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# Early markers of kidney dysfunction in patients with essential hypertension

# Wczesne wykładniki uszkodzenia nerek u pacjentów z pierwotnym nadciśnieniem tętniczym

[1]Joanna Pollak, [2]Grzegorz Janikowski, [1]Grażyna Odrowąż-Sypniewska, [1]Aneta Mańkowska, [3]Paweł Stróżecki, [3]Michał Kozłowski, [3]Marek Kretowicz, [3]Jacek Manitius

[1]Department of Laboratory Medicine, Nicolaus Copernicus University, Collegium Medicum, Bydgoszcz, Poland,
[2]Medical Center "Zachód", Bydgoszcz,
[3]Department of Nephrology, Hypertension and Internal Diseases, Nicolaus Copernicus University, Collegium Medicum Bydgoszcz, Poland

*Summary*

*The aim of study was to evaluate concentration and activity of selected markers of kidney dysfunction in non-treated patients with newly recognized hypertension. Markers of kidney dysfunction were measured in 49 patients, aged 40-65 years, with newly recognized non-treated hypertension and compared with results obtained from age-matched reference group. The values of most measured parameters were within reference range but serum cystatin C, urine creatinine, albumin and UACR were significantly higher in hypertensive patients.*

*We have found that kidney dysfunction is present already in patients with newly recognized first and second degree hypertension. Measurement of early markers of kidney dysfunction, especially albuminuria, may be a very useful tool for screening patiens with newly diagnosed, nontreated essential hypertension.*

*Streszczenie*

*Celem niniejszej pracy była ocena wczesnych zmian funkcji nerek u pacjentów z nowo rozpoznanym nieleczonym nadciśnieniem tętniczym. Badaniem objęto 49 osób z nadciśnieniem tętniczym, w wieku 45-65 lat, oraz grupę odniesienia - 49 osób z prawidłowym ciśnieniem tętniczym dobranych pod względem wieku. U pacjentów z nadciśnieniem tętniczym oceniano różne wskaźniki uszkodzenia nerek i porównywano je z wynikami uzyskanymi w grupie odniesienia. Uzyskane wyniki w grupie badanej mieściły się w zakresach wartości referencyjnych jednak stężenie cystatyny C w surowicy, kreatyniny oraz albuminy w moczu, a także wartość wskaźnika UACR były istotnie wyższe w grupie badanej w porównaniu do grupy odniesienia.*

*Stwierdzono, że u osób ze świeżo rozpoznanym nieleczonym nadciśnieniem tętniczym pierwszego i drugiego stopnia dochodzi już do uszkodzenia nerek a oznaczane parametry, w szczególności albuminuria, mogą stanowić szybki i prosty test dla oceny funkcji nerek w tej grupie pacjentów.*

**Key words:** hypertension, albuminuria, cystatin C, kidney dysfunction

**Słowa kluczowe:** nadciśnienie tętnicze, albuminuria, cystatyna C, uszkodzenie nerek

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## Introduction

Hypertension is the main cause of kidney dysfunction and often leads to chronic kidney diseases (CKD). It was shown that hypertension is the second leading cause of end-stage renal disease (ESRD) in the elderly. Higher blood pressure (systolic blood pressure ≥140 mmHg; diastolic blood pressure ≥90 mmHg) predicts the development of nephropathy and proteinuria (1). Even less severe kidney dysfunction is associated with an increase in cardiovascular risk, especially in hypertensives. Nowadays, it is extremely important

to select patients with higher risk of development of kidney dysfunction, especially in high risk hypertensive group. Data show that changes in kidney function start very early and at the beginning of the pathologic process when the values of traditional biomarkers do not exceed the refrence range.

Albuminuria was for a long time related to incidence of hypertension and disturbed endothelial function (2). Abnormal glomerulus endothelial function is considered as an early symptom of essential hypertension and may lead to increased blood pressure. The mechanisms of this process are still uncertain. Hypertension causes hyperfiltration and glomeruli impairment which lead to imbalance in electronegative filtration barrier and consequently to albumin leakage. Some data suggested that in diabetic, hypertensive patients there is a strong impact of inflammation, insulin resistance, endothelial dysfunction and disturbances in coagulation (3). To lower the influence of these factors, and also time influence on albumin excretion, urine albumin should be measured in 24-hours urine sample. However, as it comes from professional experience correct 24-hour urine sampling is quite difficult to obtain. To gain correct results, independent of above mentioned factors, urine albumin is very often presented as UACR- urinary albumin to creatinine ratio. Measurement of albumin and creatinine are performed in the first morning urine sample and the urinary albumin-to-creatinine ratio is calculated (4).

Very important in determining renal impairment in hypertensive patients is the estimation of glomerular filtration based on serum creatinine concentration. The most often used formulas for GFR calculation are: Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (C-G). *Klocek* at al suggested that in hypertensive patients the value derived from MDRD equations identifies significantly higher numbers of individuals with chronic kidney disease then assessed by C-G formula (5).

Nowadays, most of authorities consider also uric acid as an important risk factor for renal or cardiovascular risk particularly in patients with hypertension, obesity, metabolic syndrome or kidney disease (6,7). Even mild hyperuricemia is associated with early signs of renal damage (6).

Among the new markers of kidney function cystatin C seems to be of high clinical validity. Cystatin C is a cysteine proteinase inhibitor that is an endogenous marker produced at a constant rate by all nucleated cells. Patients with hypertension appear to have higher circulating cystatin C concentrations what makes them at the same time to be in higher cardiovascular risk group. Furthemore, cystatin C appears to be a useful marker for identifying individuals at a higher risk for cardiovascular events among patients belonging to a relatively low-risk category as estimated by both creatinine and estimated glomerular filtration values (8).

In practice, most renal diseases, including hypertensive nephropathy, are only detected when severe kidney dysfunction occurs. The aim of this study was to evaluate concentration and activity of selected markers of kidney dysfunction in non-treated patients with newly recognized hypertension. Early screening of kidney dysfunction in non-treated hypertensive patients is of great importance.

**Material and methods**

*Patients*

Forty nine patients with newly recognized hypertension were included into the study. Hypertension was defined according to ESH/ESC 2007 (European Society of Hypertension/ European Society of Cardiology) criteria as an average 24-hour blood pressure ≥125-130/80 mmHg, average from day time ≥130-135/85 mmHg, and average from night time ≥ 120/70 mmHg for ABPM (Ambulatory Blood Pressure Monitoring) (9). Physical examination revealed no other associated diseases. In 49 patients with essential, non-treated hypertension renal ultrasound scan showed normal-sized kidneys, routine clinical and laboratory examinations excluded other secondary forms of hypertension. In that group of 23 females and 26 males the mean age was 52,1 years (range 40-65 years). Anthropometric parameters were also measured/calculated. Fasting blood was collected to obtain serum that was stored frozen in small aliquots at -70˚C. First void morning urine was collected from all subjects and stored frozen at -70˚C. At the time of analysis they were thawed and centrifuged, with the supernatant being used for the assays.

Reference group was consisted of 49 apparently healthy volunteers with no history of renal diseases, cardiovascular disease or hypertension. Normotensives had blood pressure respectively lower than hypertensive patients according to ESH/ESC 2007 Guidelines (9). The median age of that group of 27 females and 16 males was 50,7 years (range 40-65 years).

All participants gave written informed consent. The present study was accepted and approved by the Bioethical Committee of Collegium Medicum in Bydgoszcz, University of Nicolaus Copernicus in Torun.

*Measurement of cystatin C*

Serum cystatin C was measured by particle-enhanced nephelometric immunoassay (N Latex Cystatin C, Dade Behring Diagnostics) on the BN II nephelometer. Reference values: 0,53-0,95 mg/L.

*Measurement of uric acid*

Uric acid concentration both in serum and in urine was evaluated by enzymatic reaction based on Trivedi's and Kabasakalian's reaction on the ARCHITECT® ci8200 System analyzer (Uric Acid, Abbott Laboratories). Reference values: serum/plasma: females: 2,6-6,0 mg/dL; males: 3,5-7,2 mg/dL; urine: 16-100 mg/dL.

*Measurement of GFR*

Serum and urinary creatinine were determined by a fully automated Jaffe kinetic method on a ARCHITECT® ci8200 System analyzer (Creatinine, Abbott Laboratories). Reference values: serum/plasma: females: 0,6-1,1 mg/dL; males: 0,7-1,3 mg/dL; urine: 50-265 mg/dL.

The MDRD equation was employed for estimating GFR (eGFR MDRD) (10):

| | |
|---|---|
| eGFR MDRD (mL/min/1.73m²) | eGFR= 186,3 x ((creatinine) (mg/dL))$^{-1,154}$x (age)$^{-0,203}$x 0,742 (if female) |

In addition creatinine clearance was calculated according to the Cockcroft-Gault formula (11):

| | |
|---|---|
| Creatinine clearance Cockcroft-Gault (ccC-G) (mL/min) | ccC-G=(140-age) x weight (kg)/[(72 (ml/min) x creatinine (mg/dl) x 0.85 (if female)] |

Normal values: eGFR > 90 ml/min/1,73 m$^2$

*Measurement of albumin and calculation of UACR*

Urinary albumin was measured by a nephelometric immunoassay on the BN II nephelometer (Dade Behring Diagnostics) in fresh first morning void urine samples. Reference value: urine ≤ 20 mg/L. Limit of detection: 2,27 mg/L.

Urinary albumin to creatinine ratio (UACR) was calculated based on urine albumin and urine creatinine concentration and expressed as milligrams per millimole of urine creatinine (mg/mmol Cr). Albuminuria was defined as an UACR >2,5 mg/mmol in males and >3,5 mg/mmol in females.

*Measurement of urinary N-acetyl-beta-D-glucosaminidase*

The urinary N-acetyl-beta-D-glucosaminidase (NAG) levels were measured by a spectrophotometric method using a commercial kit: N-acetyl-β-D-glucosaminidase (NAG) (ROCHE). The absorbance of the samples was obtained photometrically at 580 nm against the blank. Urinary NAG activity was corrected by creatinine excretion, and expressed as units per millimole of urine creatinine (U/mmol Cr).

Statistical Analysis

The results were expressed as mean ± standard deviation (SD) or median and low and high quartile (Q1; Q3). To check for Gaussian distributions, data were evaluated by the Kolgomorov-Smirnov test, taking p <0,001 as significant. Student's *t*-test and U-Mann Whitney test were used to compare differences. All analyses were run on the statistics package Statistica 8, StatSoft®. A probability level of p<0,05 was considered statistically significant.

**Results**

General characteristics of study groups is presented in Table I. Mean value of SBP and DBP obtained from 24 hours ABPM, day time and night time and BMI were significantly higher in patients with hypertension comparing to normotensives. There were no significant differences between groups in: age, BSA (body surface area), WHR (waist/hip ratio) and waist circumference although these values were slightly higher in hypertensive patients.

The glucose concentration was within reference values and there were no significant differences among analyzed groups. We found patients with dyslipidaemia in hypertensive group. The most often occured: high total cholesterol concentration (71,4%) and high LDL-cholesterol concentration (61,2%) (total cholesterol>190 mg/dL, LDL-cholesterol >115 mg/dL- according to ESH/ESC 2007 Guidelines (9)). There were no hypertriglicerydemia cases. There were no significant differences among hypertensives with dyslipidaemia and normolipidaemia in analyzed markers of kidney dysunction.

There were no significant differences in GFR values evalu-

**Table I.**
**General characteristics of study groups. Results presented as mean ±SD or median (Q1;Q3)**

| | Normotensives n=49 | Hypertensives n=49 | p < |
|---|---|---|---|
| SBP (24 hours (mm Hg) | 118,1 ± 8,6 | 140,2 ± 11,3 | 0,001 |
| DBP (24 hours) (mm Hg) | 74,0 ± 6,8 | 85,1 ±8,4 | 0,001 |
| SBP (day) (mm Hg) | 121,9 ± 8,9 | 145,0 ± 10,8 | 0,001 |
| DBP (day) (mm Hg) | 75,0 ± 7,0 | 88,4 ± 8,0 | 0,001 |
| SBP (night) (mm Hg) | 105,0 (100,0; 114,0) | 129,0 (119,0; 137,0) | 0,001 |
| DBP (night) (mm Hg) | 66,0 (61,0; 70,0) | 75,0 (72,0; 83,0) | 0,001 |
| Age (years) | 50,7 ± 6,3 | 52,1 ± 6,6 | NS |
| BMI [kg/m$^2$] | 26,10 ± 3,61 | 28,02 ± 4,06 | 0,0008 |
| BSA (m$^2$) | 1,90 ± 0,22 | 1,97 ± 0,24 | NS |
| WHR | 0,88 (0,81; 0,92) | 0,90 (0,84; 0,95) | NS |
| Waist circumference(cm) | 88,0 ± 10,5 | 92,4 ± 12,1 | NS |

**Table II.**
**GFR estimated with different formulas in normotensives and hypertensives**

| eGFR | Normotensives n=49 | Hypertensives n=49 | p < |
|---|---|---|---|
| eGFR MDRD (ml/min/1.73m²) | 79,0 (74,0; 91,0) | 79,0 (73,0; 87,0) | NS |
| cc C-G (ml/min) | 99,8 (82,1; 110,5) | 98,4 (88,4; 118,1) | NS |

ated with conventional formulas: MDRD and C-G between normotensives and hypertensives (Table II). Median values of GFR were over the cut-off (>60 ml/min –according to ESH/ESC 2007 Guidelines (9)) for hypertensive patients.

Analysis of biochemical markers of kidney dysfunction in hypertensive patients and normotensive group is shown in Table III. Concentration of serum cystatin C, urine creatinine and albumin and value of UACR were significantly higher in patients with hypertension. However, there were no significant differences in concentration of serum creatinine and uric acid, urine uric acid and NAG activity between groups.

Urine NAG activity was slightly lower in hypertensive group. Concentration of serum creatinine in individuals from both groups was in the reference range (0,6-1,1 mg/dL in females, 0,7-1,30 mg/dL in males) as well as serum uric acid in females and in males (2,6-6,0 mg/dL in females, 3,5-7,2 mg/dL in males). There was no difference among groups in urine concentration of uric acid.

In both groups mean value of cystatin C was within the reference range (0,53-0,95 mg/L) but elevated values of cystatin C were observed in 28,3 % of patients with hypertension. Mean UACR among hypertensives was below the currently used cut-off values (in females >3,5 mg/mmol, in males >2,5 mg/mmol (15)), however the frequency of UACR values above the cut off was 22 % among females and 19 % in males. Prevalence of elevated values of UACR was shown in Table IV. When UACR was used, instead of albumin concentration in the urine, as a criterion for albuminuria the frequency of elevated UACR in patients with hypertension was three-fold higher.

**Table III.**
**Biochemical markers of kidney dysfunction in normotensives and hypertensive patients.**

| Parameter/ratio | Normotensives n=49 | Hypertensives n=49 | p < |
|---|---|---|---|
| Cystatin C (mg/L) | 0,78 ± 0,10 | 0,89 ± 0,15 | 0,001 |
| Serum creatinine (mg/dL) | 0,86 (0,77; 0,97) | 0,82 (0,77; 0,94) | NS |
| Serum uric acid (mg/dL) | 4,0 (3,4; 4,3) | 4,1 (3,6; 5,4) | NS |
| Urine creatinine (mg/dL) | 96,7 (58,0; 119,6) | 139,2 (80,7; 177,2) | 0,002 |
| Urine uric acid (mg/dL) | 42,4 ± 14,9 | 44,1 ±17,6 | NS |
| Albuminuria (mg/L) | 3,42 (2,3; 6,3) | 6,25 (4,69; 12,2) | 0,001 |
| NAG (U/g Cr) | 1,7 (0,7; 2,8) | 1,4 (0,9; 3,3) | NS |
| UACR (mg/mmol) | 1,23 (0,80; 1,69) | 1,72 (1,20; 2,84) | 0,002 |

**Table IV.**
**Frequency of elevated values of measured/calculated parameters in patients with hypertension**

| Parameter | Frequency in hypertensive group % (n) |
|---|---|
| UACR > 3,5 mg/mmol (F) > 2,5 mg/mmol (M) | 20,4% (10) |

F- females, M-males, n-number.

**Discussion**

A complex character of hypertension, creates a necessity for early and accurate diagnosis of this disease and it's complications which results in early treatment of metabolic imbalance and subclinical organ damage (12). In complicated hypertension pathogenesis is rather difficult to recognize to the momment where complications appear. That is why it is still necessary to search for sensitive and specific bio-

markers useful in routine diagnostics in patients with new onset, untreated hypertension that will allow detection of early symptoms of organ damage and treatment in apropriate way.

Among markers of kidney and endothelial dysfunction measurement of albuminuria seems to be very important. "Microalbuminuria" or further within this range low-grade albuminuria (LGA) is a well- known independent risk factor for kidney and cardiovascular disease and of mortality in diabetics, hypertensives and in general population. Elevated albumin concentration in the urine, although considered as normal by current guidelines, is also associated with obesity (12-14). It is suggested that urinary albumin excretion, in considerably lower concentration than currently accepted as normal, reflects subclinical organ damage and higher cardiovascular risk, especially in patients with hypertension. There are also data showing that lowering of albumin concentration after antihypertensive treatment confirms association of urine albumin excretion with hypertension (15). Occurrence of "microalbuminuria" was observed in relatives of patients with chronic kidney disease with frequency of 8,5% whereas in individuals with no such relatives in only 1,4%.

Studies showed that urinary albumin allows to identify individuals with high probability of hypertension development (16). Albuminuria may be a marker of early vascular complications in hypertensive patients (17). However, albuminuria may be also a prediction factor of cardiovascular diseases in hypertensives patients even those without certified vascular complications, independently from blood pressure level (18).

Our results show that despite the fact that albuminuria in most subjects with newly recognized hypertension was within the reference range values of both, urine albumin and UACR, were significantly higher than in normotensive individuals regardless of elevated BMI in both groups. UACR, that is gender dependent, seems to reflect better early kidney dysfunction than albumin concentration in the urine or what was suggested recently the threshold for optimal albuminuria should be lowered. *Wu* and coworkers suggested that measurement of albuminuria would be a very helpful tool in selection of patients with higher risk among those with hypertension (12).

As it was shown very recently, patients with elevated cystatin C concentration are in the risk group exposed to chronic kidney disease and cardiovascular diseases. Among hypertensive patients in our study over 28% had above normal cystatin C concentration. Sekizuka and coworkers suggested also that increase of cystatin C concentration may show not only kidney impairment but also formation of atherosclerosis plaque (19). *Young* and coworkers suggested that cystatin C concentration may be associated with kidney function and with the amount of fat tissue and using formulas for estimating GFR based on creatinine concentration is not enough sensitive method for middle aged persons and older adults. Creatinine concentration depends largely on muscle mass and is lower in weak and older individuals and routinely used MDRD formula may give higher GFR results in older patients. It has been suggested that adipocytes secrete cystatin C and its concentration is related to BMI, which suggest it's role in obesity pathogenesis and accompanying mechanisms. *Stevens* and coworkers showed stronger association of cystatin C concentration than creatinine with BMI, body mass and gender (20).

In clinical practice, the most often tool used for assesment of kidney function is creatinine concentration and glomerular filtration rate based on it, calculated with MDRD or Cockcroft-Gault formula. However, creatinine level in the serum and indirectly GFR is influenced by many factors, such as: glomerular excretion, age, gender, muscle mass, physical acivity, and diet. Even low GFR decrease below normal value is a strong predictor of development cardiovascular diseases both in general population and in patients with hypertension (5). *Klocek* and coworkers suggested that using MDRD formula allows identification of greater percentage of individuals with CKD among patients with hypertension than using Cockcroft-Gault formula (5). We found no significant differences in GFR estimated with MDRD and C-G formulas in patients with new onset, non- treated hypertension comparing with normotensive individuals.

Recently, serum uric acid concentration, a marker of kidney function, was considered as a sensitive indicator of cardiovascular complications. Long time uric acid was regarded only as an antioxidant (21). However nowadays hyperuricemia plays a significant role in the development of hypertension, renal disease, metabolic syndrome and cardiovascular diseases (6,22). In our group of patients with hypertension of the first and second degree, serum uric acid concentration was within the reference range. Hyperuricemia can be regarded as a risk factor of cardiovascular diseases and prediction factor of hypertension also in those without diabetes and metabolic syndrome (23,24). *Kosugi* suggested that uric acid concentration is associated with patient's age and only selected types of hypertension, such as hypertension associated with metabolic syndrome (25). Uric acid is considered as a mediator in subclinical organ damage in patients with hypertension and in diabetic patients. *Zhang* et al suggested that higher concentration of uric acid in the serum elevated the risk of hypertension in Chinese population, and that association is influenced by obesity (7). There is also evidence that in patients with recognized, untreated hypertension hyperuricemia is associated with microalbuminuria (26). It is still unknown whether the association of uric acid with cardiovascular risk is causal or accidental.

**Conclusions**

Early screening of kidney dysfunction in patients with newly diagnosed untreated hypertension is of great importance. A quick, non-invasive and easy measurement of biomarkers of kidney dysfunction such as albuminuria (urinary albumin concentration or UACR) and cystatin C can be a very use-

ful tool for screening purposes in patients with hypertension characterized by yet unchanged eGFR.

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**Adres Autorów:**

Department of Laboratory Medicine, Collegium Medicum,
Nicolaus Copernicus University,
85-094 Bydgoszcz, ul. Marii Skłodowskiej-Curie 9
e-mail: kizdiagn@cm.umk.pl



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