Does early insulin treatment decrease the risk of microangiopathy in non-obese adults with diabetes?

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Submitted: 21 March 2007
Accepted: 23 May 2007

Arch Med Sci 2007; 3, 2: 129-135

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Abstract

Introduction: In the clinical practice classification of diabetes type in adult patients is often difficult. In non-obese adults distinguishing between Latent Autoimmune Diabetes in the Adult and type 2 diabetes leads to introduction of different treatment strategies. The aim of the present study was to assess relationship between introduction of insulin therapy at the diagnosis and occurrence of chronic microangiopathic complications of diabetes in non-obese patients aged above 35 years.
Material and methods: The group of 71 non-obese patients (BMI <30 kg/m^2) with diabetes diagnosed after the age of 35 was estimated. At diagnosis 24 patients were treated with insulin (group A) and 47 patients with oral hypoglycaemics (group B).
Results: No significant differences in presence of microangiopathic complications were noted between the groups after 6 years of duration of diabetes. In the multivariate logistic regression analysis, risk factors for the development of any type of diabetic microangiopathy were: longer duration of diabetes (RR 1.12, 95%CI: 1.00-1.27, p=0.04), higher HbA1c value (RR 2.00, 95%CI: 1.21-3.31), and higher BMI (RR 1.25, 95%CI: 0.99-0.25, p=0.048). Moreover the risk factors for microangiopathy were: CRP concentration (RR 1.36, 95%CI: 1.03-1.80, p=0.025) and smoking status (RR 4.37, 95%CI: 1.33-14.44, p=0.013).
Conclusions: Initial insulin therapy in non-obese patients with diabetes diagnosed above the age of 35, after 6 years of duration of diabetes, does not decrease significantly the risk of micro and macroangiopathic complications. Main risk factors for development of microangiopathic complications are: longer duration of diabetes, worse metabolic control of diabetes, higher body mass index, higher C-reactive protein (CRP) level and smoking.

Key words: Latent Autoimmune Diabetes in the Adults, microangiopathy, treatment of diabetes.

Introduction

Distinction of patients who require insulin at diagnosis of diabetes and patients with type 2 diabetes remains difficult. There is a group of adult phenotypic type 2 diabetic patients among whom autoantibodies typical for type 1 diabetes can be found. This type of diabetes is classified as having Latent Autoimmune Diabetes in the Adults (LADA). The results of the recent studies report that prevalence of LADA is around 10-30% among patients classified as type 2 diabetic at diagnosis. The frequency of LADA increases even to 50% among non-obese patients. LADA occurs mostly among persons aged between 30 and 50 years. The progression of autoimmune β-cell failure tends to be slower than in classical type 1

diabetes. LADA patients present therefore relatively better metabolic control on oral hypoglycemic agents for at least 6 months after diagnosis of diabetes. However these patients require insulin much earlier than those with type 2 diabetes [1].

The diagnosis of LADA is based on detection of circulating islet autoantibodies, especially against glutamic acid decarboxylase (GADA) [2]. In clinical practice measurement of GADA is not widespread because of its cost and a proportion of LADA patients is misclassified as having type 2 diabetes. Distinguishing between autoimmune and type 2 diabetes is connected with treatment decisions. The Tokyo Study confirmed that early insulin treatment delays destruction of beta cells in LADA patients and maintains endogenous insulin secretion. This resulted in better metabolic control of diabetes [3, 4]. Proved impaired β-cell function at diagnosis of LADA supports the opinion that insulin therapy should be the initial treatment of choice. It is important to recognize that at the beginning of immunological diabetes ketoacidosis, polyuria, polydypsia and weight loss may not be present. Response to diet and oral hypoglycaemic agents is often good at diagnosis in LADA patients but this treatment strategy may lead more rapidly to clinical insulin dependency. The possibility of LADA should be considered among patients with normal BMI and relatively young age at diagnosis of diabetes or among patients with coincidence of other autoimmunological diseases. The presence of hypertension and hypercholesterolemia is lower in LADA patients than in type 2 diabetes as these patients have fewer features of metabolic syndrome [5-7].

Table I. Clinical characteristics of study group

N	71
Sex F/M	37/34
Age at the onset of diabetes (years)	46.0±7.1
Duration of diabetes (years)	6.4±5.3
FPG (mmol/l)	7.7±2.2
PPG (mmol/l)	10.2±2.7
Mean 24 h glycaemia (mmol/l)	8.3±2.0
HbA1c (%)	8.7±1.5
Total cholesterol (mmol/l)	5.4±1.0
HDL-cholesterol (mmol/l)	1.7±0.4
LDL-cholesterol (mmol/l)	3.3±0.9
Triglycerides (mmol/l)	3.4±2.4
BMI (kg/m^2)	24.1±3.1
Systolic blood pressure (mmHg)	127±14
Diastolic blood pressure (mmHg)	79±8
CRP (mg/dl)	2.47±2.93
C-peptide (ng/ml)	0.7±0.5
Insulin requirement (IU/kg/day)	0.5±0.2
Microangiopathy (n)	27
Retinopathy (n)	19
Nephropathy (n)	6
Neuropathy (n)	12
Macroangiopathy (n)	10

The goal of our study was to determine relationship between introduction of insulin therapy at diagnosis and occurrence of long-term microangiopathic complications in non-obese diabetic patients at age above 35 years.

Material and methods

The group of 85 non-obese patients (BMI <30 kg/m^2) with diabetes diagnosed after the age of 35 and hospitalised in the Department of Internal Medicine and Diabetes between January 2004 and March 2006 was evaluated. Patients with unknown treatment at diagnosis were excluded from the study. Finally 71 patients (37 women and 34 men) were included into analysis. Among evaluated patients 68 were initially diagnosed as having type 2 diabetes. Mean age at the onset of diabetes was 46±7 years, mean diabetes duration was 6.4±5.3 years, mean BMI was 24.1±3.1 kg/m^2.

Microangiopathic complications were present in 27 patients (retinopathy – 19, nefropathy – 6, neuropathy – 12 patients), macroangiopathic complications were present in 10 patients. Positive family history for type 1 or 2 diabetes was registered in 32 patients. Autoimmunological disorders were coexisting in 15 patients. 22 patients smoked cigarettes. 9 patients suffered from hypertension at diagnosis of diabetes, 36 patients were receiving hypotensive medication at hospitalisation.

At diagnosis 24 patients were treated with insulin (group A) and 47 patients with oral antyhyperglycemic agents [metformin and/or sulfonylurea derivatives (gliclazyde or glimepiryde)] (group B).

In group B mean time of treatment with oral antyhyperglycemic agents was 2,3±7 years. When evaluated all patients were treated with insulin. The basic characteristics of the investigated groups are shown in Tables I and II.

Microangiopathy was defined as presence of retinopathy (background retinopathy, pre-proliferative, maculopathy, proliferative diabetic retinopathy) and/or nephropathy and/or neuropathy. To detect and classify diabetic retinopathy direct ophtalmoscopy after pupil dilatation was performed by ophtalmologist. Nephropathy was diagnosed on the basis of albumin-to-creatinine ratio above 30 µg/mg in a random spot urine collection or albumin excretion larger than 30 mg/24 h in 24-hour urine collection. Two of three specimens collected within 3-6 months should be

Table II. Comparison of group of patients treated at diagnosis of diabetes with insulin (group A) and with oral hypoglycemic agents (group B). Mann-Whitney U test

Evaluated factors	Group A (n=24)	Group B (n=47)	p-value
Age at the onset of diabetes (years)	48.0±7.5	44.9±6.7	0.09
Duration of diabetes (years)	6.3±5.4	6.5±5.3	0.97
FPG (mmol/l)	7.1±1.9	7.5±2.3	0.18
PPG (mmol/l)	10.8±2.5	9.9±2.6	0.16
Mean 24 h glycaemia (mmol/l)	**8.8±1.5**	**8.0±2.2**	**0.01**
HbA1c (%)	8.8 ±1.5	8.6±1.6	0.46
Total cholesterol (mmol/l)	5.5±0.9	5.3±1.1	0.63
HDL-cholesterol (mmol/l)	1.6±4.2	1.5±0.4	0.13
LDL-cholesterol (mmol/l)	3.2±0.9	3.3±0.9	0.79
Triglycerides (mmol/l)	3.2±3.4	3.5±1.8	0.058
BMI (kg/m^2)	24.1±3.1	24.1±3.1	0.99
Systolic blood pressure (mmHg)	**122±11**	**129±15**	**0.03**
Diastolic blood pressure (mmHg)	**75±9**	**81±7**	**0.006**
CRP (mg/dl)	2.29±3.24	2.54±2,73	0.86
C-peptide (ng/ml)	0.6±0.4	0.7±0.5	0.77
Insulin requirement (IU/kg/day)	**0.6±0.2**	**0.4±0.2**	**0.015**
Microangiopathy (n)	7	20	1.00
Retinopathy (n)	4	15	0.772
Nephropathy (n)	2	4	0.640
Neuropathy (n)	3	9	1.00
Macroangiopathy (n)	5	10	0.519

abnormal, after exclusion of the states that may elevate urinary albumin excretion.

The diagnosis of distal sensory neuropathy was based on a symptom score and clinical examination. The clinical examination consisted of measurements of sensory perception by 10-g Semmes-Weinstein monofilament, vibration sensation (using a 128-Hz tuning fork) and Achilles tendon reflex.

Macroangiopathy was considered in subjects who met one of the following conditions: history and/or absence of angina and/or permanent ischemic electrocardiogram abnormalities at rest or ischemic abnormalities in a stress, claudication and/or abolished peripheral pulses and/or foot lesions due to vascular disease demonstrated by Doppler echography and history of stroke and/or significant carotid stenosis (>50%) as assessed by Doppler echography.

Fasting plasma glucose (FPG), postprandial plasma glucose (PPG), mean 24 hour glycaemia based on 7-point profile, glycated haemoglobin (HbA1c), body mass index (BMI), total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure, C-peptide level, daily insulin requirement (IU/kg/day), serum C-reactive protein (CRP) concentration were evaluated.

Statistical analyses were performed with Statistica, version 7.0 PL (StatSoft, Poland). Data were presented as means ±SD unless otherwise indicated. Significance of differences between groups was assessed with Mann-Whitney U test and Fisher's exact test for categorical variables. P value <0.05 was considered significant.

Results

Group of patients treated with insulin since the onset of diabetes (group A) in comparison with group initially treated with oral antihyperglycemic agents (group B) did not differ in age at the diagnosis of diabetes, duration of disease and HbA1c value. Higher systolic (129±15 vs. 122±11 mmHg, p=0.03) and diastolic blood pressure (81±7 vs. 75±9 mmHg, p=0.006) was observed in patients treated with oral antyhyperglycaemic agents at the onset. Higher serum triglyceride concentration was also noticed in this group (3.5±1.8 vs. 3.2±3.4, p=0.058). Patients initially treated with insulin had higher mean daily glycaemia (8.8±1.6 vs. 8.1±2.2 mmol/l, p=0.015) and higher daily insulin requirement (0.6±0.2 vs. 0.4±0.2 IU/kg/day, p=0.015) (Table II).

No signifficant differences in presence of micro-angiopathic complications (retinopathy, nephropathy

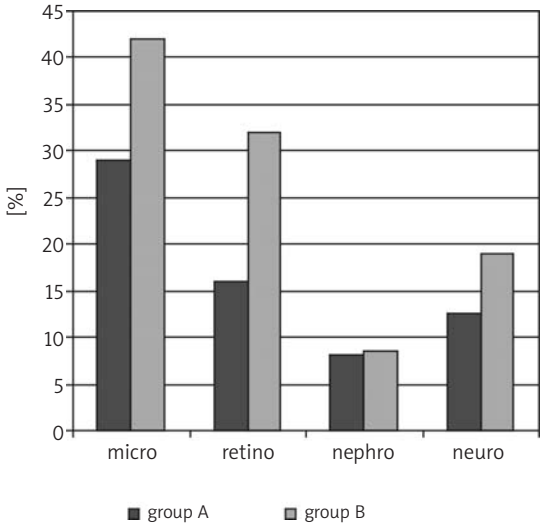

Figure 1. Presence of any microangiopathy, retinopathy, nephropathy and neuropathy in patients treated at diagnosis of diabetes with insulin (group A) and with oral hypoglycemic agents (group B)

and neuropathy) were noted in both groups after 6 years of duration of diabetes (Figure 1). The time of treatment with oral hypoglycemic agents did not influence the risk of microangiopathy among patients that were not treated with insulin from the beginning of diabetes.

In the multivariate logistic regression analysis, risk factors for the development of any type of diabetic microangiopathy and for the development of retinopathy alone were: longer duration of diabetes (respectively RR 1.12, 95%CI: 1.00-1.27, p=0.04 and RR 1.16, 95%CI: 1.02-1.31, p=0.019), higher HbA1c value (respectively RR 2.00, 95%CI: 1.21-3.31, p=0.006 and RR 1.81, 95%CI: 1.03-3.18, p=0.03), and higher BMI (respectively RR 1.25, 95%CI: 0.99-0.25, p=0.048 and RR 1.31, 95%CI: 1.01-1.72, p=0.04). The multivariate logistic regression model included duration of diabetes, HbA1c value, BMI, gender and insulin treatment from the onset of diabetes. Moreover the risk factor for microangiopathy were: CRP concentration (RR 1.36, 95%CI: 1.03-1.80, p=0.025) and smoking status (RR 4.37, 95%CI: 1.33-14.44, p=0.013) (Tables III-IV).

Table III. The relative risk of any microangiopathy adjusted for the duration of diabetes [RR(95%CI)]

Evaluated factors	RR (95%CI)	p
Sex (female)	0.78 (0.27-2.23)	0.639
Age at the onset of diabetes (years)	0.98 (0.9-1.06)	0.567
FPG (mmol/l)	1.01 (0.99-1.02)	0.353
PPG (mmol/l)	1.00 (0.99-1.01)	0.895
Mean 24 h glycaemia (mmol/l)	1.01 (1.00-1.03)	0.101
HbA1c (%)	**2.00 (1.21-3.31)**	**0.006**
Total cholesterol (mmol/l)	1.00 (0.99-1.01)	0.893
HDL-cholesterol (mmol/l)	0.97 (0.93-1.01)	0.102
LDL-cholesterol (mmol/l)	1.00 (0.99-1.02)	0.914
Triglycerides (mmol/l)	1.00 (0.99-1.00)	0.500
BMI (kg/m²)	**1.25 (0.99-0.25)**	**0.048**
Systolic blood pressure [mmHg]	1.00 (0.96-1.03)	0.832
Diastolic blood pressure [mmHg]	1.00 (0.94-1.07)	0.883
Presence of hypertension at diagnosis of diabetes	4.59 (0.84-24.95)	0.072
Current presence of hypertension	2.19 (0.75-6.39)	0.144
CRP (mg/dl)	**1.36 (1.03-1.80)**	**0.025**
C-peptide (ng/ml)	1.87 (0.37-9.04)	0.436
Insulin requirement (IU/kg/day)	12.68 (0.71-226.37)	0.079
Insulinotherapy at diagnosis	0.54 (0.17-1.68)	0.280
Duration of treatment with oral hypoglycemic agents (years)	0.96 (0.77-1.20)	0.717
Family history of diabetes	1.88 (0.61-5.77)	0.262
Smoking	**4.37 (1.33-14.44)**	**0.013**

Table IV. The relative risk of retinopathy in after adjustment for duration of diabetes [RR(95%CI)]

Evaluated factors	RR (95%CI)	p
Sex (female)	0.70 (0.21-2.30)	0.546
Age at the onset of diabetes (years)	0.99 (0.91-1.09)	0.899
FPG [mmol/l]	1.01 (0.99-1.02)	0.453
PPG [mmol/l]	1.00 (0.99-1.01)	0.997
Mean 24 h glycaemia [mmol/l]	1.00 (0.99-1.02)	0.655
HbA1c [%]	**1.81 (1.03-3.18)**	**0.03**
Total cholesterol [mmol/l]	1.00 (0.98-1.01)	0.650
HDL-cholesterol [mmol/l]	0.99 (0.95-1.03)	0.670
LDL-cholesterol [mg/dl]	1.00 (0.98-1.02)	0.886
Triglycerides [mmol/l]	0.99 (0.98-1.00)	0.107
BMI [kg/m²]	**1.31 (1.01-1.72)**	**0.04**
Systolic blood pressure [mmHg]	0.99 (0.94-1.03)	0.517
Diastolic blood pressure [mmHg]	1.02 (0.95-1.10)	0.608
Hypertension at diagnosis	5.24 (0.81-33.97)	0.076
Current presence of hypertension	1.92 (0.57-6.49)	0.286
CRP [mg/dl]	1.19 (0.95-1.49)	0.129
C-peptide (ng/ml)	1.76 (0.25-12.41)	0.552
Insulin requirement (IU/kg/day)	4.52 (0.21-99.74)	0.330
Insulin treatment at diagnosis of diabetes	0.40 (0.10- 1.59)	0.185
Duration of treatment with oral hypoglycemic agents [years]	0.99 (0.79-1.25)	0.964
Family history of diabetes	2.95 (0.77-11.30)	0.107
Smoking	3.56 (0.95-13.41)	0.055

Discussion

In clinical practice many doubts often occur in classification of diabetes among adults newly diagnosed patients. Distinguishing between LADA and type 2 diabetes is of value. There is almost no data that assess development of chronic complications of diabetes in LADA patients. In our study we tried to find the connection between the way of treatment from the beginning of the disease and occurrence of microangiopathic complications in non-obese patients with diabetes diagnosed after the age of 35. Our findings indicate possibility of such relationship. However, we did not find significant differences in occurrence of chronic complications after 6 years of duration of diabetes.

The main reason of increased death and disability rate among diabetic patients are chronic complications of this disease. Hyperglycaemia is the essential risk factor for developing macro- and microangiopathy. In *Diabetes Control and Complications Trial* (DCCT) and its follow up *Epidemiology of Diabetes Interventions and Complications Study* (EDIC), it has been shown, that better metabolic control of diabetes results in decreased risk of prevalence of retinopathy, nephropathy and neuropathy among patients with type 1 diabetes [8, 9]. This has been also confirmed among patients with type 2 diabetes mellitus in *United Kingdom Prospective Diabetes Study* (UKPDS). This study indicated that reduction of HbA1c by 1% results in microvascular risk reduction by 37% [10]. Results of *EURODIAB Prospective Complication Study* indicated that hypertension, high level of triglycerides and higher waist to hip ratio significantly increase the risk of progression of retinopathy and nephropathy [11]. UKPDS has reported that each 10 mmHg decrease in updated mean systolic blood pressure was associated with 13% risk reduction for microvascular complications [12].

It is now believed that LADA patients should be treated with insulin from the diagnoses of diabetes. Previous analyses report, that early insulin treatment among this group of patients assure better metabolic control. However, there is no unequivocal data about treatment of this type of diabetes in medical literature. Pozzilli et al. have suggested, that LADA patients can be treated with oral hypoglycemic agents at the beginning of diabetes if good metabolic control is achieved [13]. By contrast Szepietowska et al. have affirmed that

the treatment with insulin at the onset of immunological diabetes in adults is of special clinical benefits. Early treatment of these patients with insulin may improve their quality of life, potentially saving β-cell function and perhaps diminishing the risk of microvascular complications [14]. It was shown in the study of Arikan et al. that among patients first considered as type 2 diabetes these with GADA positive subgroup more frequently developed nephropathy and retinopathy [15]. Fremantle Diabetes Study has proved that patients who were GADA-positive had double the prevalence of retinopathy than those who were GADA-negative. It is important to notice that the GADA positive group has worse metabolic control than group without autoantibodies. In the logistic regression model, diabetes duration, HbA1c, systolic blood pressure and current smoking are each significantly and independently predictive of retinopathy, but GADA status is not [16]. In Botnia study, patients with LADA have similar presence of retinopathy to those with type 2 diabetes, with similar glycaemic control in both groups [17].

In our study metabolic control of diabetes in both evaluated groups (from the onset of diabetes treated with insulin or with oral hypoglycemic agents) was not satisfactory (mean HbA1c 8.6%) and average 24 hour glycaemia was significantly higher in the group treated with insulin from the onset of diabetes. Poor glycaemic control was an important factor contributing to prevalence of microangiopathy among patients evaluated in our study. Microangiopathy was significantly associated with longer duration of diabetes, increased body mass index, higher serum CRP concentration and current history of smoking. In a group treated with oral hypoglycemic agents from the onset of diabetes we showed higher systolic and diastolic blood pressure and higher triglycerides level that are considered to be risk factors for micro- and macroangiopathy.

Elevated blood pressure in patient initially treated with oral antihyperglycemic agents could be related with more prevalence to cardiovascular complications in this group, even now it is not clinically detected. It is also known that presence of microangiopathic complications of diabetes, especially the nephropathy, is connected with the increased ratio of hypertension. Latest research has indicated that a great percentage of LADA patients demonstrate insulin resistance as well as they may be at significant risk of consequences of insulin resistance such as development of hypertension. LADA patients without features of metabolic syndrome were rather similar to classical type 1 diabetes with tendency to ketosis and impaired islet function [19, 20]. On the other hand the effect of the treatment with oral antihyperglycemic agents on the cardiovascular system have to be discussed. Not surprisingly, treatment with metformin by profitable influence on insulin resistance has been reported to decrease the blood pressure [21]. Sulfonylureas stimulate insulin secretion by blocking ATP-sensitive K (ATP) potassium channels and binding to the sulfonylurea receptor (SUR1) subunit of the channel in the pancreatic β-cell membrane. K(ATP) channels are also present in other tissues but contain different types of SUR subunits (e.g., SUR2A in heart and SUR2B in smooth muscle). The sensitivity and reversibility of these different types of K(ATP) channels to sulfonylureas is variable. Glibenclamide blocks all channel with similar affinity and is poor reversible on cardiac channels. In contrast gliclazyde block the β-cell, but has very low affinity to the cardiac and smooth muscle types of channels. Glimepiryde has powerful affinity to SUR1 and SUR2 receptors but reversible and short-time effect. Blocking of the K(ATP) channels may have vasoconstrictor effect [22]. Peuler et al. have suggested the possibility to increase the blood pressure by some sulfonylureas such as gliburide [23]. In our study patients mostly used new generation of sulfonylureas in the past with little effect into cardiovascular system. Their contribution to development of cardiovascular complication of diabetes is not confirmed.

We did not prove benefits of early insulin treatment in non-obese diabetic patients after 6 years since diagnosis of diabetes. This suggests that when there are no clinical indications for insulin treatment and C-peptide level is relatively high, therapy with oral hypoglycemic agents can be started. When treatment with oral hypoglycemic agents is not successful, insulin therapy should be introduced. We are plannig prospective assessment of chronic complications development in patients with LADA confirmed serologically and treated with insulin from the beginning of the disease.

Conclusions

1. Treatment with insulin at diagnosis of diabetes in non-obese adults after the age of 35 does not decrease the risk of diabetic microangiopathy after 6 years of duration of diabetes.
2. The main risk factors for development of microangiopathic complications in non-obese adult diabetic patients are: longer duration of diabetes, worse metabolic control of diabetes, higher body mass index, higher C-reactive protein level and smoking.

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