DOI 10.1515/cclm-2012-0798 — Clin Chem Lab Med 2013; 51(7): 1529–1534

Charline M.J. Wehlou, Marijn M. Speeckaert, Tom Fiers, Marc L. De Buyzere and Joris R. Delanghe*

α_1-Microglobulin/albumin ratio may improve interpretation of albuminuria in statin-treated patients

Abstract

Background: Statins can cause tubular proteinuria by inhibiting tubular reabsorption of urinary proteins. To distinguish between microalbuminuria originating from glomerular leakage of albumin and tubular microalbuminuria due to statin therapy, the α_1-microglobulin/albumin ratio is evaluated in patients taking statins and compared to untreated patients.

Methods: Ten apparently healthy subjects were given 40 mg of simvastatin and tested for urinary α_1-microglobulin, albumin, creatinine and cystatin C, up to 24 h after administration. Additionally, urine samples of 76 statin-treated and 456 untreated patients presenting with micro-albuminuria (albuminuria range between 20 and 200 mg/L) were tested for α_1-microglobulin and albumin. α_1-Microglobulin/albumin ratios were compared. Total cholesterol was measured in 50 patients on statin therapy.

Results: In the 10 apparently healthy subjects, a significant temporary increase of α_1-microglobulin, albumin and α_1-microglobulin/albumin ratio was observed after statin intake. In the group of 532 patients showing microalbuminuria, those treated with statins showed a significantly higher mean urinary α_1-microglobulin/albumin ratio then untreated patients. Urinary albumin concentrations were significantly higher in patients taking simvastatin than in patients on rosuvastatin treatment and they were also higher in patients on statin therapy with a total serum cholesterol concentration below 3.88 mmol/L than in patients with a total serum cholesterol concentration above 5.17 mmol/L.

Conclusions: Tubular proteinuria, caused by the use of statins, can be distinguished from glomerular proteinuria by a higher urinary α_1-microglobulin/albumin ratio.

Keywords: albumin; α_1-microglobulin; proteinuria; statins.

***Corresponding author: Joris R. Delanghe,** Department of Clinical Chemistry, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium, Phone: +32 9 3322956, Fax: +32 9 3324985, E-mail: joris.delanghe@ugent.be

Charline M.J. Wehlou and Tom Fiers: Department of Clinical Chemistry, Ghent University Hospital, Gent, Belgium

Marijn M. Speeckaert: Department of Nephrology, Ghent University Hospital, Gent, Belgium

Marc L. De Buyzere: Department of Cardiology, Ghent University Hospital, Gent, Belgium

Introduction

Statins lower cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase [1], which converts HMG-CoA to mevalonate. Derivates of mevalonate, such as geranylgeranyl pyrophosphate (GGPP) play a major role in post-translational modification of a lot of proteins, especially GTP-binding proteins [2]. These proteins are involved in the process of receptor-mediated endocytosis (RME), which occurs in the proximal tubular cells for albumin uptake [3–6]. This process involves megalin and cubilin receptors, which require the presence of prenylated GTP-binding proteins [7].

By inhibiting HMG-CoA reductase and reducing prenylation of GTP-binding proteins, statins inhibit protein uptake by the human proximal tubule. The reduced uptake of plasma proteins by the tubules may result in proteinuria in some patients treated with statins [2, 8]. Patients on statin therapy often suffer from conditions that can cause proteinuria, such as diabetes and arterial hypertension. In these patients, interpretation of microalbuminuria is hampered by the fact that microalbuminuria may either originate from glomerular leakage of albumin or from a statin-induced reduction of albumin uptake by the renal tubules. Proteinuria associated with statins may be a physiologic and benign response, related to altered protein reabsorption rather than an indication of diminished glomerular membrane integrity or frank toxicity. As microalbuminuria monitoring is recommended in the

follow-up of patients with diabetes and arterial hypertension, correct interpretation is of practical importance [9–11].

Correcting albuminuria for a disturbed tubular reabsorption can theoretically be achieved by comparing albuminuria to the concentration of a tubular marker protein which is taken up by the same receptor protein. Urinary α_1-microglobulin is a very stable protein and is considered as a robust marker for tubular reabsorption of proteins [12].

In the present study, we evaluated the α_1-microglobulin/albumin ratio to differentiate between proteinuria caused by risk factors and proteinuria caused by use of statins. Albumin and α_1-microglobulin are both ligands of the cubilin/megalin receptors and increased urinary concentrations of these proteins will be found in statin-induced tubular proteinuria [12, 13].

Materials and methods

A group of 10 apparently healthy subjects (6 males, 4 females; 31±13 years) who were not treated with statins, angiotensin converting enzyme inhibitors or angiotensin receptor blockers were administered 40 mg of simvastatin. Due to ethical concerns, we have only administered very modest amounts of weak statins (simvastatin is only a weak statin) in a single dose regimen: 40 mg of simvastatin (Zocor®) corresponds to only 5 mg of rosuvastatine (Crestor®). Urine specimens were collected prior to the intake of the drug, then hourly until six samples were obtained and finally 24 h after statin intake. α_1-microglobulin, albumin, cystatin C and creatinine were measured in urine.

Urinary albumin and serum cystatin C levels were measured by nephelometry (BN II). Urinary α_1-microglobulin was measured by turbidimetry and total serum cholesterol was measured with a standard colorimetric assay using Roche reagents on a Cobas 8000 analyzer. Urinary creatinine was measured using a compensated Jaffe method on a Cobas 6000 analyzer (Roche). Urinary protein was assayed according to Orsonneau et al. [14]. Concentrations of urinary proteins were expressed as mg protein/g creatinine.

Between January 2011 and October 2011, urine samples from 532 patients (364 females, 168 males; 45±19 years) showing micro-albuminuria were obtained. Seventy-six of them were taking statins: simvastatin (n=43), atorvastatin (n=18), rosuvastatin (n=12) and pravastatin (n=3). Specimens were tested for urinary albumin, urinary α_1-microglobulin and total urinary protein. In contrast to the group of healthy subjects (n=10), urinary creatinine was not measured in the patient group. Concomitantly, in 50 patients taking statins, total cholesterol was measured in serum.

The study was approved by the Ethics Committee review board of the University Hospital of Ghent (EC 2012–374). The study complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. A written informed consent was obtained from all participants. Statistical analysis was performed with the statistical program Medcalc (Medcalc, Mariakerke, Belgium). p-Values lower than 0.05 were considered statistically significant. Data are reported as mean±SD or median with interquartile range (IQR). Wilcoxon test for paired samples, Mann-Whitney U-test and Kruskal-Wallis tests were used as appropriate.

Results

In the group of apparently healthy subjects who had been administered a single dose of 40 mg of simvastatin, a transient increase of both α_1-microglobulin and albumin was observed (Figure 1). At baseline, all 10 subjects had urinary albumin levels below 20 mg/L and urinary α_1-microglobulin concentrations below 8 mg/L. Maximal concentrations were reached after 3±1 h (albumin/creatinine) and after 4±2 h (α_1-microglobulin/creatinine and α_1-microglobulin/albumin). Maximal values for urinary α_1-microglobulin and albumin were respectively 16.7±9.8 mg/g creatinine and 14.5±5.0 mg/g creatinine. The increase of α_1-microglobulin/creatinine, albumin/creatinine and α_1-microglobulin/albumin ratio was significant (p=0.004, p=0.048 and p=0.002). Twenty-four hours after the administration of 40 mg of simvastatin, the levels of α_1-microglobulin and albumin returned to levels not significantly different from those prior to administration. All urinary cystatin C levels were below 1.04 mg/L at baseline, during the 6 h after administration and also 24 h after administration of simvastatin.

From the group of patients who were treated with statins (76 patients), 28 patients showed microalbuminuria (albuminuria between 20 and 200 mg/L) and 10 patients had albuminuria >200 mg/L. The median albuminuria was 20.2 mg/L (IQR=9.9–105.0 mg/L) in the statin group vs. 35.3 mg/L (IQR=9.1–103.0 mg/L) in the non-statin group (p=0.59). Median urinary concentration of α_1-microglobulin was 9.3 mg/L (IQR=3.6–21.9 mg/L) in the statin group vs. 4.0 mg/L (IQR=1.3–9.7 mg/L) in the non-statin group (p<0.0001). Median ratio of urinary α_1-microglobulin/albumin in the statin group was 0.4 (IQR=0.1–0.8) vs. 0.1 (IQR=0.0–0.4) in the non-statin group. The ratios differed significantly between the treated and the untreated group (p<0.0001) (Table 1).

Linear regression for the urinary albumin and α_1-microglobulin concentrations was performed for the statin group and the non-statin group. The regression equation for the non-statin group was y (urinary albumin, mg/L)=74.3 (mg/L)+0.6×(urinary α_1-microglobulin, mg/L), for the statin group y (urinary albumin, mg/L)=76.5 (mg/L)+1.2×(urinary α_1-microglobulin, mg/L). As the slopes differed between the two groups, a mathematical correction could be proposed in order to compensate for

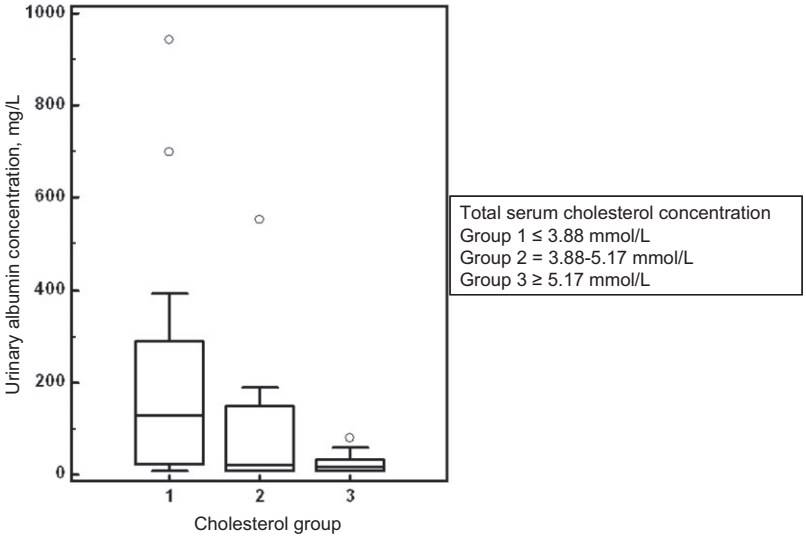

Figure 1 Urinary albumin concentration according to serum cholesterol level.
The patient group (n=50) was divided in three groups: group 1 (n=20) with a total serum cholesterol concentration ≤3.88 mmol/L, group 2 (n=13) with a total serum cholesterol concentration ranging from 3.88 to 5.17 mmol/L and group 3 (n=17) with a total serum cholesterol concentration ≥5.17 mmol/L. In the high cholesterolemia group (serum cholesterol exceeding 5.17 mmol/L), albuminuria is significantly (p=0.02) lower than in the low cholesterolemia group (cholesterolemia below 3.88 mmol/L).

the effect of tubular reabsorption of albumin. As every mg increase of urinary α_1-microglobulin corresponded to a microalbuminuria of 74.3 mg+0.6×(urinary α_1-microglobulin) in the non-statin group vs. a microalbuminuria value of 76.5 mg+1.2×(urinary α_1-microglobulin) in the statin group, the following mathematical correction could be made in patients on statin therapy: microalbuminuria (corrected, mg/L)=microalbuminuria (measured, mg/L)−0.6×(urinary α_1-microglobulin, mg/L).

Urinary α_1-microglobulin, albumin and α_1-microglobulin/albumin ratios were compared between the different types of statins: α_1-microglobulin levels did not differ significantly between the patients taking atorvastatin, pravastatin, rosuvastatin and simvastatin (p=0.9). Albuminuria was significantly different among the various types of statins prescribed (p=0.04): urinary albumin was significantly higher in patients taking simvastatin (n=43) than in patients taking rosuvastatin (n=12) (Table 2). No significant difference was found for the urinary α_1-microglobulin/albumin ratio between the different type of statins (p=0.3).

From 50 patients who were on statin therapy, the concentration of total serum cholesterol was measured. Patients were divided in three groups: patients with total serum cholesterol below 3.88 mmol/L, total serum cholesterol between 3.88 mmol/L and 5.17 mmol/L and total serum cholesterol exceeding 5.17 mmol/L. The urinary albumin concentration was significantly higher in patients with serum cholesterol values below 3.88 mmol/L than in patients with a serum cholesterol concentration exceeding 5.17 mmol/L (p=0.02). Urinary albumin levels were not significantly different between the patients with a serum cholesterol level between 3.88 and 5.17 mmol/L and the two other groups. No significant difference was found for urinary α_1-microglobulin levels and α_1-microglobulin/albumin ratio between the three groups.

Median total serum cholesterol concentrations of six patients taking rosuvastatin (1×10 mg/day, 3×20 mg/day

Table 1 Comparison of α_1-microglobulin, albumin and the α_1-microglobulin/albumin ratio in urine for the statin vs. the non-statin group.

	Statin group (n=76)	Non-statin group (n=456)	p-Value
α_1-Microglobulin, mg/L	9.3 (3.6–21.9)	4.0 (1.3–9.7)	<0.0001
Albumin, mg/L	20.2 (9.9–105.0)	35.3 (9.1–103.0)	0.59
Ratio α_1-microglobulin/albumin	0.4 (0.1–0.8)	0.1 (0–0.4)	<0.0001

α_1-Microglobulin concentrations and the α_1-microglobulin/albumin ratio were significantly higher in the statin vs. the non-statin group (p<0.0001). Data were reported as median and interquartile range.

Table 2 Urinary α_1-microglobulin, albumin, α_1-microglobulin/albumin ratio and total serum cholesterol levels in the different types of statins.

	Simvastatin (n=43)	Atorvastatin (n=18)	Rosuvastatin (n=12)	p-Value
Urinary albumin, mg/L	26.7 (11.5–135.7)	26.0 (9.1–135.0)	14.4 (9.1–20.7)	0.04
Urinary α_1-microglobulin, mg/L	11.2 (4.2–21.5)	7.6 (4.9–20.6)	4.7 (2.0–30.5)	0.9
α_1-Microglobulin/albumin ratio (urine)	0.4 (0–0.8)	0.2 (0.1–0.5)	0.5 (0.2–1.5)	0.3
Total serum cholesterol, mmol/L	4.14 (2.59–6.23)	4.16 (3.44–4.32)	5.56 (4.76–5.66)	0.07

Urinary albumin was significantly higher in patients taking simvastatin than in patients taking rosuvastatin (p=0.04). Data were reported as median with interquartile range. Pravastatin was not included in the data because the group is too small (n=3).

and 2×40 mg/day) and 26 patients on simvastatin therapy (19×20 mg/day and 7×40 mg/day) were compared because the urinary albumin concentration was significantly different in both groups. Median total serum cholesterol level was 5.56 mmol/L (IQR=4.76–5.66 mmol/L) in the patients on rosuvastatin therapy vs. 4.14 mmol/L (IQR=2.59–6.23 mmol/L) in patients on simvastatin therapy.

Discussion

The aim of the study was to distinguish microalbuminuria originating from glomerular leakage of albumin and tubular microalbuminuria due to statin therapy. All 10 healthy subjects who were administered a single dose of 40 mg simvastatin, showed a significant increase in urinary α_1-microglobulin, albumin and α_1-microglobulin/albumin ratio. This increase was transient as 24 h after administration, all urinary protein levels decreased to levels as before administration. Urinary cystatin C levels at baseline were all below 1.04 mg/L. After administration, up to 24 h after administration, levels never exceeded this value.

In patients, treated with statins, microalbuminuria can be observed in a large number of patients. These data are in agreement with earlier findings [2, 8, 15]. In a study of van der Tol et al. [16], statins were independently associated with an increased prevalence of microalbuminuria, even after correction for 'bias by indication'. The researchers created a propensity score for statin use to correct for this 'bias by indication'. Propensity score analysis is a well-established method to adjust for confounding factors by indication in observational trials [17, 18]. The propensity model included the following variables that were deemed to be possibly related to statin use: age, gender, body mass index (BMI), waist circumference, systolic blood pressure, previous cardiovascular event, C-reactive protein (CRP), fasting glucose, diabetes, serum uric acid, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, use of angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) and smoking. Except for uric acid, the authors did not take renal function parameters into account, such as cystatin C.

α_1-Microglobulin is a marker of tubular proteinuria which occurs in patients with a normal glomerular filtration rate, but with a diminished capacity of the proximal tubules to reabsorb and catabolize proteins [12]. The quantitative measurement in urine of total protein, albumin, α_1-microglobulin, IgG and α_2-macroglobulin is useful to differentiate the origin of proteinuria and hematuria [19–23]. Apart from α_1-microglobulin, many other urinary proteins are catabolized by the same megalin/cubilin pathway: vitamin D-binding protein [24, 25], β_2-microglobulin [26], transferrin [27] and retinol-binding protein [28], which are all markers of tubular proteinuria. The excretion of urinary α_1-microglobulin was significantly higher in statin-treated patients compared to statin untreated patients. Kostapanos et al. showed that rosuvastatin induced a small but significant increase in the excretion of α_1-microglobulin (by 16%, $p<0.05$), indicating that statin-related proteinuria involves low-molecular-weight proteins and is of proximal tubular origin [29]. The present study demonstrated that the urinary α_1-microglobulin/albumin ratio differs significantly between statin-treated and untreated individuals. One explanation may be that albumin and α_1-microglobulin are taken up by the same megalin/cubilin receptor, localized in the renal tubules, which requires the presence of small GTP-binding proteins. However, as mentioned earlier, statins inhibit the biosynthesis of several intermediates of the mevalonate pathway. Statin-induced microalbuminuria should also be differentiated from a possible renal bleeding, which is characterized by an α_1-microglobulin/albumin ratio <0.7 in combination with a positive urine dip test result (test strip for hemoglobin positive + + +). The additional measurement of the

IgG/albumin and α_2-macroglobulin/albumin ratios might be helpful in this condition [22, 23]. However as the clinical presentation of a patient with a renal hemorrhage is totally different from the presentation of a patient with microalbuminuria from tubular overflow (statin)-induced microalbuminuria, it should be easy for clinicians to differentiate both conditions.

Although the urinary albuminuria values induced by statins are only slightly above the reference range, our mathematical formula is important as it makes it possible to distinguish this mild proteinuria from microalbuminuria caused by glomerular damage. The reported changes in urinary α_1-microglobulin concentration (and in urinary α_1-microglobulin/albumin ratio) are statistically significant as the values increase by a factor of 2.32. For a sensitive assay with a CV of a few percent, this significant temporary increase illustrates an impaired protein reabsorption capacity by the tubules. In the present study, starting α_1-microglobulin levels of the volunteers taking statins were within the reference values (as expected for a good control group). However, a 232% increase remains impressive in people with a normal tubular function. Due to ethical concerns, only very modest amounts of weak statins (simvastatin is only a weak statin) were administered in a single dose regimen.

There was a difference between the urinary albumin levels in patients taking either rosuvastatin or simvastatin. Patients on simvastatin therapy had significantly more urinary albumin than patients on rosuvastatin therapy. When we investigated the cholesterol levels in serum in 50 patients on statin therapy, lower serum cholesterol levels (below 3.88 mmol/L) were significantly associated with higher urinary albumin concentrations than in patients with serum cholesterol values exceeding 5.17 mmol/L. This could be explained by a more profound effect of statins in these patients and as a consequence a higher prevalence of microalbuminuria. So the urinary albumin levels are not dependent on the drug but on the cholesterol levels.

The data clearly highlight the difficulties in interpreting microalbuminuria values in patients treated with statins, since two distinct mechanisms might be involved: glomerular damage and an impaired tubular reabsorption. As the statin-induced microalbuminuria is mostly of tubular origin, it is uncertain and rather unlikely whether it has the same prognostic impact for renal and cardiovascular disease as endothelial dysfunction-induced glomerular microalbuminuria [16]. The suggested correction factor is based on the difference between the slopes of urinary albumin and α_1-microglobulin concentrations between the treated and untreated patients. When microalbuminuria is measured in a patient on statin therapy, this value could be corrected with the following mathematical correction: microalbuminuria (corrected) (mg/L)=microalbuminuria (measured) (mg/L)−0.6×(urinary α_1-microglobulin, mg/L). This formula is particularly useful for patients with microalbuminuria to estimate the effect of statin use on the proteinuria level. Also in conditions of mixed (glomerular and tubular) proteinuria, our findings should be taken into account. However in case of macroalbuminuria, the clinician should look for an underlying renal pathology. It was not the aim of our study to differentiate statin-induced proteinuria from other conditions associated with tubular proteinuria. However, we definitely propose to include the urinary α_1-microglobulin/albumin ratio in a standard laboratory form, as this ratio could be helpful in distinguishing glomerular proteinuria from tubular overflow (statin)-induced albuminuria.

In conclusion, albuminuria caused by increased glomerular leakage can better be distinguished from the effect of concomitant tubular proteinuria by using a mathematical correction when microalbuminuria is measured in a patient on statin therapy.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

Received November 22, 2012; accepted December 13, 2012; previously published online January 11, 2013

References

1. Tobert J. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. Nature Rev Drug Disc 2003;2:517–26.
2. Verhulst A, D'Haese P, De Broe M. Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in human kidney proximal tubular cells. J Am Soc Nephrol 2004;15:2249–57.
3. Sidaway JE, Davidson RG, McTaggart F, Orton TC, Scott RC, Smith GJ, et al. Inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase reduce receptor-mediated endocytosis in opposum kidney cells. J Am Soc Nephrol 2004; 15:2258–65.

4. Ellis S, Mellor H. Regulation of endocytic traffic by rho family GTPases. Trends Cell Biol 2000;10:85–8.
5. Pizon V, Desjardins M, Bucci C, Parton RG, Zerial M. Association of Rap1a and Rap1b proteins with late endocytic/phagocytic compartments and Rap2a with the Golgi complex. J Cell Science 1994;107:1661–70.
6. Somsel Rodman J, Wandinger-Ness A. Rab GTPases coordinate endocytosis. J Cell Science 2000;113:183–92.
7. Christensen EI. Pathophysiology of protein and vitamin handling in the proximal tubule. Nephrol Dial Transplant 2002;17:57–8.
8. Deslypere JP, Delanghe J, Vermeulen A. Proteinuria as complication of simvastatin treatment. Lancet 1990;336:1453.
9. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. European Society of Hypertension; European Society of Cardiology. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 2007;16:135–232.
10. National Institute for Clinical Excellence. Type 1 diabetes: diagnosis and management of type 1 diabetes in adults. July 2004. Available from: http://www.nice.org. Accessed on 15 October 2012.
11. National Institute for Clinical Excellence. Management of type 2 diabetes. Renal disease – prevention and early management. Feb 2002. Available from: http://www.nice.org. Accessed on 15 October 2012.
12. Penders J, Delanghe JR. Alpha-1-microglobulin: clinical laboratory aspects and applications. Clin Chim Acta 2004;346:107–18.
13. Verroust PJ, Birn H, Nielsen R, Kozyraki R, Christensen EI. The tandem endocytic receptors megalin and cubulin are important proteins in renal pathology. Kidney Int 2002;62:745–56.
14. Orsonneau JL, Douet P, Massoubre C, Lustenberger P, Bernard S. An improved pyrogallol red-molybdate method for determining total urinary protein. Clin Chem 1989;35:2233–6.
15. Advisory Committee Briefing Document. Pharmacology/toxicology. NDA 21–366 Crestor July 9, 2003.
16. van der Tol A, Van Biesen W, Van Laecke S, Bogaerts K, De Lombaert K, Warrinnier H, et al. Statin use and the presence of microalbuminuria. Results from the ERICABEL trial: a non-interventional epidemiological cohort study. Plos ONE 2012;7:e31639.
17. Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. Eur Heart J 2011;32:1704–8.
18. Zhehui L, Gardiner JC, Bradley CJ. Applying propensity score methods in medical research: pitfalls and prospects. Med Care Res Rev 2010;67:528–54.
19. Boesken WH, Rohrbach R, Schollmeyer P. Vergleich von Histologie und Urinproteinanalyse (SDS–PAA-Discelektrophorese) bei Nierenerkrankungen. Nieren Hochdruckkrh 1978;5:206–14.
20. Boesken WH, Diagnostic significance of SDS–PAA-electrophoresis of urinary proteins different forms of proteinuria and their correlation to renal diseases. Curr Prob Clin Biochem 1979;9:235–48.
21. Hofmann W, Rossmüller B, Guder WG, Edel HH. A new strategy for characterizing proteinuria and haematuria from a single pattern of defined proteins in urine. Eur J Clin Chem Clin Biochem 1992;30:707–12.
22. Guder WG, Hofmann W. Differentiation of proteinuria and haematuria by single protein analysis in urine. Clin Biochem 1993;26:277–82.
23. Regeniter A, Siede WH, Scholer A, Huber P, Frischmuth N, Steiger JU. Interpreting complex urinary patterns with MDI LABLINK: a statistical evaluation. Clin Chim Acta 2000;297:261–73.
24. Nykjaer A, Dragun D, Walther D, Vorum H, Jacobsen C, Herz J, et al. An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D_3. Cell 1999;96:507–15.
25. Speeckaert M, Huang G, Delanghe JR, Taes YE. Biological and clinical aspects of the vitamin D binding protein (Gc-globulin) and its polymorphism. Clin Chim Acta 2006;372:33–42.
26. Orlando RA, Rader K, Authier F, Yamazaki H, Posner BI, Bergeron JJ, et al. Megalin is an endocytic receptor for insulin. J Am Soc Nephrol 1998;9:1759–66.
27. Kozyraki R, Fyfe J, Verroust PJ, Jacobsen C, Dautry-Varsat A, Gburek J, et al. Megalin-dependent cubilin-mediated endocytosis is a major pathway for the apical uptake of transferrin in polarized epithelia. Proc Natl Acad Sci USA 2001;98:12491–6.
28. Christensen EI, Moskaug JO, Vorum H, Jacobsen C, Gundersen TE, Nykjaer A, et al. Evidence for an essential role of megalin in transepithelial transport of retinol. J Am Soc Nephrol 1999;10:685–95.
29. Kostapanos MS, Milionis HJ, Gazi I, Kostara C, Bairaktari ET, Elisaf M. Rosuvastatin increases α-1 microglobulin urinary excretion in patients with primary dyslipidemia. J Clin Pharmacol 2006;46:1337–43.