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Microvascular Complications and the Associated Factors among Adult Diabetic Out-Patients in a County Teaching and Referral Hospital in Kenya

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Data on the magnitude of microvascular complications and the associated factors is scarce in resource-limited settings. A descriptive cross-sectional was carried out among 100 adult diabetic outpatients at Jaramogi Oginga Odinga Teaching and Referral Hospital in Kenya to determine the prevalence, management and the factors associated with development of microvascular complications. Results showed the prevalence rates of neuropathy, nephropathy and retinopathy were 58.0%, 26.0% and 25.0%, respectively. Retinopathy (p=0.001), neuropathy (p=0.016) and nephropathy (p=0.048) were significantly associated with the duration of diabetes. Hypertension (OR=3.457; CI: 0.942-12.686), smoking (OR=3.143CI:1.190-8.308) and consumption of alcohol (OR=2.784, CI: 1.111-6.976), each independently increased the likelihood of development of nephropathy three-fold. Microvascular complications were mainly managed using renin inhibitors (67.0%), anticonvulsants (33.0%) and pyridoxine (30.0%). Results suggest that diabetic patients should be continually advised on lifestyle habits to retard the development of chronic complications. Future studies should correlate the management of complications and their clinical outcomes.

Key Words: Microvascular Complications, Diabetes Mellitus, Diabetic outpatients, Management

INTRODUCTION

Diabetes mellitus (DM) affects 370 million people globally and is projected to hit 552 million mark by 2030[1]. In sub-Saharan Africa (sSA), 7.1% of the population is affected [2], while in Kenya the estimated prevalence is about 3.5-5%.[3] Furthermore, reports indicate that two-thirds of the Kenyan population at risk of diabetes go undiagnosed.[3]

DM causes economic and social costs attributed to long term complications.[4] Diabetic patients show a diverse range of chronic complications including microvascular complications such as retinopathy, nephropathy, and neuropathy[5] but patients are unaware of their consequences and optimal management.[6] Diabetic retinopathy causes loss of vision or blindness, nephropathy leads to end-stage renal disease (ESRD) while neuropathy is associated with nerve damage.[2]

The European diabetes prospective complications study group (EURODIAB) indicated that the prevalence of diabetic nephropathy among patients with type 1 and 2 diabetes mellitus is 12.6% and 33%, respectively.[7] In sSA, the prevalence of diabetic nephropathy ranges from 6% to 16% and retinopathy at 4%-17%.[8] Studies in Rwanda revealed that the prevalence of peripheral neuropathy was at 59% among women and 45% in men.[9] Furthermore, erectile dysfunction, a common autonomic neuropathy among diabetic men in Tanzania was reported at 55.1% with advanced age being the most significant predictor.[10]

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The EUROBIAD study indicated that neuropathy was related to levels of glycosylated hemoglobin and hyperglycemia.[11] Additionally, poor glycemic control, hypertension, and dyslipidemia are associated with poor diabetic management strategies and the associated complications. [12,13] Furthermore, the United Kingdom prospective diabetes study (UKPDS) showed tight blood pressure control reduces the incidence of retinopathy by up to 34%. [14] Epidemiology of diabetes interventions and complications study (EDIC) showed majority of patients who were on strict glycemic control presented with microalbuminuria compared to patients on conventional treatment after eight years, although at the same levels of blood glucose control. [15,16]

In an epidemiological study on the management of diabetic complications, the researchers noted that in nephropathy, angiotensin converting enzyme inhibitors (ACEIs) are the first line. If not well-tolerated, angiotensin receptor blocker (ARB) can be used at the maximum anti-hypertensive dose. ACEIs/ARBs have a strong anti-proteinuric effect and increasing their dose reduces proteinuria in diabetics. [17] Oxybutynin can be used to manage symptoms of urinary incontinence[18], while flavoxate can treat urinary incontinence, urgency, painful urination and nocturia.[19] A double-blind cross-over study comparing flavoxate and oxybutynin produced the same urodynamic parameters but oxybutynin had more side effects.[20] Moreover, studies have indicated that neuropathic pain is managed by the following medications; amitriptyline, imipramine, paroxetine, pregabalin, gabapentin, sodium valproate, dextromethorphan, morphine sulphate, tramadol, oxycodone duloxetine and transdermal lignocaine. [21]

Treatment of erectile dysfunction includes the use of oral phosphodiesterase-5 (PDE-5) inhibitors, intra-urethral alprostadil, sublingual apomorphine, vacuum constriction devices and penile prosthesis implantation. [22] Alprostadil, a vasodilator, is administered via transurethra or intracavernosa to patients who fail on the PDE-5 or oral therapy is ineffective or contraindicated. Papaverine and phentolamine were the most widely used injection therapies.[23]

A systematic review and meta-analysis of studies conducted from 1975 to 2013 showed the effectiveness and safety of calcium dobesilate in managing diabetic retinopathy. Calcium dobesilate improves retinal microaneurysms, retinal hemorrhages, blood cholesterol, and reduces intraocular pressure significantly. [24]The present study aimed at characterizing the magnitude, associated factors, and management of microvascular complications among adult diabetic outpatients at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOORTH) in Kenya.

METHODOLOGY

Research design and area

This was a descriptive cross-sectional study carried out at the Jaramogi Oginga Odinga Teaching and Referral Hospital (JOORTH) in Kisumu. JOORTH is a 467-bed capacity hospital and a major referral center for the former Nyanza and Rift Valley provinces of Kenya. It serves a population of more than 5 million people. The annual outpatient visit is 197, 200 while the inpatient admission is 21,000.

Target population

The target population was all adult diabetic patients attending the outpatient clinic of JOORTH. Patients aged ≥ 18 years with a documented diagnosis of DM and those who provided written informed signed consent were eligible to participate. Patients who had DM but with concurrent severe chronic heart disease, renal and liver disease were excluded because the confounding effects of the management of those diseases. In addition, patients with

debilitating mental disorders or those who refused to consent to participate were left out.

Sample size and sampling method

Data from the JOORTH diabetic clinic indicated that the monthly attendance ranged from 118-225 patients. Using this information, the sample size was estimated using the Yamane (1967:886) formula [25] at a 95% confidence interval. The minimum sample size was computed as 91 participants but a 10% was added to cater for non-completeness giving a final sample size of 100 patients. Convenience sampling was employed as patients came for clinic appointment until the sample size was attained.

Study methods

Study approval was sought and granted by the Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (KNH/UoN-ERC) vide reference number (KNH-ERC/A/195). Authority to carry out the study was also granted by the Ethics and Research committee of JOORTH under reference number ERC.IB/VOL.1461.

An explanation of the purpose of the study was provided to each of the eligible participants as well as a detailed consenting process. A semi-structured questionnaire, which had a unique alphanumerical serial number, was administered to eligible patients to capture the sociodemographic variables such as age, gender, occupation, highest education level, marital status, denomination, tobacco smoking, alcohol consumption status, and body mass indices. A systematic review of body systems using predesigned relevant questions was also done to capture the presence or absence of microvascular complications including neuropathy, nephropathy and retinopathy. The data on management of the observed complications was extracted from the patients' medical files. The data was kept confidential by excluding information that could identify the participants.

Data entry and statistical analysis

The questionnaires were accurately completed at the closure of each day and the raw data entered into the Microsoft Excel version 2016 to create a database. Data cleaning was undertaken and exported to STATA® version 14 statistical software for analysis. Frequencies were run for the participants' sociodemographic variables, the prevalence of microvascular complications and their management patterns. To determine the factors associated with microvascular complications, Pearson's Chi square or Fischer's exact statistic was computed between the sociodemographic characteristics and the presence of microvascular complications. Variables whose $p \leq 0.05$ were considered statistically significant.

RESULTS

The sociodemographic and clinical characteristics of the study participants are shown in Table 1. There was female preponderance (67.0%). The mean age of the participants was 57.0 ± 12.3, with a range of 24-88 years. The age group ≥50 years comprised the majority of patients at 73% (n=73). The mean duration since diagnosis of DM was 7.5 (± 5.8) years. The prevalence rates of investigated microvascular complications are shown in **Figure 1**. Neuropathy was the most prevalent complication (58%) followed by nephropathy (26 %) and retinopathy (25.0%). The associations between the participants' sociodemographic and clinical characteristics with the presence or absence of microvascular complications are displayed in **Table 2.** Duration of diabetes since diagnosis was statistically significantly associated with the development of retinopathy (χ^2=15.5, p=0.001),.neuropathy (χ^2=10.33, p=**0.016**) and nephropathy (χ^2=7.91, p=0.048). There were no statistically significant associations between other participants' characteristics and microvascular complications (**Table 2).**

Table 1: Socio-Demographic and Clinical Characteristics of the Respondents (N=100)

Variable	Category	Frequency (%)
Age (Years)	18-30	2(2.00)
	30-39	7(7.00)
	40-49	18(18.00)
	≥50	**73(73.00)**
Residence	Urban	57(57.00)
	Rural	43(43.00)
Gender	Male	33(33.00)
	Female	**67(67.00)**
Body Mass Index	Underweight	2(2.00)
	Normal Weight	22(22.00)
	Overweight	34(34.00)
	Obese	42(42.00)
Marital Status	Single	4(4.00)
	Married	68(68.00)
	Divorced	1(1.00)
	Widowed	22(22.00)
	Separated	5(5.00)
Occupation	Salaried	16(16.00)
	Self-employed	45(45.00)
	None	38(38.00)
Level of education	Primary	36(36.00)
	Secondary	40(40.00)
	Tertiary college	16(16.00)
	Informal	8(8.00)

SD-Standard Deviation

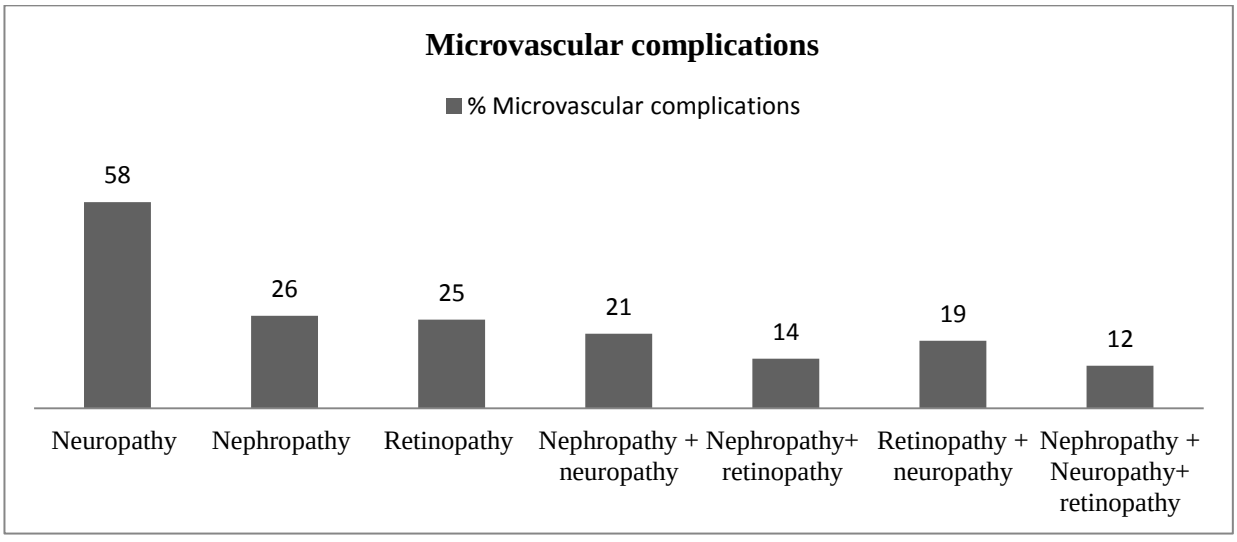

Figure 1: Prevalence of microvascular complications

Table 2: Associations between socio-demographic characteristics and microvascular complications (N=100)

Variable	Category	Retinopathy		Neuropathy		Nephropathy	
		Yes {n (%)}	No {n (%)}	Yes {n (%)}	No {n (%)}	Yes {n (%)}	No {n (%)}
Age(years)	18-30	0(0.00)	2(100.00)	0(0.00)	2(100.00)	0(0.00)	2(100.00)
	30-39	0(0.00)	7(100.00)	4(57.14)	3(42.86)	1(14.29)	6(85.71)
	40-49	4(22.22)	14(77.78)	8(44.44)	10(55.56)	4(22.22)	14(77.78)
	>=50	21(28.77)	52(71.23)	46(63.01)	27(36.99)	21(28.77)	52(71.23)
	Chi Square; *p*-value	χ^2=3.6266; *p*= 0.305		χ^2=4.8751; *p*= 0.181		χ^2=1.0058; *p*=0.800	
Residence	Urban	11(19.30)	46(80.700	33(57.89)	24(42.11)	11(25.58)	32(74.42)
	Rural	14(32.56)	29(67.44)	25(58.14)	18(41.86)	15(26.32)	42(73.68)
	Chi Square; *p*-value	χ^2=2.2984; *p*=0.130		$\chi^{2=}$0.0006; *p* = 0.980		χ^2=0.0069;	*p* = 0.934
Body Mass Index	Underweight	0(0.00)	2(100.00)	0(0.00)	2(100.00)	0(0.00)	2(100.00)
	Normal Weight	6(27.27)	16(72.73)	13(59.09)	9(40.01)	7(31.82)	15(68.18)
	Overweight	10(29.41)	24(70.59)	20(58.82)	14(41.18)	10(26.47)	25(73.53)
	Obese	9(21.43)	33(78.57)	25(59.52)	17(40.48)	0(0.00)	2(100.00)
	Chi Square; *p*-value	χ^2=1.3659; *p* =0.714		$\chi^{2=}$2.8222;	*p* = 0.420	χ^2=1.1984;	*p* = 0.753
Marital Status	Single	0(0.00)	4(100.00)	0(0.00)	4(100.00)	0(0.00)	4(100.00)
	Married	14(20.59)	54(79.41)	41(60.29)	27(39.71)	17(25.00)	51(75.00)
	Divorced	0(0.00)	1(100.00)	1(100.00)	0(0.00)	1(100.00)	0(0.00)
	Widowed	8(36.36)	14(63.64)	14(63.64)	8(36.36)	6(27.27)	16(72.73)
	Chi Square; *p*-value	χ^2=7.1544; *p* =0.128		$\chi^{2=}$7.3468;	*p* = 0.119	χ^2=4.8148;	*p* = 0.307
Occupation	Salaried	3(18.75)	13(81.25)	8(50.00)	8(50.00)	10(31.25)	11(68.75)
	Self-employed	10(22.22)	35(77.78)	26(57.78)	19(42.22)	5(22.22)	35(77.78)
	None	12(31.58)	26(68.42)	23(60.53)	15(39.47)	11(28.95)	27(71.05)
	Chi Square; *p*-value	χ^2=1.7290; *p* =0.630		$\chi^{2=}$1.2450;	*p* = 0.742	χ^2=1.0859 ;	*p* = 0.780
Level of education	Primary	29(80.56)	7(19.44)	21(41.67)	15(58.33)	12(33.33)	24(66.67)
	Secondary	10(25.00)	30(75.00)	21(47.50)	19(52.50)	10(25.00)	30(75.00)
	Tertiary college	5(31.25)	11(68.75)	11(68.75)	5(31.25)	3(18.75)	13(81.25)
	None	3(37.50)	5(62.50)	5(62.50)	3(37.50)	1(12.50)	7(87.50)
	Chi Square; *p*-value	χ^2=1.5926; *p* = 0.661		$\chi^{2=}$1.3239;	*p* = 0.723	χ^2=2.2219;	*p* = 0.528
Duration of diabetes since diagnosis	Less than a year	1(100.00)	0(0.00)	1(100.00)	0(0.00)	1(100.00)	0(0.00)
	1-6 years	6(11.76)	45(88.24)	22(43.14)	29(56.86)	11(21.57)	40(78.43)
	7-10 years	5(23.81)	16(76.19)	14(66.67)	7(33.33)	3(14.29)	18(85.71)
	More than 10 years	13(48.15)	14(51.85)	21(77.78)	9(22.22)	11(40.74)	16(59.26)
	Chi Square; *p*-value	**χ^2=15.4966; *p*=0.001**		**$\chi^{2=}$10.3319; *p* = 0.016**		**χ^2=7.9137; *p* = 0.048**	

Table 3: Associations between the participants' characteristics and development of microvascular complications

		Retinopathy		Neuropathy		Nephropathy	
		No; n(%)	**Yes, n(%)**	**No, n(%)**	**Yes, n(%)**	**No, n(%)**	**Yes, n(%)**
Hypertension	No	21(80.8)	5(19.2)	12(46.1)	14 (53.9)	23(30.3)	51(69.7)
	Yes	54(73.0)	20 (27.0)	30(40.5)	44(59.5)	3(13.0)	23(87.0)
p -value, OR; 95%CI		*p*=0.430, OR=1.556; CI:0.517-4.683		*p*=0.619, OR=1.257; CI:0.511 -3.092		***p*=0.038, OR=3.457; CI:0.942-12.686**	
Tobacco Smoking	No	58(77.3)	17(22.7)	39(48.1)	42(51.9)	60(80.0)	15 (20.0)
	Yes	17(68.0)	8(32.0)	9(36.0)	16(64.0)	14(56.0)	11(44.0)
p -value, OR; 95%CI		*p*=0.359, OR=1.606; CI:0.591-4.361		*p*=0.480, OR=1.397 CI:0.548 -3.559		***p*=0.022, OR=3.143 CI:1.190-8.308**	
Alcohol Consumption	No	45(75.0)	15(25.0)	25(41.7)	35(58.3)	49(81.7)	11(18.3)
	Yes	29(74.3)	10(25.7)	17(43.6)	22(56.4)	24(61.5)	15(38.5)
p -value, OR; 95%CI		*p*=0.943,OR=1.034; CI:0.967- 2.610		*p*=0.850, OR=0.924 CI:0.409-2.088		***p*=0.027; OR=2.784 CI:1.111-6.976**	

CI = Confidence Interval; OR = Odds Ratio

Hypertension, smoking, or consumption of alcohol, significantly increased the likelihood of development of nephropathy three-fold (**Table 3**). Table 4 demonstrates the pharmacological management patterns of the microvascular complications. The most commonly used agents were enalapril (36%), losartan (31%), pyridoxine (30%), and pregabalin (23%).

Table 4: Management of microvascular complications

Complications	**Drugs**	**Frequency (%)**
Retinopathy	Calcium dobesilate	3 (3.0)
Neuropathy	Pyridoxine	**30 (30.0)**
	Pregabalin	**23 (23.0)**
	Gabapentin	7 (7.0)
	Sildenafil	6 (6.0)
	Carbamazepine	3(3.0)
	Alprostadil	1 (1.0)
Nephropathy	Enalapril	**36 (36.0)**
	Losartan	31(31.0)
	Carvedilol	2(2.0)

DISCUSSION

The present study has characterized the types, associated factors and management of microvascular complications among diabetic patients in a busy County referral hospital in Kenya. The study revealed a high prevalence of microvascular complications with varied management patterns. The prevalence of diabetic neuropathy was the highest at 58% though previous related studies had indicated varying but lower prevalence rates: 46% in Iran [11] and 32% in Italy. [26] In addition, the rate was 30% among the Chinese [27] and 26% among the Europeans. [28]

The other microvascular complications including nephropathy and retinopathy had prevalence rates of more than 20% although studies in China revealed nephropathy at 7% and retinopathy at 18%. [27] These varying prevalence rates could be attributable to the different study methodologies employed. In addition, the higher prevalence rates in Kenya could be due to resource limitations which affect the degree of glycaemic control and hence the development of microvascular complications. There is also a possibility that the high prevalence of microvascular

complications was due to a long history of diabetes characterized by a mean duration of 7.5(±5.8) years since diagnosis and advanced age of participants which corroborates other studies.[29] Studies have shown that long standing diabetes is an important factor in developing diabetic complications such as nephropathy. [30] Furthermore, the present study revealed that the duration of years since diagnosis of diabetes was significantly associated with the development of all the three microvascular complications studied.

The important determinant for diabetic nephropathy was a history of high blood pressure. Participants who reported high blood pressure were three times more likely to develop nephropathy than the ones who did not which corroborated related studies done in India. [31] In addition, smoking and alcohol consumption were also significantly associated with nephropathy as has been indicated in related studies.[32]

The management of microvascular complications also varied greatly. For instance, diabetic neuropathy was mainly managed using pyridoxine which has been shown to improve neurophysiological functions in neuropathic pain.[23] Patients also received pregabalin and gabapentin, which are recommended in related studies. [23] However, some studies have indicated amitriptyline and duloxetine as the first-line for diabetic neuropathic pain management .[23] In the present study, less than 5% of the participants were on carbamazepine though studies have recommended the synergistic combination of carbamazepine and gabapentin for DM neuropathic pain.[33] The associated autonomic neuropathy of erectile dysfunction was managed with sildenafil in five percent of patients, which was similar to a study done in China. [34]

Although the prevalence of diabetic retinopathy was high, calcium dobesilate was used for its management in 3% of the participants. Related studies suggest that calcium dobesilate may be used for the management of diabetic nephropathy and drug-induced kidney injury. [35] Perhaps its unavailability in most of the resource-limited settings as well as prohibitive cost restricted its use. Moreover, the American Diabetic Association recommends that the risk factors for retinopathy such as chronic high blood sugar, blood pressure, kidney disease, and dyslipidemia should be optimally managed to avert retinopathy. [36]

In the management of nephropathy and the associated high blood pressure, our study revealed that 67% of the participants were on renin inhibitors, enalapril or losartan. Kidney disease improving global outcomes (KDIGO) recommends that hypertension in the chronic kidney or end-stage renal disease should be treated using of renin inhibitors .[37] Furthermore, studies have shown that renin- aldosterone blockade reduces albuminuria and dyslipidemia in diabetic nephropathy. [38]

The study had a few limitations. Firstly, this was a hospital-based cross-sectional study and the causality of the risk factors to microvascular complications cannot be adequately established. Secondly, the confounding was difficult to control and patients could have overrated or underrated their experiences.

CONCLUSION

There was a high prevalence of diabetes microvascular complications. The correlates for the development of microvascular complications were the duration of diabetes since diagnosis suggesting that glycaemic control was poor for a prolonged period of time. Management of neuropathy, retinopathy, and nephropathy was suboptimal due to the fewer treatment options available. Intensification of glycaemic control after DM diagnosis should be encouraged to prevent the disabling long-term microvascular complications. Diabetic patients should be continually advised on lifestyle habits to retard the development of chronic complications. Future studies

should ascertain the risk factors and clinical outcomes of the management of microvascular complications associated with DM.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Nyagwencha D. Nyamweya conceptualized the idea, wrote the concept, collected and analyzed the data, and drafted the manuscript. **David G. Nyamu** assisted with proposal development, data analysis and interpretation as well as drafting of the manuscript. **George A. Mugendi** helped in manuscript writing. All authors approved the final manuscript for publication.

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