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Morbi - Mortality of Diabetic Patients Hospitalized at the Unit of Endocrinology at the Joseph Raseta Befelatanana Hospital, Antananarivo

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Abstract: Introduction: Diabetes mellitus is a chronic pathology related to chronic hyperglycemia. Its seriousness is based on its complications, which are often a source of hospitalization and death. Our aim was to identify both the main causes of hospitalization and death in Malagasy diabetic patients. Methods: We conducted a descriptive and analytical cross-sectional study including all diabetic patients hospitalized between January and June 2020 at the unit of Endocrinology at the Joseph Raseta Befelatanana hospital, Antananarivo. Results: The mean age of our patients was 56.66 ± 13.03 years, the sex ratio was 0.82. Diabetes mellitus were known before admissions to hospital in 81.95% cases. Type 2 diabetes mellitus was found in the majority of our patients. The mainly causes of hospitalization were cardiovascular, in particular stroke, nephropathy and heart failure. The second cause of hospitalization was infections with a predilection on the pulmonary tract. The causes of hospital mortality were also cardiovascular, dominated by heart failure. Heart failure was a significant factor influencing mortality in these diabetic patients (OR = 4.65; 95% IC = 1.80 – 11.85; p < 0.01). Conclusion: To know the causes of morbi-mortality in diabetic patients may guide from the initiation of the preventions to the most precise multidisciplinary decisions. Prior investigations regarding diabetic patients with heart failure are needed. Thus, influences on the treatments, on follow-up and on subsequent researches may be appeared.

Keywords: Cardiovascular Diseases, Diabetes Mellitus, Heart Failure, Hospitalization, Mortality

1. Introduction

Diabetes mellitus is a chronic disease characterized by the presence of carbohydrate metabolism disorders causing glycemic disorders with all its consequences [1]. It is a real public health problem. Its burden is reflected not only in the increasing number of diabetic patients but also in the rising number of related premature deaths [2]. Diabetes mellitus accounted for an estimated 463 million people worldwide.

The number of deaths attributable to diabetes and its complications is estimated at 4.2 million [3]. In advanced countries, diabetes mellitus is the reason for excess hospitalization followed by related complications [2]. More than three quarters of people with diabetes is found in developing countries and there is a significant increase in the number of hospital admissions related to diabetes mellitus [3-5].

In the case of Madagascar, the World Health Organization

(WHO) report in 2016 estimated the prevalence of diabetic patients at more than 6% of the population [6]. However, there are only few data available concerning the reasons for hospitalization and the causes of death of diabetic patients in our country. To know these data would provide us with many answers on how to prevent the complications of this disease as much as possible and to reduce its related mortality.

This is why we carried out this study to identify the sociodemographic and clinical profiles of hospitalized diabetic patients, the main causes of hospitalization and death as well as the predictive factors of death at the unit of Endocrinology at Joseph Raseta Befelatanana University Hospital in Antananarivo.

2. Methods

We carried out a cross-sectional study with a descriptive and analytical aim. It took place in the unit of Endocrinology at Joseph Raseta Befelatanana University Hospital in Antananarivo, Madagascar for a period of six months (from January 1 to June 30, 2020).

To be included in the study, the patients should be diabetics and hospitalized at this site, even those discovered on admission. Incomplete records were excluded. The parameters studied were age, gender, profession, the duration of the de development of diabetes, the antidiabetics drugs taken before the hospitalization as well as diabetes control profile. This is followed by the comorbidity associated with diabetes including cardiovascular risk factors (CVRF) such as advanced age over 50 years in men, over 60 years in women, high blood pressure, smoking status and the chronic diseases consisting of neurological, ocular, chronic respiratory, liver and inflammatory diseases, heart failure and neoplasia. The causes of hospitalization are divided into cardiovascular, infectious and acute metabolic complications. After talking about the patient outcome (alive or dead), the causes of death are divided in the same way into cardiovascular, infectious and acute metabolic complications. Diabetes diagnosis and typing were made according to the criteria of the American Diabetes Association (ADA) [7].

After the descriptive study, we performed a statistical analysis of the diabetic patients' outcome according to their sociodemographic parameters, characteristics of the diabetes, CVRF, known diabetes complications and associated comorbidities.

Data were collected using a pre-test and validated questionnaire. Statistical analysis was performed using Epi-info^{TM} software version 7. The results are represented in absolute value, in percentage and in average. We used Pearson's Chi-Square Test to test for correlation with significance level p value < 0.05.

Anonymous was preserved by a coding method.

3. Results

During the study period, from 420 patients admitted to hospital, we selected 277 diabetic patients who met the

eligibility criteria. It gives a proportion of 65.95% within those hospitalized patients. Their mean age was 56.66 ± 16.03 years with extremes 13 years and 87 years. The sex ratio M/F was 0.82 (125 men and 152 women). The majority of our patients were employed in the tertiary sector (32.13%), followed by the unemployed (27.44%) people and the retirees (26.35%). Table 1 summarizes the clinical data of the admitted diabetic patients.

Table 1. Characteristics of hospitalized patients.

Variables	Frequency	Percent (%)
Gender		
Male	125	45.13
Female	152	54.87
Profession		
Tertiary sector	89	32.13
Unemployed	76	27.44
Retirees	73	26.35
Primary sector	31	11.19
Secondary sector	8	2.89
Characteristics of diabetes (N = 277)		
T1DM	38	13.72
T2DM	239	86.28
Circumstances of discovery of diabetes		
Known diabetic	227	81.95
New hyperglycemia	50	18.05
Antidiabetic drugs taken * (n_1 = 227)		
No treatment	72	31.72
Sulfonylureas	78	34.36
Insulin premix	62	27.31
Insulin rapid	59	25.99
Metformin	46	20.26
Madeglucyl^{TM}	07	3.08
Insulin basal	05	2.20
DPP-4-i	4	1.44
Diabetes control profile		
A1c not performed	174	62.82
A1c< 7%	23	8.30
A1c: 7 - 9	29	10.47
A1c > 9%	51	18.41
Cardiovascular risk factors and comorbidities associated with diabetes mellitus (N =277)		
High blood pressure	167	60.29
Age	160	57.76
Smoking status	31	11.19
Heart failure	30	10.83
Eye disease	13	4.69
Neurological disorders	10	3.61
Neoplasia	09	3.25
Chronic inflammatory disease	04	1.44
Liver disease	02	0.72
Chronic pulmonary disease	01	0.36
*High blood pressure treatments * (n_2 = 167)*		
Angiotensin receptor blockers	62	37.13
Calcium channel blockers	57	34.13
Angiotensin-converting enzyme inhibitor	28	16.77
Thiazide diuretics	18	10.78
Beta-blockers	13	7.78
Central antihypertensive drugs	04	2.40

* Patients might take one or more classes of drugs.
T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus; DPP-4-i: dipeptidyl-peptidase-4-inhibitor; A1c: glycated haemoglobin.

In regard to the characteristics of diabetes, 239 patients (86.28%) were type 2. For 50 patients (18.05%), diabetes

was discovered during hospitalization or even when complications occured. The average duration of diabetes in those already known was 6.28 ± 5.79 years (1 month to 31 years). Seventy-two (31.72%) of the 227 patients known to be diabetic had not received any antidiabetic treatment. Among those who had already received such treatment, seventy-eight patients (34.36%) were treated with sulphonylureas, forty-six patients (20.26%) with metformin and sixty-two patients (27.31%) with insulin mix. It should be noted that a patient may have been treated with one or more antidiabetic drugs. With regard to the diabetes control profile, only 103 patients (37.18%) were able to have their glycated hemoglobin (HbA1c) measured during hospitalization. This includes 80 patients (28.88%) who had uncontrolled diabetes; 51 patients (18.41%) had an HbA1c level exceeding 9%. The mean HbA1c value was $9.22 \pm 2.79\%$. The characteristics of the diabetes were summarized in table 1.

High blood pressure (60.29%) and advanced age (57.76%) were the most common cardiovascular risk factors associated with diabetes mellitus. In the treatment of high blood pressure, Angiotensin 2 Receptor Blockers (ARB) and calcium channel blockers were most frequently used in the treatment of high blood pressure in the ambulatory setting (37.13% and 34.13% respectively). A patient may have taken one or several therapeutic classes.

Thirty patients (10.83%) had heart failure, thirteen (4.69%) had ophthalmological complications, and ten (3.61%) had neurological pathologies.

Two hundred and sixty-seven patients (96.39%) of those admitted to hospital had complications related to diabetes mellitus. The causes of hospitalization were dominated by cardiovascular complications (47.65%). Among the cardiovascular causes, the most frequent were stroke (11.91%), nephropathy (11.19%) and heart failure (10.83%). Undercurrent infectious complications and acute metabolic complications came second and third with a frequency of 28.16% and 20.58% respectively. Infectious complications were dominated by respiratory infection (11.19%), followed by urinary tract infection (5.78%) and digestive tract infection (5.42%). Diabetic ketoacidosis was identified as the cause of hospitalization for 28 patients (10.11%) and hypoglycemia for 23 patients (8.30%). The causes of hospitalization are summarized in Table 2.

Table 2. *Causes of hospitalization ($n_1 = 277$; $n_2 = 26$).*

Variables	Frequency	Percent (%)
Causes of hospitalization for all diabetic patients ($n_1 = 277$)		
Cardiovascular complications	132	47.65
Stroke	33	11.91
Nephropathy	31	11.19
Heart failure	30	10.83
Coronaropathy	16	5.78
Retinopathy	13	4.69
Obliterative arteriopathy of the lower limbs	7	2.53
Neuropathy	2	0.72
Infectious complications	78	28.16
Respiratory system	31	11.19
Urinary tract	16	5.78
Digestive	15	5.42
Bones and joints	11	3.97
Skin	3	1.08
Neuro-meningitis	2	0.72
Oral	0	0
Oto-rhino-laryngological sphere	0	0
Genital	0	0
Acute metabolic complications	57	20.58
Diabetic ketoacidosis	28	10.11
Hypoglycemia	23	8.3
Hyperosmolar non-ketotic hyperglycemia	6	2.17
Lactic acidosis	0	0
Other causes	10	3.61
Causes of hospitalization of deceased patients ($n_2 = 26$)		
Cardiovascular complications	15	57.69
Infectious complications	10	38.46
Acute metabolic complications	3	11.54
Combination of several complications	2	7.69

Twenty-six patients died, giving a mortality rate of 6.2%. In the deceased patients, the complications encountered were mainly cardiovascular (57.69%) (Table 2). In the analysis of factors influencing death, among the factors as well as comorbidities and causes of hospitalization, a statistically significant relationship was found between congestive heart

failure and fatal outcome of hospitalization (p<0.01). Neither sociodemographic variables, nor diabetes characteristics, nor CRF, nor causes of hospitalization were associated with death (Table 3).

Table 3. Hospitalized diabetic patients outcomes (n₁ = 26; n₂ = 251).

Variable	Deaths (n₁ = 26)	Survivors (n₂ = 251)	OR	95% CI	p-value
Characteristics of hospitalized diabetic patients					
Age (years)	5.88 ± 11.89	56.43 ± 13.14	-	-	0.36
	(32 - 78)	(13 - 87)	-	-	
			-	-	
Sex-ratio	1.16	0.79	0.67	0.30 - 1.52	0.34
Known diabetic	22 (84.62%)	205 (81.67%)	-	-	0.87
Unrecognized diabetes	04 (15.38%)	46 (18.33%)	-	-	0.87
Diabetes history	5.1 ± 6.49 years	6.41 ± 5.71 years	-	-	0.38
Type of diabetes			-	-	
T1DM	2 (7.69%)	36 (14.34%)	-	-	
T2DM	24 (92.31%)	215 (85.68%)	-	-	0.66
CVRF and comorbidities associated					
Smoking status	03 (09.68%)	28 (90.32%)	1.02	0.28 - 3.61	-
High blood presure	13 (07.78%)	154 (92.22%)	0.62	0.48 - 1.41	0.26
CHD	01 (06.25%)	15 (93.75%)	0.62	0.07 - 4.96	-
CHF	08 (26.67%)	22 (73.33%)	4.62	1.8 - 11.85	<0.01
Ischemic stroke	01 (03.03%)	32 (96.97%)	0.27	0.03 - 2.09	0.33
CKD	5 (23.81%)	16 (76.19%)	3.49	1.16 - 4.96	-
Neoplasia	01 (11.11%)	08 (8.89%)	1.21	0.14 - 10.11	0.59
Chronic inflammatory disease	0 (0%)	04 (100%)	-	-	-
Chronic pulmonary disease	0 (0%)	01 (100%)	-	-	-
Neurological disorders	01 (10%)	09 (90%)	1.07	0.13 – 8.84	-
Liver diseases	0 (0%)	02 (100%)	-	-	-
Eye disease	0 (0%)	13 (100%)	-	-	0.61

OR: Odds-ratio; CI: confidence interval; T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus; CVRF: cardiovascular risk factor; CHD: coronary heart disease; CHF: congestive heart failure.

4. Discussion

The majority of patients admitted in this unit were diabetics, reflecting its main preoccupation with Endocrinology in Madagascar.

The mean age of our patients was significantly younger than Hertz et al (58.8 years) in Tanzania, Nichols et al in the United States of America (59.1 years) and Yoo et al in Korea (57.28 years) found [8-10]. This difference could be attributed to an older population seen in these countries faced with our vulnerable health care system.

The female predominance of our patients was in line with the results of the literature and would confirm the greater attention of women to their health status [8, 11, 12]. They are more likely to be hospitalized than men. But in a country like ours, the hospitalization of a man, a head of the family, who is most of the time the breadwinner, would have a strong impact on the family earnings. He would prefer to be treated on ambulatory or refuse care at all. Indeed, as this study was carried out in a public hospital where care is free, it is normal that the majority of patients were worse off financially. This principle of free care adopted in Madagascar is similar to that found in some African countries [13]. Moreover, physical activity is limited in some people who work in the tertiary sector. This sedentary lifestyle contributes to the onset of diabetes mellitus. In the same case, their weaknesses related to the malnutrition and an inappropriate health care survey would tend them to hospitalizations. This problem of access and adherence affects this category of patient, especially those with a poor socio-economic level [14].

The predominance of type 2 diabetes found both in our study and that of the Kefale team (74.2%) can only be related to the high prevalence of type 2 diabetes compared to other types of diabetes mellitus in the world [15]. Moreover, determining the type of diabetes mellitus in such countries is very difficult. The reason is that these needed tests are not available yet [16]. In our country, despite the technological advances and the increase in screening sessions, complications represent one of the major occasions to discover a diabetes status. Eighteen percent of our patients were diagnosed during hospitalization. Raherison and his team had already reported 17.8% of new diabetics among hospitalized diabetic patients between December 2002 and November 2003 [17]. Efforts must therefore be stepped up for mass screening for diabetes, or even systematic screening of all hospitalized patients. For those already known with diabetes, the average duration of the diabetes mellitus (6.28 years) gives time for degenerative complications to occur [18, 19].

For pre-hospital management of diabetes mellitus, 31.72% of our patients did not receive any antidiabetic drugs, a proportion close to the 41% reported in Cambodia [20]. Drug discontinuation would mainly have related to cost and access of drugs. In addition to a lack of education based on the chronicity of diabetes mellitus. As seen here and in other countries, there is a significant role for traditional practitioners claiming that diabetes mellitus is curable. Research carried by

Raharinavalona et al and Bigdeli et al have been reported this in prior studies [20, 21]. For those who had ever received treatments, sulonylureas (34.36%) predominated over the other classes. This result differs from the literature. In a study from the United Kingdom by Khalid et al, 87.8% of patients received biguanide versus 11.6% for sulonylureas [22]. Generally, despite the limited number of oral antidiabetic drugs available in Madagascar, a majority in our population require insulin. In addition, sulphonylureas and insulin remain the most well-known antidiabetic drugs and therefore the most well prescribed [21]. In fact, the undesirable effects of metformin, particularly its digestive effects, can be a source of hesitation in its prescription. This situation leads to patients with highly unbalanced diabetes before hospitalization, as evidenced by an average HbA1c of 9.22%. This rate exceeded that reported by Blecker et al. in New York (8.2%) where the health care system is more efficient [23].

According to the literature, severely unbalanced diabetes, with an HbA1c level above 9%, is significantly associated with increased in hospitalization for heart failure and also an increased risk of all-cause mortality [23]. Less than 4 out of 10 patients had HbA1c testing in our study. Indeed, the cost of this examination limits its realization since paraclinical examinations are charged to the patients in our hospital establishments. On the other hand, as HbA1c reflects the control of diabetes over the three previous months, the management of pathologies that lead to hospitalization takes priority over the search for long-term glycemic control. Most of the time, patients are insulin-treated during hospitalization in order to facilitate the management of glycemic fluctuations as recommended in the literature [24].

Our findings confirm the frequent binomial association of diabetes and hypertension. A study carried out in China joined this result since essential hypertension appeared in the the first comorbidity associated with type 2 diabetes (58.4%) [25]. The same is true for Nowakowska et al, in England, with a frequency of hypertension of 42.8% in women and 45.8% in men with diabetes [26]. The use of ARB (37.13%), and calcium channel blockers (34.13%) as the main antihypertensive treatments followed the European Society of Cardiology (ESC) Guidelines on the choice of renin-angiotensin-aldosterone system (RAAS) blockers over beta-blockers and diuretics in the control of blood pressure in prediabetes, and initiation of dual therapy consisting of RAAS blockers with calcium channel blockers or thiazide diuretics [27]. Karinja et al, in Kenya, reported a majority of patients on calcium channel blockers, mainly nifedipine in 49.5% [28]. The limited place of central antihypertensive drugs implies the aim of limiting their contrast with the vegetative dysautonomic signs of diabetic neuropathy.

All this requires the implementation of a social security programmer and universal health coverage which remains unimproved or not implemented compared to services dedicated to communicable diseases [29].

Complications related to diabetes are discovered during hospitalization. Sarfo-Kantanka et al in Ghana even reported a frequency of 79% [4]. In the literature, the causes of hospitalization were mainly cardiovascular [18, 30]. Our findings tend too to cardiovascular complications but the vascular aspect involved differs from country to country. Pearson-Stuttard et al found a predominance of ischemic heart disease [2]. The studies carried out by Khalid et al in the United Kingdom and by Sarfo-Kantanka et al in Ghana pointed to nephropathy [4, 22]. In fact, our study showed a high frequency of stroke. The study by Tabbalat et al in the United States revealed stroke in an older population [31]. Diabetes is an independent risk factor for stroke with a 2.5 to 3-fold higher incidence than in non-diabetic subjects [32]. Furthermore, the advanced age of the population allows time for cerebrovascular complications to develop. This age-based difference in cerebrovascular injury patients could be related to the strict management of cardiovascular risk factors associated with diabetes, supported by a defect in the early detection of CVRF.

Diabetes mellitus also leads to heart failure through multiple types of heart disease or worsens the resulting heart failure [33]. Our finding is similar to registry studies by Afaf et al in Kuwait [18]. In this context, heart failure is a public health problem in both developed and developing countries. It is due to an increase in the prevalence of the elderly population and the effort made towards significant progresses in the treatment of associated comorbidities [34].

Diabetic patients are at high risk for both common and rare infections. In our case, a predominance of respiratory infections was identified. This was consistent with the literature [2, 18]. However, a urinary tract predilection was found in the United States, putting respiratory infection in the third place after the skin infections [35]. In Ethiopia, skin infections predominated [15]. Various infectious sites of diabetic patients were reported. In particular, our study has found a high frequency of stroke, often discovered at later stages. It can lead to decubitus complications, notably inhalation pneumonitis. Furthermore, type 2 diabetes increases the risk of developing respiratory infections; the duration of diabetes, diabetes mellitus related complications, and poor long-term glycemic control increase this risk [36].

The predominance of ketoacidosis among the acute metabolic components can be seen in our study as well as in the Ethiopian study [15], despite our population with a majority type 2 diabetes. In addition, reasons for diabetic ketoacidosis could be related to a greater use of insulin therapy which involves appropriate use and adherence [37]. Hypoglycemia on the other hand would be an indicator of advanced malnutrition, severe systemic illness, various medication use focusing on sulphonylurea and insulin.

Regarding the outcome of our patients, the hospital mortality rate was 6.2%, similar to the results collected by Rafamantanantsoa et al (5.4%) and in Korea by Yoo et al (8.26%) [10, 38]. The mean age of the deceased patients was 58.88 ± 11.89 years, closer to that observed in Congo (57.2 ± 10.3 years) [39].

In his study as well as in other surveys, cardiovascular disease is the major cause of death in diabetic patients [38, 40]. Among the factors and comorbidities associated with

deaths, congestive heart failure (26.67%) were the most important and found a significant association. This result was similar to that compiled by Tirfe et al in Ethiopia (17.2%) [41]. This is despite the fact that the etiology of the cardiac decompensation could not be determined. The discovery of clinical signs at the advanced stage of heart failure, thus delaying hospital management, would be linked to the death of patients. Although Bivigou et al, in Gabon, underlined the lethality of heart failure, there was a strong correlation between the bi-variate association of hypertension and diabetes with the risk of death in patients (OR = 2.2; 95% CI = 1.2 - 6.6, p < 0.01) [42]. Coronary artery disease was widely reported in a Canadian study (55%), although it did not show a statistically significant association in our study [40]. Indeed, the concomitant presence of diabetes, hypertension and smoking status accelerate the progression of cardiovascular disease.

It must be considered that our study had several limitations. The sample size was limited and involved only one site, whereas many diabetic patients may be hospitalized in other sites or even in other hospitals. In addition, this study focused more on the causes of hospitalization despite the fact that there are various other problems seen in the management of diabetic patients.

5. Conclusion

The present study made possible to identify the various reasons for hospitalization and the causes of death in diabetic patients. Thus, in order to improve management, we suggest early detection of diabetes, screening and follow-up of complications discovered. It's the same for comorbidities and other cardiovascular risk factors associated with diabetes mellitus, which should always have been taken into account. Then, there is a need to improve the investigations requested with the intention of a well-targeted treatment; especially next to the finding of high frequency and association between heart failure and diabetic patients 'issues. All this requires an improvement in the health and social security system. Finally, it should not be forgotten that diabetes mellitus is a chronic disease. Its prior vascular complications could be slowed down by preventive measures taken at an earlier stage. A chance of survival in diabetes population may be given according to the reduction of both mortality and hospitalizations.

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