UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

PhD THESIS
-Abstract-

”INSULIN RESISTANCE MARKERS IN DIABETIC KIDNEY DISEASE IN TYPE 1 DIABETES MELLITUS”

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CONTENTS

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1. **CURRENT STAGE OF KNOWLEDGE**

Chronic kidney disease (CKD) represents a worldwide healthcare problem, affecting over 50 million people. In Romania, according to the PREDATORR Study (National Study on Diabetes, Prediabetes, Overweight, Obesity, Dyslipidemia, Hyperuricemia and Chronic Kidney Disease), CKD has a prevalence of 6.74%. The most frequent causes of CKD are: DM (49.8%) and arterial hypertension (HT) (27.3%). DKD manifests in 20-40% of the DM patients, representing the main cause of the *end stage renal disease* (ESRD), which involves a substitution therapy of renal function (STRF) all over the world. Studies have shown that insulin resistance (IR) is involved in the increased incidence of micro- and macrovascular complications (including DKD) in type 1 DM persons.

1.1 Diabetic kidney disease (DKD) - definition, epidemiology, physiopathology

CKD was defined as: the presence of structural or functional kidney abnormalities, for at least 3 months, with an impact on the general health state.

The CKD diagnosis criteria - at least 1 from the 2 modified criteria (2 consultations are required in a >3 months period of time): filtration glomerular rate (FGR) determined through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) <60 ml/min/1.73m^2 or the urinary albumin/creatinine ratio (ACR) from spontaneous urine ≥ 30mg/g.

DKD represents a CKD diagnosed in a DM patient; it includes all the anatomical, clinical and functional modifications of the kidney in a DM patient, as a result of the interaction between various metabolic and hemodynamic factors in the renal flow, with an substrate of the individual susceptibility for this disease.

The DKD diagnosis in type 1 DM may have a reliability in 95% of the patients, if they present a long duration of DM, diabetic retinopathy (DR) and microalbuminuria, a relatively preserved kidney size, in the absence of a marked proteinuria and hematuria.

DKD manifests in 20-40% of the DM patients.

The pathogenetics mechanisms involved in DKD are represented by: genetic susceptibility, glomerular hyperfiltration/ hyperfunction, oxidative stress, extracellular mesangial matrix accumulation, IR.

1.2 Type 1 Diabetes Mellitus (DM) - epidemiology

DM represents a progressive chronic disease that affects an ever growing number of people worldwidely, in 2014 globally being registered 387 million persons with DM. In 2014, at every 7 seconds, there was recorded a death caused by DM. In Europe, there live 52 million persons with DM, with a prevalence of 7.9%. The DM prevalence in Romania, according to PREDATORR, a study including patients aged between 20 and 79 years old, is 11.6%. Estimations for 2035 are going towards a global increase of the DM prevalence up to 592 million people.

Type 1 DM represents approximately 5-10% of the total DM cases, being recorded 30 million patients with type 1 DM worldwidely. The annual increase of type 1 DM incidence is of 2-5%; there is a high variability of type 1 DM incidence according to the geographical location, age, sex, ethnicity and season.

1.3 Insulin resistance (IR) in type 1 DM - mechanisms and markers of IR

Although IR represents a fundamental disorder of type 2 DM, there are also known the IR implications in type 1 DM, in the etiopathogenesis and progress of micro- and macrovascular complications.

The possible mechanisms involved in reducing insulin sensitivity in type 1 DM are represented by: changes in insulin release in the portal flow, changes in glucagone regulation, increase of ectopically accumulated free fatty acids, family history of greater IR and/ or type 2 DM family history.

The association between IR and microvascular complications in type 1 DM patients has been studied ever since 1968 by Martin et al., then by Yip et al. in 1993, Orchard et al. showed that eGDR (an IR marker) predicts clinical nephropathy in type 1 DM in the Pittsburgh EDC study.

For the IR estimation in type 1 DM, there may be used various indicators, like: waist circumference (WC), body mass index (BMI), waist to hip ratio (WHR), WC/ height (H) ratio, Homeostatic Model Assesment - Insulin Resistance (HOMA-IR) calculated with C-peptide, C-peptide, index 20/[fasting C-peptide (nmol/L) x fasting glycemia (mmol/L)], C-peptide Index (CPI), insulin sensitivity index (ISI), the Reaven score (TG/HDL cholesterol ratio - expressed in mmol/l ≥ 3), estimated Glucose Disposal Rate (eGDR).

1.4   **Metabolic syndrome (MS) in type 1 DM - definition, prevalence**

MS was described in literature for the first time in 1998 by Reaven, who combined under the name of the "X Syndrome" the following conditions: IR and compensatory hyperinsulinemia, hypertrygliceridemia, HT and lower HDL-cholesterol. The last criteria for defining MS are from 2009 - the consensus of IDF, National Heart, Lung, Blood Institute (NHLBI), American Heart Association (AHA), World Heart Federation (WHF), International HBPerosclerosis Society (IAS), International Association for the Study of Obesity (IASO), including at least 3 of the following 5 criteria for diagnosing MS: abdominal obesity (AO) (in European people, WC values ≥80 cm in women, WC ≥94 cm in men), TG ≥150 mg/dl, HDL-chol <40 mg/dl in men, HDL-chol <50 mg/dl in women, HT (sBP ≥130 mmHg and/or dBP ≥85 mmHg or antihypertensive treatment), fasting glycemia ≥100 mg/dl (or antidiabetic treatment). A possible mechanism of MS in type 1 DM persons could be: intensive insulin therapy in type 1 DM patients, used for obtaining an optimal glycemia control, in order to reduce complications, with side effects like an increased rate of hypoglycemia and subsequent weight gain, approximate 50% of type 1 DM patients being overweight or obese. MS and IR determine chronic complications of type 1 DM. The MS prevalence in type 1 DM patients varies very much, between 8-39.4%, according to the diagnosis criteria, geographical region and clinical and biological characteristics of the studied groups.

1.5 Importance of the substitution therapy of renal function (STRF) caused by DKD in type 1 DM

CKD represents a major health problem worldwide, involving huge costs and affecting the quality of life, due to its progress to ESRD that requires STRF and associated complications (anemia, mineral and bone metabolism disorders, HT, cognitive disorders). The costs for healthcare services for a patient with CKD are 1.8 times higher than a patient without CKD, while the average cost for a dialysis patient seems to be 10.3 times higher than in a patient without CKD.

Regarding the mortality rate, there was shown that at the same level of FGR, the patients with DKD presented a higher mortality rate in comparison to the non-diabetic CKD. The mortality risk for type 1 DM patients in the FinnDiane study increases with the degree of kidney damage (a 2.8 times higher risk for the microalbuminuria patients, 9.2 times higher for the patients with macroalbuminuria and 18.3 times higher in the ESRD patients).

2. PERSONAL CONTRIBUTIONS

2.1 Study objectives:

• Determining the DKD and MS prevalence in patients with type 1 DM with DM duration >10 years

• Identifying some correlations between the IR markers: *WC, BMI, WHR, WC/H ratio, daily insulin necessary (iu/kg/day), C-peptide, HOMA-IR calculated with C-peptide, eGDR, index 20 / [fasting C-peptide (nmol/L) x fasting glycemia (mmol/L)], C-peptide index (CPI), insulin sensitivity index (ISI), the Reaven score (TG/HDL-chol ratio expressed in mmol/l ≥3), Chol T/HDL-chol ratio ≥5) and DKD presence in patients with type 1 DM* with DM duration > 10 years

• Identifying some correlations between the IR markers and the other chronic complications of type 1 DM in patients with DM duration> 10 years, according to the DKD presence

• Identifying some correlations between the MS, DKD presence and other chronic complications of type 1 DM

• Identifying some correlations between cardiovascular risk (CVR) and the smoker status in patients with type 1 DM with DM duration> 10 years, according to the DKD presence

2.2 Material and methods

The study was observational, cross-sectional, lasting for 3 years (2010-2013) within the Clinical Centre of Diabetes, Nutrition and Metabolic Diseases - County Emergency Hospital of Craiova. In the study, there were included 140 patients, who complied with the inclusion and exclusion criteria, after signing the informed consent. The patients were fully evaluated at study inclusion.

Inclusion criteria: patients with type 1 DM (DM duration>10 years) who received a permanent insulin treatment initiated during the first year since DM diagnosis and before the age of 40 years old, previously having signed an informed consent.

Exclusion criteria: DKD presence having a different cause than DM; the presence of potentially nephrotoxic substances in the permanent drug list; the HT diagnosis preceedes the DM diagnosis; other causes for affecting proteinuria.

The informed consent was signed by every participant in the study, fully informed about the situation. The research was performed in accordance with the ethical principles from the Declaration of Helsinki, and are in accordance

with the GCP and present national and international regulations. The development of all activities in the research project was performed by complying with the legal standards provided by Act no. 206/2004 regarding proper conduct in research activity, technological development and innovation.

The statistical analysis was performed using the SPSS (Statistical Package for Social Sciences), 22 software (IBM Corporation, Armonk, NY, SUA). Used tests: the t-test, the Mann-Whitney test, the Kolmogorov-Smirnov test, the Chi-square test, the Kruskal-Wallis test, the ANOVA. The results were considered statistically significant when $p < 0.05$.

2.3 Results and Discussions

We included in the study 140 patients with type 1 DM (DM duration>10 years): 58 (41.43%) women and 82 (58.57%) men.

The DKD prevalence in the whole group is 58.57%, a higher statistically significant value in men than in women (68.29% vs. 44.83%).

The MS prevalence in patients with type 1 DM with DM duration >10 years is 55%, significantly higher in DKD patients than in the ones without DKD (62.2% vs. 44.8%) and higher in men than in women (62.2% vs. 44.8%). The maximum MS prevalence was recorded in patients aged between 40 and 59 years old, then in the ones aged between 60 and 79 years old, followed by the ones aged between 19 and 39 years old.

The DKD patients present a higher proportion than the ones without DKD: HT (p=0.002), hypertrygliceridemia (p=0.004), lower HDL (p=0.066), but not WC.

Patients with DKD presents a lower eGDR (thus a higher IR) than the patients without DKD (5.84 ± 2.24 vs. 7.16 ± 2.24 mg x kg^{-1} x min^{-1}), a statistically significant difference. The percentage of patients with DKD is higher corresponding to the Q1 and Q2 quartiles of eGDR (corresponding to a higher IR), lower corresponding to the Q3 and Q4 of eGDR, thus presenting a statistical significant.

The optimal cutt-off value of eGDR for the MS diagnosis is 5.806 mg x kg^{-1} x min^{-1}, having an 88.9% sensitivity and 72.7% specificity.

The DKD patients present lower values of WC, BMI, WC/H ratio, daily insulin necessary, C-peptide, HOMA-IR calculated with C-peptide, CPI and ISI, in comparison to patients without DKD, and higher values of the WHR, index 20 / [fasting C-peptide (nmol/L) x fasting glycemia (mmol/L)], but the differences are not statistically significant.

In the DKD patients there are statistically significant correlations between peripheral arterial disease (PAD) with the WC/H ratio, WHR, eGDR, eGDR quartiles, the correlations between diabetic peripheral neuropathy (DPN) with the daily insulin necessary, eGDR, ISI, DR correlations with C-peptide, C-peptide quartiles, CPI and myocardial infarction (MI) correlation with HOMA-IR.

The patients who associates DKD with one of the others chronic complications of type 1 DM presents a lower eGDR than the patients with only one chronic complication (either DKD or one of the other chronic complications).

DKD patients presents a higher percentage of the association between MS and another chronic complication - DR, DPN, chronic ischemic heart disease (CIHD), MI, except for PAD, in comparison to those without DKD, with statisitcally significant differences.

DKD patients presents a significantly higher CVR than the patients without DKD. In the patients without DKD, CVR is positively correlated with WC, the WC/H ratio, WHR, and negatively correlated with eGDR and the daily insulin necessary. In the patients with DKD, CVR is positively correlated with WC, the WC/H ratio, WHR, BMI and negatively correlated with eGDR, CPI, ISI.

The MS patients (both the ones with DKD and those without DKD) have a statistically higher CVR than the patients without MS. The DKD patients (both the ones without MS and those with MS) presents a statistically higher CVR than the patients without DKD.

CVR is higher in the smoking DKD patients than in the non-smoking DKD patients, with a statistically significant difference; also in the case of patients without DKD, CVR is higher in smokers than in non-smokers, but the difference is not a statistically significant one in this case.

Smoking DKD patients present a significantly lower eGDR than the non-smoking DKD patients.

The smoking DKD patients have a lower eGDR than the non-smoking DKD patients, therefore smoking increases the IR degree in the DKD patients; as a further argument, by studying the whole group of type 1 DM patients, there could be observed that the smokers had a lower eGDR than the non-smokers, a statistically significant difference.

The smoking DKD patients presented a lower CPI (thus a higher IR) than those without DKD, a statistically significant difference.

Of the DKD patients, the smokers presented in higher percentage than the non-smokers: HT (p=0.014), hypertriglyceridemia (p=0.028), higher WHR (p=0.003), lower HDL-chol (p=0.083).

DKD patients presented statistically significant correlations between the smoking status and DR, DPN, PAD.

2.4 Conclusions

1.   The DKD prevalence in the whole group of type 1 DM patients, with a DM duration>10 years, is high, being 58.57%, statistically more significant in men.
2.   The MS prevalence in type 1 DM patients, with a DM duration>10 years, is very high (55%), statistically more significant in DKD patients, in comparison to those without DKD (62.2% vs. 44.8%).
3.   Of all the studied IR markers, eGDR seems to be the most accurate for IR, which was higher in DKD patients, compared to those without DKD.
4.   The optimal cutt-off value of eGDR for the MS diagnosis is 5.806 mg x kg^{-1} x min^{-1}, having an 88.9% sensitivity and 72.7% specificity.
5.   The DKD patients present a statistically higher CVR than the patients without DKD (with or without MS); also, the patients with MS (with or without associated DKD) have a significantly higher CVR than those without MS.
6.   Of the DKD patients, the smokers presented a higher percentage than the non-smokers: HT (p=0.014), hypertrygliceridemia (p=0.028) and increased WHR (p=0.003).
7.   Smoking patients with type 1 DM presented a significantly lower eGDR (p=0.001), thus a higher IR than the non-smoking patients.
8.   Smoking amplify IR degree in type 1 DM patients (DM duration> 10 years) with DKD, smoking patients with DKD presenting a significantly lower eGDR than non-smoking patients with DKD.