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Diabetic nephropathy 2010 – an omen of change in clinical practice?

Nefropatia cukrzycowa 2010 – zapowiedź zmian w praktyce klinicznej?

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S u m m a r y

Recently published data on the pathogenesis of glomerular changes in diabetes, and on the outcomes of big randomised clinical trials, stress the importance of strict glycaemia control in preventing diabetic nephropathy. Hyperfiltration does not cause albuminuria in the early phase of diabetic nephropathy. Hyperglycaemia results in over-expression of ACE on the glomerular endothelium and decreases the ACE2 activity on podocytes, which increases angiotensin II and initiates albuminuria. Inhibition of renin-angiotensin system does not prevent diabetic nephropathy, but decreases albuminuria in the early phase of diabetic nephropathy without impeding the progression of the disease. In more advanced stages of diabetic nephropathy inhibition of renin-angiotensin system impedes the progression of renal failure only in hypertensive patients. The decreased inactivation of increased amount of angiotensin II by ACE2 harm the podocyte skeleton, second to the augmented local angiotensin II activity. This results in shedding podocytes into urine /podocyturia/, which uncovers the basal membrane and initiates glomerular hyalinisation and sclerosis. Thus, albuminuria and renal failure are not causally linked to each other, and there is no ground for interpreting albuminuria as a marker of diabetic nephropathy, nor to consider changes in albuminuria a prognostic marker of nephroprotection. Prescribing ACEi and/or ARBs as nephroprotection to every patient with diabetes, which is a routine today, should be limited to patients with coexisting hypertension and albuminuria. The indication to prescribe ACEi/ARBs in preventing macroangiopathy is kept. Controlling hypertension is important for nephroprotection along with controlling glycaemia. The target of therapy is to normalize blood pressure and to keep A1C < 7.0%, also in diabetes type 2. In advanced nephropathy ACEi are especially useful and, in case of intolerance should be replaced with ARBs. The ACE2-mimetics, which are under development, raise hope for further improvement of nephroprotection in diabetes.

Key words: diabetic nephropathy, albuminuria, nephroprotection, ACE2

S t r e s z c z e n i e

Opublikowane w ostatnim czasie dane dotyczące patogenezy zmian kłębuszkowych w cukrzycy oraz wyniki kontrolowanych dużych badań klinicznych wskazują na istotną rolę optymalnej kontroli glikemii dla prewencji nefropatii cukrzycowej. Hiperglikemia prowadzi bowiem do zwiększenia ekspresji ACE w endotelium naczyń kłębuszkowych i zmniejsza aktywność ACE2 na podocytach, co ma prowadzić do albuminurii. Hamowanie układu renina angiotensyna we wczesnych etapach nefropatii cukrzycowej zmniejsza albuminurię ale nie spowalnia progresji choroby. Hiperfiltracja we wczesnych stadiach cukrzycy nie jest najprawdopodobniej przyczyną białkomoczu. Zmniejszone unieczynnianie angiotensyny II przez ACE2 ma też prowadzić do uszkadzania struktury podocytów i ich utraty do moczu, co ma skutkować szkliwieniem kłębuszków. Zatem albuminuria i niewydolność nerek nie są ze sobą powiązane i traktowanie albuminurii jako markera nefropatii cukrzycowej i skuteczności nefroprotekcji nie ma uzasadnienia. W późniejszych stadiach nefropatii cukrzycowej hamowanie układu reniana-angiotensyna jest skuteczne tylko przy współistnieniu nadciśnienia tętniczego. Dlatego zalecane dotychczas rutynowe stosowanie ACEi i/lub ARB w hamowaniu jej progresji musi być ograniczone do pacjentów z nadciśnieniem tętniczym. Utrzymane natomiast muszą być zalecenia co do hamowania układu renina-angiotensyna w prewencji makroangiopatii. Kontrola glikemii i nadciśnienia tętniczego mają kluczowe znaczenie dla nefroprotekcji w cukrzycy. Celem leczenia jest uzyskanie odsetka HbA1c < 7,0%, także w DM2, i normalizacji ciśnienia tętniczego. W zaawansowanej nefropatii cukrzycowej szczególnie przydatne dla nefroprotekcji są inhibitory ACE, które w przypadku nietolerancji można zastąpić sartanami. Nadzieję na poprawę nefroprotekcji w cukrzycy rokują opracowywane ACE2mimetyki.

Słowa kluczowe: nefropatia cukrzycowa, albuminuria, nefroprotekcja, ACE2

In the last decade diabetic nephropathy (DN) became a more and more frequent reason for starting chronic renal replacement therapy – in Poland, in 2007 DN affected 25.3% of incident dialysis patients (1). The incidence of dialysis consequent to DN positively correlates with the prevalence of diabetes in general population (2). Type 2 diabetes (DM2) is more prevalent in dialysis patients as compared to diabetes type 1 (DM1). The only procedure to establish the definite diagnosis of DN is renal biopsy. This procedure can be abandoned, if feasible for technical reasons, only in patients presenting with isolated albuminuria, long-lasting diabetes (over 5 years in DM1, and 10 years in DM2), diabetic retinopathy and slowly deteriorating renal function. Lack of any of the four aforementioned conditions should alert the physician to consider the (co)existence of non-diabetic glomerulopathy, including the crescentic glomerulonephritis.

ALBUMINURIA AND PROTEINURIA FOR DIAGNOSING DN

Contrary to the common opinion, albuminuria is not an early marker of DN (3), for it can present in advanced DN only, or never. Exactly for the same reason, albuminuria is not a good marker of advanced DN, as well. Even the proteinuria accompanying extrarenal diabetic microangiopathy is not a proof of DN – the diabetic retinopathy was present in 10% of DM2 patients with biopsy-proven non-diabetic glomerulopathy (4). Moreover, retinopathy was present only in 70.8% (4)-72% (5) DM2 patients with biopsy-proven DN. However, in DM1 patients presenting DN the retinopathy is usually present.

ALBUMINURIA AND PROTEINURIA IN DN PROGRESSION

Proteinuria, regardless of its range – from microalbuminuria to nephrotic syndrome – in diabetic patients is, like in general population, an universally accepted morbidity and cardiovascular (macroangiopathy) and renal (microangiopathy) mortality risk factor. However, the diagnostic significance of albuminuria seems to change in the course of disease.

Proteinuria was proven to damage renal tubules and promote renal interstitial fibrosis (6, 7), but cannot be considered the exclusive reason of renal filtration decrease in DN. Many patients with membranous (MGN) or minimal change glomerulopathy (MCD) do not progress to renal failure, despite the massive, perennial proteinuria. Also in experimental conditions, the massive proteinuria, second to damaging the slit diaphragm with antinephrin antibodies does not result in renal interstitial fibrosis and renal failure (8). On the other hand, smoking cessation 35 and body mass reduction (9), factors which do not affect glomerular structure directly, diminish proteinuria and decelerate glomerular filtration loss (nephroprotection). Thus, the proteinuria per se should not be considered the only nor the sufficient condition of nephropathy progression (10, 11).

The response to hypotensive therapy meta-analysed in 33 clinical trials (77 therapeutic groups) unambiguously revealed, that the diminishing the proteinuria correlated with the retardation of renal failure progression only in advanced DN (DM1, $r = -0.67$, $p = 0.03$; DM2, $r = -0.57$, $p = 0.02$). Such a correlation could not be observed at early stages of DM1, normotensive DM2, nor hypertensive DM2 (12). Contrary to what is observed in advanced DN, the decrease in albuminuria second to pharmacological intervention was not a predictor of efficient nephroprotection at early DN (12).

The above observations suggest that in diabetic patients proteinuria and loss of glomerular filtration could reflect different disease processes, not necessarily of distinct aetiology. For the renal failure appears to develop and progress independently from albuminuria, at least at early stage of DN, neither the albuminuria should be considered a predictor of renal failure, nor changes in albuminuria should in DN be used as an index of risk in renal function changes.

The clinical observations mentioned above got lately a further reinforcement from the experimental research on the pathophysiology of diabetic glomerulopathy, which gave a well documented rationale to separate the pathogenesis of albuminuria from that of renal failure progression.

PATHOGENESIS OF ALBUMINURIA IN DIABETIC NEPHROPATHY

Typical diabetic changes in kidneys are present mainly in glomeruli. These are mesangial cell proliferation and mesangial matrix expansion, thickening of the glomerular basement membrane, loss of podocytes, and changes in their morphology –foot processes effacement, and finally the hyalinisation and sclerotisation of glomerular capillaries. These changes augment, in DM1 and DM2, along with the increase of proteinuria (13, 14) secondary to the damage to both, the glomerular filtration barrier and to the impairment of podocyte cytoskeleton.

In early DN, hyperfiltration is very common. Contrary to the universal belief, the hyperfiltration does not seem to cause albuminuria – after 15 years of follow-up in DM1 patients, the prevalence of proteinuria in presenting hyperfiltration at inclusion, did not differ as compared to these with normal filtration at the beginning of observation (19% and 23%, respectively) (15).

The basic indicator of diabetic damage to the glomerular filtration barrier is the decreased content of nephrin in the slit membrane (16, 17). The content of other proteins linked to nephrin -podocin and podocalixin, remains unchanged in DN (18). The decreased activity of nephrin appears to result from the over-activity of angiotensin II (AngII), for the inhibition of the angiotensin system restores nephrin expression under experimental conditions (19). The increased

AngII activity appears to be of particular importance to damaging the podocyte cytoskeleton (20), second to activation of the protein kinase C (PKC). The last one is hold responsible also for mesangial proliferation, which occurs along with the inhibition of apoptosis, secondary to the hyperglycaemia-induced decrease in p21 activity (21). It can be clearly seen, from the above, that AngII is of fundamental importance to changes in glomerular morphology and function, even if other factors, like the increased catepsin L (CatL) activity (22), are also involved.

The increased glomerular AngII activity results from both, hyperglycaemia and local deregulation of the ACE and ACE2 activity. The ACE2, first described in 2000, converts both, angiotensin I (AngI) into inactive angiotensin 1-9 (Ang1-9), and AngII into angiotensin 1-7 (Ang 1-7). The last acts antagonistically to AngII, what is schematically shown on Figure1.

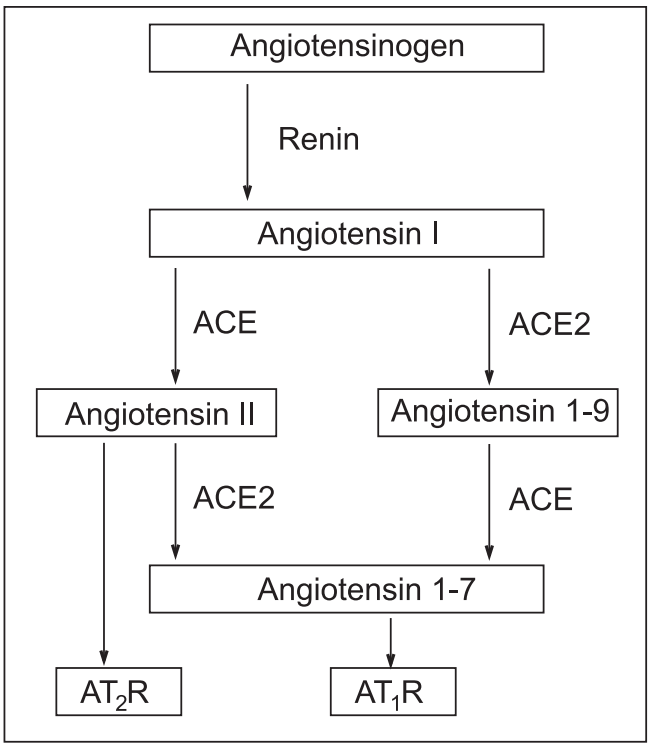

Fig. 1. The simplified Renin-Angiotensin-Aldosterone axis in renal glomerulus.

Within the glomerular tuft the ACE is localised mainly, if not exclusively, on the endothelial cells, and ACE2 can be identified exclusively on the podocyte surface23. The diagram below illustrates the biochemical consequences of such space-separation of ACE from ACE2.

Ang 1-9 ← ACE 2 + | Ang I + ACE → Ang II | + ACE2 → Ang 1
podocyte | endothelium/mesangium | podocyte

The inhibition ACE2, under experimental conditions, results in proteinuria, which is absent if AT1 receptors are blocked (23). The opposite effect – diminished proteinuria, can be seen after recombinant human ACE2 (rhACE2) is given to the diabetic mice (24).

In DM the glomerular ACE2 activity is diminished, which along with the increased ACE activity, can result in local AngII over-production, followed by slit diaphragm dysfunction/damage (23) and consequent albuminuria. Thus, one can conclude, the key factor in pathogenesis of diabetic proteinuria is a damage to the podocyte slit diaphragm resulting from the increased Ang II activity secondary to hyperglycaemia.

PATHOGENESIS OF RENAL FAILURE IN DIABETIC NEPHROPATHY

Urine of diabetic patients contains increased amount of podocytes, as compared to healthy controls. The increase in podocyturia is proportional to proteinuria. This is supposed to discriminate renal failure of diabetic origin from that caused by any other glomerulopathy (25). The inhibition of RAA activity with trandolapril normalised podocyturia both, in diabetic patients presenting micro- and macroalbuminuria (19). **Thus, one can stipulate, with high level of probability, that diabetic glomerular damage results from the loss of podocytes caused by the increased AngII activity, not from proteinuria itself.**

Hyperfiltration, podocyte effacement, and the dysfunction of the slit diaphragm seem to be fully reversible in early DN. Most probably the loss of numerous podocytes, secondary to prolonged or massive podocyturia, lays bare the basement membrane and results in irreversible glomerular hyalinisation and sclerotisation and consequent renal failure (26). The glomerular hyalinisation reduces the glomerular filtration area which results in renal failure, which can be further augment by the protein-induced tubular damage resulting in renal interstitial fibrosis.

ANGIOTENSIN II – THE COMMON ETIOLOGIC FACTOR OF DIABETES-INDUCED PROTEINURIA AND RENAL FAILURE

The pathophysiological data presented above, strongly suggest that early DN proteinuria results from the increased AngII activity, which impacts podocytes and results in a reversible dysfunction of slit diaphragm. The prolonged, or extremely intensive, AngII activity can also cause podocyte shedding, which results in reduction of area covered by podocytes on glomerular capillaries. This might explain, why there is no direct interrelationship between albuminuria/proteinuria and glomerular filtration loss in early DN. However, both phenomena are consequent of locally increased AngII activity. **This, in turn, could explain why some diabetic patients present renal failure without albuminuria/proteinuria and some do not present renal failure despite long-lasting increased albumin excretion. The clinical practice clearly suggests the above reasoning could be meaningful.**

Many clinical trials have proved that AngII AT1-receptor blockers (ARB) transiently slow down the progression of DN. Lately, it has been shown in a 56-month-long observation of a large cohort of 5927 adult patient nontolerant of ACE inhibitors, presenting with high risk of vasculopathy, normal renal function and no cardiac insufficiency, that telmisartan, as compared to placebo, resulted in slower increase in albuminuria (32% [CI, 23-41%] vs. 63% [CI, 52-76%]; P < 0.001), at a cost of increased risk of doubling plasma creatinine concentration (hazard ratio = 1.59 [CI, 1.04 to 2.41]; P = 0.031), and of greater reduction in eGFR (-3.2 mL/min per 1.73 m(2) [SD, 18.3] vs. -0.26 mL/min per 1.73 m(2) [SD, 18.0]; P < 0.001) (27). Also the three randomised trials with candesartan 32 mg/d given for 4,7 years (DIRECT – Diabetic Retinopathy Candesartan Trials) did not show any preventive capacity against microalbuminuria neither in normotensive patients with DM1, nor with DM2 (28). The above presented results, strongly suggest that ACEi or ARB in patient with normal kidney function or albuminuria indicative of diabetic angiopathy,, neither prevent albuminuria nor slows down DN progression to renal failure. Also, the decrease of proteinuria following ACEi and/or ARB should not be the only index of successful nephroprotection. Moreover, it is highly probable that in hypertensive diabetic patients the ACEi/ARB reduce proteinuria and slow down the renal failure progression second to blood pressure reduction and not to intrarenal AngII inhibition.

EARLY DIAGNOSIS OF DIABETIC NEPHROPATHY

In spite of the above presented reservations as to the diagnostic value of albuminuria in diabetic nephropathy, the albuminuria usually precedes the deterioration of renal function in DN. This is why the Polish Diabetes Association (PDA) suggests, the diabetic patients have urine albumin checked once every year, in order to detect the onset of diabetic nephropathy. In DM2 patients the screening should start at the diagnosis and in DM1 patients during the 5th year of the disease. The albuminuria check should follow a standard urinalysis to detect/diagnose proteinuria accompanying leucocyturia, suggestive of urinary tract infection.

The albuminuria screening, an immunochemistry dipstick procedure, should be done in a random urine sample (positive test indicates urinary albumin concentration exceeding 20 mg/l).

The positive screening test should be followed by albumin excretion rate (AER) examination, based on qualitative determination of albumin concentration in 24-h or overnight urine collection. The AER can be also estimated as albumin/creatinine index, calculated from quantitative examination of both substances in a random urine sample. The positive AER test should be repeated 2-3 times within 3-6month. The positive test on two of these occasions is indicative to diagnose albuminuria. The interpretation of results is presented in table 1.

Table. 1.

Category	Random Urine sample	24 h urine collection
Units	**[μg/mg creatinine]**	**[μg/min]**
Test	**screening**	**diagnostic**
Normoalbuminuria	< 30	< 20
Albuminuria	30-299	20-200
Proteinuria	≥ 300	> 200

Unfortunately, the tests advised by the PDA result in underestimated values, since the majority of albumin is not detected using the anti-albumin antibodies, for the presence of immuno-unreactive albumin fraction (29, 30, 31, 32).

The polish National Nephrology Consultant's Team in the Area of Nephrology interchangeably indicates that the regular plasma creatinine concentration should be checked regularly in every patient with renal damage, from the onset (33). Based on this value the glomerular filtration rate should be estimated (eGFR). This is consistent with PDA indications to calculate the eGFR based on the MDRD formulas given below Błąd! Nie zdefiniowano zakładki:

1. For blood/plasma creatinine (Cs) in mg/dl:
   – GFR [ml/min/1,73 m^2] = 186 × [Cs] – 1,154 × (age) – 0,203 × 0,742 (women)
   – GFR [ml/min/1,73 m^2] = 186 × [Cs] – 1,154 × (age) – 0,203 (men)
2. For blood/plasma creatinine (Cs) in μmol/l:
   – GFR [ml/min/1,73 m^2] = 186 × [Cs/88,4] – 1,154 × (age) – 0,203 × 0,742 (women)
   – GFR [ml/min/1,73 m^2] = 186 × [Cs/88,4] – 1,154 × (age) – 0,203 (men)

After the albuminuria is diagnosed the proper therapy and yearly follow-up should be instituted (see below). The nephrologist's opinion should be sought obligatorily, second to the PDA experts, in every patient with eGFR below 30 ml/min/1,73 m^2. In diabetic patients with eGFR 30-60 ml/min/1,73 m^2, or presenting poor blood pressure control, the referral to nephrologists should only be considered **Błąd! Nie zdefiniowano zakładki.** In my opinion this approach is wrong – for every patient with eGFR < 60 ml/min/1,73 m^2 should be seen by a nephrologists, at least to exclude nondiabetic causes of renal failure. It also of value to commence early the prevention/therapy of multiorgan damage from renal failure. The nephrologist's opinion should be also sought for a patient with proteinuria and absent retinopathy, when the proteinuria enters the nephrotic range, when the albuminuria is accompanied by erythrocyturia/hematuria or when the renal function deteriorates very fast (> 1 ml/min/m-th).

Diabetic patients shall be protected from developing diabetic nephropathy (prevention), and if it develops, all efforts should be made to stop its progression (nephroprotection).

The nowadays accepted measures to prevent diabetic nephropathy, recommended by diabetic and nephrological associations, are as follows:

– optimal blood glucose control
– optimal blood pressure control
– optimal lipemia control
– tobacco smoking cessation – smoking is an independent risk factor of nephropathy development and progression in DM2 (and probable in DM1) (34, 35).

To decelerate the diabetic nephropathy progression it is necessary to continue (or implement, if yet not done) the above preventive measures and to institute RAA system blockers, nondihydropyridine calcium channels blockers, and diuretics in adequate doses.

Despite of lack of proof for the existence of direct link between albuminuria and renal failure progression in diabetic nephropathy, there is a common belief that decreased albuminuria is protective to renal filtration. This is why both, the American Diabetes Association (ADA) (57) and the PDA **Błąd! Nie zdefiniowano zakładki.** recommend protein intake reduction to ≤ 0,8 g/kg bw. (ca. 10% of daily calorie intake) in proteinuric (> 300 mg/24 h) patients with diabetes. This traditional approach has no ground in the results of modern clinical trials – the low-protein diets effective in decelerating renal failure progression in non-diabetic patients (36), proved absolutely inefficient in this respect in diabetic nephropathy (37).

ACEi AND ARB IN DIABETIC NEPHROPATHY

In the opinion of the PDA, based on the published research outcomes, both, ACEi and ARBs, separately or jointly, diminish albuminuria and proteinuria in diabetic nephropathy, and thus should be introduced to the therapy independently of the level of albuminuria/ /proteinuria.

ACEi proved to decelerate progression of nephropathy exclusively in patients with:
– type 1 diabetes with concomitant hypertension and albuminuria
– type 2 diabetes with concomitant hypertension and albuminuria

ARBs decelerate progression of nephropathy in patients with:
– type 2 diabetes with concomitant hypertension, albuminuria and eGFR < 60 ml/min (retard the conversion of microalbuminuria to macroalbuminuria)
– type 2 diabetes with concomitant hypertension and albuminuria (retard renal failure)

In patients intolerant of one group the representative of the other should be tried.

As of today, there is no evidence that the ACEi/ARBs decelerate progression of renal failure in diabetic patients, both type 1 and type 2, with no concomitant hypertension and albuminuria. Thus.

Neither ACEi nor ARB are effective in preventing proteinuria. There are no guidelines to dealing with (micro)albuminuria/proteinuria in normotensive diabetic patients, with or without concomitant renal failure, in patients with normal glomerular filtration, and intolerant of RAA inhibitors. In albuminuric patients intolerant of ACEi or ARBs the nondihydropyridine calcium channel blockers (CCBs), betaadrenolytics and diuretics should be considered. The dihydropyridine CCBs should be restricted to supportive therapy, since as a first-line therapy these medications are of no capability to decelerate progression of nephropathy.

Spironolactone 25 mg/d was also successful in reduced the deterioration of renal filtration in a subgroup of patients with diabetic nephropathy.

In case the ACEi, ARBs, or diuretics (including the aldosterone antagonists), plasma creatinine and potassium should be regularly monitored.

Thiazydes can be used, second to PDA, if eGFR ≥50ml/min/1,73m^2; otherwise (eGFR < 50ml/min/1,73m^2) the loop diuretic should be chosen. The ADA place the limit to thiazyde at 30 ml/min (61).

RAA inhibition reduces proteinuria of advanced diabetic nephropathy (38) **and decelerates the progression of renal failure in diabetic patients with concomitant proteinuria and renal failure** (39, 40, 41).

DIABETES CONTROL IN PATIENTS WITH RENAL FAILURE

Until recently it has been commonly believed, the intensive glycaemia control in DM2 most probably decelerates cardiovascular complications, including diabetic nephropathy. However, strict blood glucose control seems to be ineffective in slowing down renal failure progression, regardless of diminishing proteinuria (42). The DCCT and UKPDS studies (DM1 and DM2, respectively) indicate strong positive correlation exists between HbA1c level and the progression of diabetic retinopathy and nephropathy (43, 44). However, a reduction in all cardiovascular complications with lower HbA1c, could be observed only in DM1 (45, 46), but not in DM2 (47, 48, 49). A meta-analysis of five clinical trials in 33040 DM2 patients followed by 163000 patient years revealed, the 0,9% reduction in HbA1c decreased non-fatal myocardial infarction by 17% (OR, odds ratio,= 0,83; 95%; CI = 0·75-0·93) and the incidence of cardiovascular events by 15% (OR = 0·85; 95%; CI = 0,77-0,93), but did not affect the incidence of stroke (OR = 0·93; 95%; CI = 0,81-1,06), nor the all-cause mortality (OR = 1,02; 95%; CI = 0,87-1,19) (50). The near-normal glycaemia concentrations prior to vasculopathy reduced the probability of diabetic microangiopathy, including retinopathy and nephropathy, in both DM1 (51, 52) and DM2 (53, 54, 55).

The clinical observation presented above clearly demonstrate that the diabetic nephropathy, and probably all other forms of angiopathy, in DM2 slightly differ from those in DM1. Moreover, the diagnostic and prognostic significance of albuminuria resulting from glomerulopathy is different at early stage of diabetes as compared to the advanced disease.

The current ADA (American Diabetes Association) and PDA guidelines suggest, the HbA1c < 7% could indicate adequate glycaemia control. However, the

results of ACCORD, ADVANCE, and VADT trials, published in 2008, convince of benefits which may be expected from more tight glucose control in patients with diabetes of short duration, absent angiopathy or with long life-expectancy, if hypoglycaemia is not too frequent (56). Of similar opinion is the IDF (International Diabetes Federation), which recommends keeping HbA1c below 6,5% in all diabetic patients, provided this target does not result in frequent hypoglycaemia (57), for 6.1% is the upper normal value in nondiabetic patients (58).

The American Diabetes Association and European Association for the Study of Diabetes, 2009 (59) consensus algorithm to treat DM2 is as follows:

- reach HbA1C < 7.0%,
- commence the treatment with life style changes and metformin,
- instantly change the therapeutic schema once proved unsuccessful in reaching the target,
- implement insulin early, once life style change and oral hypoglycaemic agents proved unsuccessful in reaching the target.

In the 2007 were published the National Kidney Foundation guidelines to the use of oral hypoglycaemic agents in renal failure, which are subject to verification in 2011. In diabetic patients with renal failure of any degree, including those on dialysis glipizide and gliclazide (second generation sulphonylurea derivatives), repaglinide, pioglitazone, rosiglitazone and exenatide can be used with no dose reduction (60). First generation sluphonylureas, gliburide, glimepiride, acarbose, miglitol and nateglinide are absolutely contraindicated in patients on dialysis. In all other cases the dose of oral agent should be reduced in patients with renal failure. Metformin can be used in patients with cardiac failure, till the renal function is relatively normal (plasma creatinine < 1.4 mg/dl). Moreover, metformin should be avoided in patients with circulatory decompensation or hospitalised due to exacerbated cardiac insufficiency (61).

SUMMARY

The recently published results of experimental and clinical research presented, suggest a need for deep re-evaluation of commonly accepted guidelines to the approach to patients presenting with diabetic nephropathy. The more critical aspects in this respect are listed below:

- Prevention of diabetic nephropathy and deceleration of its progression at the early stage, shall be based on strict blood glucose control.
- Blocking the renin-angiotensin system in normotensive diabetic patients neither prevents the development nor decelerates the progression of diabetic nephropathy.
- Albuminuria is not a good marker of diabetic nephropathy.
- Microalbuminuria fluctuations and changes in glomerular filtration do not correlate, thus the albuminuria alterations should not be considered a marker of nephroprotection.
- Early and late stages of diabetic nephropathy should be treated dissimilarly – the inhibition of RAA in early phase should be achieved with strict glucose control, and the ACEi should be implemented only in patients with co-morbid hypertension and albuminuria.
- At the advanced stage, the approach to treating the DM2 nephropathy should be similar to that in DM1 nephropathy – it should be more aggressive, more frequently based on insulin as compared to the current clinical practice, but the use of sartans is more justified, and the diagnosis should be more frequently based on histological findings on renal biopsy.
- The ACE2-mimetics may prove in future to be a useful therapeutic tool in diabetic nephropathy protection and prevention.

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