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Microangiopathic complications in type 1 diabetes mellitus: differences in severity when isolated or associated with autoimmune polyendocrinopathies

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Context: The development and evolution of different chronic diabetic complications may present variations among the different types and conditions of this disease. **Objective:** To evaluate the degree of microangiopathy in Type 1 diabetes mellitus (DM1) associated with autoimmune polyendocrinopathies (OSAD) or isolated DM1 (iDM1). **Patients:** OSAD (n=17) and iDM1 (n=13) were over 15 years old at diagnosis of DM and were matched for diabetes duration (13.9 ± 8.2 and 13.2 ± 5.9 years, respectively) and metabolic control (HbA1c: 6.4 ± 1.9 and $6.8 \pm 1.4\%$). **Main Outcome Measures:** Urinary albumin excretion (UAE; ELISA), the inversion of serum creatinine (1/C) level and indirect ophthalmoscopy. **Results:** Although the prevalence of hypertension was similar in both groups, the OSAD had inferior levels of UAE (7.4 ± 2.5 vs. 17.3 ± 9.2 $\mu\text{g}/\text{min}$; $p < 0.05$). Nephropathy was detected in 12% of the OSAD (none of them macroproteinuric) and in 39% of the iDM1. The UAE in the iDM1 correlated negatively with 1/C values ($r = -0.7$, $p < 0.005$), but the same did not occur in the OSAD ($r = 0.2$, ns). Among patients with retinopathy, the severe form was found in 29% of the OSAD and in 46% of the iDM1. **Conclusions:** OSAD was associated with a lower degree of microangiopathy, in spite of age at diagnosis, duration of diabetes and the metabolic control. In contrast with the iDM1, the increase in UAE of OSAD was not associated with reductions in GFR.

Uniterms: Microangiopathy. Type 1 diabetes mellitus. Autoimmune polyendocrinopathies.

INTRODUCTION

The development and evolution of different chronic diabetic complications may present variations among the different types and conditions of this disease. There may therefore exist different pathogenic mechanisms for specific diabetes complications. Several factors, especially in type 1 diabetes, such as duration of disease,¹ time beyond puberty,^{2,3} arterial hypertension,^{4,7}

metabolic control^{8,9} and a family history of hypertension^{10,11} can significantly modify the course of these complications. In parallel, residual insulin secretion is related to better metabolic control,¹² which has a relationship with development and progression of chronic diabetic complications.^{8,9,13,14}

An association between type 1 diabetes mellitus (DM1) and other autoimmune diseases has been reported several times in the last three decades.¹⁵⁻¹⁷ The associations between the many organ-specific autoimmune diseases (OSAD) have been classified as Polyglandular Autoimmune Syndromes (PGAS), divided into two major groups.^{18,19} In PGAS-I, DM1 occurs in children and is uncommon, whereas in PGAS-II, DM1 appears in almost half the cases and it begins in the third or fourth decade of life. When the onset of DM1 occurs at an adult age, as in OSAD PGAS-II patients, this disease appears to have a

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better evolution, with slower loss of b-cell function and a longer asymptomatic period before diabetes diagnosis than the classical DM1.^{3,12,20,21}

Microangiopathic diabetic complications have never before been studied comparatively in these two groups of DM1 patients. We do not yet know whether the persistence of residual insulin secretion found in OSAD diabetic patients or the associated polyendocrinopathies can modify the course of complications in these patients. Thus, the aim of this study was to investigate the degree of microangiopathy in two groups of type 1 diabetes mellitus, associated with PGAS-II or otherwise, and matched for metabolic control, duration and age at diagnosis of diabetes mellitus.

METHODS

Thirty patients were randomly recruited from among DM1 patients attending the Diabetes and Hypertension Clinic of São Paulo Hospital, Federal University of São Paulo, City of São Paulo, Brazil. We classified our DM1 in accordance with the National Diabetes Data Group criteria.²²

Seventeen DM1 patients presenting an association with one or more organ-specific autoimmune diseases (OSAD) and 13 patients showing isolated DM1, i.e. without other endocrinopathy or family history of these diseases (iDM1), were retrospectively studied.

All the patients studied had an onset of clinical diabetes at or after 15 years of age and their diabetes lasted for more than 5 years. The patients of both groups (iDM1 and OSAD) were matched for diabetes duration and metabolic control.

The diagnosis of associated diseases was made (by PTM, MBSF or SAD) via clinical and laboratorial reports of specific glandular dysfunction and/or presence of specific autoantibodies (anti-thyroidglobulin, anti-thyroperoxidase). Patients with confirmed primary endocrine deficiencies were receiving appropriate replacement hormone therapy, and those with active Grave's Disease were treated with antithyroid drugs.

Clinical Evaluation

The two groups of patients were compared for age, age at diagnosis of diabetes, family history of diabetes or other autoimmune diseases, diabetes duration, daily insulin requirement (units of insulin per body weight unit per day), presence of hypertension (if the patient was under any treatment) and body mass index (kg/m²).

Arterial blood pressure (ABP) was measured in the left arm, in a sitting position after a ten minute rest, using

a standard 12.5 cm cuff mercury sphygmomanometer (Korotkoff phase I-V sounds). Indirect optical funduscopy was performed by the same ophthalmologist (N.B.S.M.) after mydriasis and angiofluorescence when necessary. Retinopathy was classified according to the Diabetic Retinopathy Research Group.²³ The patients were divided according to whether they had the incipient form of retinopathy (background) or the severe form (pre-proliferative or proliferative).

Laboratorial Evaluation

The patients were matched for the metabolic control achieved by mean glycemia and glycosuria, obtained from patients' records from the last 5 years (from 3 months to 12 years). The last glucosilated hemoglobin (HbA1c) obtained via affinity chromatography (normal value 3.5 - 5.3%)²⁴ was also used for accessing metabolic control.

The grade of diabetic nephropathy was evaluated (exercise, drugs and urinary infection excluded) by urinary albumin excretion rate. This was analyzed in nocturnal urinary samples by ELISA (normal value < 20 µg/min)²⁵ and classified as microalbuminuria in the range 20-200 µg/min (incipient nephropathy) or macroalbuminuria if >200 µg/min (overt/clinical nephropathy).^{26,27} The inverse of serum creatinine (1/C) level was taken as an indirect index of glomerular filtration rate (GFR).²⁸

All patients were evaluate for thyroid autoantibodies: TgAb (antithyroglobulin; ELISA)²⁹ and TPO (thyroid peroxidase antibodies; ELISA).³⁰

Statistical Methods

The differences between groups were analyzed using the unpaired Student's t-test when normally distributed; otherwise the Mann-Witney test was used. A finding was considered significant if $p < 0.05$ on a two-tailed test. Distribution of hypertension, retinopathy and overt and/or incipient nephropathy were tested using Fisher's exact test. Correlations were tested with the Spearman rank-order correlation. All results are given as mean (\pm SD) if normally distributed, or otherwise as median ranges. The albuminuria values were converted to logarithmic scale to achieve a distribution near the normal curve, so the geometric median was used (mean \pm SD).

RESULTS

Organ-specific autoimmune diseases associated with Type 1 diabetes in this group were: Hashimoto's

Thyroiditis (6/17, 35.3%); Grave's Disease (5/17, 29.4%); antithyroid autoantibodies alone - TgAb or TPO (3/17, 17.6%); precocious menopause (1/17, 5.9%); and vitiligo (2/17, 11.8%).

The clinical and laboratorial characteristics are shown in Table 1. As the groups were matched, they had the same period of clinical diagnosis of DM: median 12 years, variation from 5 to 35 years in OSAD vs. median 12 years with range from 5 to 27 in iDM1 and metabolic control. The mean of fasting glycemia in the last 6 years was 256 mg/dl (OSAD) and 268 mg/dl (iDM1); HbA1c was 6.4% (3.3 to 7.5% - OSAD) vs. 6.8% (3.2 to 8.8 - iDM1). The diabetic groups had similar ages: 50 years old (28 to 71 - OSAD) vs. 37 years old (29 to 61 - iDM1); and age at DM diagnosis: 32 years old (16 to 53 - OSAD) vs. 26 years old (17 to 48 - iDM1). The patients of the two groups also had similar insulin requirements: 0.7 U/kg/day (0.4 to 1.0 U/kg/day - OSAD) vs. 0.7 U/kg/day (0.5 to 1.8 U/kg/day - iDM1); and body mass index: 23.5 kg/m² (19.7 to 29.5 kg/m² - OSAD) vs. 24.2 kg/m² (18.8 to 26.5 kg/m² - iDM1). Furthermore, neither the systemic mean blood pressure (97.7 ± 8.4 - OSAD vs. 105.2 ± 16.7 mmHg - iDM1), nor the systolic and diastolic blood pressure were statistically different.

The prevalence of retinopathy was 82% (14/17) in the OSAD group and 69% (9/13) in the iDM1 group (ns). But, when we looked at the severity of this complication in these two groups, we found that among OSAD patients with retinopathy, only 36% had the severe form, in contrast to 67% of the iDM1 patients with retinopathy, although this was not statistically significant.

Only two (12%) of the 17 OSAD patients had nephropathy, and both had this in the incipient form. Five of the 13 iDM1 patients (39%) had nephropathy, and 15% had clinical nephropathy. The urinary albumin excretion was lower in the OSAD group (7.4 ± 2.5 µg/min) than among the iDM1 patients (17.3 ± 9.2 µg/min; p < 0.05). The glomerular filtration rate was not statistically different. There was an inverse correlation between urinary albumin excretion and glomerular filtration rate in the iDM1 group (rs = -0.7, p < 0.05). However, this correlation was not observed in the OSAD group (Figure 1). Moreover, the prevalence of hypertension was similar: 53% in the OSAD group and 61.5% in the iDM1 group (ns). There was a significant association between nephropathy and hypertension in the iDM1 group (p = 0.04), but not in the OSAD group (ns).

Table 1
Clinical and laboratorial characteristics of type 1 diabetes alone (iDM1) and associated with polyendocrinopathies (OSAD).

Variable	OSAD	iDM1	significance
Number	17	13	p
AGE (yr)	50 (28 - 71)	37 (29 - 61)	ns
TDDM (yr)	12 (5 - 35)	12 (5 - 27)	ns
ADMD (yr)	32 (16 - 53)	26 (17 - 48)	ns
IR (U/kg/day)	0.7 (0.4 - 1.0)	0.7 (0.5 - 1.8)	ns
HYP (%)	53 %	61.5%	ns
MBP (mmHg)	97.7±8.4	105.2±16.7	ns
SBP(mmHg)	128.8±11.7	135.5±21.1	ns
DBP (mmHg)	81.8±9.3	89.8±15.1	ns
BMI (kg/m ²)	23.5 (19.7 - 29.5)	24.2 (18.8 - 26.5)	ns
FGLY (mg/dl)	256 (125-311)	268 (143-296)	ns
HBA1c (%)	6.4 (3.3 - 7.5)	6.8 (3.2 - 8.8)	ns
DR I/S(n)	9/5	3/6	ns
UAE (mg/min)	7.4x/ ,2.5	17.3x/ ,9.2	< 0.05
C (mg/dl)	0.7±0.2	1.0±0.6	ns

Values as Mean±SD or Median (variation). UAE in geometric average x/ , SD

TDDM: Time of Diagnosis of Diabetes Mellitus; ADMD: Age at Diabetes Mellitus Diagnosis; IR: Insulin Requirement; HYP: prevalence of Systemic Arterial Hypertension; MBP: Mean Blood Pressure; BMI: Body Mass Index; FGLY (mean of fasting glycemia in the last 5 years); HbA1c: glycosylated haemoglobin; DR I/S (Diabetic Retinopathy Incipient/Severe); UAE: Urinary Albumin Excretion Rate; C: serum creatinine

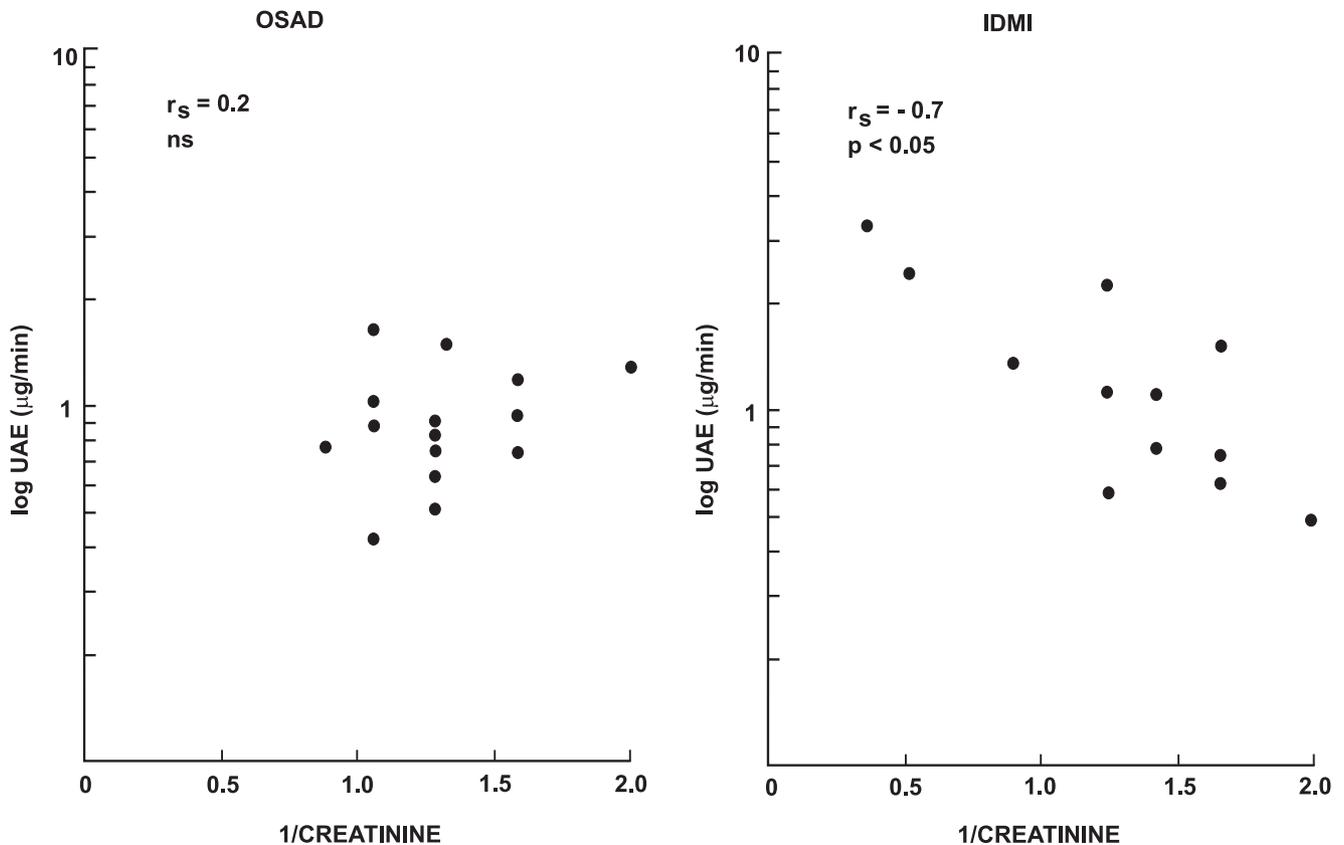


Figure 1 - Correlation between urinary albumin excretion (UAE, expressed as logarithm) and the inverse of serum creatinine values (1/C, as an indirect index of glomerular filtration rate) in the OSAD and IDMI groups.

DISCUSSION

This study demonstrates the differences in severity of diabetic complications, under the same conditions, between isolated type 1 diabetes and that associated with other autoimmune endocrinopathies, for the first time to our knowledge. The two groups were matched for diabetes duration and metabolic control over the last 6 years. They also had the same daily insulin requirement, which may imply a similar residual insulin secretion.^{12,13}

In an old study by Bottazzo et al,³¹ when looking for an association between thyrogastric autoantibodies and islet-cell autoantibodies among the families of juvenile diabetes sufferers, they observed that the families with evidence of organ-specific autoimmunity appeared to have a higher frequency of vascular complications. However, the patients were not matched for diabetes duration (the OSAD patients had diabetes for a longer time), nor for diabetes glycaemic control. Also, only the macroproteinuric

nephropathy phase was evaluated. Another study analyzed the prevalence of retinopathy in the presence of coincident autoimmune disease to a degree sufficient for producing thyroid failure or thyrotoxicosis, and found that it neither protects against nor contributes to retinopathy.³² These patients were not matched for diabetes control.

Microvascular complications develop in many patients with DM1, but their prevalence and severity are influenced by various genetic^{10,11} and metabolic^{8,9} factors, and there may be other, as yet unknown factors. Regarding retinopathy, although the background form is virtually universal after 20 years of diabetes duration, the proliferative forms affect 70% of DM1 subjects after 30 years of the disease.^{4,7} On the other hand, nephropathy, the strongest predictor of premature death and cardiovascular diseases in diabetic patients, occurs in only 40% of diabetic patients, even in cases of long diabetes duration.⁶

In general, the progression and intensity of retinopathy are related to poor metabolic control,^{14,28,33}

smoking,⁷ systemic pressure levels 4.34 (especially diastolic blood pressure)³⁵ and genetically determined immunopathic mechanisms.³⁶ The degree of metabolic control achieved in both groups studied was the same, and it can be considered good because glycosylated hemoglobin levels remained no more than 1.5% above the upper limit for normality (6.2 and 6.8 vs. 5.3%). There were no differences related to prevalence of hypertension and pressure control between the two groups studied, although hypertensive patients were treated. In the OSAD group a greater but not statistically different prevalence of all retinopathy was observed. However, in the iDM1 group with the same diabetes duration and metabolic control, a tendency to greater severity in retinopathy was observed. We should also take into account that the true diabetes duration could be underestimated in the OSAD group due to its sometimes more insidious onset.³⁷

Comparing our data with the epidemiological study of Parving et al,³⁸ which analyzed DM1 patients of comparable age (42 years old) and slightly longer diabetes duration (21 years) than our groups, we can see almost the same prevalence of hypertension (41% vs. 61.5% in our iDM1 and 53% in OSAD) and total retinopathy (78% vs. 69% in our iDM1 and 82% in OSAD). However, the prevalence of proliferative retinopathy in our iDM1 patients was much higher (47% vs. 23% in OSAD and 36% in Parving's study). Another study showed that the incidence of proliferative retinopathy was 33% in a 40-year follow-up.³⁹ It is worth remembering that the prevalence of hypertension in the two groups studied was almost the same. Another point is that in other studies there may also be OSAD patients, with diabetic control and adherence to treatment, but with different genetic and social situations.

The prevalence of nephropathy in our iDM1 patients was almost the same as found in Parving's study (39% vs. 41%, respectively),³⁸ as was the prevalence of microalbuminuria (23% vs. 22%, respectively). However, clinical nephropathy (macroalbuminuria) was found in 12% of our iDM1 patients and in 19% in the Scandinavian study against none (0%) of the OSAD patients studied.

The prevalence of clinical nephropathy in other studies was much higher (35 to 42%).^{40,41} In the classical

evolution of nephropathy in type 1 diabetes, the main associated factor is the presence of hypertension,^{7,10,35,42,43} as well as the metabolic control.^{1,9,34} However, hypertension was associated with nephropathy in the iDM1 group, as expected, but not in the OSAD group. Another fact was that albuminuria, which is a classical marker of nephropathy,^{26,27,44} was higher and it was not correlated with glomerular filtration rate in OSAD patients in spite of the inverse correlation in the iDM1 group.

The correlation between albuminuria and glomerular filtration rate is controversial, with different behaviour in patients with type 1 diabetes. Some studies have found a strong correlation, whereas others have not.⁴⁵ The variability in albuminuria measurements and the hyperfiltration shown by these patients could explain these differences.⁴⁵ Even so, the presence of hypertension and/or abnormal levels of urinary albumin excretion does not seem have the same prognostic value in type 1 diabetes, whether associated with PGAS or not, and OSAD patients could contribute to the confusion in the establishment of a relationship between EUA and GFR.

The genes related to PGAS-II may be in linkage disequilibrium with other genes that raise the microvascular risks.^{18,46-48} Therefore genetic factors should be associated with this particular course of diabetic complications in the OSAD group. Furthermore, the pancreas immunological destruction process rate in OSAD and iDM1 is also different. The OSAD patients remain with high levels of anti-islet cell antibodies for a long time, sometimes for more than 10 years without clinical diabetes, different to what can occur in iDM1 patients.⁴⁹⁻⁵⁴ This study suggests that chronic microangiopathic complications in type 1 diabetes associated with polyendocrinopathies may have different behavior in relation to isolated type 1 DM. It has apparently less severe evolution of diabetic microvascular complications than type 1 diabetes alone, in spite of the diabetes duration, age at onset of diabetes and metabolic control. Albuminuria and hypertension in these patients are probably not associated with the level of renal impairment. More studies on this particular group of patients should be done in order to evaluate new, previously unrecognized genetic, immunological or endocrinological influences on the course of diabetic microangiopathies.

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RESUMO

Contexto: O desenvolvimento e evolução das complicações crônicas do *diabetes mellitus* podem apresentar diferenças entre os vários tipos e condições desta doença. **Objetivo:** Avaliar o grau de microangiopatia em pacientes com diabetes mellitus do Tipo 1 (DM1) associado (OSAD) ou não (DM1i) a endocrinopatias auto-ímmunes. **Pacientes:** Os OSAD (n= 17) e os DM1i (n= 13) eram pareados para o tempo de duração do diabetes (13.9 ± 8.2 e 13.2 ± 5.9 anos, respectivamente) e controle metabólico (HbA1c: 6.4 ± 1.9 e $6.8 \pm 1.4\%$). **Variáveis Estudadas:** A excreção urinária de albumina (EUA), o inverso da creatinina sérica (1/C) e o grau de retinopatia diabética (oftalmoscopia indireta). **Resultados:** A prevalência de hipertensão arterial foi semelhante nos grupos e os OSAD tinham níveis inferiores de EUA (7.4 ± 2.5 vs. 17.3 ± 9.2 $\mu\text{g}/\text{min}$; $p < 0.05$). A nefropatia diabética foi detectada em 12% dos OSAD (nenhum deles com macroproteinúria) e em 39% dos DM1i. Nos DM1i havia uma correlação inversa entre a EUA e o 1/C ($r = -0,7$, $p < 0,005$), o mesmo não ocorria no OSAD ($r = 0,2$, ns). Retinopatia em grau severo: 29% do OSAD e 46% do DM1i. **Conclusões:** O presente estudo sugere que os OSAD apresentam uma evolução melhor das microangiopatias quando comparado ao DM1i nas mesmas condições. Nos DM1i o aumento da EUA estava inversamente associada ao RFG e o mesmo não ocorria nos OSAD.