Prevencija progresije kronične bubrežne bolesti u 12 koraka

12 Essential Steps for Prevention of Chronic Kidney Disease Progression

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SAŽETAK: Cilj je rada pružiti spoznaje za uspješno usporivanje progresije kronične bubrežne bolesti (KBB) vodeći se najnovijim dokazima i preporukama. *Medline* i *Web of Science* baze podataka pretražene su uporabom kombinacije ključnih riječi „kronična bubrežna bolest", „progresija" i „prevencija". Relevantni istraživački radovi te trenutačne smjernice nacionalnih i međunarodnih društava analizirani su kako bi se ekstrapolirale preporuke i prilagodbe prakse optimalne za usporivanje progresije KBB-a. Neovisno o etiologiji i tipu KBB-a, postoji mogućnost usporivanja napredovanja bolesti. U ovome je radu predočeno 12 mogućih intervencija za usporivanje KBB-a, i to: dijetne preporuke, liječenje anemije, novi antagonisti mineralokortikoidnih receptora, inhibitori kotransportera natrij glukoze-2, liječenje hiperuricemije, adekvatna tranzicijska skrb hipertenzije od pedijatrijske prema adultnoj dobi, renalna denervacija, utjecaj post-COVID-a i bubrežnog oštećenja, važnost onkonefrologije, utjecaj zagađenja zraka, nove metode procjene bubrežnog oštećenja i liječenje dislipidemije. Iako je KBB po svojoj prirodi pojava s neizbježnom progresijom tijekom vremena, mnogo se može učiniti da bi se smanjila stopa progresije te na taj način poboljšali kvalitetu života bolesnika i učinkovitost korištenja resursima zdravstvenog sustava.

SUMMARY: This paper aims to provide a concise guide on how to successfully slow down chronic kidney disease (CKD) progression, with references to the latest evidence and recommendations. The Medline and Web of Science databases were used as the sources of medical literature, based on the combinations of keywords "chronic kidney disease", "progression", and "prevention". The relevant original research papers and current national and international society guidelines were analyzed to extract recommendations and practice modifications for the optimal reduction of kidney disease progression. Regardless of etiology and type, there are certain interventions that have been proven to reduce the rate of CKD progression. Twelve of those will be examined and discussed herein: dietary intervention, anemia therapy, new mineralocorticoid receptor antagonists, inhibitors of sodium-glucose cotransporter-2, treatment of hyperuricemia, appropriate transition of care from pediatric to adult hypertension, role of renal denervation, post-COVID and kidney injury, onconephrology, air pollution, diffusion kurtosis imaging, and dyslipidemia. While chronic kidney disease is by its very nature an entity that inevitably progresses with time, much can be done to reduce the rate of its progression and, by extension, improve both the patient quality of life and the efficiency of healthcare system resource utilization.

KLJUČNE RIJEČI: kronična bubrežna bolest, prevencija, progresija.

KEYWORDS: chronic kidney disease, prevention, progression.

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Uvod

Kronična bubrežna bolest (KBB) karakterizirana je oštećenjem bubrežne funkcije tijekom najmanje 3 mjeseca (prezentacija albuminurijom ili hematurijom ili patološkim sedimentom, patološki slikovni prikaz bubrega) ili nižom procijenjenom glomerularnom filtracijom (pGF) <60 mL/min/1,73 m^2, koja traje najmanje 3 mjeseca

Introduction

Chronic kidney disease (CKD) is characterized by kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, present for at least 3 months[1]. Based on the KDIGO 2012 and 2022 classification, it is divided into six clinical stages based on eGFR (G1, G2, G3a, G3b, G4, G5) and three stages based on al-

sa znakovima bubrežnog oštećenja ili bez tih znakova[1]. Prema KDIGO klasifikaciji, KBB se na temelju pGF-a dijeli u šest kliničkih stadija (G1, G2, G3a, G3b, G4, G5) te tri stadija na osnovi albuminurije (A1, A2, A3)[2]. Početna (G1 – G3) KBB u pravilu je asimptomatska bolest, te je teško procijeniti prevalenciju KBB-a u općoj populaciji. Prema relevantnim podatcima, procjenjuje se prevalencija između 10 % i 14 %[3]. Ako se želi procijeniti globalno opterećenje uzrokovano KBB-om, smatra se da ono iznosi 1% godina života prilagođenih invaliditetu i da je zbog KBB-a 1 – 3 % izgubljenih godina života[4].

S obzirom na to da KBB pogađa osobe različitih dobnih skupina, rasa i spola, ne preporučuje se liječenje pojedinačnoga kliničkog entiteta. Do sada je bilo nekoliko pokušaja klasifikacije tipova KBB-a primjenom različitih obilježja i kriterija. Važnijom se pokazala podjela koja naglašava različite stope slabljenja bubrežne funkcije, a može se podijeliti u dvije glavne skupine. Skupina s KBB-om odnosi se na osobe iz opće populacije u kojih je dijagnosticirano bubrežno oštećenje te većinom obuhvaća populaciju starijih koji imaju aterosklerotsku bolest, arterijsku hipertenziju i šećernu bolest. Stopa slabljenja bubrežne funkcije u toj se grupi procjenjuje na između 0,75 i 1 mL/min/1,73 m^2 godišnje nakon dobi od 50 godina[5]. Budući da su oni izloženi različitim rizičnim kardiovaskularnim (KV) čimbenicima tijekom duljeg razdoblja, veća je učestalost velikih neželjenih srčanih događaja (MACE), a manje završnoga stupnja KBB-a. U samo 1 % bolesnika s KBB-om G3 i u 20 % s KBB-om G4 razvije se završni stadij KBB-a G5 (ESRD) i razvije se potreba za nadomjesnom bubrežnom terapijom, dok 24 % bolesnika s KBB-om G3 i 45 % s KBB-om G4 umire zbog posljedica MACE-a[6].

Druga se skupina odnosi na populaciju bolesnika koji su zbog nasljednih bolesti poput policistične bubrežne bolesti odrasle dobi (ADPKD) ili stečene nefropatije (dijabetička bolest bubrega, tubulointersticijalna bolest ili glomerulonefritis) odmah upućeni nefrologu. U njih je brzina progresije KBB-a vrlo varijabilna zbog različitih osnovnih mehanizama.

Neovisno o etiologiji i uzroku, određene intervencije dokazano mogu smanjiti brzinu progresije KBB-a. U radu je navedeno 12 najznačajnijih mjera intervencije koje su detaljnije objašnjene.

Dijetne intervencije

Nemali broj puta raspravlja se o korisnosti dijetnih intervencija u prevenciji progresije KBB-a. Najveći je razlog velik broj mogućih prehrambenih intervencija, različite vrste dijeta, te velik broj pojedinačnih istraživanja. Sustavni Cochraneov pregled rezultata različitih vrsta prehrambenih intervencija na napredovanje KBB-a i cjelokupno zdravlje bolesnika s KBB-om objavljen je 2017. godine, a obuhvatio je 17 istraživanja i 1639 bolesnika s KBB-om. Oko 10 % oboljelih imalo je transplantaciju bubrega, 20 % je bilo na hemodijalizi, a 70 % je imalo KBB do stadija G5, no bez dijalize[7]. Zbog dizajna uključenih istraživanja, učinak prehrambenih intervencija na progresiju bolesti do završnoga stadija KBB-a G5 nije bio jasan. Prema izračunima autora, procijenjeno je da dijetetičke intervencije mogu spriječiti progresiju KBB-a u završni stadij u jednog od svakih 3000 bolesnika liječenih tijekom godine dana. Uočeni su dodatni učinci dijetnih mjera nakon prehrambenih intervencija poput smanjenja sistoličkog (MD −9,26 mmHg) i dijastoličkog tlaka (MD −8,95 mmHg) te viša pGF i koncentracija albumina u serumu. Osim toga, mediteranska prehrana

buminuria (A1, A2, A3)[2]. Since mild to moderate CKD is often asymptomatic, it is quite difficult to precisely quantify the general prevalence of CKD. However, according to the most complete data available, its prevalence is estimated to lie between 10% and 14% of the general population[3]. When looking at the proportion of the global burden of disease that CKD carries, around 1% of disability adjusted life years and 1-3% of life years are lost because of CKD[4].

Because CKD affects patients within a wide age, race, and sex range, treating it as a single clinical entity is not recommended. Several attempts have been made to classify types of CKD using different features and criteria, but one of the most sensible approaches is probably the community versus referred CKD. This split emphasizes the different rates of renal function decline in the two groups. The community CKD group refers to patients from the general population in whom kidney failure is diagnosed and comprises mostly elderly patients who have been suffering from atherosclerosis, arterial hypertension, and diabetes mellitus for a longer time. The rate of renal function decline in this group is estimated between 0.75 and 1 mL/min/1.73 m^2 per annum after the age of 50[5]. Since these patients are exposed to different cardiovascular (CV) risk factors for long time periods, they often suffer from major adverse cardiac events (MACE), rather than complete loss of renal function. For example, one study showed that 1% of patients with CKD G3 and 20% of patients with CKD G4 increased to end stage renal disease (ESRD) and demanded renal replacement therapy. However, 24% of G3 patients and 45% of G4 patients died from MACE[6].

In comparison, referred CKD describes patients who have been referred directly to the nephrologist and their disease was diagnosed there, as in cases of hereditary (ADPKD) or acquired nephropathy (diabetic kidney disease, tubulointerstitial disease, or glomerulonephritis). The rate of CKD progression in these patients is highly variable due to widely differing mechanisms of the underlying disease processes affecting them.

Regardless of etiology and type, there are certain interventions that have been proven to reduce the rate of CKD progression. Twelve of those will be examined and discussed in the text below.

Dietary interventions

The question of the utility of dietary interventions in CKD progression prevention is often debated, and the path to finding the answer is often complicated due to the large number of possible dietary interventions, different types of diets, and the inherent bias of studies relying on self-reporting. However, an attempt to systematically review the outcomes of various types of dietary interventions on CKD progression and overall health of patients with CKD has been made in the form of a Cochrane review published in 2017[7]. The review included 17 studies and 1639 patients with CKD. Approximately 10% of patients were kidney transplant recipients, 20% were on hemodialysis, and 70% had active non-dialysis CKD. Due to the design of the included studies, the effect of dietary interventions on progression to ESRD was not clear or certain. According to the authors' calculations, they estimated that dietary interventions may prevent progression of CKD to ESRD in 1 out of every 3000 patients treated for one year. Additionally, several other beneficial effects were observed following dietary in-

omogućila je snizivanje masnoća, odnosno postizanje manje koncentracije LDL-a u serumu (MD –1 mmol/L). Drugi sustavni pregled procijenio je učinkovitost kombiniranih intervencija u prehrani i važnost savjetodavne funkcije dijetetičara u usporivanju progresije KBB-a[8]. Jedno je istraživanje pokazalo znatno smanjenje pada pGF-a tijekom 3 godine u bolesnika koji su imali prehranu s visokim unosom povrća i/ili voća (–10,0; 95 % CI = –10,6 –9,4 mL/min/1,73 m^2) ili unosom bikarbonata peroralno (–12,3; 95 % CI = –12,9 –11,7 mL/min/1,73 m^2) u usporedbi s kontrolnom uobičajenom prehranom (–18,8; 95% CI = –19,5 –18,2 mL/min/1,73 m^2)[9].

Liječenje anemije

Anemija u KBB-u dobro je poznat problem i istražena klinička pojava, s novim mogućnostima liječenja koji se danas sve češće uvode u svakodnevnu praksu. Najvažnije otkriće liječenja anemije jest signalizacija preko hipoksijom inducibilnog faktora (HIF) koji djeluje kao senzor za kisik. Primjena inhibitora faktora prolil hidroksilaze (HIF-PH) povećava koncentraciju hemoglobina (Hb) u serumu koordiniranim eritropoetičkim odgovorom na fiziološki način[10]. Analiza iz 2020. godine pokazala je kvantificiranje povećanja rizika od progresije KBB-a kod različitih stupnjeva težine anemije[11]. Rezultati su pokazali omjer rizika (HR) za progresiju KBB-a od 1,65 (95 % CI 1,36 – 2,00) za bolesnike sa serumskim koncentracijama Hb <100 g/L i 1,41 omjer rizika (95 % CI 1,27 – 1,56) za bolesnike s koncentracijom Hb u serumu od 100 do 120 g/L. Dokazana je renoprotektivna prednost liječenja anemije: HR za progresiju KBB-a je 0,85 za svakih 10 g/L povećanja serumske koncentracije Hb.

Finerenon

Antagonisti mineralokortikoidnih receptora (MRA) lijekovi su s dokazanim djelovanjem za liječenje bolesnika s hipertenzijom, proteinurijom ili KBB-om. Postoji nekoliko različitih klasa tih lijekova unutar iste skupine: eplerenon (selektivni), spironolakton i kanrenon (neselektivni) i finerenon (nesteroidni). Cochraneova analiza iz 2020. godine procijenila je učinke MRA-a na proteinuriju, sistolički tlak i sniženje bubrežne funkcije[12]. Rezultati 14 istraživanja koja su uključila 1193 bolesnika pokazali su da liječenje MRA-om uz ACEi ili blokatore angiotenzinskih receptora (ARB) smanjuje proteinuriju (SMD -0,51, 95 % CI: -0,82 do – 0,20). U 14 istraživanja koja su uključila 911 bolesnika zabilježeno je sniženje sistoličkog tlaka (MD -4,98 mmHg, 95% CI: -8,22 do -1,75), a u 13 istraživanja s 1165 bolesnika i sniženje pGF-a (MD -3,00 mL/min/1,73 m^2, 95 % CI: -5,51 do -0,49). Nesteroidni MRA poput finerenona dokazao je dodatne učinke liječenja KBB-a u populaciji bolesnika s dijabetesom tipa 2 (T2D). Pregled objavljenih ispitivanja o prednostima i ograničenjima finerenona u bolesnika s KBB-om i T2D izdvojeni su iz istraživanja FIDELITY te sjedinjeni u analizi dvaju istraživanja faze 3 (FIDELIO i FIGARO-DKD)[13,14]. Istraživanje FIDELITY procijenilo je dva različita primarna ishoda, od kojih je jedan kombinacija KV neželjenih događaja (nefatalni moždani udar, nefatalni infarkt miokarda, hospitalizacija zbog zatajivanja srca ili KV smrt), dok je drugi kompozitni ishod bubrega (smanjenje pGF-a najmanje 57 % s obzirom na početne vrijednosti ili smrt zbog bubrežnih uzroka). Sekundarni je ishod procijenio zatajenje bubrega, smanjenje pGF-a od najmanje 40 % u odnosu prema početnoj vrijednosti ili

terventions, namely a reduction of systolic (MD -9.26 mmHg) and diastolic pressure (MD -8.95mmHg) and higher eGFR and serum albumin concentrations. Furthermore, the Mediterranean diet provided the benefit of lowering serum LDL concentrations (MD -1 mmol/L). Another systematic review evaluated the effectiveness of combination interventions in diet and dietician engagement on slowing the progression of CKD[8]. Among the twelve studies included, one of them showed a significant decrease in eGFR decline over three years in patients with high base-producing vegetable and/or fruit (-10.0; 95% CI: -10.6 to -9.4 mL/min/1.73 m^2) or oral bicarbonate (-12.3; 95% CI: -12.9 to -11.7 mL/min/1.73 m^2) intake compared with usual care (-18.8; 95% CI: -19.5 to -18.2 mL/min/1.73 m^2)[9].

Treatment of anemia

Anemia in CKD is a well-known and researched clinical entity, with novel treatment modalities rapidly emerging and being implemented into daily practice, the newest of which are hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors, which have been shown to increase serum hemoglobin (Hb) concentrations by as much as 9.1 g/L[10]. One systematic review from 2020 undertook the task of quantifying the increase in CKD progression risk in various degrees of anemia severity[11]. The results showed a hazard ratio (HR) for the progression of CKD of 1.65 (95% CI: 1.36-2.00) for patients with serum Hb concentrations of <100g/L and a 1.41 hazard ratio (95% CI: 1.27-1.56) for patients with serum Hb concentrations of 100-120 g/L. The renoprotective benefits of successful anemia treatment were also demonstrated: the HR for CKD progression was 0.85 for every 10g/L increase in serum Hb concentration.

Finerenone

Mineralocorticoid receptor antagonists (MRA) are a long-standing therapeutic staple of managing patients with hypertension, proteinuria, or CKD. There are several different subclasses of these drugs within the same group: eplerenone (selective), spironolactone and canrenone (non-selective), and finerenone (non-steroidal). A Cochrane review from 2020 evaluated the effects of MRAs on proteinuria, systolic pressure, and decline of renal function[12]. The results of 14 studies with 1193 patients showed that MRA therapy concomitant with ACEi or angiotensin receptor blocker (ARB) use decreases proteinuria (SMD -0.51, 95% CI: -0.82 to -0.20). In 14 studies with 911 patients, there was a decline in systolic pressure (MD -4.98 mmHg, 95% CI: -8.22 to -1.75), and eGFR decline was observed in 13 studies with 1165 patients (MD -3.00 mL/min/1.73 m^2, 95% CI: -5.51 to -0.49). Non-steroidal MRAs such as finerenone have shown promising results in CKD treatment in the population of patients with type 2 diabetes mellitus (T2D). A review of the currently published trials quantified the available findings on the benefits and limitations of finerenone[13]. The most current and complete data on finerenone in patients with CKD and T2D was obtained from FIDELITY[14], a pooled analysis of two phase 3 studies (FIDELIO and FIGARO-DKD). The FIDELITY study evaluated two different primary outcomes, one of which was a composite of CV adverse events (nonfatal stroke, nonfatal myocardial infarction, hospitalization due to HF or CV death), while the other was a renal composite outcome (sustained eGFR decrease of at least 57% from baseline or death from renal causes). The secondary outcome evaluated renal failure,

smrt uzrokovanu bubrežnim uzrocima. Sažeto, finerenon je smanjio neželjeni KV ishod za 14 % (p = 0,002), „smanjenje pGF-a od 57 % s obzirom na početnu vrijednost" za 23 % (p = 0,0002), „smanjenje eGFR-a od 40 % s obzirom na početnu vrijednost" za 15 % (p = 0,0004), napredovanje do dijalize za 20 % (p = 0,04) u usporedbi s kontrolnom skupinom. Na temelju istraživanja pokazano je da finerenon nema značajan učinak na razinu HbA1c ili tjelesnu masu i ne povećava sklonost štetnim neželjenim događajima poput ginekomastije. Pokazan je diskretan učinak na smanjenje arterijskoga tlaka (AT). U bolesnika s KBB-om i zatajivanjem srca (HF) sa smanjenom ejekcijskom frakcijom (HFrEF), finerenon pokazuje superiornije učinke na očuvanje bubrežne funkcije u usporedbi s eplerenonom, nižu smrtnost u usporedbi s spironolaktonom i niže stope povišene razine kalija (hiperkalemija) u usporedbi s eplerenonom ili spironolaktonom[13].

SGLT2 inhibitori

Lijekovi iz skupine inhibitora SGLT2 (SGLT2i) primarno su otkriveni kao lijekovi za liječenje T2D. Ova je klasa lijekova danas nezaobilazna pri liječenju bolesnika s HF-om i KBB-om. DAPA-CKD je najvažnije ispitivanje za dokazivanje učinkovitosti SGLT2i, koje je pokazalo 44 %-tno sniženje opadanja pGF-a, pogoršanja KBB-a do G5 stadija ili smrti od bubrežnih uzroka (p <0,001)[15]. Podatci KV istraživanja sa SGLT2i podupiru njihovu učinkovitost u sprječavanju progresije KBB-a. Metaanaliza kojom se kvantificiraju bubrežni ishodi u KV istraživanjima SGLT2i (VERTIS CV, EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS) pokazala je sniženje od 42 % u ishodu kontinuiranog sniženja ≥40 % s obzirom na početnu vrijednost pGF-a, progresije KBB-a do stadija G5 ili završnog stadija te smrti zbog bubrežnih uzroka u usporedbi s placebom [HR 0,58 (95 % CI 0,51 – 0,65)][16]. Inhibitori SGLT2 pokazali su se učinkovitima u bolesnika s KBB-om stadija G4. Objavljena metaanaliza pokazala je znatno smanjenje od 23 % sniženja pGF-a, smrti ili razvoja do završnoga stadija zbog bubrežnih uzroka terapijom s SGLT2i kod uznapredovale KBB/KBB G4 (15 – 30 mL/min/m^2) u usporedbi s kontrolnom skupinom (p = 0,04)[17]. Autori su izračunali razliku u godišnjem sniženju pGF-a u skupini koja je uzimala SGLT2i u usporedbi s kontrolnom skupinom, pokazujući sniženje pada od 1,24 mL/min/1,73 m^2/godinu u skupini sa SGLT2i (95 % CI: 0,06 do – 2,42, p = 0,04).

Liječenje hiperuricemije

Iako je dokazano da je visoka razina urične kiseline novi rizični čimbenik *de novo* pojavosti KBB-a, uloga u progresiji KBB-a ostaje nejasna. To je stoga što je KBB najčešće uzrokovan dvjema bolestima poput dijabetesa i hipertenzije. U istraživanju MDRD u nedijabetičara s KBB-om stadija G3 i G4 visoka razina urične kiseline nije bila izolirani rizični čimbenik progresije KBB-a[18]. Analiza Švedskog registra bubrežnih bolesti nije dokazala povezanost hiperuricemije sa sniženjem pGF-a ili vremenom do početka hemodijalize u bolesnika s KBB-om stadija G3 – G4[19]. No nekoliko opservacijskih istraživanja pokazalo je povezanost hiperuricemije sa sniženjem bubrežne funkcije, poput osmogodišnje longitudinalne analize u Kini na 700 bolesnika[20]. Smatra se da žene imaju veću povezanost sniženja bubrežne funkcije uzrokovane hiperuricemijom, što je pokazano u nekoliko istraživanja provedenih u Japanu[21,22].

eGFR decrease of at least 40% from baseline, or death due to renal causes. In summary, finerenone decreased the CV outcome by 14% (p=0.002), the "reduction of eGFR 57% from baseline" by 23% (p=0.0002), the "reduction of eGFR 40% from baseline" by 15% (p=0.0004), and progression to dialysis by 20% (p=0.04) when compared with control group. Finerenone seems to have no outcome on HbA1c or body mass and does not increase the propensity for adverse side effects such as gynecomastia but has a modest impact on reduction of blood pressure (BP). In patients with CKD who have heart failure (HF) with reduced ejection fraction, finerenone displayed better renal outcomes in comparison with eplerenone, better mortality outcomes in comparison with spironolactone, and lower rates of high potassium compared with eplerenone or spironolactone[13].

SGLT2 inhibitors

While the first instances of the use of SGLT2 inhibitors (SGLT2i) were in the role of antidiabetic medications, this class of drugs is rapidly becoming a ubiquitous treatment staple in HF and CKD. DAPA-CKD was the most important trial to demonstrate efficiency of SGLT2i, which showed a 44% reduction of decline in eGFR, worsening to CKD stage 5, or death from kidney-related causes (p<0.001)[15]. Data derived from primarily CV outcome studies of SGLT2i medications also support their efficiency in prevention of CKD progression: a meta-analysis quantifying renal outcomes in cardiovascular SGLT2i studies (VERTIS CV, EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS) demonstrated a 42% depletion in the outcome of a constant ≥40% decline from baseline in eGFR, progression to CKD stage 5, or ESRD and death due to renal causes with SGLT2i therapy in comparison with placebo [HR 0.58 (95% CI: 0.51-0.65)][16]. SGLT2 inhibitors have also been shown to be effective in patients with advanced CKD stage 4. A recently published meta-analysis showed a significant 23% reduction in eGFR decline, death, or progression to ESRD due to renal causes with SGLT2i therapy in patients with advanced CKD (15-30 mL/min/m^2) when compared with the control group (p=0.04)[17]. The authors also calculated the difference in yearly eGFR decline between SGLT2i and placebo, demonstrating a reduction in decline of 1.24 mL/min/1.73 m^2/year with SGLT2i therapy (95% CI: 0.06-2.42, p=0.04).

Treatment of hyperuricemia

While high levels of uric acid have been demonstrated as a new risk factor for *de novo* CKD occurrence, its role in CKD progression remains somewhat unclear due to conflicting evidence. This may be a consequence of manifest CKD being the product of several different risk factors, such as diabetes, hypertension, etc. However, even in patients with nondiabetic CKD stage III and IV, such as those in the MDRD study, high levels of uric acid were not a separate risk element for progression of CKD[18]. Furthermore, an analysis of Swedish Renal Disease Registry (SRR-CKD) found no association of hyperuricemia with eGFR decline or time to initiation of hemodialysis in patients with CKD stages III-V[19]. On the other hand, several observational studies have demonstrated an association between hyperuricemia and renal function decline, one of which was an 8-year longitudinal analysis of more than 700 Chinese patients[20]. Another interesting finding related to hyperuricemia is that women seem to be more susceptible to renal function decline caused by hyperuricemia, as demonstrated by several Japanese studies[21,22].

Liječenje hiperuricemije osobito u slučaju gihta dovodi do usporivanja progresije KBB-a. Cochraneova analiza iz 2017. godine navodi u 2 istraživanja s 83 bolesnika niži serumski kreatinin (MD -73,35 µmol/L, 95% CI: -107,28 do -39,41), kao i u jednom istraživanju koje je obuhvaćala 113 bolesnika oporavak pGF (MD 5,50 mL/min/1,73 m^2, 95% CI: 0,59 do 10,41) uporabom lijekova za snizivanje povišene urične kiseline s obzirom na placebo nakon godine dana[23]. No isti se učinak gubi nakon dvije godine. Metaanaliza koja je obuhvatila 19 randomiziranih kliničkih istraživanja (RCT) s 992 sudionika pokazala je znatan porast pGF-a u skupini koja je uzimala alopurinol u usporedbi s kontrolnom grupom (3,2 mL/min/1,73 m^2, 95 % CI 0,16-6,2 mL/min/1,73 m^2, p = 0,039)[24]. Druga meta-analiza iz 2018, koja je uključila 12 RCT s 832 sudionika, uspoređivala je liječenje bilo kojim lijekom koji snizuje povišene urate s obzirom na kontrolnu skupinu/placebo. Pokazana je statistička značajnost u porastu pGF-a pri uzimanja bilo kojeg lijeka koji snizuje povišene urate (3,88 mL/min/1,73 m^2, 6,49 mL/min/1,73 m^2, p = 0,004)[25]. Posljednja metaanaliza iz 2022. uspoređivala je različite lijekove te dokazala da uzimanje topiroksostata dovodi do znatnog oporavka ili porasta pGF-a u bolesnika s KBB-om i s hiperuricemijom ili bez nje (MD 1,49 mL/min/m^2, 2,90 mL/min/m^2, p = 0,038), dok je febuksostat znatno oporavio pGF samo u bolesnika s hiperuricemijom (MD 0,85 mL/min/m^2, 1,67 mL/min/m^2, p=0,04), a peglotikaza i alopurinol nisu pokazali protektivan učinak na bubrežnu funkciju[26].

Primjerena primopredaja skrbi u prijelazu iz pedijatrijske u hipertenziju odrasle dobi

Jedna od najpodcjenjenijih i najmanje proučenih tema vezanih uz zbrinjavanje arterijske hipertenzije jest primjerena primopredaja skrbi u prijelazu iz pedijatrijske u odraslu dob. Postoji nekoliko čimbenika koji ovu temu čine teškom i problematičnom, među kojima se ističe nedostatak postupnika organizirane primopredaje skrbi te dodjeljivanja nadležnog liječnika svakom bolesniku na prijelazu iz dječje u odraslu dob. Također je problematičan nedostatak jasne dobne granice za definitivan prijelaz iz pedijatrijske u odraslu zdravstvenu skrb. Sukladno navedenom, stručna društva nastoje uskladiti smjernice za hipertenziju u pedijatrijskih i odraslih bolesnika, pojednostavnjujući time skrb za obje dobne skupine, kao i samu primopredaju skrbi[27]. Tijekom sastavljanja smjernica za zbrinjavanje hipertenzije u autorstvu *American College of Cardiology/American Heart Association* i *American Academy of Pediatrics* za 2017. godinu, navedena su se društva odlučila za nominiranje određenog broja autora za preporuke u skupini za pedijatrijsku i skupini za odraslu dob, čime se nastojao postići kontinuitet između dviju smjernica te prepoznati potencijalne probleme. Rezultat opisanog načina rada jesu ujedinjene smjernice za pedijatrijsku/odraslu hipertenziju napisane do sada te svakom liječniku koji se skrbi za bolesnike u fazi tranzicije preporučujemo da pročita čitav dokument (dostupan u referencama).

Neke od najvažnijih točaka iz navedenih smjernica jesu:

a) Dijagnostička obradba potrebna za prepoznavanje sekundarne hipertenzije i oštećenja ciljnih organa.

b) Identični stadiji i vrijednosti za stupnjevanje hipertenzije za sve osobe starije od 13 godina.

Be that as it may, urate lowering therapy seems to provide at least a modest reduction in the rate of renal function decline. A Cochrane review from 2017 on 2 studies with 83 patients reported lower creatinine in serum (MD -73.35 µmol/L, 95% CI: -107.28 to -39.41) and recovery of eGFR (MD 5.50 mL/min/1.73 m^2, 95% CI: 0.59 to 10.41) in 1 study with 113 patients with urate lowering therapy compared with placebo after one year[23]. However, the benefit seems to disappear after two years. A meta-analysis that included 19 RCTs with 992 participants found a statistically significant rise in eGFR with allopurinol therapy compared with placebo (3.2 mL/min/1.73 m^2, 95% CI: 0.16-6.2 mL/min/1.73 m^2, p=0.039)[24]. Another meta-analysis from 2018, which included 12 RCTs with 832 participants, compared treatment with any urate lowering agent to placebo and found a statistically significant rise in eGFR with any urate lowering agent (3.88 mL/min/1.73 m^2, 6.49 mL/min/1.73 m^2, p=0.004)[25]. Finally, a meta-analysis from 2022 that compared different urate lowering agents found that topiroxostat significantly improved eGFR in patients with CKD with and without hyperuricemia (MD 1.49 mL/min/m^2, 2.90 mL/min/m^2, p=0.038), that febuxostat significantly improved eGFR only in a patient with hyperuricemia (MD 0.85 mL/min/m^2, 1.67 mL/min/m^2, p=0.04), and that pegloticase or allopurinol showed no effects on renal function[26].

Appropriate transition of care from pediatric to adult hypertension

One of the most underestimated and understudied topics in hypertension management is the proper transition from pediatric care to adult antihypertensive care. While there are several factors in play that contribute to this problem, including the lack of an organized transition of care algorithm and attending physician allocation for each patient in the transitory period, along with an undefined age for definite transition, there has been an attempt to establish congruency between pediatric and adult hypertension guidelines, thus streamlining and simplifying care for both groups as well as the transition itself[27]. As the 2017 American College of Cardiology/American Heart Associations (ACC/AHA) and American Academy of Pediatrics (AAP) Hypertension Guidelines were being composed, the societies decided to appoint authors to both groups to achieve congruency between the two guidelines and identify potential issues. This resulted in the most congruent pediatric/adult hypertension guidelines created so far, and we strongly recommend each provider caring for hypertensive patients in the pediatric-adult transition period to read the whole document (available in the references). Some of the most important highlights from the document are:

a) Diagnostic assessments designed to identify secondary hypertension and target organ damage.

b) The hypertension grading stages and thresholds are identical for children aged 13 and older and adults.

c) The number of BP measurements in the doctor's office necessary for diagnosis of hypertension are 2 for adults and 3 for pediatric patients.

d) Both guidelines recommend drug treatment initiation for stage 2 hypertension (BP> 140/90 mmHg in those over 13 years of age), with pediatric guidelines allowing for a weight loss trial in obese children before initiating medical treatment. In children aged 13 and older and adults, the tre-

c) Za postavljanje dijagnoze hipertenzije na temelju mjerenja vrijednosti AT-a u ordinaciji potrebna su 2 mjerenja za odrasle, a 3 mjerenja za djecu.

d) Obje smjernice preporučuju započinjanje liječenja antihipertenzivnim lijekovima za hipertenziju 2. stupnja (AT >140/90 mmHg u svih starijih od 13 godina), dok pedijatrijske smjernice dopuštaju pokušaj smanjivanja tjelesne mase u pretile djece prije započinjanja medikamentnog liječenja. U svih bolesnika starijih od 13 godina ciljna je vrijednost AT-a <130/80 mmHg, dok u djece mlađe od 13 godina ciljna vrijednost iznosi <90. centile AT-a za dob bolesnika.

e) Odluka o započinjanju liječenja za 1. stupanj hipertenzije (AT >130/80 mmHg te <140/90 mmHg u svih starijih od 13 godina) ovisi o procjeni rizika i u odraslih i u pedijatrijskih bolesnika. Ipak, sam se postupak procjene rizika razlikuje ovisno o dobi bolesnika: u svih pedijatrijskih bolesnika s hipertenzijom preporučuje se učiniti ehokardiografiju prije započinjanja liječenja. Nekoliko je bolesti navedeno kao nužan „okidač" za neodgodivo započinjanje medikamentnog liječenja neovisno o drugim čimbenicima rizika u pedijatrijskih bolesnika, među kojima su sekundarna hipertenzija, KBB i šećerna bolest.

f) Što se same primopredaje skrbi tiče, smjernice preporučuju: adolescenti s povišenim vrijednostima AT-a, neovisno o tome uzimaju li antihipertenzivnu terapiju, trebali bi prijeći u skrb i praćenje liječnika koji se bavi odraslim bolesnicima do 22. godine života (uz napomenu da postoje pojedinačni slučajevi u kojih se navedena dobna granica može povisiti, prije svega mladi ljudi s posebnim zdravstvenim i ostalim potrebama). Tijekom prelaska u skrb liječnika koji se bavi odraslim bolesnicima, treba osigurati jasan i pouzdan prijenos informacija vezanih uz etiologiju, kao i prethodne manifestacije i komplikacije bolesnikove hipertenzije.

Arterijska hipertenzija kao čimbenik napredovanja bubrežne bolesti – pozicija denervacije renalnog pleksusa

Utjecaj pojačane aktivnosti simpatikusa na napredovanje bubrežne bolesti i pogoršanje hipertenzije proučava se više od 50 godina, počevši od 1972. godine, kada je skupina autora otkrila da hipertenzivni bolesnici s KBB-om/uremijom imaju mnogo više vrijednosti perifernoga žilnog otpora od nehipertenzivnih bolesnika s KBB-om/uremijom[28]. Također je pokazano da je aktivnost simpatikusa u mišićima obrnuto proporcionalna pGF-u u bolesnika s KBB-om, potvrđujući ulogu pojačanog tonusa simpatikusa u napredovanju bubrežne bolesti[29]. Bolesnici s KBB-om i hipertenzijom nose najveći rizik od preuranjene smrti, a nepridržavanje propisanog terapijskog režima znatno smanjuje učinkovitost antihipertenzivnih lijekova. Stoga su potrebne dodatne intervencije za bolesnike s hipertenzijom[30]. Renalna denervacija ili denervacija renalnog pleksusa (RDN) dodatna je komplementarna metoda liječenja bolesnika s različitim oblicima hipertenzije, među kojima je najpoznatija rezistentna hipertenzija[30].

RDN temeljena na kateteru uključuje uporabu radiofrekventne energije kako bi se izvršila ablacija bubrežnih simpatičkih živaca kroz stijenku renalne arterije, čime se smanjuje funkcija i senzoričkih i motoričkih živaca. Dodatno pitanje za RDN postupak u bolesnika s KBB-om bio je učinak snizivanja AT-a i preaktivnog simpatičkog tonusa na perfuziju bubre-

atment target is 130/80 mmHg, while in children younger than 13, it is <90th percentile of BP for patient age.

e) The decision to initiate treatment for stage 1 hypertension (130/80 mmHg<BP<140/90 mmHg in those over 13 years of age) is dependent on risk evaluation in both pediatric and adult patients; however, the risk evaluation itself differs based on patient age: in all pediatric patients with hypertension, obtaining an echocardiogram is recommended prior to treatment initiation. Also, several conditions have been listed as an immediate trigger for initiation of treatment regardless of other risk factors in pediatric patients, those being: secondary hypertension, CKD, or diabetes mellitus.

f) Regarding transition of care itself, the guidelines recommend: "Adolescents with elevated BP or HTN (whether they are receiving antihypertensive treatment) should typically have their care transitioned to an appropriate adult care provider by 22 y of age (recognizing that there may be individual cases in which this upper age limit is exceeded, particularly in the case of youth with special health care needs). There should be a transfer of information regarding HTN etiology and past manifestations and complications of the patient's HTN."

Hypertension in progression of renal disease –the role of renal denervation

The impact of heightened sympathetic system activity on the advancement of renal disease and the worsening of hypertension was first studied over 50 years ago, in 1972, when a group of researchers found that among uremic patients, those with hypertension had significantly higher values of peripheral vascular resistance than those without hypertension[28]. It has also been demonstrated that muscle sympathetic nerve activity (MSNA) is inversely proportional to eGFR in patients with CKD, further confirming the role of increased sympathetic tone in the progression of renal disease[29]. Patients with CKD and hypertension bear the highest risk for mortality, and non-compliance with anti-hypertensive therapy significantly hampers the effectiveness of drug therapies. It is evident that additional interventions beyond medication are necessary for hypertensive patients[30]. Renal denervation (RDN) is an alternative and additional rather than a competitive method of treating patients with various form of hypertension (not only for resistant hypertension)[30].

Catheter-based RDN involves utilizing radiofrequency energy to ablate the renal sympathetic nerves through the renal arterial wall, effectively interrupting both sensory and motor nerves. Initial investigations into renal denervation have shown a marked reduction in arterial pressure in most patients. The first question and concern when performing renal denervation on patients with chronic kidney disease was the effect of reduced BP and sympathetic tone on renal perfusion, but studies have shown that renal perfusion did not significantly change 3 months after renal denervation and showed no statistically significant decrease in eGFR from baseline in patients with preserved renal function, meaning that the procedure is safe for patients with CKD[30-32]. One of the first studies on renal denervation in patients with CKD showed not only significant decreases in BP at 12 months follow-up, but also a trend towards improvement of several important CKD disease parameters, namely elevated hemoglobin concentra-

ga, no istraživanja su pokazala da se bubrežna perfuzija ne snizuje znatno 3 mjeseca nakon postupka RDN-a, a pGF ne opada u usporedbi s početnom, što znači da je RDN sigurna za bolesnike s KBB-om[30-32]. Jedno od prvih istraživanja koja su proučavala postupak RDN u bolesnika s KBB-om pokazala je znatno sniženje AT-a 12 mjeseci nakon postupka, kao i trend prema poboljšanju nekoliko važnih parametara vezanih uz KBB, među kojima su povišenje hemoglobina te smanjenje koncentracije moždanoga natriuretskog peptida, omjera albumina naspram kreatinina u urinu, proteinurije te udjela glikoliziranog hemoglobina[33]. Drugo je opservacijsko istraživanje iz 2013. prikazalo znatno usporivanje opadanja pGF-a u hiperenzivnih bolesnika koji su podvrgnuti postupku RDN-a (−4,8 ± 3,8 mL/min/1,73m^2 godišnje prije RDN-a, nakon RDN-a pGF se povisila za +1,5 ± 10 mL/min/1,73 m^2 tijekom 12 mjeseci; p = 0,009)[34]. Novija istraživanja pokazuju slične rezultate u bolesnika s KBB-om – učinkovito sniženje AT-a te blago poboljšanje pGF-a nakon 3 mjeseca, bez znatnijih promjena nakon 12 mjeseci[35] Istražene su i dokazane sigurnost i učinkovitost RDN-a u snizivanju AT-a i u bolesnika s KBB-om stadija G5[36,37].

Post-COVID i bubrežno oštećenje

COVID-19 zahvatio je znatan udio svjetskog stanovništva, s više od 660 milijuna potvrđenih slučajeva zaraze te više od 6,5 milijuna smrti zbog bolesti COVID-19 zabilježenih u svijetu[38]. Zbog afiniteta SARS-CoV-2 virusa za angiotenzin konvertirajući enzim 2 (ACE2), koji se eksprimira u živčanom, gastrointestinalnom, žilnom, srčanom i drugim tkivima[39], zamijećeno je da se COVID-19 manifestira različitim kliničkim simptomima ovisno o zahvaćenom tkivu te može uzrokovati dugoročne posljedice nakon što se bolesnik oporavi od akutne infekcije[40]. Retrospektivna analiza više od 190 000 post-COVID bolesnika pokazala je da se u 14 % proučene populacije razvio barem jedan novi klinički entitet koji je zahtijevao medicinsku intervenciju[41]. SARS-CoV-2 uzrokuje bubrežnu ozljedu izravnim i neizravnim negativnim djelovanjem na bubreg[42]. Potvrda postojanja izravnog djelovanja SARS-CoV-2 virusa na bubreg jest prisutnost čestica virusa u tubularnim stanicama i podocitima dokazana elektronskom mikroskopijom[43], kao i prisutnost RNA i proteinskih čestica u svim bubrežnim odjeljcima zaraženih bolesnika, s jasnim afinitetom prema nakupljanju u glomerularnom tkivu[44]. Kod nehospitaliziranih bolesnika koji su preboljeli COVID-19 dokazan je brži pad pGF-a (otprilike 3,26 mL/min/1,73m^2 godišnje) u usporedbi s kontrolama koje nisu preboljele COVID-19[45]. Retrospektivno istraživanje iz tercijarne ustanove koje je analiziralo bubrežne ishode nehospitaliziranih post-COVID bolesnika pregledanih u hitnom prijmu, ambulanti za hipertenziju i u općoj internističkoj ambulanti procijenilo je incidenciju novonastale bubrežne bolesti nakon bolesti COVID-19 na 6 %[40]. Drugo istraživanje koje je proučavalo većinom nehospitalizirane post-COVID bolesnike predložilo je sustav standardiziranog probira („screeninga") 6 do 9 mjeseci nakon akutne bolesti COVID-19, koji se sastoji od procjene bubrežne, srčane, plućne i venske funkcije i strukturnog integriteta[46].

Onkonefrologija

Pojam onkonefrologije, discipline ili supspecijalizacije nefrologije posvećene zbrinjavanju bubrežne bolesti u onkoloških bolesnika, aktualan je unatrag više od 10 godina, kada je *American Society of Nephrology* osnovalo onkonefrološki fo-

tion and the gradual reduction of various factors such as plasma brain natriuretic peptide levels, urinary albumin to creatinine ratio, proteinuria, and plasma HbA1c levels[33]. Another observational study from 2013 demonstrated a significant reduction in the annual eGFR decline in hypertensive patients who underwent renal denervation (-4.8±3.8 mL/min/1.73 m^2 per year before RDN, whereas after RDN eGFR improved by +1.5±10 mL/min/1.73 m^2 at 12 months; p=0.009)[34]. Newer studies have shown similar results in patients with CKD – both the effective lowering of BP and a mild improvement in eGFR at 3 months, with no significant changes at 12 months[35]. More recent studies have also demonstrated both the safety and efficiency of RDN on BP reduction in patients with ESRD[36,37].

Post-COVID and kidney injury

COVID-19 has affected a significant portion of the human population, with the number of confirmed infections surpassing 660 million and causing over 6.5 million cumulative death worldwide[38]. Owing to the affinity of the SARS-CoV-2 virus for angiotensin converting enzyme 2 (ACE2), which is expressed in neural, gastrointestinal, vascular, cardiac, and other tissues[39], it has been reported that COVID-19 not only manifests with different clinical symptoms depending on the tissue affected, but also causes lasting clinical sequelae even after the patient's recovery from the acute infection[40]. A retrospective analysis of over 190 000 post-COVID patients found that 14% of the studied population manifested at least one novel clinical entity that required treatment[41]. SARS-CoV-2 has been shown to cause renal injury through both direct and indirect pathways[42]. A confirmation of the existence of a direct pathway of renal injury is the presence of viral particles proven in both tubular cells and podocytes through electron microscopy[43], as well as SARS-CoV-2 viral load (RNA and protein particles) detected in all renal compartments of infected patients, with a clear preference for glomerular tissue[44]. There is evidence of excess eGFR decline (approximately 3.26 mL/min/1.73 m^2 per year) in non-hospitalized patients who had COVID-19, compared with non-infected controls[45]. A retrospective study from a tertiary care center that analyzed renal outcomes of non-hospitalized post-COVID patients examined in the emergency department, hypertension clinic, and general internal medicine found an incidence of new-onset renal injury following COVID-19 of 6%[40]. Another study on mainly non-hospitalized patients post-COVID suggested a system of standardized screening 6 to 9 months following active COVID-19 that consists of evaluating renal, cardiac, pulmonary, and venous structural and functional integrity[46].

Onconephrology

The concept of onconephrology, a discipline or perhaps even a subspecialty of nephrology dedicated to the management of renal pathology in oncology patients, is hardly novel, with the OncoNephrology forum established over 10 years ago under the American Society of Nephrology[47]. Although the scope of onconephrology practice was not precisely defined in its initial phase, a paper published in 2016 attempted to describe and outline the ten crucial practice points for future onconephrologists[48]. These were, in no specific order:

(1) Acute kidney injury and the development of chronic kidney disease in patients with cancer.

rum[47]. Iako tijekom samog nastanka pojma opseg prakse onkonefrologije nije precizno definiran, članak iz 2016. pokušao je opisati i predložiti deset područja interesa onkonefrološke prakse[48]. Tih deset točaka, nasumičnim redoslijedom, jesu:

(1) akutno bubrežno oštećenje i razvoj KBB-a u osoba s malignom bolešću
(2) nefrotoksični učinci onkološke terapije, koja podrazumijeva tradicionalnu kemoterapiju, kao i nove terapije koje ciljaju na specifične molekule
(3) bubrežne komplikacije povezane s paraneoplastičnim sindromima
(4) zbrinjavanje bolesnika koji su nefrektomirani u sklopu liječenja maligne bolesti bubrega
(5) nadomjesna bubrežna terapija tijekom aktivnoga onkološkog liječenja
(6) transplantacija bubrega u bolesnika izliječenih od maligne bolesti te procjena rizika za razvoj maligne bolesti u bolesnika s ESRD-om
(7) onkološka terapija u bolesnika koji su primatelji transplantiranog bubrega
(8) zbrinjavanje boli u bolesnika koji boluju od maligne bolesti i bubrežne bolesti
(9) razvoj jasnih smjernica za zbrinjavanje onkonefroloških bolesnika
(10) klinička istraživanja namijenjena proučavanju onkonefroloških problema.

Iste je godine objavljeno više preglednih radova koji proučavaju različite modele oštećenja bubrega mehanizmima vezanima uz pojedinačne skupine onkoloških lijekova[49-52].

Zagađenje zraka

Promjena gledišta od promatranja bolesnika kao izoliranih pojedinaca do proučavanja bolesnika u kontekstu njihove svakodnevne okoline i okolnosti dovela je do razvoja novih ekoloških teorija i istraživačkih pitanja. Nedavno objavljena metaanaliza koja je uključila 14 članaka proučavala je povezanost između incidencije KBB-a i stanovanja u blizini petrokemijskih pogona[53]. Rezultati su pokazali znatno povećan rizik od KBB-a (OR = 1,70, 95 % CI: 1,44 – 2,01), niži eGFR (OR = 0,55, 95% CI: 0,48-0,67) i viši serumski kreatinin (OR = 1,39, 95 % CI: 1,06 – 1,82) u bolesnika koji stanuju pokraj izvorišta nafte i prirodnoga plina ili petrokemijskih pogona, u usporedbi s bolesnicima koji imaju nisku do neznačajnu razinu izloženosti navedenim čimbenicima. Analiza podataka iz Kineske nacionalne ankete o KBB-u proučavala je povezanost između urbanizacije, zagađenja zraka i KBB-a te utvrdila da povećanje koncentracije finih čestica promjera <2,5 mm za 10 μg/m^3, povećanje koncentracije dušikova dioksida za 10 μg/m^3 te povećanje indeksa noćnoga svjetla snažno koreliraju s višim rizikom od povećane prevalencije KBB-a [OR = 1,24 (95 % CI: 1,14, 1,35); OR = 1,12 (95 % CI: 1,09, 1,15); OR = 1,05 (95 % CI: 1,02, 1,07)][54]. Sljedeća metaanaliza, koja je obuhvatila 13 istraživanja pronašla je slične rezultate[55]. Nedavno objavljeno istraživanje proučavalo je povezanost između zagađenja zraka i razvoja progresije KBB-a, definirane kao smanjenje pGF-a za više od 25 % s obzirom na početne vrijednosti. Autori su pratili 5301 bolesnika tijekom 30 mjeseci te su ustanovili jasnu povezanost između izloženosti zagađenom zraku i progresije KBB-a na idući način: bolesnici u najvišem kvartalu izloženosti ugljikovom monoksidu [HR = 1,53 (95% CI: 1,24, 1,88)], dušikovu monoksidu [HR = 1,38 (95% CI: 1,11, 1,71)], NO_2 [HR = 1,63 (95% CI: 1,36, 1,97)], SO_2 [HR = 2,27 (95% CI: 1,83, 2,82)], $PM_{2,5}$ [HR = 7,58 (95% CI: 5,97, 9,62)], i PM_{10} [HR = 3,68 (95% CI: 2,84, 4,78)] imali su značajno veći rizik od progresije bubrežne bolesti u usporedbi s onima u najnižem kvartalu izloženosti[56]. Preporučujemo detaljnije proučavanje literature iz područja medicine okoliša[57,58].

(2) Nephrotoxic effects caused by cancer treatments, which can include traditional chemotherapy drugs as well as newer molecularly targeted therapies.
(3) Renal complications associated with paraneoplastic syndromes.
(4) Management of patients who have undergone nephrectomy as a treatment for kidney cancer.
(5) Renal replacement therapy in conjunction with ongoing cancer treatments.
(6) Kidney transplantation in cancer survivors and the evaluation of cancer risk in patients with ESRD.
(7) Oncological therapies for kidney transplant recipients.
(8) Pain management for patients coping with both cancer and kidney disease.
(9) Development of comprehensive guidelines for onco-nephrology patients.
(10) Clinical trials designed specifically for onco-nephrology.

That same year, reviews of various renal injury patterns and mechanisms associated with specific anti-cancer medication groups were published[49-52].

Air pollution

The move from considering patients as isolated individuals to examining them in the context of their everyday living environment and circumstances has allowed for novel theories and research questions. A recent meta-analysis that included 14 papers investigated the association between the incidence of CKD and living near petrochemical plants[53]. The results showed a statistically significant increased risk for CKD (OR = 1.70, 95% CI: 1.44-2.01), lower eGFR (OR = 0.55, 95% CI: 0.48-0.67) and higher serum creatinine (OR = 1.39, 95% CI: 1.06-1.82) in patients who were situated near oil and natural gas sources or petrochemical plants, in contrast to groups with lower or no exposure to air pollution from the agents. An analysis of the data from the China National Survey of Chronic Kidney Disease examined the link between urbanization, air pollution, and CKD and found that a 10-μg/m^3 increase in $PM_{2.5}$ (fine particulate matter <2.5 mm in diameter) at 3-year moving average, a 10-μg/m^3 increase in NO_2 (nitrogen dioxide) at 5-year moving average, and a 10-U increase in NLI (night light index). The 5-year moving average was strongly linked to higher odds of increased CKD prevalence [OR = 1.24 (95 % CI: 1.14, 1.35); OR = 1.12 (95 % CI: 1.09, 1.15); OR = 1.05 (95 % CI: 1.02, 1.07)][54]. Another meta-analysis covering 13 studies found similar results[55]. Finally, a recent study examined the connection between air pollution and the development of CKD progression, defining progression as a decrease in eGFR of more than 25% from the baseline. A population of 5301 patients was followed for a mean of 30 months, and the authors established a clear association between exposure to air pollution and progression of CKD in the following manner: patients with the highest quartile exposure to CO [HR = 1.53 (95% CI: 1.24, 1.88)], NO (nitric monoxide) [HR = 1.38 (95% CI: 1.11, 1.71)], NO_2 [HR = 1.63 (95% CI: 1.36, 1.97)], SO_2 [HR = 2.27 (95% CI: 1.83, 2.82)], $PM_{2.5}$ [HR = 7.58 (95% CI: 5.97, 9.62)], and PM_{10} [HR = 3.68 (95% CI: 2.84, 4.78)] had notably greater risk of renal progression compared with those in the lowest quartile of exposure[56]. We recommend a deeper dive into the environmental medicine literature[57,58].

kovu monoksidu [HR = 1,53 (95 % CI: 1,24, 1,88)], dušikovu monoksidu [HR = 1,38 (95 % CI: 1,11, 1,71)], dušikovu dioksidu [HR = 1,63 (95 % CI: 1,36, 1,97)], sumporovu dioksidu [HR = 2,27 (95 % CI: 1,83, 2,82)] te česticama promjera >2,5 mm [HR = 7,58 (95% CI: 5,97, 9,62)] i česticama promjera <10 mm [HR = 3,68 (95% CI: 2,84, 4,78)] imali su mnogo viši rizik od progresije KBB-a u usporedbi s bolesnicima u najnižem kvartalu izloženosti navedenim čimbenicima[56] Zainteresiranim čitateljima preporučujemo detaljnije iščitavanje literature vezane uz okolišnu medicinu[57,58].

Oslikavanje odstupanja difuzije od normalne razdiobe

Oslikavanje odstupanja difuzije od normalne razdiobe (DKO) nov je način oslikavanja magnetnom rezonancijom koji se prvi put spominje unatrag 10 godina, primarno kao metoda procjenjivanja mikrostrukture moždanog tkiva u kontekstu infarkta, ishemije traume ili tumora[59]. DKO je neinvazivno rješenje za procjenu i prognozu progresije KBB-a i bubrežne fibroze te bi se trebalo primjenjivati ako je dostupno.

Iako su tehnički aspekti ovog modaliteta oslikavanja previše kompleksni da bi se točno objasnili u ovom segmentu, pozdravljamo čitateljevu znatiželju i pokušaj da ih samostalno shvati, pa stoga pružamo iduću referencu kao početnu točku[60]. Nekoliko je istraživanja provedeno sa svrhom procjenjivanja korisnosti DKO-a kao prognostičkog alata za bolesnike s KBB-om. Jedno je takvo istraživanje pratilo 42 bolesnika tijekom 43 mjeseca kako bi se odredila povezanost između markera dobivenih kroz DKO i opadanja pGF-a. Mjera nazvana pojavnim difuzijskim koeficijentom (ADC) pokazala se kao precizan prognostički marker za razvoj ESRD-a (površina ispod krivulje 0,936, osjetljivost 92,31 %, specifičnost 82,76 %) te kompozitni ishod opadanja pGF-a za više od 30 % i ESRD-a (površina ispod krivulje 0,811, osjetljivost 66,67 %, specifičnost 96,3 %)[61]. Drugo je istraživanje proučavalo 70 bolesnika s KBB-om i 20 zdravih dobrovoljaca te je pronašla snažnu korelaciju između ADC-a i pGF-a te je odredila da DKO pruža bolju dijagnostičku preciznost od difuzijski mjerenih slika (DWI)[62]. Japansko je istraživanje pokazala da se DKO može primjenjivati i za procjenu stupnja bubrežne fibroze u bolesnika s KBB-om primjenom histograma[63].

Vrijednost LDL kolesterola i kronična bubrežna bolest

Istraživanja o ulozi LDL kolesterola na razvoj i progresiju KBB-a provode se tijekom duljeg razdoblja. Prva istraživanja koja povezuju dislipidemiju s progresijom KBB-a objavljena su prije više od 30 godina, kada je skupina autora proučavala povezanost između apolipoproteina B i E u bubrežnome tkivu i stupnja bubrežnog oštećenja. Zaključili su da bolesnici čiji su bubrežni bioptati bili pozitivni na odlaganje navedenih apolipoproteina imaju naprednije stadije KBB-a[64]. Istraživanje iz 1995. koja je pratilo 2702 sredovječna muškarca s dislipidemijom pokazalo je da bolesnici s HDL-C/LDL-C omjerom većim od 4,4 imaju 20 % veću stopu slabljenje bubrežne funkcije (procijenjene na osnovi koncentracije serumskog kreatinina) od bolesnika koji imaju HDL-C/LDL-C omjer manji od 3,2[65]. Ispitivanje koje je uspoređivalo atorvastatin u bolesnika s KBB-om liječenih ACEi ili ARB-om s placebom pokazalo je statistički značajno smanjenje proteinurije i sporije opada-

Diffusion kurtosis imaging

Diffusion kurtosis imaging (DKI) is a novel mode of magnetic resonance imaging that emerged in the last decade, primarily as a method of evaluating the microstructure of cerebral tissue in infarctions, ischemia, trauma, and neoplasms[59]. DKI provides a non-invasive solution for both the evaluation and prognosis of CKD progression and renal fibrosis and should be used when available.

While the technical aspects of this imaging modality are far too complex to be properly addressed and explained in this segment, the reader is more than welcome to obtain more detail information, so we provide a reference as a starting point[60]. The clinical aspects are a different story altogether: in recent years, several studies have been performed to evaluate the viability of DKI as a prognostic tool for patients with chronic kidney disease. One such study followed 42 patients for a median of 43 months to determine the relationship between markers obtained with DKI and eGFR decline. A measurement called apparent diffusion coefficient (ADC) was demonstrated to be a reliable and precise prognostic marker for both ESRD [area under the curve (AUC) 0.936, sensitivity 92.31%, specificity 82.76%] and the composite endpoint of a decline in eGFR >30% or ESRD (AUC 0.881, sensitivity 66.67%, specificity 96.3%)[61]. Additionally, the ADC values were statistically significantly associated with the eGFR slopes, both with the first-last time point slope ($p<0.001$) and with the regression slope ($p<0.001$). Another study with a population of 70 patients with CKD and 20 healthy volunteers also found a strong correlation between ADC and eGFR and determined that DKI offered better diagnostic performance for renal pathology than diffusion weighted imaging (DWI)[62]. Finally, a Japanese study has shown that DKI can also be used to estimate the degree of renal fibrosis in patients with CKD using histograms[63].

LDL-C and CKD

Research on the role of LDL-cholesterol is hardly novel. The first mentions of a connection between dyslipidemia and CKD progression date back more than 30 years, when a group of authors studied the association between the presence of apolipoproteins B and E in renal tissue and the degree of renal injury, finding more advanced stages of renal tissue damage in patients whose renal biopsy tissues were positive for deposits of those apolipoproteins[64]. A study on 2702 middle-aged men with dyslipidemia from 1995 found that patients with an HDL-C/LDL-C ratio of more than 4.4 had a 20% higher rate of decline in renal function (estimated by creatinine levels) than those with an HDL-C/LDL-C ratio of less than 3.2[65]. An open label trial comparing atorvastatin in patients with CKD treated with ACE inhibitors or ARBs to no treatment found a statistically notable decrease in proteinuria and a more gradual decline in creatinine clearance in patients on atorvastatin[66]. However, there is also evidence pointing to little or no benefit of statin therapy on prevention of CKD progression. A study from the SHARP research group randomized patients with CKD to either 20 mg of simvastatin plus 10 mg of ezetimibe or placebo and followed them for 4.8 years. The findings indicated an average decrease in LDL-C levels of 0.96 in the simvastatin/ezetimibe group, but with no significant effect on the rate of eGFR decline[67]. Additionally, the CRIC study showed no statistically significant correlation between LDL-C levels

nje klirensa kreatinina (naziv ranije rabljen umjesto naziva pGF) u bolesnika koji su uzimali atorvastatin[66]. Ipak, postoje i dokazi koji upućuju na izostanak pozitivnog učinka terapije statinima na usporivanje progresije KBB-a. Istraživanje koje je provela SHARP grupa istraživača randomiziralo je bolesnike s KBB-om na 20 mg simvastatina + 10mg ezetimiba ili placebo i pratilo ih tijekom 4,8 godina. Rezultati su pokazali prosječno sniženje LDL-C-a za 0,96 mmol/L u skupini koja je uzimala simvastatin/ezetimib, ali bez značajne razlike u brzini opadanja pGF-a[67]. CRIC istraživanje također je pokazala izostanak statistički značajne korelacije između serumske koncentracije LDL kolesterola i brzine progresije KBB-a[68]. Potencijalno objašnjenje za ovu heterogenost dostupne literature možda se nalazi u doziranju terapije statinima: metaanaliza iz 2015. koja je uključila 10 istraživanja pronašla je znatno usporivanje godišnjeg opadanja pGF-a [3,35 (95% CI: 0,91 do 5,79) mL/min/1,73m^2] u bolesnika koji su uzimali terapiju statinima visokog intenziteta, ali takav učinak nije zamijećen u bolesnika koji su uzimali statinsku terapiju niskog ili umjerenog intenziteta[69]. Druga je metaanaliza uključila 57 istraživanja i 143 888 bolesnika te je pokazala statistički značajno usporivanje godišnjeg opadanja pGF-a u bolesnika koji se koriste statinima [0,41 (95 % CI: 0,11 – 0,70) mL/min/1,73m^2] i statistički značajno smanjenje proteinurije ili albuminurije[70]. Ista je metaanaliza također pokazala statistički značajan pad rizika od neželjenih kardiovaskularnih događanja u bolesnika s KBB-om koji uzimaju statine (OR, 0,69; 95 % CI: 0,61 – 0,79; p <0,001).

Zaključak

Iako je sigurno da teme obrađene u ovom članku nipošto nisu jedini čimbenici koji utječu na progresiju KBB-a, vrlo je vjerojatno da je riječ o područjima u kojima su se unatrag nekoliko godina pojavili uvjerljivi dokazi koji mijenjaju svakodnevnu praksu pa su stoga izrazito zanimljivi i važni kliničarima.

and the rate of CKD progression[68]. The reason for this discrepancy in the evidence might lie in the dosing of statin therapy: a meta-analysis from 2015 that included 10 studies found a significant decrease in the rate of eGFR decline per year [3.35 (95% CI: 0.91 to 5.79) mL/min/1.73 m^2] in patients using high-intensity statin therapy, but no such decrease in patients on low or moderate-intensity statins[69]. Another meta-analysis included 57 studies and 143 888 patients and showed a statistically significant decrease in eGFR decline per year in patients using statins [0.41 (95% CI: 0.11-0.70) mL/min/1.73 m^2] and a statistically significant decrease in proteinuria or albuminuria[70]. The same meta-analysis also demonstrated a statistically significant decrease in risk for CV events in patients with CKD using statins (OR = 0.69; 95% CI: 0.61-0.79; p<0.001).

Conclusion

While the topics and talking points discussed in this article are far from the only factors influencing the progression of CKD, they are certainly areas in which significant and practice-changing evidence has emerged in the last few years and are therefore of utmost interest for the practicing physician.

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