Dijabetička nefropatija i prevencija dijabetičkom nefropatijom uzrokovanog bubrežnog zatajenja

Diabetic nephropathy and the prevention of renal failure caused by diabetic nephropathy

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Šećerna bolest (ŠB) je obilježena povišenom koncentracijom glukoze u krvi, iznad točno određenih vrijednosti natašte ili u testu opterećenja sa 75 grama glukoze uzete peroralno zbog potpunog ili relativnog nedostatka inzulina. Bolesnici s potpunim nedostatkom inzulina imaju ŠB tip 1, a bolesnici s relativnim ŠB tip 2. Nastaje uslijed autoimunih, genetskih ili okolinskih čimbenika. Prati ju niz komplikacija, akutnih i kroničnih, vaskularnih i nevaskularnih.

Dijabetičku nefropatiju (DN) ubrajamo zajedno s dijabetičkom retinopatijom i neuropatijom u mikrovaskularne komplikacije. Njen najraniji znak je mikroalbuminurija, nalaz više od 30, a manje od 300 mg albumina u 24-satnom urinu. Mikroalbuminuriju dakle mogu imati i šećerni bolesnici s normalnom 24-satnom proteinurijom. Preporuka je da se mikroalbuminurija i proteinurija odrede u

Diabetes is diagnosed by an increased concentration of blood glucose level, above specific values on an empty stomach or in oral glucose tolerance tests (with 75 grams of glucose) due to complete or relative deficiency of insulin. Patients with a total insulin absence have type 1 diabetes, whereas patients with relative insulin deficiency have type 2 diabetes. This occurs due to autoimmunity, genetic and environmental factors and is followed by a series of complications, acute and chronic, vascular and non-vascular.

Diabetic nephropathy (DN) with diabetic retinopathy and neuropathy are microvascular complications. The earliest sign is microalbuminuria (30-300mg albumin in a 24-hour urine). Diabetic patients can therefore have microalbuminuria with a normal 24-hour proteinuria. It is recommended that microalbuminuria and proteinuria be determined in patients with type 1 diabetes after 5 years from di-

bolesnika sa ŠB tip 1 nakon 5 godina postojanja bolesti ili u pubertetu, a u bolesnika sa ŠB tip 2 odmah nakon dijagnoze bolesti. Bolesnici s mikroalbuminurijom imaju 3 do 4 puta veću šansu nastanka patološke proteinurije i završnog stupnja kroničnog bubrežnog zatajenja (KBZ) od dijabetičkih bolesnika bez mikroalbuminurije. Međutim, samo 20-45% bolesnika sa ŠB tip 1 i mikroalbuminurijom tijekom narednih 10 godina razvija patološku proteinuriju, 20-25% njih postane normoalbuminuričnih, a preostalih 30-60% ostaju s mikroalbuminurijom.

Glomerularna filtracija počinje padati tek nakon što 24-satna proteinurija dostigne patološke vrijednosti, obično iznad 300 mg. Prije toga obično je u normalnom rasponu, a neposredno nakon otkrivanja ŠB može biti čak i povišena. U ranim stupnjevima bolesti nije moguće razlučiti koji će bolesnici sa ŠB razviti DN, a koji neće.

DN je posljedica dugotrajnih metaboličkih promjena, a hiperglikemija je neophodna za njen nastanak. Brojne studije su pokazale da dobra regulacija glukoze smanjuje rizik nastanka DN i u bolesnika sa ŠB tip 1 i tip 2. Uz hiperglikemiju za nastanak DN neophodne su karakteristične hemodinamske promjene u glomerulima, glomerularna hiperfiltracija i porast tlaka u glomerularnim kapilarama. Glomerularna hiperfiltracija direktno dovodi do nakupljanja vanstaničnog mezangijskog matriksa. Utjecaj arterijskog tlaka (AT) vrlo je bitan u nastanku DN. Prevladava mišljenje da su genetski čimbenici ipak najvažniji u njenom nastanku.

Glavno morfološko obilježje DN je nakupljanje vanstaničnog matriksa u glomerularnim i tubularnim bazalnim membranama. Dominantno se nakuplja u mezangijumu, pa je on proširen, a glomerularna i tubularna bazalna membrana zadebljana. Posljedica je promjena selektivne propusnosti glomerularnih kapilara i smanjenje glomerularne filtracije. U 40-50% bolesnika proširenje mezangija uslijed nakupljanja vanstaničnog mezangijskog matriksa je samo mjestimično, u obliku nodula. Ovaj oblik DN nazvan je zbog toga nodularnom ili Kimmelstiel-Wilsonovom. Promjene u DN nađu se i u intersticiju te u aferentnoj i eferentnoj arterioli.

Renoprotekcija, pokušaj odgode nastanka dijabetičke nefropatije

Poboljšanje kontrole glikemije, dobra regulacija AT, korekcija bubrežne anemije eritropoetinom, regulacija kvantitativnih i kvalitativnih poremećaja metabolizma lipoproteina plazme, uvođenje ACE inhibitora i smanjenje unosa bjelančevina, sve negenetskih čimbenika, usporit će gubitak bubrežne funkcije u nekih od ovih bolesnika. Svejedno, još uvijek će značajan broj dijabetičkih bolesnika razviti DN i završni stupanj KBZ.

Dobrom regulacijom glukoze smanjen je rizik nastanka mikroalbuminurije u bolesnika sa ŠB tip 1 i 2 za čak 54%. Američko dijabetološko društvo preporučuje zbog toga HbA1c ispod 7%, a japansko ispod 6,5%. Procjenjuje se da je adekvatno liječenje arterijske hipertenzije (AH) važnije u smanjenju srčanožilnih komplikacija i u usporenju gubitka bubrežne funkcije bolesnika sa ŠB od regulacije koncentracije glukoze. Preporučuje se da bolesnici s AH liječenjem održavaju AT ispod 130/85 mmHg, odnos-

agnosis or in puberty, and in patients with type 2 diabetes immediately following diagnosis of the disease. Patients with microalbuminuria have 3-4 times a greater chance of developing pathological proteinuria and the final stage of chronic kidney failure than diabetic patients without microalbuminuria. However, only 20-45% of patients with type 1 diabetes and microalbuminuria in the next 10 years develop pathological proteinuria, 20-25% of them become normoalbuminuric, while the remaining 30-60% has microalbuminuria.

Glomerular filtration begins to decrease, only after 24-hour proteinuria reaches pathological values, ordinarily above 300mg. Prior to this, it normally increases, and directly following discovery of diabetes can even be elevated. In the early stages of the disease, it is not possible to differentiate what patients with diabetes will develop DN and what patients will not.

DN is the result of long-term metabolic changes, while hyperglycemia is essential for its occurrence. Numerous studies have shown that good regulation of blood glucose reduces the risk of DN occurrence even in patients with type 1 and type 2 diabetes. Along with hyperglycemia, DN is also caused by characteristic hemodynamic changes in glomerulus, glomerular hyperfiltration and an increase of pressure in the glomerular capillaries. Glomerular hyperfiltration directly leads to the accumulation of extracellular mesangial matrix. The impact of blood pressure (BP) is very important in the occurrence of DN. Opinion prevails that genetic factors are nonetheless the most important in the occurrence of DN.

The main morphological characteristics of DN are the accumulation of extracellular matrix in glomerular and tubular basal membranes. It primarily accumulates in the mesangium, hence it expands, while glomerular and tubular basal membrane become thicker. The results are changes in the selective permeability of the glomerular capillaries and a reduction in glomerular filtration. In 40-50% of patients, expansion of the mesangia during accumulation of extracellular mesangial matrix occurs only sporadically, and in the form of nodules. This type of diabetes is consequently called nodular or Kimmelstiel-Wilson diabetes. Changes in DN are also found in interstitia and in the afferent and efferent arteriole.

Renoprotection, an attempt to delay the occurrence of diabetic nephropathy

Improving the control of glycemia, good regulation of BP, corrections to renal anemia through erythropoietin, regulation of quantitative and qualitative disorders in the lipid metabolism, introducing ACE inhibitors and a reduction in the intake of proteins, all of which are non-genetic factors, will delay the loss of kidney function in some of these patients. Nonetheless, a significant number of diabetic patients will develop DN and reach the final stage of chronic kidney failure (CKF).

Good regulation of blood glucose reduces the risk of microalbuminuria occurring in patients with type 1 and 2 diabetes by even 54%. The American Diabetic Society recommends that HbA1c be under 7%, while the Japanese Diabetic Society claims it should be under 6.5%. It has been estimated that adequate treatment of arterial hypertension (AH) is more important in the reduction of cardiovascular

no ispod 130/80 mmHg ako im je 24-satna proteinurija <1g, a ispod 125/75 mmHg ako je iznad toga.

Pri tome je vrlo bitan korišteni antihipertenziv. Meta analiza 100 studija bolesnika sa ŠB tip 1 i 2 pokazala je da je usporenje gubitka bubrežne funkcije postignuto dobrom regulacijom AT neovisno o korištenom antihipertenzivu, ali da je to usporenje uz ACE inhibitore bilo neovisno o utjecaju na AT. Zbog toga se ovi antihipertenzivi preporučuju dijabetičarima s mikroalbuminurijom i kada nemaju povišen AT. Niz studija pokazao je da korekcija anemije humanim rekombinantnim eritropoetinom (rHu-Epo) usporava daljni gubitak bubrežne funkcije. Jungers i sur. su zaključili da je početak liječenja bubrežnog zatajenja dijalizom u bolesnika kojima je bubrežna anemija korigirana rHu-Epom odgođen prosječno za šest mjeseci. Meta analiza trinaest kontroliranih studija pokazala je da statini u bolesnika s KBZ smanjuju proteinuriju i usporavaju gubitak preostale bubrežne funkcije. Nakamura i sur. pak nisu našli da statini smanjuju albuminuriju i usporavaju gubitak glomerularne filtracije u bolesnika s KBZ i ŠB tip 1. To je uspjelo Lamu i sur. u bolesnika sa ŠB tip 2. Zbog svega navedenog sada su primarna i sekundarna prevencija srčanožilnih bolesti glavni razlog liječenja poremećaja metabolizma lipoproteina u šećernih bolesnika. Jedno komparativno ispitivanje pokazalo da i umjereno ograničenje unosa proteina značajno smanjuje rizik nastanka završnog stupnja KBZ u bolesnika sa ŠB tip 1 i kroničnim bubrežnim zatajenjem 2. stupnja. Preporučuje da bolesnici sa ŠB i KBZ 1. — 4. stupnja unose 0,8 g proteina/kg tjelesne težine dnevno te da proteinima ne osiguravaju više od 20% dnevno potrebnih kalorija.

Veličina problema

U novije vrijeme ŠB je najčešći uzrok nastanka završnog stupnja KBZ. Prosječno u 30-40% novih bolesnika sa završnim stupnjem KBZ uzrok nastanka je ŠB. U SAD taj udio je još i veći, iznad 40%.

Tijekom 2004. godine u SAD započelo je liječenje dijalizom 339 bolesnika na milijun stanovnika, u Njemačkoj 194, u Južnoj Europi 129, a u Sjevernoj 110. Udio bolesnika sa ŠB bio je 149 na milijun stanovnika u SAD, 66 u Njemačkoj, 28 u Južnoj i 24 u Sjevernoj Europi. Prema podacima iz Hrvatskog registra nadomještanja bubrežne funkcije liječenje dijalizom tijekom 2005. godine započelo je 144 bolesnika na milijun stanovnika, a udio bolesnika sa ŠB iznosio je 30%.

Između 2002. i 2004. godine broj novih bolesnika koji su razvili završni stupanj KBZ zbog ŠB u SAD smanjen je za 2,1%. Godine 1996. završni stupanj KBZ razvilo je 305 od 100.000 bolesnika sa ŠB, a 2002. godine njih samo 232. Ali, pitanje je hoće li ovakav trend imati i druge zemlje ili će se u nekima od njih, kao što je Njemačka, još jedno vrijeme bilježiti porast stope incidencije dijabetičkih bolesnika koji razvijaju završni stupanj KBZ.

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complications and in delaying the loss of kidney functioning in diabetic patients than regulation of glucose concentrations. It is recommended that patients with AH through treatment maintain BP below 130/85mmHg, or below 130/80 mmHg if their 24-hour proteinuria is <1g, and below 125/75mmHg if it exceeds this value.

Therefore, it is important to use antihypertensive. Meta analysis of 100 studies of patients with type 1 and 2 diabetes has shown that delaying the loss of kidney functioning is achieved through good regulation of BP regardless of the use of antihypertensive, but this delay along with ACE inhibitors, was not dependent on impact on BP. Consequently, these antihypertensive are recommended to diabetic patients with microalbuminuria and when without high BP. A series of studies have shown that a correction in anemia using human recombinant erythropoietin (rHu-Epo) delays further loss of kidney function. Jungers et al. have concluded that the commencement of treatment of kidney failure in patients using dialysis, whose renal anemia is corrected by using rHu-Epo is delayed on the average by 6 months. Meta analysis of 13 controlled studies has shown that statins in patients with CKF reduces proteinuria and slows down the loss of the remaining kidney functioning. Nakamura et al., however, did not find that statins reduce albuminuria and slow down the loss of glomerular filtration in patients with CKF and type 1 diabetes. This was succeeded by Lam et al. in patients with type 2 diabetes. In accordance with all mentioned above, primary and secondary prevention of cardiovascular diseases are the main reason for treating disorders in the metabolism of lipoproteins in diabetic patients. A comparative test has shown that even limited intake of proteins significantly reduces the risk of the final stage of CKF occurring in type 1 diabetic patients and in stage 2 CKF. It is recommended that patients with type 1 diabetes and CKF between stage 1 and 4 take 0.8 grams of protein per kilogram of body mass on a daily basis and that using such proteins, patients do not ensure more than 20% of their daily required calories.

The size of problem

In recent times, diabetes was most frequent cause of the final stage of CKF. On the average in 30-40% of new patients with final stage CKF, the cause is diabetes. In the USA, this percentage is even greater, more than 40%.

In 2004 in the USA, treatment of 339 patients per million inhabitants using dialysis began, in Germany 194, in southern Europe 129, and in northern Europe 110 patients. The percentage of patients with diabetes was 149 per million inhabitants in the USA, 66 in Germany, 28 in southern and 24 in northern Europe. Based on the data from the Croatian Registry, treatment of kidney functioning using dialysis in 2005 was carried out by 144 patients per million inhabitants, while the percentage of patients with diabetes amounted to 30%.

Between 2002 and 2004, the number of new patients developing the final stage of CKF due to diabetes in the USA was reduced by 2.1%. In 1996 the final stage of CKF occurred in 305 out of 100,000 patients with diabetes, while in 2002 there were only 232 such patients. But the question remains, whether other counties will experience this trend or whether some of these countries, such as Germany, will continue to experience an increase in the number of incidents of diabetic patients who develop the final stage of CKF.