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CLINICAL FEATURES (CHARACTERISTICS) ASSOCIATED WITH AMPUTATION IN TYPE 2 DIABETES

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Diabetes mellitus (DM) is often associated with a wide range of comorbidities and complications.
The objective of this study was to assess the association of DM related complications, the presence of non-specific chronic cardiovascular (CV) and non-cardiovascular conditions and their association with lower extremity amputation (LEA), and to report their incidence in a population of patients with type 2 diabetes (T2D) from a surgery clinic.
Methods: This was a hospital based descriptive study of 290 patients that associated type 2 DM admitted for the management of diabetic foot (DF) lesions, over a 2 year period. All data was identified and collected from electronic medical records from hospital archive. Data analyzed was as follow: routine laboratory tests, age, gender, paraclinical measurements for diagnosis of diabetes specific complications (neuropathy, arteriopathy), diabetes related CV comorbidities and types of amputations performed.
Results: Median duration of T2D was 18 years, male was predominant gender (68.6%), age between 35–95 y/o, the majority of patients were on insulin treatment (56,2%), medium fasting plasma glucose was 212±92 mg/dl. Wet gangrene represented 66.21% of cases while dry gangrene represented 33.79% of cases. As regards to specific diabetes-related vascular complication, peripheric artery disease (PAD) was observed in 85,25%, followed by nephropathy 34,5%. Patients with PAD associated wet gangrene 53.8% and dry gangrene 31.4%. PAD was associated with smaller medium values of plasma glucose. The presence of 1 previous major CV event such as stroke or myocardial infarction was described in 20.7% of cases and atrial fibrillation (AFib) had a 5.9% incidence. Also, most of patients (61%) had only one reported diabetes-related specific complication.

Key words: diabetes mellitus, neuropathy, arteriopathy, amputation.

INTRODUCTION

810,134 patients were estimated with diabetes mellitus (DM) in Romania (2014), 83,2% on oral antidiabetic drugs (OAD), 16,75% insulin-treated; 9.3% national prevalence, 10.8% cost of the total healthcare budget (2011)[1, 2]. According to the WHO, the diabetic foot syndrome is defined as "ulceration of the foot (*distally from – and including – the ankle)* associated with neuropathy and different grades of ischemia and infection"[30]. The diabetic foot implies significant health care costs – 20–40% of (diabetes) health care resources are spent on DM related foot complications[31, 32], representing 25% of all hospital stays for DM patients[4, 6]; being the most common cause of non-traumatic lower extremity amputation (LEA).

Diabetic neuropathy and peripheric artery disease (PAD) have been reported as classical risk factors for diabetic foot ulcer (DFU)[1, 4], but few studies' demonstrate the association between DFU and microangiopathy complications, including albuminuria (Alb) and diabetic retinopathy (DR). Patients with advanced DR or Alb are likely to develop diabetic neuropathy or PAD. The reduction in visual acuity is a risk factor for DFU[4, 5]. Albuminuria and elevated serum creatinine have been reported as risk factors for DFU[6, 7]. Less it is known about association of other type of diabetes complications and comorbidities[28, 29] in DM patients – with DFU and LEA risk.

In the present study we focused on the association of diabetes complications, chronic

cardiovascular (CV) and non-cardiovascular conditions – with lower extremity amputation (LEA); diabetic individuals with DR and Alb were at an increased risk of developing DFU. From the perspective of a diabetic patient's evaluation of risk, the presence of asymptomatic DR and/or Alb may not be considered serious; hence, early intervention and long-term follow-up programs and identifying supplementary risk factors are crucial to prevent DFU and lower extremity amputations.

MATHERIALS AND METHODS

We made a hospital based descriptive study of 290 patients. The identification of all patients with type 2 diabetes mellitus (T2DM) was based on selecting from the database each patient who had been diagnosed with T2DM at any point in their lives, or who had been prescribed diabetes medication during the evaluation period. 100 (34.5%) patients with previous LEA and 190 (65.5%) without previous LEA were admitted for the management of DF lesions, in the "I. Juvara" *Surgery Department* within the Dr. I. *Cantacuzino* Clinical Hospital in Bucharest. We identified and collected the patient data and all risk factors-related information from electronic medical records from hospital archive using the aforementioned keywords. Amputations caused by other reasons than diabetes mellitus (*e.g.* trauma, acute arterial thrombosis) were excluded from this study. We excluded from the study group the patients diagnosed with type 1 diabetes mellitus or those with unspecified diabetes mellitus.

The clinical variables considered were: age, sex and existence of complications and comorbidities (whether or not associated to type 2 diabetes mellitus). Hospital admission because of major amputation was also considered. To study the chronic diseases, we developed a list of health problems and defined specific criteria to consider that particular disease as active during the period. In most cases, patients had been previously diagnosed with a specific illness and they were receiving a specific treatment for that disease.

Routine laboratory tests were performed including fasting glucose for each patient. Glycated hemoglobin (HbA1c) determination was not routinely assessed on surgery department.

We assessed the following diabetes related complications: the **nephropathy** (by persistent decrease in glomerular filtration rate (GFR) <60 ml/min/1,73 m^2 or by presence of persistent proteinuria on 2 or more lab measurements); The **diabetic neuropathy** was defined as decrease or loss in sensation (vibration, touch, pain and thermal sensibility) in a stocking distribution or loss of deep tendon reflex and absence of perception of the Semmes-Weinstein monofilament (10 g) at 2 of 10 standard plantar sites; the **retinopathy** was assessed by the fundoscopy; the presence of **peripheral artery disease** (PAD) was assessed by history or ankle-brachial index. The presence of **hypertension** was assessed either if patient was on antihypertensive treatment or if he had blood pressure higher than 140/90 mmHg in at least two measurements. **Coronary ischemic disease** (CID) was defined based on the patient history when admitted to hospital for either myocardial infarction (MI) or angina, or positive ECG for ischemic lesions history of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

RESULTS AND DISCUSSIONS

Although type 2 diabetes can occur at any age, we selected patients with age range between 35–95 y/o. The mean age was 65.25, median age was 65 y/o, the maximum incidence of patients age was in group 56–65 y/o (32.7%) followed by 21–40 years of diabetes duration (27.2%) (Fig. 1).

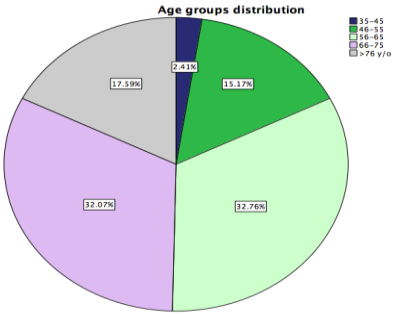

Figure 1. Age groups distribution.

Male was predominant gender (68.6%) with a median value of diabetes duration of 18 years and predominantly interested side for amputation was right (n = 154, 53,1%).

As regarding the diabetes mellitus treatment, the majority of patients were treated with insulin (56,2%) (p < 0,001). Medium fasting plasma glucose during hospitalization was **212±92 mg/dl**, with a median value of 194 mg/dl.

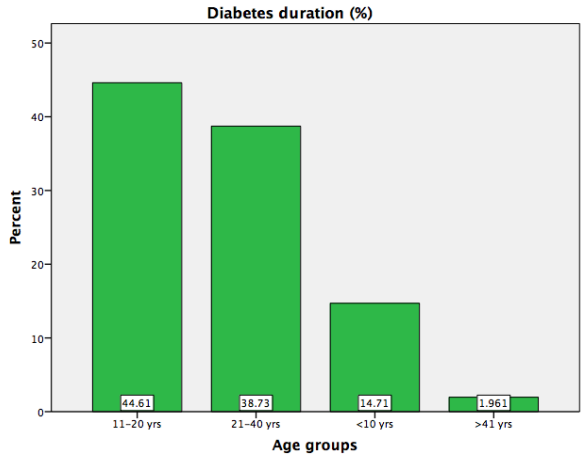

Figure 2. Distribution of patients according to diabetes duration.

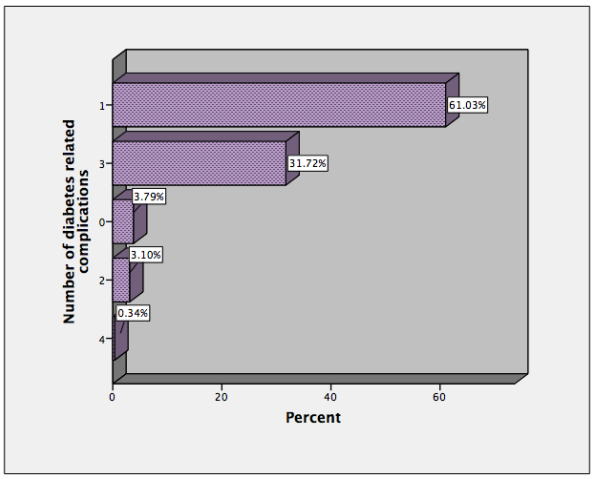

Figure 3. Number of associated complications – incidence.

The medium hospitalization duration was 8,69 ± 4,8 days. Regarding the duration of DM most patients had 11 to 20 years duration, with a median of 18 years (Fig. 2).

Looking at specific diabetes-related vascular complication, PAD was observed in 85,25%, followed by nephropathy 34,5%, while the most common associated comorbidity was hypertension (59,3%) (Fig. 3). Surprisingly PAD was associated with smaller medium values of plasma glucose ($p < 0,001$) – the smaller was medium value of plasma glucose, the higher was the incidence of PAD (possibly due to the existence of glycemic variability in those patients, which was not evaluated in this study). The presence of one previous major CV event such as stroke or myocardial infarction was observed in 20.7% and also atrial fibrillation had a 5.9% incidence. Most of patients (61%) had only one reported diabetes-related specific complication.

Patients who are at surgical reintervention were mostly treated with insulin (17.6%). DM treatment (insulin or OAD) did not correlate with diabetes related specific complications but correlated positive with the number of complications, the shorter was the duration of diabetes, the higher was the probability of the patient being insulin treated ($r = –0,226$, $p = 0,001$).

The incidence of patients who presented previous surgical amputation was 34.5%, while 65.5% presented with new onset necrosis or gangrene extended to different levels as follows: extensive foot necrosis (42.41%), one finger necrosis (40.34%), calf necrosis (6.55%), two finger necrosis (6.21%), three finger necrosis (3.79%) and four finger necrosis (0.69%) (Table 1).

Table 1

Baseline characteristics, complications and comorbidities

Sex	
Female (F)	91 (31,4%)
Male (M)	199(68,6%)
Fasting glucose	212±92 mg/dl, Median-194 mg/dl
Duration of DM type II	
<10 years	30(10.3%)
11–20 years	91(31.4%)
21–40 years	79(27.2%)
>40 years	4(1.4%)
No data	86(29.7%)
Diabetes medication	
Insulin	163 (56,2%)
Oral hypoglycemic agent	127 (43,8%)
Surgery type	
Necrosis excision	44(15.2%)
Finger resection	125(43.1%)
TMT resection	15(5.3%)
Calf resection	60(20.6%)
Hip resection	46(15.8%)
Diabetes related complications	
Neuropathy	28(9.7%)
Nephropathy	100(34.5%)
Retinopathy	59(20.3%)
Arteriopathy	247(85.2%)
Cardiovascular complications	
Hypertension	172(59.3%)
Ischemic heart disease	78(26.9%)
Atrial fibrillation	17(5.9%)
Stroke/Myocardial infarction	60(20.7%)

Majority of patients (61%) presented only one reported complication of DM. Hypertension and diabetes related specific complications as nephropathy and retinopathy did not correlated statistically significant with type of surgical amputation.

Patients who had a previous surgical amputation (and were at reintervention) were predominant insulin treated (17.6%) with a statistically significant difference between groups (p = 0,01); they also associated a higher CID rate (r = 0.161, p = 0.006); as a consequence, patients with CID have a higher reintervention risk.

Patients with a long duration of diabetes 20–40 years duration of the disease treated with OAD have a higher rate of complications than insulin treated ones; fact that shows that insulin has a protective effect on complications development. Surprisingly, the shorter was diabetes duration, the higher was the incidence of those patients to be on insulin treatment. The surgical reintervention frequency does not rise with age. Almost 1/3 of OAD treated patients have one reintervention; reintervention rate was higher in insulin treated group. From associated cardiovascular complications, 37% of patients presented non-major CV events (stable and unstable angina), while 20% presented stroke or myocardial infarction. The low percent of neuropathy-associated cases can be due to an underreporting of this complication because of the application of sensitivity tests on a surgery clinic, but without EMG evaluation. It is known that neuropathy has been reported as a risk factor for low extremity amputation. Our study, and also a meta-analysis published in 2017 by Shin *et al.*[26] showed no association between neuropathy and lower limb amputation.

An explanation for this result could be the association of neuropathy with diabetes duration and also the need for other risk factors associated that lead to amputation (infection or ischemia).

Although the surgical amputation type didn't correlate with hypertension, this was the most common associated CV related comorbidity.

Nephropathy is known to be a marker of PAD and published studies also showed this association. Despite that, in our study there wasn't any statistically significant association of nephropathy or retinopathy with surgical amputation.

The lower was the value of serum glucose, the higher was the association rate of PAD. This may be due to high intra-individual glycemic variability, which has not been evaluated in this study.

In conclusion, similar to diabetes and pre-diabetes, PAD is a complication that is often undiagnosed or under diagnosed until the disease has progressed and as a result, the risk of severe complications like surgical amputations is high. The actual study has a few limitations. The type of PA could not be precisely described. The results obtained are from one hospital and this cannot necessary be generalized to other hospitals.

CONCLUSIONS

In the type 2 diabetes mellitus population group from "I. Juvara" *Surgery Clinic* within the *Cantacuzino* University Hospital in Bucharest incidence rates of complications present a high prevalence of diabetes-related and unrelated diseases that associate to amputation. Multimorbidity is very common in our study group and is a factor to be taken into account to ensure correct clinical management. The associated risk factors for amputation were age above 65 Y/o, presence of PAD, OAD treatment and previous foot amputations (with underlying cause being recurrent foot lesions). Microangiopathic complications were not associated with amputation risk. Chronic complications of diabetes have a strong negative impact on population with type 2 diabetes. Therefore, an expansion of epidemiological knowledge and a well-established screening program should be a public health priority, to address the social, psychological and health implications and to develop interventions that enable better management of these patients.

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