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Factors associated with the presence of microangiopathy in type 2 diabetics outpatients in Antananarivo, Madagascar, in 2023

Rija E. Raherison*, Thierry Razanamparany, Miora M. A. Andrianiaina, Radonirina L. Andrianasolo, Andrianirina D. P. Rakotomalala

Department of Endocrinology, Joseph Raseta Befelatanana University Hospital in Antananarivo, Madagascar

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*Correspondence: Dr. Rija E. Raherison,

E-mail: rijaherison@yahoo.fr

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ABSTRACT

Background: The microvascular complications of diabetes correspond to diabetic microangiopathy including retinopathy, nephropathy and neuropathy. Few data are available on diabetic microangiopathy in Madagascar. The aims of the present study were to determine the prevalence of microangiopathy and their associated factors in a population of type 2 diabetics seen as outpatients in the Endocrinology Department of Joseph Raseta Befelatanana Hospital, in Antananarivo, Madagascar.

Methods: Cross-sectional, descriptive and analytical study was conducted over a 6-month period. Retinopathy was diagnosed by specific abnormalities on fundus examination, nephropathy by albuminuria ≥ 30 mg/24h, and peripheral neuropathy by symmetrical distal sensory symptoms beginning in the lower limbs, a DN4 score $\geq 4/10$ and/or impaired foot sensitivity.

Results: Of the one hundred type 2 diabetics included in the study, sixty-two (62%) had presented with one or more diabetic microangiopathy. Associated factors were diabetes duration \geq 10 years (OR=3.28; 95% CI: 1.17-9.22), abdominal obesity (OR=1.72; 95% CI: 1.06-2.77) and HbA1c >10% (OR=3.72; 95% CI: 1.02-13.48). Albuminuria was significantly higher in type 2 diabetics with microangiopathy than in without (p<0.01) while estimated glomerular function rate was significantly lower (p=0.04).

Conclusions: Diabetic microangiopathy was frequent. Optimal management of hyperglycemia, obesity and associated cardiovascular risk factors is essential to avoid or limit their occurrence.

Keywords: Associated factors, Microangiopathy, Prevalence, Type 2 diabetes mellitus

INTRODUCTION

Diabetes is a major public health problem. It is a metabolic disorder characterized by the presence of hyperglycemia attributable to a defect in insulin secretion and/or insulin action. The chronic hyperglycemia is associated with fairly specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk of cardiovascular disease. Les specific ocular complications, more specifically retinal or retinopathy, renal or nephropathy and neurological or neuropathy, are grouped under the term diabetic microangiopathies.

Diabetic retinopathy (DR) remains a major cause of visual impairment and the leading cause of blindness in people under 60 in industrialized countries.³

Diabetic nephropathy (DN) occurs in 30% of insulindependent diabetics and 25% of non-insulin-dependent diabetics. It is characterized by a progressive and continuous deterioration of glomerular function, leading to irreversible renal failure. It is one of the most frequent causes of end-stage renal failure.⁴ Diabetic neuropathy is the most frequent complication of diabetes, with prevalence ranging from 8% to 60%, depending on the criteria used. It can affect the peripheral nervous system corresponding to the diabetic peripheral neuropathy (DPN) as well as the autonomic nervous system corresponding to the diabetic autonomic neuropathy (DAN).⁵

These complications tend to appear over time, impair quality of life and can even be fatal. In addition, they increase health expenditure.

So, early detection of microangiopathy is important in type 2 diabetic (T2D) patients to manage them as soon as possible in order to reduce their burden especially in low and middle income countries like ours.

The duration of diabetes and its poor control are among the factors incriminated in the occurrence of these microangiopathies according to the literature.⁶

In Madagascar, few data are available about microangiopathies and their associated factors. The main objective of this study was to determine prevalence of microangiopathy and identify their associated factors in a population of Malagasy T2D patients. This data will allow us to better target and improve our therapeutic interventions on diabetes management.

METHODS

This is a descriptive and analytical retrospective cross-sectional study conducted during the period from April 1, 2023 to September 31, 2023 (6 months) including exhaustively all T2D patients seen as outpatients in the Endocrinology Department of Joseph Raseta Befelatanana university hospital in Antananarivo, Madagascar. The sample size was 107.

Inclusion criteria

Patients included were adult T2D over 18 years of age, who had been screened for diabetic microangiopathies by fundus examination for retinopathy, 24-hour albuminuria assay for nephropathy and clinical examination for peripheral neuropathy.

Exclusion criteria

Pregnant patients, patients with incomplete parameters and patients with one or more factors making the diagnosis of microangiopathy uncertain or impossible were excluded.

Thus, patients with cataracts or insufficient pupil aperture hindering the diagnosis of DR were excluded.³

Those presenting with a urinary tract infection, fever, decompensated heart failure, ketonuria, menstruation were excluded, as these situations could influence

albuminuria levels and lead to confusion about the existence of ${\rm DN.}^7$

Similarly, those with a pathology or situation likely to give rise to neuropathy were excluded, including chronic alcoholism, spinal cord compression, neurotoxic drugs such as chemotherapy, hypothyroidism and Human Immunodeficiency Virus (HIV) infection.⁸

Parameters studied

Socio-demographic parameters including age and gender.

The characteristics of the diabetes, including its duration and insulin therapy if diabetes is previously known.

The associated cardiovascular risk factors (CVRF) including high blood pressure (HBP), smoking, a blood level of high density lipoprotein cholesterol (HDL-c) <40 mg/dl (1.03 mmol/l) and the existence of early-onset family atherosclerotic cardiovascular disease (ASCVD).

Clinical characteristics: current systolic and diastolic blood pressures, body mass index (BMI), abdominal circumference, presence of abdominal obesity, presence of macroangiopathy including ischemic stroke or transient ischemic attack (TIA), coronary artery disease (CAD), occlusive peripheral arterial disease (OPAD)/amputation.

Bbiological characteristics including fasting blood glucose, random blood glucose, glycosylated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), 24-hour albuminuria, blood level of HDL-c, blood level of low density lipoprotein cholesterol (LDL-c), triglyceridemia (TG).

Clinical and paraclinical data

DR was diagnosed in the presence of abnormalities on fundus examination after pupillary dilation.⁹

DN was attested by the presence of albumin ≥30 mg in urine collected over 24h, with or without impaired glomerular filtration.⁹

The diagnosis of DPN was purely clinical. It is retained by the existence of distal symmetric sensory symptoms starting in the lower limbs, a score \geq 4/10 on the DN4 questionnaire defining neuropathic pain, and/or altered sensitivity of the feet on examination with a 10 g monofilament or 128 Hz graduated tuning fork.

The diagnosis of newly diagnosed diabetes was based on the American Diabetes Association (ADA) 2023 criteria.¹⁰

The duration of diabetes was expressed in years for diabetics previously known before the consultation. Those whose diabetes had just been diagnosed were classified as newly diagnosed with diabetes.

HBP was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or use of antihypertensive treatment.

Smokers were defined as those who had not yet weaned off smoking or had stopped smoking less than three years previously.

Early-onset family ASCVD included myocardial infarction or sudden death before age 55 in the father or a first-degree male relative; or before age 65 in the mother or a first-degree female relative.¹¹

BMI was calculated using the formula: BMI (kg/m^2) = weight (kg)/height² (m^2) .

Abdominal obesity is characterized by an abdominal circumference \geq 80 cm in a woman and \geq 94 cm in a man. ¹²

The presence of macroangiopathy, including ischemic stroke or TIA, CAD and OPAD, was determined according to specific anamnestic, clinical and paraclinical criteria for each complication. ^{13,14}

Glycosylated hemoglobin (HbA1c) was determined by high-performance chromatography and expressed as a percentage (%).

Albuminuria was measured using the turbidimetric method and expressed in mg/24h.

Creatinine levels were determined using the alkaline picrate method. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula expressed in ml/min/1.73m².

Total cholesterol (TC), HDL-c and triglyceridemia (TG) were determined enzymatically. LDL-c was calculated using Friedwald's formula: LDL-c (mmol/l) = TC (mmol/l) - HDL-c (mmol/l) - (TG(mmol/l) x 0.45).

Data collection

Parameters were collected using a pre-established information form in Microsoft Office Word 97 - 2003[®].

Statistical analysis

The data were then transcribed and analyzed using IBM SPSS® version 26 software. The statistical analysis began with a description of the patients according to each variable studied. We calculated frequencies for qualitative variables and means \pm standard deviations for quantitative variables.

Then, for the analytical study, we compared the frequency of each variable studied in diabetics with microangiopathy (M +) and those without (M -). The statistical tests used for the comparative analysis were the Chi 2 test for qualitative variables and the Student's t test for quantitative variables.

A p value ≤0.05 was considered statistically significant. The measure of association used was the odds ratio (OR) retained significant when the value 1 was not included in the 95% confidence interval [95% CI].

RESULTS

One hundred and seven T2D patients were enrolled during the study period. Seven were excluded including 4 with urinary tract infections and 3 with decompensated heart failure. In the end, one hundred patients were selected.

The general characteristics of the 100 patients selected for the study are summarized in Table 1.

Table 1: General characteristics of patients (n=100).

Variables	Results
Mean age (years)	60.53±9.36
Sex ratio	0.67
Newly diagnosed with diabetes, N (%)	9 (9%)
Previously known diabetics, N (%)	91 (91%)
Mean duration of previously known diabetes (years)	7.77±7.56
Insulin therapy if previously known diabetics, N (%)	29 (29)
HBP, N (%)	80 (80)
Tobacco, N (%)	20 (20)
HDL-c<40 mg/dl (1.03 mmol/l), N (%)	26 (26)
Early-onset family ASCVD, N (%)	13 (13%)
Mean SBP (mmHg)	141.81±18.27
Mean DBP (mmHg)	87.90 ± 15.12
Mean BMI (kg/m²)	26.00 ± 3.85
Mean abdominal circumference (cm)	93±8.81
Patients with macroangiopathies, N (%)	30 (30)
Ischemic stroke/TIA, N (%)	4 (4)
CAD, N (%)	24 (24)
OPAD/amputation, N (%)	4 (4)
Mean HbA1C (%)	8.00±2.12
Mean albuminuria (mg/24h)	107.19±164.09
Mean eGFR (ml/min/1.73m²)	90.76±23.98
Mean HDL-c (mmol/l)	1.16±0.33
Mean LDL-c (mmol/l)	2.30±2.06
Mean triglyceridemia (mmol/l)	1.54±1.65

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycosylated hemoglobin; HBP: high blood pressure; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; OPAD: occlusive peripheral artery disease; SBP: systolic blood pressure

Sixty-two patients presented with 1 or more microangiopathies, giving a prevalence of 62%. Twenty-seven (27%) patients had DR, 35 (35%) DN and 36 (36%)

DPN. Among these 62 patients, thirty-six had presented with a single type of microangiopathy, 17 and 9 had presented with 2 and 3 types of microangiopathy respectively.

The mean age of patients with microangiopathy was 62.72±8.36 years, with a sex ratio of 0.72. None of the socio-demographic parameters was associated with the presence of microangiopathy (Table 2).

Concerning the characteristics of diabetes and other associated cardiovascular risk factors, among those with

microangiopathy, eight (12.9%) were newly diagnosed with diabetes and 54 (87.10%) were previously known diabetics. The mean duration of diabetes for those whose diabetes was previously known was 9.06±7.24 years. Diabetes duration of more than 10 years was associated with the presence of microangiopathy (p=0.02; OR=3.28 [1.17-9.22]).

Fifty (80.65%) of the patients with microangiopathy have HBP, compared with 30 (78.95%) of those without. However, no cardiovascular risk factors were associated with the presence of microangiopathy (Table 3).

Table 2: Relationship between socio-demographic characteristics of patients and presence of microangiopathy (n=100).

Variables	M+ (n=62)	M - (n=38)	P value
Mean age (years)	62.72±8.36	59.16±10.87	0.07
sex ratio	0.72	0.58	
Male, N (%)	26 (41.94)	14 (36.84)	0.61

M+: patients with microangiopathy M-: patients without microangiopathy

Table 3: Relationship between characteristics of diabetes and associated cardiovascular risk factors of patients and the presence of microangiopathy (n=100).

Variables	M+ (n=62)	M - (n=38)	OR[IC95%]	P value
Newly diagnosed with diabetes, N (%)	8 (12.90)	1 (2.63)	5.48 (0.66-45.69)	0.14
Previously known diabetics, N (%)	54 (87.10)	37 (97.37)	0.18 (0.02-1.52)	0.14
Mean duration of previously known diabetes (years)	9.06±7.24	5.56±5.42		0.01
Less than 5 years, N (%)	18 (33.33)	21 (56.76)	0.38 (0.16-0.90)	0.03
5 to 9 years, N (%)	15 (27.78)	10 (27.03)	1.04 (0.40-2.65)	0.93
10 years and over, N (%)	21 (38.89)	6 (16.22)	3.28 (1.17-9.22)	0.02
Insulin therapy if previously known diabetic				
Yes, N (%)	18 (33.33)	11 (29.73)	1.18 (0.48-2.92)	0.72
No, N (%)	36 (66.67)	27 (70.27)	1.10 (0.46-2.92)	
HBP, N (%)	50 (80.65)	30 (78.95)	1.11 (0.41-3.03)	0.84
Tobacco, N (%)	14 (22.58)	6 (15.79)	1.56 (0.54-4.47)	0.41
HDL- c<40 mg/dl (1.03 mmol/l), N (%)	16 (25.81)	10 (26.32)	1.14 (0.45-2.89)	0.79
Early-onset family ASCVD, N (%)	6 (9.68)	7 (18.42)	0.47 (0.15-1.54)	0.21

ASCVD: atherosclerotic cardiovascular disease; HBP: high blood pressure; HDL-c: high density lipoprotein cholesterol; M+: patients with microangiopathy; M-: patients without microangiopathy

Table 4: relationship between clinical characteristics of patients and the presence of microangiopathy (n=100).

Variables	M+ (n=62)	M - (n=38)	OR[IC95%]	P value
Mean SBP (mmHg)	143.71±24.27	140.82±16.69		0.79
Mean DBP (mmHg)	87.06±13.14	88.81±9.92		0.48
Mean BMI (kg/m²)	26.03±4.45	25.70±3.73		0.70
Mean abdominal circumference (cm)	94±10.30	91.82±9.61		0.31
Abdominal obesity, N (%)	43 (69.35)	18 (47.37)	1.72 (1.06 - 2.77)	0.029
Macroangiopathies	19 (30.65)	11 (28.95)	1.08 (0.45 - 2.63)	0.86
Ischemic stroke/TIA	2 (3.23)	2 (5.26)	0.60 (0.08 - 4.47)	0.63
CAD	14 (22.58)	10 (26.32)	0.82 (0.32 - 2.08)	0.67
OPAD/amputation	3 (4.84)	1 (2.63)	1.88 (0.19 - 18.77)	1.00

BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; M+: patients with microangiopathy; M-: patients without microangiopathy; OPAD: occlusive peripheral artery disease; SBP: systolic blood pressure; TIA: transient ischemic attack

Clinically, only abdominal obesity was associated with the presence of microangiopathy (p=0.029; OR=1.72 [1.06 - 2.77]). Neither blood pressure, BMI nor the presence of macroangiopathy were associated with microangiopathy (Table 4).

On biological tests, diabetes control influenced the presence of microangiopathy. HbA1c >10% was

associated with the presence of microangiopathy (p=0.049; OR=3.72 [1.02 - 13.48]).

Furthermore, in T2D with microangiopathy, albuminuria was significantly higher $(58.31\pm125.11~\text{mg/24h}~\text{vs.}\ 10.72\pm7.31~\text{mg/24h};\ p<0.01)$ while eGFR was significantly lower than in TD2 without microangiopathy $(82.58\pm26.98~\text{vs.}\ 93.76\pm23.77~\text{ml/min/1.73m}^2;\ p=0.04)$ (Table 5).

Table 5: Relationship between biological characteristics of patients and the presence of microangiopathy (n=100).

Variables	M + (n=62)	M - (n=38)	OR[IC95%]	P value
Mean fasting blood glucose (mg/dl)	156.66±99.57	132.36±48.65		0.34
Mean random blood glucose (mg/dl)	161.89±86.53	153.26±58.56		0.57
Mean HbA1C (%)	8.41±2.32	7.32 ± 1.56		0.01
HbA1C >10%, N (%)	15 (24.19)	3 (7.89)	3.72 (1.02-13.48)	0.049
Mean albuminuria (mg/24h)	58.31±125.11	10.72±7.31		< 0.01
Mean eGFR (ml/min/1.75m ²)	82.58±26.98	93.76±23.77		0.04
Mean HDL-c (mmol/l)	1.11±0.33	1.19±0.32		0.34
Mean LDL-c (mmol/l)	2.44±1.53	2.19±0.96		0.76
Mean triglyceridemia (mmol/l)	1.36±0.67	1.79±1.39		0.38

DISCUSSION

We found a high prevalence of microangiopathy in our study population (62%). This observation was close to the microangiopathy frequencies described in the studies by Nachi et al in Algeria (66.8%) and Li et al in China (57.5%), but much higher than that reported by Messaoudi et al in Morocco (32%).15-17 In fact, our study population was similar to those of the Nachi and Li teams, which included only type 2 diabetics followed up on an outpatient basis, unlike Messaoudi's study, which included hospitalized diabetics. Indeed, for outpatients, it would be easier to investigate the various complications of diabetes; whereas for inpatients, the priority would be to diagnose and treat the main reason for hospitalization. Many situations, such as episodes of decompensated heart failure or urinary tract infections, make it impossible to confirm certain microangiopathic complications, such nephropathy.

Diabetic peripheral neuropathy was the most frequent microangiopathic complication (36%), followed by DN (35%) and DR (27%) in our study. These frequencies were close to those reported by Nachi et al and Raman et al. ^{15,18} While for Bui et al in China, DPN (23.5%) was followed by DR (17.4%) and DN (10.8%). ¹⁹ These differences may be explained by differences in studied populations, including duration of diabetes, comorbidities, race, region, economic level, and diagnostic criteria for microangiopathies.

Like Shillah et al in Tanzania, we found no relationship between patient age and the presence of microangiopathy.²⁰ This was in contradiction with the results reported in studies by Li et al in China and Seid et al in Ethiopia. 16,21

The female predominance of our patients was similar to that of Messaoudi et al.¹⁷ Similarly, gender was not associated with the presence of microangiopathy in us, as in Algeria and China.^{15,16} Thus, microangiopathies should be investigated regardless of patient age and gender.

Microangiopathies can be present as early as the diagnosis of type 2 diabetes. This explains the presence of microangiopathy in 8 newly diagnosed with diabetes in our study. This is due to the fact that this type of diabetes evolves quietly for several years before being discovered, leaving time for complications to develop.²² For this reason, it is recommended that vascular complications must be systematically investigated as soon as diabetes is diagnosed, so as not to delay their management.^{7,23}

We found a statistically significant relationship between the duration of diabetes and the presence of microangiopathy. This result is in line with the literature. Indeed, like the results reported in the studies by Arambewela et al in Sri-Lanka and Tracey et al. in Ireland, duration of diabetes of more than 10 years was a risk factor for diabetic microangiopathy in our patients. ^{24,25} Indeed, the duration of diabetes reflects exposure to risk factors for vascular degenerative complications over time. ²⁵

In our case, insulin therapy was not associated with the presence of microangiopathy, contrary to the findings of some studies.^{19,26,27} In fact, insulin therapy is more of an indicator of poorly controlled diabetes than a factor of complications. Moreover, while in these other countries, insulin therapy is only initiated when the combination of

several oral antidiabetic agents fails, in Madagascar, it is prescribed fairly rapidly because the combination of several antidiabetic drugs is too expensive and insulin therapy seems cheaper. It should be noted that the insulin most widely used in Madagascar is still regular insulin.

Like Bonora et al, we didn't find any association between HBP and microvascular complications, contrary to the results of other studies. 25,27,28

This difference could be explained by the fact that the history of HBP in our patients was retained only by their assertion in the majority of cases.

Our study showed that the mean blood pressure in both diabetic patients with and without microangiopathy was above the blood pressure target of <130/80 mmHg.²⁹ However, as its value during the medical consultation was a point value, several parameters such as the white coat effect, or its measurement under poor conditions could influence it. Indeed, Single-occasion blood pressure measurements overestimate true hypertension.³⁰ This could also explain the absence of a relationship between blood pressure and microangiopathy in our study.

Nevertheless, it is recognized that blood pressure control reduces the onset and development of microvascular complications in patients with type 2 diabetes.³¹

Clinically, only abdominal obesity was associated with the presence of microangiopathy in our study. Indeed, abdominal obesity is the main factor in insulin resistance. It reflects lipid accumulation and triggers and amplifies oxidative stress. Oxidative stress in turn is accompanied by pancreatic β -cell failure and vascular damage. 32

We found no relationship between the presence of diabetic macroangiopathy and microangiopathy. Negussie et al in Ethiopia also made the same finding, while Hussein et al in Sudan found an association between the presence of CAD and microangiopathy. These differences may be explained by differences in diagnostic methods for macroangiopathies and microangiopathies in these different countries. In any case, systematic, early and regular screening for all types of vascular complications is essential for all type 2 diabetics, especially in low-income countries such as ours, where the management of diabetic complications is very difficult.

Poor diabetic control was associated with microangiopathy in our study. Other authors have also demonstrated this relationship.^{24,33} This chronic hyperglycemia is evidenced by high glycosylated hemoglobin levels rather than by blood glucose levels, which were measured only occasionally during medical consultations. Pathophysiologically, chronic hyperglycemia promotes the formation of advanced glycation end products (AGEs). The accumulation of AGEs leads to alterations in intracellular, matrix and secreted proteins, resulting in endothelial dysfunction via activation of specific

receptors, including RAGE. The binding of AGEs to RAGE triggers an inflammatory cascade and induces oxidative stress. This leads to structural changes in microvessels, which explain diabetic microangiopathies.^{35,36}

Our patients with microangiopathy had significantly higher mean albuminuria than those without. This is in line with the observation of Bhavya et al in India.⁴

Similarly, like Babaliche in India, Teliti in Italy, we found an inverse relationship between eGFR value and the presence of microangiopathy.^{37,38} In fact, increased albuminuria, starting with the microalbuminuria stage, is already indicative of diabetic nephropathy. And microalbuminuria is recognized as an important factor in GFR decline.³⁹

The limitation of this study is that the results may not be applicable to the total population, as it only involved outpatients, most of whom were active or retired public servants whose biological check-ups were paid for by the state. Blood pressure values could be biased, as they were taken only once. The same applied to albuminuria measurements. As the study was cross-sectional, it was impossible to determine the causal relationship between the associated factors and diabetic microvascular complications.

CONCLUSION

This study revealed a very high prevalence of microangiopathy in our type 2 diabetic patients. The long duration of diabetes, its poor control and abdominal obesity were the factors associated with microagiopathic complications. However, some patients already have microangiopathy when their diabetes is discovered. Hence the importance of systematic screening as soon as diabetes is diagnosed, the need for good glycemic control, active management of obesity and other cardiovascular risk factors associated with diabetes, and the use of antidiabetic treatment for both metabolic and cardiovascular purposes.

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