Impact of Overweight on Chronic Microvascular Complications in Type 1 Diabetic Patients

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OBJECTIVE — To investigate a possible association of BMI with retinopathy and neuropathy in type 1 diabetes. Retinopathy and neuropathy may not only be related to glycemic control and diabetes duration but also to blood pressure and BMI.

RESEARCH DESIGN AND METHODS — A total of 592 type 1 diabetic patients without nephropathy were studied (M/F: 324/268; age: 41 ± 12 years; duration: 19 ± 11 years; HbA_{1c} [A1C]: 7.9 ± 1.1%). Patients were subdivided according to BMI: 168 men and 146 women with BMI <25 kg/m^2, and 156 men and 122 women with BMI ≥25 kg/m^2. Retinopathy was examined by fundoscopy and neuropathy by electromyography.

RESULTS — Hypertension (>130/85 mmHg) was present in 40%, retinopathy in 53%, and neuropathy in 43% of patients. Overweight subjects had more retinopathy (63 vs. 45%, $P < 0.0001$, odds ratio [OR] = 2.1) and neuropathy (49 vs. 38%, $P = 0.008$, OR = 1.6) than normal-weight patients. Patients with retinopathy were older (45 ± 12 vs. 37 ± 11 years, $P < 0.0001$) and had a longer diabetes duration (25 ± 10 vs. 12 ± 8 years, $P < 0.0001$), a higher A1C (8.0 ± 1.1 vs. 7.7 ± 1.1%, $P = 0.001$), and a higher BMI (25.8 ± 4.1 vs. 24.7 ± 4.2 kg/m^2, $P = 0.001$) than individuals without retinopathy. The same results are found in neuropathy. Logistic regression analysis showed that diabetes duration ($\beta = 0.15$, $P < 0.0001$), blood pressure ($\beta = 0.22$, $P = 0.0047$), and A1C ($\beta = 0.24$, $P = 0.01$), but not BMI, lipid levels, sex, or age, were independent risk factors for retinopathy. Likewise, duration ($\beta = 0.05$, $P < 0.0001$), age ($\beta = 0.04$, $P = 0.0001$), A1C ($\beta = 0.35$, $P < 0.0001$), and sex ($\beta = 0.74$, $P = 0.0001$) but not BMI, lipid levels, or hypertension were independently associated with neuropathy. Men had more neuropathy than women (50 vs. 34%, $P < 0.0001$, OR = 1.9). Leptin and adiponectin levels did not differ between individuals with or without microvascular complications.

CONCLUSIONS — Retinopathy and neuropathy are more prevalent in overweight (BMI ≥25 kg/m^2) type 1 diabetic subjects. However, logistic regression analysis showed that diabetes duration and A1C remain the main determinants for retinopathy and neuropathy.

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Overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2) are becoming increasingly prevalent in the industrialized world (1), not only in type 2 but also in type 1 diabetic patients (2–4). Besides physical inactivity, intensive insulin therapy to obtain good metabolic control to reduce complications is associated with weight gain (4,5). The relationship between metabolic control and the development of chronic complications (retinopathy, neuropathy, and nephropathy) is a primary concern of clinicians. Factors involved in the development of vascular complications of diabetes include long diabetes duration, poor glycemic control, smoking, hypertension, and dyslipidemia, but the role of body weight/BMI is unclear.

Retinopathy may not only be related to glycemic control and diabetes duration but also to blood pressure and BMI for patients with type 2 diabetes, as was shown by the U.K. Prospective Diabetes Study and the Hoorn Study (6–8). However, information on the possible role of BMI on retinopathy in type 1 diabetes is scarce. Zhang et al. (9) revisited data from the Diabetes Control and Complications Trial and observed that besides diabetes duration and metabolic control, BMI had a significant predictive value in developing retinopathy. In Sweden, Henricsson et al. (10) observed that time to develop retinopathy was related to high HbA_{1c} (A1C) and high BMI. Only one recent report suggested a role of BMI in neuropathy (11). Adipocytokines, products from adipose tissue, have biological activities on the vascular system and may affect diabetic microangiopathy. Despite the abundance of studies on adipocytokines among type 2 diabetic patients or healthy individuals, there is only one study dealing with adiponectin and macrovascular complications in type 1 diabetes (12). Because overweight is becoming increasingly prevalent and can be managed by lifestyle intervention (nutrition, exercise, and education), it seems appropriate to study the impact of overweight, which may reduce the impact of good metabolic control, on diabetes complications.

This study aimed to assess the prevalence of being overweight in type 1 diabetes and to examine relationships between BMI, glycemic control, microvascular risk factors, and retinopathy and neuropathy. Moreover, in a subgroup of 130 type 1 diabetic patients, we assessed the relationship between overweight and plasma adipocytokine levels (leptin and adi-

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ponectin) and a possible association with the degree of diabetic retinopathy and neuropathy.

RESEARCH DESIGN AND METHODS

— A group of 620 type 1 diabetic patients was studied (age at onset <40 years), but 28 subjects with major cardiovascular disease, amputation, creatinine >1.5 mg/dl, or diseases (e.g., dysthyroidism) or drugs influencing BMI were excluded. All patients fulfilled the criteria of type 1 diabetes (13). Patients were subdivided according to BMI: 168 normal-weight men (BMI <25 kg/m^2), 146 normal-weight women, 156 overweight men, and 122 overweight women. The study was approved by the University Hospital of Antwerp Ethics Committee. Informed consent was obtained in accordance with the Helsinki Declaration.

Weight was measured using a balance-beam scale, and height was measured using a wall-mounted stadiometer with patients in their underwear and without shoes. Blood pressure was taken with a standardized method (Dynamap) after a 10-min rest, and a mean of four measurements was used. Hypertension was defined as blood pressure >130/85 mmHg (14) or active antihypertensive medication intake by the patient. A1C was determined by high-performance liquid chromatography (Variant Hemoglobin A1c; Bio-Rad; normal range 4.8–6%). A mean of four annual determinations of A1C was used to assess overall metabolic control. Plasma lipid levels were determined after a 12-h overnight fast. Cholesterol and triglycerides were measured using a Boehringer Mannheim kit; HDL cholesterol was determined in whole plasma after precipitation of LDL and VLDL with 4% sodium phosphotungstate in the presence of 2 mol/l $MgCl_2$. LDL levels were derived from the Friedewald formula, where LDL = total cholesterol − HDL − triglycerides/5. None of the patients had a triglyceride level ≥400 mg/dl. Leptin was measured using a radioimmunoassay kit (Biosource Europe, Nivelles, Belgium) (sensitivity 0.5 ng/ml; within- and between-assay coefficient of variation [CV]: 4.6 and 5.0%, respectively; normal fasting range: men: 3.8 ± 1.8 ng/ml, women 7.4 ± 3.7 ng/ml). Adiponectin was measured using a radioimmunoassay kit (DRG Instruments, Germany) (sensitivity 1 ng/ml; within- and between-assay CV: 3.6 and 9.1%, respectively).

Retinopathy was examined by fundoscopy (Airlie House classification) and scored as follows: R0: no abnormalities; R1: mild to moderate nonproliferative retinopathy (microaneurysms with or without one of the following: retinal hemorrhage, hard or soft exudates, intra-retinal microvascular abnormalities, venous beading); R2: severe nonproliferative retinopathy (microaneurysms plus one or more of the following: soft exudates, hard exudates, intra-retinal microvascular abnormalities, venous beading); R3: proliferative retinopathy (proliferation of new vessels, macular edema); R4: photocoagulation and preretinal or vitreous hemorrhages; R5: blindness (15).

Other causes of neuropathy than diabetes (e.g., familial, alcoholic, nutritional, uremic, toxic, monoclonal gammopathies) were excluded. Electromyographic examination with nerve conduction velocity tests, including motor (peroneal and tibial) and sensory (sural) nerves, H-reflexes, and F-waves, were performed by a skilled neurophysiologist. Nerve conduction tests, H-reflexes, and F-waves were scored as normal or abnormal. Neuropathy severity was graded as follows: N0: no neuropathy; N1: mild neuropathy: abnormal H-reflex or F-wave; N2: decreased conduction velocity without axonal injury; N3: signs of demyelinization and axonal degeneration; and N4: muscle atrophy or malum perforans (16).

Statistical analysis

Results were analyzed using SPSS (SPSS, Chicago, IL). Distributions of continuous data were tested for normality by the Kolmogorov-Smirnov test. The unpaired *t* test, Mann-Whitney *U* test, or ANOVA were used to determine differences between groups. Bonferroni adjustments for multiple comparisons were made. The Spearman rank correlation test was used. Differences in distributions of categorical data were evaluated by χ^2 or Fisher's exact test. Stepwise forward logistic regression and multivariate linear regression was used to assess the strength and independency of associations. A two-tailed $P < 0.05$ was considered significant.

RESULTS

— The study population comprised 324 men and 268 women with type 1 diabetes, consisting of 168 normal-weight men (BMI <25 kg/m^2), 146 normal-weight women, 156 overweight men, and 122 overweight women. The study population had a mean age of 41 ± 12 years, a mean diabetes duration of 19 ± 11 years, and an average A1C of 7.9 ± 1.1%. In both sexes, the prevalence of overweight and obesity increased with age ($P < 0.0001$) and duration of diabetes ($P = 0.006$). The level of A1C and the insulin dose were not significantly different between overweight and normal-weight type 1 diabetic patients.

Hypertension (>130/85 mmHg) was present in 40%, retinopathy in 53%, and neuropathy in 43% of patients. Hypertension was more prevalent in overweight than normal-weight subjects (47 vs. 33%, $P = 0.001$; odds ratio [OR] = 1.77 [95% CI 1.27–2.47]) (Table 1). With increasing BMI, total cholesterol ($r = 0.26$, $P < 0.0001$), LDL cholesterol ($r = 0.31$, $P < 0.0001$), non-HDL cholesterol ($r = 0.37$, $P < 0.0001$), and triglycerides ($r = 0.21$, $P < 0.0001$) increased, whereas HDL cholesterol ($r = -0.15$, $P = 0.006$) decreased significantly in men but not in women. The higher the BMI, the more severe the retinopathy ($P < 0.0001$) and neuropathy ($P = 0.007$).

Overweight subjects had more retinopathy (63 vs. 45%, $P < 0.0001$, OR = 2.05 [1.48–2.85]) and neuropathy (49 vs. 38%, $P = 0.008$, 1.57 [1.13–2.18]) than normal-weight patients (Table 2). Patients with retinopathy were older ($P < 0.0001$) and had a longer diabetes duration ($P < 0.0001$), a higher A1C ($P = 0.001$), a higher BMI ($P = 0.001$), and a worse lipid profile (total cholesterol: $P = 0.001$; non-HDL cholesterol: $P < 0.0001$; LDL cholesterol: $P = 0.001$) than individuals without retinopathy. Patients with retinopathy were more likely to present with neuropathy (58 vs. 26%, $P < 0.0001$, 3.82 [2.70–5.42]). Logistic regression analysis showed that diabetes duration ($\beta = 0.15$, $P < 0.0001$), blood pressure ($\beta = 0.22$, $P = 0.0047$), and A1C ($\beta = 0.25$, $P = 0.01$) but not BMI, insulin dose/kilogram body weight, age, sex, or lipid values, were independent risk factors for retinopathy. However, after excluding blood pressure from this model, diabetes duration ($\beta = 0.16$, $P < 0.0001$), A1C ($\beta = 0.25$, $P = 0.011$), non-HDL cholesterol ($\beta = 0.01$, $P = 0.0067$), and BMI ($\beta = 0.05$, $P = 0.042$) were withheld as risk factors for retinopathy.

Similar to the situation of retinopathy, patients with neuropathy were older ($P < 0.0001$) and had a longer diabetes duration ($P < 0.0001$), a worse A1C ($P <$

0.0001), a higher BMI ($P = 0.047$), and a higher non-HDL cholesterol concentration ($P < 0.0001$). Men were more likely to present with neuropathy than women (50 vs. 34%, $P < 0.0001$, OR = 1.94 [1.39–2.70]) (Table 2). Diabetes duration ($\beta = 0.05$, $P < 0.0001$), age ($\beta = 0.04$, $P = 0.001$), A1C ($\beta = 0.35$, $P < 0.0001$), and sex ($\beta = 0.74$, $P = 0.001$) but not BMI, insulin dose/kilogram body weight, lipid levels or blood pressure, were independent risk factors for neuropathy.

In the last 130 patients recruited for this study, adipocytokines were measured. Compared with levels in women, leptin (16.1 ± 10.8 vs. 6.7 ± 4.9 ng/ml, $P < 0.0001$) and adiponectin (18.5 ± 6.9 vs. 14.1 ± 5.8 μg/ml, $P < 0.0001$) levels were lower in men. Leptin levels correlated positively with BMI ($r = 0.64$, $P < 0.0001$) and waist ($r = 0.36$, $P < 0.0001$). In contrast, adiponectin levels correlated negatively with BMI ($r = -0.31$, $P < 0.0001$), waist ($r = -0.40$, $P < 0.0001$), waist-to-hip ratio ($r = -0.37$, $P < 0.0001$), and triglycerides ($r = -0.20$, $P = 0.021$) and positively with HDL cholesterol ($r = 0.45$, $P < 0.0001$) and A1C ($r = 0.25$, $P = 0.005$). As shown in Table 2, no differences could be observed in the levels of leptin and adiponectin between patients with or without retinopathy and neuropathy.

CONCLUSIONS — The prevalence of being overweight has increased steadily over the last 20 years (1), which is concurrent with a rising incidence of type 1 diabetes (2). The relationship between the effects of weight gain on glycemic control, on microvascular risk factors (blood pressure, lipid profile), and on chronic complications in type 1 diabetes is unclear. Clinicians faced with the individual variability of patients often wonder why some patients under good metabolic control (A1C ≤7.0%) still develop complications, whereas others remain free of such complications despite poorly controlled diabetes.

Intensive insulin therapy, as shown in the Diabetes Control and Complications Trial, is associated with an increase in body weight (5). Possible explanations for weight gain with improvement of glycemic control include elimination of caloric loss from glycosuria, shift in fuel use from fatty acids to glucose, and an insulin-induced increase in appetite (17,18). Insulin sensitivity is impaired in subjects

Table 1—*Baseline characteristics of 592 type 1 diabetic patients, subdivided according to BMI*

	Normal-weight men (group 1)	Normal-weight women (group 2)	Overweight men (group 3)	Overweight women (group 4)	ANOVA (P)	Post hoc	
						Group 1 vs. 3	Group 2 vs. 4
n	168	146	156	122			
Age (years)	40 ± 12	39 ± 11	44 ± 12	42 ± 12	<0.0001	0.003	NS
Duration (years)	17 ± 10	17 ± 10	21 ± 12	21 ± 10	0.001	0.019	0.014
BMI (kg/m^2)	22.5 ± 1.8	22.3 ± 1.6	28.0 ± 3.5	29.1 ± 4.1	<0.0001	<0.0001	<0.0001
Insulin dose (units/kg)	0.73 ± 0.24	0.69 ± 0.24	0.71 ± 0.25	0.72 ± 0.26	NS		
A1C (%)	7.8 ± 1.2	7.8 ± 1.2	7.9 ± 1.1	7.9 ± 1.1	NS		
Total cholesterol (mg/dl)	181 ± 33	199 ± 35	198 ± 38	199 ± 37	<0.0001	<0.0001	NS
Non-HDL cholesterol (mg/dl)	119 ± 32	113 ± 38	142 ± 36	110 ± 33	<0.0001	<0.0001	NS
LDL cholesterol (mg/dl)	101 ± 29	122 ± 40	119 ± 33	126 ± 39	<0.0001	<0.0001	NS
HDL cholesterol (mg/dl)	62 ± 17	75 ± 18	56 ± 18	73 ± 17	<0.0001	0.011	NS
Triglycerides (mg/dl)	91 ± 49	87 ± 61	118 ± 87	81 ± 33	0.001	0.002	NS
Leptin (ng/ml) (tested: 130)	4.8 ± 2.7	10.5 ± 4.8	8.6 ± 5.9	25.9 ± 11.3	<0.0001	0.087	<0.0001
Adiponectin (μg/ml) (n = 130)	15.3 ± 5.5	20.1 ± 7.3	12.9 ± 5.9	15.7 ± 5.4	<0.0001	NS	0.028
					χ^2		
Hypertension	50 (30)	55 (38)	84 (54)	47 (39)	<0.0001	1 + 2 vs. 3 + 4: $P = 0.001$	
Retinopathy	81 (48)	60 (41)	98 (63)	76 (62)	<0.0001	1 + 2 vs. 3 + 4: $P < 0.0001$	
Neuropathy	73 (43)	46 (31)	90 (58)	46 (38)	<0.0001	1 + 2 vs. 3 + 4: $P = 0.008$	

Data are means ± SD or n (%), unless otherwise indicated. Overweight is defined as a BMI ≥25 kg/m^2 and hypertension as blood pressure >130/85 mmHg. Leptin and adiponectin were tested in a subgroup of 130 patients.

Table 2—*Characteristics of patients with and without retinopathy and neuropathy*

	With retinopathy	Without retinopathy	*P*	OR (95% CI)	With neuropathy	Without neuropathy	*P*	OR (95% CI)
n	315	277			255	337		
Sex (M/F)	179/136	145/132	NS		163/92	161/176	<0.0001	1.9 (1.4–2.7)
Age (years)	45 ± 12	37 ± 11	<0.0001		46 ± 12	38 ± 11	<0.0001	
Duration diabetes (years)	25 ± 10	12 ± 8	<0.0001		23 ± 11	16 ± 9	<0.0001	
BMI (kg/m^2)	25.8 ± 4.1	24.7 ± 4.2	0.001		25.8 ± 4.3	24.9 ± 4.2	0.047	
Insulin dose (units/kg)	0.71 ± 0.24	0.71 ± 0.25	NS		0.70 ± 0.25	0.71 ± 0.24	NS	
A1C (%)	8.0 ± 1.1	7.7 ± 1.1	0.001		8.1 ± 1.2	7.7 ± 1.1	<0.0001	
Total cholesterol (mg/dl)	199 ± 35	188 ± 36	0.001		198 ± 35	191 ± 37	0.023	
Non-HDL cholesterol (mg/dl)	128 ± 36	115 ± 36	<0.0001		128 ± 36	117 ± 37	<0.0001	
LDL (mg/dl)	121 ± 36	111 ± 36	0.001		119 ± 33	114 ± 39	0.08 (NS)	
HDL (mg/dl)	62 ± 19	61 ± 18	NS		61 ± 19	62 ± 18	NS	
Triglycerides (mg/dl)	102 ± 65	99 ± 74	NS		105 ± 71	97 ± 66	NS	
Leptin (ng/ml) (n = 130)	12.2 ± 9.9	10.9 ± 9.7	NS		10.5 ± 10.3	12.3 ± 9.3	NS	
Adiponectin (μg/ml) (n = 130)	17.3 ± 7.5	15.3 ± 5.9	0.12 (NS)		17.3 ± 7.2	15.7 ± 6.6	NS	
Neuropathy	182 (58)	73 (26)	<0.0001	3.8 (2.7–5.4)	—	—	—	—

Data are means ± SD or *n* (%), unless otherwise indicated.

with normal glucose tolerance who exceed a critical threshold of obesity, corresponding to an ideal body weight of 120% (BMI ≥26.8 kg/m^2) (19). This may have important implications for desirable weight goals. Obesity-associated insulin resistance increases insulin secretory demands and upregulates the β-cells metabolically, thereby accelerating their loss through glucotoxicity (20) or by increasing antigen presentation (21). However, this could not be observed in the present study; overweight and non-overweight subjects injected a similar insulin dose/kilogram body weight. Theoretically, insulin resistance could contribute to the development of chronic diabetes complications.

Recent studies of type 1 diabetic patients have shown that a higher BMI is associated with hypertension and an atherogenic lipid profile as part of the insulin resistance syndrome. The adverse lipid profile consists of higher triglyceride and LDL cholesterol levels and lower HDL cholesterol levels (22). Adverse effects of lipoproteins may be mediated through effects on coagulation, fibrinolysis, vascular tone, insulin resistance, or susceptibility of lipoproteins to oxidation (23). A1C correlated positively with total and LDL cholesterol and triglyceride in men (23). We observed a positive correlation between BMI and total cholesterol, LDL cholesterol, and non-HDL cholesterol in men but not in women. Overweight men had a more unfavorable risk profile than overweight women, with higher blood pressure and worse lipid profile. Sex differences in vascular disease risk factors, including dyslipidemia, may contribute (23). Beneficial effects of intensive insulin therapy on lipid levels were reported in individuals with modest weight gain, but not anymore in people with excessive weight gain (BMI >30 kg/m^2), who had an increased risk of coronary artery disease (4,22). This may be another reason to (modify glycemic goals to) prevent further weight gain.

Low adiponectin levels are associated with obesity (24), severity of insulin resistance (24), and coronary artery disease (12,25). Adiponectin levels correlate negatively with visceral and subcutaneous fat areas (25). We and others observed that adiponectin values were higher in women than in men (26) and correlated negatively with BMI (26,27), waist-to-hip ratio, and plasma triglycerides (25,27) but positively with HDL cholesterol (25,27) and A1C (27). In contrast to reports of patients with type 2 diabetes (25,28), we could not observe lower adiponectin concentrations in patients with diabetic retinopathy than in patients without diabetic retinopathy.

Plasma leptin levels are elevated in obesity and correlate positively with both visceral and subcutaneous fat areas (25). Female patients have higher leptin levels than male patients (29). Pertinent to diabetic retinopathy, recent findings show that leptin promotes vascular endothelial cell proliferation and angiogenesis in vitro and neovascularization in vivo (30). However, in contrast to findings in type 2 diabetes (29), we could not confirm a link between the existence or stages of diabetic retinopathy and serum leptin levels in type 1 diabetes. Matsuda et al. (31) suggested that leptin may play a role not only in angiopathy but also in neuropathy in type 2 diabetes. We could not extend these findings to type 1 diabetes.

The prevalence of retinopathy in this study was 53% after a mean diabetes duration of 19 years, which is lower than the reported 82% in Europe (32), suggesting a good standard of diabetes care. Risk factors for diabetic retinopathy are the level of metabolic control (A1C) (5,32–36), diabetes duration (5,32–34), blood pressure (33–35), and triglycerides (33,36). Patients with nephropathy are known to have a higher risk of developing other diabetes complications (37). To avoid such interference, subjects with a creatinine level >1.5 mg/dl were excluded from this study. Whether BMI is a contributing factor is not well known. Zhang et al. (9) revisited data from the Diabetes Control and Complications Trial and observed that besides diabetes duration and metabolic control, BMI had a significant predictive value in developing retinopathy. However, the actual prognostic impact of BMI was limited (~1% risk increase by kg/m^2) unless it reached scores indicative of obesity. Dorchy et al. (38) confirmed this observation. Henricsson et al. (10) observed that time to develop retinopathy

was related to high A1C and high BMI. We studied ~600 patients after ~20 years of type 1 diabetes and observed that, with increasing BMI, the severity of retinopathy increased. Overweight subjects were twice as likely to present with retinopathy. However, logistic regression analysis identified diabetes duration, A1C, and blood pressure as independent risk factors, but not BMI. However, BMI was strongly associated with blood pressure, and after excluding this covariate in the logistic regression model, BMI and non-HDL cholesterol were also withheld as risk factors.

The prevalence of polyneuropathy varies between 28 and 54% in adult type 1 diabetic patients (39–42). In the Pittsburgh Epidemiology of Diabetes Complications Study, the prevalence of neuropathy was 59% in individuals aged ≥30 years, and in the Eurodiab Study, it was 42% for those patients with a diabetes duration >15 years, in comparison with 43% in this study. Risk factors for polyneuropathy are age (11,39), diabetes duration (5,11,40,41), glycemic control (5,11,39–41), blood pressure (11,42), smoking (11,39,40), low HDL cholesterol, high triglycerides (11,39), and high LDL cholesterol (40). As in the study by Dyck et al. (41), we observed a good correlation between the retinopathy level and the severity of neuropathy. Tesfaye et al. (11) recently reported that BMI was an independent risk factor for polyneuropathy in type 1 diabetes. We observed that overweight subjects had an almost twofold increased risk for neuropathy. In addition, the severity of neuropathy increased with increasing BMI. However, logistic regression analysis identified diabetes duration, age, sex, and A1C as independent risk factors, but not BMI.

As for A1C, high scores for BMI are deleterious and low scores are preventive. Overweight is associated with hypertension and an atherogenic lipid profile. Association is not causation, but overweight may be an important factor in a cascade leading toward insulin resistance and the development of complications. Improved glycemic control, more exercise, weight loss, smoking cessation, and lipid-lowering and antihypertensive treatment may favorably influence the diabetic risk profile for late complications. The American Diabetes Association proposed evidence-based nutrition recommendations for the treatment/prevention of diabetes and its complications (43).

Although no data are available for type 1 diabetic patients, studies have shown weight loss and a concurrent major risk reduction of developing diabetes from structured intensive lifestyle programs, including a low-fat diet, increased physical activity, and educational sessions (44,45). Management of hypertension includes reducing weight and sodium intake (46). The average systolic and diastolic blood pressure reductions per kilogram of weight loss are 2 and 1 mmHg, respectively (47). The DASH (Dietary Approach to Stop Hypertension) diet lowered systolic and diastolic blood pressure by 6 and 3 mmHg, respectively (48). Similar trends are to be expected in type 1 diabetes.

In conclusion, significant overweight is present in type 1 diabetic patients. Because weight gain can be managed by means of lifestyle intervention (nutrition, exercise, education), it seems appropriate to study the impact of overweight on diabetes complications. Retinopathy and neuropathy are more prevalent in overweight (BMI ≥25 kg/m^2) type 1 diabetic subjects. BMI showed a strong positive correlation with blood pressure, lipid profile, and severity of retinopathy and neuropathy. However, logistic regression analysis showed that diabetes duration and A1C remain the main determinants of chronic complications. BMI was not an independent risk factor but may nevertheless be an important factor in a cascade leading toward insulin resistance and the development of chronic complications. The clinical significance of adipocytokines in terms of a causative role in metabolic disorder and microangiopathy in type 1 diabetes should be further elucidated in a prospective longitudinal study. Lifestyle intervention studies are needed to study the pathogenic role of BMI in diabetes complications.

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