

UNIVERSITY OF MEDICINE AND PHARMACY

CRAIOVA

DOCTORAL SCHOOL

DOCTORATE THESIS

- Summary –

**”RISK FACTORS OF DIABETIC
CHRONIC KIDNEY DISEASE”**

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Keywords: diabetic chronic kidney disease, risk factors, diabetes duration, glomerular filtration rate

1. Current state of knowledge

1.1 Diabetic renal disease

Diabetic chronic kidney disease (CKD) is a clinical syndrome characterized by persistent albuminuria > 300 mg / day or > 200 mg / min, confirmed in at least two occasions within 3-6 months, sustained decline in glomerular filtration rate (GFR) and increased blood pressure.

CKD affects about 10-13% of the general population with a small proportion of end stage renal disease requiring renal replacement therapy and kidney transplantation. CKD is the ninth leading cause of death in the United States. CKD prevalence increases with age. Diabetes is responsible for 50% of cases of CKD represents the most common cause. Diabetic CKD is the most common cause of chronic kidney disease involving renal replacement therapy worldwide, especially in patients with type 2 diabetes mellitus (T2DM) . DM is responsible for 30-40% of cases of end-stage renal disease in the United States. In the past 30 years the rate of patients with type 1 diabetes mellitus (T1DM) requiring renal substitution therapy significantly decreased due to improved treatment strategies for diabetes and hypertension.

1.2 The main risk factors associated with the presence of diabetic CKD

Diabetic nephropathy is the result of many factors, family interaction, intrauterine perinatal, metabolic and hemodynamic. The main risk factors are:

- demographic factors: age, sex, ethnicity,
- metabolic factors: hyperglycemia (age of onset of diabetes, duration of diabetes), dyslipidemia, hyperuricemia, obesity
- hemodynamic factors: anemia, hypertension
- family factors: family history of CKD, family history of DM, degree relatives with premature cardiovascular disease
- intrauterine and perinatal factors: low birth weight
- lifestyle: smoking, increased protein intake, physical activity, inactivity, viral and occupational exposures
- genetic factors

Patients with CKD have generally evolved with progressive loss of renal function, the major risk is the end stage requiring renal replacement therapy. Rate of progression depends on the patient's age, presence of comorbidities associated for successful implementation of secondary prevention measures individualized for each patient.

2. Personal contributions

2.1 Aim of study

The aims of study are:

- to determine the prevalence of CKD in patients with T1DM
- to determine the prevalence of CKD in patients with T2DM
- to determine the prevalence in the general population CKD
- to assess the degree of renal impairment in patients with diabetes and the general population
- to identify risk factors associated with the presence of diabetic CKD
- to establish some correlations between risk factors and the presence of CKD
- to evaluate the CKD prognosis
- to elaborate conclusions

2.2 Material and methods

The study was conducted over a period of three years (2010-2013) including patients with diabetes hospitalized in the Clinic of Diabetes Nutrition and Metabolic Diseases and unselected patients without diabetes registered at family doctors in Dolj County.

The study is an epidemiological, transversal, non-interventional type, with unselected patients and it has been conducted by analyzing 600 subjects divided into three groups, as it follows:

- group 1 included 200 patients with type 1 DM
- group 2 included 200 patients with type 2 DM
- group 3 (control) included 200 subjects, randomized, without DM

Inclusion criteria: caucasians; patients diagnosed with T1DM who are permanent insulin treatment initiated in the first year after diagnosis of DM before the age of 40 years; patients diagnosed with T2DM by ADA criteria 2010

(minimum two fasting blood glucose ≥ 126 mg / dl, glucose ≥ 200 mg / dl at any time of the day in the presence of specific clinical signs: polyuria, polydipsia, polyphagia, HbA1c ≥ 6.5 % glucose 2 hours after glucose load ≥ 200 mg / dl); subjects signed informed consent.

Exclusion criteria: acute metabolic imbalance; presence in the current treatment of potentially nephrotoxic drugs; diagnosis of hypertension precedes the diagnosis of diabetic CKD; patients with symptoms of urinary infection.

Patients with diabetes were unselected recruited from those who presented to the outpatient specialist consultations of Clinical Emergency County Hospital Craiova and met the criteria for inclusion.

Informed consent was signed by each participant in the study, in full knowledge, having been informed of all relevant aspects in the decision. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with GCP and national and international regulations in force, respecting the right to the integrity, confidentiality, withdrawal option of the subject at any time in the study.

The following data were analyzed: demographic data (age, sex), anthropometric data (weight, height, body mass index, waist circumference, hip circumference), physiological personal history (menarche, births, abortions, fetal macrosomia, menopause), pathological personal history (age of diabetes onset, age, time from diagnosis to the occurrence of CKD), data about blood pressure, cardiovascular disease (chronic ischemic heart disease, stroke, myocardial infarction, peripheral venous disease, dyslipidemia), cardiovascular risk, other microvascular complications of diabetes (retinopathy, diabetic neuropathy, diabetic nephropathy), treatment of comorbidities, family history (diabetes, hypertension, dyslipidemia, stroke, heart attack, obesity, autoimmune diseases, etc.), smoking.

Venous blood was collected by periphery venipuncture in EDTA vacutainers of 3 ml and the following analyzes were performed: serum creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol calculated using the Friedwald formula, triglycerides, uric acid, hemoglobin levels. Sampling was done in the morning after at least 12 hours of fasting. From urine sample it was

determined albumin and creatinine and then it was calculate the albumin/creatinine ratio.

2.3 Results

We conducted a study of 600 subjects (289 women and 311 men), divided into 3 groups. The distribution on sex of the subjects from the 3 lots has been relatively balanced, as it follows: the patients integrated in the study in lot 1 were 84 (42%) women, 116 (58%) men, in lot 2 were 101 (50%) women and 99 (50%) men, and in the controlling lot 104 (52%) women and 96 (48%) men.

The analyzed subjects were distributed on age groups, as it is shown in table 1. It may be observed that, as expected, the patients from the insulin-dependent group had a younger age.

Table 1. The distribution on age groups of the 3 lots

Age	Group 1	Group 2	Controlling group
0 - 19 years old	4 (2%)	-	-
20-39 years old	103 (51.5%)	3 (1.5%)	34 (17%)
40-59 years old	88 (44%)	60 (30%)	74 (37%)
60-79 years old	5 (2.5%)	134 (67%)	91 (45.5%)
Over 80 years old	-	3 (1.5%)	1 (0.5%)

The duration of DM comes under the presented intervals in table 2, observing a longer duration of type 1 DM compared to type 2 DM.

Table 2. The duration of diabetes mellitus

Duration	Group 1	Group 2
0-9 years	55 (27.5%)	131(65.5%)
10-19 years	84 (42%)	56 (28%)
20-29 years	48 (24%)	11(5.5%)
30-39 years	7 (3.5%)	2 (1%)
Over 40 years	6 (3%)	-

2.4. The presence of diabetic renal disease

We evaluated the presence of renal disease in each of the 3 groups. Based on the 2012 KDIGO criteria I had three choices of patients diagnosed with BCR. In group 1, patients with type 1 diabetes, diabetic CKD was found in 44,5%; in group 2, patients with type 2 diabetes, diabetic CKD was found in a proportion of 53.5% and in the control group was 8%.

2.5. Degree of renal impairment

Patients analyzed were found in varying degrees of CKD after the 2012 KDIGO classification. Thus, in group 1, most patients were in stage 2 of the CKD (53.93%), followed by stage 1 (25.85%), stage 3 (11.23%), stage 3b and G4 (3.37%), stage 5 representing 2.25%.

In group 2, most patients were in stage 2 of CKD (42.99%), followed by the third stage (26.16%), then stage 1 (20.57%), stage 3b (7.48%), stage 4 0.94% and 1.86% in stage 5.

In the control group, half of the patients were in the third stage (50%), followed by stage 2 (18.75%), stage 3b and stage 4 each in proportion of 12.5% and stage 5 (6.25%).

2.6. Corelations risk factors – diabetic CKD

We performed correlations between risk factors of diabetic BCR for the 3 groups, and between BCR micro and macrovascular diabetic and complications of diabetes.

2.6.1 Multivariate analysis of parameters associated with diabetic renal disease

Multivariate logistic regression analysis type of the most important parameters associated with CKD in type 1 DM used hypertension, hyperuricemia, chronic ischemic heart disease, peripheral vascular disease, proliferative diabetic retinopathy, family history of hypertension and stroke. The resulting ROC curve, with the area under the curve of 0.906, indicating these factors as having a significant influence on the presence of chronic kidney disease in type 1 DM.

Multivariate analysis of the most important parameters associated with CKD in type 2 DM using dyslipidemia, chronic ischemic heart disease, diabetic neuropathy, and family history of obesity. The resulting ROC curve with the area under the curve

of 0.689 indicates a lower rate of these factors influence the presence of chronic kidney disease in type 2 DM.

Multivariate analysis of the most important parameters associated with CKD in the control group using hypertension and family history of hypertension. The resulting ROC curve with the area under the curve of 0.695 indicates a low influence of these factors for chronic kidney disease in this control group.

2.6.2 Corelations eGRF – age and eGRF – duration of DM

In type 1 diabetes Spearman correlation coefficient was calculated GFR and age variables and obtained the value -0.473, $p < 0.001$, statistically significant, the GFR decreases with age of patients.

In type 2 diabetes Spearman correlation coefficient was calculated GFR and age variables and obtained the value -0.326, $p < 0.001$, statistically significant, the GFR decreases with age of patients.

The control group Spearman correlation coefficient was calculated GFR and age variables and obtained the value -0.358, $p < 0.001$, statistically significant, the GFR decreases with age of patients.

In type 1 diabetes Spearman correlation coefficient was calculated for GFR and duration of diabetes and obtained a value of - 0.430 with $p < 0.001$, statistically significant., The GFR decreases with increasing duration of diabetes.

In type 2 diabetes, the GFR and duration of diabetes was obtained Spearman correlation coefficient -0.129 with $p = 0.069$, not statistically significant. In type 2 diabetes decreased GFR did not correlate with duration of diabetes.

2.7 The prognosis of diabetic renal disease according to eGFR and albuminuria

We assessed the outcome of CKD, eGFR and albuminuria according to KDIGO criteria from 2012 that predicts the risk of overall mortality, cardiovascular risk and risk of progression to dialysis of CKD.

The risk is low in patients with stage 1 and 2 of the CKD without albuminuria present, is moderately increased in patients with stage 1 and 2 with moderately elevated albuminuria and normal albuminuria stage 3a. The risk is increased in patients with stage 1 and 2 of the CKD with severe albuminuria increased or greatly increased in patients with stage G3a severe albuminuria increased G3B with

moderate and severe albuminuria increased or stages G4 and G5 with or without albuminuria .

In the group with type 1 diabetes, more than half of patients (55.5%) had a lower risk of development of CKD and development of complications, 12.5% moderately increased risk and 26% were high risk. Only 6% of patients had very high risk.

In type 2 DM group, 46.5% of patients had a lower risk of development of CKD and development of complications, 34.5% moderate risk and 19% had very increased risk. There were no high-risk patients in the group of patients with type 2 diabetes.

In the control group, 92% of patients were at low risk, there was no patient with high risk and only 1.5% patients had moderate risk and 6.5% had very high risk.

Correlation tests showed statistically significant differences ($p < 0.0001$) in the risk of patients with type 1 diabetes versus control, in those with type 2 diabetes versus control ($p < 0.0001$), showing that diabetes is a factor prognosis for CKD. There are also statistically significant differences between patients with type 1 diabetes risk compared with patients with type 2 diabetes ($p < 0.0001$). The type 1 diabetes is somewhat predictable, while for type 2 diabetes predicting prognosis is difficult and unpredictable.

DISCUSSIONS

Chronic kidney disease is common in patients with diabetes compared with the general population. The presence of chronic kidney disease in patients with type 1 diabetes versus type 2 is similar in the present study.

Age of developing chronic kidney disease is lower in patients with type 1 diabetes compared to those with type 2 and the general population. The incidence and prevalence of chronic kidney disease increases with age. Old age seems to be a negative predictor for the occurrence of end stage BCR.

In our study we encountered a predominance of chronic kidney disease in men with type 1 diabetes. Chronic kidney disease occurs 5-10 years after diagnosis of type 1 diabetes, but can be present at diagnosis of type 2 diabetes development duration of diabetes correlated with the presence of chronic kidney disease is higher in type 1 diabetes with an average of 19.69 years, compared with patients with type 2 diabetes with a mean disease duration of 8.23 years in the study groups.

Family history of cardiovascular disease risk was not associated with increased risk of CKD in the present study. The literature suggests that heredity influences the development and progression of CKD.

Current smoking status in our study did not correlate with the presence of chronic kidney disease in patients with diabetes, but was smoking status in patients with type 1 diabetes, raising suspicion necessary interruption of smoking when major complication. Smoking has been found in several studies as an independent risk factor for different degrees of CKD.

Patients with type 1 diabetes and chronic kidney disease have a higher incidence of microvascular complications. In our study, patients with type 1 diabetes and diabetic peripheral sensorimotor neuropathy had a 5.5 times higher risk of associated chronic kidney disease, those with diabetic retinopathy at any stage risk 9.5 times high at 11.6 times when associated with proliferative diabetic retinopathy.

Hypertension, dyslipidemia, hyperuricemia are important risk factors associated with the presence of chronic kidney disease.

Dyslipidemia has been incriminated in numerous studies to play an important role in the initiation and progression of diabetic renal disease. In our study, patients with type 1 diabetes and dyslipidemia risk 6.4 times greater than aprezenta chronic kidney disease or in type 2 diabetes risk 2.2 times higher.

Hyperuricemia may contribute to the onset and progression of chronic kidney disease.

In our study, patients with type 1 diabetes and anemia risk 5.3 times more likely to associate chronic kidney disease, a correlation was not observed this in the group of patients with type 2 diabetes Anemia is a common complication of CKD but several studies have shown that it is also an independent predictor of risk of kidney disease.

Although the literature recognize obesity as a risk factor for impaired renal function in our study did not reveal a link between obesity and chronic kidney disease.

CONCLUSIONS

The study, including individual and comparative analysis of clinical and paraclinical parameters incriminated as potential risk factors in the development of chronic kidney disease in diabetes development has led to the development of conclusions that may be of importance and practical application in the prevention and delay disease progression.

- ◆ Diabetes is identified as a disease with a strong impact on health in association with micro-and macrovascular complications.
- ◆ Chronic kidney disease is a serious complication associated with premature mortality, decreased quality of life, increased costs necessary patient care. It thus requires prevention, early identification and treatment of associated risk factors.
- ◆ It is necessary screening type 2 diabetes because most of patients are already diagnosed in some stage of chronic complications.
- ◆ A screening of chronic kidney disease should be done to diagnose diabetes and at least once a year of diagnosis.
- ◆ diabetes is an important risk factor for the occurrence of CKD and also a negative prognostic factor for patients with CKD .Prognosis of patients with type 1 diabetes is somewhat predictable, while in the case of type 2 diabetes is more difficult to assess prognosis and unpredictable.
- ◆ Along with diabetes should not be underestimated and risk factors such as hypertension, dyslipidemia, hyperuricemia, anemia.