Diabetes mellitus is one of the most common groups of metabolic diseases, characterized by chronic hyperglycemia. Due to its prevalence, diabetes is one of the most significant problems of global public health. Diabetes mellitus type 1 (DM1) is characterized by autoimmune destruction of pancreatic cells, which produce insulin. The onset of DM1 is most often in childhood or adolescence. The main symptoms include increased liquid and food intake as well as frequent urination. Diagnosis is based on the confirmation of hyperglycemia, defined as the fasting glucose serum level ≥ 7.0 mmol/L (126 mg/dL) or ≥ 11.1 mmol/L (200 mg/dL) in a glucose tolerance test. Treatment is based on keeping the glycemia in the normal range. In DM1, this is achieved by administering exogenous insulin. Traditionally, insulin is administered subcutaneously by patient, several times a day. The doses are determined on the glycemia measurements performed by the patient with the same frequency. Such insulin therapy allows to maintain the normoglycemia for about 28% of the time of the day. Diabetes leads to numerous complications. Acute complications include ketoacidosis and severe hyperosmolar hyperglycemia. An improper insulin therapy may lead to hypoglycemic coma. Chronic complications include retinopathy, nephropathy, cardiovascular disease, diabetic foot and diabetic gastroparesis. Neurological complications are mostly chronic and include peripheral neuropathy and cognitive impairment. According to previous studies, diabetic neuropathy develops in half of patients. It may affect sensory, motor and autonomic fibers. Symptoms include sensory loss, hyperalgesia, allodynia and paresthesias as well as neuropathic pain. The involvement of autonomic fibers results in orthostatic hypotension, thermoregulatory disturbances, constipation or diarrhea, and sexual dysfunction. Neurological signs include impaired touch and vibration sensation, as well as increase in pain, heat and cold threshold. With progression, deep tendon reflexes decrease and become absent. Muscles may become weak and wasted and fasciculations may occur. The main mechanism of the development of neuropathy is microangiopathy. The main risk factors are older age, longer disease duration, and higher glycated hemoglobin (HbA1c) level. Other factors include dyslipidemia, obesity, hypertension, smoking, alcohol abuse and greater body height. Fluctuations of glucose level, including even transient and small deviations may impair conduction of distal nerve fibers, which was confirmed by examining the plantar nerves. Cognitive impairment in DM1 affects executive functions, memory, verbal intelligence and others. The risk factors for cognitive impairment are higher age, age of diabetes onset, duration of the disease, chronic hyperglycemia, as well as episodes of severe hypoglycemia and episodes of ketoacidosis. Similarly to neuropathy, the risk of cognitive impairment is increased by higher HbA1c, higher BMI and smoking. The main mechanism of cognitive impairment is macroangiopathy, which

leads to atherosclerosis of cerebral vessels as well as strokes and other morphological changes, especially in the white matter. The effect of angiopathy has been documented, among others, by showing the correlation of cognitive impairment with increased thickness of the intima-media complex of the common carotid arteries. The frequency and severity of neurological complications in DM1 can be reduced with modern therapeutic options. One of such options is increase in frequency of manual glycaemia measurements and insulin injections. Such treatment results in tighter glycemic control, which, according to meta-analysis from the Cochrane Library significantly reduces the occurrence of complications. In the last decade therapeutic techniques in DM1 have been further developed with the aim to provide the most physiological level of glycemia. These techniques include continuous glucose monitors (CGMs), which are small devices permanently attached to the patient's body. Using transdermal or subcutaneous sensor CGMs measure blood glucose every one to five minutes and reacts if the glucose level exceeds the normal range, or if the dynamics of the glucose level change becomes too steep. Other component of the modern insulin therapy are the insulin pumps. They are small devices worn by patients, capable to administer insulin automatically. The optimal therapeutic system, which becomes increasingly popular is the combination of CGM with an insulin pump, called a closed loop system. Therapy with the closed loop system was associated with reduction of HbA1c in the group of twenty young people from 10.5 to 7.6%. Moreover, the proportion of time spent in normoglycemia increased from 27.6 to 66.5% and in some studies reached even 85%, which corresponds to near-perfect glycemic control.

Aims of the study

The first aim was to assess the incidence of neuropathy and angiopathy in the population with DM1 treated with the insulin pump.

The second aim was to identify factors, which contribute to the development of neurological complications in patients with DM1 treated with the insulin pump.

Methods

This was a prospective and observational study. Patients with DM1, of both sexes, who were treated with the insulin pump in the Diabetes Clinic of the Department of Metabolic Diseases, University Hospital in Kraków, as well as subjects from the control group were included. Age, height and weight, as well as education level of each included person were recorded. Further demographic data included regular sport activity and the alcohol consumption. The clinical data of the patients was read from the medical records and from the

insulin pumps. This data included disease duration, duration of therapy with the pump, doses of insulin, the most recent HbA1c level, autonomic and sensory symptoms of neuropathy, presence of cardiovascular diseases, hypothyroidism and other comorbidities. A structured interview and neurologic examination for neuropathic symptoms and signs were performed using the Michigan Neuropathy Screening Instrument (MNSI). Further assessment of neuropathy included the nerve conduction study of the sural nerve on the non-dominant side. Attitude towards the disease was assessed using the Diabetes Locus of Control Scale (DLCS) and the Diabetes Self-Management Questionnaire (DSMQ). The quality of life was assessed with the Medical Outcomes Study 36-Items Short Form Health Survey (SF-36) and the Satisfaction with life scale (SWLS), as well as the Sexual Satisfaction Questionnaire (Kwestionariusz Satysfakcji Seksualnej – KSS) and the Body Esteem Scale (SOC). The mood was assessed with the Center for Epidemiologic Studies Depression Scale - Revised - CESD-R. Signs of macroangiopathy were investigated by measuring the thickness of bilateral intima-media complex of the common carotid arteries.

Results

The study included 90 (53 women) patients with DM1 and 45 (23 women) controls. The mean age was 30.5 ± 10.9 in patients and 27.7 ± 7.1 ($p<0.30$) in the control group. Patients suffered more frequently from hypertension, hypothyroidism, skin problems, gastrointestinal symptoms, as well as symptoms specifically related to neuropathy, i.e. burning and / or tingling of the hands and / or feet, and vasovagal symptoms. The mean score of the first part of MNSI was 1.17 ± 1.62. The mean score of the second part was 0.61 ± 1.12 and the average total score was 1.74 ± 2.36. In 15 (17%) patients, the total score amounted to four or more, which suggested neuropathy. No differences were found between patients and controls regarding amplitude of the response from the sural nerve and conduction velocity. However, comparison of the proportion of abnormal conduction results showed more abnormalities in DM1 group (χ=4.45, $p<0.035$). The mean intima-media thickness for both internal carotid arteries was 0.39 ±0.11mm in the patient group, which was significantly more than in the controls (0.33 ±0.06mm, $p<0.015$). The results of CESD-R, KSS, SF-36, SWLS and SOC tests and questionnaires showed no differences between both groups. The subgroup of patients with DM1, complaining of neuropathic symptoms such as numbness and tingling, showed higher age, higher BMI, longer disease duration, and lower quality of life in the SF-36. The MNSI score correlated with age and with SF-36. The amplitude of the response from the sural nerve showed significant inverse correlations with age (R=-0.52, p=0.000), disease duration (R=-0.40, p=0.000), intima-

media thickness (R =-0.36, p=0.018) and with BMI (R=-0.25, p=0.025). Similarly, the thickness of the intima-media complex correlated with age (R=0.57, p=0.000), disease duration (R=0.56, p=0.000), and BMI (R=0.39 p=0.008). However, significant correlations were also found with CESD-R, with DSMQ and with some sub-scores of SOC and DLCS.

Discussion

This study revealed increased occurrence of peripheral neuropathy and angiopathy in DM1 despite treatment with insulin pump. Thus, even modern therapy with a very high percentage of time spent in normoglycemia (65-85%) does not completely prevent the development of neurological complications of DM1. On the other hand, the incidence of neuropathy symptoms was much lower than in the populations treated without tight glucose control, which is in line with previous studies.

Surprisingly, differences were found in factors contributing to the development of peripheral neuropathy and angiopathy. Both were related to age, disease duration and BMI. However, the angiopathy showed also relation to psychological factors, such as attitude towards the disease (DLCS), body perception (SOC) and therapeutic strategy (DSMQ). Concurrently, the correlation of BMI with the thickness of the intima-media complex was stronger than with the signs of neuropathy. Such results suggest that BMI determines both the thickness of the intima-media complex and the body perception, together with the attitude to the disease. In this light, the relationship between psychological factors and the thickness of the complex is only indirect. This thesis is supported by the lack of differences in the results of psychological tests between the patient group and the controls. In contrast to studies on patients with DM1 treated with manual insulin dosing, neurological diabetic complications in the currently studied population were not related to the level of HbA1c, which was slightly elevated, but on the other hand significantly lower than in the previous studies on patients without tight glucose control. This data indicates that the reduction in the HbA1c level after treatment with the insulin pump effectively eliminates the influence of elevated HbA1c on the development of neurologic complications of DM1.