Menopauza i klimakterij kao rizik za razvoj bubrežno-srčanih bolesti

Menopause and climacteric as a risk factor for renal and cardiovascular disease

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SAŽETAK: Rizik za razvoj srčanožilne bolesti znatno se povećava u razdoblju menopauze, koja je udružena s ubrzanim razvojem vaskularne bolesti i osteoporoze. Razvoju srčanožilne bolesti pridonose povišen arterijski tlak, dislipidemija, preddijabetes i dijabetes, kao i kronična bubrežna bolest. Smanjenje bubrežne funkcije povećava ukupnu smrtnost i kardiovaskularnu smrtnost, neovisno o tradicionalnim čimbenicima rizika.

SUMMARY: The risk of cardiovascular disease increases significantly in menopause, which is associated with faster development of vascular disease and osteoporosis. Elevated blood pressure, dyslipidemia, pre-diabetes and diabetes, and chronic kidney disease contribute to cardiovascular disease development. Impaired kidney function increases total mortality and cardiovascular mortality independently of the traditional risk factors.

KLJUČNE RIJEČI: žene, menopauza, kardiovaskularna bolest.

KEYWORDS: women, menopausis, cardiovascular disease.

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Kronična bubrežna bolest (KBB) važan je javnozdravstveni problem, s prevalencijom od 10,5 do 13,1%[1]. Globalno postoje brojni čimbenici rizika za njezin nastanak, kao što su starija dob, muški spol i šećerna bolest, ali i čimbenici rizika koji pogoduju razvoju KBB-a, kao što su arterijska hipertenzija, proteinurija i hiperuricemija[2]. Brojnost čimbenika rizika komplicira prevenciju i liječenje te bolesti. Mlađe bolesnice s KBB-om imaju preuranjenu menopauzu zbog manjka estrogenih hormona, što uzrokuje niz strukturnih i funkcijskih promjena u svim organskim sustavima. Hormonsko nadomjesno liječenje važan je oblik liječenja menopauznih tegoba koje povećava kvalitetu života. Nakon istraživanja *Women's Health Initiative* stvorena je tzv. vremenska hipoteza, prema kojoj koristi od terapije postoji ako se ona uvede u žena mlađih od 60 godina i unutar 10 godina nakon menopauze.

Menopauza

Menopauza je definirana prestankom menstruacije u trajanju od godinu dana. Menopauza je udružena s ubrzanim razvojem vaskularne bolesti i osteoporoze, tako da se rizik za razvoj srčanožilnih bolesti (SŽB) znatno povećava[2]. Ra-

Chronic kidney disease (CKD) is a major public health issue with a prevalence of 10.5%-13.1%[1]. Generally, many risk factors for CKD onset have been identified, such as advanced age, male sex and diabetes mellitus, as well as the risk factors favoring CKD development, such as arterial hypertension, proteinuria and hyperuricemia[2]. The multitude of risk factors makes the prevention and treatment of CKD highly challenging. Younger female CKD patients experience premature menopause due to estrogenic hormone deficiency, leading to a number of structural and functional changes in all organ systems. Hormone replacement therapy is an important treatment option for menopausal discomforts, which can successfully improve the patient quality of life. The Women's Health Initiative study has resulted in designing the so-called timing hypothesis, according to which hormone therapy benefits can only be expected if introduced in women below 60 years of age and within 10 years of the menopause onset.

Menopause

Menopause is defined by the cessation of menstruation for a one-year period. Menopause is

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zvoju SŽB-a pridonose arterijska hipertenzija, šećerna bolest i dislipidemija, ali i sama KBB[2]. Smanjenje bubrežne funkcije povećava ukupnu i kardiovaskularnu smrtnost neovisno o tradicionalnim čimbenicima rizika[3].

Menopauza je često udružena s pojavom vazomotornih simptoma koji perzistiraju oko sedam godina u većine žena[4]. Međunarodne smjernice preporučuju postmenopauznu hormonsku terapiju za liječenje vazomotornih simptoma[4,5]. Terapija estrogenima je „zlatni standard" postmenopauzne hormonske terapije, može biti kombinirana s progesterenom u žena s intaktnim uterusom, ali i sa selektivnim modulatorima estrogenskih receptora.

Kronična bubrežna bolest i rana menopauza

Pogoršanjem bubrežne funkcije, uz poremećaje drugih tjelesnih sustava, u žena se pojavljuju i menstruacijski poremećaji, neplodnost i rana menopauza[6]. Uz starenje opće populacije, raste i prevalencija KBB-a, kao i broj postmenopauznih žena s KBB-om (4 % godišnje)[6]. Rana menopauza udružena s hipoestrogenizmom česta je u žena s KBB-om. Menopauza u žena s KBB-om pojavljuje se 4 godine ranije nego u žena u općoj populaciji[6]. Primjena postmenopauzne hormonske terapije u općoj populaciji obuhvaćena je aktualnim smjernicama, ali nema jasne upute za liječenje žena s visokim rizikom, odnosno žena s KBB-om.

Bubreg ima važnu ulogu u regulaciji spolnih hormona[5]. Tijekom razvoja KBB-a nastaje poremećaj funkcije jajnika zbog poremećaja osi hipotalamus-hipofiza-jajnici, što uzrokuje anovulatorne cikluse, ranu menopauzu te povećani rizik od razvoj malignih bolesti endometrija[5]. Ciklično oslobađanje gonadotropin oslobađajućeg hormona (GnRH) smanjeno je u bolesnica s KBB-om, što preko luteinizirajućeg hormona (LH) i folikulstimulirajućeg hormona (FSH) dovodi do smanjene sekrecije estrogena i anovulatornih ciklusa. Hiperprolaktinemija u KBB-u rezultat je povećane proizvodnje zbog rezistencije na inhibicijski učinak dopamina te smanjenoga bubrežnog izlučivanja. Povišena razina prolaktina utječe na smanjenje ciklične sekrecije GnRH i posljedičnoga smanjenja pulsne sekrecije LH i FSH, što uzrokuje smanjeno oslobađanje estrogena, a to se klinički manifestira poremećajima menstruacijskog ciklusa, neplodnošću i funkcionalnom menopauzom[5].

Disfunkcija hipotalamusa može se djelomično oporaviti uz intenziviranje liječenja hemodijalizom ili nakon transplantacije bubrega. Pojava menopauze može ubrzati progresiju KBB-a i postmenopauzna hormonska terapija nije učinkovita u smanjenju tog utjecaja. Hormonska terapija pozitivno utječe na kvalitetu života, seksualnu želju i prevenciju gubitka koštane mase u postmenopauznih žena liječenih dijalizom[7,8].

Utjecaj spolnih hormona na bubrežnu funkciju

Utjecaj spolnih hormona na bubrežnu funkciju još uvijek nije dovoljno razjašnjen. Renoprotektivni učinak ženskih spolnih hormona nije izravno dokazan. Eksperimentalna istraživanja na laboratorijskim životinjama pokazala su razlike u estrogenskim receptorima na bubrežnim stanicama, kao i utjecaj spolnih hormona na sintezu i aktivnost nekih citokina, čimbenika rasta i vazoaktivnih tvari. Dokazano je da estrogen ima

associated with faster development of vascular disease and osteoporosis, thus considerably increasing the risk of cardiovascular disease[2]. Arterial hypertension, diabetes mellitus and dyslipidemia, as well as CKD itself, contribute to the development of cardiovascular disease[2]. Impaired renal function increases the overall and cardiovascular mortality independently of the traditional risk factors[3].

Menopause is frequently associated with the occurrence of vasomotor symptoms that persist for about seven years in most women[4]. International guidelines recommend postmenopausal hormone therapy to treat vasomotor symptoms[4,5]. Estrogen therapy is the gold standard of postmenopausal hormone therapy; in women with intact uterus, it can be combined with progesterone, as well as with selective estrogen receptor modulators.

Chronic kidney disease and premature menopause

Impairment of kidney function, along with disorders in other body systems leads to menstrual impairments, infertility and premature menopause in women[6]. The prevalence of CKD and the proportion of postmenopausal women with CKD increase with the general population aging (4% *per* year)[6]. Premature menopause associated with hypoestrogenism is common in CKD women. The onset of menopause occurs four years earlier in CKD women than in women from the general population[6]. Current guidelines include administration of postmenopausal hormone therapy in the general population but there are no clear instructions on the treatment of high-risk women including those with CKD.

Kidney has a major role in the regulation of sex hormones[5]. During the course of CKD, ovarian function disorder occurs due to impairment in the hypothalamic-pituitary-ovarian axis, which leads to anovulatory cycles, premature menopause, and an increased risk of malignant endometrium disease[5]. Cyclic release of the gonadotropin-releasing hormone (GnRH) is reduced in CKD patients, which leads to decreased estrogen secretion and anovulatory cycles *via* luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Hyperprolactinemia in CKD is the result of increased prolactin production due to resistance to the inhibitory effect of dopamine and reduced renal excretion. Elevated prolactin level leads to reduced cyclic GnRH secretion and consequential reduction in LH and FSH pulse secretion, which in turn results in a reduced estrogen release that clinically manifests by menstruation cycle irregularities, infertility, and functional menopause[5].

Hypothalamic dysfunction can be partially recovered with intensified hemodialysis or following kidney transplantation. The onset of menopause may accelerate CKD progression, and postmenopausal hormone therapy is inefficient in reducing this effect. Hormone therapy has favorable impact on the patient quality of life, sexual desire, and prevention of bone mass loss in postmenopausal women on dialysis[7,8].

Effect of sex hormones on kidney function

The effect of sex hormones on kidney function has not yet been fully clarified. There is no direct evidence for the renoprotective effect of female sex hormones. Studies on experimental animals have shown differences in estrogen receptors

važnu ulogu u aktivaciji reninsko-angiotenzinsko-aldosteronskog sustava, kao i da nedostatak estrogena ubrzava progresiju glomeruloskleroze te da hormonska nadomjesna terapija može utjecati na progresiju KBB-a u laboratorijskih životinja.

Za razliku od opće populacije, ne postoje smjernice za uporabu postmenopauzne hormonske terapije u bolesnica s KBB-om. Učinak postmenopauzne hormonske terapije procjenjuje se kroz smanjenje srčanožilnog rizika i rizika od prijeloma, dok utjecaj postmenopauzne hormonske terapije na bubrežnu funkciju nije potpuno razjašnjen[8]. Istraživanja su dala različite rezultate, ovisno o načinu primjene postmenopauzne hormonske terapije, o dodanim drugim sastojcima, kao i o vremenu početka liječenja. Nedostaju prospektivna istraživanja odnosa bubrežne funkcije i menopauze, kao i utjecaja postmenopauzne hormonske terapije na ishod bolesnica s KBB-om.

Učinci potencijalnih čimbenika rizika koji su jedinstveni za žene očituju se napose u razdoblju menopauze, a posebno su potrebna buduća istraživanja koja će uključiti učinke hormonske terapije u malim dozama, kao i u transrodnoj populaciji[9,10].

Nuspojave postmenopauzne hormonske terapije u općoj populaciji jesu venska trombembolijska bolest te zloćudne bolesti dojke, jajnika i endometrija, što zahtijeva pažljivu procjenu rizika u populaciji žena s KBB-om, koje se dodatno u slučaju preuranjene menopauze (prije 45. godine) nalaze u skupini povišenoga srčnožilnog rizika[11,12].

Zaključak

Internisti, ali i ostale struke, relativno rijetko sa svojim bolesnicama razgovaraju o menstruacijskim poremećajima, plodnosti i menopauzi. Ovi problemi kroničnih bubrežnih bolesnica, kao i njihovo liječenje zahtijevaju daljnja istraživanja i stvaranje jasnih smjernica liječenja ove visokorizične skupine bolesnika za kardijalni i/ili cerebrovaskularni neželjeni događaj.

on renal cells, as well as the effect of sex hormones on the synthesis and activity of some cytokines, growth factors and vasoactive substances. It has been demonstrated that estrogen plays a major role in the activation of the renin-angiotensin-aldosterone system and that hormone replacement therapy can influence the progression of CKD in laboratory animals.

Unlike the general population, there are no guidelines on the use of postmenopausal hormone therapy in female CKD patients. The effect of postmenopausal hormone therapy is assessed through cardiovascular and fracture risk reduction, whereas the effect of postmenopausal hormone therapy on kidney function has not been completely elucidated[8]. Studies have shown variable results, depending on the mode of postmenopausal hormone therapy administration, other components added to therapy, and timing of treatment initiation. Prospective studies of the kidney function and menopause relationship and of the impact of postmenopausal hormone therapy on the outcome of female CKD patients are lacking.

Effects of the potential risk factors exclusively associated with female patients manifest most intensively in menopause; in the future, studies should also tackle the effects of hormone therapy administered in low doses and in the transgender population[9,10].

The side effects of postmenopausal hormone therapy in the general population include venous thromboembolism, and malignant diseases of the breast, ovary and endometrium, thus requiring careful risk assessment in the population of women with CKD, as they fall in the group at an increased cardiovascular risk in case of premature menopause (before age 45)[11,12].

Conclusion

Internists and other specialists relatively rarely talk to their female patients about menstruation problems, fertility and menopause. In female CKD patients, these problems and their treatment require additional research and development of strict therapeutic guidelines for this group of patients at a high risk of undesired cardiac and/or cerebrovascular event.

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