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β-cell dysfunction and insulin resistance in relation to pre-diabetes and diabetes among adults in north-western Tanzania: a cross-sectional study

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Abstract

OBJECTIVE Studies on phenotypes of diabetes in Africa are inconsistent. We assessed the role of β-cell dysfunction and insulin resistance on pre-diabetes and diabetes.

METHODS We included 1890 participants with mean age of 40.6 (SD11.9) years in a cross-sectional study among male and female adults in Tanzania during 2016 to 2017. Data on C-reactive protein (CRP), alpha-acid glycoprotein (AGP), HIV, oral glucose tolerance test (OGTT), body composition and insulin were collected. Insulinogenic index and HOMA-IR were used to derive an overall marker of β-cell dysfunction and insulin resistance which was categorised as follows: normal β-cell function and insulin sensitivity, isolated β-cell dysfunction, isolated insulin resistance, and combined β-cell dysfunction and insulin resistance. Pre-diabetes and diabetes were defined as 2-hour OGTT glucose between 7.8–11.0 and ≥ 11.1 mmol/L, respectively. Multinomial regression assessed the association of β-cell dysfunction and insulin resistance with outcome measures.

RESULTS β-cell dysfunction, insulin resistance, and combined β-cell dysfunction and insulin resistance were associated with higher pre-diabetes risk. Similarly, isolated β-cell dysfunction (adjusted relative risk ratio (aRRR) 4.8 (95% confidence interval (CI) 2.5, 9.0), isolated insulin resistance (aRRR 3.2 (95% CI 1.5, 6.9), and combined β-cell dysfunction and insulin resistance (aRRR 35.9 (95% CI 17.2, 75.2) were associated with higher diabetes risk. CRP, AGP and HIV were associated with higher diabetes risk, but fat mass was not. 31%, 10% and 33% of diabetes cases were attributed to β-cell dysfunction, insulin resistance, and combined β-cell dysfunction and insulin resistance, respectively.

CONCLUSIONS β-cell dysfunction seemed to explain most of diabetes cases compared to insulin resistance in this population. Cohort studies on evolution of diabetes in Africa are needed to confirm these results.

keywords β-cell dysfunction, insulin resistance, pre-diabetes, diabetes, HIV

Sustainable Development Goals (SDGs): 3.3, 3.4

Introduction

Non-communicable diseases (NCDs) including type 2 diabetes are becoming major health problems in sub-Saharan Africa (SSA) [1]. Diabetes develops as a result of either insulin resistance, reduced insulin secretion or both [2] and is established when plasma glucose reaches certain cut-points, where complications (seen in high-income populations) start to appear [3]. In SSA, diagnosis relies mostly on plasma glucose; thus, more detailed assessment of islet auto-antibodies and insulin or C-peptide secretion to determine whether patients have either insulin resistance or reduced secretion or both is rare. Similarly, a suggestion to sub-divide type 2 diabetes into five subgroups with varying levels of insulin resistance/insulin secretion combinations [4] may not be feasible due to

lack of detailed investigation. Furthermore, in SSA, we may see a completely different group of type 2-like entities that do not fit the traditional type 2 phenotype, nor the five sub-group classification due to differences in genetics and pre- and post-natal exposures such as malnutrition potentially affecting diabetes aetiology, risk and presentation [5]. These limitations hinder prevention strategies and proper patient management.

Reviews suggest that the clinical manifestations of type 2 diabetes are due to both insulin resistance and reduced insulin secretion [6]. However, field studies have shown considerable inconsistency, with some indicating the predominance of insulin resistance [7] and others the predominance of reduced secretion [8]. In SSA, the increasing diabetes burden [1] is partly thought to be driven by overweight, particularly seen in urban settings where it is associated with intake of high-calorie low-fibre diets and decreased level of physical activity [9]. These could result in insulin resistance [10] leading to type 2 diabetes. However, the rising diabetes burden could also be contributed by reduced insulin secretion likely caused by widespread infections including HIV and tuberculosis (TB) and other adverse environmental exposures, but data are limited [11].

In SSA, research on the causes driving the diabetes epidemic is very scarce but urgently needed to guide approaches to both prevention and treatment which are currently informed by studies conducted in other settings. In this analysis conducted in a large diabetes risk factors cohort study among Tanzanian adults, we investigated the relative contribution of β-cell dysfunction and insulin resistance to pre-diabetes and diabetes and tested if these were modified by HIV infection.

Methods

Study design and setting

This was a cross-sectional study using baseline data of participants recruited from the Chronic Infections, Comorbidities and Diabetes in Africa (CICADA) study, a cohort study investigating risk factors for diabetes among HIV-uninfected and HIV-infected adults in north-western Tanzania from 2016 to 2021 and registered at clinical.trials.gov as NCT03106480. During October 2016 to November 2017, CICADA recruited 1947 participants. Participants with both glucose and insulin data were eligible for inclusion in this paper.

Participants

The study population and main methods have been reported elsewhere [12]. Briefly, participants who were recruited in previous tuberculosis and HIV nutritional supplementation trials in Mwanza from 2006 to 2013 (i.e. Nutrition, Diabetes and Pulmonary Tuberculosis (TB-NUT) [13,14] and Nutritional Support for African Adults Starting Antiretroviral Therapy (NUSTART) [15]) and were known to be alive were invited to participate. TB-NUT trial recruited HIV-infected and uninfected TB patients [13,14] and non-TB controls [16], whereas NUSTART trial recruited undernourished HIV-infected patients [15]. In addition, HIV-infected people who visited antiretroviral therapy (ART) clinics in Mwanza City from October 2016 to November 2017, who were preparing to start ART and were not part of TB-NUT or NUSTART trials were invited in the study as a new HIV cohort, if they were aged ≥ 18 years and residents of Mwanza City. Finally, we randomly took half of the new HIV cohort participants and selected HIV-uninfected participants for frequency matching. Criteria for HIV-uninfected participant selection were as follows: lived within the same neighbourhood as the HIV index participant (defined as living in the same street or sub-village), HIV-uninfected based on HIV rapid tests, had lived in Mwanza City for at least 3 months, aged ≥ 18 years and age difference with HIV-infected index participant not more than 5 years, and same sex as the HIV-infected index participant. All study participants were recruited if they intended to stay in the study area in the next 3 years and after they consented to be enrolled in the study.

Data collection

Risk factors. Data on demographics and NCDs risk factors were collected based on the WHO STEPS manual questionnaire [17]. According to previously reported analysis, of the lifestyle factors, only physical activity was associated with diabetes [12], so was the only such variable included here. Less than 600 MET (metabolic equivalent of tasks) minutes per week was considered as being physically inactive [18]. Information on ART use was retrieved from patients' treatment cards and clinic records and used to derive HIV-ART status groups.

Anthropometry and body composition. Anthropometric measurements were determined using standardised methods. While barefoot and with minimal clothing, weight of the patient was determined to the nearest 0.1 kg using a digital scale (Seca, Germany) and height measured to the nearest 0.1 cm using a stadiometer fixed to the wall (Seca, Germany). Anthropometric measurements were taken in triplicate, and medians were used during analysis. Based on weight and height measurements, body mass index (BMI) was calculated as mass (kg)/height

$(m)^2$. Participants underwent bio-impedance analysis to estimate fat mass and fat-free mass (Tanita BC418, Tokyo, Japan) which were categorised into tertiles (i.e. lower, middle and upper) for analysis.

Glucose assessment. Following 8 h of fasting, plasma glucose (Hemocue AB, Angelholm, Sweden) was determined using venous blood. Participants underwent an oral glucose tolerance test (OGTT) and were provided with 82.5 g of dextrose monohydrate (equivalent to 75 g of glucose anhydrous) diluted in 250 ml drinking water to drink within 5 min. The OGTT glucose assessment was done at 30 min and 2 h. According to WHO guidelines [3], participants whose 2-hour OGTT glucose level was ≥ 7.8 to < 11.1 mmol/L were classified as impaired glucose tolerance (IGT), in this study termed pre-diabetes, and those with glucose level of ≥ 11.1 mmol/L were classified as diabetes. Pre-diabetes and diabetes were used as outcome measures of this study.

Insulin, C-reactive protein (CRP), alpha-acid glycoprotein (AGP) and HIV status. Venous blood samples drawn at the same time as those for glucose assessment were separated into serum for insulin (fasting, 30 and 120 min) and inflammatory markers (CRP and AGP; fasting only) assessments and stored at −80°C pending analysis. ELISA technique was used to assess insulin in Denmark using dual-monoclonal antibodies (ALPCO, Salem, NH, USA) whereas CRP and AGP were measured using sandwich ELISA in Germany [19]. HIV testing was done using two rapid antibody tests (SD HIV- 1/2 3.0 SD standard diagnostics Inc, and The Uni-Gold, Trinity Biotech, IDA Business Park, Bray, Co. Wicklow, Ireland). Discordant samples were tested using Uniform II vironostika-HIV Ag/Ab Micro-Elisa system (Biomerieux bv, The Netherlands).

Derivation of an overall marker of β-cell dysfunction and insulin resistance

Using fasting and 30 min glucose and insulin data, we computed several indices of β-cell function and insulin resistance including insulinogenic index, early-phase insulin release index, first- and second-phase Stumvoll indices and homeostatic model assessment (HOMA)-β as markers of β-cell function[20] and HOMA-insulin resistance (IR) and Matsuda index as markers of insulin resistance [21,22] (Table S1). Then, we generated receiver operating characteristics (ROC) curves and used area under the curves (AUCs) to investigate the probabilities of these markers in predicting pre-diabetes and diabetes using non-parametric approach [23] (Table 1). Based on this comparison, insulinogenic index and HOMA-IR, the markers with highest AUCs, were selected as markers of β-cell function and insulin resistance, respectively, as in previous work [24]. These markers correlate well with reference techniques [20,21,25] and are not derived from 2-hour glucose, which could have led to spurious associations with pre-diabetes and diabetes. We dichotomised them using optimal cut-points for predicting diabetes computed using Liu's method [26]. The cut-points optimally predicting diabetes among this study population were as follows: <0.71 (mU/L/mg/dL) for insulinogenic index and > 1.9 (mU/L)/(mmol/L) for HOMA-IR. Based on these cut-off points, we derived an overall marker of β-cell function and insulin resistance dividing participants into four groups, that is normal β-cell function and insulin sensitivity (insulinogenic index ≥ 0.71 and HOMA-IR ≤ 1.9), isolated β-cell dysfunction (insulinogenic index < 0.71 only), isolated insulin resistance (HOMA-IR > 1.9 only), and combined β-cell dysfunction and insulin resistance (insulinogenic index < 0.71 and HOMA-IR > 1.9) [24].

Table 1 Area under receiver operating characteristic curves for markers of insulin secretion and resistance in predicting pre-diabetes or diabetes

Marker	AUC (95% CI)	*P*
Pre-diabetes		
Insulin secretion		
Insulinogenic index*	0.59 (0.56, 0.61)	–
HOMA-β-cell function*	0.55 (0.52, 0.58)	0.01†
Early insulin release index*	0.56 (0.53, 0.58)	0.01†
First-phase Stumvoll*	0.58 (0.55, 0.61)	0.44†
Second-phase Stumvoll*	0.58 (0.55, 0.60)	0.33†
Insulin resistance		
HOMA-IR	0.53 (0.51,0.56)	–
Matsuda insulin sensitivity index	0.41 (0.39, 0.44)	<0.0001‡
Diabetes		
Insulin secretion		
Insulinogenic index*	0.82 (0.77, 0.87)	–
HOMA-β-cell function*	0.67 (0.62, 0.72)	<0.0001†
Early insulin release index*	0.78 (0.73, 0.82)	0.09†
First-phase Stumvoll*	0.64 (0.57, 0.71)	<0.0001†
Second-phase Stumvoll*	0.71 (0.64, 0.77)	0.0004†
Insulin resistance		
HOMA-IR	0.55 (0.50, 0.60)	–
Matsuda insulin sensitivity index	0.38 (0.33, 0.44)	0.004‡

AUC, area under the receiver operating characteristic curve; HOMA-IR, homeostatic model assessment – insulin resistance; HOMA-β, homeostatic model assessment – β-cell function.
*Inverse of the predictor was used in calculations to meet test requirements.
†Compared with AUC of insulinogenic index.
‡Compared with AUC of HOMA-IR.

Ethics

Ethical clearance was provided by the National Institute for Medical Research (NIMR) in Tanzania and the London School of Hygiene and Tropical Medicine in UK. Consultative approval was provided by the National Committee on Health Research Ethics in Denmark. Participants were enrolled after written informed consent, and those with diabetes and other illnesses were referred to Sekou-Toure referral hospital for care.

Data management and statistics

Data were double entered in CSPro database and analysed in STATA version 13 (Station College, TX, USA). Demographic characteristics, body composition, physical activity, inflammatory markers, and β-cell dysfunction and insulin resistance markers were compared between participants without diabetes *vs*. those with pre-diabetes or diabetes using means, medians, percentages or graphs as appropriate. Comparisons between two groups were done using t-test or Mann–Whitney U-test (if the distribution was not normal) for continuous variables and by chi-squared test for categorical variables.

To understand the role of β-cell dysfunction and insulin resistance on pre-diabetes and diabetes, we fitted multinomial logistic regressions. We examined the association of the β-cell dysfunction and insulin resistance overall marker with pre-diabetes or diabetes and included age, sex, CRP, AGP, HIV/ART, fat mass, fat-free mass and physical activity in models. HIV/ART, fat mass, fat-free mass and physical activity were included in models because they were previously found to be associated with diabetes in univariate or multivariable analysis in this study population [12], whereas CRP and AGP were included because inflammation is known to be important in both HIV and insulin resistance and may explain the effect of HIV on insulin resistance. Minimally adjusted multinomial logistic regression models included age and sex and final models included all predictor variables. We also tested if effects of β-cell dysfunction and insulin resistance marker on pre-diabetes or diabetes were modified by HIV/ART status. To investigate relative contribution of β-cell function and insulin resistance on pre-diabetes and diabetes, we computed population attributable fraction (PAF) using the formula PD[(aRRR-1)/aRRR], where PD was proportion of cases (pre-diabetes or diabetes) exposed to the risk factor and aRRR was adjusted Relative risk ratio[24]. The associations were presented as aRRR with 95% confidence intervals. In all analyses, a significance level of $P < 0.05$ was used.

Results

Glucose and insulin data were obtained for 1890 participants (Figure S1). The prevalence of diabetes was 6.5% ($n = 123$) and that for pre-diabetes was 43.9% ($n = 829$), similar to what was reported in a full CICADA cohort [12]. The mean (±SD) age was 40.6 (±11.9) years, and 60% (1128) were females. Participants with pre-diabetes and diabetes were older, and the latter had a lower proportion of females, compared to those without diabetes (Table 2). In addition, BMI was lower in participants with diabetes than those without diabetes (21.0 *vs*. 22.0 kg/m^2, $P = 0.01$), although this was driven by HIV infection (Table S2). Insulinogenic index was lower in participants with pre-diabetes and diabetes than those without diabetes (0.9 and 0.3 *vs*. 1.2 mU/L/mg/dL, $P < 0.0001$, all) whereas HOMA-IR was higher among participants with pre-diabetes (1.6 *vs* 1.4 mU/L, mmol/L, $P = 0.02$) but only marginally higher in those with diabetes (1.5 *vs* 1.4 mU/L, mmol/L, $P = 0.08$). Overall, the prevalence of isolated β-cell dysfunction was 25.3% (478), isolated insulin resistance was 27.9% (527), and combined β-cell dysfunction and insulin resistance was 9.5% (180); these were different between those without diabetes and those with pre-diabetes or diabetes ($P < 0.0001$, all). During the 2-hour OGTT, we found insulin was higher at 30 min but lower at 120 min among those without diabetes compared to those with pre-diabetes or diabetes, whereas glucose was lower at both 30 and 120 min among the group without diabetes compared to the group with pre-diabetes or diabetes (Figures 1 and 2).

Predictors of pre-diabetes and diabetes

Table 3 presents the association of β-cell dysfunction and insulin resistance on pre-diabetes or diabetes. In final models adjusted for age, sex, CRP, HIV, fat mass and fat-free mass, and physical activity, isolated β-cell dysfunction (aRRR = 1.6, 95% CI: 1.2, 2.0), isolated insulin resistance (aRRR = 1.6, 95% CI: 1.2, 2.1), and combined β-cell dysfunction and insulin resistance (aRRR = 2.1, 95% CI: 1.6, 2.6) were associated with higher risk of pre-diabetes. Similarly, isolated β-cell dysfunction (aRRR = 4.8, 95% CI: 2.5, 9.0), isolated insulin resistance (aRRR = 3.2, 95% CI: 1.5, 6.9), and combined β-cell dysfunction and insulin resistance (aRRR = 35.9, 95% CI: 17.2, 75.2) were associated with higher risk of diabetes. CRP was associated with higher risk of pre-diabetes and diabetes whereas AGP was associated with higher risk of diabetes only (Table S3). As already reported in analyses not including an overall marker of β-cell dysfunction and insulin resistance as a predictor

Table 2 Background characteristics, β-cell function and insulin resistance, and inflammatory markers by diabetes status

	Normal (*N* = 938)	Pre-diabetes (*N* = 829)	Diabetes (*N* = 123)	*P**	*P*†
Age (years), mean (sd)	39.4 (11.5)	41.3 (12.0)	45.3 (12.2)	0.001	<0.0001
Female sex, *n* (%)	578 (61.6)	494 (59.6)	56 (45.5)	0.38	0.001
Body mass index (kg/m^2), mean (sd)	22.0 (4.3)†,‡	21.9 (4.7)	21.0 (4.9)	0.70	0.01
Fat mass (kg), mean (sd)	13.8 (9.1)§	13.8 (9.7)‖	11.5 (8.9)¶	0.87	0.01
Physical activity (MET min per week), *n* (%)**					
Not active (≤ 600 MET min per week)	89 (9.5)	141 (17.1)	34 (27.6)	<0.0001	<0.0001
Active (>600 MET min per week)	845 (90.5)	686 (82.9)	89 (72.4)		
β-cell function and insulin resistance markers					
Fasting insulin (mU/L), median (IQR)	5.2 (3.4, 7.8)	5.3 (3.4, 8.3)	4.7 (2.7, 8.2)	0.58	0.36
30 min insulin (mU/L), median (IQR)	44.4 (27.6, 71.4)	41.0 (25.9, 62.3)	23.3 (15.3, 39.7)	0.01	<0.0001
120 min insulin (mU/L), median (IQR)	29.7 (19.2, 46.1)**	44.9(28.7,67.8)**,‡‡	49.9 (31.4, 82.8)‡,‖	<0.0001	<0.0001
Insulinogenic index (mU/L/mg/dL), median (IQR)	1.2 (0.7, 2.1)	0.9 (0.5, 1.7)	0.3 (0.2, 0.8)	<0.0001	<0.0001
HOMA-IR (mU/L, mmol/L), median (IQR)	1.4 (0.9, 2.3)	1.6 (1.0, 2.5)	1.5 (0.9, 2.8)	0.02	0.08
β-cell function and insulin resistance status, *n* (%)					
Normal β-cell function and insulin sensitivity	413 (44.0)	276 (33.3)	16 (13.0)	<0.0001	<0.0001
Isolated reduced β-cell function	203 (21.7)	227 (27.4)	48 (39.0)		
Isolated insulin resistance	261 (27.8)	248 (29.9)	18 (14.6)		
Reduced β-cell function and insulin resistance	61 (6.5)	78 (9.4)	41 (33.4)		
Inflammatory markers					
C-reactive protein (mg/L), median (IQR)	1.7 (0.7, 4.5)‡,‖	2.7 (1.0, 9.0)	8.3 (2.6, 61.5)	<0.0001	<0.0001
Raised (>5 mg/L), n (%)	209 (22.1)‡,‖	308 (37.2)	82 (67.2)	<0.0001	<0.0001
Alpha-acid glycoprotein (g/L), median (IQR)	0.7 (0.5, 1.0)‡,‖	0.8 (0.6, 1.4)	1.5 (0.8, 3.1)	<0.0001	<0.0001
Raised (>1 g/L), *n* (%)	276 (29.1)‡,‖	307 (37.1)	81 (66.4)	<0.0001	<0.0001
HIV status					
Not infected	367 (39.1)	241 (29.1)	26 (21.2)	<0.0001	<0.0001
HIV-infected not on antiretroviral therapy	405 (43.2)	441 (53.2)	87 (70.7)		
HIV-infected on antiretroviral therapy	166 (17.7)	147 (17.7)	10 (8.1)		

HOMA-IR, homeostatic model assessment – insulin resistance; IQR, interquartile range; sd, standard deviation.
*Difference between non-diabetes and pre-diabetes groups by t-test or Mann–Whitney U-test (when distributions were not normal).
†Difference between non-diabetes and diabetes groups by t-test or Mann–Whitney U-test (when distributions were not normal).
‡One participant missing.
§18 participants missing.
‖22 participants missing.
¶Six participants missing.
**Four participants missing.
‡‡Nine participants missing.

[12], HIV infection was associated with higher risk, physical activity was protective of diabetes, whereas fat and fat-free mass were not predictors (Table S3).

Regarding PAFs, we found that pre-diabetes could have been due to β-cell dysfunction in 10.3% (95% CI: 4.6, 13.7), isolated insulin resistance in 11.2% (95% CI: 5.0, 15.7), and combined β-cell dysfunction and insulin resistance in 4.9% (95% CI: 3.1, 6.5) of cases. We also found that diabetes could have been due to isolated β-cell dysfunction in 30.9% (95% CI: 23.4, 34.7), isolated insulin resistance in 10.0% (95% CI: 4.9, 12.5), and combined β-cell dysfunction and insulin resistance in 32.5% (95% CI: 31.5, 33.0) of cases. HIV/ART did not modify the role of an overall marker of β-cell dysfunction and insulin resistance on pre-diabetes ($P = 0.31$) or diabetes ($P = 0.93$).

Discussion

In this study, we investigated the relative contribution of β-cell dysfunction and insulin resistance on pre-diabetes and diabetes among Tanzanian adults and found that β-cell dysfunction and insulin resistance were associated

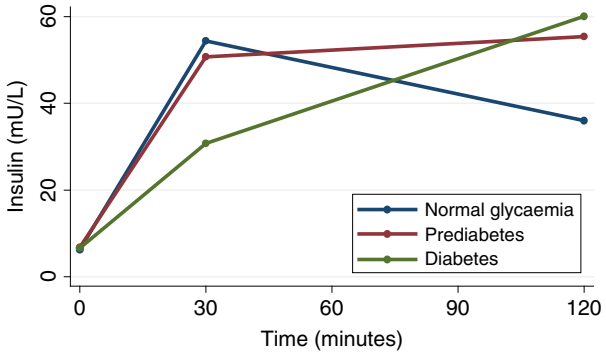

Figure 1 Insulin secretion during 2-h oral glucose tolerance test by diabetes status. Differences in median insulin level at 0 min: Normal glycaemia and prediabetes groups ($P = 0.52$), Normal glycaemia and diabetes groups ($P = 0.33$); Differences in median insulin level at 30 min: Normal glycaemia and prediabetes groups ($P = 0.02$), Normal glycaemia and diabetes groups ($P < 0.0001$); Differences in median insulin level at 120 min: Normal glycaemia and prediabetes ($P < 0.0001$), Normal glycaemia and diabetes groups ($P < 0.0001$). All comparisons by Mann Whitney *U* test. [Colour figure can be viewed at wiley onlinelibrary.com]

with higher risk of having pre-diabetes and diabetes. We found that 31% of diabetes cases could have been attributed to isolated β-cell dysfunction alone whereas only 9% could be attributed to isolated insulin resistance indicating that in this population β-cell dysfunction is a major contributor to diabetes.

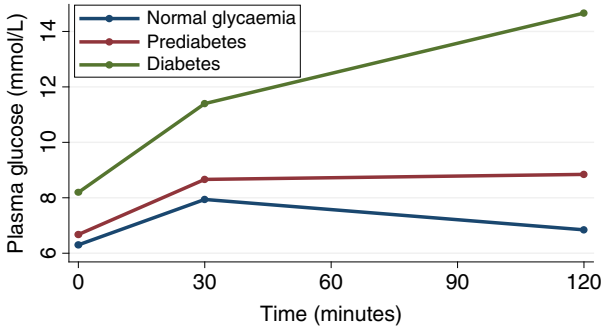

Figure 2 Glucose level during 2-h oral glucose tolerance test by diabetes status. Differences in mean glucose at 0 min: Normal glycaemia and prediabetes groups ($P < 0.0001$), Normal glycaemia and diabetes groups ($P < 0.0001$); Differences in mean glucose at 30 min: Normal glycaemia and prediabetes groups ($P < 0.0001$), Normal glycaemia and diabetes groups ($P < 0.0001$); Differences in mean glucose at 120 minutes: Normal glycaemia and prediabetes groups ($P<0.0001$), Normal glycaemia and diabetes groups ($P<0.0001$). All comparisons by t-test. [Colour figure can be viewed at wileyonlinelibrary.com]

β-cell dysfunction

Previous research has hypothesised that diabetes develops when both insulin resistance and β-cell dysfunction exist [27]. Based on work mostly in western countries, it has been suggested that insulin resistance and thereby hyperglycaemia precede β-cell damage and decreased insulin secretion [28]. Some studies have found diabetes to be associated with both insulin resistance and lack of first-phase or diminished second-phase insulin response to glucose challenge [29]. However, in this analysis, we found that only 33% of diabetes patients had combined β-cell dysfunction and insulin resistance, while 15% had isolated insulin resistance and 39% had isolated β-cell dysfunction. In regression analysis adjusted not only for HOMA-IR but also CRP and AGP, other proxies of insulin resistance [20], isolated β-cell dysfunction was significantly associated with diabetes suggesting that in some patients β-cell dysfunction may be the only defect leading to diabetes.

Several other observations point to the importance of β-cell dysfunction in the pathogenesis of diabetes in this study population. In the analysis of β-cell dysfunction across the continuum of diabetes, we found that there was progressive loss of β-cell function as individuals moved from normal glycaemia to diabetes and that isolated β-cell dysfunction was associated with higher risk of pre-diabetes suggesting that even before clinical diabetes, potential patients have lost substantial β-cell function. Furthermore, based on OGTT, an approach to confirm pattern of insulin secretion among diabetes patients, we found lower insulin at 30 min but higher at 120 min among those with diabetes compared to those without diabetes, which is a characteristic feature of diabetes associated with β-cell dysfunction [27]. In OGTT, the intake of glucose stimulates secretion of insulin; however, in individuals with diabetes there is delayed insulin response at 30 min, but increased secretion by 2 h and persistent hyperglycaemia in comparison with those without diabetes similar to what we observed. A few other studies have investigated the role of β-cell dysfunction on diabetes in Africa. In a prospective study among 128 South African Indians, it was reported that IGT was associated with early β-cell dysfunction [30], while other studies among southern Africans and Ghanaians suggested that early loss of β-cells preceded insulin resistance in diabetes patients [31,32]. These studies further suggested that the pathogenesis of diabetes in black Africans was different from white populations in western countries where insulin resistance seemed to precede loss of β-cell function [33]. These data point to the primacy of β-cell dysfunction as a major driver of diabetes in African populations, but further studies are needed. We do not know what are the major factors driving β-cell function

Table 3 Multinomial logistic regression of β-cell function and insulin resistance as predictors of pre-diabetes and diabetes

	Model*		Model†		
	RRR (95% CI)	*P*	RRR (95% CI)	*P*	PAF (95% CI)
Pre-diabetes					
β-cell function and insulin resistance status					
Normal β-cell function and insulin sensitivity	Reference		Reference		–
Isolated β-cell dysfunction	1.7 (1.3, 2.1)	<0.0001	1.6 (1.2, 2.0)	0.001	10.3 (4.6, 13.7)
Isolated insulin resistance	1.5 (1.2, 1.9)	0.001	1.6 (1.2, 2.1)	<0.0001	11.2 (5.0, 15.7)
Combined β-cell dysfunction and insulin resistance	1.9 (1.3, 2.7)	0.001	2.1 (1.5, 3.2)	<0.0001	4.9 (3.1, 6.5)
Diabetes					
β-cell function and insulin resistance status					
Normal β-cell function and insulin sensitivity	Reference		Reference		
Isolated β-cell dysfunction	5.7 (3.1, 10.2)	<0.0001	4.8 (2.5, 9.0)	<0.0001	30.9 (23.4, 34.7)
Isolated insulin resistance	2.0 (1.0, 4.2)	0.04	3.2 (1.5, 6.9)	0.003	10.0 (4.9, 12.5)
Combined β-cell dysfunction and insulin resistance	17.7 (9.3, 33.9)	<0.0001	35.9 (17.2, 75.2)	<0.0001	32.5 (31.5, 33.0)

PAF, population attributable fraction (%); RRR, relative risk ratio.
*Adjusted for age and sex.
†Adjusted for age, sex, C-reactive protein, alpha-acid glycoprotein, HIV/antiretroviral treatment, fat mass, fat-free mass and physical activity level.

loss in African populations; however, it has been hypothesised that genetic pre-disposition, environmental factors and chronic infections [5] could contribute to β-cell dysfunction.

Insulin resistance

Using HOMA-IR, the proxy of insulin resistance used in this study, we found that 15% of diabetes patients in the study population had insulin resistance and that both isolated insulin resistance and insulin resistance in combination with β-cell dysfunction were significantly associated with pre-diabetes or diabetes, indicating that in some of our participants insulin resistance was probably the only abnormality explaining the occurrence of diabetes. Insulin resistance is hypothesised to develop when the body becomes obese due to physical inactivity and intake of high-energy but low-fibre diet compromising insulin uptake in muscles. In this analysis, we found that fat mass was not associated with either pre-diabetes or diabetes suggesting that the effect of adipose tissue on glycaemia may have been mediated by HOMA-IR, a marker of insulin resistance used in this study, although it may also be that the effect of adipose tissue on glycaemia occurs at lower threshold than that found in other populations possibly also explaining our previous findings [12]. Excessive adipose tissue in the visceral organs like liver, mesenteric region and kidneys could have led to higher glucose level due to insulin resistance without changes in total body fat mass; however, we did not have imaging equipment to assess this in the current study [27]. In our previous work, we had shown that obesity, which is a conventional risk factor for NCDs, may not be associated with diabetes among Tanzanians [34]. Similarly, Ghanaian studies found that diabetes occurred independent of high BMI and developed in younger age in comparison with other settings [32,35]. It could also be that in these populations, insulin resistance is not primarily determined by obesity but rather by other factors leading to inflammation including infections [36]. In this population, we found that the prevalence of raised CRP (the proxy marker of inflammation) increased from 22% in participants without diabetes to 67% in participants with diabetes and that inflammation was associated with both pre-diabetes and diabetes independent of HIV infection. Future work should explore if strategies to reduce inflammation would help reduce risk of pre-diabetes and diabetes in this population.

Strengths and limitations

This was a large study including both HIV-uninfected and HIV-infected people in SSA, and thus, results can be generalised to similar populations. Insulinogenic index is validated against hyperglycaemic glucose clamp whereas HOMA-IR is validated against hyperinsulinemic–euglycemic clamp technique which are gold standard techniques for assessing insulin secretion and resistance, respectively [21,37–40]. Probability of insulinogenic index to predict diabetes was excellent whereas that for HOMA-IR was only satisfactory, but was better than the Matsuda insulin sensitivity index, the other measure of insulin resistance, which we derived but did not use in this analysis.

We included CRP and AGP, other measures of insulin resistance to complement the role of HOMA-IR. In multivariable models including both CRP, AGP and marker of β-cell dysfunction and insulin resistance, we found that both CRP and AGP were significant predictors of diabetes suggesting that both may have contributed to insulin resistance which could not be explained by HOMA-IR. This was a cross-sectional study so causality cannot be confirmed. In addition, we used populations with different backgrounds including those with previous TB as well as undernutrition and other potential β-cell dysfunction and insulin resistance determinants including childhood undernutrition and childhood diseases which could have confounded our results. However, we adjusted for important potential confounders.

Conclusions

To conclude, in this large cross-sectional study we found that β-cell dysfunction seemed to be a major contributor of diabetes in this study population, although insulin resistance was also a key contributor. Longitudinal studies are needed to understand evolution of diabetes as well as contributors of insulin insufficiency and resistance in African populations. These studies will help generate evidence for development of strategies to prevent a diabetes epidemic and to inform clinicians on appropriate management approaches, as aetiology may affect choice of treatment. Given that HIV-infected participants on ART continued to have elevated levels of inflammation, it would be critical to further investigate long-term health of HIV-infected patients since these could be at higher risk of developing diabetes and other NCDs in future due to ongoing inflammation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Participants flow diagram.

Table S1. Markers of insulin secretion and resistance.

Table S2. Body composition, β-cell function and insulin resistance, and inflammatory markers by diabetes and HIV treatment status.

Table S3. Multinomial logistic regression of inflammatory markers and other factors as predictors of prediabetes and diabetes.

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