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Frequency of risk factors and long-term complications in a female population with previously diagnosed diabetes mellitus in rural Nepal

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Student thesis in endocrinology
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Abbreviations

2PG	2-hour Plasma Glucose
AER	Albumin Excretion Rate
ACR	Albumin:Creatinine Ratio
ADA	American Diabetes Association
BHC	Bolde Health Center
BMI	Body Mass Index
BP	Blood Pressure
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DH	Dhulikhel Hospital
DHKUH	Dhulikhel Hospital Kathmandu University Hospital
DM	Diabetes Mellitus
DM1	Diabetes Mellitus type 1
DM2	Diabetes Mellitus type 2
ESRD	End Stage Renal Disease
FPG	Fasting Plasma Glucose
HbA1c	Hemoglobin (A1c)
HPLC	High Performance Liquid Chromatography
HT	Hypertension
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
IQR	Interquartile Range

LMIC	Low- and Middle Income Countries
NCD	Non Communicable Disease
NHANES	National Health and Nutrition Examination Survey
NICE	The National Institute for Health and Care Excellence
nonDM	non Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
PDM	Prediabetes
SBP	Systolic Blood Pressure
SD	Standard Deviation
WC	Waist Circumference
WHO	World Health Organization

Abstract

Frequency of risk factors and long-term complications in a female population with previously diagnosed diabetes mellitus in rural Nepal

Background: Diabetes mellitus (DM) is a noncommunicable disease causing 1.5 million deaths annually in 2012. Its global prevalence is growing dramatically, projecting to 10.4% of the adult population in 2040. Almost 75% of those with DM reside in developing countries, including Nepal. In the current study, we attempted to verify the DM diagnosis and to investigate for risk factors and DM-related complications among a small sample of women in rural Nepal.

Methods: This is a descriptive follow-up study of rural women previously identified with DM according to HbA1c measured by the Nycocard method. Data concerning demographics, lifestyle and symptoms were retrieved. Anthropometric measurements, collection of blood and urine samples, and examinations for DM-related complications were carried out. HbA1c was analyzed by a High Performance Liquid Chromatography (HPLC)-technique, cholesterol by a colorimetric assay and urine albumin by Nycocard affinity chromatography. DM and anthropometric measurements were categorized according to guidelines from ADA, WHO and NICE[1].

Results: Of 100 invited women, 72 participated in the study. The overall prevalence of DM, prediabetes (PDM) and non-diabetes (nonDM) was 16.9%, 63.4% and 19.7%, respectively. Median HbA1c was 6.0% (IQR 0.6). Higher age in the PDM and DM groups was observed. Median body mass index was 25.1 kg/m^2 (IQR 7.8), 66.6% being overweight or obese. BMI was similar in those with DM, PDM and nonDM. In the whole study population, 36.2% had hypertension (HT), and 15.5% had high total cholesterol levels. The latter was more frequent in those with DM, HT and older age. Prevalence of complications was as follows: 6.25% nonproliferative retinopathy, 18.6% cataract and 2.9% microalbuminuria. Symptoms and findings giving suspicion of neuropathy occurred in 76.1%. However, this percentage is unreliable due to the foot status of the women with thick and hard skin under the soles. Retinopathy, cataract and microalbuminuria were more frequent in the combined PDM/DM groups compared to nondiabetics, although not significant. Nonproliferative retinopathy and microalbuminuria were seen only in PDM/DM, while the other complications were seen in all groups. Only 45.8% had heard of DM.

Conclusion: We were able to confirm the presence of DM only in 12 of the women, while the majority had PDM. Altogether, 80.3% had PDM or DM. The occurrence of overweight/obesity and HT was high in the study population, and hypercholesterolemia was also frequent, consistent with metabolic syndrome. The prevalence of retinopathy and microalbuminuria was low, while cataract was more common. However, the low number of women with DM and several sources of errors prevented us from drawing firm conclusions on the prevalence of complications. Finally, we observed that the awareness of DM was poor. Our data show the need for implementation of preventive public health actions to reduce modifiable risk factors and increase awareness in rural Nepal.

[1] American Diabetes Association, World Health Organization and National Institute of Health and Care Excellence

Introduction

Noncommunicable diseases (NCDs) are a global burden, being the premier cause of death and disability worldwide with a mortality rate of 38 million a year. The four main groups of diseases are cardiovascular diseases (CVDs), cancers, chronic respiratory diseases and diabetes mellitus (DM). Together, these groups account for 82% of all NCD deaths. The NCDs, including DM, disproportionately affect low- and middle-income countries (LMIC) where almost three quarters of NCD deaths occur[1].

A dramatic rise in the prevalence of DM has occurred over the recent decades: it has nearly doubled since 1980, increasing from 4.7% to 8.5% in 2014 in the adult population[2 3]. In 2015, the global prevalence of DM was approximately 8.8% in adults aged 20-79 years and was projected to be 10.4% in 2040[4]. The estimated annual death rate was 1.5 million in 2012[2 3]. About 75% of those with DM reside in LMIC[5], and so the burden of the disease largely falls on developing countries. Close to one-fifth of all adults with DM live in South East Asia, where about 8.5% of the adult population (78 million people) have DM[6]. China has the highest prevalence of DM worldwide, followed by India[7]. The number of people with DM in South East Asia is expected to increase to 140 million by 2040, i.e. 10.7% of the adult population[6]. The projected increase parallels rapid cultural and social changes with ageing populations and increasing urbanization.

DM, risk factors and related long-term complications

DM is characterized by hyperglycemia and glucose intolerance, due either to insulin deficiency, as in type 1 diabetes (DM1), or to disorders of insulin resistance and insulin secretion, either of which may be the predominant feature in type 2 diabetes (DM2). DM2 is the most common form of DM, comprising 90% of people with DM around the world, and hence the increasing global prevalence of DM reflects that of DM2.

The development of DM2 is largely driven by modifiable risk factors, particularly physical inactivity, overweight and obesity[8]. Family history, urban residency, age, higher body mass index (BMI), sedentary lifestyle and hypertension (HT) are all associated with a greater DM2 risk. The metabolic syndrome, referring to the co-occurrence of several important cardiovascular risk factors such as central obesity, raised BP and FPG, and an abnormal lipid profile, contribute to a five time greater risk of developing DM2[9 10]. Symptoms of DM

include polyuria, polydipsia, weight loss, vision change and fatigue. In DM2 these symptoms are often less marked than in DM1, and therefore, diagnosis may be delayed by several years after onset, when complications have already arisen[3].

Long-term complications of DM are common in both DM1 and DM2. Chronic exposure to hyperglycemia leads to microvascular and macrovascular damage, affecting several tissues. The most prevalent microvascular complications are retinopathy, nephropathy and neuropathy. Recently, osteoporosis has also emerged as a complication of DM[11]. These complications may eventually result in blindness, kidney disease and osteoporotic fractures. Macrovascular complications include CVD and peripheral vascular disease that may finally lead to leg amputations[12]. Age and duration of DM are significant risk factors for all complications in diabetic patients.

Globally, diabetic retinopathy is the most frequent cause of preventable blindness in adults. In a major meta-analysis, Yau et al. examined the prevalence and major risk factors for diabetic retinopathy from 35 studies across the world, including data from 22.896 individuals with DM[13]. The prevalence of any diabetic retinopathy was estimated to 34.6%, with 10.2% having vision-threatening retinopathy. Longer DM duration and poorer control of blood sugar and blood pressure (BP) were strongly associated with diabetic retinopathy[13]. In a review, addressing diabetic retinopathy in 12 developing countries, the prevalence varied from 12-61%[14].

Neuropathy is considered the most common microvascular complication in both DM1 and DM2, and also a main risk factor for amputation[15]. Around 50% of diabetics have some form of peripheral neuropathy, as well as autonomic neuropathy. The latter includes cardiovascular autonomic dysfunction, which is manifested as abnormal heart rate and impaired vascular control[16].

Diabetic nephropathy is the leading cause of end stage renal disease (ESRD) in Western countries, and develops as a clinical syndrome in 25-40% of Caucasian diabetic patients with either DM1 or DM2. Subjects diagnosed with DM2 account for approximately 90% of DM-related ESRD. According to a study by Adler et al. in the UK in 2003, including more than 5000 subjects with DM2, progression to microalbuminuria occurred at 2.0% per year. During ten years of follow-up, 24.9% developed microalbuminuria and 5.3% macroalbuminuria. A

rise in risk of CVD death with increasing nephropathy was also observed [17]. In a study including ten Asian countries, albuminuria was observed in around 20-40% of hypertensive patients with DM2[18].

Data on prevalence of diabetic complications in developing countries are scarce. Also, estimates vary widely between the countries[15]. Multiple studies show association between worse metabolic control and lower socio-economic status and rural settings[15].

CVD is the primary cause of death globally, and currently, over 80% of CVD deaths occur in LMIC[8]. According to the World Health Organization (WHO), DM, HT, and obesity are some of the main risk factors for CVD deaths worldwide. Adults with DM are 2-4 times more likely to develop CVD than nondiabetics, and CVD is the most common cause of morbidity and mortality among these patients. HT, hyperlipidemia and hyperglycemia contribute to the increased risk of CVD complications in the diabetic population[19].

DM is associated with significant morbidity, diminished quality of life and reduced life expectancy, due to related long-term complications. In addition, the disease is a huge economic burden for the individuals, their families and the society[2]. All of these can be reduced significantly with earlier detection and treatment of risk factors and the disorder.

Diagnostic criteria

Plasma glucose estimation remains the basis for the diagnosis of DM (WHO/IDF Report 2006): fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL) or 2-h plasma glucose (2PG) after oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L (200 mg/dL). These criteria recognize a group with significantly increased premature mortality and increased risk of microvascular and CVD complications[20]. Asymptomatic individuals are also identified. In 2009, a WHO expert committee issued an addendum report to the 2006 published diagnostic criteria, recommending HbA1c (average blood glucose levels over a 2- to 3-month period of time) as a diagnostic test for DM with a 6.5% cut point. However, a value less than 6.5% does not exclude DM diagnosed using glucose tests[21]. Moreover, there is no full concordance between HbA1c levels and FPG/OGTT tests, and the National Health and Nutrition Examination Survey (NHANES) data indicate that an HbA1c cut point of 6.5% identifies one-third fewer cases of undiagnosed DM than a FPG test (cut point of 7.0 mmol/L)[22].

Prediabetes (PDM) refers to an intermediate condition between normality and DM, with increased risk of developing DM, having higher than normal glucose levels, but not meeting the DM criteria. According to the American Diabetes Association (ADA) an impaired fasting glycemia (IFG) with FPG = 5.6-6.9 mmol/L (100-125 mg/dL) and/or impaired glucose tolerance (IGT) with 2PG = 7.8-11 mmol/L (140-199 mg/dL). HbA1c of 5.7-6.4% could similarly predict the prediabetic state[23]. (Table 1)

Table 1. Diagnostic values for DM and prediabetic state according to the American Diabetes Association

	FPG mmol/l (mg/dL)	**2h PG mmol/l (mg/dL)**	**HbA1c %**
DM	≥ 7.0 (126)	≥ 11.1 (200)	≥ 6.5
IGT		7.8-11.0 (140-199)	
IFG	5.6-6.9 (100-125)		
Prediabetes			5.7-6.4

DM = Diabetes mellitus. IGT = Impaired glucose tolerance. IFG = Impaired fasting glycaemia

Early stage of diabetic kidney disease is characterized by microalbuminuria, which is defined as an albumin excretion rate (AER) of 20-200 μg/min (30-300 μg/d) or an albumin:creatinine ratio (ACR) of 2.5-25 mg/mmol in males and 3.5 – 35 mg/mmol in women. The traditional descriptive term diabetic nephropathy is defined specifically with persistent macroalbuminuria, associated with an elevated BP and a decline in glomerular filtration rate. Macroalbuminuria is defined as an AER > 200 μg/min (> 300 μg/d) or an ACR > 25 mg/mmol in males and > 35 mg/mmol in women[24].

Diabetic retinopathy may be clinically detected by fundus ophthalmoscopy, and is classified as nonproliferative diabetic retinopathy and proliferative diabetic retinopathy. Nonproliferative retinopathy includes microaneurysms, small hemorrhages, and intraretinal microvascular abnormalities. Proliferative retinopathy comprises neovascularization of the retina and of the optic disc, in addition to hemorrhage into the vitreous[25].

Diabetic sensorimotor polyneuropathy can be assessed by the following parameters: presence of symptoms, such as pain, dysesthesias (burning, tingling), and numbness, impaired nerve conduction and motor reflexes of ankle and knee, and reduced vibration and light touch perception (monofilament)[26].

Asians are predisposed for DM2 at a younger age and lower BMI than Caucasians[27 28 29 30], consequently, lower cutoff levels are set for BMI to classify overweight and obesity in Asians: ≥ 23 kg/m^2 indicates overweight, ≥ 27.5 kg/m^2 obesity (compared to European values, 25 kg/m^2 and 30 kg/m^2, respectively)[31 32]. Asians also have a higher percentage of body fat at a given BMI than Caucasians[33], indicating abdominal adiposity. The International Diabetes Federation (IDF) sets the WC limit to 80 cm and 90 cm for Asian women and men, respectively[34].

Table 2. BMI values according to the WHO

	Principal BMI cutoff (kg/m^2)	**Asian criteria BMI cutoff (kg/m^2)**
Underweight	< 18.5	< 18.5
Normal	18.5 – 24.9	18.5 – 22.9
Overweight	25 – 29.9	23 – 27.4
Obesity	≥ 30	≥ 27.5

BMI = Body Mass Index. WHO = World Health Organization.

Table 3. Ethnic specific values for waist circumference (as measure of central obesity)

Country/Ethnic group		**Waist circumference**
Europids	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm

Nepal

Nepal is a small, landlocked country in South East Asia, located between China and India. Its 150 000 square kilometers inhabit approximately 29 million people of many diverse ethnicities, comprising more than 120 ethnic groups and languages. Three ecological zones characterize Nepal's geography: mountain (north), hill (center) and Terai (plains, south). The country is among the poorest and least developed in the world, 25% of its population living below the national poverty line. The unemployment rate was 46% in 2008 and literacy is estimated at 63.9%. The population has more than doubled during the last four decades; the estimated annual growth rate in 2016 was 1.24% with a birth rate of 19.9/1000, and the life expectancy at birth has increased to 70.7 years. Rural poverty, malnutrition, poor sanitation

and inadequate health service are contributing to the high infant mortality (28.9 deaths per 1000 live births)[35]. Nepal is a predominantly rural country, with 81% of the population living in rural settings. It is also the fastest urbanizing nation in South Asia, with a 3.18% annual change rate. However, the rapid urbanization has been accompanied by lower economic growth than in other South Asian countries[36].

Development and growth of Nepal's public sectors face many challenges: a landlocked, rugged and mountainous geography, poor infrastructure, proneness and vulnerability to natural disasters (among them the massive earthquakes in 2015), political instability and public dissatisfaction, are all barriers for change and advance in the economical and social conditions. This also applies to the health sector.

The health situation in Nepal

The Government has recognized health care as a basic fundamental right with a right for free basic health service from the state (2007 Interim Constitution and 2015 Constitution of Nepal[37]). However, poverty and turbulent political times have made implementation of this difficult. The health system is troubled by the unequal distribution of health care services, geographical constraints with poor or lacking infrastructure, inadequate supply of essential medication, poor retention of human health resources in public service and rural areas, unorganized growth of the private health sector, and insufficient financing for health.
In 2011, it was reported that Nepal had only 0.67 doctors and nurses per 1000 population (0.17 doctors/1000, 0.5 nurses/1000), which is significantly less than the WHO recommendation of 2.3 doctors, nurses and midwives per 1000 population, and is also low compared to other countries in South Asia[38 39].

The estimated total health expenditure in 2014 was 5.8% of the gross domestic product[35]. The government sector covers less than a quarter of total health spendings, and external resources finance nearly half of governmental health expenses. Also, a considerable growth in the private sector makes it an important part of the health financing system. Around half of all health care expenditure comes from payments by individual households. Thus, as a result of seeking health care, households can experience financial hardship and often impoverishment[40].

During the last decades, various programs have been implemented in the health sector. Since 2004, the Ministry of Health has organized the Nepal Health Sector Program, with renewal every 5th year. Improving the health of the poor and marginalized groups, and the extension of free services, have been the main focus. Community-based health insurance schemes have been and are being piloted in some districts, though this has in most cases not helped to avoid catastrophic personal expenditure as there is no other official public health insurance system in the country[41].

Some health programs have shown significant improvement in the Human Development Index, especially regarding maternal and child health. Maternal mortality rate has decreased by 80% between 1991 and 2011, and under five-child mortality has also diminished considerably[42].

Female empowerment is another important issue in Nepal. Domestic violence and men's control in many aspects of a woman's life, among them accessibility to health care and family economy, are reasons for poor health and insecurity among women. In the 2011 Nepal Demographic and Health Survey[43], the majority of women reported at least one problem that would pose a barrier to seek health care for themselves: getting permission, money, distance to a health facility and not wanting to go alone. Those living in rural areas and having no education were more likely to have these problems.

DM in Nepal

At present, Nepal is facing a double burden of disease: high rates of communicable diseases and the increasing prevalence of NCDs are together a big challenge for the country's health care system. DM is the 4th major group among NCDs worldwide; in Nepal there is a considerable rise in DM prevalence both in rural and urban regions, making it a leading public health problem.

According to the IDF, the estimated national prevalence of DM in the age group 20-79 years in 2013 was 4.5%, increasing to 5.4% by 2035[44]. A survey from 1991 to 2001 observed DM in 14.6% in urban and 2.5% in rural areas. Another study showed a national increase of DM prevalence from 7.5 to 8.2% in 2010 and 2014, respectively[45]. The rapid rise in the prevalence of DM might largely be driven by the transition to a more urban lifestyle, including dietary factors and physical inactivity. A recent systematic review and meta-analysis of DM2

concluded with a national prevalence of 8.4% in Nepal[46]. The need to establish local DM registries to better understand the burden of the disease has been discussed[47].

DM as a chronic disease requires broad self-care knowledge and management. Poor level of overall awareness of the disease can account for a higher rate of long-term complications[48 49]. A hospital-based descriptive study of diabetic complications among 100 out-patients (99% DM2) in Dharan in 2010 reported a high frequency of complications: neuropathy (44.4%), CVD and retinopathy (27.7%), and nephropathy (16.6%)[50]. In South Asian Association for Regional Cooperation (SAARC) countries, including Nepal, the large, poor population has lower DM prevalence rates than the rich, but have higher frequency of complications. Delay in diagnosis and identification of risk factors, and poorer management are essential reasons[51]. It is therefore important to increase awareness of the disease, and improve accessibility to health centers and management of health care costs. A survey published in 2015 using World Health Survey data from 35 LMIC showed the trend of catastrophic expenditure, also regarding DM[52]. Even with insurance, diabetics were more likely to experience such expenditure and to lack appropriate medication for their treatment. Diabetics in developing countries often delay seeking medical care until after they have developed complications[52], again resulting in higher costs. Paralleling the survey, a study in urban Nepal (2014) noted DM as the third illness most frequently associated with catastrophic expenditure[41].

Several studies have been conducted of DM and complications in different parts of Nepal, showing varying frequency. As the geographical characteristics, population density, ethnicity and culture, lifestyle and urbanization, differ widely between regions, it is difficult to compare the studies and conclude concerning overall prevalence of DM and its complications. Few studies have been carried out to assess the complication rate in rural Nepal. In a previous study on NCDs in women in the rural Kavre region, about 14% were found to have DM according to HbA1c (Syversen et al, unpublished data). In the current study we aimed to verify their DM and investigate for risk factors and DM-related complications.

Methods and subjects

Study population

The study was a follow-up study of a population-based cross-sectional study conducted in joint collaboration with Dhulikhel Hospital Kathmandu University Hospital (DHKUH) and

the Norwegian University of Science and Technology. Altogether, 1500 married non-pregnant women from the Kavre region of Nepal were included for studies of gynecological diseases[53] and NCDs (Syversen et al, unpublished data). HbA1c was analyzed in about 1100 of these women, applying the Nycocard method (Axis shield PoC As, Oslo, Norway).

Altogether, 100 women were identified with DM according to their HbA1c value (≥ 6.5%) and invited to participate in the follow-up study. The project was conducted in October 2016 in Bolde village where one of the outreach health centers of Dhulikhel Hospital (DH) is located, and in neighboring villages within the Kavre District: Pokhari Narayansthan, Thuloparsel and Sirsuekharka. The women were invited to the various health posts in the region, and investigated by a team consisting of a senior medical physician from Bolde Health Center (BHC), a first year resident ophthalmologist, a biochemical lab technician and a staff member from the Department of Community Programs from DH, a Bachelor's student of Public Health from Purbanchal University, and the thesis student.

Data collection

The women answered a questionnaire including sociodemographic data, diet, smoking habits, alcohol consumption, symptoms of DM, CVD and diseases in the family. Measurements of BP, height, weight and WC were performed. Urine samples were collected for determination of microalbuminuria at the arrival to the health posts. Blood samples were obtained for measurement of HbA1c and total cholesterol. Microvascular complications were investigated, including: visual acuity (Snellen chart), pupil-dilated (tropicamide 1% eye drops) retinal fundus evaluation by direct ophthalmoscopy, sensibility assessment with 10g monofilament on plantar and dorsal aspects of the feet, ankle and knee reflex, feet inspection for callus or ulcers, and recording of the pulse in arteria tibialis posterior and arteria dorsalis pedis.

Blood and urine samples

The blood samples were collected and divided in two vials (full blood and serum). The serum was either centrifuged on-site or stored in dry ice until centrifugation at BHC the same day. Thereafter the samples were stored at BHC at -80˚C, following transportation in dry ice to DH and storage at -80˚C. The HbA1c analyses were conducted by biochemists at DH using the High Performance Liquid Chromatography (HPLC) technique. This method is certified by the National Glycohemoglobin Standardization Program[54]. Total cholesterol was measured with colorimetric assay. DM was indicated by HbA1c levels ≥ 6.5% and PDM by 5.7-6.4%, in

accordance with the guidelines of the American Diabetes Association[55] and the WHO[21]. Cholesterol levels were categorized as: desirable < 200 mg/dL (5.2 mmol/L), borderline high = 200-239 mg/dL (5.2-6.2 mmol/L) or high ≥ 240 mg/dL (6.2 mmol/L). Urine albumin was measured on-site in spot (random) urine sample with Nycocard affinity chromatography and categorized as: normal < 20 mg/L, microalbuminuria = 20-200 mg/L or clinical albuminuria > 200 mg/L.

Physical examination

BP measurement was conducted manually using a standard sphygmomanometer by experienced health workers. Only one cuff size was available, BP was measured once and the women did not sit for a standardized period before measurement. HT was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, in accordance with the guidelines of the Joint National Committee[56]. Body weight was measured without footwear, but with clothing. No specific equipment was available for measurement of body height, thus, a measuring tape was applied. BMI cutoff value for overweight was set at 23 kg/m^2, obesity at 27.5 kg/m^2 and underweight at 18.5 kg/m^2, as recommended by the WHO and NICE guidelines for Asian populations[32 57]. WC limit was set to 80 cm, in accordance with guidelines by the WHO and IDF for South Asian populations[58]. Monofilament results were categorized as normal, diminished or absent. Knee and ankle reflexes were noted as normal, diminished or absent. One or more abnormal findings among the variables monofilament, reflex and tingling/itching foot-sensation were registered as "associated neuropathy". Retinopathy was classified as nonproliferative retinopathy, with the presence of at least one microaneurysm, hemorrhage or exudates in either of the eyes, or proliferative retinopathy, presence of new vessels or vitreous hemorrhage. Presence of clinically significant macular edema was also inspected.

Statistical analyses

All statistics were performed using the IBM SPSS statistics version 24 software (IBM, Chicago, US). Figures and tables were made in Microsoft Excel 2010 (Microsoft Corp, WA, US). All data were tested for normal distribution using the Shapiro-Wilk test. Between groups differences in continuous variables were analyzed with one-way ANOVA with a post-hoc Tukey test. A univariate general linear model, with confounding factors age and/or BMI as covariates, was used to calculate adjusted between-groups differences (ANCOVA). Logarithmic transformation was performed on data that were not normally distributed before

analyzing. Between-groups differences for categorical variables were analyzed by a Pearson Chi Square test. Correlations between variables were assessed by Spearman or Pearson tests. Data are presented as mean (± standard deviation (SD)) or median (interquartile range (IQR)), depending on normal distribution or not. A two sided *p*-value ≤ 0.05 was considered significant for all analyses.

Ethical aspects

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway and the DHKUHs Institutional Review Committee. On the day of examinations, participants received information about the study from the health workers at the various health posts. Informed consent was given as a thumb print due to illiteracy. Participation was free of charge and withdrawal from the study was accepted at any time. The results from urine and blood samples will be conveyed to the participants through their neighboring health posts.

Results

A total of 100 women with previously identified DM according to HbA1c were invited, and 72 participated. The remaining women had migrated, lived too far away from the health posts or had died. Blood samples were collected from all, except for one. The response rate was 94% or more in the majority of the study parameters.

Baseline characteristics

The mean (± SD) age of the participants was 51.40 (± 12.7) years. The age distribution is shown in Figure 1.The median BMI was 25.1 kg/m^2 with an IQR of 7.8. Forty-eight women (66.6%) had a BMI ≥ 23 kg/m^2, thus being overweight (23 women) or obese (25 women). A negative correlation between BMI and age was seen (r = -0.288, *p* = 0.014). Mean WC was 76.4 (± 10.5) cm, and 34.7% of the participants had central obesity (≥ 80 cm). The median SBP and DBP was 110.0 (IQR 25) and 80.0 (IQR 20) mmHg, respectively. Due to missing equipment, BP was not measured in three of the women. In total, 25 women (25/69 = 36.2%) exhibited systolic and/or diastolic HT. Baseline characteristics including anthropometric measures and results of blood analyses are summarized in Table 4.

Figure 1 - Distribution of particpants by age (n=72)

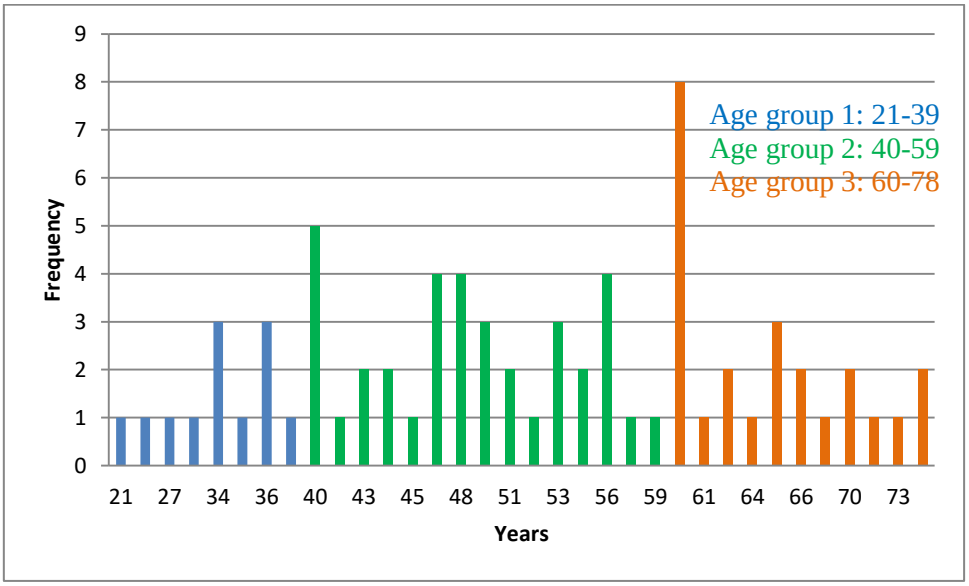


Table 4 - Baseline characteristics of the total population

		Frequency n	Percentage %	Mean	SD	Median	IQR
Age years (n=72)				51.4	12.7		
BMI kg/m^2 (n=72)						25.1	7.8
WC cm (n=72)				76.4	10.5		
SBP/DBP mmHg (n=69)						110 / 80	25 / 20
HT (n=69)		24	34.8				
Serum							
HbA1c % (n=71)						6	0.6
	NonDM	14	19.7			5.4	0.3
	PDM	45	63.4			6	0.4
	DM	12	16.9			6.6	0.5
Total cholesterol mg/dL (n=71)						189	53
Stimulant							
Alcohol (n=72)		15	20.8				
Smoke (n=72)							
	Yes	25	34.7				
	Never	35	48.6				
	Quitted	12	16.7				
Awareness							
DM awareness (n=72)		33	45.8				
Known DM (n=72)		4	5.6				

BMI = body mass index. WC = Waist Circumference. SBP = Systolic BP. DBP = Diastolic BP. BP = Blood Pressure. HT = Hypertension. DM = Diabetes Mellitus. IQR = Interquartile Range.

HbA1c levels

The median HbA1c value was 6.0% (IQR 0.6), with 16.9% and 63.4% of participants having an HbA1c of ≥ 6.5% (DM) and 5.7-6.4% (PDM), respectively. According to the novel HbA1c results the population was divided into three groups: non-diabetes (nonDM), PDM and DM. Among the diabetics the median HbA1c level was 6.6% (IQR 0.5), among prediabetics 6.0% (IQR 0.4) and nondiabetics 5.4% (IQR 0.3). A significant positive association between HbA1c level and age was noted (r = 0.306, p=0.009).

Baseline characteristics in three groups (Table 5)

Mean age was higher in the DM group compared to the nonDM group (p = 0.031). Median BMI did not differ significantly between the three groups (p = 0.526) or between the nonDM and combined PDM and DM group (p = 0.595). Table 5 shows the prevalence of overweight in the groups. WC was significantly higher in the DM group compared to the other groups (DM vs PDM: p = 0.004, DM vs nonDM: p = 0.005). Overall, the awareness of DM was 45.8%. A higher percentage had heard of DM in the DM group compared to the nonDM group (DM vs nonDM: p = 0.02). Three of those with DM were treated with metformin, the others were not aware that they had DM (HbA1c levels of 6.5%, 11.2% and 11.7%, respectively).

Table 5 - Baseline characteristics of the groups: nonDM, PDM, DM

		Total n	NonDM (n = 14)	PDM (n = 45)	DM (n= 12)	*p*-value
Age years		71	44.5 (± 14.1)	52.1 (± 11.0)	56.3 (± 13.4)	*0.031**
	21-39	12	5 (35.7%)	7 (15.6%)	0	
	40-59	35	6 (42.9%)	24 (53.3%)	5 (41.7%)	
	60-78	24	3 (21.4%)	14 (31.1%)	7 (58.3%)	
BMI kg/m^2		71	26.3 (10.4)	24.4 (6.6)	26.9 (8.7)	*0.526*
	Underweight	4	1 (7.1%)	3 (6.7%)	0	
	Normal	20	4 (28.6%)	13 (28.9%)	3 (25%)	
	Overweight	23	2 (14.3%)	14 (31.1%)	6 (50%)	
	Obesity	25	7 (50%)	15 (33.3%)	3 (25%)	
WC cm		72	72.5 (± 9.3)	75.0 (± 9.6)	86.2 (± 11.7)	*0.002**
	< 80	47	12 (85.7%)	31 (68.9%)	3 (25%)	
	≥ 80	25	2 (14.3%)	14 (31.1%)	9 (75%)	
BP						
	SBP mmHg	68	110 (20)	110 (30)	120 (20)	*0.619*
	DBP mmHg	68	75 (10)	80 (20)	80 (20)	*0.332*
	HT (n)	23	1 (7.1%)	17 (39.5%)	5 (45.5%)	*0.031**

Serum						
HbA1c %		71	5.4 (0.3)	6.0 (0.2)	6.6 (0.5)	
Total cholesterol mg/dL		71	172.0 (23)	196.0 (52)	224.0 (57)	*0.085*
	Desirable	43	13 (92.9%)	26 (57.8%)	4 (33.3%)	
	Borderline high	17	1 (7.1%)	12 (26.7%)	4 (33.3%)	
	High	11	0	7 (15.6%)	4 (33.3%)	
Stimulants						
Alcohol		15	3 (4.2%)	9 (12.5%)	3 (4.2%)	*0.933*
Smoke						*0.179*
	Yes	25	2 (2.8)	16 (22.2)	7 (9.7)	
	Never	34	9 (12.5)	22 (30.6)	3 (4.2)	
	Quitted	12	3 (4.2)	7 (9.7)	2 (2.8)	
Awareness						
Awareness DM n		71	3 (21.4%)	22 (48.9%)	8 (66.6%)	*0.061*
Known DM n		4		1 (1.4%)	3 (4.2%)	

Mean (± SD), median (IQR), n (%).
nonDM = non DM. PDM = Prediabetes. DM = Diabetes Mellitus. BMI = Body Mass Index. WC = Waist Circumference. BP = Blood Pressure. SBP = Systolic BP. DBP = Diastolic BP. HT = Hypertension.
p-value: overall between-groups (adjusted for age). *: statistically significant
Percentage is according to respective group. Total n can be lower than total frequency of the whole study population, due to missing HbA1c value used for group determination.
One subject who reported known DM had PDM according to new HbA1c level.

BP and lipid status

No significant differences in SBP or DBP were found between groups ($p = 0.619$ and $p = 0.332$, respectively). The 24 individuals with HT were significantly older than those with normal BP (55.2 (± 12.8) and 48.9 (± 10.6) years, respectively, $p = 0.043$). Twenty-two women (30.6%) reported having any kind of BP-related problems. Two used BP-medication for their hypertensive condition, one of these had still an elevated BP (150/100 mmHg). HT was more frequent in the DM and PDM groups compared to the nonDM group (DM vs nonDM: $p = 0.023$, PDM vs nonDM: $p = 0.013$).

In the total population the median value of total cholesterol was 189 (IQR 53). Eleven women (15.5%) had high levels, seven in the PDM and four in the DM group. Cholesterol levels were higher in the DM group compared to the PDM and nonDM groups ($p = 0.058$ and $p = 0.007$, respectively). After adjusting for age, a borderline significance between groups persisted ($p = 0.085$). Age and BP were positively correlated with cholesterol (age: $r = 0.493$, $p < 0.01$ and SBP: $r = 0.495$, DBP: $r = 0.543$, SBP/DBP: $p < 0.01$).

Among the total study population, 31 (43.1%) displayed one of the risk factors HT, high/borderline high total cholesterol, or overweight/obesity. Eighteen (25%) of the study subjects had two, and 11 (15.3%) all three.

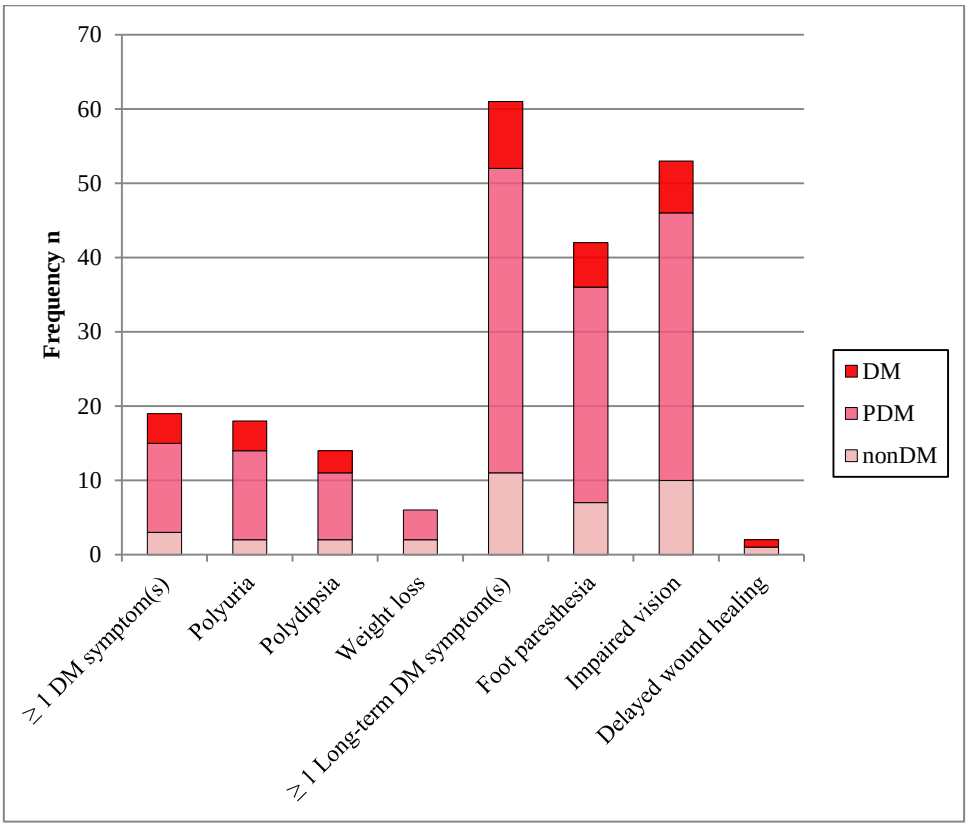
Stimulants

Among the 72 women, 34.7% (25) were current smokers, 48.6% (35) had never smoked and 16.7% (12) reported previous smoking. BP and HbA1c were similar among smokers and never-smokers. Alcohol consumption was reported by 20.8% (15) of the women. No significant differences in stimulant status were seen between the groups (smoke $p = 0.179$, alcohol $p = 0.933$).

DM symptoms

Altogether, 26.4% (19) reported having one or more DM symptoms (polyuria, polydipsia, weight loss). The combination polyuria and polydipsia was the most common (16.7%). Regarding symptoms associated with long-term complications of DM (itching/tingling foot-sensation, impaired vision, delayed wound healing), 86.1% (62) women reported having experienced one or more symptoms, foot paresthesia and problem with vision being the most common of the three. The frequency of symptoms among the groups is shown in Figure 2. There were no significant differences in the frequency of those reporting symptoms or long-term DM-related symptoms between the three groups ($p = 0.792$, $p = 0.262$, respectively).

Figure 2. Frequency of symptoms among groups

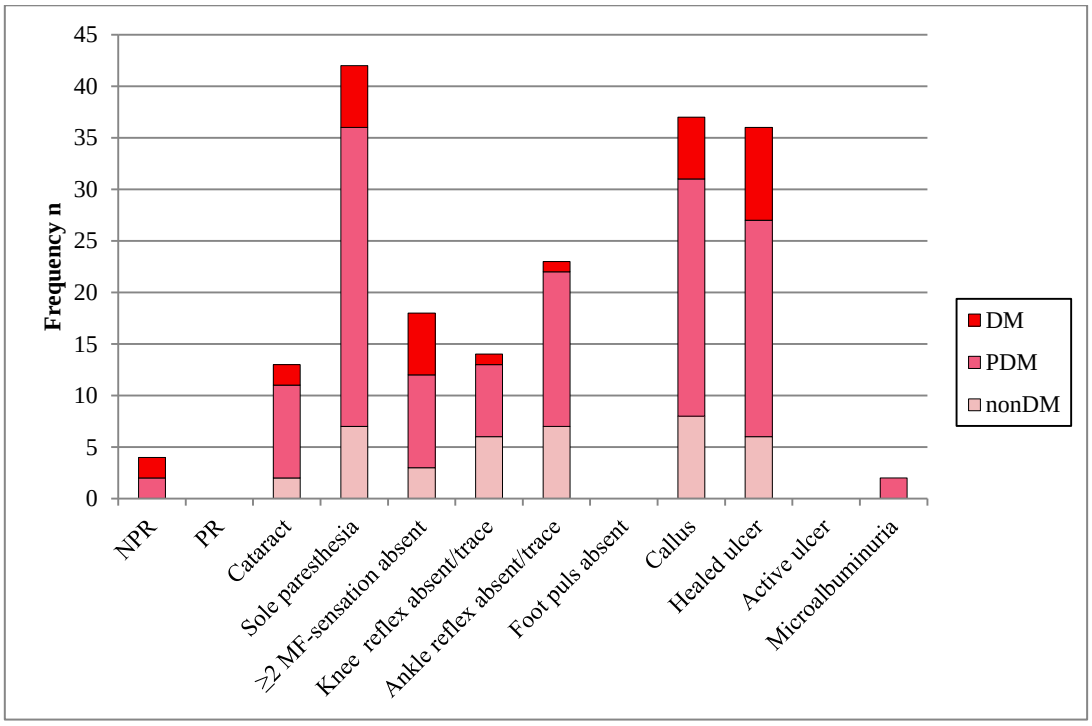


nonDM = non DM. PDM = Prediabetes. DM = Diabetes Mellitus

Complications

The observed prevalence of complications in the study population was as follows: 6.25% nonproliferative retinopathy, 18.6% cataract, 76.1% neuropathy-associated factors, 2.9% microalbuminuria. With the exception of nonproliferative retinopathy and microalbuminuria, complications were seen in all groups (Figure 3). The combined PDM and DM groups showed a higher frequency of cataract, retinopathy and microalbuminuria than the nonDM group (although not significant, $p = 0.616$, $p = 0.170$, $p = 0.333$, respectively).

Figure 3 - Frequency of complications among groups



NPR = Nonproliferative Retinopathy. PR = Proliferative Retinopathy. MF = Monofilament. nonDM = non DM. PDM = Pre-diabetes. DM = Diabetes Mellitus.

Nonproliferative retinopathy and proliferative retinopathy

Fundus evaluation of 64 women revealed that four subjects (6.25%), two with PDM and two with DM, had some form of nonproliferative retinopathy. All four had soft exudates, two (DM or PDM) had in addition hemorrhages and microaneurysms, respectively. No proliferative retinopathy was observed. A total of eight participants were not examined of unknown causes.

Cataract

18.6% (13) of 70 women had cataract, ten of them bilaterally. Figure 3 shows the distribution of cataract among the three groups. There was no difference between those with and those without cataract regarding HbA1c values ($p = 0.764$), and no difference between groups in cataract status was found ($p = 0.869$). The prevalence of cataract increased by age ($p < 0.001$), with 30.8% in those 40-59 years old and 69.2% in those 60-78 years old. A higher frequency of cataract was also seen in those with HT compared to those without HT (p = 0.044). Two women were not investigated.

Neuropathy-associated variables

Diabetic neuropathy was evaluated among 71 participants; 76.1% (54) reported one or more of the defined parameters. The parameters were non-specific for DM and most of the findings were unreliable due to poor understanding and skin status at the feet. Frequency of variables were similar in all groups: 75% of the diabetics, 73.3% of the prediabetics and 85.7% of those without DM were noted with one or more of the parameters, while 23.9% (17) participants reported none. Itching or tingling in the feet were reported by 58.3% of the 72 participants, of which only 14.6% (8.5% of 71) were diabetic. Results from monofilament sensation were attained from 69 of the 72 women, with 26.1% reporting two or more sites absent; the distribution among the groups is shown in Figure 3. Among those with one absent sensation site uni- or bilaterally, 77.3% (17) had impaired sensation at the heel, with a comment of hard and thick skin. Abnormal knee and ankle reflexes (absent or trace) were noted in 19.7% (14) and 32.4% (23) of 71 participants, respectively. Distribution among the groups is shown in Figure 3.

Foot status

Of the 12 diabetic women who were evaluated for diabetic foot complications, none had absence of foot pulses, six had calluses, nine reported healed ulcers, and none active ulcers. In the total study population, callus formation and healed ulcers were present in 52.1% and 50.7%, respectively.

Urine albumin

Urine samples were provided by 68 of the 72 (94.4%) participants. 97.1% (66) were normal and 2.9% (2) had microalbuminuria (33.0 and 49.0 mg/L, respectively). Both abnormal samples were from women with PDM. 70.6% (48) of the participants had a urine albumin value of less than 5 mg/L.

Discussion

This study was a follow-up of a study on NCDs among married women in rural Kavre, Nepal, where 100 women were found to have DM according to HbA1c (Syversen et al, unpublished data). We now aimed to verify their DM and to examine for risk factors and DM-related complications. Due to various reasons, including migration, long distance to health post and death, 28% were not able to participate. Surprisingly, presence of DM was confirmed in only

12 (16.9%) of the participants, while 45 (63.4%) had PDM. Three of those with DM were treated with metformin, the others were not aware that they had DM. All women were examined with the assumption that they had DM, as the results of the new HbA1c measurements were not available before later.

It should be noted that the method used for analysis of HbA1c in the current study was HLPC, while the Nycocard method was applied in the previous project from 2013. According to the ADA, HPLC is an accurate and stable method for HbA1c-determination[59]. Evaluations of the numerous HbA1c measurement techniques are divergent in their findings. Some conclude that the Nycocard system, involving several manual steps, is imprecise and does not meet the quality requirements for HbA1c testing[60 61]. Others state the system as effective and showing significant linear association with the HLPC method[62]. It cannot be ruled out that there has been a decline in HbA1c in some of the women since the previous measurements due to alterations in lifestyle or other factors.

Although the DM prevalence was lower than anticipated, the majority of the women had elevated HbA1c (80.3% PDM and DM). In addition, those with normal HbA1c (19.7%) had values in the upper reference range. DM is usually diagnosed by FPG or 2PG following an OGTT. These tests are not in full concordance with HbA1c, and as reported by the NHANES, a FPG $\geq$ 7 mmol/L identifies one-third more DM cases than an HbA1c $\geq$ 6.5%. Thus, the prevalence of DM in the current study might be higher than 16.9%. In our study it was more feasible with HbA1c, as the women walked to the health posts and arrived at different time points of the day, making it difficult to obtain fasting blood samples.

The median HbA1c level of the diabetics was 6.6%. Eight (66.7%) of them had an HbA1c below 7%, which is the recommended level, also for prevention of complications[63]. Consequently, lifestyle changes could be sufficient for the majority. Of the three women with known DM who reported taking metformin, only one met the advised target of 6.5%[64], whereas the other two had unfavorable levels (11.2% and 11.7%). Measurement of antibodies to assess the presence of DM1 was unfortunately not performed. However, DM2 is the most common type of DM, and is most likely in these women aged 40 to 78 years. However, latent autoimmune diabetes in adults (LADA) cannot be excluded.

We experienced difficulty in estimating neuropathy in these women, both because of occasional poor understanding of instructions and because of foot status. Since most of them had thick and hard skin under their soles, we did not achieve representative results from monofilament testing. The women reported walking barefoot at home and during work in the fields, also explaining ulcers, and had unsuitable footwear ("flip-flops") for longer distances. Accordingly, it was impossible to differentiate between diabetic neuropathy and other etiologies.

Retinopathy is another diabetic complication of major concern. Unfortunately, the ophthalmological evaluation was not always made under ideal conditions. At some study sites investigations were performed outside, some participants were not adequately pupil dilated and some were not examined. Thus, we may have missed a number of cases with retinopathy. We observed the presence of retinopathy in four women, two prediabetics and two diabetics.

Cataract, another eye complication of DM, is the leading cause of blindness in the world[65] and in Nepal, accounting for more than two-thirds of blindness in the country[66]. Most cataracts are related to ageing, and risk factors include DM, prolonged exposure to sunlight, tobacco use and alcohol drinking[67]. Numerous studies report an association between cataract development and hyperglycemia. Both those with PDM and DM are considered to be at greater risk[68 69 70 71]. In our study, 18.6% had cataract, two of the diabetics, nine of those with PDM and two of those with normal HbA1c. Cataract was more prevalent in the elderly, suggesting the presence of senile cataract. UV radiation and high altitudes contribute to development of lens opacities[72 73 74], which could also be a causal factor in our study population. Sun-protective eyewear is probably little used and could be an important preventable measure.

Diabetic nephropathy is a major cause of chronic kidney disease and end stage renal failure globally[75]. In the current study, only two women with PDM displayed microalbuminuria. Several studies report the presence of microvascular complications[76], including microalbuminuria[77 78], in PDM. In the rural setting of our study, only collection of a spot (random) urine sample was possible. Prevalence of microalbuminuria is reported to be higher when determined by spot urine samples compared to first morning void[79], making our results uncertain.

Due to the low number of women with DM we could not draw any firm conclusion on the prevalence of diabetic complications. It must also be noted that the complications are not specific for DM. Since neuropathy was difficult to assess, these data were excluded from further analyses. No significant differences in occurrence of other complications were found between the three groups. When combining those with PDM and DM, we observed higher frequency of cataract, retinopathy and microalbuminuria than in the nonDM group, although not significant.

Globally, obesity is a major risk factor for DM, and its prevalence is growing rapidly in LMIC such as Nepal. The WHO national STEPwise approach to Surveillance (STEPS) survey (2015) noted a high occurrence of overweight and obesity (21%) in Nepal, even greater among urban residents (31%)[80]. South Asians are reported to have the highest prevalence of abdominal obesity[81], the epidemic also propagating to children and adolescents. In the current study, 66.6% were overweight or obese. However, BMI did not differ significantly between the three groups or between the nonDM and combined PDM and DM group. This is in contrast to previous studies in Nepal[46 82] and globally[83 84], showing a relationship between DM and BMI.

Studies conducted in the Kavre region in 2008[85] and 2013 suggest a BMI of 22 kg/m^2 as an appropriate cutoff value for the detection of individuals at risk of developing DM in the area. The current study population had a higher BMI, with overweight in all three groups. Unlike previous studies[81], we observed a negative correlation between age and BMI. The high prevalence of overweight mirrors the trend of increasing obesity and reduction in physical activity in recent years in Nepal[46]. It might also reflect the fact that excess body fat is considered healthy and of higher status in rural than in urban areas. Measures to raise awareness on its role in disease are necessary.

WC correlates more closely with abdominal adipose tissue than BMI, and data suggest that WC is a better indicator than BMI of the DM risk[58]. A total of 25 women (34.7%) in the study had central obesity with a WC of 80 cm or above. A significant higher WC was seen in those with DM and PDM compared to the nonDM group, in concordance with a study conducted in the Kavre district in 2009[86].

Elevated levels of total cholesterol were observed in 15.5 % of the study population, while 23.9% had borderline levels. The increased cholesterol levels were more frequently seen in prediabetics and diabetics. In accordance with other studies[80], those with DM, HT and higher age displayed the highest cholesterol levels. Unfortunately, we do not have data on HDL and LDL, and total cholesterol in the reference range does not rule out unfavorable levels of these parameters. Due to problems to obtain fasting blood samples, triglycerides were not measured.

HT is twice as common in diabetics than in nondiabetics, affecting 20-60%, depending on obesity, ethnicity and age[87]. In line with this, we observed that HT was more frequent in the DM and PDM groups compared to the nonDM group. HT is often present as part of the metabolic syndrome in DM2, while it may reflect the onset of diabetic nephropathy in DM1[88]. HT greatly increases the risk of both macrovascular and microvascular complications. In our study, there was a significant difference between those with and without HT regarding cataract, similar to other studies which show HT as a risk factor for cataract[89 90].

To conclude, a substantial proportion of the participants were overweight or obese (66.6%), had HT (36.2%) and/or had borderline or high total cholesterol (39.4%). Thirty-one (43.1%) of the study subjects displayed one of these risk factors, 18 (25%) had two, and 11 (15.3%) all three. This suggests a high rate of the metabolic syndrome and increased risk for CVD[91].

Awareness and participation rate

According to the main study, many participants refused to give blood due to cultural prejudice and superstition. In the current study, the few with reservations were convinced without difficulty of the benefits of a blood test. As a result, no participant refused to give the required amount of blood. Since these women have already experienced giving blood in the previous project, the participation ratio might not be representative for women in rural Nepal. Community-based awareness programs and education prior to conducting a study can greatly increase the participation rate. A study on community-based health education in rural Nepal by Shakya et al.[92] showed significant impact on attitude towards cervical cancer screening, willingness to participate rising from 15.6% before to 100% after the education.

Level of DM awareness and its risk factors is low in Nepal and other South Asian populations, also among diabetics[93 94 95]. This might be one of many causes for the increasing

prevalence of the disease and its complications. For successful prevention, it is necessary to improve knowledge regarding DM in the general population[96]. National investment in education to decrease illiteracy is important. DM2 has many modifiable risk factors, and increased awareness can result in individual and community empowerment to choose healthier lifestyle. Mohan et al. provided mass awareness programs regarding the benefits of physical activity in Indian communities as a prevention strategy of DM and other NCDs. As a result, one of the communities created a public park with their own funds, significantly raising the physical activity level of local residents[97]. Additionally, being aware of DM complications might further encourage individuals to seek medical care when symptoms of DM or complications first occur. Especially in remote areas, it can be both time and economically efficient to educate some individuals who can share information. Women's groups and female community health volunteers (FCHVs) are examples of successful social networks linking communities to the governmental health system in rural Nepal[98].

Expenditure and higher complication rate

Health care expenditure can be an important barrier to seek medical help and treatment[99 100]. Consequently, the expenses associated with DM can contribute to inappropriate treatment, increasing the risk for development of DM-related complications. DM is a huge economic burden because of its chronic nature and severe complications, and can lead to catastrophic expenses for the individuals and their families. Moreover, for people in remote areas, the nearest hospital or health post might be far away, thus making transportation costs an additional financial strain[39].

Limitations

In the current study several limitations are noteworthy. The sample size was small and the results may not be representative for rural Kavre. The use of HbA1c in diagnosing DM, may lead to an underestimation of the number of diabetics. As aforementioned, factors such as thick skin under the soles, understanding of instructions, spot urine samples and ophthalmological limitations contributed to unreliable findings. Assessment of reflexes was difficult in many of the participant as they did not relax the extremity. Furthermore, WC and body weight values were probably overestimated, since the participants did not remove all layers of clothing prior to measurement. Another source of error is that different health workers were conducting the anthropometric measurements at the various study sites. WC and BMI data should therefore be interpreted with caution. Furthermore, for measurement of BP,

only one cuff-size was applied, the measurements were performed by changing health personnel and were not repeated. The BP results are thus likely to be inaccurate[101 102].

Conclusion

In the current study, the number of women with DM was lower than anticipated, however a significant proportion of the participants were prediabetic. Altogether, 80.3% had PDM or DM. Due to several sources of errors, we were not able to assess the prevalence of neuropathy. The prevalence of retinopathy and microalbuminuria was low, while cataract was more frequent. When combining those with PDM and DM, we observed higher frequency of these three complications than in the nonDM group, although not significant. The occurrence of overweight/obesity and HT was high in the study population, with no differences between the groups, while hypercholesterolemia was more frequent in those with DM. Our findings indicate presence of the metabolic syndrome in a high percentage of the women. Finally, we observed that the awareness of DM was poor. It is of major importance to implement preventive public health actions in rural Nepal to increase awareness of DM and to reduce modifiable risk factors.

Appendix 1

Questionnaire प्रश्नावली

व्यक्तिगत विवरण :					कोड
A1	**a.** जिल्ला : District	काभ्रे Kavre			
	b. गाउँ विकास समितिको नाम :	1 बोल्दे Bolde			
		2 सरसीउनखका Sarsewkharka			
		3 पोखरी नारायण स्थान Pokhari narayansthan			
		4 चपखोरी Chapakhori			
		5 सरमथली Saramthali			
		6 मेछे Mechhe			
		7 ठूलो परसेल Thulopersel			
	c. वडा नम्बर Ward No.	**d.** गाउँ बस्ती वा टोलको नाम Name of locality	**e.** घर नम्बर : Household No.	**f.** सम्पर्क फोन नम्बर Contact No.	
A2	गत जन्म मितिमा तपाई कति उमेरको हुनु भयो ? What was your age in last birthday?		बर्ष Years _____ _____	पूरा भएको वर्ष उल्लेख गर्नुहोस् Mention the years completed	बर्ष – –
A3	के तपाई आर्थिक क्रियाकलापमा संम्लग्न हुनु हुन्छ ? Are you involved in any income generating activities? 1. छ Yes 0. छैन No 3. नभनेको Not mentioned			यदि छ भने प्रश्न a र b सोध्नुहोस् ।	
	a. यदि छ भने तपाईको आर्थिक श्रोत के हो ? Do you have any source of income? 1 जागिर Service 2 पसल र व्यापार Bussiness 3 गृहिणी Housewife 4 पशुपालन Animal Husbandry 5 अन्य Others			अन्य भए उल्लेख गर्नुहोस् Mention if any others	
	b. तपाईको कमाइको पैसा खर्च गर्ने निर्णयमा मुख्य भुमिका कस्को हुन्छ ? Who makes a decision on the expense of your earning? 1 आफ्नै Self 2 आफु र श्रीमान Self and husband 3 श्रीमान मात्र Husband only 4 परिवारको अन्य सदस्य Other family members 5 नभनेको				

			समुह Groups	छ Yes	छैन No	
A4	के तपाई यी कुनै समूहहरुमा संलग्न हुनुहुन्छ ? Are you involved in any groups	1	आमा समुह Mothers group	1	0	अन्य भए उल्लेख गर्नुहोस्
		2	बचत समुह Saving groups	1	0	
		3	स्वास्थ्य समुह Health groups	1	0	
		4	अन्य Others			

Non Communicable Diseases नसर्ने रोगहरु

B1 **के तपाई साकाहारी हो** ? Are you vegetarian?

1	हो Yes		0	होईन No

B2 **के तपाई चाँउचाँउ खानुहुन्छ** ? Do you eat noodles?

1	खान्छु Yes		0	खादिँन No →B4

B3 **तपाई चाउचाउ खानुहुन्छ भने कति खानुहुन्छ** ? If yes, how often do you eat noodles?

1	हप्तामा एक पटक नि खान्न	Once or twice in a month
2	हप्तामा एकचोटि	Once in a week
3	हप्तामा २ ,४ पटक	2-4 times in a week
4	हप्तामा चारपटक भन्दा बढी	More than 4 times a week

B4 **के तपाई दुध पिउनु हुन्छ** ? Do you drink milk?

1	पिँउछु Yes		0	पिँउदिन No→B6

B5 **यदि पिउनुहुन्छ भने कति पटक पिउनु हुन्छ** ? If yes, how often do you drink milk?

1	हप्तामा एक पटक नि खान्न	Once or twice in a month
2	हप्तामा एकचोटि	Once in a week
3	हप्तामा २-४ पटक	2-4 times in a week
4	हप्तामा चारपटक भन्दा बढी	More than 4 times a week

B6 **तपाईले मधुमेहको बारेमा सुन्नुभएको छ?** Have you heard about diabetes?

1	छ Yes		0	छैन No→B8

B7 **यदि सुन्नुभएको छ भने कुन माध्यम बाट सुन्नुभयो** ? If yes, what is the source of your information?

		छ Yes	**छैन** No
1. टेलिभिजन	TV	1	0
2. रेडियो	Radio	1	0
3. पत्रिका	Newspaper	1	0
4. स्वास्थ्य केन्द्र	Outreach Centre	1	0
5. अस्पताल	Hospitals	1	0
6. अन्य	Others	1	0

B8 **तपाईलाई मधुमेह भएको छ** ?Do you have diabetes?

1	छ Yes		0	छैन No→B11

B9 **यदि मधुमेह छ भने कस्तो प्रकार** ?If yes, what type of diabetes you have?

	1	प्रकार १ Type 1		2	प्रकार २ Type 2			
B10	**मधुमेह भएको खण्डमा तपाईले कस्तो उपचार गराईरहनुभएको छ ?**What type of treatment you are receiving for your type of diabetes? 1 चक्की सेवन Intake of tablets 2 इन्सुलीन इन्जेक्सन Injecting insulin 3 खाना सम्बन्धि सुझाब Dietary suggestions 4 कुनै पनि छैन None							
B11	**तपाईले निम्न लक्ष्णहरु महसुश गर्नु भएको छ ?** Have you experienced diabetes-like symptoms?			**छ** Yes	**छैन** No			
	धेरै पल्ट पिसाप लाग्न Frequency of urination			1	0			
	धेरै तिर्खा लाग्ने Excessive thirst			1	0			
	तौल घट्ने Weight loss			1	0			
B12	**तपाई धुम्रपान गर्नुहुन्छ?** Do you smoke? 1 गर्छु Yes →B13 2 कहिल्यै गरेको छैन Never →B14 3 छोडेको समय Quitted a. कहिले छोड्नु भएको हो ? When did you quit smoking? DD दिन MM महिना YY वर्ष							Use month during coding.
B13	**तपाई धुम्रपान गर्नुहुन्छ भने दिनको कतिवटा गर्नुहुन्छ ?** If yes, how many cigarettes do you smoke in a day? 1 ५ वटा भन्दा कम Less than 5 2 ५ देखि १० वटा 5 to 10 3 १० देखि १५ वटा 10 to 15 4 १५ देखि २० वटा 15 to 20							
B14	**के तपाईले कहिल्यै रक्सीजन्य चिजहरु जस्तैस बियर, वाइन, जाँड आदि पिउनु भएको छ ?** Do you drink alcohol? 1 पिउछु Yes 0 पिउदिन No							
B15	**तपाई कस्तो प्रकार को रक्सीजन्य चीज हरु पीउनु हुन्छ ?** What type of drinks do you drink? 1 बियर Beer 2 जाँड Jaad 3 तोंग्बा Tongba 4 रक्सि Raksi 5 छ्यांग Chyang 6 निंगर Ningar							

B16	**तपाईले बिगतका १२ महिनामा कुनै रक्सीजन्य चिजहरु कम्तिमा पनि एकपटक कतिको पिउनु भएको छ ?** During the past 12 months, how frequently have you had at least one standard alcoholic drink? 1 दैनिक Daily; 2 ५-६ दिन / हप्ता 5-6 days per week; 3 ३-४ दिन / महिना 3-4 days per week; 4 १-२ दिन / हप्ता 1-2 days per week; 5 १-३ दिन / महिना 1-3 days per month		
B17	**तपाईले कति पिउनु हुन्छ ?** How much do you drink when you drink? ..... माना		
B18	**तपाईको जिवन क्रीयाशील छ ?**Is your life active? 1 छ Yes; 2 छैन No		
B19	**तपाईले काम गर्दा कुनै अंग मा दुखाईको महसुस गर्नुभएको छ ?** Have you ever felt pain in any of your body parts while working? 1 छ Yes; 0 छैन No		
B20	**तपाईको पैताला चिँलाउने वा झमझमाउने गर्दछ ?** Do the soles of your feet ever get itching or have a tingling sensation? 1 गर्छ Yes; 0 गर्दैन No		
B21	**तपाईको पैतालामा कुनै त्यस्तो घाउ छ जुन कहिल्यै बढ्दैन ?** Do you have wounds on your soles that took long time to heal? 1 छ Yes; 0 छैन No		
B22	**तपाईले कहिल्यै आफ्नो दृष्य शक्ति कमजोर वा पुरै नदेख्ने हुनु भएको छ ?** Have you ever felt weak of vision or had blindness? 1 छ Yes; 0 छैन No		

Hereditary or personal diseases वंशाणु वा व्यक्तिगत रोगको बारे			
C1	**तपाईको परिवारमा कसैलाई मधुमेह भएको थियो ?** Did anyone from your family have diabetes?		

	1	छ Yes		0	छैन No			
C2	तपाईको परिवार मध्ये कसैलाई मुटु सम्बन्धि वा रक्तचाप को रोग लागेको छ ? Did any of your family members have any kind of heart or BP-related diseases?							
	1	छ Yes		0	छैन No			
C3	तपाईलाई मुटु सम्बन्धि कुनै रोग छ ? Do you have heart related diseases?							
	1	छ Yes		0	छैन No→C6			
C4	यदि तपाईलाई मुटु सम्बन्धि रोग भएको भए कुनै औषधि लिइराख्नु भएको छ ? If yes, are you taking any medicines for it?							
	1	छ Yes		0	छैन No→C6			
C5	यदि औषधि लिनुभएको भए त्यसको नाम लेख्नुहोस् If yes, mention the name of the medicine	.....						
C6	तपाईलाई प्रेसर को समस्या त छैन ?Do you have problems of blood pressure?							
	1	छ Yes		0	छैन No→C9			
C7	तपाईलाई प्रेसर को समस्या भए कुनै औषधी त लिनुभएको छैन ?If yes, are you taking any medicines for it?							
	1	छ Yes		0	छैन No→C9			
C8	औषधी लिनुभएको छ भने नाम लेख्नुहोस् If yes, mention the name of the medicine	.....						
C9	तपाईलाई कहिले कुनै स्वस्थ कर्मी ले तपाई को कुनै हड्डी भाचियो भनेर भनेको छ ? Have you ever been diagnosed with a fracture of any of your bones by health personnel?							
	1	छ Yes		0	छैन No			
C10	तपाई लडेर चोट लागेको ठाउँ मा कुनै अंग भंग भयको छ? Have you had a fall with following deformity of the injured area?							
	1	छ Yes		0	छैन No			

Appendix 2

Examination of eyes and feet

Date	
Participant ID No.	
VDC	

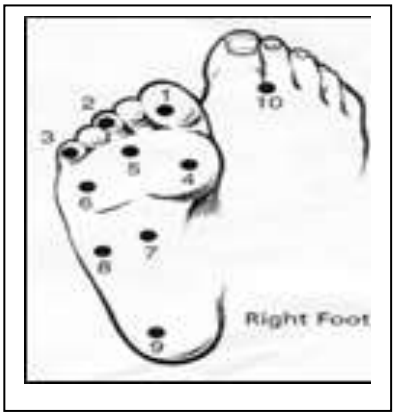
EYES. Performed by: _____

Findings		**OD**	**OS**
Visual acuity (Snellen chart)			
NPR	Microaneurysms		
	Hemorrhages		
	Hard/soft exudates		
PR	Presence of new vessels		
	Vitreous hemorrhage		
Clinically significant macular edema			

× *(cross): present. 0 (zero): absent*

MONOFILAMENT. Performed by: _____

Findings		**Right foot**	**Left foot**
Digits	1		
	3		
	5		
Metatarsal head	1		
	3		
	5		
Midfoot	Medial		
	Lateral		
Heel			
Dorsal foot			



× *(cross): present. 0 (zero): absent*

Avoid calluses/scars, as the patient will have reduced sensation in these areas.

PULS. Performed by: _____

Findings	Right foot	Left foot
A. Dorsalis pedis		
A. Tibialis posterior		

× *(cross): present. 0 (zero): absent*

FOOT INSPECTION. Performed by: _____

Findings	Right foot	Left foot
Callus		
Healed ulcer		
Active ulcer		

× *(cross): present. 0 (zero): absent*

REFLEX. Performed by: _____

Findings	Right extremity	Left extremity
Knee reflex		
Ankle reflex		

0: absent. 1+: trace. 2+: normal. 3+: brisk. 4+: nonsustained clonus. 5+: sustained clonus.

Normal: 1+, 2+, 3+ (unless asymmetric).

Hyperreflexia: 4+, 5+. Spreading to other muscles not directly being tested. Crossed adduction of opposite leg when patellar tendon is tapped.

Knee (patellar) reflex (L2-4): tap patellar ligament just below patella

Ankle jerk reflex (S1): dorsiflex the foot. Tap over Achilles tendon. Observe contraction.

LAB

Blood sample	Collected by: _____	Refused

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