

Prevention and treatment of diabetic nephropathy

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Available online 24 March 2005

Abstract

Increasing number of diabetic patients develop different stages of renal failure. However, often an inappropriate parameter, the serum creatinine is measured as a marker of glomerular function. Calculated glomerular filtration rate or endogenous creatinine clearance are suggested to be used for the estimation of the glomerular function. Important structures preventing proteinuria in the kidney are glomerular basement membrane, podocytes and proximal tubular cells. In diabetes mellitus loss of nephrin of podocytes can play a role in the development of microalbuminuria, and podocyte desquamation may result in the progression to proteinuria. In diabetes mellitus there is an increased formation of advanced glycation endproducts (AGE), of which the only elimination organ is the kidney. The AGE induce proteinuria and atherosclerosis. Therefore, in diabetes mellitus a vicious circle develops due to proteinuria, nephron loss and accumulation of AGE, which play a role in the initiation and progression of diabetic nephropathy and atherosclerosis. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers having antiproteinuric effect may decrease the risk of diabetic nephropathy and atherosclerosis. Improvement of carbohydrate metabolism with a consequential decrease in the formation of AGE is an important contributor to the prevention and treatment of diabetic nephropathy and atherosclerosis.

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Keywords: Advanced glycation endproducts; Angiotensin converting enzyme inhibitor; Angiotensin receptor blocker; Diabetic proteinuria; Podocyte

1. How to measure kidney function in diabetes?

Because of the increase of the prevalence of diabetes mellitus and because of the decrease of cardiovascular mortality due to improved therapeutic strategies, more and more diabetic patients develop different stages of renal failure. In addition, mainly an

inappropriate parameter, the serum creatinine is measured as marker of glomerular function.

Figs. 1 and 2 demonstrate that glomerular filtration rate (GFR) is a better parameter for the determination of the kidney glomerular function than serum creatinine. In Fig. 1 the exponential association between serum creatinine and GFR (calculated according Cockcroft-Gault) is shown. In our laboratory the reference range for serum creatinine is 50–120 $\mu\text{mol/l}$. Three patients with similar serum creatinine level (121, 123 and

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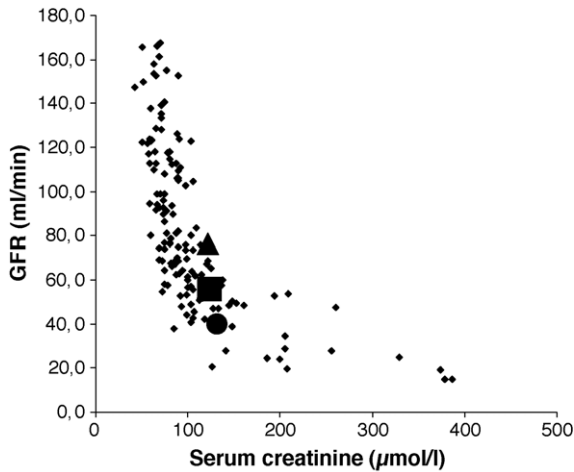


Fig. 1. Association between serum creatinine and calculated glomerular filtration rate (GFR, according to Cockcroft-Gault formula) in type 2 diabetic patients. Emphasized data are: (▲) serum creatinine, 121 $\mu\text{mol/l}$, GFR, 76 ml/min; (■) serum creatinine, 123 $\mu\text{mol/l}$, GFR, 56 ml/min; (●) serum creatinine, 132 $\mu\text{mol/l}$, GFR, 39 ml/min.

132 $\mu\text{mol/l}$) were chosen to demonstrate the need for GFR determination. Calculated GFR values related to these serum creatinine levels were 76, 56 and 39 ml/min using Cockcroft-Gault formula. These big differences among the calculated GFR values raise the possibility that this formula was not correct. Therefore, we

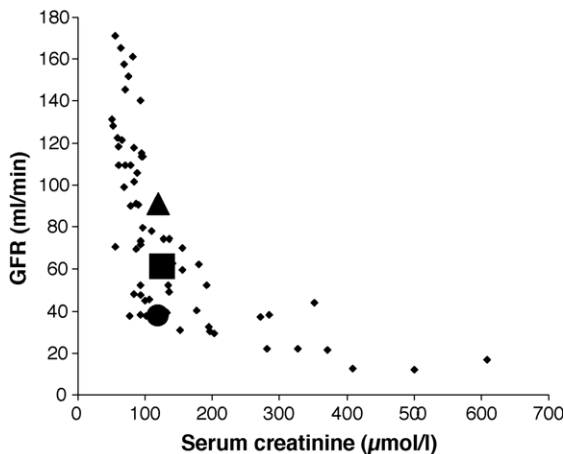


Fig. 2. Association between serum creatinine and measured glomerular filtration rate (GFR, 24 h-endogenous creatinine clearance). Emphasized data are: (▲) serum creatinine, 119 $\mu\text{mol/l}$, GFR, 91 ml/min; (■) serum creatinine, 125 $\mu\text{mol/l}$, GFR, 62 ml/min; (●) serum creatinine, 119 $\mu\text{mol/l}$, GFR, 37 ml/min.

examined the association between serum creatinine and measured 24-h endogenous creatinine clearance (Fig. 2). Despite similar serum creatinine levels in three selected patients (119, 125 and 119 $\mu\text{mol/l}$), measured GFR values ranged from normal to impaired renal function (91, 62 and 37 ml/min) demonstrating the divergence between serum creatinine and GFR as in case of calculated GFR shown above.

Recent studies, performed on big populations, proved connection between the calculated GFR and the incidence of cardiovascular and renal events [1,2]. The message of these trials is the importance of the use of GFR as a measure of the kidney glomerular function [3] as a real indicator of progression of kidney disease and cardiovascular risk.

2. Kidney-structures responsible for the prevention of urinary protein loss

Normal urinary protein excretion rate in healthy persons does not exceed 150 mg/day. There are four structures that are implied to play an important role in the prevention of further urinary protein loss, namely the capillary endothelium, the glomerular basement membrane, the podocytes with the slit membrane (Figs. 3 and 4) and the cells of the proximal convoluted tubules.

Nephrin, a component of the slit membrane was discovered upon the investigation of the gene of an autosomal recessive disease with proteinuria, the Finnish type of congenital nephrotic syndrome [4]. According to a recent study, non-enzymatic glycation and the effect of angiotensin II can constitute the background of nephrin loss [5]. Both an angiotensin-converting enzyme inhibitor (ACEI; perindopril) [6] and an angiotensin II receptor blocker (ARB, irbesartan) [7] proved to be capable of preventing nephrin loss and microalbuminuria in diabetic nephropathy.

Immunohistology has shown that there is no further decrease in the amount of nephrin in the renal tissue of macroproteinuric patients, compared with microalbuminuric patients [5]. This may imply that in the early phase the loss of nephrin may be responsible for the microalbuminuria, however another process, most probably podocyte detachment might be a major cause of macroalbuminuria (Fig. 5). The fact that both ACEI and ARB are able to decrease macroalbuminuria

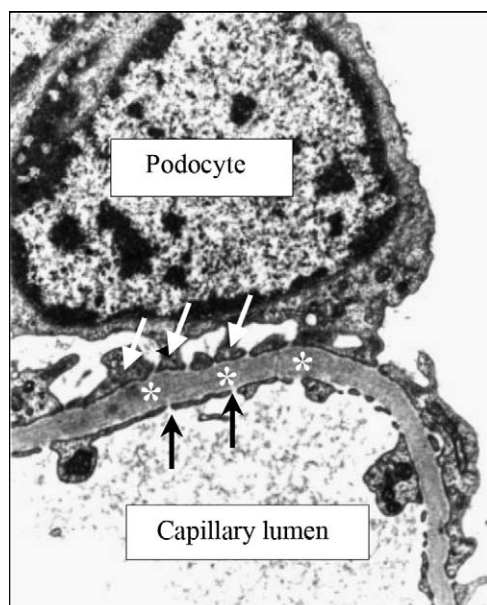


Fig. 3. Electronmicroscopic picture of the glomerulus showing foot processes of podocytes (white arrows) on the glomerular basement membrane (GBM = asterisks). The contact of the podocytes to the GBM is provided by the foot processes. The fenestrated endothelium can be seen on the other surface of the GBM, black arrows indicate the fenestrations.

suggests that these groups of drugs influence podocyte detachment, as well.

3. Development of proteinuria

Protein molecules, passing through the glomerular loops into the urine, are reabsorbed by active transport processes in the proximal tubular cells (Fig. 6). There is an upper capacity bound of tubular reabsorption, and if the amount of proteins exceeds this limit, a pathologic proteinuria will develop. Due to the ineffectiveness of reabsorption, albumin and small-sized protein molecules will appear in the urine, first micro-, and subsequently macroalbuminuria may occur.

4. Proteinuria and nephron-loss

Tubular protein reabsorption is activated by protein appearing in the primary urine. However, the long-lasting and massive protein reabsorption leads to

tubular cell damage, release of inflammatory mediators, tubulointerstitial fibrosis which lead to the final destruction of the nephron [8]. This process is also referred to as the “suicide” of the nephron [9]. This is an important self-defense mechanism, as it prevents the loss of proteins. However, in diseases in which all nephrons are involved in protein loss (e.g. diabetes mellitus), this defense mechanism becomes dangerous, as it may lead to the loss of the total renal mass and thus to renal impairment.

5. Nephron-loss and atherosclerosis

It is a well-known fact that diabetic patients with proteinuria have a higher risk of atherosclerosis compared with non-proteinuric diabetic patients. Proteinuria can lead to a progressive loss of functional renal tissue and consequential loss of renal function. In diabetes, hyperglycaemia results in an increased formation of AGE, of which the only elimination route is the kidney. AGE lead to a loss of nephrin and activate the renin-angiotensin system in the kidney, contributing this way to proteinuria [5]. Proteinuria induces the “suicide” of increasing amount of nephrons that results in a vicious circle. Renal impairment leads to further accumulation of AGE and consequently to renal failure. Besides that, AGE are atherogenic on their own [10]. Therefore, proteinuria leads to atherosclerosis via nephron loss. Fig. 6 shows a scheme of these processes and the vicious circle that develops.

Another fact supporting these observations is that drugs preventing nephron loss in diabetes and inducing a significant decrease of proteinuria (ACEIs and ARBs) are capable of preserving renal function and thus decrease the risk of atherosclerosis at the same time [11].

6. Prevention of microalbuminuria

There is evidence based epidemiological data, supporting the importance of the intensive metabolic treatment in the prevention of diabetic nephropathy in both type 1 and type 2 diabetes in the DCCT [12] and UKPDS studies [13]. ACEI therapy, used in type 2 diabetic patients with normoalbuminuria, may

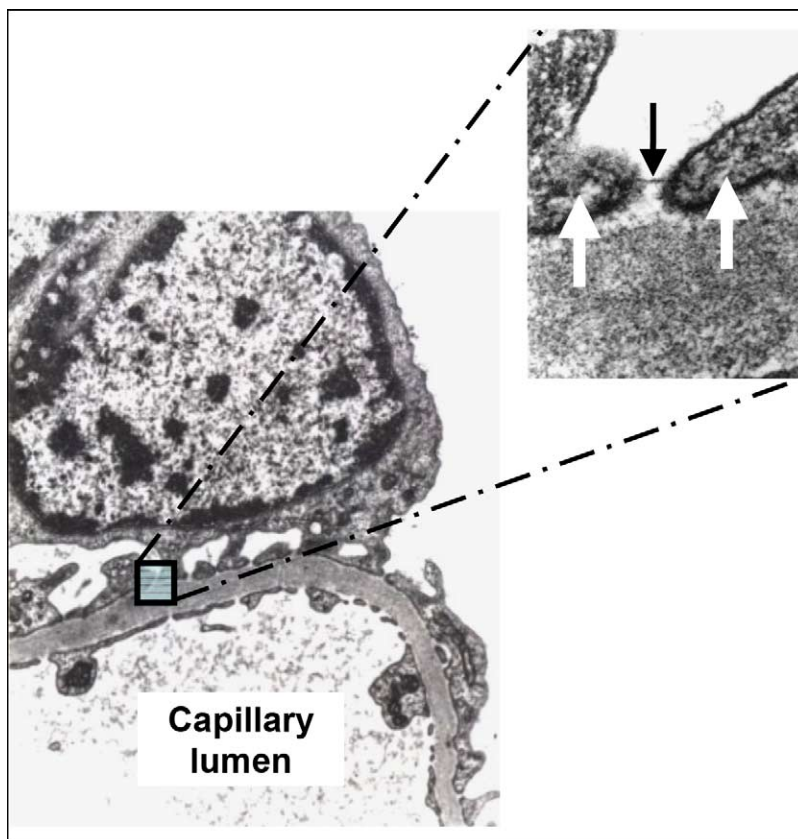


Fig. 4. Electronmicroscopic picture of a glomerular capillary loop and a podocyte. On the insert in the upper right corner, the slit membrane (black arrow facing down) can be seen between the foot processes of the podocyte (white arrows).

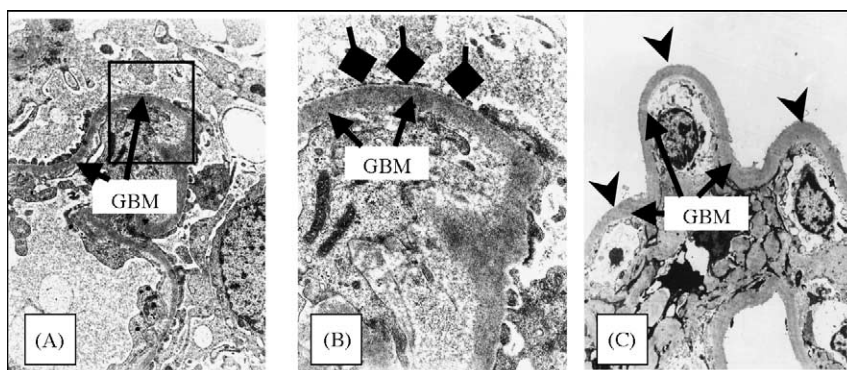


Fig. 5. Podocyte detachment in diabetic nephropathy. The area in the brick on panel A shows partial detachment of foot processes, and this area can be seen on panel B in a higher magnification. The arrows with a square-head show the remnants of the detached foot processes on the glomerular basement membrane (GBM). Complete detachment of the podocytes can be seen on panel C (arrowhead: 'nude' GBM surface towards the podocytes).

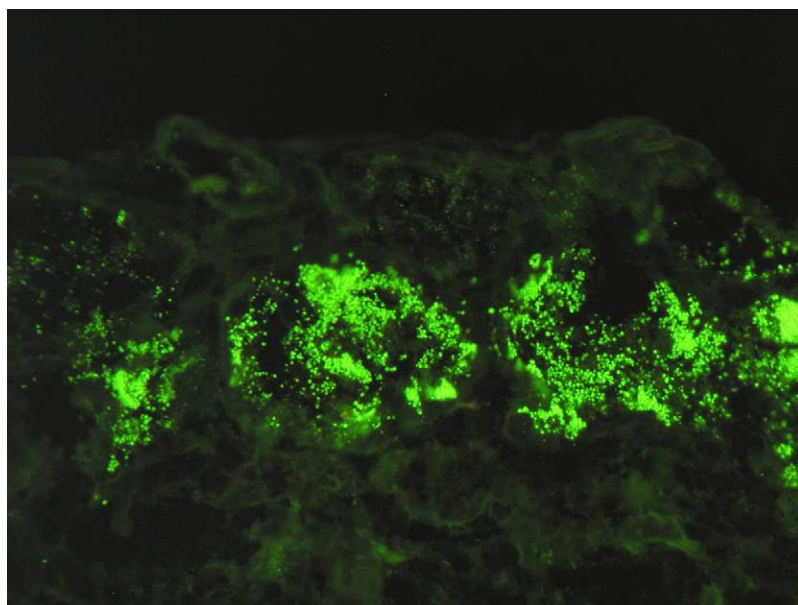


Fig. 6. Detection of tubular reabsorption of albumin in a renal biopsy specimen of a patient with diabetic nephropathy using fluorescent immunohistochemistry (direct immunofluorescence with anti-human albumin antibody).

decrease the risk of development of microalbuminuria (Table 1) [14].

7. Treatment of diabetic nephropathy

Improvement of carbohydrate metabolism (hemoglobin A_{1c} < 7.0%) decreases the risk for progression of diabetic nephropathy [12,13]. It is important to modify the dose of oral antidiabetic agents if necessary. Dose of metformin should be decreased if GFR is <90 ml/min, and has to be stopped if GFR is

lowered to <60 ml/min, because of the increasing risk of lactic acidosis [15]. Glibenclamide is contraindicated if GFR <90 ml/min because of the high risk of hypoglycemia. Other sulphonylureas (e.g. gliclazide) can be used in severe renal failure, but not in uremia. Some sulphonylureas (e.g. glipizide, and glipizide) can be given even in case of uremia [16]. Postprandial glucose regulators (glinides) are recommended even in chronic kidney failure, but they should be used with caution in end stage renal failure (GFR < 15 ml/min) [17,18]. There are insufficient data about thiazolidinediones (glitazones), but they may have beneficial effect on diabetic nephropathy and can be used even in kidney failure [19,20] (Fig. 7).

In hypertensive diabetic patients, the renoprotective effectiveness of ACEI and ARB is shown in Table 1. In normotensive, micro- and macroalbuminuric, type 1 diabetic patients ACEI is the first choice of drug and in type 2 diabetes ARB is recommended [21]. In the case of an ARB risk reduction of cardiovascular diseases was parallel to the reduction of albuminuria, which supports the hypothesis described above (Fig. 8) and suggests a new approach to the therapy taking albuminuria as a target for treatment [11]. Therapy by ACEI and ARB must not

Table 1

Renoprotective effect of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in hypertensive, type 1 and 2 diabetic patients

	Hypertensive type 1			Hypertensive type 2		
	Norm.	Micro.	Macro.	Norm.	Micro	Macro.
ACEI	+	+	+	+	+	+
ARB	ND	ND	+	ND	+	+
ACEI + ARB	ND	ND	++	ND	ND	++

Norm.: normalalbuminuria, Micro.: microalbuminuria, Macro.: macroalbuminuria, ND: no data, +: renoprotective effect, ++: combination therapy is more effective than either drug alone.

- Life-style
- Glycaemia
- Blood pressure
- Dietary protein intake
- Dyslipidaemia
- Urinary tract infections

Fig. 7. Management of diabetic nephropathy. Targets for prevention and treatment.

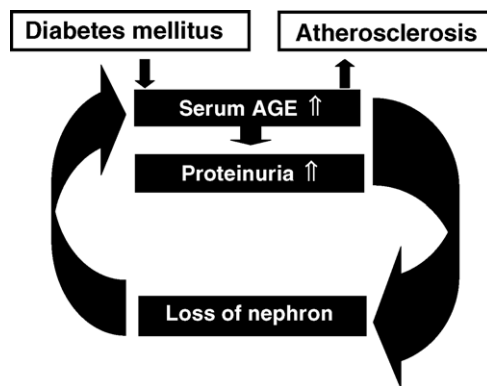


Fig. 8. Diabetes mellitus leads to nephron-loss and to a vicious circle via elevation of serum advanced glycation endproducts (AGE). This process evokes atherosclerosis.

be stopped in case of decreased GFR but a reduced dose is suggested. In order to normalize blood pressure (the target is <130/80 mmHg) thiazide, calcium channel blocker and α_1 - or β -receptor antagonist can be combined with ACEI and/or ARB, as well.

Other valuable methods in slowing progression of kidney insufficiency are the decrease of salt intake (<6 g/day) and decrease of protein content of diet in azotemia (<0.6 g/kg body weight per day) [22], and start of statin therapy [23].

8. Conclusions

Diabetic proteinuria is not only a predictor of renal failure and atherosclerosis in type 2 diabetes mellitus but also plays an important role in the development of these processes. The level of microalbuminuria is influenced by the nephrin component of the slit membrane that can be located between the foot-

processes of podocytes. This structure can be defended using ACEI or ARB therapy from the effects of diabetes. Another process, most probably the podocyte detachment, can be made responsible for the development of non-selective proteinuria and macroalbuminuria.

The fact that the increased amount of AGE contributes to the loss of nephrons and the development of atherosclerosis draws attention to the importance of the determination of GFR and reaching euglycaemia besides the preservation of renal function.

Acknowledgement

Grant support: István Wittmann received financial support from the Széchenyi István Fund, László Wagner's work was supported by the Bolyai János Grant. This work was also supported by the Hungarian National Grants: ETT 562/2003 of the Scientific Health Council of the Ministry of Health, OTKA T-043788 of the Hungarian Scientific Research Fund of the Hungarian Academy of Sciences, by FKFP 06615 (Fund for Research and Innovation in the Tertiary Education) of the Ministry of Education.

References

- [1] A.S. Go, G.M. Chertow, D. Fan, C.E. McCulloch, C.-Y. Hsu, Chronic kidney disease and the risk of death, cardiovascular events, and hospitalization, *N. Engl. J. Med.* 351 (2004) 1296–1305.
- [2] N.S. Anavekar, J.J. McMurray, E.J. Velazquez, S.D. Solomon, L. Kober, J.-L. Rouleau, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction, *N. Engl. J. Med.* 351 (2004) 1285–1295.
- [3] T.H. Hostetter, Chronic kidney disease predicts cardiovascular disease, *N. Engl. J. M.* 351 (2004) 1344–1346.
- [4] M. Kestilä, U. Lenkkeri, M. Männikkö, J. Lamerdin, P. McCready, H. Putaala, et al. Positionally cloned gene for a novel glomerular protein—nephrin is mutated in congenital nephrotic syndrome, *Mol. Cell* 1 (1998) 575–582.
- [5] S. Doublier, S. Gennaro, E. Lupia, V. Routsalainen, D. Verzola, G. Deferrari, et al. Nephrin expression is reduced in human diabetic nephropathy. Evidence for a distinct role for glycated albumin and angiotensin II, *Diabetes* 52 (2003) 1023–1030.
- [6] R.G. Langham, D.J. Kelly, A.J. Cox, N.M. Thomson, H. Holthöffer, P. Zaoui, et al. Proteinuria and the expression of the podocyte slit diaphragm protein, nephrin, in diabetic nephropathy: effects of angiotensin converting enzyme inhibition, *Diabetologia* 45 (2002) 1572–1576.

- [7] F. Bonnet, M.E. Cooper, H. Kawachi, T.J. Allen, G. Boner, Z. Cao, Irbesartan normalises the deficiency in glomerular nephrin expression in a model of diabetes and hypertension, *Diabetologia* 44 (2001) 874–877.
- [8] K. Zandi-Nejad, A.A. Eddy, R.J. Glasscock, B.M. Brenner, Why is proteinuria an ominous biomarker of progressive kidney disease? *Kidney Int.* 66 (2004) S76–S89.
- [9] C.N. Hales, Suicide of the nephron, *Lancet* 357 (2001) 136–137.
- [10] H. Sano, R. Nagai, K. Matsumoto, S. Horiuchi, Receptors for protein modified by advanced glycation endproducts (AGE)-their functional role in atherosclerosis, *Mech. Ageing Dev.* 107 (1999) 333–346.
- [11] D. de Zeeuw, G. Remuzzi, H.-H. Parving, W.F. Keane, Z. Zhang, S. Shahinfar, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy, *Circulation* 110 (2004) 921–927.
- [12] The Diabetes Control and Complications Trial Research Group, The effect of intensive therapy of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, *N. Engl. J. Med.* 329 (1993) 977–986.
- [13] UK Prospective Diabetes Study (UKPDS) Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), *Lancet* 352 (1998) 837–853.
- [14] P. Ruggenenti, A. Fassi, A.P. Ilieva, S. Bruno, I.P. Iliev, V. Brusegan, et al. Preventing microalbuminuria in Type 2 diabetes, *N. Engl. J. Med.* 351 (2004) 1941–1951.
- [15] P. Phillips, J. Braddon, Oral hypoglycaemics. When not to use what, *Aust. Fam. Physician* 31 (2002) 637–643.
- [16] G. Charpentier, J.P. Riveline, M. Varroud-Vial, Management of drugs affecting blood glucose in diabetic patients with renal failure, *Diab. Metab.* 26 (2000) 73–85.
- [17] D. Devineni, Z.H. Walters, H.T. Smith, J.S. Lee, P. Prasad, J.F. McLeod, Pharmacokinetics of nateglinide in renally impaired diabetic patients, *J. Clin. Pharmacol.* 43 (2003) 163–170.
- [18] V. Hatorp, Clinical pharmacokinetics and pharmacodynamics of repaglinide, *Clin. Pharmacokinet.* 41 (2002) 471–483.
- [19] M.C. Chapelsky, K. Thompson-Culkin, A.K. Miller, M. Sack, R. Blum, M.I. Freed, Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency, *J. Clin. Pharmacol.* 43 (2003) 252–259.
- [20] K. Budde, H.-H. Neumayer, L. Fritsche, W. Sulowicz, T. Stompor, D. Eckland, The pharmacokinetics of pioglitazone in patients with impaired renal function, *Br. J. Clin. Pharmacol.* 55 (2003) 368–374.
- [21] American Diabetes Association: Clinical Practice Recommendations 2004, Nephropathy in diabetes, *Diab. Care* 27 (Suppl. 1) (2004) S79–S83.
- [22] National Kidney Foundation: K/DOQI, Clinical practice guidelines for nutrition in chronic renal failure, *Am. J. Kidney Dis.* 35 (Suppl. 2) (2000), S1–S140.
- [23] Heart Protection Study Collaborative Group, MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial, *Lancet* 361 (2003) 2005–2016.