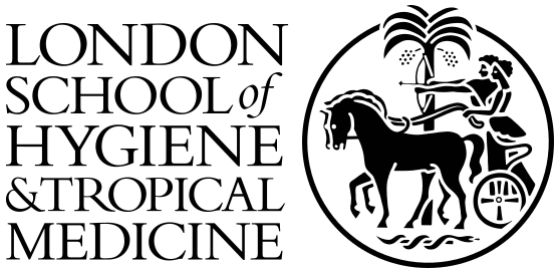

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Disease characteristics and treatment of patients with diabetes mellitus attending government health services in Indonesia, Peru, Romania and South Africa

Running title: Diabetes characteristics in four countries

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Abstract

Background

Diabetes mellitus (DM) is rising globally yet relatively little is known about the characteristics and management of DM patients from low- and middle-income countries (LMIC).

Methods

We systematically characterized consecutive DM patients attending public health services in urban settings in Indonesia, Peru, Romania and South Africa, collecting data on DM treatment history, complications, drug treatment, obesity, HbA1c, and cardiovascular risk profile; and assessing treatment gaps against relevant national guidelines.

Results

Patients (median 59 years, 62.9% female) mostly had type 2 diabetes (96%), half for >5 years (48.6%). Obesity (45.5%) and central obesity (females 84.8%; males 62.7%) were common. The median HbA1c was 8.7% (72 mmol/mol), ranging from 7.7% (61 mmol/mol; Peru) to 10.4% (90 mmol/mol; South Africa). Antidiabetes treatment included metformin (62.6%), insulin (37.8%), and other oral glucose-lowering drugs (34.8%). Disease complications included eyesight problems (50.4%), EGFR <60 ml/min (18.9%), heart disease (16.5%), and proteinuria (14.7%). Many had an elevated cardiovascular risk with elevated blood pressure (36%), LDL (71.0%), and smoking (13%), but few were taking antihypertensive drugs (47.1%), statins (28.5%) and aspirin (30.0%) when indicated. Few patients on insulin (8.0%), statins (8.4%) and antihypertensives (39.5%) reached treatment targets according to national guidelines. There were large differences between countries in terms of disease profile and medication use.

Conclusion

DM patients in government clinics in four LMIC with considerable growth of DM have insufficient glycemic control, frequent macrovascular and other complications, and insufficient preventive measures for cardiovascular disease. These findings underline the need to identify treatment barriers and secure optimal DM care in such settings.

INTRODUCTION

Diabetes mellitus (DM) is one of the largest global health emergencies of the 21st century. In 2017, there were 425 million adults estimated to be living with DM, and this number is predicted to increase to 629 million by 2045 (1; 2). An estimated 80% of people with DM live in low- or middle-income countries (LMICs) (2). Although studies are few, compared to individuals living in high-income countries, those with DM in LMIC may present at a younger age or with more advanced disease and more disease complications (3). Health care access and long-term care may be more problematic, with inadequate access to laboratory testing, medication such as insulin, health information, and limited self-management of patients (4). Also, people living with DM in tropical countries may be at higher risk for infectious diseases (5). Cardiovascular complications, the leading cause of mortality and morbidity among patients with type 2 DM (6; 7), may also be more common among people living with DM in LMICs (8-10), due to higher rates of smoking, and lower access to cardiovascular risk assessment and management (11-15). Assessment of diabetes disease characteristics, cardiovascular risk profile and medical management of people living with DM has been undertaken in some country-specific studies (16-18) and compared across LMIC countries in Asia and sub-Saharan Africa (12; 19; 20). Such studies are needed to help

improve management of DM and reduce its progression and complications.

As part of the TANDEM project on DM and tuberculosis (21), we have systematically characterized people with DM in government health clinics or hospitals in Indonesia, Peru, Romania and South Africa, four countries that are witnessing a rapid growth of DM (1). The TANDEM project has examined the prevalence of tuberculosis among individuals with DM, but this also allowed us to characterize DM patients in these four countries. Thus, the objectives of the present study were: (1) to establish disease phenotype and cardiovascular risk profile of DM patients; (2) to characterise medical treatment, and gaps between national and international guidelines and actual patient care as a 'cascade of care', and (3) to identify possible socio-demographic factors associated with inadequately controlled DM or with sub-optimal management.

METHODS

Setting and design

This study is part of The Concurrent Tuberculosis and Diabetes Mellitus (TANDEM) study which aims to develop methods for better screening and management of combined tuberculosis and DM, and to increase basic knowledge about the link between the two diseases (21). TANDEM is a multicentre prospective study with field sites in Peru, Romania, South Africa and Indonesia, countries with diverse healthcare systems and population demographics, but all with a relatively high burden of tuberculosis and an increasing prevalence of DM (1; 22). The TANDEM study recruited 2096 consecutive patients (December 2013 to June 2016) with previously diagnosed DM to be screened for tuberculosis through symptom screen, chest X-ray and sputum examination. To identify possible factors associated with tuberculosis, all patients were

uniformly and systematically characterized in terms of DM disease characteristics and management. These data were used for the current study, excluding those patients in whom active tuberculosis was diagnosed.

In Indonesia, DM patients were recruited in 25 community health centres and from the endocrine clinic in a tertiary public referral hospital in Bandung. In Peru, patients were recruited at a diabetes clinic at one tertiary level public hospital in Lima, as diabetes care in the public domain is mainly provided by hospitals. In Romania, patients with DM were recruited from two secondary level hospitals in Craiova. In South Africa, patients were recruited at three community health centres in the northern Cape Town metropolitan area. For more details of study site selection and location see Supplementary File.

Study procedures

Patients with known DM (either under care for DM or on DM medication) who were above 18 years of age were eligible; those with gestational or steroid induced diabetes were excluded. Following provision of written informed consent, research doctors conducted an interview, using a validated questionnaire, with each patient asking about their socio-demographic characteristics (age, gender, and education, and assets to link to socio-economic status), behavioural characteristics such as self-reported smoking status and alcohol consumption, and diabetes characteristics such as DM history, complications, medication, and management. Research nurses followed a standard operating procedure for taking patients' blood pressure using a digital device, and for measuring height, weight (using digital scales), and waist measurement for calculation of body mass index (BMI) and central obesity. Venous blood was taken for laboratory glycated hemoglobin (HbA1c), and urine for albumin to creatinine ratio

(ACR). All HbA1c samples were analysed in an accredited laboratory with NGSP certification, using the HPLC methods according to WHO guidelines and with DCCT aligned assays. Lipid profile and creatinine, recorded as the most recent test undertaken within the previous month, was obtained from the medical records for a sub-set of patients. Laboratory methods for both LDL and HDL used Siemens dimension clinical chemistry system. Ethical approval was received from the Observational/Interventions Research Ethics Committee, London School of Hygiene and Tropical Medicine on 18 December 2013 (LSHTM ethics ref: 6449, LSHTM amendment no: A473) and Institutional Review Boards in Indonesia, Romania, Peru and South Africa.

Data management and variables used

Demographic and clinical data were entered onto a case report form and then into a secure, centrally managed, electronic database (REDCap). Other data, such as laboratory results, diabetes history, smoking status and complications were entered directly into REDCap. Data quality was checked on a monthly basis for accuracy and completeness.

Blood pressure was categorised according to the JNC VIII (23): Normal (systolic and diastolic <120/80 mmHg); Pre-hypertension (systolic 120-139 or diastolic 80-89 mmHg); Stage I hypertension (systolic 140-159 or diastolic 90-99 mmHg); Stage II hypertension (systolic ≥160 or diastolic ≥100 mmHg). Weight and height for Indonesian patients were classified based on the Asia Pacific Criteria of Body Mass Index (24): Under-weight (<18·5 kg/m2); Normal (18·5-22·9 kg/m2); Over-weight (23·0-24·9 kg/m2); Obese I (25·0-29·9 kg/m2); Obese II (≥30 kg/m2). Weight and height for the three other sites were classified according to the World Health Organization (25):

Under-weight (<18·5 kg/m2); Normal (18·5-24·9 kg/m2); Over-weight (25·0-29·9 kg/m2); Obese (≥30 kg/m2). Central obesity for female patients in all sites was categorized as a waist circumference (WC) of ≥80 cm. Central obesity for males was categorized as a WC ≥90 cm for Indonesia and Peru and ≥94cm for Romania and South Africa (26). Laboratory HbA1c was categorised into three groups <7·0; 7·0-9·9; ≥10% (<53; 53-85; ≥86 mmol/mol) for analysis (27). ACR categories were normal (<30 ug/mg); moderately increased (30-299 ug/mg), and albuminuria (≥300 ug/mg). Low-density lipoprotein (LDL) were categorized as dyslipidemia if the result was ≥100 mg/dL (2.6 mmol/l), or if high-density lipoprotein (HDL) was ≤40 mg/dL (1.0 mmol/l) for males or ≤50 mg/dL (≤1.3 mmol/l) for females (27; 28). Estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI creatinine equation 2009 (29). Principal Component Analysis (30) was performed to build a socio-economic status index based on asset ownership by patients that included non-sellable (possession of a bank account, type of sanitation facility, household water source) and sellable assets (e.g. stove, refrigerator, washing machine, television).

Diabetes mellitus treatment guidelines for the four countries

The gap between optimal and actual treatment with insulin, antihypertensive, lipid-lowering and antiplatelet drugs was calculated using patient's HbA1c, blood pressure, LDL and cardiovascular (coronary artery disease, myocardial infarction, angina) disease history. Among patients using insulin, antihypertensive and lipid-lowering drugs, HbA1c, blood pressure and LDL values were used to examine what proportion of patients reached desired treatment targets according to national guidelines (19; 27; 28; 31; 32):

1. Patients with HbA1c ≥10% (86 mmol/mol) should have insulin added to their medications.
2. Patients with blood pressure ≥140 systolic or ≥90 diastolic should be managed with anti-hypertensive medication.
3. Cardiovascular complications should be managed with aspirin.

Macrovascular complications included infarct (coronary artery disease, angina, myocardial infarction), heart failure, cerebrovascular disease, peripheral vascular disease). Microvascular complications included a history of renal disease, neuropathy, eye problems (blindness, impaired vision, glaucoma, cataract).

Statistical analysis

Descriptive data are presented as mean and standard deviation for normally distributed data, median and inter-quartile range (IQR) for non-normally distributed data, and proportions for categorical data. Odds ratios and 95% confidence intervals were estimated using logistic regression to investigate factors associated with severe disease (defined as an HbA1c ≥10% (86 mmol/mol) or macrovascular or microvascular complications) and poor medical treatment (defined as patients not receiving insulin, anti-hypertensives or aspirin when it is indicated). We then undertook multiple logistic regression, including all the variables in the model. A test for trend was done for ordinal variables where the trend was consistent but no individual levels were statistically significant. Univariate and multivariate analysis was not undertaken for South Africa due to the small number of participants. All analyses were stratified by site, given the substantial heterogeneity expected. Statistical analyses were performed using STATA Version 12·1.

RESULTS

General patient characteristics

After excluding 28 DM patients with active tuberculosis, 2068 were included, in Indonesia (n=783), Peru (n=599), Romania (n=603), and South Africa (n=83). Baseline characteristics are shown in **Table 1.** All patients in Peru and South Africa had type 2 DM, 98% in Indonesia and 87% in Romania. Almost half of the patients (49%) had had DM for at least five years. Their median age was 59 years, 63% were female and 33% had an education of primary school or less.

Glycemic control and diabetes complications

The median HbA1c across all four sites was 8·7% (IQR 7·0-10·7%) (72; 53-93 mmol/mol). It was highest in South Africa (10·4%; 90 mmol/mol) and appeared lowest in Peru (7·7%; 61 mmol/mol), although HbA1c was missing for a substantial proportion of DM patients in Peru (**Table 1**; **Supplementary Figure 1**). The proportion of patients using metformin was 63% overall, with the greatest use in South Africa (90%), and the lowest in Indonesia (55%). Insulin, either alone or in combination with oral medication, was used by 38% of patients overall, with the highest use of insulin in Romania (67%) where patients were recruited in hospital wards, and the lowest in Peru (20%) (**Table 1**). Disease complications including heart disease, eyesight problems, micro- and macroalbuminuria, and decreased renal clearance were common across all populations (**Table 1**).

Cardiovascular risk profile

On average, patients had a moderately increased cardiovascular risk profile, as shown in **Table 2.** Overall, almost half of the DM patients had a BMI categorised as obese

(46%). This was highest for the Indonesian cohort when using the Asia Pacific Criteria of BMI (Obese I, 39·3%; Obese II, 14·2%). Eighty-five percent of females and 63% of males across sites were categorised as having central obesity. Uncontrolled hypertension in patients not on anti-hypertensives, was reported in 36% of the overall cohort and this was highest in South African patients (52%) and lowest in patients in the Peru site (15%). Current smoking was reported in 13% of patients across all sites. In a subset of patients in three sites, dyslipidemia (LDL ≥100 mg/dL (2.6 mmol/l)), for patients not on statins, was reported in 74% (Indonesia 80%; Romania 55%; South Africa 52%).

Medical treatment

Uptake of treatment and success in terms of reaching treatment targets was suboptimal, with large variation between sites. For instance, of patients with an indication for insulin (HbA1c ≥10%, 86 mmol/mol), 55% were using insulin, varying from 80% in Romania, to 73% in South Africa, 41% in Peru, and 32% in Indonesia (**Table 3**). Of patients in these sites who were on insulin, only a small proportion had their HbA1c controlled to <7% (53 mmol/mol) (**Table 4**). Similarly, of 913 patients with hypertension, less than half (47%) were taking antihypertensive drugs **(Table 3)**, while only 40% of 711 patients taking anti-hypertensive drugs had their blood pressure controlled (**Table 4**). Of 326 patients reporting cardiovascular complications, 30% were on aspirin, ranging from 86% in South Africa to 20% in Indonesia (**Table 3**). Blood lipids were only available for a subset of patients, and not for patients in Peru. Of 267 patients with dyslipidemia (LDL ≥100 mg/dL (2.6 mmol/l)), 29% were treated with statins **(Table 3).** Of 407 patients who were taking statin medication, only 8% had a LDL level of less than 100 mg/dL (2.6 mmol/l) **(Table 4).**

Factors associated with disease severity and medical treatment

Disease severity and medical treatment and underlying factors differed substantially between countries. We assessed risk factors for disease severity as defined separately by a high HbA1c, macrovascular or microvascular complications (Supplementary Tables S1-3). Older age was associated with macrovascular complications in Indonesia (OR 1.50; 95% CI 1.02-2.20) and Romania (OR 2.52; 95% CI 1.65-3.87) but not in Peru (OR 1.41; 95% CI 0.74-2.69), and with lower HbA1c in Indonesia (OR 0.45; 95% CI 0.32-0.64), but not in Romania (OR 0.83; 95% CI 0.57-1.21) or Peru (OR 0.61; 95% CI 0.35-1.06). Males were more likely to have macrovascular complications in Indonesia (OR 1.81; 95% CI 1.24-2.63). Longer DM duration was associated with more macro- and microvascular complications in Romania (6-15 years: OR 2.59; 95% CI 1.35-4.99, and OR 2.11; 95% CI 1.33-3.37, respectively; >15 years DM duration: OR 4.23; 95%CI 2.09-8.55, and OR 7.06; 95% CI 3.81-13.07, respectively), and with more microvascular complications in Indonesia (6-15 years: OR 1.75; 95% CI 1.09-2.81; >15 years: OR 3.72; 95% CI 1.94-7.13) and Peru (>15 years: OR 2.07; 95% CI 1.02-4.18). Completed high school education and Q3 socioeconomic status were associated with lower HbA1c in Romania (OR 0.43; 95% CI 0.24-0.79 and OR 0.56; 95% CI 0.33-0.97, respectively). Completed high school education was associated with less microvascular complications in Peru (OR 0.44; 95% CI 0.27-0.73) and Romania (OR 0.43; 95% CI 0.23-0.80), but not Indonesia (OR 1.08; 95% CI 0.71-1.66).

We assessed what factors were associated with non-compliance to treatment guidelines with regard to use of insulin, anti-hypertensives and aspirin (Supplementary Tables S4-6). Compared to females, males were more likely to take insulin in Indonesia (OR 2.26; 95% CI 1.16-4.42), but less likely to take anti-hypertensives when indicated

(OR 0.43; 95% CI 0.26-0.70). Older aged patients were more likely to be taking anti-hypertensives in Indonesia (OR 2.29; 95% CI 1.44-3.62), but were less likely to be taking aspirin for cardiovascular complications in Romania (OR 0.34; 95% CI 0.13-0.86). DM duration of 6-15 years was associated with increased likelihood of taking insulin in Indonesia (OR 2.70; 95% CI 1.05-6.96) and Romania (OR 2.35; 95% CI 1.09-5.03), and of taking anti-hypertensives in Peru (OR 5.73; 95% CI 1.30-25.13). No significant associations were found between education or socioeconomic status.

DISCUSSION

Numerous studies have addressed the growing burden of diabetes in low- and middle-income countries but detailed patient data like disease complications and specific drug treatment have mostly been reported in single-site studies. In the context of the TANDEM project on the interaction between diabetes and tuberculosis (21), we have pooled systematically collected detailed characteristics of more than 2000 DM patients from Indonesia, Peru, Romania and South Africa. Three main conclusions could be drawn. First, both among hospitalised and ambulatory patients in these four countries, glycemic control is often poor, disease complications are common, and the cardiovascular risk is often high. Second, across different settings many patients who qualify for insulin, anti-hypertensive, lipid-lowering drugs or aspirin do not receive these drugs. Third, of those on these drugs, only a minority reach desired treatment targets. These findings underline the need to identify treatment barriers and secure optimal DM care in low- and middle-income countries where most people with DM live.

Recent studies have addressed the ‘cascade of care’ for diabetes (19; 20; 33). For instance, based on population surveys in 12 sub-Saharan African countries it was

estimated that only 37% of DM patients were aware of their diagnosis, and only 11% received medication (19). But these studies have also stressed the lack of data regarding the burden of diabetes-related complications. Systematically collecting data from individual patients we could precisely characterize disease severity, complications and drug treatment. With regard to disease severity, hyperglycemia was common yet use of insulin was low. Poor glycemic control in Romania could be due to a selection bias as only in-patients were investigated, who are more likely to have poor disease management or infections or other disease complications leading to hyperglycemia. Among ambulatory patients in the others sites the proportion of patients with an HbA1c <7% (53 mmol/mol) ranged from 11% to 28%. Moreover, from discussion with local practitioners and evaluation of patient records it became clear that HbA1c was not routinely measured, and in Peru even during this study it proved impossible in a large proportion of patients due to the local unavailability of HbA1c tests. Lack of HbA1c monitoring probably contributes to poor glycemic control. Other factors include insufficient or inadequate use of insulin, which is often not available (34), too expensive, or difficult to use because of patients unwillingness or inability to do self-monitoring of blood glucose (35). Even metformin and sulphonylurea derivates, widely used and cheap diabetes drugs, are often not available or prohibitively expensive (36; 37).

Like poor glycemic control, disease complications as reported in other studies (7; 9; 38; 39), were common, with many patients suffering from cardiovascular disease, eyesight problems and renal disease. Local health providers may not be fully aware of disease severity of their patients, because time and resources are often lacking to conduct systematic assessment (14; 40), as was done in this study. Our study may

even underestimate the proportion of patients with disease complications as we mainly relied on patient history and medical records and did not perform electrocardiography, fundoscopy, or other related tests. Our cross-sectional study was unable to establish what proportion of complications were already present at the time of initial presentation, and how often complications develop while patients are under DM care, as a result of insufficient glycemic control and cardiovascular risk management. It is clear that both earlier detection of DM and better glycemic control and cardiovascular risk management are needed.

Cardiovascular risk profile was elevated in most patients. Obesity, uncontrolled hypertension and dyslipidemia were common. The proportion of patients smoking was less than we had expected, ranging from 6% in Peru, 14% in Indonesia, 16% in Romania and 37% in South Africa. It is possible that patients may have given socially-desirable answers, particularly as a much higher proportion reported having stopped smoking in most sites. Also, in these countries, smoking is more common among men, while almost two-thirds of study patients were female.

We found large discrepancies between guidelines and practice regarding use of insulin and cardiovascular risk management. Approximately half of those patients qualifying for insulin or antihypertensive drugs received these drugs. Similarly, of those with an indication for statins, or aspirin as secondary prevention of cardiovascular disease, only 30% were prescribed these drugs. And of those who were prescribed these drugs, targets in terms of HbA1c, blood pressure and LDL were only met for 8%, 40%, and 8% respectively. This could be due to incomplete treatment adherence, which was not assessed in this study, or insufficient dosing. Optimal glycemic control with insulin is

difficult to achieve without self-monitoring of blood glucose, but this is not routine in government clinics in any of the four sites. Similary, self-measurement of blood pressure is rarely done, and blood pressure is not measured at each clinic. Limited time and space in clinics, or low awareness or lack of training among health professionals may contribute to the poor 'cascade of care' in DM care in low-resource settings (14; 38; 40; 41).

This study suffers from limitations. As it was a cross-sectional study of patients who had had DM for a median of 5 years or more we do not know how many patients present with complications, and how many patients die from DM over time or disengage from DM care. Second, it is unlikely that our data are fully representative of the four countries. Assessment of the DM phenotype and treatment was not a primary objective of TANDEM, and patients were only recruited in a limited number of clinics. In Romania, we only included inpatients, who likely suffer from poorer glycemic control and more disease complications. Third, complications were mostly self-reported. It would have been preferable to have a formal assessment by a cardiologist, neurologist and eye physician but this was beyond the scope of this study. Fourth, for some characteristics there was a lot of missing data. For instance, recent lipid measurements, not included in the TANDEM assessment, but extracted from patient records, were not available in Peru, and only in a minority of patients from the other sites, and HbA1c was often missing in Peru and South Africa most likely due to frequent unavailability of laboratory tests. Lack of coverage from public health insurance or unawareness among health professionals may also be involved.

Despite these limitations we feel that our study, using a standardised method and addressing the most important disease and treatment characteristics, shows a clear picture of the severity of DM in these countries across four continents and of the unmet needs in terms of drug treatment. Future studies should examine these issues longitundinally, identify barriers to optimal DM care, and evaluate possible interventions to help improve the outcome of DM patients.

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Competing Interests:

The authors declare that no competing interests exist.

Author contributions:

RvC and NS conceived the idea and developed the analysis plan with input from SM and JC. SM performed the main statistical analyses with input from FP, SKB, YL and JC. NS and SM drafted the paper. All other authors contributed to the development of the overall project, data collection and manuscript writing. All authors approved the final version of the manuscript.

REFERENCES

1. IDF Diabetes Atlas [article online], 2017. Available from www.diabetesatlas.org/resources/2017-atlas.html. Accessed 4 December 2017
2. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol 2014;2:56-64
3. Misra A, Tandon N, Ebrahim S, Sattar N, Alam D, Shrivastava U, Narayan KM, Jafar TH. Diabetes, cardiovascular disease, and chronic kidney disease in South Asia: current status and future directions. BMJ 2017;357:j1420
4. Phillimore P, Zaman S, Ahmad B, et al. Health system challenges of cardiovascular disease and diabetes in four Eastern Mediterranean countries. Global Public Health 2013;8:875-889
5. van Crevel R, van de Vijver S, Moore DA. The global diabetes epidemic: what does it mean for infectious diseases in tropical countries? Lancet Diabetes Endocrinol 2016;5:457-468
6. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. World J Diabetes 2015;6:1246-1258
7. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14:88-98
8. Lim SS, Gaziano TA, Gakidou E, Reddy KS, Farzadfar F, Lozano R, Rodgers A. Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs. The Lancet 2007;370:2054-2062
9. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol 2016;12:357-370
10. Gupta R, Misra A. Epidemiology of microvascular complications of diabetes in South Asians and comparison with other ethnicities. J Diabetes 2016;8:470-482
11. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol 2010;35:72-115
12. Yeung RO, Zhang Y, Luk A, et al. Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. Lancet Diabetes Endocrinol 2014;2:935-943
13. Luk AO, Li X, Zhang Y, et al. Quality of care in patients with diabetic kidney disease in Asia: The Joint Asia Diabetes Evaluation (JADE) Registry. Diabet Med 2016;33:1230-1239
14. Attaei MW, Khatib R, McKee M, et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: an analysis of the PURE study data. Lancet Public health 2017;2:e411-e419
15. Murphy A, Palafox B, O'Donnell O, et al. Inequalities in the use of secondary prevention of cardiovascular disease by socioeconomic status: evidence from the PURE observational study. Lancet Global health 2018;6:e292-e301
16. Mohan V, Shah SN, Joshi SR, et al. On behalf of the DiabCare India Study Group. Current status of management, control, complications and psychosocial aspects of patients with diabetes in India: Results from the DiabCare India 2011 Study. Indian J Endocrinol Metab 2014;18:370-378
17. Omar MS, Khudada K, Safarini S, Mehanna S, Nafach J. DiabCare survey of diabetes management and complications in the Gulf countries. Indian J Endocrinol Metab 2016;20:219-227

18. Mafauzy M, Zanariah H, Nazeri A, Chan SP. DiabCare 2013: A cross-sectional study of hospital based diabetes care delivery and prevention of diabetes related complications in Malaysia. Medical J Malaysia 2016;71:177-185
19. Atun R, Davies JI, Gale EAM, et al. Diabetes in sub-Saharan Africa: from clinical care to health policy. Lancet Diabetes Endocrinol 2017;5:622-667
20. Manne-Goehler J, Atun R, Stokes A, et al. Diabetes diagnosis and care in sub-Saharan Africa: pooled analysis of individual data from 12 countries. Lancet Diabetes Endocrinol 2016;4:903-912
21. van Crevel R, Dockrell H. TANDEM: Understanding diabetes and tuberculosis. Lancet Diabetes Endocrinol 2014;2:270-272
22. World Health Organization. Global tuberculosis report. Geneva, World Health Organization, 2017
23. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). JAMA 2014;311:507-520
24. Yoon K-H, Lee J-H, Kim J-W, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006;368:1681-1688
25. World Health Organization: Waist circumference and waist–hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008. Geneva, World Health Organization, 2008
26. International Diabetes Federation. The IDF consensus worldwide definition of the Metabolic Syndrome. Brussels, Belgium, International Diabetes Federation, 2006
27. American Diabetes Association. Standards of medical care in diabetes - 2016 J Clin App Res Ed 2016;39:S1-S2
28. Indonesia Endocrinology Society. Konsensus Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia. 2015
29. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Int Med 2009;150:604-612
30. Vyas S, Kumaranayake L. Constructing socio-economic status indices: how to use principal components analysis. Health Policy Plan 2006;21:459-468
31. Ghid medical pentru îngrijirea pacienţilor cu diabet zaharat (Medical guideline for the management of patients with diabetes mellitus) [article online], 2016. Available from https://legeaz.net/monitorul-oficial-179-2016/oms-226-2016-ghiduri-practica-medicala/ghid-medical-pentru-ingrijirea-pacientilor-cu-diabet-zaharat-2016. Accessed 10 April 2018
32. Guía de práctica clínica para el diagnóstico, tratamiento y control de la diabetes mellitus tipo 2 en el primer nivel de atención [article online], 2016. Available from http://bvs.minsa.gob.pe/local/MINSA/3466.pdf. Accessed 4 December 2017 2017
33. Stokes A, Berry KM, McHiza Z, et al. Prevalence and unmet need for diabetes care across the care continuum in a national sample of South African adults: Evidence from the SANHANES-1, 2011-2012. PLoS One 2017;12:e0184264
34. Beran D, Ewen M, Laing R. Constraints and challenges in access to insulin: a global perspective. Lancet Diabetes Endocrinol 2016;4:275-285
35. Riza AL, Pearson F, Ugarte-Gil C, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrinol 2014;2:740-753
36. Ewen M, Zweekhorst M, Regeer B, Laing R. Baseline assessment of WHO's target for both availability and affordability of essential medicines to treat non-communicable diseases. PLOS ONE 2017;12:e0171284

37. Bazargani YT, de Boer A, Leufkens HGM, Mantel-Teeuwisse AK. Selection of Essential Medicines for Diabetes in Low and Middle Income Countries: A Survey of 32 National Essential Medicines Lists. PLOS ONE 2014;9:e106072
38. Glezeva N, Chisale M, McDonald K, Ledwidge M, Gallagher J, Watson CJ. Diabetes and complications of the heart in Sub-Saharan Africa: An urgent need for improved awareness, diagnostics and management. Diabetes Res Clin Pract 2018;137:10-19
39. Clarke PM, Glasziou P, Patel A, Chalmers J, Woodward M, Harrap SB, Salomon JA, on behalf of the ACG. Event rates, hospital utilization, and costs associated with major complications of diabetes: A multicountry comparative analysis. PLOS Med 2010;7:e1000236
40. Lee JD, Saravanan P, Varadhan L, Morrissey JR, Patel V. Quality of diabetes care worldwide and feasibility of implementation of the Alphabet Strategy: GAIA project (Global Alphabet Strategy Implementation Audit). BMC Health Serv Res 2014;14:467
41. Kane J, Landes M, Carroll C, Nolen A, Sodhi S. A systematic review of primary care models for non-communicable disease interventions in Sub-Saharan Africa. BMC Fam Pract 2017;18:46

Table 1: General characteristics of patients with diabetes according to recruitment site

	Total (n=2068) n (%)	Indonesia (n=783) n (%)	Peru (n=599) n (%)	Romania (n=603) n (%)	South Africa (n=83) n (%)
Female sex	1301 (62.9)	500 (63.9)	426 (71.1)	321 (53.2)	54 (64.1)
Age, median (IQR)	59 (52-66)	59 (53-65)	59 (52-67)	59 (51-66)	53 (47-60)
Education					
<Primary/no formal education	687 (33.4)	235 (30.0)	304 (50.8)	84 (14.2)	61 (74.4)
Secondary school completed	473 (23.0)	146 (18.6)	112 (18.7)	201 (33.9)	14 (17.1)
High school completed	641 (31.2)	226 (28.9)	163 (27.3)	247 (41.7)	5 (6.1)
College/university/post graduate	258 (12.5)	176 (22.5)	19 (3.2)	61 (10.3)	2 (2.4)
n/a*	12	0	1	10	1
Socio-economic status					
Q1: poorest	222 (10.9)	96 (12.4)	82 (13.7)	43 (7.3)	1 (1.2)
Q2: poor	332 (16.2)	111 (14.4)	121 (20.2)	93 (15.7)	7 (8.6)
Q3: middle income	378 (18.5)	121 (15.7)	126 (21.1)	119 (20.1)	12 (14.8)
Q4: upper middle income	477 (23.3)	179 (23.2)	123 (20.6)	148 (25.0)	27 (33.3)
Q5: richest	635 (31.1)	265 (34.3)	146 (24.4)	190 (32.0)	34 (42.0)
n/a*	24	11	1	10	2
Use of alcohol	660 (31.9)	14 (1.7)	288 (48.1)	338 (56.1)	21 (25.3)
Duration of diabetes					
<1 year	388 (18.8)	138 (17.6)	126 (21.1)	122 (20.3)	2 (2.5)
1-5 years	672 (32.6)	298 (38.1)	237 (39.6)	110 (18.3)	27 (33.3)
6-15 years	704 (34.1)	280 (35.8)	139 (23.2)	249 (41.4)	36 (44.4)
>15 years	299 (14.5)	67 (8.6)	96 (16.1)	120 (20.0)	16 (19.8)
n/a*	5	0	1	2	2
HbA1c,† Median %	8.7	8.3	7.7	9.5	10.4
IQR %	(7.0-10.7)	(6.7-10.2)	(6.2-10.1)	(8.1-11.3)	(9.0-12.0)
Median (IQR) mmol/mol	72 (53-93)	67 (50-88)	61 (44-87)	80 (65-100)	90 (75-108)
HbA1c					
<7% (53 mmol/mol)	433 (24.3)	220 (28.2)	144 (38.0)	65 (11.1)	4 (11.1)
7-9.9% (53-85 mmol/mol)	757 (42.5)	339 (43.5)	137 (36.2)	271 (46.1)	10 (27.8)
≥10% (65 mmol/mol)	593 (33.3)	221 (28.3)	98 (25.9)	252 (42.9)	22 (61.1)
n/a*	285	3	220	15	47
Diabetes medication‡					
No medication	180 (8.7)	63 (8.1)	87 (14.5)	29 (4.8)	1 (1.2)
Insulin	781 (37.8)	223 (28.5)	120 (20.0)	406 (67.3)	32 (38.6)
Metformin	1295 (62.6)	431 (55.0)	391 (65.3)	398 (66.0)	75 (90.4)
Other oral DM drugs	720 (34.8)	357 (45.6)	91 (15.2)	248 (41.1)	24 (28.9)
Comorbidities and complications‡					
Infarct (CAD, angina, MI)	326 (15.8)	140 (17.9)	46 (7.7)	133 (22.1)	7 (8.4)
Heart failure	14 (0.7)	13 (1.7)	1 (0.2)	0 (0.0)	0 (0.0)
Cerebrovascular disease	7 (0.3)	0 (0.0)	3 (0.5)	0 (0.0)	4 (4.8)
Peripheral vascular disease	27 (1.3)	20 (2.6)	0 (0.0)	6 (1.0)	1 (1.2)
Kidney disease	31 (1.5)	21 (2.7)	7 (1.2)	3 (0.5)	0 (0.0)
Eye problems attributable to DM	1043 (50.4)	272 (34.7)	463 (77.3)	258 (42.8)	50 (60.2)
Renal Clearance					
eGFR ≥60	949 (81.1)	216 (73.5)	184 (82.9)	502 (83.3)	47 (92.2)
eGFR 30-59	174 (14.9)	56 (19.0)	30 (13.5)	85 (14.1)	3 (5.9)
eGFR <30	47 (4.0)	22 (7.5)	8 (3.6)	16 (2.6)	1 (1.9)
n/a*	898	489	377	0	32
Urine albumin/creatinine ratio					
<30 ug/mg	854 (60.2)	387 (50.0)	n/a	422 (71.0)	45 (90.0)
30-299 ug/mg	356 (25.1)	230 (29.7)	n/a	121 (20.4)	5 (10.0)
≥300 ug/mg	208 (14.7)	157 (20.3)	n/a	51 (8.6)	0 (0.0)
n/a*	51	9		9	33

CAD: coronary artery disease; DM: Diabetes mellitus; eGFR: estimated glomerular filtration rate mL/min/1.73 m^2; IQR: Interquartile range; MI: myocardial infarction; n/a =not available

* Denominator for proportions does not include the number not available.

† Data available for a total of 1783 patients: 780 Indonesia; 379 Peru; 588 Romania; 36 South Africa.

‡ Patients may be in more than one category

Table 2. Cardiovascular risk profile and medication management of patients according to recruitment site

	Total (n=2068) n (%)	Indonesia (n=783) n (%)	Peru (n=599) n (%)	Romania (n=603) n (%)	South Africa (n=83) n (%)
Body Mass Index (kg/m^2)*					
Underweight	42 (2.0)	24 (3.1)	4 (0.7)	14 (2.4)	0 (0.0)
Normal	503 (24.4)	191 (24.4)	186 (31.2)	111 (18.6)	15 (18.5)
Overweight	577 (28.0)	149 (19.0)	210 (35.2)	188 (31.5)	30 (37.0)
Obese	936 (45.5)	419 (53.5)	197 (33.0)	284 (47.6)	36 (44.4)
n/a†	10	0	2	6	2
Central Obesity					
Females	1099/1296 (84.8)	347/500 (69.4)	408/426 (95.7)	292/317 (92.1)	52/53 (98.1)
Males	476/759 (62.7)	108/283 (38.2)	131/173 (75.7)	217/275 (78.9)	20/28 (71.4)
BP classification: patients not on anti-hypertensives‡					
Normal	357 (26.3)	104 (17.8)	196 (42.2)	54 (19.7)	3 (8.6)
Pre-hypertension	517 (38.1)	182 (31.2)	198 (42.7)	123 (44.9)	14 (40.0)
Stage I hypertension	308 (22.7)	176 (30.1)	45 (9.7)	77 (28.1)	10 (28.6)
Stage II hypertension	175 (12.9)	122 (20.9)	25 (5.4)	20 (7.3)	8 (22.9)
BP classification: patients on anti-hypertensives‡					
Normal	73 (10.3)	13 (6.5)	22 (16.3)	35 (10.6)	3 (6.3)
Pre-hypertension	208 (29.3)	45 (22.6)	54 (40.0)	96 (29.2)	13 (28.1)
Stage I hypertension	212 (29.8)	58 (29.2)	34 (25.2)	105 (31.9)	15 (31.3)
Stage II hypertension	218 (30.7)	83 (41.7)	25 (18.5)	93 (28.3)	17 (35.4)
Dyslipidemia (mg/dl): patients not on statins					
LDL ≥100 (2.6 mmol/l)	191/260 (73.5)	159/200 (79.5)	n/a	16/29 (55.2)	16/31 (51.6)
HDL ≤40 (male); ≤50 (female) (1 mmol/l (male); 1.3 (female))	127/261 (48.7)	93/200 (46.5)	n/a	15/28 (53.6)	19/33 (57.6)
Dyslipidemia (mg/dL): patients on statins					
LDL ≥100 (2.6 mmol/l)	76/107 (71.0)	59/66 (89.4)	n/a	11/24 (45.8)	6/17 (35.3)
HDL ≤40 (male); ≤50(female) (1 mmol/l (male); 1.3 (female))	65/107 (60.7)	29/66 (43.9)	n/a	21/24 (87.5)	15/17 (88.2)
Smoking status					
Current	269 (13.0)	112 (14.3)	34 (5.7)	93 (15.5)	30 (36.6)
Past	630 (30.5)	223 (28.5)	221 (37.0)	172 (28.6)	14 (17.1)
Never	1165 (56.4)	448 (57.2)	343 (57.4)	336 (55.9)	38 (46.3)
n/a†	4	0	1	2	1
Anti-hypertensive drugs	711 (34.4)	199 (25.4)	135 (22.5)	329 (54.6)	48 (57.8)
Lipid-lowering drugs (statins)	407 (19.7)	146 (18.6)	36 (6.0)	201 (33.3)	24 (28.9)
Anti-platelet drugs (aspirin)	249 (12.0)	47 (6.0)	53 (8.9)	121 (20.1)	28 (33.7)

BMI: Body mass index (kg/m^2); BP: Blood pressure; HDL: High density lipoprotein; LDL: Low density lipoprotein; WC: Waist circumference, n/a =not available

* Body Mass Index (kg/m^2) was classified as:

- Underweight (<18.5)
- Normal (18.5-22.9 Indonesia; 18.5-24.9 Peru, Romania, South Africa)
- Overweight (23.0-24.9 Indonesia; 25.0-29.9 Peru, Romania, South Africa)
- Obese (≥25.0 Indonesia; ≥30 Peru, Romania, South Africa)

† Denominator for proportions does not include the number not available

‡ Blood pressure classification according JNC VII:

- Normal = systolic and diastolic <120/80 mmHg;
- Pre-hypertension = systolic 120-139 or diastolic 80-89 mmHg;
- Stage I hypertension = systolic 140-159 or diastolic 90-99 mmHg;
- Stage II hypertension = systolic ≥160 or diastolic ≥100 mmHg.

Table 3. Treatment indication and actual treatment with insulin, antihypertensive, antiplatelet, and lipid-lowering medication according to recruitment site

	Total n/N (%)	Indonesia n/N (%)	Peru n/N (%)	Romania n/N (%)	South Africa n/N (%)
HbA1c ≥10 (86 mmol/mol)*	593/1783 (33.3)	221/780 (28.3)	98/379 (25.9)	252/588 (42.9)	22/36 (61.1)
Patients with HbA1c≥10 (86 mmol/mol) receiving insulin	325/593 (54.8)	70/221 (31.7)	40/98 (40.8)	199/252 (80.0)	16/22 (72.7)
Hypertension†	913/2068 (44.1)	439/783 (56.1)	129/599 (21.5)	295/603 (48.9)	50/83 (59.5)
Patients with hypertension taking anti-hypertensives	430/913 (47.1)	141/439 (32.1)	59/129 (45.7)	198/295 (67.1)	32/50 (64.0)
Cardiovascular complications‡	326/2068 (15.8)	140/783 (17.9)	46/599 (7.7)	133/603 (22.1)	7/83 (8.4)
Patients with cardiovascular complications taking aspirin	98/326 (30.0)	28/140 (20.0)	21/46 (45.6)	43/133 (32.3)	6/7 (85.7)
LDL ≥100mg/dL (2.6 mmol/l)/§	267/367 (72.8)	218/266 (82.0)	n/a	27/53 (50.9)	22/48 (45.8)
Patients with LDL ≥100mg/dL (2.6 mmol/l) taking statins	76/267 (28.5)	59/218 (27.1)	n/a	11/27 (40.7)	6/22 (27.3)

* Of those with a reported HbA1c. † Systolic blood pressure (BP) ≥140 mm Hg; diastolic BP ≥90
‡ Cardiovascular complications: Includes patients categorized with coronary artery disease, angina or myocardial infarction. § Of those with a reported low-density lipoprotein (LDL)
n/a: not available

Table 4. Patients receiving insulin, antihypertensives, and lipid-lowering medication and those who have reached the treatment target according to recruitment site

	Total n/N (%)	Indonesia n/N (%)	Peru n/N (%)	Romania n/N (%)	South Africa n/N (%)
Patients on insulin	780/2068 (37.7)	223/783 (28.5)	120/599 (20.0)	405/603 (67.2)	32/83 (38.6)
Patients on insulin with a recorded HbA1c <7% (53 mmol/mol)	77/780 (8.0)	41/223 (18.4)	15/120 (12.5)	20/405 (4.9)	1/32 (3.1)
Patients on antihypertensives	711/2068 (34.4)	199/783 (25.4)	135/599 (22.5)	329/603 (54.6)	48/83 (57.8)
Patients on antihypertensives with BP systolic <140 & diastolic <90	281/711 (39.5)	58/199 (29.1)	76/135 (56.3)	131/329 (39.8)	16/48 (33.3)
Patients on statins	407/2068 (19.7)	146/783 (18.6)	36/599 (6.0)	201/603 (33.3)	24/83 (28.9)
Patients on statins with LDL <100 mg/dL (2.6 mmol/l)	31/371 (8.4)	7/146 (4.8)	n/a	13/201 (6.5)	11/24 (45.8)