
Original Article

Epidemiology and Treatment Results of Diabetic Kidney Disease in Ukraine: Clinical Trial "The Scythian", Stage I

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Abstract

Introduction. Diabetic kidney disease (DKD) remains the leading cause of chronic kidney disease (CKD) requiring renal replacement therapy (RRT). A diagnosis of DKD is based on the finding of microalbuminuria and change in glomerular filtration rate (GFR). Hypertension affects the majority of patients with DKD. The true extent of renal damage is quite difficult to be assessed due to both an incomplete recognition of diabetes type 2 and insufficient activity of screening programs. The purpose of the present study was to determine the prevalence and progression of DKD in subjects with type 2 diabetes in Ukraine (the first stage of «The Scythian» trial).

Methods. The open-label prospective randomized study was conducted in 32 endocrinology departments in Ukraine and included 1802 patients diagnosed with type 2 diabetes mellitus, according to the ADA criteria. The following criteria were selected for the diagnosis of DKD: 1) eGFR, calculated by the Cockcroft & Gault formula when creatinine clearance estimates were less than 90 ml/min, and Reberg Tareev test for detection of hyperfiltration, and 2) albuminuria ≥ 30 mg. The rise in blood pressure (BP) $\geq 130/80$ mm Hg was considered as an additional index.

Results. The majority of subjects (95.5%) had BP levels higher than 130/80 mm Hg, 89% demonstrated changes in GFR (reduction in 76% and hyperfiltration in 13%), and albuminuria was found in 74% (micro in 71% and macroalbuminuria in 3%). In 23% cases the decline in GFR less than 90 ml/min coincided with microalbuminuria. In this group, GFR below 30 ml/min was documented in 6%, 31-60 ml/min in 26%, 61-90 ml/min in 51%, above 120 ml/min in 17% of subjects. 43% of them used antihypertensive drugs regularly, 34% - with some degree of regularity, 22% - occasionally, and main drugs were ACE inhibitors (78%) and diuretics (45%).

Conclusion. The results demonstrate that a change in glomerular filtration rate can be expected in 8 out of 10 patients suffering from DM type 2 for more than one year. Elevation of BP above 130/80 and particularly above 140/90 mm Hg precedes increase/reduction in glomerular filtration rate. Microalbuminuria is probably

the third most important informative sign indicating kidney damage from diabetes.

Keywords: diabetic kidney disease (DKD), epidemiological data, glomerular filtration rate (GFR), hypertension, microalbuminuria

Introduction

Although the importance of diabetes as a major cause of CKD has been stabilized and even tends to decline [1], DKD remains the main condition when renal replacement therapy is required (RRT) [2]. In 2003, AHA began to consider subjects with CKD as a group at highest risk of cardiovascular disease [3], and cardiovascular events are the main cause of mortality in subjects with DKD, both prior to dialysis and during RRT.

Hypertension, albuminuria and GFR are regarded as independent risk factors that reflect progression of the diabetic kidney disease [1]. According to KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease, patients with diabetes type 2 should be screened for DKD by measurements of urinary albumin-creatinine ratio in a spot urine sample (B) and measurement of serum creatinine and estimation of GFR (B). The Guidelines state that most people with diabetes and CKD have hypertension and treatment of hypertension slows the progression of CKD [4].

In Ukraine, diabetic kidney disease is the second major cause of CKD with its share of about 10% of all chronic kidney diseases [5]. With regard to CKD stage, diabetic kidney disease has the following pattern of distribution in Ukraine: 1 stage – 73,4 %, 2 stage - 17,5 %, 3 stage – 6,2 %, 4 stage – 1,4 %, 5 stage – 1,5 %.

The goal of the this study was to establish the real prevalence of diabetic kidney damage in Ukraine in order to improve medical care and to reduce the rate of development of terminal renal failure and cardiovascular death in these patients (the first stage of the «The Scythian» trial).

Patients and methods

Open-label, prospective, randomized cross-sectional trial «The Scythian» was designed in Ukraine in 2 stages. The first stage (2008-2009) investigated epidemiologic prevalence and severity of renal damage in type 2 diabetes mellitus (Figure 1). The second stage (2009-2010) studies the ACEi+ potential for treatment of diabetic nephropathy in a prospective design. Randomization was performed by envelope method for prescribing perindopril + indapamid either another ACEi + diuretic.

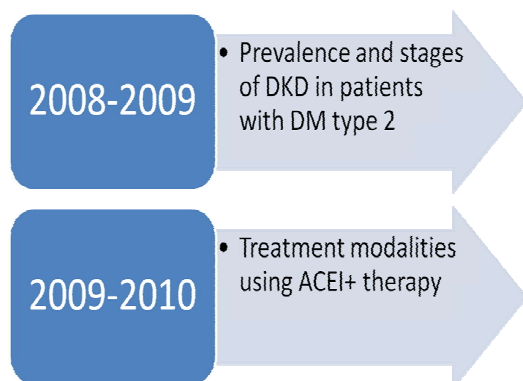


Fig. 1. Stages of «The Scythian» trial

«The Scythian» is derived from the Ukrainian abbreviation for glomerular filtration rate (GFR). The screening of diabetic kidney impairment is based upon this criterion only, which allows recognition of the C.E.Mogensen's first stage of diabetic nephropathy. Albuminuria ≥ 30 mg was also regarded as a diagnostic criterion for DKD. All patients with BP $\geq 130/80$ were additionally registered. The study was conducted in 32 endocrinology departments in Ukraine and involved 1802 patients diagnosed with type 2 diabetes at least 1 year prior to enrolment (Figure 2).

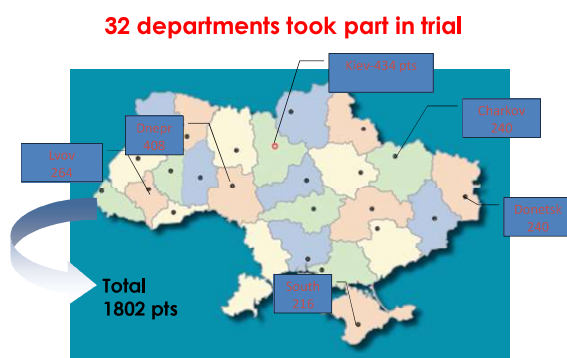


Fig. 2. Regions of Clinical Trial Conduct

Inclusion criteria were the following: subjects over 40 years of age, documented diagnosis of type 2 diabetes mellitus according to the American Diabetic Association (ADA, 2008). Exclusion criteria were the following:

diagnosis of type 1 diabetes mellitus; arterial hypertension stage III; symptomatic hypertensions requiring specific treatment methods; severe concomitant diseases with a life expectancy less than one year.

There were 46% male and 54% female patients included in this study. The age distribution was the following: under 50 years – 12.29 %, 51-60 years – 40.42 %, 61-70 years – 29.70 %, over 70 years – 17.59 %. Obesity was diagnosed when the body mass index exceeded 30 kg/m^2 and was found in 53% of patients. The majority of patients evaluated received glucose-lowering tablets (sulphonilurea derivatives or/and metformin), and 16% of patients were prescribed insulin either as monotherapy or in combination with oral hypoglycaemic agents. Regarding the duration of diabetes patients were distributed in the following manner: 1 to <3 years – 33.48 %, 3 to <5 years – 18.13 %, 5 to <10 years – 27.54 % and 10 years and above – 20.85 %. 58% of patients had manifestations of ischemic heart disease in the past, 13% had history of stroke or transitory ischemic attacks. In all cases, patients had no prior history of chronic renal disease.

GFR index was calculated on the basis of serum creatinine levels by the Cockcroft & Gault formula [6]:

for male subjects:

$$\text{CrCl} = [140 - \text{age (years)}] \times \text{body mass (kg)} / \text{serum creatinine } (\mu\text{mol/l}) \times 0,8$$

and for female subjects:

$$\text{CrCl} = [140 - \text{age (years)}] \times \text{body mass (kg)} \times 0,85 / \text{serum creatinine } (\mu\text{mol/l}) \times 0,8.$$

Serum creatinine was measured utilizing the modified Jaffe method. Hyperfiltration was evaluated by the Reberg-Tareev clearance test.

The presence of microalbuminuria was assessed by dipsticks. Urinary albumin excretion was determined by using timed overnight urine specimen. BP level evaluations were made by an office measurement in three consecutive days.

Prevalence proportion (prevalence) was calculated as quantity of DKD (exposed and affected + unexposed and affected) attributed to all patients included [7]. Incidence proportion (risk) was calculated as event to patients at risk ratio, odds – as probability over the complement of probability [7].

The correlation coefficient r (also called Pearson's product moment correlation), characterising degree of linear dependence between DM duration and hypertension (BP above 130/80 mm Hg), micro-, macroalbuminuria and eGFR (less than 90 ml/min) was calculated by [8]:

$$r = \frac{\sum_{i=1}^n (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^n (x_i - \bar{x})^2 \sum_{i=1}^n (y_i - \bar{y})^2}}$$

Results

Arterial hypertension (BP above 130/80 mm Hg) was found in the overwhelming majority ($n=1721$, 95,5%) of evaluated patients on the background (or without) of regular use of antihypertensive drugs. BP values $\geq 140/90$

were detected in 94%. 0.8% patients were first diagnosed with hypertension in the course of the trial. Stage 2 of arterial hypertension (systolic arterial pressure 160-

179 and diastolic 100-109 mm Hg) was documented in 706 (41%) of subjects and in 14% with either separate elevated systolic or diastolic BP (Figure 3).

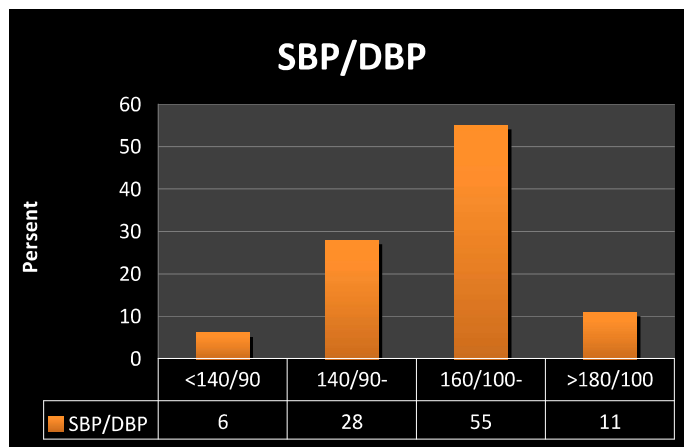


Fig. 3. Blood Pressure Characteristics in Evaluated Patients

Thus, elevated blood pressure in the majority of patients indicated: 1) a high cardiovascular risk, and 2) an insufficient BP control.

The patients had already treated their elevated blood pressure prior to the study entry by the following anti-hypertensive drugs: ACE inhibitors – 77.93 % of patients, angiotensin II receptor blockers – 11.18 %, calcium channel blockers – 24.46 %, beta-adrenoblockers – 44.57 %, diuretics – 44.68 % and central antihypertensive drugs – 8.73%. However, regular use of antihypertensive drugs was reported by 43% of patients only: 18.8% receiving ACEI, 12.14% - ACEI+β-blockers + diuretics, 10,7% -ACEI+β-blockers.

Analysis of GFR demonstrated presence of hyperfiltra-

tion (GFR >120 ml/min.) in 139 patients (13 %) and 11 % of patients (198) showed the GFR values in the range 90 to 120 ml/min. In majority of patients (48%), a certain reduction in GFR in the order of 60-90 ml/min was found. A more significant renal dysfunction with GFR values below 60 ml/min (30-60 ml/min) was detected in 24 % of patients. In 4% of subjects, a reduction in GFR was considerable (below 30 ml/min), which corresponded to CKD 4. Thus, the prevalence proportion of DKD based on abnormal GFR among patients with Diabetes type 2 with hypertension stage 1-2 was 0.89 and odds - 8,0. The risk of hyperfiltration in elevated BP was 0.08, decreased GFR – 0.85.

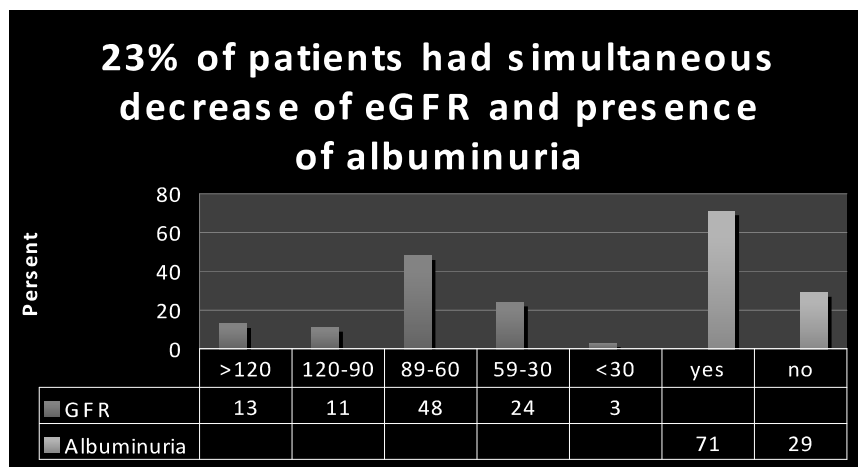


Fig. 4. eGFR and albuminuria in patients evaluated in «The Scythian» trial

The markers of diabetic kidney disease including micro- and macroalbuminuria were detected in 71% of patients (1279) with prevalence rate of 0.71 and odds 2.44 (Figure 4). Twenty three percents showed a decline in GFR

(below 90 ml/ min) simultaneously with microalbuminuria with calculated risk 0.23. In this group, GFR values were distributed in the following

manner: below 30 ml/min in 6%, 31 to 60 ml/min in ml/min in 17%.

Thus, the markers of renal impairment, including elevated BP, reduced glomerular filtration and presence of micro-macroalbuminuria, are distributed in the following manner: the majority of patients (1721; 95.5%) showed BP readings above 130/80 mm Hg, in 89%

26%, 61 to 90 ml/min in 51%, over 120 (1604) a change in GFR (reduction in 76% and hyperfiltration in 13%) was observed and in 74% (1334) subjects albuminuria (micro- in 71% and macroalbuminuria in 3%) were detected.

The results of diabetes duration in comparison with elevated BP, eGFR and albuminuria are shown in Figure 5.

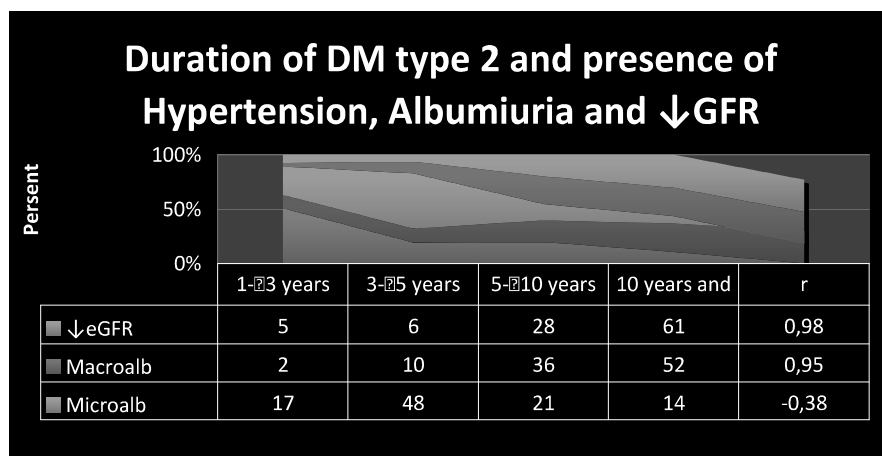


Fig. 5. Comparison of duration of a current of diabetes with elevated BP, eGFR and albuminuria

The presented results testify that with increase in diabetes duration the number of patients with hypertension, renal worsening and transition from microalbuminuria to macroalbuminuria was enlarged. There was a strong positive correlation (r) between duration of DM type 2 and hypertension, macroalbuminuria and decreasing renal function as well as a negative weak correlation with microalbuminuria.

Forty three percents of these patients (740) used antihypertensive drugs regularly, 34 % (585) - with some degree of regularity, 22 % (379) - occasionally, and main medications were ACEI (78%) and diuretics (45 %).

Discussion

«The Scythian» trial involved great and by far a representative number of patients with diabetes mellitus type 2, distributed evenly by sex and age. Subjects in the study represented quite typical population of patients with diabetes mellitus type 2 with regard to age and body mass index. The absolute majority of patients received glucose-lowering tablets and only relatively small number were taking insulin. Renal dysfunction was detected by an active screening in 76% of subjects, and in 13% diabetic nephropathy was first established by detecting hyperfiltration. The results obtained suggest that in 8 out of 10 patients suffering from DM type 2 for more than one year, some change in glomerular filtration rate is to be expected.

The vast majority of patients evaluated within the program «The Scythian» showed elevation of blood pressure. Our finding of systolic blood pressure below 140mm Hg only in 6% of patients deserves a special attention

(although this level is higher than the known target value of 130/80 mm Hg, recommended for diabetic patients by ADA, 2010). Interestingly, the majority of subjects were aware of arterial hypertension they had, and even used antihypertensive drugs, but, apparently, irregularly, in non-adequate dosage or in an ineffective combination.

Hypertension is a rather frequent finding in patients with CKD and DKD. Thus, the data obtained in the Centers for Disease Control and Prevention (CDC) from National Center for Health Statistics [9] indicate that hypertension defined as SBP \geq 140 mm Hg or 130 mm Hg or DBP \geq 90 or 80 was found in 81.8 % of those with CKD and 76.8 % of those with diabetes. The prevalence of hypertension increased with age. Of these participants with hypertension, 68.5 % were being treated and 52.9% of those under treatment had their hypertension in control. Women and men had similar treatment rates, but control tended to be higher in men than in women (56.5 % vs 49.4 %, respectively). Overall, 23.1 % of individuals without cardiovascular comorbidities had hypertension compared with 51.8 % to 81.8 % ($P < 0.01$).

The staging classification by C.E. Mogensen assumes development of hypertension and microalbuminuria after development of hyperfiltration. The results of our study give evidence that BP elevation over 130/80 and most commonly over 140/90 mm Hg precedes the increase/decrease of glomerular filtration rate. Microalbuminuria becomes here the third most important in inflammatory sign indicating the kidney involvement in diabetic patients.

Arterial hypertension and DM type 2 are certainly important risk factors of cardiovascular mortality. Classic

cardiovascular risks, however, imply no relation between cardiovascular mortality and glycaemia. The present data have indicated that cardiovascular risk increases prior to hyperglycaemic manifestations of type 2 diabetes mellitus. Nevertheless, smoking in 12%, glucose level above 4.9 mmol/l in 21%, high cholesterol levels in 45% and hypertension in 47% caused mortality in patients with ischemic heart disease (IHD) [1]. According to the results of the Norwegian trial HUNT [10], an elevation of HbA_{1c} values by 1% provides an increase of mortality risk by 20% even in those patients who are free of cardiovascular diseases, and a good control of glucose levels in patients with DM 2 allows to reach the same mortality risk associated with IHD as in patients without DM. Thus, a combination of reduced GFR and microalbuminuria, documented in our trial in 23% of patients, uncontroversially increases the cardiovascular risk [11].

It has to be noted that we evaluated in this trial patients with various duration of diabetes mellitus type 2. Subjects with a relatively short history of disease were prevailing, but they had a reduced GFR. This data can indicate a delayed diagnosis of diabetes mellitus type 2 in our country (i.e. the true disease history may be quite longer). On the other hand, the results obtained impose to start an active treatment of type 2 diabetes mellitus at the moment when the disease is diagnosed, while patients with short history of diabetes may already have quite significant renal dysfunction.

In conclusion, kidney damage and low GFR develop often in patients with type 2 diabetes mellitus, and frequently remain unrecognized. Arterial hypertension is one of the leading factors in the development of renal damage in patients with diabetes.

The results obtained in «The Scythian» trial dictate imperatives for an active recognition of kidney damage in subjects with type 2 diabetes mellitus and more intensive treatment of arterial hypertension aimed at reduction of the renal failure risk in such patients, which we are implementing in the second stage of «The Scythian» trial in 2009-2010.

Conclusions

Arterial hypertension develops in 94-96 % of patients with DM type 2, being probably the first manifestation and the cause of the subsequent renal impairment.

Changes in GFR, and later microalbuminuria, follow the elevated blood pressure reflecting kidney damage from DM type 2. The results obtained in «The Scythian» trial dictate imperative for an active recognition of kidney damage in subjects with type 2 diabetes mellitus, more intensive treatment of arterial hypertension aimed at reduction of the risk of renal failure in such patients.

Conflict of interest statement. The clinical trial was conducted with a financial support of Servier company. The authors received lecture fees from Servier.

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