The Relationship of Metabolic and Endocrine Parameters with Associated Diseases in Diabetes Mellitus

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The most common comorbidities in patients with diabetes mellitus are cardiovascular diseases, obesity, dyslipidemia, thyroid disorders but other associated diseases may frequently occur. Laboratory tests are useful investigation methods that may reveal the subclinical manifestations of the disease but they are also essential for patient monitoring. The aim of the study was to assess laboratory parameters and associated diseases in diabetic subjects and to implement a scoring system with a predictive role in the evolution of the cases. Material and methods: The study group consisted of 195 subjects with documented type 1 or type 2 diabetes. About half of the cases were collected from the Procardia outpatient unit, and the rest were patients admitted to the Diabetology Clinic in Tîrgu Mures. The study was performed between January - June 2017. The results of the laboratory tests, as well as the information regarding comorbidities and treatment, was collected and patients' body mass index was calculated. Based on the clinical data, a scoring system, called Diabetes Complication Severity Index (DCSI) with a predictive role, was implemented. The diabetic outpatients presented significantly better carbohydrate metabolic balance compared to the hospitalized subjects. No significant differences could be observed regarding kidney function, hepatic status and lipid profile of the two subgroups of diabetic subjects. The most important comorbidity observed in both patient groups was arterial hypertension. The hospitalized diabetic subjects had significantly higher incidence of ischemic heart disease and significantly lower incidence of thyroid disorders compared to the outpatients. The DCSI scoring system revealed that comorbidities are more frequently present in the hospitalized patients compared to the ambulant diabetic subjects. Evaluation of clinical status and laboratory results in diabetic patients followed by implementation of a scoring system based on the data obtained regarding comorbidities could help clinicians to set up an individual treatment plan for these patients, focusing on preventing other complications.

Keywords: diabetes mellitus, dyslipidaemia, hypertension, laboratory parameters, thyroid diseases

Diabetes mellitus is a disease with growing incidence worldwide; it represents a serious public health problem of the modern society, a real epidemic (1, 2). Recent statistics revealed a 75% increase in the number of persons with diabetes mellitus in all age-groups in the period 1988-2010 (1, 3)

In several cases, associated pathologies occur in diabetic patients, especially cardiovascular diseases, such as arterial hypertension or even heart failure. Arterial hypertension affects around one-third or half of the population in most of the countries (4, 5). Due to the presence of comorbidities the therapeutic plan becomes more difficult as side effects of the medication should be taken into consideration (6). Type 2 diabetes and hypertension are related to modern life habits, such as sedentary lifestyle, unhealthy diet and stress exposure (7).

Nowadays the most frequent endocrine disorders in the clinical practice are diabetes mellitus and thyroid dysfunction. Non-recognized thyroid disorders may have a negative influence on the metabolic control of diabetic individuals and may increase the risk for the development of cardiovascular complications (8).

Abnormalities of the thyroid gland function deeply affect the metabolism of lipoproteins and the patients' lipid profile, influencing their risk of cardiovascular diseases, thus any kind of thyroid disorder in diabetic individuals should be diagnosed and treated. A close relationship could be observed between the values of serum TSH (thyroid-stimulating hormone) and some laboratory parameters, such as total cholesterol concentration, LDL (low-density lipoprotein) cholesterol and triglycerides, these parameters being positively correlated with the TSH value and a negative correlation occurred between HDL (high-density lipoprotein) cholesterol levels and serum TSH concentration (9).

Patients with chronic kidney disease (CKD), which occurs frequently in the background of diabetic or hypertensive nephropathy, reveal high risk for developing hypothyroidism and cardiovascular disease, especially in advanced stages of CKD. Increased triglyceride concentration and hypercholesterolemia with low HDL cholesterol, increased LDL cholesterol are common in patients suffering from CKD (10).

The aim of our study was the assessment of biochemical, endocrine parameters and associated diseases in type 1 and 2 diabetic patients who regularly attended the Procardia outpatient medical unit and in patients admitted to the Diabetology Clinic of the Emergency County Hospital in Tirgu-Mures during the first six months of the current year.

Experimental part

Material and methods

We processed the data of 96 diabetic patients who attended the Procardia outpatient clinic between January – June 2017, and 99 patients with diabetes mellitus admitted to the Diabetology Clinic of the Emergency County Hospital in Tirgu Mures during the same period.

Biochemical and endocrine laboratory results were collected together with data regarding associated diseases

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and medication; body mass index (BMI) was calculated based on patients' height and weight.

Measurement of glycated hemoglobin (HbA1c) levels was performed by reflectometry using the Nycocard Reader equipment from the laboratory of the Procardia medical unit. Metabolic investigation of the patients included serum glucose, total cholesterol, triglycerides, HDL (high-density lipoprotein) and LDL-cholesterol (low-density lipoprotein). Kidney function was evaluated by serum creatinine measurement and the glomerular filtration rate was calculated based on the creatinine value. Other biochemical parameters followed were serum urea, uric acid and serum transaminase activity for assessment of hepatic status. The Konelab 20XTi analyzer was used to carry out these laboratory tests with Diagnosticum reagent kits. Endocrine investigations were performed using ELISA methodology (Stat Fax 505 equipment) with Diametra reagent kits. The parameters followed were serum TSH (thyroid stimulating hormone), FT4 (free thyroxine) and ATPO (anti-thyroid peroxidase antibodies).

The laboratory analyses for the hospitalized patients were performed in the Central Laboratory of the Emergency County Hospital in Tirgu-Mures. The biochemical tests were carried out on the Cobas 6000 analyzer system while the endocrine parameters were obtained by a chemiluminescence method on an Immulite One analyzer.

We evaluated both groups of patients for the presence of subclinical hypothyroidism based on TSH values exceeding 4.20μUI/mL and FT4 values between 0.93-1.7 ng/dL. Subclinical hyperthyroidism was considered in the presence of TSH concentration under 0.27 μUI/mL and FT4 in the reference range (0.93 -1.7 ng/dL). Clinical hypothyroidism was defined by TSH values exceeding 4.20 μUI/mL and FT4 under 0.93 ng/dL, and clinical hyperthyroidism by TSH values under 0.27 μUI/mL and FT4 concentration over 1.7 μUI/mL. Autoimmunity can be considered in case of ATPO levels exceeding 35 IU/mL (8).

Based on the clinical data, a scoring system was calculated having a predictive role in the evolution of the patients' medical condition, called Diabetes Complication Severity Index (DCSI). This system takes into consideration the incidence of diabetic complications, the score gets higher according to the number of associated pathological conditions, the points are ranging from 0 to 2 for each type of abnormality, the maximum obtainable score being 13. This score is proven to have a prognostic value predicting both hospital admission and mortality (11).

SPSS version 22 and GraphPad InStat were used for statistical processing of the experimental data. The significance threshold was set to p value under 0.05.

Results and discussions

The mean age of the ambulant patients was 64.58 years ± 11.19 (SD), while the hospitalized diabetic group was slightly younger, with an average age of 58.97 ± 14.49 (SD).

The ambulant diabetic subjects had better carbohydrate metabolic balance compared to the patients admitted to hospital during the same period of time. The mean HbA1c value for the outpatients was 6.73 % ± 1.06 (SD), significantly lower compared to 8.88 % ± 2.05 (SD) in the hospitalized group ($p<0.0001$). A similar pattern could be observed by comparing the serum glucose values in these two groups: the average was 133.25 mg/dL ± 35.62 (SD) in the outpatients' group and 170.45 mg/dL ± 62.09 (SD) in case of the diabetic subjects admitted to hospital ($p<0.0001$). These results are closely related to those obtained by comparing the incidence of glucosuria in these two groups of diabetic patients (table 1, fig. 1).

No significant differences could be observed with respect to the lipid profile of the two subgroups of diabetic patients. The average serum total cholesterol level was 188.11 mg/dL ± 50.16 (SD) in the outpatients' group and 193.51 mg/dL ± 61.18 (SD) in the hospitalized diabetic subjects ($p=0.5172$). The mean serum triglyceride concentration was 163.04 mg/dL ± 94.05 (SD) in the ambulant patients compared to 186.62 mg/dL ± 141.44 (SD) found in the hospitalized group ($p=0.1908$). Comparison between HDL and LDL cholesterol obtained in the two groups could not be performed, due to the lack of data in case of the hospitalized patients. In the outpatients' group, 22.22% of the subjects had elevated LDL-cholesterol level, which represents a cardiovascular risk factor.

No significant difference could be observed in the serum transaminase activity between the two groups of patients. Evaluation of the kidney function based on creatinine values and GFR calculation showed no significant difference in the two studied groups of diabetic subjects. The mean glomerular filtration rate was 68.82 mL/min ± 17.54 (SD) in case of the outpatients, and the GFR average was 67.57 mL/min ± 27.48 (SD) in the hospitalized group ($p=0.8117$). We found significantly higher serum urea results in the hospitalized group compared to ambulant diabetic patients: the mean value was 37.27 mg/dL ± 11.91 (SD) in the outpatients and 42.67 mg/dL ± 21.37 (SD) in the patients admitted to the Diabetology Clinic ($p=0.0423$).

Hypertension occurs in case of 51.51% of the hospitalized patients and in 41.66% of the cases concerning outpatients. A statistically significant difference ($p=0.0019$) could be observed regarding the burden ischemic heart disease, which was more frequent in the hospitalized group and the incidence of thyroid pathology which was significantly

Table 1
DISTRIBUTION OF NORMAL AND PATHOLOGICAL VALUES IN THE HOSPITALIZED AND OUTPATIENT GROUPS

Parameter	Value type	Outpatients (Number)	Hospitalized patients (Number)
Glycaemia	High	75	90
	Normal	21	9
Hb1Ac	High	37	50
	Normal	59	49
BMI	High	36	66
	Normal	60	33
Uric acid	High	7	14
	Normal	89	85
Glucosuria	Present	15	34
	Absent	81	65

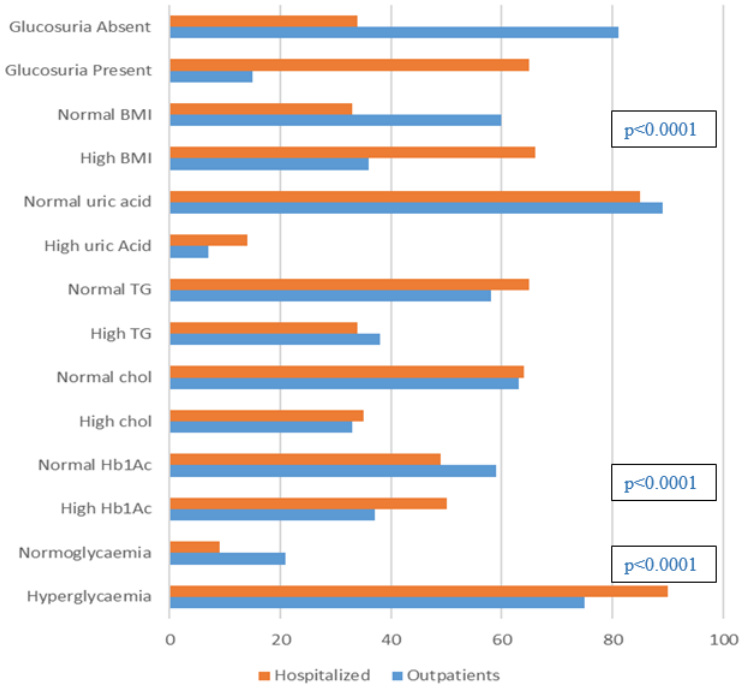

Fig. 1. Distribution of the normal and pathological values in the hospitalized and outpatient groups

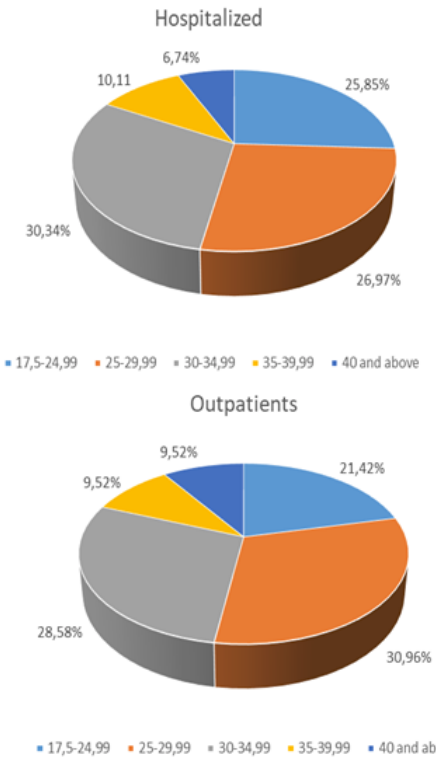

Fig. 2. Distribution of body mass index results in the two groups of patients

Table 2
DCSI SCORES CALCULATED FOR THE TWO GROUPS OF DIABETIC PATIENTS

DCSI score	Hospitalized patients (count)	Ambulatory patients (count)
0	0	83
1	8	7
2	62	5
3	48	1
4	36	0
5	20	0
6	12	0
7	7	0

higher (p=0.0140) in the outpatient group.

Subclinical hyperthyroidism could be observed in 4.61% of the patients, subclinical hypothyroidism in 3.07 and 2.54% of the studied diabetic patients presented laboratory values corresponding to clinical hypothyroidism during the evaluation period. No cases with clinical hyperthyroidism could be observed based on the recent laboratory results probably due to the current treatment of the patients diagnosed with this disease. ATPO values were within the normal range for all the patients where this parameter was available.

Applying the Diabetes Complications Severity Index scoring system to our database we could observe a higher frequency of comorbidities in the hospitalized diabetic subjects compared to the outpatients suffering from this disease. The total DCSI score obtained for the ambulant patients was 96, while in the group of diabetic subjects admitted to hospital the total DCSI score was 209. The frequency of the DCSI scores in the two groups is presented in table 2.

Glycated hemoglobin has an important seasonal variation in diabetic individuals, showing higher values during late autumn, winter and early spring compared to other periods of the year (12). The background of these changes is related to the differences in diet and the patients' physical activity (13). This variation was taken into consideration in the design of our study by means of collecting the data regarding outpatients and hospitalized diabetic subjects during the same interval of the year.

As we expected, the diabetic subjects admitted to hospital had significantly worse carbohydrate metabolic balance compared to the ambulant patients. An interesting outcome of our study is the relatively young mean age of the hospitalized diabetic subjects, which might reflect the tendency of presenting complications early during the evolution of the disease and underlines the importance of secondary prevention, especially in case of cardiovascular diseases.

An important aspect is the evaluation of microvascular status, which was performed by our research team in several hypertensive diabetic patients (including some subjects which belong to this study group) based on ophthalmologic examination and assessment of cognitive status using three validated questionnaires. Impairment of cognitive function leading to dementia is a very severe associated disease in diabetic patients having a complex pathological mechanism, including chronic hyperglycemia, repeated hypoglycemic episodes, insulin resistance, amyloid deposits, vascular dysfunction (aggravated by coexisting hypertension). Poor

carbohydrate metabolic control increases the risk of developing dementia (14).

Huge variations of glycemia is considered to be a serious risk factor in diabetic patietns for developing long-term complications of the disease; a special manifestations, difficult to be controlled, which contributes to this variation is the dawn phenomenon (15). According to recent research data collected in 2014, unhealthy eating habits (irregular meals, eating during watching TV) are very common in the Romanian population. Together with a diet rich in fat and carbohydrates, these factors contribute to the high incidence of overweight and obesity in our country, especially in the age group between 40-80 years (16).

The assessment of thyroid gland function is frequently performed for diabetic subjects on the diabetologists' and the general practitioners' requests. This screening has an important role in revealing the subclinical forms of thyroid disorders.

DCSI score can be used in a simple way in order to predict hospital admission and mortality in diabetic patients. According to this score, hospitalized patients from our study will probably have a high rate of hospital readmission and mortality.

Several other scoring systems are described in the medical literature, the most complex ones take into consideration clinical and laboratory investigation results (17). Other research groups evaluated the risk of developing metabolic syndrome in subjects having genetic polymorphisms of factors involved in the development of this complex disease (18).

It would be necessary to complete the laboratory investigation of the hospitalized diabetic patients with analysis of different lipoprotein fractions (HDL, LDL-cholesterol) to achieve a better evaluation of the cardiovascular risk factors, which may influence the treatment plan.

Conclusions

Several differences could be observed between hospitalized diabetic subjects and outpatients suffering from this disease. The main difference regarding laboratory results could be detected between the carbohydrate metabolic balances of the two groups, this being significantly worse in the hospitalized patients. Cardiovascular diseases are the most frequent comorbidities in case of these diabetic subjects, especially arterial hypertension. Associated ischemic heart disease, obesity, dyslipidemia and thyroid disorders were found in several subjects.

Scoring systems based on clinical and laboratory data, like the one we used, can have a predictive role in the evolution of the cases and can help the clinician to focus on those patients who are most exposed to complications in order to implement efficient preventive strategies adapted to individual characteristics and necessities. More financial resources would be necessary to complete the laboratory investigation of the diabetic patients.

Acknowledgements: The financial support for laboratory analyses and microvascular status evaluation in case of some patients involved in this study group has been provided by the Hungarian Academy of Science, contract nr. 0346/26.02.2016.

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Manuscript received: 15.09.2017