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Major Micro vascular Complications and Associated Risk Factors among Diabetic Outpatients in Southwest Ethiopia

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Abstract

Background: Diabetic complications and comorbidities, mainly due to poorly controlled diabetes, are the common causes of hospital admissions and mortalities among diabetic populations. Although studies from Ethiopia show high incidence of complications, data on associated risk factors is scarce. The current study was aimed to assess the potential risk factors contributing to microvascular diabetic complications in the study area.

Methods: Hospital-based, cross-sectional study was conducted during October and December of 2015 among systematically selected diabetic patients, at outpatient clinic of Jimma University Specialized Hospital (JUSH), Southwest Ethiopia. At recruitment, 5 ml of venous blood was collected without any prior special preparation such as fasting, and used for $HbA1_C$ level determination. Data on sociodemographic and diabetic complications was documented for each patient on the format prepared for this study. Binary logistic-regression analysis was used to identify the risk factors associated with the microvascular complications. A p-value <0.05 was considered significant.

Results: The sample analyzed consisted of 236 diabetic patients: 53.4% male, 58.5% Type 2 diabetics, 40% overweighed, and 75.0% younger than 60 years and with diabetes for less than 7 years. The mean ± SD of $HbA1_C$ was 9.1 ± 2.8%. Nearly two-third (65%) of the patients had $HbA1_C$ greater than 8.0%, indicating poor glycemic control. Self-reported genetic risk factors were evident in almost 20% of the study population. At least one major microvascular complication was recorded in 41.5% of the sampled population. The overall prevalence of the major microvascular complications was associated with high $HbA1_C$ level (≥ 8.0%), female sex and genetic risk factors, as evidenced by adjusted odds of 2.7, 2.2 and 3.2, respectively.

Conclusions and recommendation: The overall prevalence of microvascular complications was high. To reduce the risk of the costly complications, new diabetes care policies objectively targeting a stringent glycemic goal of $HbA1_C$ <8.0% should be implemented.

Keywords: Diabetes mellitus; Glycosylated hemoglobin; Glycemic level; Microvascular complication; Genetic risk factors; Jimma University; Southwest Ethiopia

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. A more recent estimate suggests that DM has become the fifth leading cause of death worldwide; the seventh in US, with an estimated 3.8 million deaths each year [2,3]. A few years ago, the rate of DM among Africans appears to have been 1-6%; the national prevalence estimated for Ethiopia being 2.9% [4]. According to the 2016 Diabetes country profiles (WHO report), age adjusted prevalence particularly among Ethiopian youngsters less than 37 years is about 4.2% with an estimated 1.3 million cases, the prevalence that exceeds that of the world and Africa [5].

All forms of poorly controlled DM increase the risk of acute and chronic complications that affect virtually every system of the body. Such complications include diabetic foot, renal disease, eye problem, cardiovascular disease, neuropathy, and skin and/or subcutaneous infections [6-10]. In the western world, DM is the leading cause of blindness, non-traumatic lower limb amputation and chronic renal failure, which are on very much increase [11-13]. The situation in developing world, particularly in Africa, is even worse due to late diagnosis and poor access to diabetic care [6-10]. Diabetes in sub-Saharan Africa greatly increases the risk of serious costly complications including emotional distress, heart attack, stroke, kidney damage, blindness, neural damage leading to amputation, and reduction of life expectancy [14-17]. Moreover, recent evidence is emerging that diabetes is associated with cognitive impairment, depression, incontinence, fracture risk, and cancer risk and prognosis [18].

In clinical practice, single glycosylated hemoglobin ($HbA1_C$) assay value provides reliable information about the status of glycemia over the preceding three months [19-21]. Besides, $HbA1_C$ is becoming a screening tool of patients at increased risk of chronic diabetic complications [22,23]. Considering the benefits of $HbA1_C$ assay, several international bodies such as American Diabetes Association [24] and WHO [25] recommend $HbA1_C$ test at least twice yearly. Nevertheless, $HbA1_C$ assay is not readily available in diabetic care system in Ethiopia.

Recent studies from Ethiopia show high incidence (25-52%) of diabetic complications among adult diabetic outpatients [9,10,26]. However, data on the associated risk factors is scarce. Moreover, none of the available literatures reported the associations between

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diabetic complications and the level of $HbA1_C$ in Ethiopian diabetic population [27-29]. The current study was aimed to assess the factors associated with the overall prevalence of major microvascular diabetic complications and evaluate if there is any association between $HbA1_C$ level and microvascular complications among diabetic outpatients at Jimma University Specialized Hospital (JUSH), Southwest Ethiopia.

Methods and Participants

Study area, design and subjects

A facility-based descriptive cross sectional study design with quantitative data collection method was conducted from October 20 to December 15, 2015 at Jimma University Specialized Hospital (JUSH) outpatient clinic, which is located in Jimma City, 335 km Southwest of Addis Ababa. The hospital is a teaching and referral hospital that gives health service for more than 10 million people living in Southwest Ethiopia [30,31]. The hospital has many chronic follow-up clinics for both pediatric and adult patients. The diabetes clinic runs twice weekly (on Monday and Tuesdays) and provides integrated diabetic care for both Type 1 and Type 2 diabetics. All adult diabetic patients attending the chronic clinic of JUSH were our source populations while those consenting and fulfilling our inclusion criteria during the study period taken as study population.

The minimum sample size was determined using the single population proportion formula based on the following assumptions: 25% prevalence rate (p) of diabetic complications from previous studies in Ethiopia [9,10,26]; 5% margin of error (d); and 95% confidence interval. This yield an initial sample size of 288. Every week, about 100-160 patients visit the clinic whilst 400-640 patients are treated per month. During the two months study period, a maximum of 1280 patients were expected to visit the clinic. We used this number as a sampling frame. After correcting for the finite study population less than 10,000 and considering a 10% incomplete questionnaire, the final sample size was 258. Accordingly, every fourth diabetic patient who fulfilled the study criteria and gave informed consent was recruited consecutively as a study participant from the cohort of patients attending the follow-up clinic during the two-month study period.

Participants inclusion and exclusion criteria

For the purpose of this study, all adult diabetic patients aged 18 years or older (WHO criteria), willing to participate and gave informed consent were included. Patients with the following conditions were excluded: age less than 18, pregnant women, hospitalized and/or with psychiatric disorder during the data collection time (since there is blood collection for assessment of $HbA1_C$ and questionnaire investigation), and those who were not willing to participate. Since there is assessment of $HbA1_C$ as a measure of level of glycemic control during the last two to three months preceding data collection and record of complication is to be reviewed, patients with diabetes follow-up history for less than three months were also excluded. Moreover, participants diagnosed with hypochromic anemia (as revealed by measured total hemoglobin) were excluded not from the study but from the analysis related to $HbA1_C$.

Data collection procedures

Five clinical nurses and four laboratory technicians were participated in data and blood sample collection and laboratory determination. After receiving informed verbal consent from each patient, 5 ml venous blood sample was collected from the median cubital vein randomly at the time of the clinic visit with no advanced instructions concerning fasting, into haparinized EDTA tubes and used for $HbA1_C$ level determination. The blood samples were sent to the hospital clinical laboratory for chemistry analyses immediately.

In addition, socio-demographic data such as age, sex, residence, data on diabetic duration and type, was collected using interviewer administered questionnaires. The study patients were also interviewed for behavioral (smoking and alcohol consumption) and treatment related characteristics and current symptoms, as well as family history of diabetes, hypertension and other cardiovascular comorbidities (CVCs) in any of their family. Moreover, the patient or patient's next of kin was interviewed if there was any $HbA1_C$ assay before and knowledge about the test. The interview was conducted in a separate room with complete privacy. Currently recorded on anthropometric data (weight and height), and data on type of diabetes and diabetic duration, as well as previous laboratory data if there is any (e.g. $HbA1_C$), information on eye evaluations, neurologic examinations, and other diabetic complications and comorbidities including hypertension, diabetic foot, skin and subcutaneous infections, were retrieved from patient charts on a prepared checklist. The data collection instruments used were prepared for this study after reviewing several related literatures [26-31].

Quantitative *In vitro* determination of $HbA1_C$

$HbA1_C$ was measured from a whole blood with ABX Pentra 400 Automated Clinical Chemistry Analyzer (Horiba ABX SAS, 34184 Montpellier, France) using a standard kit for Latex-enhanced immunturbidmetry method provided by the supplier [32]. For each whole blood sample, the test output consists two total hemoglobin concentrations (in µmol/l), $HbA1_C$ concentration (in µmol/l) and $HbA1_C$ percentage. The assay kit consists of five reagents: Antibody Reagent (R1), diluted with Diluent I (R5), Agglutinator Reagent (R2), Hemolysis Reagent (R3) and Total Hemoglobin Reagent (R4).

The EDTA whole-blood sample is first mixed with the Hemolysis Reagent (R3) by the analyzer: The red blood cells are lysed and the hemoglobin chain is hydrolysed by the action of a protease present in the reagent. The Total Hemoglobin Reagent (R4) is used to determine total hemoglobin. The method is based on the conversion of all forms of hemoglobin into alkaline haematin in an alkaline solution of non-ionic detergent as described elsewhere [32]. The reaction is triggered off by the addition of a blood sample pre-treated with the Total Hemoglobin Reagent (R4), resulting in a green coloration of the solution. The conversion of the different types of hemoglobin into alkaline haematin with a defined absorbance spectrum allows the calculation of the total hemoglobin concentration, using an end-point method at 550 nm.

The latex agglutination inhibition test is used to measure specific $HbA1_C$. An agglutinin (synthetic polymer containing multiple copies of the immunoreactive portion of $HbA1_C$) causes the agglutination of the latex particles covered with monoclonal mouse antibodies specific for $HbA1_C$. In the absence of $HbA1_C$ in the sample, the agglutinin in the Agglutinator Reagent (R2) and the micro particles covered with Antibody Reagent (R1) agglutinate. The agglutination leads to an increase in the absorbance of the suspension. The presence of $HbA1_C$ in the sample reduces the rate of agglutination, for $HbA1_C$ enters into competition with the Agglutinator Reagent (R2) at the micro particles' antibody docking sites. The greater the amount of $HbA1_C$ in the sample, the lower the agglutination rate. The reaction was measured by absorbance at 550 nm and the agglutination rate was used for calculation of $HbA1_C$ concentration from a calibration curve. For each whole blood sample, in addition to $HbA1_C$%, the chemistry machine yields $HbA1_C$ concentration (in µmol/l) and two total hemoglobin values (in µmol). The machine provides $HbA1_C$% test values between

4.0 and 16.5%. When the test result is outside this range, the machine does not provide any test result, rather a comment 'low linearity'.

Study variables

The dependent variable (outcome variable) of this study was overall prevalence of microvascular diabetic complications, a package composed of composite measure of four major complications (DPN, visual disturbance, diabetic foot ulcer and skin and subcutaneous infections). The occurrence of each complication was recorded as 'Present', coded as '1', and otherwise categorized as 'Absent' and coded as '0'. The responses on the four complications were added to four (0-4) for each participant. A patient with a total score of 1 or more was considered with prevalent major microvascular complication.

The major independent variables investigated were the level of glycemic control, as measured by $HbA1_C$; and presence or absence of self reported genetic risk factors for microvascular complications. Other co-variables include age, gender, type of DM, diabetic duration, body max index, and two total hemoglobin values (in µmol). The average of the hemoglobin values was used to determine hypochromic anemia.

Operational Definitions

- **Microvascular diabetic complication**: It is defined as the presence of any one or more of the following complications: peripheral diabetic neuropathy (DPN), diabetic foot ulcer, visual disturbance and/or diabetic retinopathy, and skin and subcutaneous infections.
- **Good glycemic control:** a patient characteristic referring to a patient has successfully achieved a therapeutic goal of $HbA1_C$ below 8.0%.
- **Poor glycemic control:** a patient characteristic referring to a patient with an $HbA1_C$ values between 8.0 and 10.0%.
- **Very poor glycemic control:** a patient characteristic referring to a patient with an $HbA1_C$ value above 10.0%.
- **Cardiovascular comorbidity:** any health problem including cardiac problem and hypertension identified in the diabetic patients, excluding all non-diabetic causes.
- **Genetic risk factors/genetic predisposition:** presence self reported family history of diabetes, hypertension, renal complication and other cardiovascular comorbidities (CVCs) in any of their family.
- **Hypochromic anemia:** total hemoglobin concentration less than 20 µmol/l or symptoms of anemia recorded by the physician.

Data Analysis

The prevalence of microvascular complication was the outcome variable, treated as a dichotomous data with absent/present options, while level of glycemic control achieved by each participant, determined using his/her $HbA1_C$ value, was the major independent variable evaluated. Based on their glycemic level, patients were classified into three groups: good glycemic control ($HbA1_C$<8.0%), poor glycemic control ($8.0 \geq HbA1_C\% \leq 10.0$) and very poor glycemic control ($HbA1_C$ >10.0%). Descriptive analysis was done by computing proportions and summary statistics. Bivariate analysis was done by using χ^2 cross-tabulation or t-tests, according to whether the variable was continuous or categorical, to see associations between the dependent and independent variables. Then, all variables having P-value, 0.25 were considered as candidates for the final model, that explored the the association between the three levels of $HbA1_C$ and overall prevalence of microvascular complications while adjusting for other covariates like sex and self reported genetic risk factors. In all analysis, group of patients with the lowest $HbA1_C$ level (good glycemic control i.e. $HbA1_C$ less than 8.0%, mean, 6.2%) was used as a reference for calculating the relative odds. The Odds ratio and 95% confidence interval was reported in each logistic regression analysis. All analyses were performed using IBM-SPSS software for windows version 20.0 [33] and all statistical tests were two-tailed with a p-value <0.05 considered significant.

Ethical Considerations

The protocol was reviewed and approved by the ethical clearance board of College of Health Sciences, Jimma University (Ref. No. RPGC/06/2015), according to the standardized principle and a procedure designed in line with the national or regional guidelines and the Helsinki Declaration of the 1975, as revised in 1983. In addition, a written permission was sought from the hospital medical director to perform the laboratory tests and retrieve patients chart from records and archives. All the study subjects were unpaid volunteers who had informed of the study purpose and gave verbal consent to participate. All the participants' information was kept confidential using coding system and no direct benefit was provided for the participants, except the cost free total hemoglobin and $HbA1_C$ tests performed for each participant without being asked for any form of payment. The laboratory test result and its implication was communicated with the patients and their providers immediately on the next clinic visit to assist them improve diabetic care and adjust therapy. Moreover, patients with severe anemia were recommended for further treatment.

Results

Sociodemographic and clinical characteristics of the study participants

After exclusion of 12 subjects, the final sample analyzed consisted of 236 adult diabetic patients, 126 males and 110 females, aged between 18 and 81 years. The reason for exclusion was as follows: eight subjects due to lack of linearity in hemoglobin test values and evidence of hypochromic anemia and four subjects due to under 18 age. Around 59% (138 out of 236) of the analyzed patients had Type 2 DM, Type 1 DM accounting for the remaining 41%. Major characteristics of the study participants were stratified by the outcome variable and presented in Tables 1 and 2. The mean (± SD) and median (IQR) age of participants was 47.8 (± 13.8) years and 48.0 (37.0, 59.8) years, respectively. Moreover, 28.8% of the study subjects were below the age of 40 years, and every fourth subject was aged 60 years or older (Table 1). The duration of diabetes range from 1 to 22 years with a mean (± SD) duration of 5.3 ± 4.7 years. Three-forth of the participants had the diabetes for less than seven years.

Out of the total study participants, only two patients (1.0%) reported themselves as smoker and none was alcohol consumer. Only two women were pregnant during the study period and excluded from the analysis. Mean BMI (± SD) for the overall data was 24.6 (± 4.8) kg/m^2 (Table 2); and almost 60% of the participants had a BMI <25.0 kg/m^2 (normal weight), while the remaining (40%) were overweight (BMI ≥ 25.0 kg/m^2) (Table 1). Cardiovascular comorbidity (CVC) was prevalent in 31.4% (in 74 patients among 236 participants). Self-reported family history of DM, hypertension, family CVC, and family renal complication were used as a measure of genetic predisposition/factors for microvascular complications. Patient answered 'Yes' to any one or more of the questions like "Is there DM/hypertension/cardiac problem/kidney disease in any of your parents?" was considered as positive evidence for genetic risk factors, otherwise the index diabetic patient was considered negative for evidence of genetic risk factors.

According to the patients' response, genetic risk factors were evident in almost 20.0% of the sampled population (Table 1).

Level of glycosylated hemoglobin ($HbA1_C$) and glycemic control

Total hemoglobin and glycosylated hemoglobin percentage ($HbA1_C$%) were the main independent variables measured for 178 patients in this study. Regarding history of $HbA1_C$ assay and pervious knowledge about the assay, none of the patients had $HbA1_C$ test ever and all of them never heard about the assay before. The current $HbA1_C$ assay was therefore the first in history for all of the patients; chart review showed absence of previous record of $HbA1_C$ for all study patients.

For the purpose of this study, eight patients diagnosed with hypochromic and gestational anemia were excluded from the analysis. The reason for the exclusion was due to the fact that such factors are known to influence of HbA1c values as this was supported by lack of linearity of the test result provided by the machine. The mean ± SD of total hemoglobin and $HbA1_C$% for the overall data was 36.8 ± 11.8 µmol/L and 9.1 ± 2.8%, respectively. When these dataset were stratified for microvascular complications, an independent-samples t-test showed no significant difference (p>0.05) between those with history of microvascular complication and those without, for both of these test variables (Table 2). Level of the current glycemic control achieved by each patient was evaluated based on his/her $HbA1_C$ test value. Based on their glycemic level, patients were classified into three groups: good glycemic control ($HbA1_C$<8.0%), poor glycemic control (8.0 ≥ $HbA1_C$% ≤ 10.0) and very poor glycemic control ($HbA1_C$ >10.0%). The result showed only 35.3% of the study patients achieved a glycemic goal of $HbA1_C$ <8.0% with a mean score of 6.2%. The prevalence of poor glycemic control was 33.5% (95% CI: 27.1, 40.6%) with a mean score of 9.1%. Moreover, very poor glycemic control was apparent in 31.2% of the study patients with a mean score of 12.2% (Table 2).

Overall prevalence of major microvascular complications and associated factors

Microvascular diabetic complication was defined as the presence of any one or more of the following major complications: peripheral diabetic neuropathy, diabetic foot ulcer, visual disturbance and/or diabetic retinopathy, and skin and subcutaneous infections. Accordingly, 98 patients had already a record of at least one of these four complications during the study period, making the overall prevalence of major microvascular complications 41.5% (95% CI: 34.7 -

Variable	All cases, n (%)	Cases n (%), with complication	Cases n (%), with no complication	χ^2-statistic*	p-value
Gender					
Male	126 (53.4)	42 (33.3)	84 (66.7)	7.471	0.006
Female	110 (46.6)	56 (50.9)	54 (49.1)		
Type of DM					
Type 1	98 (41.5)	41 (41.8)	57 (58.2)	0.007	0.935
Type 2	138 (58.5)	57 (41.3)	81 (58.7)		
Age group					
20 - 39 years	68 (28.8)	26 (38.2)	42 (61.8)	0.413	0.937
40 - 49 years	53 (22.5)	22 (41.5)	31 (58.5)		
50 - 59 years	56 (23.7)	23 (41.1)	33 (58.9)		
60⁺ years	59 (25.0)	25 (42.4)	34 (57.6)		
BMI categories[a]					
<25.0 kg/m²	130 (59.9)	52 (40.0)	78 (60.0)	0.041	0.839
≥ 25.0 kg/m²	87 (40.1)	36 (41.4)	51 (58.6)		
Duration of diabetes[a]					
<7 years	161 (74.9)	67 (41.6)	94 (58.4)	0.703	0.402
≥ 7 years	54 (25.1)	26 (48.1)	28 (51.9)		
Family history of DM					
Absent	167(88.4)	62 (37.1)	105 (62.9)	5.683	0.017
Present	22 (11.6)	14 (63.6)	8 (36.4)		
$HbA1_C$ level and level of glycemic control[a]					
Good ($HbA1_C$ <8.0%)	60 (35.3)	16 (26.7)	44 (73.3)	4.765	0.092
Poor ($HbA1_C$=8.0 -10.0%)	57 (33.5)	25 (43.9)	32 (56.1)		
Very poor ($HbA1_C$ >10.0%)	53 (31.2)	23 (43.4)	34 (56.6)		
Hypertension					
Absent	177 (75.0)	67 (37.9)	110 (62.1)	3.932	0.047
Present	59 (25.0)	31 (52.5)	28 (47.5)		
Cardiovascular co-morbidities					
Absent	162 (68.6)	58 (35.8)	104 (64.2)	4.286	0.038
Present	74 (31.4)	38 (51.4)	36 (48.6)		
Genetic predisposition/risk factors[b]					
Absent	189 (80.1)	70 (37.0)	119 (63.0)	7.874	0.005
Present	47 (19.9)	28 (59.6)	19 (40.4)		

*=Pearson Chi-Square Tests; [a] indicates totals do not add up to 236 due to missing data; BMI=body mass index; DM=diabetes mellitus; $HbA1_C$=glycosylated hemoglobin; [b] refers to the presence of any one or more of the following conditions in the family tree: history of DM, hypertension, cardiovascular and renal complications.

Table 1: Sociodemographic and clinical correlates of microvascular complications among diabetic outpatients, Jimma University Specialized Hospital, Southwest Ethiopia.

47.9%). Diabetic peripheral neuropathy (DPN) was the most prevalent microvascular complication evident in 60 (25.4%) subjects, followed by visual disturbance in 48 (20.3%), skin and subcutaneous infection in 23 (9.7%) patients, and diabetic foot in 20 (8.5%) subjects. The number of microvascular complications recorded per patient stratified by glycemic level was shown in Figure 1. As shown, among the 98 subjects with record of complication, 33 subjects (33.7%) had two or more of the microvascular complications under study. The incidence of microvascular complication was higher among patients with poorly controlled DM.

On bivariate analysis, gender, CVC and genetic risk factors were significantly ($p<0.05$) associated the prevalence of microvascular complications, while $HbA1_C$ level and glycemic control marginally ($p<0.25$) associate with the outcome. These variables, notably $HbA1_C$ level, gender and genetic risk factors, which showed absolute or marginal univariate association with the outcome, were included in the multivariate binary-logistic regression analysis. As shown in Tables 1 and 2, other variables like age or age at onset, body mashttps://doi.org/10.1007/s00592-009-0093-8, type of DM and diabetic duration had no significant association with the overall prevalence of major microvascular complications, and hence not included into the multivariate analysis.

Table 3 shows summarized results from the multivariate regression analysis for factors associated with microvascular complications. As shown, all the three variables ($HbA1_C$ level or glycemic control, gender and genetic risk factors) entered into the multivariate model were significantly associated with the microvascular complications. The prevalence of microvascular complication was 26.7% in good glycemic

Variable	All cases, Mean (SD)	Cases with complication	Cases with no complication			
		Mean (SD)	Mean (SD)	df	t-static [a]	p-value
$HbA1_C$%	9.1 (2.8)	9.2 (2.4)	9.0 (3.0)	168	0.282	0.779
Total hemoglobin (µmol/l)	36.8 (11.8)	38.2 (11.3)	35.9 (12.1)	167	1.217	0.226
Current age (years)	47.8 (13.8)	48.1 (13.3)	47.6 (14.1)	234	0.305	0.760
Duration of illness (years)	5.3 (4.7)	5.71 (4.8)	5.03 (4.6)	213	1.041	0.299
Age at onset of DM (years)	42.8 (13.4)	42.8 (13.6)	42.7 (13.3)	202	0.070	0.945
Body mass index (kg/m^2)	24.6 (4.8)	24.6 (3.9)	24.6 (5.3)	215	0.026	0.979

[a] Independent samples T-tests between diabetic outpatients with record of microvascular complications and those without; HbA1c=glycosylated hemoglobin; SD=standard deviation; *df*=degree of freedom.

Table 2: Mean scores of various characteristics of diabetic outpatients by record of microvascular complication, Jimma University Specialized Hospital, Southwest Ethiopia, 2015.

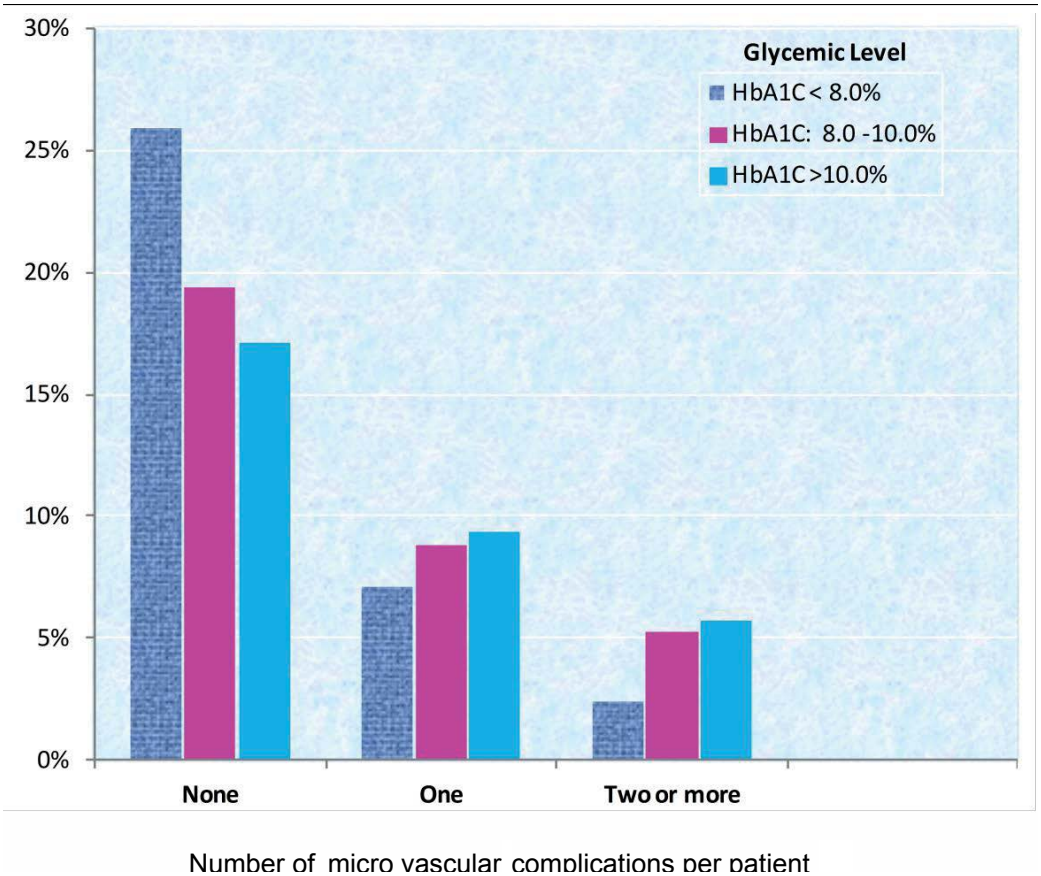

Figure 1: Number of major microvascular complications stratified by glycemic level at the outpatient clinic of Jimma University Specialized Hospital, Southwest Ethiopia, 2015

Variable	All cases, n (%)	Cases, n (%) with complication[a]	Adjusted OR* [95% CI]	Wald statistic	P value
$HbA1_c$ level (%) and level of glycemic control[b]					
Good ($HbA1_c$ <8.0%)	60 (35.3)	16 (26.7)	1.00 (Reference)	5.694	
Poor (HbA1C = 8.0 - 10.0%)	57 (33.5)	25 (43.9)	2.65 [1.15, 6.12]	5.196	0.023
Very poor (HbA1C >10.0%)	53 (31.2)	23 (43.4)	2.23 [0.96, 5.18]	3.447	0.063
Gender					
Male	126 (53.4)	43 (34.1)	1.00 (Reference)		
Female	110 (46.6)	53 (48.2)	2.21 [1.14, 4.28]	5.518	0.019
Genetic predisposition/risk factors					
Absent	168 (71.2)	60 (36.0)	1.00 (Reference)		
Present	67 (28.8)	40 (59.6)	3.16 [1.37, 7.26]	7.319	0.007

[a] the figure in the bracket indicated the proportion of patients with record of complication in that specific category of the variables under study; *binary logistic-regression analysis for factors associated with microvascular complications; OR=odds ratio; CI=confidence interval; [b] totals do not add up to 236 due to missing data.

Table 3: Multivariate analysis for the independent predictors of microvascular complications among diabetic outpatients at Jimma University Specialized Hospital, Southwest Ethiopia, 2015.

level ($HbA1_C$ <8.0%) and increased progressively to 43.9% and 43.4% in patients with poor ($HbA1_C$: 8.0 - 10.0%) and very poor ($HbA1_C$ >10.0%) glycemic levels, respectively (Table 3). After adjustment for gender and genetic predisposition, the risk of microvascular complication was increased with the level of $HbA1_C$ by 97.4% (p=0.023) in poor glycemic level and by 80% (p=0.063) in very poor glycemic level, compared to patients with good glycemic control. As compared to patients achieving good glycemic level ($HbA1_C$ <8.0%), those patients with poor glycemic level ($HbA1_C$: between 8.1% and 10.0%) had double-folded adjusted odds (AOR= 2.65; 95% CI: 1.15 - 6.12, p=0.023) of microvascular complication. Likewise, patients with $HbA1_C$ values greater than 10.0% (very poor glycemic level) had increased relative risk of microvascular complications by a factor of 2.22 compared to patients with values in the lowest range (Table 3). This shows the relative risk rose steeply with the level of $HbA1_C$ value up to 10% after which it raised steadily.

When level of $HbA1_C$ or glycemic level is adjusted in multivariate analysis, gender and genetic risk factors were significantly associated with microvascular complications (Table 3). After adjustment for levels of $HbA1_C$ and genetic predisposition, female patients were two-times prone to microvascular complications (AOR=2.21; 95% CI: 1.14 - 4.28, p=0.019) than male subjects. As compared to patients with no self reported genetic risk factors, subjects with evidence of genetic predisposition had three-fold more adjusted relative odds for the complications (AOR=3.16; 95% CI: 1.37 - 7.27, p=0.007) when adjusted for other covariates. Among 47 patients with genetic risk factors, at least one major microvascular complication was recorded in 28 (59.6%) subjects.

Discussion

In clinical practice, the use of $HbA1_C$ assay compared with measures of fasting blood glucose avoids the problem of day-to-day variability of glucose values, and importantly removes the need for the person to fast and to have preceding dietary preparations. These advantages have made it the preferred test to judge the adequacy of the ongoing diabetes care and adjust therapy. Moreover, $HbA1_C$ test is gold standard and reliable in screening patients at high risk of diabetic complications [34-36]. Nonetheless, $HbA1_C$ assay is not readily available for Ethiopian diabetic patients in the public health sector and not used in clinical practice. It was against this background that this study was designed to undertake HbA1c assay and use the test results for evaluating level of glycemic control and assess its association with the overall prevalence of major microvascular complications among diabetic patients attending the outpatient clinic of JUSH.

For this purpose, HbA1c assay was objectively performed for 178 study patients and the test result and its implication was communicated with the patients and their providers. Before the current study, most patients did not know the test and not aware of the implication of its test results. Thorough patient chart review also showed that none of the study patients had $HbA1_C$% test earlier, probably due to inaccessibility of the test at this institution and unaffordability in some private sectors. The mean $HbA1_C$% for the overall data was 9.1% and this is comparable with earlier study reports from the same clinic, 7.6 - 8.5% [26,27], and with 7.8% report (Northwest Ethiopia) [36], but somewhat lower than other reports; 12% from Gondar Ethiopia [37] and 11% from Mekele [10]. Furthermore, the mean $HbA1_C$ of 9.1% obtained in this study was slightly higher than similar reports around the world; 7.2% from china [38], 7.4% from Germany [39], 7.2% from European cohort of 2023 [19], and 8.2% from the Diabcare Africa study [40]. Various diabetes care bodies around the world are currently working to achieve a glycemic goal of $HbA1_C$<10% in 90% of the diabetic patients [41,42]. Only 69.4% of diabetic patients in the current study achieved a glycemic goal of $HbA1_C$<10%, implicating the urgent need for adoption and implementation of similar polices in local diabetes care system of Ethiopia.

Major microvascular complications and associated factors

People with poorly controlled diabetes over a longer period have a risk of developing a number of microvascular chronic complications involving microscopic blood vessels supplying the retina, kidneys, nerves, genital organs and teeth [14-17]. In addition, people with diabetes also suffer from developing infections. In almost all high-income countries, diabetes is a leading cause of blindness, kidney failure, and lower limb amputation [22,23,34]. In the current study, the overall prevalence of major microvascular complications (DPN, diabetic foot ulcer, visual disturbance, and skin and subcutaneous infections) was 41.5%; the proportion which is comparable with 52.9% prevalence report from Waktola et.al [26], but much higher than the prevalence reported from other studies [9,10]. The relatively low prevalence shown in other studies in Ethiopia and other African countries [6-8] could be associated with the repeatedly reported low screening frequency for chronic complications. Besides, the progression of poorly controlled DM to costly complications overtime should not be deserted.

Studies have clearly demonstrated that persons with higher level of adherence to their treatment regimens and lower level of $HbA1_C$% have better glycemic control and thus less likely to develop diabetic complications [43-45]. In contrary, persistently higher levels of $HbA1_C$% (poorly controlled DM) increases the risk of developing diabetic complications [46-50]. In the current study, overall prevalence of major microvascular complications was found strongly associated

with poor glycemic control ($HbA1_C$>8.0%), female sex and self-reported genetic risk factors. In line with literature, in this study $HbA1_C$ significantly predicted major microvascular complications. In literature, the mortality risk of established diabetes is generally mediated largely through HbA1c concentration [51-53]. Even though there is different cut-off values for different populations worldwide at least partially due to geographical, sociodemographic and genetic predisposition, diabetic patients with $HbA1_C$ >7.0% are considered poor glycemic control and hence with a higher risk of developing diabetic complications and subsequent co-morbidities and mortalities [46-50]. For Ethiopian diabetic population, $HbA1_C$ level was not standardized. Therefore, a cutoff value of 8.0% as poor glycemic level in this study was mainly arbitrarily and partially based on the method of the assay [32]. The increasing risk of major microvascular complications among patients with poor glycemic level implicated urgent need for improvement in glycemic care at the current clinic in order to minimize the apparent risk of complications.

In addition to high levels of $HbA1_C$ or poor metabolic control, interlay of other factors including gender and genetic risk factors were significantly associated with major microvascular complications in the current study. Regarding the relationship between gender and incidence and severity of microvascular complications, severe complications were frequently reported in female subjects [22]. In concordant with literature, the incidence of microvascular complication in the current study population was two-times higher in female subjects as compared to the proportion in male subjects while adjusting for glycemic level and genetic predisposition.

In the current study, presence of history of DM, hypertension and CVC in the family members was considered positive evidence for genetic risk factors. As a result, genetic risk factor was prevalent in almost 20% of the study population, and these patients were found three-times more susceptible to the development of microvascular complications, independent of $HbA1_C$ level. Use of the variables as a major of genetic risk factors in the current population was original. Data on the association between family history of DM, hypertension and/or other cardiovascular comorbidities (CVC), and family history non-traumatic renal disease, as a measure of genetic risk factor for microvascular complications is scarce [54-56].

The overall prevalence of major microvascular complications in the current study was independent of type of DM, current age or alternatively age at onset, diabetic duration, and BMI. These findings are not supported by the literature [9,10] in which patients suffering from chronic complications of diabetes are usually overweigh subjects with advancing age. Regarding the relationship between types of DM and incidence and severity of microvascular complications, severe complications were frequently reported in patients with Type 1 DM [11-13]. Literature evidence also shows positive association between BMI and the development of microvascular complications [50,55-57]. In the current study however, BMI has no univariate association with microvascular complications, and hence omitted from multivariate analysis. Regarding the relationship between diabetic duration and incidence and severity of microvascular complications, our result lacks literature support, as severe complications were frequently reported in patients with longer diabetic duration [9,22]. The root cause of this discrepancy needs further large prospective studies. However, absence any meaningful association between age, and alternatively age at onset, diabetic duration and major microvascular complications could be at least partially due to recall bias among the respondents during data collection. Our hypothesis was based on the difficulty we faced while attempting to crosscheck the data with what is recorded in patient chart. The challenge was lose of older patient charts along with data recorded on due to poor chart keeping and handling. This problem was even worse among patients with theoretically long history of follow-up at the clinic, as the patient cards are exhaustively torn away and lost. This problem is potentially avoidable. In the last decade, nations are using digital registry of diabetes database not only to alleviate the problem of poor patient chart keeping, but also as one effective chronic disease management strategy [58]. A recent report from Eritrea, Ethiopia's close neighbor in the northern, shows effectiveness of diabetes registry in providing evidence-based prevention and control of the disease. For effective evidence-based prevention and control of diabetes, establishment of diabetes registry in Ethiopia is therefore crucial.

Limitations of the Study

Several limitations of this study should be considered. First, this study is a facility-based cross-sectional study, which is not free from all inherent limitations of cross-sectional data. Secondly, a single institutional based nature of the study and the relatively small sample size might limit the generalizability of the findings for all diabetic populations in Ethiopia or elsewhere around the world.

Poor chart keeping resulted in loss of older patient charts along with information recorded on them. This limited us from getting reliable data on diabetic duration, age at onset, previous laboratory tests and earlier treatment regimens and chronic complications. Absence of full patient's information on a specific complication leads to wrong conclusion that the patient is free of that complication, but in reality, the patient may be suffering from the complication. Moreover, due to lack of central registry and diabetes database in the current health facility and in Ethiopia as a whole, there is no apt way to undergo all round analysis on the issues like the trend and incidence of diabetes and its associated health problems overtime.

Conclusions

Despite all the potential limitations stated, the following key conclusions can be drawn from the findings of this study. Although HbA1c assay is a gold standard and an index of glycemic control and screening tool for patients at increased risk of complications, the test is not readily available in clinical practice, at least at JUSH. Result from an $HbA1_C$ assay for the diabetic patients at the outpatient clinic of JUSH showed mean $HbA1_C$ of 9.1%, which was by far above the worldwide recommendations for better glycemic goal. The overall prevalence of major microvascular complications was high; almost 42% of the diabetic outpatients had record of at least one complication. The associated risk factors include poor glycemic control ($HbA1_C$ >8.0%), female sex and family history of genetic risk factors.

Recommendations

Large prospective studies are also necessary to validate the current findings. The higher level of microvascular diabetic complication in subjects with poorly controlled diabetes highlights the need for more effective diabetes management/therapeutic alternatives to minimize the development of such costly and life threatening complications. Besides, $HbA1_C$ level should be standardized for Ethiopian diabetic populations and use of $HbA1_C$ as screening tool for patients at increased risk of complications should be an emerging issue in Ethiopian public health sector. In order to facilitate ease availability of reliable diabetes related data for care providers, researchers and policy makers, establishment of a centralized digital registry and diabetes database in Ethiopia is indispensable.

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Authors Contributions

All authors contributed almost equally to the work. TAN and BZ conceived the research concept, ADW involved in the research plan and grant writing. WC assisted in the process of $HbA1_c$ determination. TGG, ST and YM developed tools, supervised data collection and carried out analysis; EM and SG drafted and produced the final document. All authors read and approved the final manuscript.

Competing Interests

No competing interest to declare.

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