GINGIVAL MUCOSA, ENDOTHELIAL DISFUNCTION AND MENOPAUSE

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Increased incidence of complications and parodontopathies in women in postclimax as well as the therapeutic benefits resulting from the application of techniques by bleeding or using lambous of gingival mucosa can be understood only gums. Histologically and biochemically, turntable processes of destruction and regeneration tissue is as well in parodontopathies, the regulating vascular unit: endothelial cell-myocyte.This bipolar whole responds extemporaneusly to variations of the physical, umor or hormone-vegetative factors, secreting substances-hormone with paracrine action, activator in secondary of neww mechanisms responsable for trophicity and tissue regeneration. Among these favourable factors, etiopathogenic of hormone type in women is also menopause. This presentation is a review of the literature data concerning the role and biochimics mechanisms in periodontal diseas, their etiopathogenic involvement, form of menopausis.

Key words: Gingival mucosa; Postclimax; Trophicity and tissue regeneration; Parodontopathies.

The quality of mastication is mainly determined by the masticatory force developed and by the duration of this force. The influence of both masticatory parameters is conditioned by the state of the dentition, with the efficiency of the mastication progressively diminishing as the triturating surface diminishes. On the other hand, the factors which contribute to shortening mastication time (because of pain), but also the tooth's lifespan (through its fixation ring) is the morphological state of the gum [1]. This is because anatomic-functionally, the tooth-gum complex is a unit, the gum forming a fixation ring around every tooth, but also a sulcus, physiologically, with a role in absorption [2]. Pathologically, this can favor the development of paradontopathies with important functional repercussions, especially in the advanced stages of suffering [3,4]. Fulfilling the physiological role of the gum is, however, dependant of maintaining trophicity, of its capacity to regenerate and of the physical, chemical and biocenosical characteristics of the two compare-tments of the oral cavity, but especially from the gum's sulcus fluid.

Gingivitis, although seemingly local pains, are actually a link of a systemic vascular pathology in which the parietal stress and the intramural tension of the microcirculation are the common elements which condition the metabolic exchange of oxygen and nutrients between the capillary-interstitial blood and the cells of the layers which form the soft periodontium. Amongst the physiological factors that determine the normal variation limits of these exchanges, there's sex and age [5]. Menopause, as a physiological sex-related stage, is characterized by progressive ceasing of the ovarian

secretion activities, as result of the stock reduction of the primordial follicles capable of maturing under the influence of the hypophysary hormones [4,6,7]. Dysendocrinia, in the line of estrogen hormones (mainly β-estradiol), for a woman in a post climax, becomes a terrain modifying factor which, cumulated with other factors over time, determines the predisposition to developing certain diseases, including some outside the oral cavity segment[8, 9, 10].

The trophic effect of estrogen on the gum is a component in maintaining vascular support, in general, and the necessity of a local vascular network, functionally normal, derives from its role to:

– ensure the local necessary input of nutrients and local oxygen [6, 7];

– bring other bioactive substances necessary for maintaining their viability to the target cells [9];

– limit the ionic concentration variations in the gum interstice [2];

– remove the hydrogen ions, the local catabolites generated through glycolysis and other reactive species of oxygen (ROS), which can induce cellular destruction if accumulated locally in excess (see Fig.1).

The gums mucous' capacity to regenerate depends not only on the size and the quality of the exchange surface wall, but also on the local blood debit. The clinical argument, supporting the local hemodynamic factor is the "white gum".

Knowing that the blood debit (Q), in a bowl, is a function of the medium blood flow speed value (v) and the surface of the bowl (S), which in turn depends on the bowl's diameter (D):

$$Q = v \times S$$

Since the bowl is circular shaped, $S = \pi r^2$ and $D = 2r$; then $r = D/2$.

$$S = \pi (D/2)^2$$

Substituting in the last formula, the blood debit (Q) becomes:

$$Q = v \pi (D/2)^2$$

Adapting the blood flow and exchanges to the variable necessities of circulation leads to the obligation of correlating the capillary circulation with the arterial and the venular one (functional unity of the microcirculation). These vascular components of the masticator gum structure behave like elastic tubes during the blood flow, behavior set by the existence of reticular and elastic fibers (easily extendable) and collagen ones (a bit harder to extend) in the vessel wall structure. Because the flow in elastic tubes is influenced by the elasticity coefficient, it's necessary that the interpretation of the blood flow parameters to be correlated with the vascular wall resistance (stronger in the gums, where most of the arteries have a diameter below 2 mm). The value of the resistance developed by these is directly influenced by the vascular tonus, which is in turn generated by the state of contraction/relaxation of the precapillary myocyte.

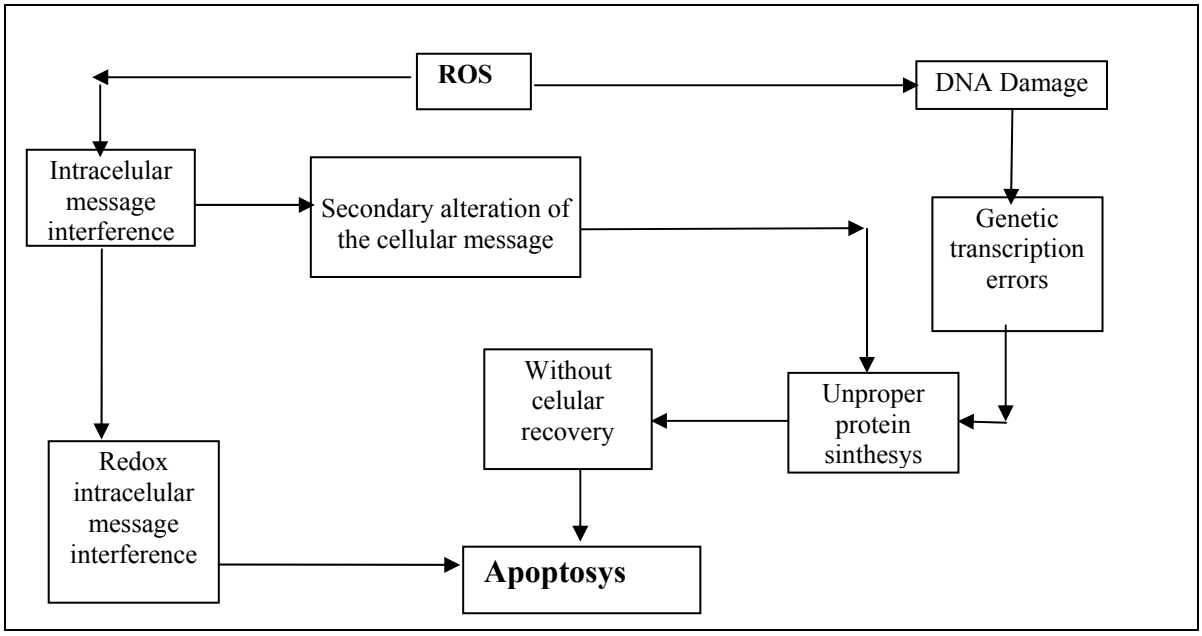

Fig. 1. Synthetic representation of the ROS action mechanism in the genesis of tissue destructive lesions.

This means that modifying the vascular caliber is the main parameter through which the local tissue hemodynamic is controlled. Regulating the micro-circulation in the gum is, alike to other segments of the vascular system, double (nervous and humoral), the latter one being dominant [1, 11].

Coordinating the local vascular-motor phenomenon is dependant, however, of the electronic functioning mode of the morpho-fucntional unit smooth vascular cell – endothelial cell [mio-endothelial regulating unit [11, 12]. Specific to the endothelial cell membrane is the capacity to be stimulated by physical, chemical and neurohormonal factors [2, 9, 14] (Table 1).

The vascular endothelium's capacity of response to stimulation differs territorially, because it correlates with the anatomical origin of various arteries and it forms in the synthesis and secretion of message bearing factors:

– contracting or relaxing, with paracrinic action over the smooth vascular myocyte [11, 14, 15];

– modification of vascular permeability;

– amplifying the adhesiveness of the cells involved in phgocytosis and inflammation to the endothelial vascular cell, quasipresent processes at a woman in menopause, even if only by the fact that developing atherosclerosis implies the existence of an inflammatory process [2, 11, 17] (Table 2).

Besides the direct action exercised by the secretion of some factors with action over the muscular tonus, the endothelium influences the blood debit locally and indirectly through its capacity to absorb and locally metabolize the vasoactive substances [3,10].

Table 1

Main stimulators of the vascular endothelium cell secretion

Physical factors (stretch activated)	– stretch tension of the vascular wall (stretch stress), created by the blood pressure – tangential forces resulted from the blood's laminar flow (shear stress);
Chemical factors (type I messengers)	– arterial oxygen concentration (P_aO_2); – substances with a varied chemical structure: nitric oxide, prostaciclyn, PAF, histamine, bradikine, serotonin, adenine nucleotides (adenosine), PDGF, thromboxane A_2; – reactive derivates of oxygen (hydrogen peroxide, hidroxil etc.) – unspecific acid catabolites: H^+, CO_2, lactic acid;
Neuro-hormonal factors (type II messengers)	– circulatory hormones with systemic action: catecholamines, ADH; – local action hormones: endothelin, substance P, VIP, peptide correlated with the calcitonin gene, angiotensin; – neuromediators: acetilcoline, catecholamines; – cotransmitters of norandrenaline: ATP, neuropeptide Y; – cytokine: interleukine 1(IL 1), TNFα, IFNγ

Table 2

Factors involved in adjusting the functional unity of microcirculation

Factors with a role in adjusting vasomotricity.	– responsible for vasoconstriction: endothelin, angiotensin II, thromboxane A_2, PDGF – responsible for vasodilatation: NO, PAF, prostacyclin etc;
Factors that influence vascular permeability	– arterial oxygen concentration (P_aO_2); – histamine [responsible for endothelial cell contraction (by fixating on its H_1 -receptors) and opening the intercellular junctions, especially the level of the juxtacapillary end of the venula] – serotonin, prostanglandin; – cytokine: TNFα, IL 1, IFNγ; – unspecific acid catabolites: H^+, CO_2, lactic acid;
Factors that act on the adhesion molecules.	– local action hormones: endothelin, substance P, VIP, peptide correlated with the calcitonin gene, angiotensin; – preformed adhesion molecules: selectins, integrins; – endothelially synthesized adhesion molecules; – chemical substances with the role of favorizing the display of preformed adhesion molecules on the membrane of the endothelial cell: PAF, histamine, IL 1, IFNγ, ICAM-1, VCAM-1.

THE PHYSIOLOGICAL EFFECTS INDUCED BY THE MAIN ENDOTHELIAL STIMULATORS OVER THE ADJUSTING MIO-ENDOTHELIAL UNIT OF MICROCIRCULATION

Adjusting the gum hemodynamic, through a humoral and locally nervous mechanism, a process of self-adjustment in fact, depends on four factors:

a. the intensity of local activity, which is the state of mechanical compression and decompression of the masticating gum [5];
b. the physical, chemical and microbial properties of the fluid in the gum sulcus [2, 16, 17];
c. the presence or the absence of the inflammation at soft peridontium(gum component);
d. the chemical and microbial composition of the saliva, with indirect action [16, 18].

Studies regarding microcirculation have proven that the signals for inducing the metabolic vasodilatation in the precapillary sector does not act directly, but correlated with the vessels found downwards. Functionality is secured through debit dependant relaxation, as a result of leading the perturbations of membrane potential, through the connections of the communicating junctions [5].

a. Implying the complex inter-relationship EDRF – menopause in the local control of gum microcirculation

The physical action of estrogens over the vessels is exercised directly, but also through the complex of relaxing factors deriving from the endothelium (EDRF).

a. Directly exercised vasomotricity is the result of connecting estrogen hormones to receptors ERα and ERβ, but also to the ones with a role, still arguable, in transmitting fast estrogenic signals – GPER (GPR_{30}) from the vascular wall. Today it is unanimously accepted that for a woman, age, through the quantity circulating variations of estrogen influences the local blood debit, mediating vasodilatation [18, 19, 20].

b. Relatively recently, it has been proven that up to 40% of the local blood flow is mainly adjusted through gas transmitters, in correlation with the quantity of nitrogen monoxide released by the endothelial cell. This, together with PGI_2 and the still controversial hyperpolarizing factor derived from endothelium (EDHF) are components of the EDRF. The NO synthesis from L-arginine requires the presence of the endothelial form of the nitrous-synthesis calcium-moduline-dependent and the presence of NADPH, and the vasodilatating action is the effect of the guanylate cyclase activated in the muscular cell of the vessels. The growth of NO and PGI_2 secretion by the estrogens takes place only after the hydrolisys of the estrone, state in which it can fixate at the specific receptors in the membrane of the endothelial cell. The process of stimulating the prostacyclin I_2 synthesis requires accentuating the COX_1 synthesis. The state of the arterial tonus, as studies have shown on rats, especially for the vasodilatating action is mediated through the endothelial hyperpolarizing factor.

The responsibility of releasing the factors involved in determining or inhibiting the myocyte's contraction goes to the ion of Ca^{2+} whose intracytoplasmic concentration grows from two sources: cellular influx, by activating the operating calcium canals and by releasing from the deposits attached to the mitochondrial membranes and to the endoplasmatic reticulum. The consequence of reaching a concentration of intracytoplasmic calcium of at least 10^{-5}mol/l is double: creating a connection between Ca^{2+} and calmodulin-M and activating numerous enzymes amongst which: phospholipase, endonuclease and protease. In reverse, by depriving the smooth vascular muscular cell of the calcium ions (reduction of the influx and stimulation of the reflux of Ca^{2+}), the enzyme specific to this type of muscle, myosin-light-chain-kinaza (MLCK) can no longer activate the easy chains of the meromyosin (LLM) and the initiation of the actin-mioyin coupling is no longer made through it, resulting in vasodilatation [1, 11] (see Fig. 2).

The vasodilatating and myorelaxant action of NO is amplified, in pathological cases, through direct or indirect reactions, by the presence of carbon dioxide, of acid catabolites and of components of the oxidative stress.

The importance of estrogen hormone participation over the trophic capacity and the tissue regeneration derives from the role they play outside the target organs (ovaries, uterus and breasts), selectively on the tegument and mucus at many cellular levels:

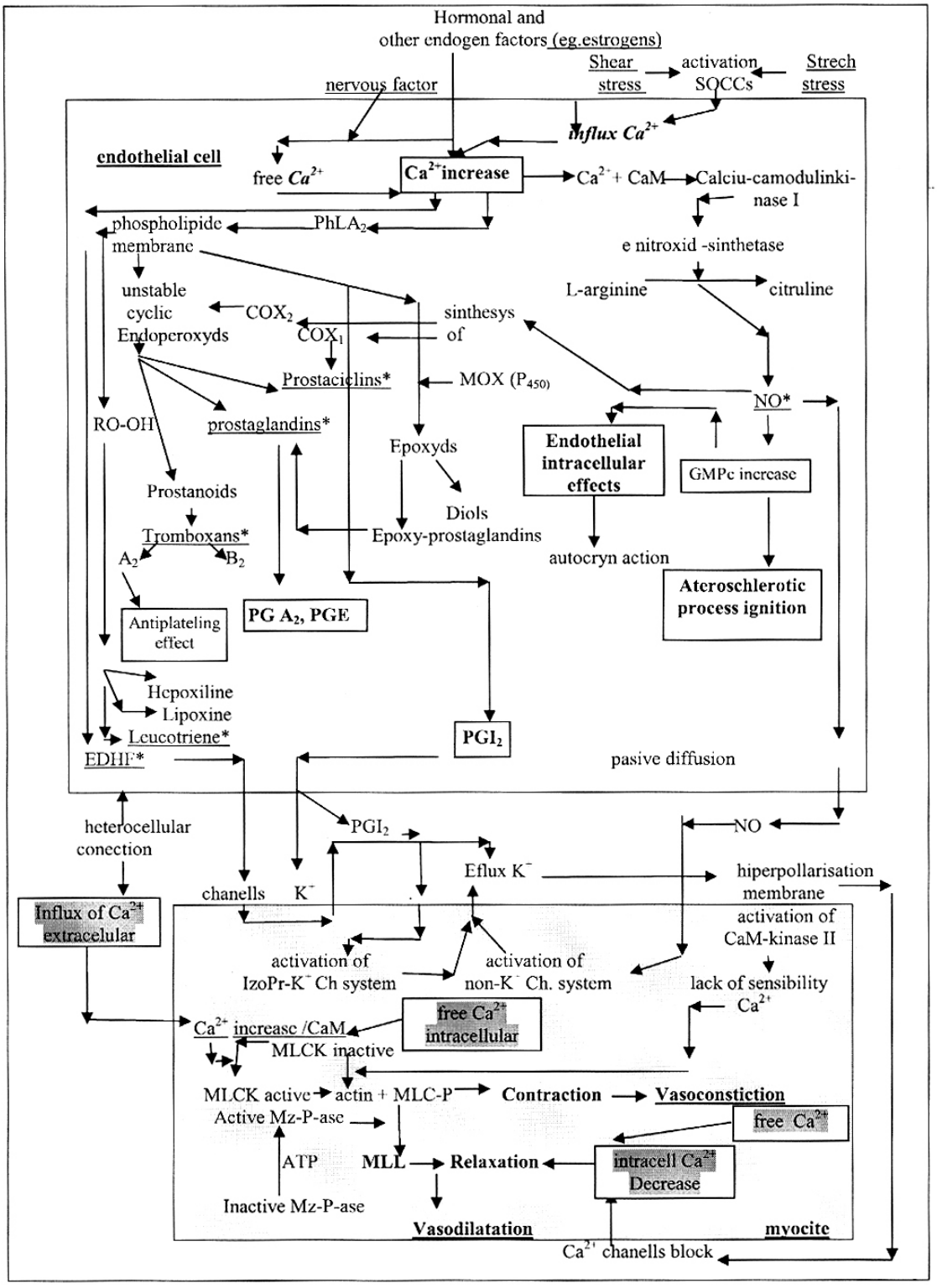

Fig. 2. The local control of microcirculation through the factors of the adjusting myo-epithelial unit.

PGI_2 – prostaglandin I_2; eNOS – endothelial synthetase;
$PhLA_2$ – phospholipase A_2; SOCCs – the reserve operating calcium canals; COX_1: constitutional cycloxygenase; COX_2: stimulated cycloxygenase; LOX: lipoxygenase;
CaM – calmodulin; NO – nitric oxide; Mz: myosin-phophatase
EDHF – hyperpolarizing endothelial factor; RO-OH – hydroperoxides; Mz-P-ase – myosin-phosphatase;
Rec.IzoPr – isoprostane receptors; MLC – phophatase of the easy chain of the myosin; K^+Ch – various K^+ canals; activated: by Ca^{2+}, the reduction of ATP, voltage-dependant or with rectification towards the inside; Green color – myorelaxant ways.

1. The vascular endothelium, through the quantitative control of secretion of the complex of factors derived by the endothelium, influences the dynamics of the atherosclerosis process and the oscillation of blood pressure values, evolution which, in postclimax, as a result of releasing less NO, is accelerated [5,14]. The effect is demonstrated by clinical studies which showed the growth of vasodilatation and local blood flow, being more and more intense as the women in post menopause received substitute estrogenic treatment for a longer period. The mechanism through which the physiological action mentioned is obtained, although still imprecisely determined, seems to be connected to the degree of membrane expression of the estrogenic receptors and to the accentuating of the eNO-synthetase [19].

2. Clinically, the hypoestrogenism from the menopause period is responsible for excessive desquamation in gingivitis, which occurs with a high incidence (80%), compared to the one in the fertile period (28%).

b. Other roles of the estrogen hormones with repercussions on the microcirculation wall

Estrogens induce:

– the reduction of conversion from angiotensin I to angiotensin II, through internalizing the A_1 receptors, with a double effect: reducing vasoconstriction and the local concentration of ROS;

– the suppression of transcription of pro-mitogenic factors, such as: the growth factor derived from plaquettes, interleukina-1 or interleukina-6.

– through their metabolites, not only arterial protection but also limiting the venous risks (dilatation, thrombosis). An argument for this is the presence of the varicella on the pelvic members, which associates high circulating levels of estrogen, which seem to act through the enzymes of the extra-cellular matrix.

c. The role of the vascular endothelin in the degenerative process of the small vessel wall

Amongst the human endothelins, the vascular endothelin ET_1 is responsible for running some processes:

a. physiological, such as:

– adjusting the local blood debit, by modifying the vascular lumen; thus, by fixating on its specific receptors, of the type ET_A at the vascular myocyte membrane, it induces vasoconstriction, and through connecting at the type ET_B located on the membrane of the endothelial cell, it indirectly determines arteriodilatation, by stimulating the synthesis of NO and prostacyclin [21].

– running the first stages of phagocytosis, by easing the expression of the leucocyte adhesion molecules and the chemotactical factors [22].

b. pathological, from arteriosclerosis, where it stimulates the release of fibroblasts and myocytes.

The high incidence of arterial hyper-pressure, at women in post menopause, accelerates, indirectly, the vascular parietal proliferative stimulation process, which grows even more in the coexistence of dyslipidemia, only if for the fact that the endothelial cells are involved in the metabolism of the circulating lipoproteins [14, 21].

d. Involving the estrogen hormones in maintaining the fluido-coagulant balance of blood

Although data from specialized literature regarding the fluido-coagulant balance of blood shows somewhat contradicting data, most researchers admit that estrogens are responsible for the growth of thrombocytic adhesiveness and the reduction of fibrinolytic activity of the vascular endothelium. In post-climax, the laboratory studies have proven, showing the growth of blood fluidity, consequence of:

a. reduction of the thromboxane synthesis, with a consecutive shrinking of plaque aggregation;

b. the growth of fibrinolytic activity at a endothelial level, as well as at the gum fluid level, because the estrogens, physiologically, modulate the enzymes involved in forming the extra-cellular matrix (matrix metalloproteinases) and the plasminogen activators. The growth of matrix-metalo-protein activity, especially of those of types 2, 3, 7 and 9, can initiate the inflammatory gingivitis process, and also the activation on fibrinolysis, because in contact with the fibrine, it generates plasmin. An argument for this is the presence of the plasmin-plasmin inhibitor complex at the gum-liquid interface found in the gum sulcus. The presence of the inhibitor as α_2-antiplasmin proves the activation of the plasminogen (see Fig. 3).

Activation is induced by two of the tissue activators found in the vascular wall: urokinase plasminogen activator (u-PA) and tissue plasminogen activator (t-PA). The post-climax diminish of estrogenism leads to reduced plasmine action, process which involves the the fibrionlytic capacity of the fluid in the gum sulcus.

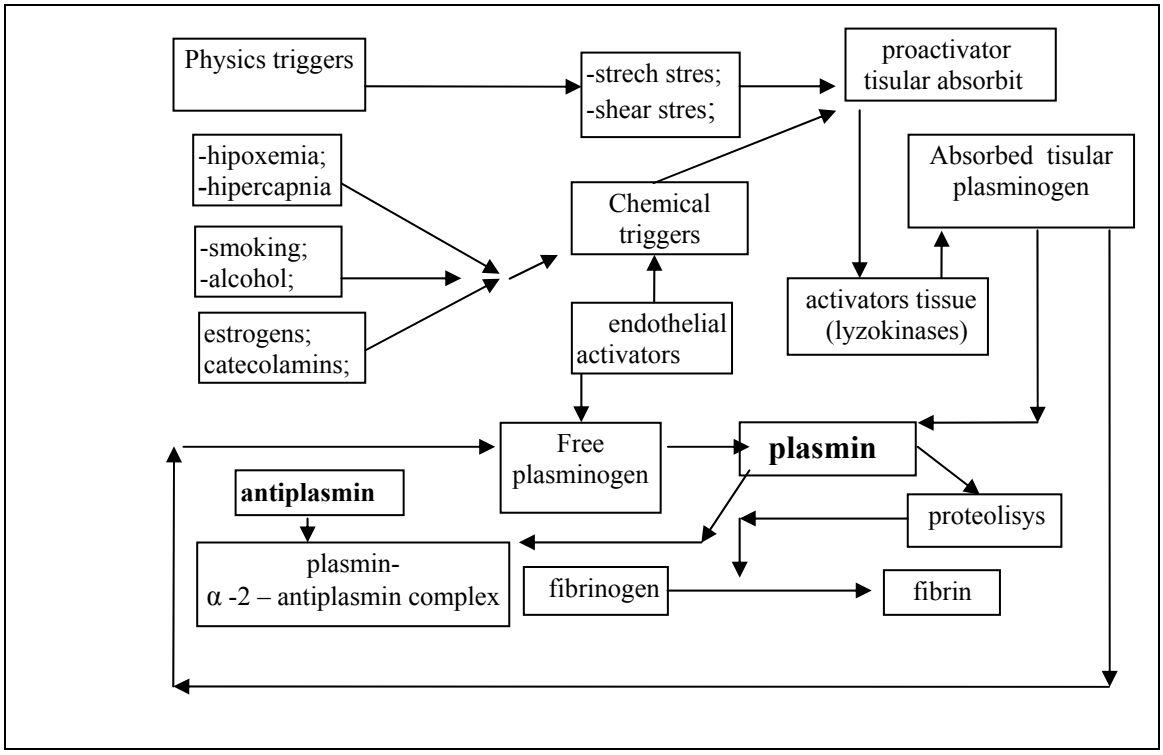

Fig. 3. Activating the fibrinolytic system by stimulating the endothelial cell.

In the base of the biochemical mechanisms described, the interest in post-climax, of the fluido-coagulating balance, through diminishing the fibrinolyic component, explains, at a general level, the lack of difference between sexes when it comes to atherosclerosis incidence and thrombosis incidence, and in the oral cavity pathology, by its action as a favoring factor, it justifies:

a. The high incidence of paradontopathies which appear as an expression of the reduction of unspecific defense mechanisms anti-inflammation. The consequence is the possibility of intersection between the fixation ring and the alveolo-dental ligament, with direct repercussions on the fixation state of the teeth.

b. The possibility of cumulating hypoestrogenism from post-climax with situations that compromise the integrity of the local defense barriers (of physical and chemical nature), such as local traumas or diverse therapies which favor the installation of opportunist infections [11, 15, 25].

e. The functional estrogen – glucocorticoid link in post-climax. The intervention in the inflammatory process

1. Overall, the anfibrinolytical direct action induced by the menopause hypoestrogenism sums up algebraically with the effect generated by affecting the level of secretion through hypoestrogenism, but also of the cortizol transport. Physiologically, at a fertile woman, it is unanimously admitted that the estrogens have the capacity to raise the function of the cortico-suprarenal gland in two ways:

– through interfering in the short feed-back between the hypothalamus and the hypophyse, stimulating the secretion of the coritcotropin-releasing-hormone [23];

– by augmenting the transporter protein secretion of the glucocorticoids: corticosteroid binding globulin (CBG).

The proof that comes to support the intervention of such mechanisms is the particular way of women aged under 47–50, to respond, on an endocrine line, to aggression, through a higher secretion of ACTH compared to men. After menopause has set, the reduced estrogenic plasmatic level diminishes the influence over the glucocorticoid secretion function, with primordial indirect consequences to the trophicity of the gum, through the effect exercised, physiologically, by these hormones on the local protein metabolism and on the lipid one in other tissues, generating dyslipidaemia.

2. Negatively overlapping, in post-climax, of the secretion rate of the two categories of hormones, along with the diminishment of the rate

of connection of the cortizol with the plasmatic transporters, with the predominance of the free cortizolemy, explains the evolution of an inflammatory hive (including the paradental one), comparative to the male [24]. Although, on a quick approximation, the diminishment of the glucocorticoid secretion function seems to have a beneficial effect, the one of reducing the inflammatory processes, the time evolution of the inflammation is quite contrary. This is because the process of amplifying the protein synthesis, induced by the same relative hypocorticism associates with the one of diminishing the protein synthesis, generated through direct action by the hypoestrogenism from the post-climax. An important negative effect of the hypoestrogenism-relative hypocorticism link, in the post-climax, is the interference in one of the phagocytosis stages, through:

a. diminishing the secretion of L- and P-selectin, with consequences on the marginalization process and a slow attachment of the polymorphonuclears on the vascular endothelium [22,25];

b. reducing secretion of E-selectin and integrins, with a direct result of shrinking the process of firm attachment of polymorphonuclears on the vascular endothelium [24]. At the same time, the polymerizing process of the actin G in actin F is reduced, which finally leads to reducing the diapedeses and the movement in the privacy of the tissue interstice of the polymorphonuclears.

c. inhibition of migration towards the inflammatory hive of the leucocytes with phagocytosis capacity;

d. stabilizing the lysosome membranes, with repercussions on the process of releasing hydrolases [26];

e. intensifying the forming of components of the still and mobile phagocytary system (monocytes and macrophage), by activating the AMP_c synthesis of some chemotactism inhibiting peptides, which results into removing the polymorphonuclears from the inflammatory hive;

f. inhibition of the prostaglandin synthesis [25];

g. diminishing the process of forming defense antigen-antibody complexes;

h. inhibition of kinin and plasmin forming (see Fig. 4).

Today, it is unanimously accepted that the intensity of the pro or anti inflammatory response depends not only on the estrogenic metabolism at the vascular wall level, but also on the cytokines involved in mediating the inflammation, which modulates the degree of expression and the intensity of the steroid-sulfatase activity and the estrogenic sulfotransferase [3, 11, 16]. A good example of this is the role of interleukine-1β, which reported to the local level of the 17β-estradiol, induces inhibition of the steroid-sulfatase and the stimulation of the estrogenic sulfotransferase [22]. The two sulfate enzymes intervene indirectly, by forming catechol-estrogenic complexes, form in which the estrogens are catabolised by the COMT.

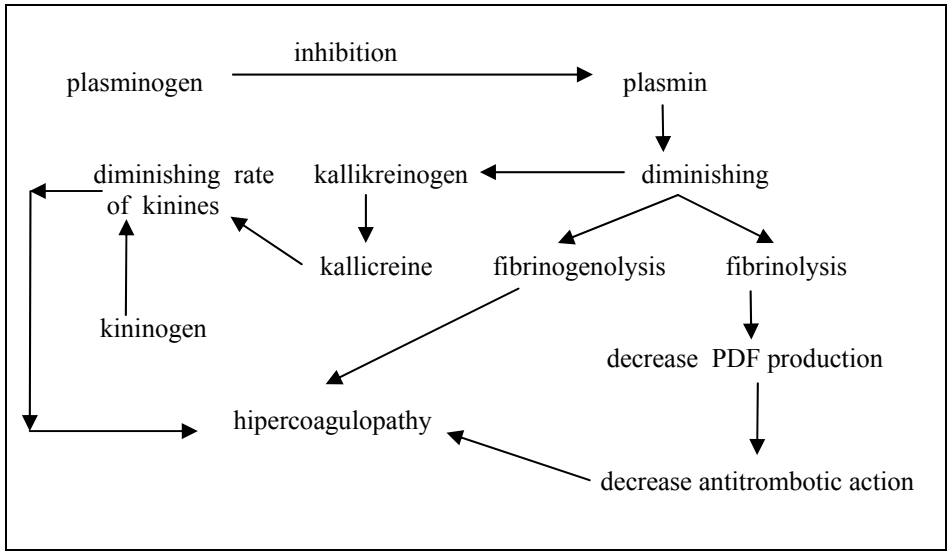

Fig. 4. Interference of the fibrinolytic system through relative hypocorticism with free hypercotizolemia, from post-climax.

3. As a follow-up of the installment of hypoestrogenism, at climax, and of the reduction of the stimulus that amplifies glucocorticoid secretion, comes the diminishment of the histamine and serotonin synthesis processes, with the reduction of the physiological vascular action of these. At an arterial level, the result is a growth of the parietal tonus, with a direct consequence on the local blood debit and on the limit of pain sensitivity at the most varied levels, including paradental [26, 27]. As a follow-up, various stimuli of the triturating dental surfaces are perceived, in post-climax, as having a higher intensity, element which justifies the lack of concordance between the intensity of local pain and the severity of the lesions on the same level.

4. Post-menopause hypoestrogenism, aside from reducing histamine-synthesis, also induces a diminishment of sensitivity in the endothelial venous cells under the action of this vascular amine, effect proved through experiments.

f. The functional estrogen-adrenergic neurotransmission link, in post-climax

Maintaining the vascular tonus is tied to the functionality of the sympathetic nervous system, whose activity is modulated estrogenically by forming cathecol-estrogenic complexes at the receptors (2-hidroxiestradiol and 4-hidroxi-estradiol)[19, 24]. The consequence of these complexes forming, which show an affinity for tyrosinase, is the diminishment of the cathecolamino-synthesis and the COMT activity. The diminishing activity of the cathecol-O-methyl transferase is a competitive one, because the enzyme catabolises both adrenaline and noradrenaline as well as estrogen hormones.

g. The involvement of the hypoestrogenism, from post-climax, in the processes of tissue regeneration

1. The action mechanism of the estrogens, mainly of the 17-β-estradiol in the microcirculation, implies the intracellular endothelial hormonal transport, through diffusion, with fixation on the specific cytosolic receptors, in connection to their concentration in the blood. Forming the cytosolic-estrogen receptor complex is a satiable phenomenon, because the number of specific cytosolic receptors is limited [24, 28]. The next stage is the translocation of the complex formed in the nucleus, where reactions of messenger-ARN synthesis reactions are triggered, which determine the synthesis of structural or functional proteins at the ribosomal level, necessary at a local level (cytokine, chemokine), or at a distance. At a local level, the action is exercised inside the endothelial cell, or paracrine, on adjacent cells, (including on the vascular myocyte) through the junction connections, and at distance after a blood transport (see Fig.5).

The poor protein synthesis in the post-climax period is randomly compensated by the effect of hypoestrogenism, exercised through reduction of secretive functions of the fascicular area of the cortico-suprarenal. Diminishing the secretion of glucocorticoids results in the ADN and ARN synthesis activation, interferingly and ribosomal, so that the processes of tissue regeneration are not too affected.

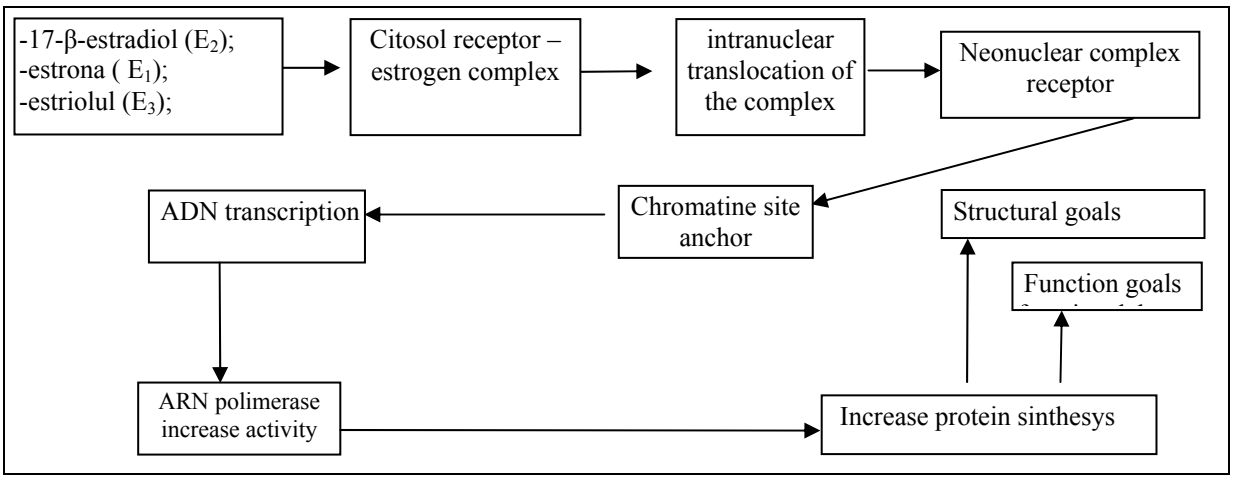

Fig. 5. The synthesis mechanism in the endothelial cell of the relaxing and contracting factors of the vascular myocyte.

2. Accentuating the fibrinolysis process in post-climax determines the growth in the blood concentration of matrix-metaloproteinase [9], with an accentuated process of fibrin degradation, along with other structurally related proteins from all structures where the enzyme can be activated. The enzymatic mechanism described adds itself to the similar one in the process of growing old. Acting at the same time, the two processes become synergic effect-wise, affecting the intra-alveolar fixation of the tooth's root. At this level, the tissue proteolysis process becomes so much more intense, as the thrombosis or inflammation adds itself locally [19]. The coexistence of the local thrombosis for an area of the gum microcirculation, leads to the growth of the local concentration of matrix-metaloproteinase [9], especially in zone where the thrombus adheres to the arterial wall and at the surface of the clot "washed by the blood flow", in situations of incomplete or obstructing thrombus [26]. The presence of arteriosclerosis and of thrombosis implies the already proven coexistence of the inflammatory parieto-vascular process, which has repercussions over the evolution of healing in paradontopathies [3, 10].

3. The scarring of the gum mucus, with the presence of neovascularization, as a result of dental extractions is dependant, amongst other factors, of the level of estrogen, the involvement of steroid hormones in angiogenesis being well known [28, 29]. The physiological action diminishes in post-climax, through the reduction of the number and the quality change of the precursor forming colonies in the red bone marrow, as a result of reduced synthesis of growth factors and molecular adhesion, such as: factor-2 of fibroblast growth, the endothelial growth factor, various others [27, 25].

h. The involvement of estrogen hormones in the lipidic and proteic metabolism, and ROS

Lipidic metabolism

The compared clinical studies have proven, without a doubt, the anti-atherogenic action of estrogen hormones and the growth of incidence of atherosclerotic, after menopause. Biochemically, it is also proven that after the climax, at a woman of 47-50 year old, the following occur: growth of fat tissue mass, of total lipemia and of cholesterol (LDL rises and HDL decreases), with the insignificant reduction of the blood level of triglycerides. Overall, the metabolic-lipidic effects described are responsible for inducing athermatosis, which in post-climax appears with a frequency similar to that met in males [13, 19, 28]. The physio-pathological explanation of the mentioned things, is a result of the diminishing of the role estrogen hormones play in involving themselves at menopause, in the lipido-protidic metabolism and in the DNA transcription process, via the nuclear respiratory factor-1 (NRF-1) [17, 24]. Thus, as a result of hypoestrogenism, it diminishes: inhibition over the grade of expressing the lipogenic gene, cathecol-aminic stimulated lipolysis in adipocytes and the functionality of the lipo-oxidative paths from the myocyte level [13, 30]. The action is a result of composing the effects of estrogenic stimulation of the SREBP-1c genes and PPAR-δ adjusting the expression grade of the lipolytic genes, the direct effect on energy-generating protein kinase and fixating on the ES_1 receptors, which leads to modifying the apolipoprotein-1. At a fertile woman, the estrogens in normal circulating levels, acting on the mitochondrial function, modulate the state of the endothelium in correlation with age. In post-climax, hypoestrogenism, via the free radicals derived from oxygen (ROS) induces the alteration of mitochondrial functions, growing more intensely as the metabolic tissue activity is more intense [27, 31].

Protein metabolism

In the protein metabolism plan, the direct physiological action of estrogens is the activation of the protein synthesis, via nucleus, where it stimulates the ADN transcription, forming ARN_m. The hypoestrogenism characteristic to menopause increases the production not only of structural proteins necessary for tissue regenerations, but also of protein-enzymes, with roles in cellular functionality [19, 24]. The coexistence of the two action mechanisms, in a clinical plan, leads to the gum's retraction, a late healing and poor local defense (see Table 4).

The effect of estrogen in the protein metabolism is an indirect one as well, exercised through the ROS, which in pathological concentrations disturbs either the good flow of protein endergonic reactions, either it destroys ADN, especially from the vascular muscular cell [28, 31].

ROS metabolism

The presence of ROS in the endothelial cell, at physiological levels is the result of the processes of oxidative phosphorilation and the leucotrien and prostaglandin synthesis [12]. Secondary to these, oxidant equivalents are being produced, which generate through successive energetic gain, singlet oxygen, or through electron gain, in the extra-cellular matrix, superoxide, and with the presence of hydrogen from oxygenated water, the hidroxile and molecular oxygen radicals [17, 26] (see Fig. 6).

Table 4

Hipoestrogenic status consequence on main enzymes functionality (after Miller MV şi Duckles PS, modifycated)

Action	Final physiological effects
Decrease of the turnover of the inductive factor of ornithine-decarboxylase	Growth of cell proliferation
Growth of phosphorilation of the telomarese	
Activation of the matrix metalloproteinases-7 Secretion	Permeability augmentation
Reducing the synthesis of glycosiltransferase	Diminishing the time of halving the gluco-corticoid-hormones
Growth of the expression of propyl-hidroxilase-1	Induces the insensitivity of cells to hypoxia
Growth of the link protein of ARN $_M$ to the receptors of angiotensin-1	Membrane interiorization of the angiotensin-1 receptors
Coordinating the phosphorilation processes with the stimulation of the secretion of co-activating steroid receptors	Growth of the control over the ligand dependant of the nuclear transcription

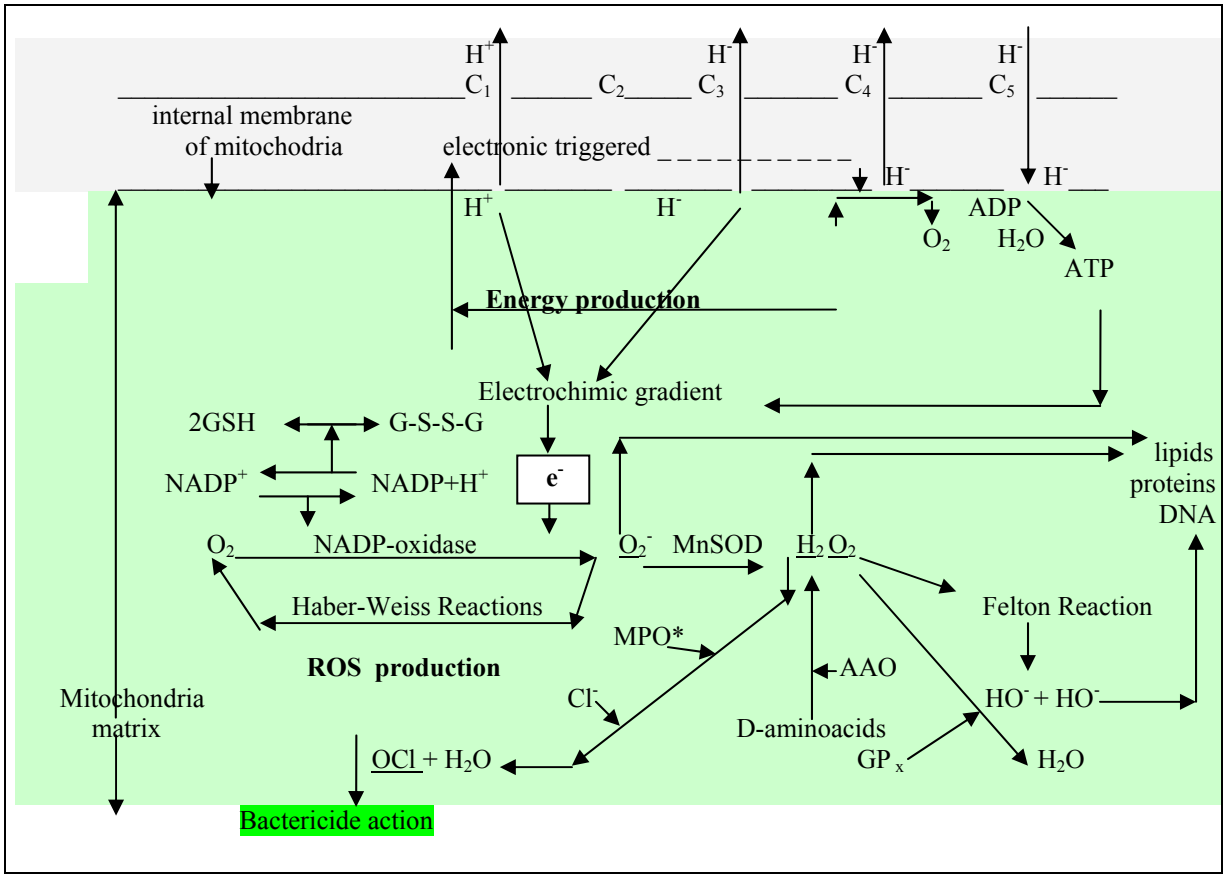

Fig.6. ROS synthesis at the vascular endothelial cell level.

C_1, C_2, C_3, C_4, C_5, C_6 – enzymatic oxidative phosphorilant system;
GP_x – glutation-peroxidases; Mn SoD – mangan-superoxide dimutase;
MPL – mieloperoxidases; ROS – superoxide (O_2), oxygenated water (H_2O_2), radical hidroxile (HO^-);
AAO – D-aminoacidoixdases
* The bactericide action present as a defense mechanism in paradontopathies, takes place at the vascular myocytes and the locally migrated microphages.

Besides the mitochondrial origin, inside the endothelial cell, the ROS can come from other sources as well, which imply activating various enzymes, such as: lipoxigenases, eNO-synthesases, xantinoxidases, nicotinamid-adenindinucleotide-oxidases, etc. The presence at this level of ROS, over the capacities of local inactivation constitutes in vascular oxidative stress, with vascular physio-pathological consequences, especially on cellular exchange [26]. As in the case of other tissues, and at the oral cavity, the trophicity and the capacity to regenerate mucus depends on the proximity of the cells to the source of oxygen and the nutriments brought by the blood. Physiologically, the distribution system of the local microcirculation ensures minimizing this distance of diffusion (maximum 25µ from any cell to the closest capillary), and structuring the capillary wall allows the double exchange capillary-cell, preventing the raise of the interstitial volume, element which would have repercussions, finally, over the integrity and gum functions. Arteriosclerosis, as a favored disease of hypoestrogenism, intervening in the endothelium and the vascular wall, meddles in this trophic exchange [12]. The estrogen hormones influence, indirectly, the local ROS concentrations through the influence they have in the vascular muscular cell [31]. In the vascular myocytes, ROS induce, on one hand, the reduction of angiotensin II synthesis, local hormone which potentiates the ROS synthesis, and on the other hand, the growth of the transcription rate of information of genes responsible for the synthesis of mangan superoxide-dismutase, with a direct consequence of increasing the cellular and extra-cellular levels of the enzyme; at the same time, a diminishment of the NADPH-oxidase activity coexists [13].

CONCLUSION

The effects of estrogen on the gums, benefic for a fertile woman and poorly exercised at the woman in post-climax, are the local expression of the action of these hormones in order to protect the cardiovascular system. The main physiological correlations are: the involvement in the lipidic metabolism, the growth of production in the endothelial cell of factors of the endothelial relaxation complex (nitric oxide and prostacyclin), the interference of vascular oxidative stress, the suppression of the inflammatory response with the augmentation of the growth of endothelial cells and of the angiogenesis. At this moment is accepted unanimously that endothelium's function is dependant on the topography of the vessel and it decreasing with age growing, as result of diminishing exchanges. In these processes, the estrogen hormones have the role of delaying the settling of vascular lesions.

On the other hand, the differential expression of the estrogenic receptors on every endothelial cell and vascular myocyte, like the different capacity of elements in blood able to interact with the structures of the vascular wall, are factors that associate themselves with the heterogeneous affinity of different estrogenic metabolites to membrane receptors.

As far as medical practice goes, there is a therapy indication in cases of peeling gingivitis to use potions or creme-pastes with glucocorticoids. In the advanced paradontopathies the estrogenic substitution therapy can be a solution but only under endocrinological supervision.

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