SUMMARY

The aim of the study was to investigate whether obesity, independently or associated with other risk factors, increases the risk for diabetic retinopathy, nephropathy and neuropathy in type 2 diabetic persons. Data of 156 diabetic persons that had consecutively attended the Outpatient Department during a two-month period were studied. According to body mass index (BMI) they were divided into three groups: group 1 (BMI ≤ 25; n=49), group 2 (BMI 26-29.9; n=52), and group 3 (BMI ≥ 30; n=55). The three groups did not differ according to age, duration of diabetes, treatment, cholesterol, HDL-cholesterol and triglycerides. A significant deterioration of HbA1c and significant increase in LDL-cholesterol, and systolic and diastolic blood pressure were observed with the increase in BMI. The prevalence of retinopathy increased significantly with higher body weight (p<0.05) alone as well as in combination metabolic control (HbA1c) and systolic blood pressure. The prevalence of nephropathy and polyneuropathy correlated significantly and independently with body weight (p<0.01). Therefore, obesity alone or in combination with quality of metabolic control (HbA1c), systolic and diastolic blood pressure, and LDL-cholesterol was demonstrated to be a risk factor for microvascular and neuropathic complications in diabetes.

INTRODUCTION

Diabetes is a common disease that is associated with high mortality and morbidity from macrovascular and microvascular complications (1,2). Whereas macrovascular complications, particularly cardiovascular diseases, substantially reduce the life expectancy of diabetics in all age groups, microvascular complications lead to blindness, renal failure and amputation, which require expensive health care resources. As the diagnosis of type 2 diabetes is usually preceded by years of undiagnosed hyperglycemia (3), at the time of first diagnosis 8% of patients already have cardiovascular disease, 37% have microaneurysms or more severe retinopathy in one eye, 18% have retinopathy in both eyes, 18% have microalbuminuria (4), and 2.3% and 15.2% have polyneuropathy defined by clinical signs and according to electrophysiological criteria, respectively (5).

The frequency of microvascular diabetic complications is clearly correlated to the duration of diabetes, quality of metabolic control (HbA1c) and systolic blood pressure (6-8). Besides these risk factors, obesity, hyperlipidemia and insulin resistance have a considerable impact on the development and progression of macrovascular diabetic complications (9-11).
Only a few investigations have focused on the role of obesity in the development or progression of microvascular complications. However, it is known that obesity correlates with deterioration of metabolic control and a higher prevalence of hyperlipoproteinemia and hypertension (12-14), which are considered to be the risk factors for microvascular diabetic complications.

The aim of the present study was to investigate whether obesity alone or associated with other risk factors increases the risk of diabetic retinopathy, nephropathy and neuropathy in type 2 diabetic persons.

PATIENTS AND METHODS

The study was conducted at the Vuk Vrhovac Institute, University Clinic for Diabetes, Endocrinology and Metabolic Diseases in Zagreb. A total of 156 persons with type 2 diabetes that had consecutively attended the Outpatient Department during a two-month period were included. Their age ranged from 50 to 70 years, and diabetes duration from 10 to 15 years. They were on either oral hypoglycemic agent (OHA) therapy or insulin therapy. According to body mass index (BMI), they were divided into three groups: group 1 (BMI ≤ 25; n=49), group 2 (BMI 26-29.9; n=52), and group 3 (BMI ≥30; n=55).

The following biochemistry parameters were assessed: HbA1c, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and albumin. HbA1c was determined by an automated immunoturbidimetric assay (reference values 3.5 – 5.7%) (15). Cholesterol was measured by an enzymatic colorimetric test (reference value <5.18 mmol/l) (16), HDL-cholesterol by the method based on precipitation with polyethylene glycol (reference value >1.40 mmol/l) (17), and LDL-cholesterol by Friedwald method (reference value <3.37 mmol/l) (18). Triglycerides were determined by the colorimetric method with peroxidase (reference values M 0.45 - 1.81 mmol/l, F 0.40 - 1.53 mmol/l) (19), whereas turbidimetric immunoassay (reference value <30 mg/24 h) was used for albumin determination in 24-h urine (20).

Blood pressure was measured on every visit using an ambulatory sphygmomanometer and the mean of three measurements was calculated.

Each diabetic patient underwent funduscopy by a skilled ophthalmologist. The diagnosis of nephropathy was made when urinary albumin excretion exceeded 30 mg/24 h. Late neuropathic complications were assessed by standardized clinical tests for sensitivity and peripheral vibration sensation.

Data were analyzed by the Statistica for Windows software version 6.0. Values are reported as mean ± standard deviation. Relationship between the level of obesity and diabetic complications was analyzed using Pearson’s correlation. Comparison between groups was performed using ANOVA for continuous variables. Nominal scaled data were tested by use of $\chi^2$-test.

RESULTS

The study included 156 persons with type 2 diabetes (74 male and 82 female). The three groups divided according to BMI did not differ according to age, duration of diabetes and current therapy. Women had a significantly higher BMI than men (Table 1). After about 12 years of diabetes, at the age of ~62, retinopathy was present in 56.4%, nephropathy in 42.3% and neuropathy in 66.7% of the patients (Table 2). We documented a significant increase in each diabetic complication with higher body weight. While the prevalence of retinopathy increased significantly up to BMI of 26-29.9 kg/m², the prevalence of nephropathy increased significantly up to BMI of ≥30 kg/m². The prevalence of neuropathy increased continuously and significantly with body weight increase (Figure 1).

<table>
<thead>
<tr>
<th>Table 1. Basic characteristics of type 2 diabetics (N=156) divided into three groups according to body mass index (BMI)</th>
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<tbody>
<tr>
<td>BMI ≤ 25 (n=49)</td>
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<tr>
<td>Sex (M/F)*</td>
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<tr>
<td>Age (yrs)**</td>
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<tr>
<td>Diabetes duration (yrs)**</td>
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<td>Therapy (OHA / insulin)*</td>
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<td>* %; ** mean ±SD</td>
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To analyze other factors that influence the development of diabetic retinopathy, nephropathy and neuropathy, we classified metabolic and clinical parameters according to BMI (Table 3). With increasing obesity, we observed a significant deterioration of HbA1c and a significant increase in LDL-cholesterol, systolic and diastolic blood pressure. The other parameters were not influenced by BMI.

Statistical analysis showed the prevalence of retinopathy to increase significantly with higher body weight alone as well as in combination with quality of metabolic control (HbA1c) and systolic blood pressure. In contrast to this observation, the increase in the prevalence of nephropathy and polyneuropathy was significantly and independently related to body weight.

**DISCUSSION**

Type 2 diabetes is, because of its high incidence and high risk of microvascular and late neuropathic complications, one of the potentially most debilitating diseases. Diabetic eye disease and its complications, especially diabetic retinopathy that leads to macular edema and retinal neovascularization, are the leading cause of blindness and visual dysfunction in adults in economically developed societies (21,22). In the United States and western Europe, diabetic nephropathy is the leading cause of end-stage renal disease. Also, the 5-year survival of patients with diabetic nephropathy who are receiving dialytic therapy is less than one-half that of patients without diabetes mellitus (23,24). An important cause of sustained disability, prolonged hospital stay and invalid status in diabetic patients is also chronic foot ulceration that often leads to amputation, and is the result of peripheral somatic neuropathy, autonomic neuropathy and peripheral vascular disease (25).

Many epidemiological studies have already shown that the frequency of microvascular and neuropathic complications in diabetes is clearly correlated with the duration of diabetes, quality of metabolic control, and systolic blood pressure (6-8). As the onset of type 2 diabetes occurs at least 4 to 7 years before the clinical diagnosis and at the time of diagnosis many patients have already developed microvascular and neuropathic complications, the period of undiagnosed disease is considered to be even more harmful (3-5). Therefore

| Table 2. Microvascular and neuropathic complications in type 2 diabetics (N=156) divided into three groups according to body mass index (BMI) |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Total | BMI ≤ 25 | 26-29.9 | BMI ≥ 30 | p |
| Retinopathy (%) | 56.4 | 40.8 | 63.4 | 63.6 | <0.05 |
| Nephropathy (%)* | 42.3 | 26.5 | 34.6 | 63.8 | <0.01 |
| Neuropathy (%) | 66.7 | 44.9 | 67.3 | 85.5 | <0.01 |

* microalbuminuria >30 mg/24 h

| Table 3. Metabolic and clinical parameters of type 2 diabetics (N=156) divided into three groups according to body mass index (BMI); results are expressed as mean±SD |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| BMI ≤ 25 | 26-29.9 | BMI ≥ 30 | p |
| HbA1c (%) | 7.55±1.1 | 8.28±1.1 | 8.57±1.0 | <0.01 |
| Cholesterol (mmol/l) | 5.60±0.8 | 6.01±1.2 | 5.92±1.0 | NS |
| HDL-cholesterol (mmol/l) | 1.28±0.3 | 1.18±0.2 | 1.20±0.3 | NS |
| LDL-cholesterol (mmol/l) | 3.41±0.7 | 3.76±1.1 | 3.77±0.9 | <0.05 |
| Triglycerides (mmol/l) | 1.92±1.1 | 2.45±1.3 | 2.35±1.5 | NS |
| Systolic blood pressure (mm Hg) | 136.6±13.5 | 150.9±11.7 | 156.7±13.0 | <0.01 |
| Diastolic blood pressure (mm Hg) | 82.2±7.1 | 85.9±7.1 | 89.2±7.6 | <0.01 |

Figure 1. Diabetic complications in relation to BMI. A significant increase of retinopathy (p<0.05), nephropathy (p<0.01) and neuropathy (p<0.01) with obesity

**Figure 1. Diabetic complications in relation to BMI. A significant increase of retinopathy (p<0.05), nephropathy (p<0.01) and neuropathy (p<0.01) with obesity**
screening for diabetic late complications in type 2 diabetes is performed from the time of its diagnosis. Strict metabolic control in both type 1 and type 2 diabetes unequivocally and significantly delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy (4,26-28). Aggressive treatment of even mild-to-moderate hypertension also reduces significantly the risk of microvascular complications (29).

Besides these well-known risk factors, overweight and obesity are also very frequently found in type 2 diabetic patients. Obesity is a chronic, stigmatized disease, its incidence being increased by nearly 50% in the past decade (30,31). Overweight is commonly defined as a BMI 25-30 kg/m² and obesity as a BMI >30 kg/m². Obesity increases the risk of type 2 diabetes and its macrovascular complications, i.e. cardiovascular, cerebrovascular and peripheral vascular diseases, and reduces life expectancy in all age groups (9-11,32). An increase in BMI also correlated significantly with deterioration of HbA1c, decrease in HDL-cholesterol, increase in triglycerides, and higher prevalence of hypertension (12-14). As described previously, our evaluation also demonstrated a significant deterioration of HbA1c and significant increase in systolic and diastolic blood pressure with the increase in BMI, however, instead of typical characteristics of type 2 diabetes lipid disorders (12,33,34) we observed a significant increase in LDL-cholesterol with increasing obesity, whereas HDL-cholesterol and triglycerides were not influenced by BMI.

According to our evaluation, the prevalence of nephropathy and polyneuropathy was clearly and significantly related to BMI, whereas the prevalence of retinopathy increased significantly with higher body weight and also correlated with deteriorating HbA1c level and higher systolic blood pressure.

Other studies also support a correlation between obesity and diabetic microvascular and neuropathic complications in patients with type 2 diabetes (12,35-38). Some of these results and conclusions are different and contradictory, likely because microvascular and neuropathic complications in diabetes are not necessarily a direct result of obesity but a consequence of a multiplicity of other risk factors. The heterogeneity of diabetic complications of as yet unclear etiology and pathogenesis, and the multifactorial genetic and environmental influences such as obesity, complicate diabetic care management and demand more aggressive treatment as well as higher level of the patients’ understanding of both diabetes and obesity.

REFERENCES


