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Risk Factors for Microvascular Atherosclerotic Changes in Patients with Type 2 Diabetes Mellitus

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A B S T R A C T

Diabetes mellitus is a metabolic disorder primarily characterized by elevated blood glucose levels and by microvascular and macrovascular complications which increase the morbidity and mortality. The aim of this study was to assess whether in high risk patients with type 2 diabetes mellitus whose blood pressure and lipid levels are well controlled still exist risk factors for microvascular changes and target organ damage (nephropathy and retinopathy). In this case control retrospective study 326 patients (111 with nephropathy and/or retinopathy and 215 controls) were enrolled. Nephropathy or retinopathy was present in 10.1% and 26.9% cases, respectively. Only 71% of patients (no significant difference between cases and controls) were treated with antidiabetic drugs. Therefore their diabetes was not properly controlled (hemoglobin A1c was 7.96% in cases and 7.58% in controls). Patients with microvascular changes had significantly longer diabetes than the controls (p < 0.05) but there were no significant differences between these two groups concerning lipids concentrations. Statins and fibrates were used by significantly less (p < 0.05) patients with microvascular complications than by those without them (21.6% vs. 36.3% and 1.8% vs. 17.2% respectively). The results of this study suggest that the duration of the disease and adequate control of glycaemia in patients with type 2 diabetes mellitus are more important for microvascular complications than the serum lipoproteins levels. Lipid-lowering treatment might have an impact on microvascular complications in patients with type 2 diabetes, irrespectively of their serum lipid levels.

Key words: *cardiovascular risk, type 2 diabetes mellitus, cholesterol, LDL-cholesterol, HDL-cholesterol, statins, fibrates*

Introduction

Diabetes is a metabolic disorder primarily characterized by elevated blood glucose levels and by microvascular and macrovascular complications. These complications increase the morbidity and mortality associated with the disease and reduces substantially the quality of life.

Cardiovascular disease (CVD) are the most important cause of death in Croatia and worldwide[1]. It is also the major cause of death in patients with type 2 diabetes mellitus because more than 60 % of patients with type 2 diabetes die from myocardial infarction or stroke[2].

On the other hand, diabetes mellitus and dyslipidaemia are, together with hypertension, smoking and obesity, the most important risk factors for coronary heart disease (CHD) and myocardial infarction (MI) as well as cerebrovascular disease[3–6]. An association between the complications of diabetes and elevated blood glucose levels was postulated many decades ago and revaluated in the follow up studies[7–9].

However, observational epidemiologic data published in the last three decades suggest that not only lower blood glucose levels, but even more, lower blood pressure and lower serum lipids might be associated with a lower incidence of micro- and macrovascular complications in patients with diabetes.

The United Kingdom prospective Study (UKPDS) was the first large intervention study which provided the evidence that tight glucose control could be effective in reducing the risk of major microvascular endpoints in patients with type 2 diabetes but the effects on CVD risk (macrovascular endpoints) were modest and did not reach the statistical significance[8]. Recently, three major trials, the Veterans Affairs Diabetes trial (VADT)[10], the Action to Control Cardiovascular risk in Diabetes (ACCORD)[11], and the Action in Diabetes and vascular Disease (AD-VANCE)[12] evaluated the impact of attaining good blood glucose control in older patients with diabetes and high cardiovascular risk and reported no significant decrease in primary cardiovascular endpoints with intensive glucose control.

Nevertheless, large observational studies show that both elevated triglycerides (either fasting or non-fasting) and reduced plasma levels of high-density lipoprotein cholesterol (HDL-C) are associated with increased cardiovascular risk, even at or below recommended low-density lipoprotein cholesterol (LDL-C) levels[13–16]. In patients with type 2 diabetes mellitus already the UKPDS study has identified decreased HDL-C as the second most important coronary risk factor, after elevated LDL-C[8].

Much more recently, it has been established that dyslipidaemia is important not only for macrovascular changes, but also in the pathogenesis of diabetic microvascular disease[17]. Elevated levels of total cholesterol as well as LDL-C are associated with the increased risk for proliferative diabetic retinopathy, and elevated levels of TG appear to be associated with progression of albuminuria[18].

The aim of this study was to assess whether in high CVD risk patients with type 2 diabetes mellitus whose blood pressure and lipid levels are well controlled still exist risk factors that might precipitate microvascular changes and target organ damage, particularly nephropathy and retinopathy.

Methods

The study was a case-control retrospective study and it was conducted in University Hospital Center Zagreb.

Patients population and inclusion criteria

Cases and controls were high risk patients (dyslipidemia + arterial hypertension ± target organ damage as defined bellow) with type 2 diabetes, and with optimal blood pressure (BP) control (defined as BP ≤140/90 mmHg) as well as with LDL-C less than 3.4 mmol/L. Arterial hypertension was defined as BP before the treatment ≥ 140/90 mmHg or usage of antihypertensive drugs. Blood pressure was measured according to recent guidelines[19]. Cases were patients with diabetes mellitus type 2 and at least one recorded microvascular complication (nephropathy, retinopathy, diabetic macular edema).

Controls were patients with type 2 diabetes mellitus with no documented evidence of any microvascular complications.

Case definitions

Nephropathy was defined as proteinuria >300 mg/L, albuminuria, or estimated glomerular filtration rate <60 ml/min/1.73[2]. Albuminuria was measured and defined as > 30 mg/24 h in a 24-hour urine. A low glomerular filtration rate was estimated by the MDRD formula. Serum creatinine level was detected by colorimetric Jaffe method.

Retinopathy was defined as laser treatment for diabetic retinopathy or Diabetic Retinopathy Disease Severity Scale 3,4 or 5 shown by dilated ophthalmoscopy; or maculopathy defined as moderate or severe using Diabetic Macular Edema Disease Severity Scale.

Measurements

All data were obtained from reviews of medical records. The lipid values were from blood taken in the fasting state. Total cholesterol, HDL-C, LDL-C (measured directly or calculated) and triglycerides were assayed within the 6 months prior to the date of the index visit. Data obtained included age, sex, duration of diabetes, body weight, height, ethnicity, history of hypertension, blood pressure, current medical treatment, medications, smoking, cardiovascular diseases, fasting blood glucose, and hemoglobin A_{1c}.

Statistical analysis

Data are expressed as means ± standard deviation (SD). All data were analyzed by two-way ANOVA or the Student's t-test as appropriate. A p value less than 0.05 was considered to be statistically significant.

Results

A total of 326 patients were enrolled who matched inclusion criteria. Among them 111 cases were matched by gender and age to 215 controls. Nephropathy was present in 33 cases and retinopathy in 88 cases (10.1% and 26.9% respectively). Characteristics of the cases and controls are shown in Table 1.

Surprisingly only about 71% patients with type 2 diabetes, (no significant difference between cases and controls), were treated with antidiabetic drugs. This is the reason why their diabetes was not satisfactory regulated, with mean hemoglobin A1c 7.96% for cases and 7.58% for controls (7.71% overall).

As expected, 78.4% cases and 63.3% controls had arterial hypertension which was well controlled (BP<140/90 mmHg) in all of them.

Patients with microvascular diabetes complications had significantly longer (p<0.05) diabetes than the controls but there were no significant differences between these two groups concerning their lipids concentrations.

TABLE 1
DESCRIPTIVE STATISTICS OF SUBJECTS INCLUDED IN THE STUDY

	N	Cases 111	Controls 215
Demographics	Males [N, (%)]	62 (55.9%)	111 (51.6%)
Lipids	Age,years (mean, SD)	66.59 (8.95)	62.09 (10.56)
	*Diabetes duration, years (mean, SD)	14.29 (9.03)	5.25 (5.48)
	Total cholesterol (mmol/L)	5.07 (1.28)	4.68 (1.11)
	LDL-cholesterol (mmol/L)	2.74 (0.62)	2.46 (0.79)
	HDL-cholesterol (mmol/L)	1.25 (0.36)	1.26 (0.41)
	Triglycerides (mmol/L)	1.98 (1.13)	2.08 (1.49)
*Hemoglobin A1C		7.96% (1.41%)	7.58% (1.52%)
Medication	*Fibrate use [N, (%)]	2 (1.8%)	37 (17.21%)
	*Statin use [N, (%)]	24 (21.62%)	78 (36.28%)
	antidiabetic drugs use [N, (%)]	79 (71.17%)	154 (71.63%)
Clinical condition	Nephropathy [N, (%)]	33 (29.73%)	0
	Retinopathy [N, (%)]	88 (79.28%)	0
	Hypertension [N, (%)]	87 (78.38%)	136 (63.26%)

* significantly different between groups

Statins and fibrates were used by significantly less (p<0.05) patients with microvascular complications than those without them (21.6% vs. 36.3% and 1.8% vs. 17.2% respectively).

Discussion

Our results suggest that adequate control of glycaemia in patients with type 2 diabetes mellitus is more important for microvascular complications than the serum lipoproteins levels. Microvascular complications of diabetes remain the leading causes of blindness and renal failure in the developed world and it seems that they are much more closely associated with hyperglycemia than macrovascular complications[20].

Intensive glucose control in the ADVANCE study which included 11140 patients with type 2 diabetes showed a reduction in the development of new or worsening of existing nephropathy and modest, but significant reduction in new-onset microalbuminuria. However, no significant benefit on retinopathy could be proven[21]. The UKPDS, one of largest studies of glycaemia control in patients with type 2 diabetes, has shown that tighter glucose control did not reduce the incidence of major renal outcomes, but has found evidence of a reduction in the development of microalbuminuria and overt proteinuria after a prolonged follow-up period[21]. A clear reduction in nephropathy demonstrated in the ADVANCE trial is important, because indexes of renal impairment are strongly associated with the future risk of major vascular events, end-stage renal disease, and death in patients with diabetes[22].

Intensive glycaemia therapy significantly reduced the risk of progression of diabetic retinopathy in the AC-CORD Eye study[23]. ACCORD eye study provides evidence that the beneficial effect of intensive glycaemia therapy on retinopathy progression, in patients with type 2 diabetes that was newly diagnosed or not yet accompanied by hypertension, lipid abnormalities, or established CVD, applies also to patients with type 2 diabetes with characteristics similar to those enrolled in the ACCORD trial, who were older and at greater cardiovascular risk[24–26]. The ACCORD trial demonstrated that fenofibrate, when added to statin therapy, slows the progression of diabetic retinopathy in patients with type 2 diabetes.

Atherogenic dyslipidaemia, characterized by elevated triglycerides and low levels of HDL-C, is very common in patients with type 2 diabetes mellitus and metabolic syndrome and is associated with macrovascular and microvascular complications[16, 27]. It has been shown that such dyslipidaemia might play an important role in the pathogenesis of diabetic microvascular disease[28]. High levels of triglycerides seem to be associated with an increased risk for proliferative diabetic retinopathy and elevated levels of total cholesterol as well as LDL-C may be associated with the development of retinal hard exudates and diabetic maculopathy[23, 29–31]. The severity of retinopathy was positively associated with the levels of serum triglycerides, but negatively associated with HDL-C in the Diabetes Control and complications Trial/ Epidemiology of Diabetes Interventions and complications Study[32].

Many epidemiological studies have found an association between elevated levels of triglycerides and progression of albuminuria, a first marker of diabetic nephropathy[33, 34]. However, the association between HDL-C levels and nephropathy has been less clear. Some of the published data suggest that higher HDL-C levels may be protective against nephropathy[35].

Our patients were high risk patients having several cardiovascular risk factors. Most of them were almost optimally regulated concerning their serum lipid levels and blood pressure value but their glucose regulation was insufficient. Therefore their target organ damage presented here as microvascular complications (nephropathy and retinopathy) are most probably related to their relatively poor glycemic control. Also, much less of them were treated with statins and fibrates than the controls suggesting that lipid-lowering treatment might have an impact on microvascular complications of type 2 diabetes irrespectively of the serum lipid levels. So far, the effect of statin therapy on diabetic retinopathy has been inconclusive. The Collaborative Atorvastatin Diabetes Study (CARDS) showed no significant benefit on the progression of diabetic retinopathy with atorvastatin, but other small studies have shown a reduction in the severity of macular exudates associated with statin therapy[36, 37]. Beneficial effect of lipid-lowering treatment was demonstrated in experimental models but also in some clinical studies[38]. FIELDS study suggested that fibrates have beneficial effects on the development of microvascular complications (nephropathy and especially retinopathy) in patients with diabetes, particularly on the requirement for first laser treatment and macular oedema. In a recent review, Kouroumichakis and colleagues summarised the data from experimental and clinical studies on the emerging therapeutic potential of fibrates in diabetic nephropathy[39]. Fibrates like statins may act to decrease the progression of diabetic microvascular complications not only through their lipid-lowering effects, but even more via their pleiotropic effects.

In general, data indicate that atherogenic lipid profile (low HDL-C, elevated triglycerides) could not be directly associated so far to diabetic nephropathy or retinopathy. LDL-C levels of our patients were in recommended range for high risk diabetic patients[40].

Our study has some potential limitations. It was performed on a relatively small number of hospitalized patients. The influence of other drugs on the results which the patients were receiving (eg. RAS blockade) cannot be excluded.

Conclusion

The results of this study suggest that the duration of diabetes and adequate control of glycaemia in patients with type 2 diabetes mellitus are more important for microvascular complications than the serum lipoproteins levels. The obtained results also indicate that lipid-lowering treatment might have an impact on microvascular complications in patients with type 2 diabetes irrespectively of the serum lipid levels.

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ČIMBENICI RIZIKA ZA MIKROVASKULARNE ATEROSKELROTSKE PROMJENE U BOLESNIKA SA ŠEĆENOM BOLESTI TIPA 2

SAŽETAK

Šećerna bolest obilježena je povišenim razinama glukoze u krvi te razvitkom mikrovaskularnih i makrovaskularnih komplikacija koje su uzrok povećanom morbiditetu i mortalitetu. Cilj je ovog istraživanja bio istražiti da li u visoko rizičnih bolesnika sa tipom 2 šećerne bolesti i dobro kontroliranim arterijskim tlakom i lipidima u serumu postoje rizični čimbenici koji mogu biti uzrokom mikrovaskularnih promjena i posljedičnog oštećenja ciljnih organa, posebno nefropatije i retinopatije. U ovo "case-control" retrospektivno ispitivanje uključili smo sveukupno 326 ispitanika (111 sa nefropatilom i/ili retinopatijom i 215 bolesnika bez tih komplikacija – kontrolna skupina). 10,1% ispitanika imalo je nefropatiju, a 26.9% imalo je retinopatiju. Samo 71% ispitanika (bez značajne razlike među skupinama) bilo je liječeno antidijabeticima. Stoga ne čudi da im je regulacija glukoze u krvi bila nedostatna (hemoglobin A1c bio je 7.96% u bolesnika sa nefro/retinopatijom, a 7.58% u onih kontrolne skupine). Bolesnici s mikrovaskularnim komplikacijama u usporedbi s onima iz kontrolne skupine rjeđe su koristili statine (21.6% vs. 36.3%) i fibrate (1.8% vs. 17.2%). Bolesnici sa mikrovaskularnim promjenama bolovali su od dijabetesa značajno dulje nego oni iz kontrolne skupine (p < 0.05) ali nije bilo razlike u koncentracijama lipida između te dvije skupine. Rezultati našeg istraživanja ukazuju da su u bolesnika sa tipom 2 šećerne bolesti za razvitak mikrovaskularnih komplikacija važniji trajanje bolesti i odgovarajuća kontrola glikemije nego li koncentracije lipoproteina u serumu. Primjena lijekova za snižavanje lipida u krvi može imati učinak na mikrovaskularne komplikacije u bolesnika sa šećernom bolešću tipa 2 neovisno o koncentracijama lipida u serumu.