Spolno različita incidencija autoimunosnih bolesti u žena i povezanost s kardiovaskularnim rizikom

Sex-differentiated Incidence of Autoimmune Diseases in Women and Association with Cardiovascular Risk

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SAŽETAK: Autoimunosne bolesti imaju raznoliku kliničku sliku i mogu zahvatiti bilo koji organ ili organski sustav uzrokujući znatan kronični morbiditet i ovisnost o tuđoj pomoći. Žene imaju 2,7 puta veći rizik nego muškarci da obole od autoimunosne bolesti. Kardiovaskularni (KV) rizik bolesnica sa sustavnim lupusom i reumatoidnim artritisom upućuje na prijevremenu aterosklerozu. Pacijenti sa sustavnim lupusom imaju 5 – 8 puta veću učestalost koronarne bolesti srca nego opća populacija, što se povezuje s dislipidemijom, prisutnošću LDL fenotipa-B te istodobno prisutnom sustavnom upalom uz ostale tradicionalne KV rizike. Prerana ateroskleroza rezultat je tradicionalnih KV čimbenika, čimbenika specifičnih za autoimunosnu bolest i upalnih medijatora. S obzirom na to da su KV bolesti vodeći uzrok smrti, postavlja se pitanje o preventivnoj KV obradi. Ako se razvije bubrežno oštećenje s lupusnim nefritisom i kroničnom bubrežnom bolešću, KV rizik se multiplicira.

SUMMARY: Autoimmune diseases can cause significant and chronic morbidity and disability. Women are at a 2.7 times greater risk than men of acquiring autoimmune diseases. Cardiovascular risk in female patients with systemic lupus erythematosus and rheumatoid arthritis indicates early atherosclerosis. Patients with systemic lupus erythematosus have a 5-8 times higher incidence of coronary artery disease than the general population, which is associated with dyslipidemia, the presence of LDL-phenotype B, and simultaneously present systemic inflammation. Premature atherosclerosis in these patients is the result of traditional cardiovascular risk factors, factors specific to autoimmune disease, and inflammatory mediators. Since cardiovascular diseases are the leading cause of death, this raises the question of preventive cardiology treatment. If kidney failure develops with lupus nephritis and chronic kidney disease, the cardiovascular risk multiplies.

KLJUČNE RIJEČI: žene, autoimunosne bolesti, kardiovaskularni rizik.

KEYWORDS: women, autoimmune diseases, cardiovascular risk.

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Autoimunosne bolesti karakterizirane su oštećenjem tkiva autoprotutijelima i najčešće se pojavljuju u žena fertilne dobi (omjer žene fertilne dobi : muškarci za sustavni lupus iznosi 11 : 1). Klinička je slika vrlo raznolika i bolest može zahvatiti bilo koji organ ili organski sustav. Zahtijeva multidisciplinarni pristup zbrinjavanja, a posebnost problematike očituje se posebice u razdoblju trudnoće, kada se ne misli primarno o hipertenziji, nego o komplikacijama vezanim za autoimunosne bolesti, a to su prije svega sustavni lupus i lupusni nefritis te antifosfolipidni sindrom koji zahtijeva specifično liječenje. Sustavni lupus još uvijek pridonosi mortalitetu[1].

Autoimmune diseases are characterized by tissue damage caused by antibodies and usually manifest in women of fertile age (the ratio of women of fertile age to men for systemic lupus is 11:1). The clinical picture is very diverse, and the disease can affect any organ or organ system. It requires a multidisciplinary approach to treatment, and the unique issues are most pronounced in pregnancy, when hypertension is not the focus, but rather the complications associated with autoimmune diseases, primarily systemic lupus and lupus nephritis as well as antiphospholipid syndrome that requires specific treatment. Systemic lupus still contributes to mortality[1].

Najčešće autoimunosne bolesti

Široki spektar autoimunosnih fenomena i njihovih kliničkih ekspresija u obliku autoimunosnih bolesti uključuje više od dvadeset bolesti, koje su veća prijetnja ženama nego muškarcima[2]. U ukupnoj populaciji bolesnika 75 % oboljelih čine žene. One imaju 2,7 puta veći rizik nego muškarci da obole od autoimunosne bolesti[2]. Takve su bolesti među 10 vodećih uzroka smrtnosti žena svih dobnih skupina do 65. godine života[2]. Prevalencija najčešćih autoimunosnih bolesti iz 1997. godine u Sjedinjenim Američkim Državama po učestalosti pojavljivanja i spolnoj je distribuciji daleko u korist žena: po učestalosti pojavljivanja slijede Gravesova bolest/hipertireoidizam (1000 žena i 150 muškaraca na 100 000 stanovnika), reumatoidni artritis (630 žena i 220 muškaraca na 100 000 stanovnika) i tireoiditis (750 žena i 50 muškaraca na 100 000 stanovnika) koji čine najveći dio autoimunosnih bolesti (gotovo 90 %) u općoj populaciji (uz šećernu bolest tipa 1 i vitiligo)[2]. Procijenjeno je da 1 od 31 stanovnika ima neku od autoimunosnih bolesti[2]. Ostale autoimunosne bolesti koje su mnogo rjeđe od prethodno navedenih, poput multiple skleroze i sustavnog lupusa, češće su u žena, a uz glomerulonefritis (koji podjednako zahvaća oba spola) zahvaćaju 323 232 osoba. Prevalencija ostalih autoimunosnih bolesti je rijetka i iznosi 5,14/100 000 stanovnika. Smatra se da se svakih 5 godina broj novooboljelih s autoimunosnim bolestima povećava za 1 186 015[2].

Autoimunosne bolesti mogu zahvatiti bilo koji organ i dio tijela pa je zbog toga simptomatologija raznolika i nespecifična, a dijagnoza i liječenje izazov su za kliničara. Neke bolesti iz ovoga spektra, ako se ne dijagnosticiraju i liječe, mogu biti opasne za život kao sustavni lupus sa zahvaćenošću bubrega u obliku lupusnog nefritisa i kroničnom bubrežnom bolesti (KBB), no i pojavnošću autoimunosne bolesti srca tipa koronaritisa, endokarditisa ili perikarditisa. Dio autoimunosnih bolesti poput reumatoidnog artritisa često uzrokuju invalidnost i teško narušavaju kvalitetu života i bolesnika i cijele obitelji unatoč danas prisutnim brojnim opcijama liječenja. Za sustavnu sklerozu cijelog života treba tražiti načine uspješnog svladavanja simptoma i liječenja. Sklerodermijska kriza, iako je rijetka, za pacijentičin je život iznimno kritična i povezana je s pogoršanjem bubrežne funkcije. Postoje i druge autoimunosne bolesti kao što su Gravesova bolest i kronični tireoiditis koje se mogu uspješno liječiti, ali je problem u tome što se često ne prepoznaju na vrijeme zbog postupnog i diskretnog nastupa, a nije rijetkost preklapanje više autoimunosnih bolesti poput sustavnog lupusa i tireoiditisa.

Dijagnostičkim postupcima imunosne poremećaje razvrstavamo prema tipu imunosne reakcije (posredovane imunokompleksima, autoprotutijelima, citotoksičnim limfocitima i ostalo), a najjednostavnija je klasifikacija ona koja ih svrstava u organospecifične (Hashimotov tireoiditis, mijastenija gravis, ulcerozni kolitis, Goodpastureov sindrom, autoimunosna hemolitička anemija, primarna bilijarna ciroza) i organonespecifične (sustavni eritemski lupus, reumatoidni artritis, sustavna skleroza, nodozni poliarteritis, Sjögrenov sindrom i upalne miopatije) autoimunosne bolesti.

Uzroci povećane učestalosti autoimunosnih bolesti u žena

Žene i muškarci razlikuju se ne samo u incidenciji autoimunosnih bolesti nego i u drugim obilježjima, pa su zamijećene

Most common autoimmune diseases

The spectrum of autoimmune phenomena and their clinical presentations as autoimmune disease is very wide and includes more than 20 diseases that pose a greater threat to women than to men[2]. In the total patient population, 75% are women. Women have 2.7 times greater risk than men of acquiring an autoimmune disease[2]. Autoimmune diseases are among the 10 leading causes of mortality for women of all age groups up to 65 years of age[2]. The prevalence of the most common diseases in 1997 in the United States by frequency and sex distribution was strongly in favor of women: Graves' disease/hyperthyroidism was the most common (1000 women and 150 men per 100 000 inhabitants), followed by rheumatoid arthritis (630 women and 220 men per 100 000 inhabitants) and thyroiditis (750 women and 50 men per 100 000 inhabitants), which taken together comprise the majority of autoimmune diseases (almost 90%) in the general population (in addition to diabetes type 1 and vitiligo)[2]. It is estimated that 1 out of 31 inhabitants has an autoimmune disease[2]. Other autoimmune diseases such as multiple sclerosis and systemic lupus, which are much rarer than those listed above, are more common in women with glomerulonephritis (which affects both sexes at similar rates) and affect 323 232 persons. The prevalence of other autoimmune diseases is low at 5.14/100 000 inhabitants. It is estimated that every 5 years the number of persons with autoimmune diseases increases by 1 186 015 new cases[2].

Autoimmune disease can affect any organ or part of the body, so their symptomatology is thus varied and unspecific, and diagnosis and treatment represent a challenge for the clinician. Some diseases from this spectrum, if they are not diagnosed and treated, can be life-threatening, such as systemic lupus affecting the kidneys in the form of lupus nephritis and chronic kidney disease (CKD), but also the presence of autoimmune diseases of the heart such as coronaritis, endocarditis, or pericarditis. Some autoimmune diseases such as rheumatoid arthritis are often the cause of invalidity and severely impact quality of life for the patient and their whole family, despite the numerous treatment options available today. Systemic sclerosis requires a life-long search for ways of successful treatment and alleviation of symptoms. Scleroderma crisis, although rare, is extremely critical for the life of the patient and is associated with deterioration of kidney function. There are other autoimmune diseases such as Graves' disease and chronic thyroiditis that can be successfully treated, but the problem is that they are often not recognized on time due to their gradual and discrete progression, as well as the fact that overlap of more than one autoimmune disease, such as systemic lupus and thyroiditis, is also possible.

Diagnostic procedures are used to sort immunological disorders according to the type of immunological reaction (mediated by immune complexes, autoantibodies, cytotoxic lymphocytes, etc.), and the simplest classification is the one that sorts them into organ-specific (Hashimoto's thyroiditis, myasthenia gravis, ulcerative colitis, Goodpasture syndrome, autoimmune hemolytic anemia, primary biliary cirrhosis) and organ-nonspecific (systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polyarteritis nodosa, Sjogren's syndrome, and inflammatory myopathies).

Causes of increased incidence of autoimmune diseases in women

Women and men clinically differ not only in the incidence of autoimmune disease but in other characteristics as well; for in-

mnogo teže kliničke forme iste bolesti u žena u usporedbi s muškarcima[3]. Spolne razlike u incidenciji i težini bolesti posljedica su složenog međudjelovanja genskih, hormonskih, epigenetskih i okolišnih čimbenika, tj. cjelokupne građe, funkcije i uloge ženskog i muškog organizma u prirodi. Postoje razlike ovisno o vrhuncu incidencije, omjeru žene spram muškaraca i o razini estrogena za bolesti poput sustavnog lupusa, reumatoidnog artritisa i sustavne skleroze. Vrhunac incidencije za sustavni lupus jest generativna dob, za reumatoidni artritis perimenopauza, a za sustavnu sklerozu dob nakon 50 – 60 godina. Omjer zahvaćenosti žene : muškarci za sustavni lupus iznosi 15 : 1, za reumatoidni artritis 4 : 1, dok je za sustavnu sklerozu 14 : 1. Visoka razina estrogena povezuje se samo s reumatoidnim artritisom, dok je niska razina estrogena u negativnoj korelaciji s reumatoidnim artritisom i sustavnom sklerozom. Spolne razlike posvuda u svijetu perzistiraju kontinuirano nevezano za stupanj edukacije, medicinsku uslugu i sudjelovanje u kliničkim istraživanjima[3].

Razlike građe i funkcije imunosnog sustava

U ljudi, ali i u životinjskom svijetu, zapažena je imunosna supresija u muškaraca[4]. Žene imaju bolju imunokompetenciju i pojačanu imunosnu reaktivnost[5,6]. Muškarci imaju manji broj limfocita T, a žene u razdoblju postmenopauze smanjeni broj limfocita B i pomagačkih limfocita T. Žene proizvode veću razinu cirkulirajućih protutijela od muškaraca. Nadalje, žene razvijaju jači i humoralni i celularni imunosni odgovor na stimuluse. Zapaženo je da su prevalencija, sklonost i težina parazitarnih infekcija veće u muškaraca nego u žena. S druge strane, u žena su učestalije infekcije virusom *Herpes simplex* zbog povišene razine progesterona.

Rezidentne imunosne stanice u tkivima mogu također biti spolno ovisne i utjecati na preosjetljivost pojedinoga ciljnog organa, što se zapaža u bolestima središnjega živčanog sustava, a na eksperimentalnim se modelima dokazuje da u aktivaciji mikroglije i astrocita te u stvaranju tolerogenih dendritičnih stanica važnu ulogu ima estrogen. Zanimljivo je da se migrena, od koje boluje 15 % ukupnoga stanovništva, mnogo češće pojavljuje u žena i čimbenik je rizika ne samo moždanog udara nego i vaskularnih događaja, posebice infarkta miokarda te je danas jasno povezana s povišenim kardiovaskularnim (KV) rizikom[7,8]. Dakle, autoimunost izolirano nije dostatna za razvoj bolesti bez preosjetljivosti ciljnog organa. U imunokompetenciji ciljnog organa važne su funkcije osjetljivost na apoptozu, autofagija, funkcija mitohondrija i održavanje biokemijskih putova koji omogućuju preživljenje kao što je Th2 put[9,10].

Razlike uvjetovane reproduktivnom ulogom žene

Nastupom puberteta zapaža se veća sklonost nastanku multiple skleroze u usporedbi s pretpubertetskim razdobljem, a u ranom pubertetom rizik postaje veći. Sustavni se lupus prije puberteta pojavljuje u dječaka i djevojčica u omjeru 1:2, a nakon puberteta mnogo više u ženskom spolu nego u muškom (omjer 9 : 1)[11,12]. Problem je i u ustrajnosti terapije[13].

Ulcerozni je kolitis jednako zastupljen u obama spolovima u doba adolescencije, no u ranoj odrasloj dobi omjer se povećava na 4 : 1 u korist muškaraca[12].

stance, significantly more severe clinical forms of the same disease have been observed in women in comparison with men[3]. Sex differences in incidence and severity are the consequence of complex interrelations of genetic, hormonal, epigenetic, and environmental factors, i.e. the overall structure, function, and role of the female and male organisms in nature. There are differences depending on peak incidence, the ratio of women compared with men, and the level of estrogen for diseases such as systemic lupus, rheumatoid arthritis, and systemic sclerosis. Peak incidence for systemic lupus is generative age, perimenopause for rheumatoid arthritis, and age 50-60 for systemic sclerosis. The prevalence ration for women vs. men in systemic lupus is 15:1, 4:1 for rheumatoid arthritis, and 14:1 for systemic sclerosis. High levels of estrogen are associated only with rheumatoid arthritis, while low estrogen levels are negatively correlated with rheumatoid arthritis and systemic sclerosis. Sex differences are constant across the world regardless of education levels, health care service, and participation in clinical trials[3].

Differences in the structure and function of the immunological system

Immunological suppression has been observed human males and in the animal world in general[4]. Women have superior immunocompetence and stronger immunological reactivity[5,6]. Men have a lower T-lymphocyte count, and women have a reduced number of B-lymphocytes and helper T-cells. Women produce a higher level of circulating antibodies than men. Furthermore, women develop both stronger humoral and stronger cellular immunological responses to stimuli. It has been observed that the prevalence, susceptibility, and severity for parasite infections is higher in men than in women. On the other hand, herpes simplex infection is more common in women due to higher levels of progesterone.

Resident immunological cells in tissues can also be sex-differentiated and influence the oversensitivity of individual target organs, which can be observed in central nervous system diseases, and experimental models have demonstrated the important role of estrogen in the activation of microglia and astrocytes as well as the creation of tolerogenic dendritic cells. It is interesting that migraine, which affects 15% of the total population, is far more common in women and represents a risk factor not only for stroke but for vascular events as well, especially myocardial infarction, and is now clearly associated with elevated cardiovascular (CV) risk[7,8]. Therefore, autoimmunity in isolation is not sufficient for the development of disease without oversensitivity of the target organ. Important functions for target organ immunocompetence are sensitivity to apoptosis, autophagy, mitochondrial function, and the maintenance of biochemical pathways that allow survival such as the Th2 pathway[9,10].

Differences stemming from the reproductive role of women

A higher tendency for sclerosis has been observed with the advent of puberty in comparison with preadolescence, and the risk increases for early puberty. Before puberty, systemic lupus manifests in boys and girls at a ratio of 1:2, but the incidence is much higher for women after puberty (9:1 in favor of women)[11,12]. Long-term treatment adherence is also an issue[13].

Ulcerative colitis is equally represented in both sexes during adolescence, but in early adulthood the ratio increases to 4:1 in favor of men[12].

U trudnoći, u kojoj je majka domaćin fetusu-nositelju stranih antigena, imunosni Th1 odgovor na stimuluse nužno je suprimiran, a dominira Th2 limfocitni odgovor. Osim toga, regulacijski T limfociti posreduju aktivnu imunološku toleranciju. U trudnoći se zapaža remisija reumatoidnog artritisa i ankilozantnog spondilitisa (Th1 posredovanih bolesti). Promjena povezana s trudnoćom jest i pojava malog proteina iz obitelji *heat shock* proteina HSP 10 (chaperonin 10) koji ima povoljna imunomodulatorna svojstva. Trudnoća ne utječe jednako na težinu kliničke slike u multiploj sklerozi, dok se u ankilozantnom spondilitisu, multiploj sklerozi i reumatoidnom artritisu zapaža remisija. Suprotno tomu, sustavni lupus u većem ili manjem stupnju pogoršava se u trudnoći. Trudnoća može inducirati i prvu pojavu autoimunosne bolesti pa se tako opisuje nastup fulminantnoga autoimunosnog dijabetesa te tireoiditisa koji se očituje postpartalno. Autoimunosne bolesti u trudnoći mogu rezultirati manifestacijama bolesti u fetusa kod multiple skleroze, sustavnog lupusa, tireotoksikoze, autoimunosne trombocitopenične purpure i kožnog (kutanog) oblika lupusa. Pasivna transmisija autoprotutijela anti-Ro i anti-La u sustavnom lupusu može uzrokovati razvoja kongenitalnog bloka u novorođenčeta, odnosno znatne aritmije. Autoimunosne bolesti mogu se pojaviti i kod hiperstimulacije ovarija te u situacijama potpomognute trudnoće, primjerice u žena s multiplom sklerozom i sustavnim lupusom, a žene s antitireoidnim protutijelima u postupcima potpomognute oplodnje imaju veći rizik od pobačaja. Dakle, promjene u trudnoći specifične su za oblik autoimunosne bolesti. Specifična promjena zapažena u trudnoći jest i izmjena stanica između fetusa i majke – mikrokimerizam, što se smatra mogućim „okidačem" za razvoj autoimunosne bolesti. Stanice mikrokimere mogu perzistirati kao inaktivne dendritične stanice i limfociti i pri ekspoziciji okolišnim „trigerima", promjeni citokinskoga profilnog miljea, infekcijama i hormonskim promjenama postati aktivirane i pokrenuti razvoj autoimunosnih bolesti.

Menopauzne promjene utječu na smanjenje učestalosti relapsa u sustavnom lupusu, ali, s druge strane, uzrokuju intenzivnija oštećenja već prethodno zahvaćenih organa. U reumatoidnom artritisu pojavljuje se progresija u viši stupanj fizičke onesposobljenosti, a promjene na bubrezima uz reumatoidni artritis očituju se spektrom različitih bolesti[14]. Mogu nastati komplikacije poput sekundarne amiloidoze sa zahvaćanjem bubrega i očitovanjem nefrotskog sindroma, no i zahvaćenošću koštane srži uz nastanak teškog oblika sekundarne anemije, što uzrokuje komplikacije i razvoj sekundarnog infarkta miokarda, odnosno KV komplikacije koje su najčešći uzrok smrtnosti u ovoj populaciji[15]. Autoimunosni hepatitis pojavljuje se, osim u tinejdžerskim godinama, i nakon menopauze. Ipak, rana je menopauza poseban dio ženina života koji nosi rizik od novonastalog sustavnog lupusa i reumatoidnog artritisa[16,17]. Prikupljeni su dokazi o ulozi spolnih hormona estrogena, progesterona, androgena i prolaktina u autoimunosti. U sustavnom su lupusu limfociti T aktivirani preko estrogenskih receptora α i β, za razliku od zdravih osoba. Isto tako, u reumatoidnom artritisu koncentracija estrogena je povišena u sinovijalnoj tekućini. Progesteron ima antiinflamatorni učinak u imunosnom sustavu, a receptori za taj hormon nalaze se na mnogim imunokompetentnim stanicama.

In pregnancy, the mother is host to the fetus – a carrier of foreign antigens – so the immunological Th1 response to stimuli is necessarily suppressed, and the Th2 lymphocytic response dominates. Additionally, regulatory T-cells mediate active immunological tolerance. Remission of rheumatoid arthritis and ankylosing spondylitis (Th1 mediated diseases) has been observed in pregnancy. Changes associated with pregnancy include the presence of the small protein from the "heat shock" protein family, HSP 10 (chaperonin 10), which has beneficial immunomodulatory effects. Pregnancy does not have a unidirectional effect on the severity of the clinical picture in multiple sclerosis, but remission can be observed in ankylosing spondylitis, multiple sclerosis, and rheumatoid arthritis. Conversely, systemic lupus is exacerbated to a greater or lesser degree in pregnancy. Pregnancy can also induce the first manifestation of autoimmune disease, and the development of fulminant autoimmune diabetes and thyroiditis that becomes evident postpartum has been reported. Autoimmune diseases in pregnancy can result in disease manifestation in the fetus in the form of multiple sclerosis, systemic lupus, thyrotoxicosis, autoimmune thrombocytopenic purpura, and cutaneous lupus. Passive transmission of anti-Ro and anti-La autoantibodies in systemic lupus can lead to the development of congenital block in the newborn, as well as significant arrhythmia. Autoimmune disease can also manifest due to hyperstimulation of the ovaries and in situations related to assisted pregnancy, for instance in women with multiple sclerosis and systemic lupus, and women with antithyroid antibodies have greater risk of abortion in assisted reproduction procedures. Thus, the changes in pregnancy are specific to the form of autoimmune disease. Specific changes noted in pregnancy are also the exchange of cells between the fetus and the mother – microchimerism – which is considered a possible trigger for the development of autoimmune disease. Microchimera cells can persist as inactive dendritic cells and lymphocytes and activate due to exposure to environmental triggers, changes in the cytokine profile, infections, and hormonal changes, causing the development of autoimmune disease.

Menopausal changes influence the reduction of relapse frequency in systemic lupus, but on the other hand also lead to more intensive damage to previously affected organs. Rheumatoid arthritis progresses to a higher degree of physical incapacitation, and the changes to kidneys in rheumatoid arthritis manifest in a spectrum of different diseases[14]. Complications can occur, such as secondary amyloidosis affecting the kidneys and manifesting with nephrotic syndrome or affecting the bone marrow with the development of a severe form of secondary anemia, which leads to complications and the development of secondary myocardial infarction or CV complications, which are the most common cause of mortality in this population[15]. Other than in puberty, autoimmune hepatitis manifests after menopause as well. Still, early menopause is a special aspect of women which brings the risk of newly-acquired systemic lupus and rheumatoid arthritis[16,17]. There is ample data on the role of the sex hormones estrogen, progesterone, androgen, and prolactin in autoimmunity. In systemic lupus, T-cells are activated through estrogen receptors α and β, unlike in healthy persons. Similarly, the concentration of estrogen in synovial fluid is elevated in rheumatoid arthritis. Progesterone has an anti-inflammatory effect in the immunological system, and the receptors for that hormone can be found on many immunocompetent cells.

Doprinos genskih obilježja spolno različitoj incidenciji autoimunosnih bolesti

Genske se promjene odnose na gene ili skupinu gena koji nose preosjetljivost za bolest, nadalje, na kromosomske razlike te na epigenetske promjene. HLA geni (uglavnom DR i DQ) povezuju se s mnogim autoimunosnim bolestima kao što su mijastenija gravis, multipla skleroza i sustavni lupus, a oni imaju središnju ulogu u prezentaciji antigena CD4+ limfocitima. Povezanost HLA gena i autoimunosnih bolesti jasno se očituje u ženskom spolu. Žene imaju veću učestalost HLA DR4 od muškaraca pa time i veći rizik za nastanak bolesti koja je vezana uz taj alel – autoimunosni hepatitis tipa 1. Jaka je povezanost HLA DR2, DQ6 s multiplom sklerozom u žena. Genotip HLA DRB1*0401/*0401 povezan je s nastankom reumatoidnog artritisa u žena. U sustavnom lupusu genski rizik od HLA gena veći je u muškaraca. Od non-HLA gena važni su geni koji kodiraju molekulu CTLA-4 na limfocitima T, lokus 1 kisele fosfataze, IL-10 i apolipoprotein. Polimorfizam gena za IL-10 povezan je s težim oblikom Hashimotova tireoiditisa, reumatoidnog artritisa i s primarnim Sjögrenovim sindromom[18]. Geni na X-kromosomu također pridonose nastanku autoimunosti jer je zapažena njihova inaktivacija u autoimunosnoj bolesti štitnjače, reumatoidnom artritisu i sustavnoj skerozi, ali ne i kod sustavnog lupusa. Gubitak Y-kromosoma ovisan o godinama zapažen je kod primarne bilijarne ciroze. Od epigenetskih mehanizama važan je gubitak mikroRNA (regulira gene vezane za autoimunosne bolesti) koja je različito hormonski i kromosomski regulirana u muškaraca i žena i može pridonijeti spolnom dimorfizmu autoimunosnih bolesti.

Nefrološke komplikacije autoimunosnih bolesti tipa sustavnog lupusa s osvrtom na trudnoću

U bolesnika s autoimunosnim bolestima, pogotovo sustavnim lupusom, može se razviti sekundarni antifosfolipidni sindrom (APS). To je autoimunosni poremećaj okarakteriziran pojavom krvožilnih tromboza, a može se pojaviti i kao primarni APS u zdravih osoba[19]. Dijagnoza APS-a temelji se na specifičnim autoprotutijelima u krvi i kliničkim manifestacijama.

Zahvaćenost bubrega je jedan od najčešćih manifestacija sustavnog lupusa. U više od polovice bolesnika sa sustavnim lupusom razvije se lupusni nefritis, što je nepovoljan prognostički čimbenik koji u 17 – 25 % oboljelih vodi do završnoga stupnja KBB-a i potrebe za nadomjesnim bubrežnim liječenjem[20]. Tijek je bolesti proliferativnog lupusnog nefiritsa nepredvidljiv[13]. Patohistološki dokazana aktivna bubrežna oštećenja zahtijevaju kombinaciju imunosupresivne (ciklofosfamid ili mikofenolat mofetil) i glukokotrikoidne terapije za proliferativni (tip III./IV.) i membranski lupusni nefritis (tip V.). Rituksimab je sekundarna linija liječenja[21]. Posebnost je doba trudnoće u bolesnica sa sustavnim lupusom. Trudnice s aktivnim lupusnim nefritisom zahtijevaju redovito praćenje zbog povezanosti s većom učestalosti komplikacija za majku i dijete. U kohortnom istraživanju provedenom na 166 trudnica, proteinurija u prvome tromjesečju trudnoće rezultirala je povećanom stopom spontanih pobačaja za 2,6 puta. U istraživanju provedenom u 65 trudnica bubrežno oštećenje definirano proteinurijom, bez preeklampsije, hematurije ili staničnog

The contribution of genetic features to the sex differentiation in the incidence of autoimmune diseases

Genetic changes concern genes or groups of genes which carry oversensitivity to disease, chromosomal differences, and epigenetic changes. HLA genes (mostly DR and DQ) are associated with many autoimmune diseases such as myasthenia gravis, multiple sclerosis, and systemic lupus and have a central role in the presentation of the CD4+ gene to lymphocytes. The association of the HLA genes and autoimmune diseases is clear in women. Women have a higher prevalence of HLA DR4 than men, and thusly a higher risk of the development of disease associated with that allele – autoimmune hepatitis type 1. There is a strong association of HLA DR2, DQ6 with multiple sclerosis in women. The genotype HLA DRB1*0401/*0401 is associated with the development of rheumatoid arthritis in women. In systemic lupus, the genetic risk from the HLA gene is higher in men. Among non-HLA genes, of importance are the genes that code the molecule CTLA-4 on T-cells, acid phosphatase locus 1, IL-10, and apolipoproteins. Polymorphism of genes for IL-10 is associated with a more severe form of Hashimoto's thyroiditis, rheumatoid arthritis, and primary Sjogren's syndrome[18]. Genes on the X chromosome also contribute to the development of autoimmunity, since their inactivation has been observed in autoimmune thyroid disease, rheumatoid arthritis, and systemic sclerosis, but not in systemic lupus. The loss of the Y chromosome dependent on age has been observed in primary biliary cirrhosis. Among epigenetic mechanisms, of importance is the loss of microRNA (regulating genes associated with autoimmune diseases), which is differently regulated hormonally and chromosomally in men and women and can contribute to sexual dimorphism in autoimmune diseases.

Nephrological complications in systemic lupus type autoimmune diseases with reference to pregnancy

Patients with autoimmune diseases, especially systemic lupus, can develop secondary antiphospholipid syndrome (APS). This is an autoimmune disorder characterized by the appearance of blood vessel thrombosis, and can also manifest as primary APS in healthy persons[19]. The diagnosis of APS is based on clinical manifestations and specific autoantibodies in the blood.

One of the most common manifestations of systemic lupus is to affect the kidneys. More than half of patients with systemic lupus erythematosus (SLE) develop lupus nephritis, which is a negative prognostic factor leading to end stage chronic kidney diseases in 17-25% of patients and requiring renal replacement therapy[20]. The course of the disease in proliferative lupus nephritis is unpredictable[13]. Pathohistologically demonstrated active kidney damage requires a combination of immunosuppressive medication (cyclophosphamide or mycophenolic acid) and glucocorticoid treatment for proliferative (type III/IV) and membranous lupus nephritis (type V). Rituximab is the secondary line of treatment[21]. A unique challenge is the period of pregnancy in patients with systemic lupus. Pregnant women with active lupus nephritis require regular monitoring due to the association with higher incidence of complications for the mother and child. In a cohort study conducted on 166 pregnant women, proteinuria in the first month of pregnancy

detritusa u urinu, prognostički je čimbenik fetalnog zastoja u rastu i/ili preeklampsije. Pri izboru oblika liječenja u trudnoći potrebno je razlučiti korist od štetnosti. Liječenje tijekom trudnoće ne smije se ukinuti jer može uzrokovati ozbiljni morbiditet te mortalitet majke i djeteta[22]. Za sada još uvijek ne postoji alternativni oblik protuupalnim lijekovima i steroidima koji se danas primjenjuju za liječenje sustavnog lupusa no istraživanja navode i učinak monoklonskih protutijela poput tokalizumaba (humanizirana monoklonska protutijela na IL-6) i ekulizumaba (rekombinantni potpuno humanizirani IgG2/IgG4 monoklonsko protutijelo na komplement C5)[13]. Studije podržavaju korisnost uloge hidroksiklorokina u kontroli aktivnosti bolesti i prevenciji pogoršanja tijekom trudnoće te preporučuju prihvatljiv omjer rizika/koristi oralnih kortikosteroida, azatioprina i kalcineurinskih inhibitora (ciklosporin A, takrolimus). Mikofenolat mofetil, metotreksat i leflunomid treba izbjegavati zbog moguće ili poznate teratogenosti u trudnoći. U trudnoći su kontraindicirani i ciklofosfamidi te ACE inhibitori.

Porast serumskog kreatinina i/ili proteinurije, pojava patološkoga mokraćnog sedimenta ili smanjenje klirensa kreatinina (eGFR) kasni su pokazatelji pogoršanja bubrežne funkcije („renal flare") zbog aktivne bolesti. Relapsi se pojavljuju u 45 % bolesnika s učestalošću pogoršanja od 0,1 do 0,2 po bolesniku u godini dana. Ako se relapsi definiraju mokraćnim sedimentom (aktivni: >5 bijelih krvnih stanica po vidnom polju) i smanjenjem eGFR-a, važan su, no zakašnjeli pretkazivač pogoršanja KBB-a pa su stoga osobite važna istraživanja koja upućuju na mogućnost ranih biomarkera pogoršanja bolesti poput mikroRNA[23].

Dodatni kardiovaskularni rizik u bolesnica s autoimunosnim bolestima

U bolesnica s autoimunosnim bolestima dodatno je povišen KV rizik zbog često prisutne hipertenzije, i to posebice maskirane koja se ne može dijagnosticirati bez kontinuiranog mjerenja arterijskoga tlaka. Hipertenzija u autoimunosnim bolestima (koja se može prvotno očitovati migrenama), kao i hiperlipidemija (niski HDL te povišeni urati u sustavnom lupusu, hiperkolesterolemija i inzulinska rezistencija češća je u reumatoidnom artritisu u usporedbi sa zdravom populacijom bez autoimunosne bolesti) nedostatno su prepoznate i liječene, što dodatno povećava KV rizik[24,25]. Bolesnici sa sustavnim autoimunosnim bolestima imaju veći KV rizik, koji je nedovoljno prepoznat i podcijenjen. Kardiovaskularni rizik u bolesnica sa sustavnim lupusom i reumatoidnim artritisom upućuje na prijevremenu aterosklerozu. Pacijentice sa sustavnim lupusom imaju 5 – 8 puta veću učestalost koronarne bolesti srca nego opća populacija, što se povezuje s dislipidemijom, prisutnošću LDL fenotipa B te istodobno prisutnom sustavnom upalom uz ostale tradicionalne KV rizike[2,25]. Autoimunosna bolest sama je po sebi nezavisni KV čimbenik te bi se ta činjenica trebala uzimati u obzir pri obradi bolesnika s autoimunosnim bolestima koje su mnogo učestalije u žena. Potrebno je procijeniti ukupni KV rizik: probir visokog / vrlo visokog kardiovaskularnog rizika s trima ili više čimbenika rizika (tlak pulsa, dob žene >65 godina, pušenje, arterijski tlak, ukupni kolesterol >5,0 mmol/L, LDL kolesterol >3,0 mmol/L, glukoza >6,9 mmol/L, pretilost, obiteljska anamneza preuranjene KV bolesti), sa šećernom bolesti, hipertenzijom 2. – 3. stupnja, sa supkliničkim oštećenjem ciljnih organa

resulted in 2.6 times higher rate of pregnancy loss. In a study conducted on 65 women, kidney damage defined as proteinuria without preeclampsia, hematuria, or cell detritus in urine was a prognostic factor for intrauterine growth restriction and/or preeclampsia. When choosing the form of treatment in pregnancy, it is necessary to distinguish benefits from harm. Treatment should not be terminated during pregnancy because this can lead to serious morbidity and mortality in the mother and child[22]. There is still no alternative form of treatment to anti-inflammatory medication and steroids that are currently applied in the treatment of SLE, but studies have noted the effect of monoclonal antibodies such as tocilizumab (humanized monoclonal antibodies to IL-6) and eculizumab (recombinant fully humanized IgG2/IgG4 monoclonal antibodies to complement C5)[13]. Studies support the beneficial role of hydroxychloroquine in the control of disease activity and prevention of progression during pregnancy, recommending an acceptable risk/benefit ratio for oral corticosteroids, azathioprine, and calcineurin inhibitors (cyclosporine A, tacrolimus). Mycophenolic acid, methotrexate, and leflunomide should be avoided due to potential or known teratogenicity in pregnancy. Cyclophosphamides and ACE inhibitors are also contraindicated in pregnancy.

Elevation of serum creatinine and/or proteinuria, the presence of pathological urine sediment, or reduction in estimated glomerular filtration rate (eGFR) are late indicators of deterioration of kidney function ("renal flare") due to active disease. Relapses occur in 45% of patients, with an incidence of deterioration of 0.1 to 0.2 per patient per year. If the relapses are defined using urine sediment (active >5 white blood cells per visual field) and reduced eGFR, they are an important, though belated, prognosticator for CKD deterioration; consequently, studies that indicate the possibility of early biomarkers of disease progression such as microRNA are especially important[23].

Additional cardiovascular risk in patients with autoimmune diseases

CV risk is elevated in female patients with autoimmune diseases due to the common presence of hypertension, especially masked hypertension that cannot be diagnosed without ambulatory blood pressure monitoring. Hypertension (that can initially manifest as migraines) and hyperlipidemia (low HDL and elevated urate levels in systemic lupus; hypercholesterolemia and insulin resistance is more common in rheumatoid arthritis compared with the healthy population without autoimmune disease) in autoimmune diseases are inadequately recognized and diagnosed, which additionally increases CV risk[24,25]. Patients with systemic autoimmune diseases have higher CV risk that is underestimated and insufficiently recognized. The cardiovascular risk in female patients with systemic lupus and rheumatoid arthritis indicates premature atherosclerosis. Female patients with systemic lupus have a 5-8 times higher incidence of coronary artery disease compared with the general population, which is associated with dyslipidemia, the presence of LDL phenotype-B, and the simultaneous presence of systemic inflammation with other traditional CV risks[2,25]. Autoimmune disease is itself an independent CV factor, which should be taken into account when processing patients with autoimmune diseases, which are far more common in women. It is necessary to estimate total CV risk: screening for high/very high cardiovascular risk with three or more risk factors (pulse pressure, female age >65, cigarette smoking, blood pressure, total cholesterol >5.0 mmol/L, LDL cholesterol >3.0 mmol/L, blood

(hipertrofija lijeve klijetke, karotidnim plakom, povišenom krutošću arterija, povišenim kreatininom / sniženim klirensom kreatinina, proteinurijom), prisutnom KV bolesti (infarkt miokarda, moždani udar) ili bubrežnom bolesti. Potrebno je liječiti čimbenike rizika poput hipertenzije antihipertenzivnom terapijom, hiperlipidemiju statinima i fenofibratima, kao i liječiti osnovnu autoimunosnu bolest temeljnim lijekovima i specifičnim terapijskim mjerama[25].

Zaključak

Incidencija autoimunosnih bolesti povećava se pojavom reproduktivne sposobnosti žene i hormonskih promjena u ciklusima promjena reproduktivne funkcije. Nedostaju novi biomarkeri pravodobne dijagnostike, kao i praćenja aktivnosti autoimunosnih bolesti te bi u budućnosti rutinsko određivanje mikroRNA u krvi, mokraći ili bioptatu tkiva moglo pridonijeti smanjenju kardiovaskularnog rizika u žena.

glucose >6.9 mmol/L, obesity, family history of premature cardiovascular disease), with diabetes, hypertension stage 2-3, subclinical target organ damage (left ventricular hypertrophy, carotid plaque, increased arterial stiffness, increased creatinine/ decreased creatinine clearance, proteinuria), present CV disease (myocardial infarction, stroke), or kidney disease. It is necessary to treat risk factors such as hypertension using antihypertensive therapy, hyperlipidemia using statins and fenofibrates, and also treat the underlying autoimmune disease with basic medication and specific treatment measures[25].

Conclusion

The incidence of autoimmune diseases increases with the advent of reproductive capabilities in women and hormonal changes from cycles in reproductive function. We are lacking new biomarkers for timely diagnosis as well as monitoring the activity of autoimmune diseases; in the future, routine measurement of microRNA in the blood, urine, or biopsied tissue could contribute to the reduction of cardiovascular risk in women.

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