



Increased Prevalence of Microvascular Complications in Type 2 Diabetes Patients with the Metabolic Syndrome

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Background: Microvascular complications of diabetes contribute significantly to the disease morbidity. The metabolic syndrome is common among subjects with diabetes and is a very important risk factor for macrovascular complications. However, its contribution to the microvascular complication has not been assessed.

Objectives: To assess the risk of microvascular complications associated with the metabolic syndrome in diabetes subjects.

Methods: The study group comprised 415 diabetic subjects attending a primary care clinic. The prevalence of microvascular complications was compared between 270 diabetic subjects with metabolic syndrome (NCEP-III criteria) and 145 diabetic patients without.

Results: We found that as a group, diabetic subjects with metabolic syndrome had a significantly higher frequency of microvascular-related complications than diabetic subjects without the syndrome (46.6% and 26.8% respectively, $P = 0.0005$). These include microalbuminuria (41.5% vs. 23.9%, $P = 0.013$), neuropathy (10.4% vs. 7.5%, $P = 0.38$), retinopathy (9.6% vs. 4.1%, $P = 0.046$) and leg ulcers (7.9% vs. 2.8%, $P = 0.044$). After adjustment for age, gender, glycemic control, disease duration, lipid profile and blood pressure, metabolic syndrome was associated with a significantly higher risk of microvascular complications: odds ratio (95% confidence interval) for nephropathy 2.27 (1.53–3.34), neuropathy 1.77 (0.79–4.0), retinopathy 3.42 (1.2–9.87), and leg ulcers 3.57 (1.08–11.95).

Conclusions: In addition to hyperglycemia and disease duration, the metabolic syndrome is a significant risk factor for the development of microvascular complications in diabetic subjects.

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study groups [4]. Since increased insulin resistance is usually associated with type 2 diabetes, most subjects with this disease can be defined as having metabolic syndrome as well. Using the NCEP-III or World Health Organization criteria, 70–80% of diabetic subjects are diagnosed with the syndrome [5–7].

While macrovascular complications are associated with significant morbidity and mortality in diabetic subjects, microvascular complications also contribute significantly. About 30–45% of diabetic subjects suffer from microvascular complications, and type 2 diabetes has become the principal cause for blindness and end-stage renal disease in western countries [8]. Poor glycemic control, disease duration, hypertension and dyslipidemia are considered to be important risk factors for microvascular complications [9–11]. Although the role of metabolic syndrome in macrovascular complications has been studied extensively [12–14], only a few studies evaluated the risk of diabetic subjects with the syndrome for developing microvascular complications [15], and consequently its clinical relevance was never addressed until now. In this study we assessed the associated risk of developing microvascular complications in diabetic patients who also have metabolic syndrome.

Subjects and Methods

Study population

A cross-sectional study was conducted among 426 type 2 diabetes subjects. All were of Jewish origin and registered in a single primary healthcare clinic of Clalit Health Services. Every Israeli citizen has free access to the public health system, based on the Israeli national health plan. The primary healthcare system provides services to all its registered subjects, who belong to one of four health management organizations; Clalit is the largest (60%). Each member of Clalit has a medical file containing his/her medical history, pharmacy dispenses, laboratory results, outpatients visits, expert consultations, and hospitalizations.

Data from the files of 426 diabetic patients (all with type 2 diabetes), all registered in one regional Clalit clinic, were included in the present study. For the purposes of the study,

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The metabolic syndrome is characterized by aggregation of obesity (mainly central), dyslipidemia and hypertension. Oversecretion of insulin with peripheral resistance to insulin action is believed to underlie this syndrome [1,2]. Despite the very recent controversy regarding the definition of the syndrome [3], its internationally defined criteria had allowed an accurate clinical diagnosis and comparison between the rates of its development among different

the diagnosis of diabetes was based on the registration of diabetes in the list of diseases in the subject's medical file, the registered use of antihyperglycemic medications, and/or the documented level of fasting blood glucose above 126 mg/dl in at least two measurements. The regional clinic serves 4699 adult individuals. The mean age of all registered individuals was 53 ± 18 years (range 18–93) and the male/female ratio was 0.85.

Definition of metabolic syndrome

We used modified NCEP-III (National Cholesterol Education Program) and WHO criteria [4,5] for the diagnosis of metabolic syndrome. All study subjects had type 2 diabetes and therefore met the criterion of fasting blood glucose > 110 mg/dl. Since waist measurement was not available in the patient's record we used body mass index instead of waist circumference as a measure of obesity. The diagnosis of metabolic syndrome was made according to NCEP-III criteria if the subject had at least two of the following: a) hypertension (on antihypertensive treatment or with at least three blood pressure measurements $> 130/85$ mmHg); b) obesity (BMI > 30); c) triglycerides > 150 mg/dl (subjects treated with fibrates were considered to meet this criterion even if their triglycerides were < 150 mg/dl); d) high density lipoprotein-cholesterol < 50 mg/dl in women and < 40 mg/dl in men.

Alternatively, the diagnosis of metabolic syndrome was based on the WHO criteria if the subject had two or more of the following: a) hypertension (blood pressure > 130 mmHg systolic or > 90 mmHg diastolic); b) dyslipidemia (triglycerides > 150 mg/dl or HDL-cholesterol < 35 mg/dl in men and < 45 mg/dl in women); c) BMI > 30 kg/m²; d) microalbumin > 20 mg/24 hour urinary collection.

Since microalbuminuria is considered one of the WHO criteria for metabolic syndrome, we compared the prevalence of the syndrome in our population using both sets of criteria, including the NCEP-III for further statistical analysis. However, we also assessed the risk for development of retinopathy and neuropathy in association with metabolic syndrome using the WHO criteria [Table 1].

Definition of microvascular complications:

Retinopathy: Diagnosis based on fundoscopic examination performed by an ophthalmologist. Patients were divided into two groups: one comprised patients with diabetic retinopathy who had either a background or proliferative retinopathy, while the second consisted of diabetic patients with no evidence of diabetic retinopathy.

BMI = body mass index
HDL = high density lipoprotein

Table 1. Prevalence (%) of complications in diabetic subjects with and without metabolic syndrome diagnosed according to the NCEP-III and WHO criteria

	Metabolic syndrome (NCEP)		Metabolic syndrome (WHO)		P 1 vs. 2	P 3 vs. 4
	(1) present	(2) absent	(3) present	(4) absent		
Microalbuminuria (all patients)	41.5	23.9	NA	NA	0.013	
Microalbuminuria (no ACE inhibitors)	31.7	18.6	NA	NA	0.0482	
Neuropathy	10.4	7.5	11.1	4.7	0.38	0.0397
Retinopathy	9.6	4.1	10.4	2.8	0.046	0.0046
Leg ulcers	7.9	2.8	8.8	1.3	0.044	0.046
At least one microvascular complication	46.6	26.8	NA	NA	0.0005	

NA = not available

Microalbuminuria: Diagnosis based on 24 hr urinary collection for microalbumin. Subjects were diagnosed as having microalbuminuria if their urinary collection had > 20 mg microalbumin/24 hours, or without microalbuminuria if the level was < 20 mg microalbumin/24 hours. Microalbuminuria was confirmed by at least two urinary collections.

Neuropathy: Diagnosis of distal sensory neuropathy based on symptoms or clinical examination. Patients' complaints including distal symmetric nocturnal numbness, abnormal Achilles tendon reflexes, or lack of sensory perception were also considered diagnostic for neuropathy.

Leg ulcers: Pathophysiologically, leg ulcers are divided into two groups – ischemic and neuropathic. The former are considered a macrovascular diabetic complication, and the latter as microvascular. However, most often neuropathic ulcers develop subsequent to neuropathy or peripheral small vessel disease of the extremities, reflecting a microvascular complication, thus justifying their inclusion in our analysis. This dual effect is also exemplified by the detection of microalbuminuria, which reflects diabetic nephropathy representing microvascular disease and is a marker for macrovascular atherosclerotic disease. Leg ulcer was diagnosed if the subject had a history of skin ulceration below the ankle lasting more than a week and necessitating medical treatment.

Analytic methods

All analytic methods were carried out in a central laboratory serving Clalit Health Services in the Haifa District. Glucose was determined by the glucose oxidase method. Glycosylated hemoglobin was determined by an automated high performance liquid chromatography method. Cholesterol, HDL-cholesterol and triglycerides were measured by enzymatic, colorimetric methods. Microalbuminuria was measured in 24 hours urinary collection by means of an immunonephelometric assay. A value above 20 mg/24 hours was considered positive for microalbuminuria.

Statistical analysis

We conducted all statistical analysis using SAS software package. Data are presented as mean ± SD, or as percentage. The significance of differences between group means was tested by the *t*-test. Chi-square test was used to assess the difference between group frequencies. The difference between the frequency of the WHO and NCEP-III definitions of metabolic syndrome was tested by the McNemar test. Odds ratios were calculated with multiple logistic regression analysis. For this analysis the mean hemoglobin A1C and blood pressure measurement values during the previous year was used (on average, patients had 5.2 measurements for blood pressure and 2.1 measurements for HbA1C); and age, mean HbA1C, mean blood pressure and disease duration were used as continuous variables, and gender and metabolic syndrome as categorical variables. *P* < 0.05 was considered statistically significant.

Results

Eleven of the 426 diabetic patients were excluded from the analysis as they had incomplete data. Of the remainder, 270 had two or more components of the metabolic syndrome according to NCEP-III criteria, indicating a prevalence of 65.1% in this diabetic cohort. Table 2 presents anthropometric and metabolic characteristics of the patients according to the clustering of metabolic syndrome. Subjects with metabolic syndrome were more obese (BMI 30.8 vs. 26.0, *P* < 0.0001), younger (68.8 vs. 70.8 years, *P* = 0.058), and had shorter disease duration (8.94 vs. 9.9 years, *P* = 0.0186) than those without the syndrome. Females had metabolic syndrome more often than males. As expected, patients with the syndrome had higher systolic and diastolic blood pressure, higher triglycerides and lower HDL levels. Differences between both groups in total cholesterol, low density lipoprotein and HbA1c did not have statistical significance.

Table 2. Anthropometric and metabolic characterization of diabetic patients with and without metabolic syndrome

	Metabolic syndrome present (n=270)	Metabolic syndrome absent (n=145)	<i>P</i>
Age	68.8 ± 10.5	70.8 ± 11.8	0.058
Gender (% female)	66.8	42.8	< 0.0001
BMI	30.8 ± 5	26.0 ± 2.9	< 0.0001
Disease duration	8.94 ± 7.7	9.9 ± 9	0.0186
HbA1c	7.68 ± 1.69	7.41 ± 1.61	0.27
Cholesterol	206.1 ± 43	201.5 ± 45	0.24
LDL	116.5 ± 37	119.0 ± 33	0.081
HDL	45.4 ± 10.8	57.9 ± 4.2	< 0.0001
Triglycerides	199.0 ± 91	130.6 ± 106	0.014
Systolic BP	142.6 ± 15.6	137.3 ± 22	0.001
Diastolic BP	80.9 ± 8.5	78.1 ± 10.9	0.0039

LDL = low density lipoprotein

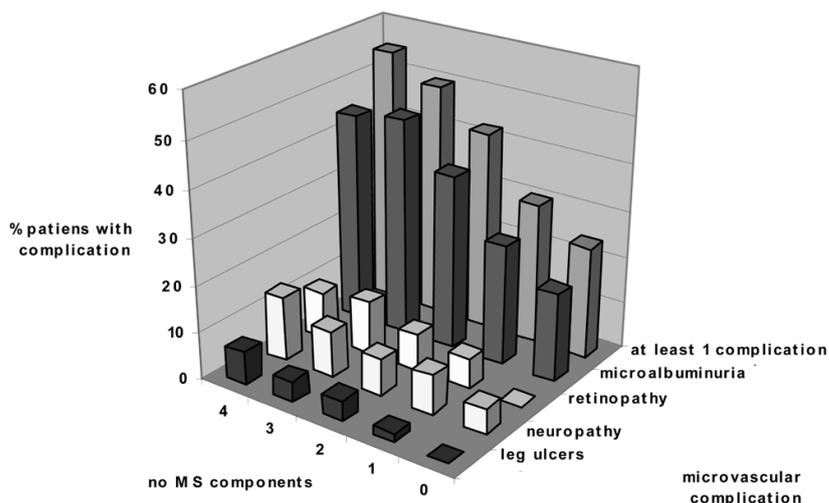


Figure 1. Prevalence (%) of different microvascular complications in relation to number of metabolic syndrome components

When WHO criteria were applied, 262 patients were diagnosed with metabolic syndrome, with a prevalence of 63.1%. The difference between both frequencies of the syndrome was not statistically significant (*P* = 0.50); 56.1% were diagnosed with metabolic syndrome according to both sets of criteria, and 29.8% did not have the entity according to both sets of criteria. Nine percent of patients fulfilled the criteria of NCEP but not of the WHO, while 7.0% fulfilled the WHO criteria but not those of NCEP.

Patients with metabolic syndrome had a higher rate of diabetes complications, and 46.6% had at least one microvascular complication [Table 1]. In addition, patients with metabolic syndrome had a significantly higher prevalence of microalbuminuria (41.5% vs. 23.9%, *P* = 0.013). The latter analysis did not include patients not receiving angiotensin-converting enzyme inhibitors or angiotensin receptor antagonist treatment since these compounds are expected to affect the level of albuminuria. Interestingly, the higher prevalence of microalbuminuria among diabetic patients with metabolic syndrome remained significantly higher (31.7% vs. 18.6%, *P* = 0.0482), even when patients treated with an ACE inhibitor or ARB were excluded from the analysis.

Retinopathy and neuropathy were also more prevalent among patients with metabolic syndrome (9.6% vs. 4.1%, *P* = 0.046, and 10.4% vs. 7.5% respectively), but the difference in the latter was not statistically significant (*P* = 0.38). However, when the WHO criteria were applied, the prevalence of neuropathy was significantly higher among diabetic patients with metabolic syndrome when compared to those without [Table 1]. Leg ulcers, considered a serious complication of neuropathy and peripheral vascular disease, were also more common among patients with metabolic syndrome (7.9 vs. 2.8%, *P* = 0.044).

When patients were grouped according to the number of

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor antagonist

Table 3. Multiple regression analysis for microvascular complications risk associated with metabolic syndrome (NCEP-III criteria), after adjustment for HbA1C, disease duration, age, gender, and blood pressure

Complication	OR	95% confidence interval
Microalbuminuria	2.27	1.53–3.34
Neuropathy	1.77	0.79–4.0
Retinopathy	3.42	1.2–9.87
Leg ulcers	3.57	1.08–11.95
Any complication	2.37	1.5–3.73

detected components of the metabolic syndrome, the prevalence of each complication increased linearly with the increasing number of components [Figure 1]. A logistic regression analysis, after controlling for the duration of diabetes, HbA1C and blood pressure, showed that the metabolic syndrome was significantly associated with higher risk for nephropathy, retinopathy and leg ulcers [Table 3].

Discussion

Our results demonstrate that diabetic subjects with metabolic syndrome, regardless of the criteria used for diagnosis, have significantly higher risk for microvascular complications than diabetic subjects without the syndrome. After adjustment for gender, lipid profile, disease duration, glycemic control and blood pressure – all well-established risk factors for microvascular complications – subjects with metabolic syndrome had a more than twofold risk of having at least one microvascular complication than diabetic patients without the syndrome [Table 3]. Furthermore, the prevalence of each microvascular complication directly and significantly correlated with the number of metabolic syndrome components [Figure 1].

A higher frequency of retinopathy was found in our diabetic patients with metabolic syndrome. Using logistic regression analysis, the odds ratio for the presence of this complication in this group of patients increased to 3.42, a risk comparable to that noted by other investigators [15]. Consistent with this finding is the reported observation that insulin resistance, assessed by a euglycemic hyperinsulinemic clamp, strongly correlates with diabetic retinopathy in subjects with type 2 diabetes [16]. Furthermore, metabolic syndrome was found to be associated with high retinal microvascular risk also in non-diabetic subjects, with an odds ratio of 1.68 for having retinal microvascular signs, similar to that observed in diabetic retinopathy (micro-aneurysms, retinal hemorrhages, arteriovenous nicking) [17]. All these observations together suggest that insulin resistance is probably an important risk factor for diabetic retinopathy.

Neuropathy was also found to be associated with metabolic syndrome, however this association was statistically significant only when using WHO criteria for the diagnosis. Other studies observed a significant association of neuropathy and metabolic syndrome but the association was weaker than with retinopathy [6]. Unlike the diagnostic methods used for the diagnosis of

retinopathy and microalbuminuria, it is difficult to assess distal neuropathy due to the common use of subjective methods which may result in larger diagnostic error. However, a recent prospective study of type I diabetes subjects identified different components of the syndrome (triglycerides, albuminuria, hypertension, BMI) as significant risk factors for the development of distal neuropathy. Interestingly, after adjustment for glycemic control and disease duration, the odds ratio for having neuropathy was found to be similar to that in the present study (1.35–1.92) [18].

Assessing the association between microalbuminuria and metabolic syndrome is somewhat problematic. Microalbuminuria is one of the criteria used by the WHO to define the syndrome. Furthermore, treatment with drugs that block the renin-angiotensin axis may affect the outcome, and it may lead to bias in diagnosing microalbuminuria. We overcame such difficulties by using the NCEP-III criteria and by excluding subjects treated with ARB and ACE inhibitors from the analysis. However, even under such conditions microalbuminuria remained strongly and significantly associated with metabolic syndrome. It should be noted that microalbuminuria is one of the strongest predictors of cardiovascular events and mortality among type 2 diabetes subjects [14,19].

Leg ulcers are associated with significant morbidity in diabetic patients. They usually develop as a consequence of neuropathy and/or peripheral vascular disease, including small vessel disease. Interestingly, they were also significantly associated with metabolic syndrome with an odds ratio of 3.57.

The prevalence of retinopathy and neuropathy in this study was lower than that reported in other studies [16], possibly due to differences in the study populations. While this study was done among diabetic subjects in the community, subjects in other studies were recruited from patients attending hospital outpatient clinics for diabetes consultation and therefore were more likely to have more severe disease and a higher rate of complications. Shorter duration of diabetes (9.3 years in this study compared to > 11) may also contribute to differences between the studies. Finally, good glycemic control observed in this study (mean HbA1C 7.52) may also have contributed to the lower prevalence of microvascular complications.

The prevalence of metabolic syndrome among diabetic subjects in this study was slightly lower than in other studies [20–22]. One explanation may be that we used BMI instead of waist circumference as a measure of metabolic syndrome-related obesity. This possibility is supported by other studies where the use of BMI as a measure of obesity, rather than waist measurement, resulted in a lower prevalence of the syndrome particularly among men [23]. However, ethnic differences may also have contributed to variations in metabolic syndrome prevalence between the different studies [24].

Other components of the metabolic syndrome (triglycerides, obesity, hypertension) should also be treated in order to reduce their contribution to the development of microvascular complications. Randomized clinical trials demonstrated that intensive, multifactorial interventions were effective in reducing both mac-

rovascular and microvascular complications in type 2 diabetes patients [25].

This study may have important clinical significance as it indicates that diabetic subjects with metabolic syndrome are at higher risk to develop microvascular complications than diabetic subjects without the syndrome. These subjects should be identified and subjected to more aggressive treatment beyond their tight glycemic control.

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A society grows great when old men plant trees whose shade they know they shall never sit in.

Greek proverb