the variability in its severity and character. It should subsequently lead to individual manners of treatment focused on specific aspects of pathophysiology. Table 1 presents the possibilities for management and treatment, which lead to an alleviation of manifestations of DED. If a patient does not respond to the given level of treatment, it is recommended to progress to the next level, and the previous therapy can then be discontinued. In general it applies that management of treatment begins with conventional and easily available over-the-counter preparations, artificial tears (for early and mild stage of DED), and then progresses to more advanced types of therapy (for more severe forms of DED). These recommendations may be adjusted on the basis of the individual profile of the client. The expected period of duration of

**Table 1. Recommendations for gradational management and treatment of dry eye disease [2]**

**Step 1:**
- Education of patient relating to condition, management, treatment and prognosis
- Modification of local environment
- Education relating to potential dietary adjustments (oral supplementing of essential fatty acids)
- Identification and potential modification/elimination of problematic systemic and local medications
- Ocular lubrication of various types (in case of dysfunction of meibomian glands consider supplements containing lipids)
- Eyelid hygiene and warm wraps

**Step 2:**
If the above procedures are insufficient, consider:
- Lubrication without preservative substances in order to minimise toxicity generated by preservatives
- Treatment with tea-tree oil for Demodex (if present)
- Protection/preservation of tears
  - Occlusion of lachrymal puncta
  - Moist chamber/swimming goggles
- Overnight treatment (e.g. grease or moist chamber)
- In surgery: physical warming and expression of meibomian glands (including therapy with the aid of equipment such as LipiFlow)
- In surgery: intensive pulse light therapy for dysfunction of meibomian glands
- Prescription drugs
  - Local antibiotic or combination of antibiotic/steroid applied to edge of eyelids for anterior blepharitis (if present)
  - Local corticosteroid (for limited time only)
  - Local substances supporting tear secretion
  - Local non-glucocorticoid immune modulation drugs (such as cyclosporine)
  - Local antigen antagonising drugs associated with lymphocyte functions (LFA-1) such as Lifitegrast
  - Oral macrolide or tetracycline antibiotics

**Step 3:**
If the above procedures are insufficient, consider:
- Oral substances supporting tear secretion
- Autologous/allogenic serum eye drops
- Therapeutic contact lenses
  - Soft contact lenses (bandage)
  - Hard scleral lenses

**Step 4:**
If the above procedures are insufficient, consider:
- Local corticosteroid for longer period
- Transplantation of amnion membrane
- Surgical occlusion of lachrymal puncta
- Other surgical procedures (e.g. tarsorrhaphy, transplantation of salivary glands)

treatment before termination due to failure relates both to the patient's response and to the therapy under consideration. The therapeutic effects are mostly observed within one to three months, even if certain therapies (e.g. cyclosporine A) may require longer. Treatment of DED is dynamic and should be based on clinical skills and abilities to assess the significance of each of the processes which may imitate DED [2,11].

## CONCLUSION

This study deals comprehensively with dry eye disease. With regard to the fact that, in the field of ophthalmology in the Czech Republic, there is an insufficient amount of modern publications dealing with the classification, pathophysiology, diagnosis, management and treatment of dry eye disease, this study sets itself the goal of presenting an integrated view of this issue.

Dry eye disease is a dynamic and complex pathology of the ocular surface and ocular adnexa with known risk factors. It represents a pathology of a cyclical character, in which the most important step is to identify the triggering factor, restore homeostasis and break the vicious circle. In each of its phases, dry eye disease requires a different strategy of diagnosis, management and treatment. The key elements in diagnosis are increased osmolarity of the tear film and inflammation of the ocular surface, which are accompanied by ocular symptoms (discomfort, disturbances of vision). However, dry eye disease may occur also without damage to the ocular surface. Our attention should be focused on inflammation, which is a universal manifestation of the disease and plays the main role. Inflammation of the ocular surface is not always associated with congestion, but can be confirmed by a number of techniques and methods, which include impression cytology of the conjunctiva, confocal microscopy, staining of the ocular surface with lissamine green, determination of metalloproteinase (MMP-9) concentration in tears etc. At the same time, new diagnostic tests are constantly being developed, which influence the future of management. Our common goal should be to optimise treatment in the individual stages of the pathology on the basis of its etiology and severity. The treatment strategy of dry eye disease must be individualised and dynamic. We must give patients time to understand the disease, ask specific questions on the conditions which worsen their symptoms, we must explain the nature of the disease to them and provide quality instruction on treatment (when and how to apply artificial tears and when to apply other preparations), which is almost always long-term. Without doubt, products not containing preservatives must be the future of treatment. Treatment should be combined, incorporating regular hygiene of the eyelids, application of artificial tears and anti-inflammatory preparations without preservative substances. An advance in the issue of dry eye disease is the development of new pharmaceuticals and therapeutic options in accordance with an improvement of pre-clinical and clinical evaluations and an understanding of pathophysiological events.

The study emphasises the provisions of the Tear Film and Ocular Surface Society, discusses the new classification and definition of dry eye disease on the basis of its pathophysiology, and places emphasis on the correct diagnostic and therapeutic approaches, which it displays in the form of algorithms.

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