Why does intensive insulin therapy implemented at the onset of type 1 diabetes not decrease prevalence of diabetic microangiopathy?

Aleksandra Araszkiewicz, Dorota A. Zozulińska-Ziółkiewicz, Magdalena Trepińska, Bogna Wierusz-Wysocka

Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Raszeja Hospital, Poznan, Poland

Submitted: 9 August 2007
Accepted: 13 September 2007

Arch Med Sci 2008; 4, 2: 167–173

Corresponding author:
Assist. Prof. Dorota Zozulińska-Ziółkiewicz
Department of Internal Medicine and Diabetology
Poznan University of Medical Sciences
Raszeja Hospital, Mickiewicza 2
60-834 Poznan, Poland
Phone/fax: +48 61 847 45 79
E-mail: zozula@box43.pl

Abstract

Introduction: The aim of this study was to assess the incidence and predictors of nephropathy and retinopathy in prospective observation of type 1 diabetic patients treated with intensive functional insulin therapy (IFIT) from the onset of disease.
Material and methods: 86 type 1 diabetic patients, mean age 23.4±5.1 years, were investigated once a year. The mean follow-up of this study was 7.1±1.5 years. We analyzed the association between various clinical features and subsequent diagnosis of diabetic microangiopathy.
Results: We detected background retinopathy in 17 subjects (20%) and positive microalbuminuria in 13 patients (15%). Five patients had both retinopathy and positive microalbuminuria. The development of retinopathy and microalbuminuria was associated with lower knowledge about diabetes (respectively, RR=3.71, 95% CI: 1.15-12.01, P=0.02 and RR=4.33, 95% CI: 0.98-19.10, P=0.04), worse self-monitoring of blood glucose (respectively, RR=5.50, 95% CI: 2.00-15.11, P=0.0003 and RR=2.86, 95% CI: 1.13-7.24, P=0.04), lower HDL cholesterol level (respectively, RR=3.06, 95% CI: 1.36-6.87, P=0.01 and RR=4.85, 95% CI: 1.95-12.00, P=0.002) and higher diastolic blood pressure (respectively, RR=7.42, 95% CI: 2.11-26.15, P=0.002 and RR=10.62, 95% CI: 3.32-33.96, P=0.0001). Additionally the risk of the development of microalbuminuria was associated with BMI (RR=2.99, 95% CI: 1.10-8.10, P=0.04), postprandial glycaemia (RR=10.66, 95% CI: 1.49-7.61, P=0.001) and high triglyceride level (RR=4.52, 95% CI: 1.97-10.33, P=0.01).
Conclusions: The presented data show that the development of microangiopathy in type 1 diabetic patients treated with intensive functional insulin therapy from the onset of the disease was associated with low diabetic knowledge and signs of insulin resistance.

Key words: type 1 diabetes, intensive functional insulin therapy, diabetic retinopathy, microalbuminuria.

Introduction

Despite great progress concerning treatment of diabetes, late diabetic complications still remain the principal cause of morbidity and mortality in patients with type 1 diabetes. The DCCT (Diabetes Control and Complications Trial) and its follow-up EDIC (Epidemiology of Diabetes Interventions and Complications) studies demonstrated that the improvement of metabolic control after implementation of intensive insulin therapy reduced the risk

of development and progression of microangiopathy [1, 2]. However, the intensive approach used in these trials was associated with increased risk of hypoglycaemic episodes and unfavourable weight gain [1]. This might result from the lack of any structured teaching programme involved in these studies. The works of the Department of Metabolic Disease and Nutrition in Düsseldorf as well as the results of the DAFNE (Dose Adjustment for Normal Eating) study group revealed the benefits of a training programme in intensive insulin therapy in producing sustained improvements of glycaemic control and quality of life without increasing the risk of hypoglycaemia [3, 4].

Intensive functional insulin therapy (IFIT) was originally defined as a systemic therapeutic programme consisting of intensified insulin substitution. This method of treatment is based on multiple daily insulin injections, including once or twice-daily NPH insulin, long acting insulin analogue or continuous subcutaneous insulin infusion, several times daily blood glucose self-monitoring and a liberalization of dietary regulations and other lifestyle restrictions [5]. The five-day structured teaching programme provided the skills to adapt regular insulin doses according to blood glucose level before main meals, physical activity and amounts of carbohydrate intake planned. Today, intensive insulin therapy seems to be the gold standard in the care of type 1 diabetic patients. The safety and efficacy of this method of treatment in maintaining near normal glycaemia has been proved in several prospective studies [3]. After publication of the results of DCCT and EDIC trials it seemed that intensive functional insulin therapy (IFIT) implemented at the onset of type 1 diabetes could prevent the development of microvascular complications. However, the patients recruited to these trials did not have newly diagnosed type 1 diabetes and thus were not educated in IFIT from the beginning of the disease.

The aim of this study was to assess the incidence and predictors of nephropathy and retinopathy in prospective observation of type 1 diabetic patients treated with intensive functional insulin therapy (IFIT) from the onset of disease.

Material and methods

Patients population

We recruited 100 consecutive patients aged below 35 years with newly diagnosed type 1 diabetes, hospitalized due to diabetic ketoacidosis (DKA) at the Department of Internal Medicine and Diabetes in Poznan between 1994 and 1999. After DKA cure and stabilization of metabolic state all the patients started the treatment in IFIT. They attended a five-day structured training programme during hospitalization providing the skills in multiple daily insulin injections with adapting short-acting insulin doses before main meals. During the course the patients also obtained general information about pathogenesis of diabetes, acute and chronic diabetic complications, physical activity and characteristics of insulin and glucagon.

Fourteen patients with acute or latent inflammatory foci, liver dysfunction, connective tissue disease, renal failure, missing the first follow-up visit and treated with drugs other than insulin were excluded from the study. Therefore, 86 individuals, of mean age 23.4±5.1 years, were investigated once a year. The mean follow-up of this study was 7.1±1.5 years. Baseline clinical characteristics of the study group one month after diagnosis of diabetes are presented in Table I.

All subjects were informed about the aim of the study and gave their consent. The study was approved by the local Ethical Committee.

Methods

At the baseline participants completed a standardized questionnaire including sex, age, education, medical history, duration of diabetes, smoking status, frequency of hypoglycaemia episodes and blood glucose monitoring. The assessment of diabetic knowledge was performed using a test consisting of 20 questions. We considered tests passed with 60% correct answers (12 scores) as a good results and above 80% (16 scores) as an excellent result.

Moreover, all the participants completed a world standardized Diabetes Treatment Satisfaction Questionnaire (DTSQ) evaluating quality of life and satisfaction with treatment regiment. It consists of six questions assessing patients' attitude to diabetes and satisfaction with the method of treatment. The scores range from 0 (very dissatisfied) to 36 (very satisfied) [6].

Blood samples were collected in a fasting state after a period of rest with minimal occlusion of the vein using the S-Monovette blood collection system (Sarstedt, Aktiengesellschaft & Co, Numbrecht, Germany). Plasma glucose, total cholesterol, high density lipoproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol and triglycerides level, and C-peptide level were measured using standard methods. HbA_{1c} (glycated haemoglobin) was measured using high-performance liquid chromatography (HPLC) with Variant Hemoglobin A1c Program (Bio-Rad Laboratories, Hercules, CA, USA) (reference range 4.1-6.5%). Serum C-reactive protein (CRP) concentration was measured by a particle-enhanced immunoturbimetric assay (Olympus Diagnostica GmbH, Hamburg, Germany) using anti-CRP gout monoclonal antibodies coupled to latex microparticles with a lower limit of detection of 0.03 mg/l.

Microangiopathy outcomes

Screening for diabetic retinopathy was performed once a year by two experienced ophthalmologists

Table I. Baseline clinical characteristic of patients with and without diabetic retinopathy and with positive and negative microalbuminuria

Parameters	Retinopathy		Microalbuminuria	
	Yes (n=17)	No (n=69)	Yes (n=13)	No (n=73)
Sex [F/M]	5/12	26/43	3/10	28/45
Age [years]	24.3±5.0	23.2±5.0	23.7±5.1	23.4±5.0
Family history of diabetes n [%]	4 (23)	21 (30)	5 (38)	22 (30)
Smoking n [%]	5 (29)	21 (30)	5 (38)	23 (31)
Higher education n [%]	4 (23)	24 (35)	**2 (15)***	**26 (36)**
Self control [number/day]	3.0±1.0	3.0±1.1	2.5±0.9	3.1±1.1
Hypoglycaemic episodes/month	4.0±4.9	3.9±4.0	2.4±2.3	4.0±4.2
Knowledge [scores]	**12.5±3.6***	**14.2±3.3**	**12.6±2.9***	**14.1±3.5**
DTSQ [scores]	27.1±4.7	29.7±4.4	26.8±6.2	29.9±4.1
C-peptide >0.5 ng/ml n [%]	6 (35)	23 (33)	**6 (46)***	**24 (33)**
BMI [kg/m^2]	23.5±3.4	23.2±3.0	**25.5±3.6***	**22.8±2.8**
FPG [mmol/l]	11.0±3.7	9.7±3.4	11.1±2.3	9.9±3.7
2hPPG [mmol/l]	9.9±1.7	9.7±2.3	10.8±1.8	9.8±2.2
HbA_{1c} [%]	**8.8±1.4***	**7.8±1.7**	8.5±1.9	7.9±1.5
Cholesterol [mmol/l]	5.8±1.5	5.3±0.9	5.9±1.7	5.3±0.9
LDL [mmol/l]	**3.5±1.0***	**2.9±0.9**	**3.6±1.2***	**2.9±0.8**
HDL [mmol/l]	1.8±0.5	1.9±0.4	**1.6±0.3***	**1.9±0.3**
TAG [mmol/l]	1.2±0.6	1.1±0.6	**1.6±1.1***	**1.0±0.4**
SBP [mm Hg]	125.1±16.8	123.7±16.0	122.4±11.5	125.4±16.6
DBP [mm Hg]	76.1±7.4	76.9±8.9	79.7±11.8	76.3±8.0
hsCRP [mg/l]	2.97±0.87	2.38±0.38	**4.04±1.07***	**1.89±0.38**

Data are the mean ± SD or n (%), Mann-Whitney test and Fisher's exact test
**p<0.05 patients with background retinopathy or positive microalbuminuria vs. subjects without complications*

using direct ophthalmoscopy through dilated pupils followed, if necessary, by fluorescent angiography. Retinal photography was taken of each eye using a Fundus Camera VISUSCAM (Zeiss, Germany). After mydriasis with Tropicamide 1%, two 45° photographs, macular and nasal, were taken of each eye. Retinopathy was classified according to the American Academy of Ophthalmology as: mild non-proliferative, moderate non-proliferative, severe non-proliferative, or proliferative diabetic retinopathy.

Assessment of microalbuminuria was performed once a year by measurement of the albumin-to-creatinine ratio in a random spot collection and urinary albumin excretion over 24 hours. Persistent microalbuminuria was defined as a urinary albumin excretion rate between 30 and 300 mg/24 hours and albumin-to-creatinine ratio above 30 mg/g in two of three samples collected during 3 months.

Neuropathy assessment was performed using pressure sensation (10 g monofilament perception), vibration perception (128-Hz tuning fork) and ankle reflex tests.

Statistical analysis

All data are expressed as means ± SD or percentage of patients. Mann-Whitney test (continuous variables) and Fisher's test (categorical variables) were used to assess differences between groups with and without diabetic complications. The logistic regression model was used to estimate the relative risk (RR) (95% CI) for diabetic retinopathy and microalbuminuria events. Differences with a probability value <0.05 were considered statistically significant.

Results

We followed 86 of a total of 100 patients newly diagnosed with type 1 diabetes between 1994 and 1999. Mean age was 23.4±5.1 years.

During a mean follow-up of seven years, we detected mild non-proliferative retinopathy in 17 subjects (20%) and positive microalbuminuria in 13 patients (15%). Five patients had both retinopathy and positive microalbuminuria.

Table II. Clinical data patients with and without diabetic retinopathy and with positive and negative microalbuminuria after seven years of observation

Parameters	Retinopathy		Microalbuminuria	
	Yes (n=17)	No (n=69)	Yes (n=13)	No (n=73)
Self control [number/day]	3.9±1.7	3.8±1.4	3.6±1.6	4.1±1.3
Hypoglycaemic episodes/month	5.8±7.1	6.0±5.7	5.3±6.0	6.2±6.3
Knowledge [scores]	**12.2±3.4***	**14.2±3.1**	**12.3±3.6***	**14.8±2.3**
DTSQ [scores]	24.7±6.7	28.1±4.5	26.0±6.01	27.9±4.8
BMI [kg/m^2]	24.1±3.8	23.8±2.9	24.1±3.6	23.7±2.9
FPG [mmol/l]	8.8±1.3	8.4±2.5	**9.8±2.4***	**7.9±2.0**
2hPPG [mmol/l]	**16.6±2.6***	**9.4±1.6**	**10.7±0.6***	**9.3±1.7**
HbA_{1c} [%]	**9.2±2.1***	**7.9±1.2**	**9.1±2.2***	**7.8±1.0**
Cholesterol [mmol/l]	5.2±0.9	4.9±0.9	5.3±1.1	4.9±0.9
LDL [mmol/l]	3.3±0.9	2.9±0.7	3.2±0.9	2.9±0.7
HDL [mmol/l]	1.6±0.3	1.6±0.3	1.6±0.3	1.6±0.3
TAG [mmol/l]	0.9±0.3	1.0±0.5	1.2±0.5	1.0±0.6
SBP [mm Hg]	124.9±13.7	122.9±17.9	120.8±19.4	124.8±15.7
DBP [mm Hg]	82.6±5.9	77.7±10.9	79.7±11.8	78.6±9.9
hsCRP [mg/l]	3.01±1.29	2.16±0.51	**4.78±1.47***	**1.39±0.24**

Means ± SD, Mann-Whitney test
**p<0.05 patients with vs. without retinopathy or microalbuminuria*

At baseline, patients with and without microangiopathy were similar for age, sex, smoking status, hypoglycaemia episodes, fasting and postprandial glycaemia, total cholesterol level and blood pressure. At baseline knowledge about diabetes was significantly lower in patients who developed retinopathy as well as microalbuminuria. Subjects who developed retinopathy had higher HbA_{1c} and serum LDL cholesterol concentration. Moreover, patients who developed persistent microalbuminuria had markedly higher C-peptide level, body mass index (BMI), serum hsCRP concentration, LDL cholesterol and triglyceride level and simultaneously lower HDL cholesterol level (Table I).

During follow-up patients with diabetic retinopathy compared to subjects without retinopathy had higher values of HbA_{1c} (9.2±2.1 vs. 7.9±1.2%, P=0.02), lower scores in the diabetic test (12.2±3.4 vs. 14.2±3.1 scores, P=0.03) and markedly higher 2h-postprandial glycaemia (16.6±2.6 vs. 9.4±1.6 mmol/l, P=0.01). Subjects with positive microalbuminuria had higher values of: fasting plasma glucose (9.8±2.4 vs. 7.9±2.0 mmol/l, P=0.01), 2h-postprandial glycaemia (10.7±2.2 vs. 9.3±1.7 mmol/l, P=0.02) and HbA_{1c} (9.1±2.2 vs. 7.8±1.0%, P=0.03) and had lower level of diabetic knowledge (12.3±3.6 vs. 14.8±2.3 scores, P=0.02) than patients without microalbuminuria. Subjects with positive microalbuminuria also had higher levels of hsCRP (4.78±1.47 vs. 1.39±0.24 mg/l, P=0.01) (Table II).

In the prospective observation of study group the risk of retinopathy was associated with low level of patients' education (RR=4.06, 95% CI: 1.26-13.11, P=0.01), low level of diabetic knowledge (RR=3.71, 95% CI: 1.15-12.01, P=0.02), infrequent self-monitoring of blood glucose (RR=5.50, 95% CI: 2.00-15.11, P=0.0003), high values of systolic blood pressure (SBP) (RR=3.43, 95% CI: 1.31-9.01, P=0.01) and diastolic blood pressure (DBP) (RR=7.42, 95% CI: 2.11-26.15, P=0.002) and low HDL cholesterol level (RR=3.06, 95% CI: 1.36-6.87, P=0.01) (Table III).

In the prospective observation of the study group the risk of development of microalbuminuria was associated with low level of diabetic knowledge (RR=4.33, 95% CI: 0.98-19.10, P=0.04), bad self-monitoring of glucose (RR=2.86, 95% CI: 1.13-7.24, P=0.04), higher values of 2h-postprandial glycaemia (RR=10.66, 95% CI: 1.49-7.61, P=0.001), overweight (RR=2.99, 95% CI: 1.10-8.10, P=0.04), higher values of DBP (RR=10.62, 95% CI: 3.32-33.96, P=0.0001), low HDL cholesterol level (RR=4.85, 95% CI: 1.95-12.00, P=0.002) and high triglyceride level (RR=4.52, 95% CI: 1.97-10.33, P=0.01) (Table III).

Discussion

There are inconsistent data concerning the incidence of microangiopathy in type 1 diabetic patients with a short history of the disease. Krolewski et al. noticed that diabetic nephropathy develops in 0.5% of subjects a year in the first 10 years of the disease [7]. We demonstrate that 20% of type 1 diabetic subjects treated with intensive insulin therapy from the onset of the disease developed

Table III. Association of baseline parameters with the risk of developing retinopathy and microalbuminuria among patients with type 1 diabetes treated with IFIT from the onset of the disease. Relative risk (95% CI)

Parameters	Retinopathy		Microalbuminuria	
	Relative risk [95% CI]	p	Relative risk [95% CI]	p
Family history of diabetes				
no	1.0		1.0	
yes	1.17 (0.49-2.83)	0.77	1.90 (0.69-5.24)	0.28
Smoker				
no	1.0		1.0	
yes	1.13 (0.47-2.71)	0.77	1.34 (0.49-3.60)	0.74
Outpatient diabetic clinic				
yes	1.0		1.0	
no	1.25 (0.54-2.89)	0.78	1.50 (0.57-3.95)	0.52
Education				
higher	**1.0**		1.0	
other	**4.06 (1.26-13.11)**	**0.01**	2.75 (0.66-11.35)	0.19
Diabetic knowledge				
>16 scores	**1.0**		**1.0**	
<12 scores	**3.71 (1.15-12.01)**	**0.02**	**4.33 (0.98-19.10)**	**0.04**
Self-control				
≥3 times/day	**1.0**		**1.0**	
<3 times/day	**5.50 (2.00-15.11)**	**0.0003**	**2.86 (1.13-7.24)**	**0.04**
Hypoglycaemia				
no	1.0		1.0	
yes	1.02 (0.43-2.38)	1.00	1.91 (0.72-5.05)	0.21
C-peptide				
positive	1.0		1.24 (0.47-3.28)	
negative	1.13 (0.37-3.45)	1.00	1.0	0.75
BMI				
<25 kg/m^2	1.0		**1.0**	
≥25 kg/m^2	1.47 (0.64-3.39)	0.40	**2.99 (1.10-8.10)**	**0.04**
FPG				
<6.1 mmol/l	1.0		1.0	
≥6.1 mmol/l	1.54 (0.23-10.08)	1.00	1.18 (0.18-7.58)	1.00
PPG				
<10 mmol/l	1.0		**1.0**	
≥10 mmol/l	2.29 (0.89-5.86)	0.06	**10.66 (1.49-7.61)**	**0.001**
HbA_{1c}				
<6.5%	1.0		1.0	
≥6.5%	1.35 (0.21-8.52)	1.00	2.89 (0.41-20.28)	0.43
LDL cholesterol				
<2.6 mmol/l	1.0		1.0	
≥2.6 mmol/l	1.53 (0.58-4.02)	0.55	2.39 (0.58-9.82)	0.31
HDL cholesterol				
≥1.6 mmol/l	**1.0**		**1.0**	
<1.6 mmol/l	**3.06 (1.36-6.87)**	**0.01**	**4.85 (1.95-12.00)**	**0.002**
Triglycerides				
<1.7 mmol/l	1.0		**1.0**	
≥1.7 mmol/l	2.40 (0.51-11.37)	0.24	**4.52 (1.97-10.33)**	**0.01**
Systolic blood pressure (SBP)				
<130 mm Hg	**1.0**		1.0	
≥130 mm Hg	**3.43 (1.31-9.01)**	**0.01**	1.83 (0.70-4.79)	0.31
Diastolic blood pressure (DBP)				
<80 mm Hg	**1.0**		**1.0**	
≥80 mm Hg	**7.42 (2.11-26.15)**	**0.002**	**10.62 (3.32-33.96)**	**0.0001**
hsCRP				
<1 mg/l	1.0		1.0	
>3 mg/l	1.05 (0.38-2.87)	1.00	2.92 (0.62-13.69)	0.19

early stages of diabetic microangiopathy during 7 years of the disease. Similarly, Donaghue et al. noticed retinopathy in 24% and microalbuminuria in 18% of type 1 diabetic patients with the same mean duration of diabetes [8]. In the group of 300 type 1 diabetic subjects with a short duration of the disease in the EURODIAB trial the prevalence of microvascular disease was also 25% [9].

Our study was performed in type 1 diabetic patients treated with intensive functional insulin therapy implemented at the onset of the disease. However, our study shows that this method of treatment does not allow good metabolic control to be achieved and does not prevent the development of microangiopathy without patients' sufficient knowledge and self-monitoring. Despite the fact that this method of treatment was equally introduced at the beginning of the disease, the patients did not achieve the same results. Subjects with lower diabetic knowledge at baseline had nearly four times greater probability of developing microangiopathy.

Hyperglycaemia seems to remain the strongest risk factor for late diabetic complications [10]. In our study HbA_{1c} was higher in patients with retinopathy and microalbuminuria. Porta et al. demonstrated that HbA_{1c} is the strongest predictor of progression to proliferative diabetic retinopathy in type 1 diabetic subjects [11]. However, we did not find this parameter of metabolic control to be a risk factor for microangiopathy. This may be partially caused by the fact that HbA_{1c} reflects only the average level of glycaemia from the last three months, whereas large fluctuations of glycaemia with high frequency of hypoglycaemia was found to generate more reactive oxygen species (ROS) and induce a greater increase in the activity of protein kinase C (PKC) than did a stable hyperglycaemia [12]. Therefore, additional risk factors are sought to better predict the development of diabetic vascular complications.

We have found that systolic (SBP) and diastolic (DBP) blood pressure as well as low HDL cholesterol at baseline are associated with the development of microangiopathy. All these variables are components of the insulin resistance syndrome that is involved in the pathogenesis of vascular complications of diabetes. Earlier studies have shown that type 1 diabetic patients with microvascular complications are more insulin resistant than subjects without vascular changes [13]. Ekstrand et al. confirmed, using a euglycaemic insulin clamp, that impaired glucose disposal precedes microalbuminuria in type 1 diabetes [14]. The EURODIAB trial revealed an association between albuminuria and plasma lipids in a large cohort of type 1 diabetic patients [15]. However, this association was also apparent among subjects with duration of diabetes exceeding 5 years. The results are consistent with the EURODIAB trial, which found diastolic blood pressure to be a risk factor for progression of retinopathy [11]. A similar association was also observed by Klein et al. in the Wisconsin Epidemiological Study of Diabetes Retinopathy (WESDR) [16]. Diastolic blood pressure was also one of the strongest determinants of persistent microalbuminuria development in the observation of The Microalbuminuria Collaborative Study Group [17].

The mechanisms which may link insulin resistance and microvascular complications in type 1 diabetes are not fully clear. The most likely candidates linking components of insulin resistance with the development of vascular complications in type 1 diabetes could be endothelial dysfunction and inflammatory process. Adipocytes release proinflammatory cytokines, mostly IL-6 and TNF-α, which induce the production of acute phase proteins by the liver [18]. Recent data from the DCCT trial showed that the activity of the inflammatory process can be modulated by weight gain [19]. Moreover, levels of triglycerides and LDL cholesterol were strongly associated with inflammatory activity in the EURODIAB trial [20]. In fact, small dense LDL particles have pro-inflammatory and pro-oxidative properties and stimulate NF-κB. In contrast HDL molecules inhibit inflammatory cascade and reduce oxidative stress [21]. In a previous study we found that in long-standing type 1 diabetes higher levels of HDL cholesterol are associated with lower likelihood of diabetic retinopathy [22]. Moreover, overdose of exogenous insulin is conducive to weight gain and insulin resistance, and thus is associated with low grade inflammatory response.

The potential role of the inflammatory process in the pathogenesis of late diabetic complications was postulated in the late 1990s. However, this relationship was primarily described in the development of macroangiopathy and cardiovascular disease [23-25]. The EURODIAB trial confirmed the increased activity of the inflammatory process in type 1 diabetic subjects and its association with microangiopathy [20, 26].

Our results may be limited by the quite long recruitment time of the study group and not a very large number of patients. Lack of randomization (intensive vs. conventional insulin treatment) results from the ethical point of view, because the method of choice for type 1 diabetic patients is intensive functional insulin therapy. However, we would like to underline that this is a unique type 1 diabetes group where the rules of intensive insulin therapy were implemented at the onset of the disease.

In conclusions, the presented data show that the development of microangiopathy in type 1 diabetic patients treated with intensive functional insulin therapy from the onset of the disease was associated with low diabetic knowledge and signs of insulin resistance.

Acknowledgments

We thank dr Jaroslaw Krasnik and mgr Irena Fafara for collaboration. We are also grateful to Anna Kowalczyk for her assistance.

References

1. The effect of Intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977-86.
2. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999; 22: 99-111.
3. Berger M, Műhlhauser I. Implementation of intensified insulin therapy: a European perspective. Diabet Med 1995; 12: 201-8.
4. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002; 325: 746-9.
5. Műller UA, Femerling M, Reinauer KM, et al. Intensified treatment and education of type 1 diabetes as clinical routine. A nationwide quality-circle experience in Germany. ASD (the Working Group on Structured Diabetes Therapy of the German Diabetes Association). Diabetes Care 1999; 22 (Suppl 2): B29-B34.
6. Bradley C. Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice. Chur, Harwood Academic Publishers; 1994.
7. Krolewski AS, Warram JH, Christlieb AL, Busick EJ, Kahn CR. The changing natural history of nephropathy in type 1 diabetes. Am J Med 1985; 78: 785-94.
8. Donaghue KC, Craig ME, Chan AK, et al. Prevalence of diabetes complications 6 years after diagnosis in an incident of childhood diabetes. Diabet Med 2005; 22: 711-18.
9. Stephenson JM, Fuller JH. Microalbuminuria is not rare before 5 years of IDDM. EURODIAB IDDM Complications Study Group and the WHO Multinational Study of Vascular Disease in Diabetes Study Group. J Diabetes Complications 1994; 8: 166-73.
10. Zozulińska D, Wierusz-Wysocka B. Hyperglycaemia and Inflammation are culprits of late complications. Arch Med Sci 2005; 1: 115-8.
11. Porta M, Sjoelie AK, Chaturvedi N, et al. Risk factors for progression to proliferative diabetic retinopathy in the EURODIAB Prospective Complications Study. Diabetologia 2001; 44: 2203-9.
12. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? J Diabetes Complications 2005; 19: 178-81.
13. Yip J, Mattock MB, Morocutti A, Sethi M, Trevisan R, Viberti G. Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. Lancet 1993; 342: 883-7.
14. Ekstrand AV, Groop PH, Grönhagen-Riska C. Insulin resistance precedes microalbuminuria in patients with insulin-dependent diabetes mellitus. Nephrol Dial Transplant 1998; 13: 3079-83.
15. Chaturvedi N, Bandinelli S, Mangili R, Penno G, Rottiers R, Fuller JH. Microalbuminuria in type 1 diabetes: rates, risk factors and glycemic threshold. Kidney Int 2001; 60: 219-27.
16. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology 1998; 105: 1801-15.
17. Predictors of the development of microalbuminuria in patients with Type 1 diabetes mellitus: a seven-year prospective study. The Microalbuminuria Collaborative Study Group. Diabet Med 1999; 16: 918-25.
18. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005; 115: 1111-9.
19. Schaumberg DA, Glynn RJ, Jenkins AJ, et al. Effect of intensive glycemic control on levels of markers of inflammation in type 1 diabetes mellitus in the diabetes control and complications trial. Circulation 2005; 111: 2446-53.
20. Schram MT, Chaturvedi N, Schalkwijk CG, Fuller JH, Stehouwer CD. Markers of inflammation are cross-sectionally associated with microvascular complications and cardiovascular disease in type 1 diabetes – the EURODIAB Prospective Complications Study. Diabetologia 2005; 48: 370-8.
21. De Winther MP, Kanters E, Kraal G, Hofker MH. Nuclear factor kB signaling in atherogenesis. Arterioscler Thromb Vasc Biol 2005; 25: 904-14.
22. Wierusz-Wysocka B, Zozulinska DA, Araszkiewicz A, Pisarczyk-Wiza D. Higher levels of HDL cholesterol are associated with a decreased likelihood of albuminuria in patients with long-standing type 1 diabetes. Diabetes Care 2006; 29: 1176-7.
23. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med 1999; 340: 115-26.
24. Libby P, Ridker P, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105: 1135-43.
25. Lopes-Virella MF, Virella G. Immune mechanism of atherosclerosis in diabetes mellitus. Diabetes 1992; 41 (Suppl 2): 86-91.
26. Schram MT, Chaturvedi N, Schalkwijk C, et al. Vascular risk factors and markers of endothelial function as determinants of inflammatory markers in type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetes Care 2003; 26: 2165-73.