

**UNIVERSITY OF MEDICINE AND PHARMACY
CRAIOVA
DOCTORAL SCHOOL**

DOCTORATE THESIS

- Summary –

**”CHRONIC COMPLICATIONS IN
PATIENTS WITH
TYPE 1 DIABETES MELLITUS
- Epidemiological study -”**

PhD Manager:

Professor PhD. Maria Moța

PhD - STUDENT:

Diana Clenciu

Craiova
2014

CONTENTS

Keywords	3
1. Current state of knowledge	
1.1. Microvascular complications in diabetes mellitus	3
1.2. Macrovascular complications in diabetes mellitus.....	3
1.3. Risk factors for chronic complicationd in diabetes mellitus	4
1.4. Insulinresistance and metabolic syndrome in type 1 diabetes mellitus.....	4
2. Personal contribution	
2.1 Aim of study	6
2.2 Material and methods	6
2.3 Results	7
2.3.1. Microvascular complications in type 1diabetes mellitus.....	7
2.3.2. Macrovascular complications in diabetes mellitus.....	7
2.3.3. Insulinresistance in patients with type 1 diabetes mellitus	7
Discussions	8
Conclusions	9

Keywords: diabetic neuropathy, microvascular complications, risk factors

1. Current state of knowledge

Microvascular complications of DM include: diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, whereas macrovascular complications are related to cardiovascular disease, cerebrovascular and peripheral vascular diseases. As a result of vascular complications, diabetes is the leading cause of blindness, is responsible for up to 40% of cases of renal failure and is a major determinant of cardiovascular morbidity and mortality.

1.1. Microvascular complications of diabetes

Diabetic neuropathy is the most common complication of diabetes that affects more than 50% of patients with type 1 and type 2 diabetes mellitus and diabetic peripheral neuropathy involves the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes after other possible causes of disease were excluded.

Diabetic retinopathy is the leading cause of blindness in people aged 25-74 years in the United States.

Currently, diabetic nephropathy is the leading cause of chronic kidney disease in the United States and other Western societies. It is also one of the most important long-term complications in terms of morbidity and mortality in patients with diabetes. Diabetes is responsible for 30-40% of cases of end-stage renal disease in the United States.

1.2. Macrovascular complications of diabetes

The presence of cardiovascular disease (CVD) in type 1 diabetes greatly affect life expectancy. Hyperglycemia resulting in an increase in oxidative stress is considered to be the key pathophysiological micro-and macrovascular complications of both.

Over the past 40 years, has been observed a reduction in cardiovascular mortality and coronary heart disease by about 70% both in diabetic patients and in non-diabetics. The cause is believed to be substantial progress in the management of CV risk factors and interventional cardiology. Moreover, in patients with type 1

diabetes, a decrease in mortality and a remarkable improvement in life expectancy over the past decades. Comparing two subcohorte Pittsburgh Epidemiology of Diabetes study Complications depending on the time of diagnosis of diabetes (1950-1964 vs 1965-1980) found an increase in life expectancy of about 14 years. However, the overall risk of CVD for persons with type 1 diabetes compared to non-diabetic persons has increased 2-3 fold in men and 3-5 fold in women. A significant increase in mortality of growing CVD HbA1c levels has been reported in type 1 diabetes.

1.3. Risk factors for chronic complications of diabetes

The association between duration of diabetes, degree of hyperglycemia and severity of microvascular complications was observed in type 1 and type 2 diabetes. The same can not be said about the relationship of glycemic control and macrovascular complications not directly proportional. The association of diabetes, especially type 2, with various vascular risk factors such as hypertension and dyslipidemia lead to an interaction of these factors that alter the risk and therefore each factor must be framed in the general context, not in isolation appreciated. Hyperglycemia is one of the major risk factors for chronic complications.

Microalbuminuria and diabetic retinopathy complications are microvascular markers, as confirmed by numerous studies have examined the relationship of glycemic control on the one hand and the onset and progression of microvascular complications on the other. However, glycemic control does not appear to influence the timing of retinopathy, except those with a very altered control (HbA1c> 13%). In addition to hyperglycemia, hypertension, hyperlipidemia, smoking and ethnic origin plays an important role in the onset and development of chronic complications of diabetes mellitus.

1.4. Insulin resistance and metabolic syndrome in type 1 diabetes mellitus

It has been shown that in type 1 diabetes, insulin resistance is present before diagnosis, at diagnosis and a few years after diagnosis. Studies showed that insulin resistance may even accelerate the progression of moderate to high risk for developing type 1 diabetes. A study in 2002 found that probable cause of insulin resistance at diagnosis as follows: acute metabolic decompensation, growth hormone

counterregulatory during puberty (e.g., growth hormone), and impaired glucose metabolism. Several studies have shown, however, that insulin resistance (IR) is more associated with older age, longer duration of diabetes, with a greater amount of fat, with a family history of type 2 diabetes, poor glycemic control and increase in lipid. Yki-Jarvinen and Koivisto noted in particular a further reduction of 40% of insulin-mediated glucose uptake in type 1 diabetes patients long term (> 1 year) than newly diagnosed (<1 year).

Two of the most important limitations in the insulin resistance patients with type 1 diabetes are lower prevalence and incidence of type 1 diabetes. Throughout the world, especially in the Asian region and the absence of non-invasive methods to measure insulin resistance in this type of diabetes. Metabolic syndrome groups cardiovascular and metabolic risk factors including central obesity, insulin resistance, dyslipidemia, hypertension. The presence of metabolic syndrome predicts the risk of cardiovascular disease in nondiabetic subjects and in patients with type 2 diabetes. There are several definitions of the metabolic syndrome, the most recent being the International Diabetes Federation consensus (IDF).

Essential for the development of metabolic syndrome seems to be the presence of increased insulin resistance. Although it is a feature commonly associated with the development of type 2 diabetes may also be a characteristic of patients with type 1 diabetes when present in type 1 diabetes patients can be interpreted as insulin resistance are likely to be at increased risk of developing cardiovascular disease.

Clinically, insulin resistance in patients with type 1 diabetes is often recognized by high insulin requirements. Using eGDR epidemiological studies that aim Pittsburgh chronic complications of diabetes has been found a high eGDR therefore, a high resistance to insulin which is associated with increased risk for diabetic nephropathy, peripheral vascular disease and coronary heart disease. The data so far show that in patients with type 1 diabetes there is an association between the presence of metabolic syndrome and diabetic nephropathy and poor glycemic control.

2. Personal contribution

2.1 Purpose of the study

This study aims are:

- ◆ to determine the prevalence of chronic complications in type 1 diabetes specific and correlation with risk factors (lifestyle, level of physical activity, nutritional status, duration of the disease, age of onset of disease, metabolic control).
- ◆ to assess the balance of carbohydrate and lipid metabolism in patients included in the study.
- ◆ to assess the correlation with insulin resistance and chronic complications.

2.2 Material and methods

This study cross-sectional observational held for a period of three years 2010-2013 the Department of Diabetes Nutrition and Metabolic Diseases Emergency County Hospital of Craiova. Calendar exploring patients in the study consisted of an initial full evaluation at inclusion in the study group.

We analyzed a sample of 200 subjects with type 1 diabetes Inclusion criteria: Caucasians; patients diagnosed with type 1 diabetes who are permanent insulin treatment initiated in the first year after diagnosis of diabetes before the age of 40 years; subjects signed informed consent. Exclusion criteria from the study: presence in the list of potentially nephrotoxic drugs permanent; diagnosis of hypertension preceding the diagnosis of diabetic nephropathy; patients with symptoms / clinical signs of positive urine culture urinary infection or other causes of impaired urinary protein.

Informed consent was signed by each participant in the study, in full knowledge of the facts, having been informed of all relevant aspects in the decision. All activities of the research project was conducted with the legal provisions under Law 206/2004 regarding conduct in scientific research, technological development and innovation.

Patients with diabetes were chosen and recruited from patients who presented to the outpatient specialty consultations of Clinical Emergency County Hospital from Craiova and met the criteria for inclusion and exclusion. After data collection was performed the initial database, using Excel program.

2.3 Results

We conducted a study of 200 subjects with type 1 diabetes (116 men and 84 women). Chronic complications and major risk factors for type 1 diabetes complications were analyzed in these patients.

2.3.1. Microvascular complications in type 1 diabetes

Diabetic neuropathy met in 126 patients representing a percentage of 61.5%. Diabetic retinopathy at any stage met in percentage of 53%, proliferative diabetic retinopathy met in 61 patients representing 30.5%. BCR diabetic met 44% of patients.

2.3.2. Macrovascular complications in type 1 diabetes

Peripheral vascular disease met in 52 patients (26%), and myocardial infarction was encountered in 6 patients (3%). Chronic ischemic heart disease was present in 39 patients (19.5%) of the 6 patients had prior myocardial infarction. Stroke (stroke) met only one patient (0.5%) with type 1 diabetes so that could not be achieved statistical analysis thereof. The patient was a male, 59 years old, had a duration of diabetes of 20 years development, the HbA1c value of 7.8% at the time of data collection and presented hypertension, dyslipidemia and hyperuricemia which were in treatment.

2.3.3. Insulin resistance in patients with type 1 diabetes

In our study, the statistical analysis performed observed that insulin resistance measured by the constant low eGDR appears associated with all chronic complications of type 1 diabetes.

Thus, insulin resistance assessed by eGDR (estimated glucose disposal rate) $\leq 7.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was found in 83 patients (41.5%), the average being $10.06 \pm 5.56 \text{ mg eGDR} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Of the 83 patients with insulin, 66.3% were male and 33.7% female.

Age, gender, positive family history of diabetes, duration of the disease, smoking, waist-hip ratio, BMI and dyslipidemia in patients with type 1 diabetes with or without insulin resistance were statistically significantly different. There is a higher prevalence of insulin resistance among patients with disease duration of more than

10 years, those with a family history of diabetes (50.6% vs 32.5%) in hypertensive (89.2% compared to 26 5%) and in those with dyslipidemia (61.9% vs 35.1%, $p < 0.001$).

DISCUSSION

31% of the 200 patients studied were found none of the chronic complications of diabetes, however 69% of patients had complications of micro and / or macrovascular.

Only microvascular or only macrovascular complications were not detected in patients with type 1 diabetes, patients had both micro and macrovascular complications.

In this study, older age, longer duration of diabetes development, insulin resistance, the presence of hypertension and dyslipidemia were common in patients with chronic micro and macrovascular complications.

Older age and longer duration of diabetes development are known factors and shown in numerous studies to be associated with the development and progression of chronic complications in diabetes, while this new concept of insulin resistance appeared lately in type 1 diabetes won land to be accepted worldwide among doctors and researchers. In this study we evaluated the prevalence of insulin resistance in patients with type 1 diabetes using clinical score eGDR, its results showing a prevalence of 41.5%, similar to that of other European countries where prevalence studies cited 32-48% is.

The results of this study showed that insulin resistance, measured by eGDR is more common in patients with chronic complications than in those without complications. In addition, showed that the low value of eGDR (increased insulin resistance) is independently associated with the presence of all chronic complications of diabetes.

This result is very interesting because the presence of insulin resistance is not universally accepted, although it may be a good indicator for all chronic complications independent of other risk factors.

CONCLUSIONS

The study includes analysis of micro and macrovascular chronic complications of diabetes, clinical and paraclinical parameters incriminated as potential risk factors in the development of diabetes complications led to the development of the following conclusions can be important and practical application in preventing and delaying disease progression.

- 69% of patients had chronic complications of diabetes and 31% showed no complications. All patients had chronic complications such as microvascular complications and macrovascular.
- The most common microvascular complication was neuropathy that was found in a proportion of 61.5%, followed by 53% in diabetic retinopathy at any stage and diabetic CKD who met in 44% of patients studied.
- If macrovascular complications, the most frequent was BVP in 26% of patients followed by CIC to 19.5% of patients. Myocardial infarction was found only in 6 patients and stroke in one patient.
- Older age, longer duration of diabetes development, insulin resistance measured by eGDR, the presence of hypertension and dyslipidemia are common in patients with chronic micro and macrovascular complications.
- IR was assessed in 41.5% of patients with type 1 diabetes was more common in patients with chronic complications than in those without complications and was associated with the presence of all chronic complications of diabetes.
- This study demonstrated the association between insulin resistance and type 1 diabetes, although it is limited by the relatively small sample size. Thus, future research is needed involving a larger sample to determine which of the factors identified are associated with insulin resistance in type 1 diabetes.
- Study has shown that IR is associated with an increased risk of chronic complications but because of the cross-sectional design, the causality relationship can not be determined. However, the existence of this causal relationship and the benefit of insulin therapy in type 1 diabetes are issues discussed in the future.
- In conclusion, our study showed that IR is the only constant factor associated with all chronic complications of type 1 diabetes and may be useful in the future to predict the risk of these complications and to reassess therapy in type 1 diabetes.