Original paper

High knowledge about diabetes decreases the likelihood of retinopathy in type 1 diabetic patients treated with intensive insulin therapy from the onset of the disease

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Abstract

Introduction: The aim of the study was to evaluate type 1 diabetic patients treated with intensive functional insulin therapy from the onset of the disease.
Material and methods: 100 patients aged under 30 with newly diagnosed type 1 diabetes, educated in intensive insulin therapy at baseline were recruited to this single-centre clinical trial. At follow-up (5.2±1.5 years) the participants underwent a test concerning their knowledge about diabetes (20 questions). According to test results the patients were divided into three groups: group A (<11 scores), group B (11-17 scores) and group C (>17 scores). The relationship between the patients' knowledge and metabolic control, hsC-reactive protein and late diabetic complications was assessed.
Results: At follow-up fasting plasma glucose 7.2±3.4 mmol/l, 2 hour postprandial plasma glucose 9.4±3.6 mmol/l, HbA1c 7.5±1.4%. In the knowledge test 20% reached <11, 62% 11-17 and 18% >17 scores (mean 14.4±3.2 scores). The hsCRP level was 4.94±1.53 mg/l. We observed statistically significant differences in hsCRP concentrations between the high and low levels of knowledge groups. The level of patients' knowledge significantly negatively correlated with hsCRP and HbA1c ($r=-0.41$, $p<0.05$ and $r=-0.31$, $p<0.05$). Background retinopathy and positive microalbuminuria were detected in 8 (9%) and 9 (10%) subjects, respectively. The risk of retinopathy was connected only with low knowledge (OR 5.67; 95% CI: 2.02-15.82, $p<0.0002$).
Conclusions: Our study confirms intensive insulin therapy and patients' knowledge about diabetes as a possibly beneficial treatment regimen in reducing the incidence of vascular complications in type 1 diabetes.

Key words: type 1 diabetes, education, C-reactive protein, late diabetic complications.

Introduction

The Diabetes Control and Complications Trial (DCCT) and its follow up Epidemiology of Diabetes Interventions and Complications (EDIC) study have demonstrated that improvement of metabolic control reduces the risk of development and progression of late diabetic complications [1, 2]. However, the intensive approach used in those trials was associated with an increased risk of hypoglycaemic episodes [1]. This might result from the lack of any structured teaching program involved in these studies. The works of the Department of Metabolic Disease and Nutrition in Düsseldorf as well as the results of DAFNE (Dose Adjustment for Normal Eating) study group have revealed the benefits of the training program in intensive insulin therapy in

producing sustained improvements of glycaemic control and quality of life without increasing the risk of hypoglycaemia [3, 4]. The intensive functional insulin therapy (IFIT) was originally defined as a systemic therapeutic program consisting of intensified insulin substitution. This program based on multiple daily insulin injections, including once or twice-daily NPH insulin, long acting insulin analog 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 program provided the skills to adapt regular insulin doses according to the blood glucose level before main meals, physical activity and amounts of carbohydrate intake planned. Today, intensive insulin therapy seems to be the point in the care of type 1 diabetic patients. The safety and efficacy of this method of treatment in maintaining near normal glycaemia have been proved in several prospective studies [3]. However, it becomes more evident nowadays that intensive insulin therapy demands a comprehensive and repeated educational program, patients' knowledge of self-management and involvement in the treatment.

Improvement of diabetic metabolic control achieved from the implementation of IFIT, is closely related to the patomechanisms of late diabetic complications. Hyperglycaemia is recognized as one of the most important mechanisms leading to endothelial dysfunction and development of vascular diabetic complications. All the consequences of a higher glucose level, including nonenzymatic glycation, formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC) and nuclear factor κ-B (NFκ-B), have been shown to result in enhanced leukocytes adhesion and aggregation, increased oxidative stress and release of cytokines, such as interleukin-1, tumor necrosis factor-α and interleukin-6. Recent data reveal the important role of low-grade inflammatory process in the development of diabetes and its late complications [6].

In response to these cytokines, predominantly interleukin-6, C-reactive protein (CRP) is synthesized by the liver. It is regarded as a sensitive acute-phase protein and is commonly used as a marker of inflammation. The predictive association between CRP and coronary artery disease has been extensively confirmed. CRP has been shown to predict myocardial infarction, stroke and the peripheral artery disease among individuals with the cardiovascular disease as well as in apparently healthy general population [7, 8]. It has emerged as one of the most important markers of atherosclerosis. Moreover, recent studies suggest that CRP may be actively involved in lesion formation through inducing endothelial dysfunction and leukocyte activation [9, 10]. Increased CRP concentrations have been also demonstrated to correlate significantly with features of the metabolic syndrome, including insulin sensitivity, triglycerides, obesity, blood pressure, fasting glycaemia, microalbuminuria and impaired fibrinolysis. Recent studies identified elevated CRP levels as a predictor of the development of type 2 diabetes [11, 12]. In comparison with type 2 diabetes, the studies of CRP and risk factors for late diabetic complications in type 1 diabetic subjects have been few and small. Two large-scale prospective studies DCCT and EURODIAB widely assessed the association between the metabolic state and inflammatory markers, and the risk of late diabetic complications. However, both these studies included patients with history of diabetes at baseline (mean duration of diabetes at baseline in DCCT and EURODIAB was respectively 2.6 and 15 years) [1, 13].

The aim of the study was to evaluate the group of type 1 diabetic patients after a mean of five years of treatment with intensive functional insulin therapy. All the patients were educated for this method of treatment at the onset of the disease. They were taught to match insulin doses to their food choice, physical activity and glycaemia, in order to keep their blood glucose level close to normal. We estimate the relationship between the level of patients' knowledge about diabetes and parameters of metabolic control, serum CRP, C-peptide concentration and the presence of late diabetic complications.

Material and methods

We recruited 100 consecutive patients aged under 30 with newly diagnosed type 1 diabetes, hospitalized due to diabetic ketoacidosis (DKA) at the Department of Internal Medicine and Diabetes in Poznań between 1994-1999. After cure DKA and stabilization of the metabolic state all the patients started the treatment in IFIT. They attended a five day structured training program during hospitalization performed by a skilled educational team. The patients obtained practical skills concerning blood glucose monitoring, calculating the amount of carbohydrates (carbohydrate exchangers) in the meal and self-adjustment of the insulin dose. During the course general information about pathogenesis of diabetes, acute and chronic diabetic complications, physical activity, characteristics of insulin and glucagon was also provided.

Twelve patients with acute or latent inflammatory focuses, liver dysfunction, connective tissue disease, renal failure and other severe diseases were excluded from the study.

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

Baseline clinical characteristics of the study group one month after the diagnosis of diabetes is presented in Table I. The prospective assessment of the study group was done every one year.

The mean follow-up of this study was 5.2±1.5 years. At follow-up the participants completed a standardized questionnaire including sex, age,

Table I. Clinical characteristics of the study group at baseline and after follow-up. Means ±SD

	Type 1 diabetic patients		
	At baseline	Follow-up	p
n	88	88	–
Sex (women/men)	33/55	33/55	–
Age (years)	24.3±6.2	29.1±5.9	–
BMI (kg/m^2)	23.5±3.2	23.6±3.2	0.41
Total cholesterol (mmol/l)	4.9±1.2	5.1±1.8	0.38
HDL cholesterol (mmol/l)	1.2±0.3	1.1±0.4	0.06
LDL cholesterol (mmol/l)	2.9±0.8	3.1±1.7	0.32
Trigliceryde (mmol/l)	1.2±0.8	1.4±1.0	0.14
Systolic BP (mmHg)*	115.2±28.2	126.8±20.4	0.002
Diastolic BP (mmHg)	66.8±16.8	62.6±12.8	0.06
FPG (mmol/l)	7.3±2.4	7.2±3.4	0.82
PPG (mmol/l)	9.6±3.8	9.4±3.6	0.72
HbA1c (%)*	8.1±1.9	7.5±1.4	0.02

**p<0.05*
BMI – body mass index; Systolic BP – systolic blood pressure; Diastolic BP – diastolic blood pressure; FPG – fasting plasma glucose; PPG – postprandial plasma glucose

education, medical history, duration of diabetes, smoking status, frequency of hypoglycaemic episodes and blood glucose monitoring. They also underwent a test concerning their knowledge about diabetes and rules of intensive insulin therapy, consisting of 20 questions. We considered the test positive with the result of 55% good answers (11 scores) and above 85% (17 scores) as an excellent result. According to these results, the patients were divided into three groups: group A (<11 scores), group B (11-17 scores) and group C (>17 scores). Moreover, all the participants completed a world standardized Diabetes Treatment Satisfaction Questionnaire (DTSQ) evaluating the 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) [14].

Retinopathy was assessed by two experienced ophthalmologists using direct ophthalmoscopy through dilated pupils followed if necessary by fluorescein angiography. Pictures of the eye fundus were collected. Retinopathy was classified as: background, non-proliferative, proliferative retinopathy and maculopathy. Urine samples were collected from the patients to determine the value of albumin excretion. Positive microalbuminuria was defined as urinary albumin excretion between 30 and 300 mg/24 h in two of three samples.

Laboratory methods. Blood samples were collected in a fasting state after a period of rest with minimal occlusion of the vein. Blood was collected using Vacutainer tubes. Plasma was stored at less than -20°C until assayed no longer than 3 months. Plasma glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides level and C-peptide level were measured using standard methods and HbA1c by using a high performance liquid chromatography. Serum CRP concentration was measured by a highly sensitive microparticle enzyme immunoassay. The test sensitivity was 0.03 mg/l.

Statistical analysis

All data are expressed as means ±SD or percentage of patients. Two-tail p-value t-test was used to compare continuous variables at baseline and after 5 years of follow-up. The analysis of variances (ANOVA) and Tukey-Kramer multiple comparison test (continuous variables) and Fisher's test (categorical variables) were used to assess differences between the groups. Correlations between the level of knowledge and continuous variables were calculated using Pearson's correlation coefficients test. The logistic regression model was used to estimate the OR (95%CI) for diabetic retinopathy and microalbuminuria events. Differences with a probability value <0.05 were considered statistically significant.

Results

After five years follow-up of the study group 19% of the subjects had a persistent function of beta cells (mean C-peptide 0.9±0.4 ng/ml). Mean fasting plasma glucose (FPG) was 7.2±3.4 mmol/l, 2 hour postprandial plasma glucose (PPG) 9.4±3.6 mmol/l and mean HbA1c 7.5±1.4%. The number of hypoglycaemic episodes was 6/individual/month but we did not observe any severe hypoglycaemia.

Table II. Differences between type 1 diabetic patients according to their level of knowledge. Group A (<11 scores the test), group B (11-17 scores), group C (>17 scores). Means ±SD

	Group A	Group B	Group C
n	17	55	16
Sex (women/men)	6/11	22/33	5/11
Age (years)	29.2±1.8	25.2±0.7	26.4±1.8
BMI (kg/m^2)	24.5±3.0	23.0±2.9	23.5±3.5
Smoking (%)	36	26	10
Duration of diabetes (years)	4.6±1.4	5.1±1.7	5.1±1.0
Diabetic diary (%)	73	45	60
Measuremets of glycaemia (n/day)	3.1±1.2	3.8±1.9	4.5±1.6
HbA1c (%)	8.6±1.8	7.5±1.3	6.9±0.9*
hsCRP (mg/l)	13.88±18.64	3.63±8.26	0.50±0.36*
C-peptide (ng/ml)	0.12±0.39	0.75±0.38	0.13±0.41
hypoglycaemia (n/individual/month)	6.3±8.8	6.7±6.3	6.3±5.9
Background retinopathy (n)	2	6	0
Microalbuminuria (n)	3	5	1

**p<0.05 group C vs group A*
hsCRP – high sensitivity C-reactive protein; BMI – body mass index

We noticed that only 68% of the patients controlled glycaemia regularly before main meals and 53% of subjects kept a diabetic diary.

In the test checking patients' knowledge about diabetes and the method of intensive functional insulin therapy 20% of the subjects reached <11, 62% 11-17 and 18% >17 scores (mean 14.4±3.2 scores of maximal 20 to achieve). All the patients were pleased with intensive insulin therapy as a method of treatment (mean 28.1±4.9 of maximal 36 scores in DTSQ).

The serum level of hsC-reactive protein was 4.94±1.53 mg/l. We observed statistically significant differences in hsCRP concentrations between the high and low levels of knowledge groups (Table II). Additionally, the level of patients' knowledge about diabetes significantly negatively correlated with hsCRP and HbA1c (respectively, r=-0.41, p<0.05 and r=-0.31, p<0.05) (Table III).

Background retinopathy was detected in 8 (9%) subjects and 9 (10%) patients had positive microalbuminuria. The risk of retinopathy was connected only with low knowledge about diabetes (OR 5.67; 95% CI: 2.02-15.82, p<0.0002).

Table III. Correlations between the level of knowledge concerning diabetes and HbA1c level, hsCRP concentration, C-peptide level, duration of diabetes, blood glucose monitoring, hypoglycaemic episodes, BMI, expressed as Pearson correlation coefficients (r)

	The level of patients' knowledge	
	r	p
HbA1c*	-0.31	0.02
hsCRP*	-0.41	0.002
C-peptide (n=9)	-0.29	0.43
Hypoglycaemic episodes	0.04	0.72
Duration of diabetes	0.24	0.07
Blood glucose monitoring	0.23	0.07
BMI	-0.08	0.58

**p<0.05*
hsCRP – high sensitivity C-reactive protein; BMI – body mass index

Discussion

Intensive functional therapy is a recommendable method of treatment of type 1 diabetes. Studies such as DCCT and DAFNE have shown that IFIT improves the metabolic control and prognosis of late diabetic complications in patients with an ongoing history of diabetes [1, 4]. Our study was performed in type 1 diabetic patients treated with intensive functional insulin therapy implemented at the onset of the disease. According to the obtained results, the method of IFIT seems to be convenient for newly diagnosed type 1 diabetic patients. Moreover, the findings are consistent with works of many authors implicating the role of this method of treatment in improving patients' metabolic control and quality of life. However, our study shows that intensive functional insulin therapy does not allow achieving these benefits without patients' self-control and sufficient knowledge. 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. The positive correlation

between patients' knowledge and HbA1c provide strong evidence that only a well educated patient may achieve good metabolic control without a higher risk of hypoglycaemia.

Moreover, the study reveals for the first time a relationship between the diabetic knowledge and C-reactive protein, reflecting the inflammatory process. This fact seems to be obvious, considering the role of a structured training program in maintaining good metabolic control as well as a possible association between the abnormal glucose level and CRP. The follow-up of our patients was relatively short to show directly the influence of diabetic knowledge on the occurrence of microangiopathy. It has been shown, however, that the mechanisms leading to chronic low-grade inflammation in diabetes could be related to hyperglycaemia and its consequences. Rodriguez et al. reveal an association between CRP levels and hyperglycaemia suggesting that higher glucose levels increase oxidative stress resulting in inflammation and dysfunction of endothelium [15]. C-reactive protein has been recently regarded as a marker as well as a mediator of inflammatory reactions. The mechanisms indicating an involvement of C-reactive protein in the interaction between endothelial and inflammatory cells has been revealed by a number of authors in patients with atherosclerosis. Those patients included subjects with coronary heart disease and type 2 diabetes mellitus [16-18]. Increased levels of CRP were found also by Kilpatrick et al. in type 1 diabetic patients with the overt coronary heart disease (CHD). They indicate age, sex, family history of CHD, BMI and HbA1c as independently associated with CRP concentrations [19]. However, the role of C-reactive protein in the pathogenesis of microangiopathy in type 1 diabetic patients still remains uncertain. Elevated concentrations of hsCRP demonstrated in our work are consistent with other studies, which additionally reveal the correlation between CRP and markers of vascular dysfunction [20, 21]. EURODIAB Prospective Complications Study showed increased levels of CRP as well as other inflammatory markers in type 1 diabetic patients with vascular complications [13, 22]. Similarly, in the EUCLID study – a 2-year prospective trial, C-reactive protein and fibrinogen were associated with albumin excretion rates and retinopathy status [23]. In the light of these facts, it might indicate that inflammatory process and endothelial dysfunction are the potential mechanisms of late diabetic complications. 60 years ago, Professor Joslin said that the higher knowledge about diabetes the longer life of people with diabetes. The results of our study seem to support his words.

Conclusion

Our study reveals a crucial role of teaching program and patients' knowledge about diabetes in maintaining good metabolic control. Moreover, it indicates intensive insulin therapy, based upon a structured training of the patients, as a possibly beneficial treatment regimen in reducing the incidence of vascular complications in type 1 diabetic patients.

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