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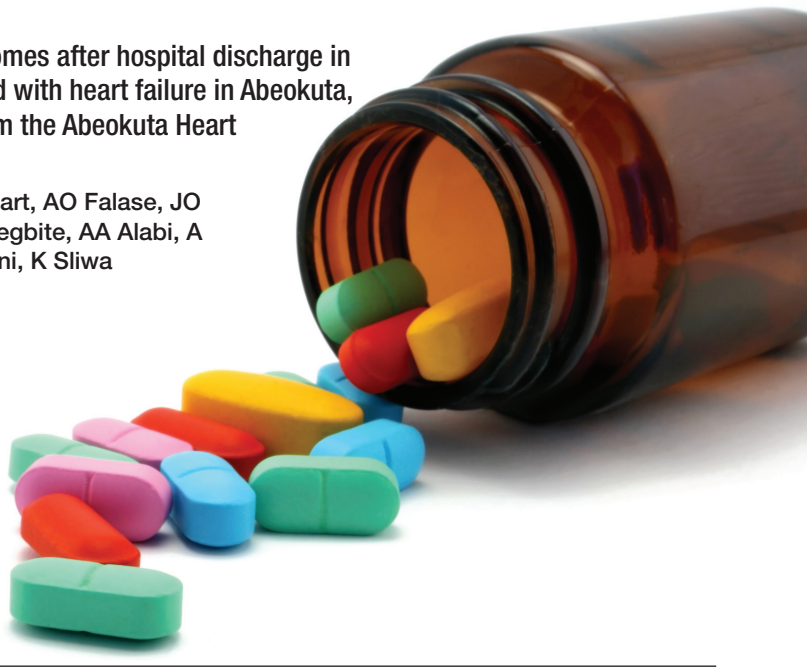
CONTENTS



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From the Editor's Desk

This issue looks at important aspects of the epidemiology of diabetes in Africa and India. Studies by Akintunde *et al*. from Nigeria (page 13), Pessinaba *et al*. from Senegal (page 27), Mondo *et al*. from Uganda (page 31) and Das *et al*. from West Bengal (page 37) all show a striking similarity in the high prevalence of hypertension, the metabolic syndrome and other cardiovascular risk factors in patients in these countries. This represents a significant health risk for diabetes and cardiovascular diseases in their populations, and specific programmes for the management and prevention of non-communicable diseases in these countries need to be urgently addressed.

Heart failure is a significant complication of many non-communicable diseases. Ogah *et al*. from Nigeria (page 20) report on data from the Abeokuta Heart Failure registry that looked at short-term outcomes after admission for heart failure. They found that this cohort in Nigeria differed from those in high-income countries. The patients were relatively younger and presented with non-ischaemic risk factors for heart failure, such as hypertensive heart disease. They concluded that region-specific strategies are required to improve health outcomes in low-income countries such as Nigeria.

Maries and Manitiu from Romania (page 40) review B-type natriuretic peptide (BNP) and the N-terminal fragment (NT-pro-BNP) and their various uses, including the diagnosis of congestive heart failure and the distinction between patients with dyspnoea of cardiac or pulmonary origin. Reference values for the tests differ depending on the patients on whom they are used and the manufacturer, therefore determination of reference values represents a challenge.

Veigne and co-workers carried out an interesting study in Cameroon on the effect of different altitudes from 13–1 600 metres above sea level, on HbA_{1c} measurements from point-of-care analysers in diabetic patients. They found little difference but recommend further calibration studies against gold-standard measures.

Hapunda and colleagues assessed the validity of a Zambian version of the Problem Areas in Diabetes (PAID) scale to determine levels of diabetes-specific emotional distress in Zambian people with diabetes. They found it to be reliable and valid to assess distress but some items needed to be simplified or clarified to enhance comprehensibility. They also found the Zambian participants had high levels of diabetes-specific distress, which needs to be addressed.

The patient leaflets look at women's and men's specific challenges with regard to diabetes, from depression to gestational diabetes in women, and erectile dysfunction as an early warning of possible health problems in men. The need for being proactive with one's health is emphasised.

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S Afr J Diabetes Vasc Dis 2016; **13**: 3

Validity and reliability of the Zambian version of the Problem Areas in Diabetes (PAID) scale: a triangulation with cognitive interviews

GIVEN HAPUNDA, AMINA ABUBAKAR, FRANS POUWER, FONS VAN DE VIJVER

Abstract

This study aimed to examine the psychometric properties of the Zambian version of the Problem Areas in Diabetes (PAID) scale and to determine the levels of diabetes-specific emotional distress in Zambian people with diabetes. A total of 157 Zambians living with type 1 and 2 diabetes completed the 20-item PAID, self-care inventory (SCI), fear for hypoglycaemia scale (HFS) and the major depression inventory (MDI) in study 1. In addition to exploratory factor analysis (EFA), reliability and validity tests were also conducted. In study 2, eight patients participated in cognitive interviews, in order to evaluate the extent to which participants were able to comprehend the scale items. EFA showed that a one-factor solution was the best interpretable solution and the PAID was a valid and reliable measure. Cognitive interviews showed that the participants were able to comprehend question intent, while a few faced some challenges with the meaning of words such as 'anxious' and 'physician', and with comprehension of some items. The Zambian version of the PAID is a reliable and valid measure to assess diabetes-specific distress. These Zambian participants with diabetes expressed high levels of diabetes-specific distress, and some items needed to be simplified or clarified to enhance comprehensibility.

Keywords: validity, reliability, diabetes, cognitive interviews, Problem Areas in Diabetes, Zambia

Introduction

Diabetes has become a major public health concern globally and sub-Saharan African (SSA) has not been spared. An estimated 15 million people in SSA are living with diabetes.[1] In Zambia alone, approximately 437 570 people are known to have diabetes, although this is potentially a gross underestimation of the magnitude of the problem, since many diabetes cases remain undiagnosed and the healthcare institutions do not keep systematic records of those who go for care. The number of people with undiagnosed diabetes in Zambia is estimated at 221 000.[1]

Evidence from mainly European and North American studies has shown that being diagnosed with either diabetes mellitus type 1 (TIDM) or type 2 (T2DM) can be daunting and demanding, and its treatment and care may impact on work, interpersonal relationships, social functioning, as well as the physical and emotional well-being of patients.[2-5] Psychosocial distress not only burdens patients but can also hamper adequate self-care behaviours, consequently compromising glycaemic control.[4,6,7]

Depression has also been reported to be a common problem in people with diabetes, which is associated with suboptimal HbA_{1c} levels, higher mortality rates and impaired quality of life.[8-14] Diabetes-specific emotional distress appears to mediate the relationship between depression and glycaemic control.[15] Hence, it is not surprising that depressive symptoms and diabetes-specific emotional distress are highly correlated; both affect glycaemic control and quality of life, among others.[15] Addressing diabetes-specific emotional distress could presumably simultaneously improve depressive mood and help improve health outcomes of patients with diabetes mellitus.

Having diabetes mellitus in Zambia differs from having diabetes in Europe or the USA. Access to care is often problematic, and cost of insulin and/or syringes is high, especially in rural areas.[16] Furthermore, as found in an earlier study in Zambia, certain cultural beliefs prevail that may impede the functioning of diabetes patients, such as 'a girl with diabetes cannot have children' or 'diabetes complications such as foot ulcers result from witchcraft'.[17] Given this array of issues specific to Zambia and Africa, a study of diabetes-specific emotional distress is needed in Zambia.

To be able to adequately monitor the levels of diabetes-specific emotional stress, there is a need to have adequately developed and standardised measures for monitoring and identifying those experiencing distress. The Problem Areas in Diabetes (PAID) scale is a widely used measure to monitor diabetes-related distress. The PAID has been translated and used to assess diabetes-specific emotional problems in many countries, such as Brazil, China, Iceland, Iran, the Netherlands, Norway, Sweden, Turkey and the USA.[3,6,7,18-24]

Given this wide use, its administration to various age groups, good psychometric properties and clinical utility, this measure has the potential to fill the gap in assessment measures in the diabetes population in Africa. However, its factor structure has been found to differ across studies. For instance, some studies reported the scale to be composed of one,[3,20] two,[6] three,[7] and four factors or scales.[18,19]

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S Afr J Diabetes Vasc Dis 2016; **13**: 4–12

This measure has not been evaluated and validated in the African context to date. Therefore, the aim of the present study was to examine psychometric properties of the PAID scale in Zambian people with diabetes and to determine the levels of diabetes-specific emotional distress in that group.

Methods

The study comprised two sets of data: quantitative data to test the validity and reliability of the PAID scale (study 1), and a cognitive interview to assess the adequacy, comprehensibility and cultural appropriateness of the PAID among the urban sample (study 2).

Study 1

The study sample comprised out-patients with either T1DM or T2DM from major hospitals in Lusaka, Ndola, Kitwe and Livingstone. Patients were classified as T1DM or T2DM based on what was indicated on the patients' hospital record cards. Patients were invited to participate in the study if they were at least 12 years old and were diagnosed at least six months before the study. In total, 157 patients signed the consent form, or with permission from guardians, assent was obtained from participants under 18 years of age. Recruitment was done over a one-year period.

Of the 157 participants, 80 were female (51%). We did not find significant differences in gender composition of the patients. Mean age was 39 ± 17 years with ages ranging from 12 to 68 years. Of the total sample, 115 (73%) were adults and 42 (27%) were adolescents. Table 1 shows the detailed demographic characteristics of the participants. Demographic variables included age, gender, educational level, properties and services owned by families of the participants, and type of diabetes. In addition, the body mass index of the participants was recorded.

Table 1. Demographic characteristics of 157 participants with type 1 and type 2 diabetes

Demographics	Number
Gender, *n* (%)	
Females	80 (51)
Age, mean (SD)	39 ± 17
Age range (years)	12–68
Type of diabetes, *n* (%)	
Type 1	93 (59)
Type 2	58 (37)
Unknown (but either type 1 or 2)	6 (4)
Developmental stage, *n* (%)	
Adolescents	42 (27)
Adults	115 (73)
BMI mean (SD)	25 (5)
Males	25 (5)
Females	26 (5)
Adolescents	22 (4)
Adults	27 (5)
Educational levels, *n* (%)	
Adolescents (*n* = 42), *n* (%)	
5–7th grade (primary school)	14 (31)
8–12th grade (secondary school)	16 (38)
Unknown	14 (31)
Adults (*n* = 115), *n* (%)	
Primary education	10 (9)
Secondary education	29 (25)
Tertiary education	22 (19)
Unknown	54 (47)
Marital status (adults *n* = 115), *n* (%)	
Single	6 (5)
Married	80 (70)
Unknown	29 (25)

The PAID is a 20-item self-report measure used to assess diabetes-specific emotional distress in a wide age group,[2] including a range of feelings such as diabetes-related anger, fear, depression, worry and guilt. Items can be responded to on a scale from 0 (not a problem) to 4 (serious problem). An overall score for PAID can be calculated by adding all of the item scores and multiplying by 1.25, which gives a total score ranging from 0 to 100. Higher scores indicate more distress. The reported Cronbach's alpha for the PAID scale was 0.84 to 0.96.[3,6,7,18-24]

The hypoglycaemia fear survey (HFS) consists of 26 items. HFS comprises two scales assessing 'worries about hypoglycaemia' and 'hypoglycaemia-related behaviours'. The items are rated on a five-point scale ranging from 1 (never) to 5 (very often). The Cronbach's alpha of 0.90 suggests high internal consistency.[25]

The 13-item self-care inventory (SCI) is a self-report measure used to assess patients' perceptions of their adherence to diabetes self-care recommendations over the previous one to two months. Individuals rate themselves on a five-point Likert scale that reflects on how well they have followed recommendations for self-care during the past month (i.e. 1 = 'never do it' to 5 = 'always do this as recommended, without fail'). Higher scores indicate more optimal diabetes self-care. Cronbach's alpha for the SCI was 0.84 for T1DM and 0.85 for T2DM.[26]

The major depression inventory (MDI) is a 12-item self-report questionnaire used to assess depression. Items of the MDI ask the patient to rate how long in the past two weeks each of the symptoms of the depressive syndrome was present on a six-point scale ranging from 0 = 'not at all' to 5 = 'all the time'. It can be used as an instrument measuring severity of depression with a range from 0 to 50. The internal consistency of the MDI appeared to be good, as indicated by Cronbach's alphas of 0.89 and 0.94.[27,28]

Zambia is a multi-lingual country with five main languages and English is the official language. Measures were administered in English and in two local languages, Nyanja and Bemba. Back translations were done by two native speakers in each language who were fluent in the other language and English. The translators met, together with the first author to discuss the translation in each language and the differences between forward and back translation versions. The goal was to maximise both linguistic and psychological equivalence. The final translation was piloted on six adolescents with type 1 diabetes and feedback on their understanding of the items was obtained.

Statistical analyses

Demographic characteristics in the total sample were examined using descriptive statistics. Missing data from the PAID were determined as missing completely at random (MCAR) and replaced using expectation maximisation/maximum likelihood (EM) in SPSS. To assess the factor structure of the PAID, exploratory factor analysis was conducted; we used direct oblique rotation (direct oblimin), Keiser–Mayer–Olkin measure of sampling and Bartlett's test of sphericity using the scree plot criterion. Keiser–Mayer–Olkin values of > 0.6 indicate that data are suitable for conducting a factor analysis.[29,30] Oblique rotation was used because factors of the PAID were expected to be moderately correlated. Factor loadings of 0.30 or higher have been recommended for a sample size of 300 or more.[31]

The reliability was evaluated using data on the type of diabetes (T1DM and T2DM) and included Cronbach's alpha and lambda 2

Table 2. One-, two-, three-, four- and five-factor solution for the PAID as reported by 157 Zambian participants (aged 12–68 years) with type 1 and 2 diabetes

	Factor solution														
	One-factor	Two-factor		Three-factor			Four-factor				Five-factor				
Shortened item content	**F1**	**F1**	**F2**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F4**	**F1**	**F2**	**F3**	**F4**	**F5**
Feeling depressed?	0.71	0.70		0.76			0.75				0.74				
Worry about low blood sugar reactions?	0.58	0.62		0.63			0.76				0.77				
Worry about complications?	0.70	0.70		0.69			0.68				0.69				
Feeling angry?	0.63	0.60		0.74		–0.40	0.72		–0.40		0.71		–0.37		
Feeling scared?	0.73	0.73		0.77			0.62				0.63				
Feeling discouraged with treatment?	0.73	0.72		0.75			0.64				0.61				
Mood related to diabetes?	0.63	0.63		0.54			0.61		0.31		0.59				
Feeling 'burned out'?	0.70	0.67		0.60			0.64				0.53				–0.40
Feelings of guilt or anxiety?	0.65	0.64		0.63			0.55				0.55				
Diabetes is taking up too much energy?	0.59	0.54		0.51			0.53				0.57				
Uncomfortable social situation?	0.63	0.65		0.60						0.76				0.76	
Feeling that others are not supportive?	0.67	0.67		0.55		0.39			0.31	0.63				0.65	–0.31
Feeling alone with your diabetes?	0.62	0.64	0.69						0.72				0.70		
Not 'accepting' your diabetes?	0.68	0.72		0.63		0.31	0.30			0.51				0.53	
Unsatisfied with diabetes physician?	0.56	0.60		0.40		0.64			0.59	0.44			0.53	0.46	
Concerned about food and eating?	0.11		0.72		0.73			0.75					0.87		
Feelings of deprivation regarding food?	0.17		0.76		0.73			0.79					0.76		
Coping with complications?	–0.00		0.69		0.75			0.66		–0.42			0.59	–0.42	
Not having clear and concrete goal?	0.36		0.43		0.43			0.38							–0.90
Feeling overwhelmed by your diabetes?	0.23		0.59		0.41	–0.59		0.49	–0.57				–0.79	–0.32	
Eigenvalue before rotation	6.69	6.69	2.14	6.69	2.14	1.35	6.69	2.14	1.35	1.14	6.69	2.14	1.35	1.14	1.02
% variance before rotation	33.45	33.45	10.70	33.45	10.70	6.73	33.45	10.70	6.73	5.71	33.45	10.70	6.73	5.71	5.12
Eigenvalue after rotation		6.65	2.39	6.58	2.41	1.78	6.03	2.39	1.55	4.08	5.91	2.11	1.41	4.17	2.22

Principle factor analysis using oblique rotation (direct oblimin).

(i.e. for PAID total alpha and alpha for each subscale). Values above 0.70 are regarded as satisfactory.[32] Concurrent validity was assessed using Pearson's correlation between PAID total score and other psychosocial variables of interest. In addition, item total correlation was computed to evaluate the degree to which differences among patients' responses to the items were consistent differences in their total PAID scores. Correlations among measures of the same attribute should be between 0.40 and 0.80.[7] A lower correlation indicates either an unacceptably low reliability of one of the measures, or that the measures are measuring different phenomena.[33] Discriminant validity was examined by conducting a multiple regression analysis to determine the extent to which PAID scores were predicted by body mass index, depression, fear of hypoglycaemia and diabetes self-care, after adjusting for age, diabetes type, gender and socio-economic status.

Results

The lowest PAID item missing value accounted for 1.3% and the highest item accounted for 3.8%. In particular, five items had the largest missing value percentages; 'feeling constantly burned out by constant effort to manage diabetes' (3.8%), 'feeling constantly concerned with food' (3.8%), 'feeling diabetes is taking up too much of your mental and physical energy' (2.5%), 'not accepting diabetes' (2.5%) and 'feeling overwhelmed by your diabetes regimens' (2.5%). These items accounted for 15.1% missing values. The Bartlett test of sphericity was highly significant [χ^2 (190) = 1005.533, $p < 0.001$]. The KMO value was 0.86. These statistics suggest that the EFA can be adequately applied.

In the second step, principal component analysis using direct oblimin was conducted and inspection of the Eigenvalues yielded a maximum of five factors: 6.69, 2.14, 1.35, 1.14 and 1.02 (values before rotation). Given the ambiguity as to the number of factors reported in the literature, we explored solutions with different numbers of factors, working back from five factors. The five-factor solution could not be used, as many items loaded on more than one factor and some of the factors could not be interpreted

Consistent with Snoek and colleagues,[18] a forced four-factor model was inspected. However, the results were not consistent with the four-factor model described by Snoek and colleagues, who had the following four factors: (1) emotional problems related to diabetes, (2) treatment problems, (3) food problems, (4) lack of social support.[18] As can be seen in Table 2, our four-factor solution was not interpretable, with the exception of factor 1, which had some resemblance to Snoek and colleagues' emotional subscale; but items from the food-related, social support and treatment-related distress subscales loaded on the same factor.

We also inspected a three-factor and a two-factor model using EFA; both solutions were not interpretable. The first factor of the two-factor solution consisted of items assessing 'diabetes stress' and a second factor containing items covering not only 'food-related problems' but also covering 'coping with complications and being overwhelmed with the diabetes regimens'. The second factor had item combinations that rendered it difficult to interpret, partly because of various secondary loadings. Therefore the two-factor solution was discarded.

Lastly, we examined a one-factor solution. Our data provided the strongest support for a one-factor model, although it had four items with low loadings below 0.30 (concerned about food and eating = 0.11, deprivation regarding food = 0.17, coping with complications = –0.00 and feeling overwhelmed by your diabetes = 0.23).The retained items had factor loadings ranging from 0.36 to 0.73. Internal consistency remained high even after removing

Table 3. Proportion of participants that endorsed an item as a 'serious problem'#

PAID 20 items	Type 1 diabetes		Type 2 diabetes		Type 1 and 2 diabetes
	Males % (*n*)	Females % (*n*)	Males % (*n*)	Females % (*n*)	males and females % (*n*)
Diabetes-related emotional problems					
Worry about low blood sugar reactions	57 (27/47)*	59 (27/46)*	61 (17/28)	63 (19/30)*	61 (95/157)*
Feeling that diabetes is taking up too much mental and physical energy	62 (29/47)*	50 (23/46)	68 (19/28)*	67 (20/30)*	60 (94/157)*
Feeling guilt/anxious when you get off track with your diabetes management	66 (31/47)*	41 (19/46)	75 (21/28)*	60 (18/30)*	58 (91/157)*
Worrying about the future and possibility of serious complications	55 (26/47)*	61 (28/46)*	71 (20/28)*	47 (14/30)	57 (90/157)*
Feeling depressed when you think about living with diabetes	55 (26/47)*	54 (25/46)*	57 (16/28)	53 (16/30)	54 (84/157)
Feeling scared when you think about living with diabetes	53 (25/47)	54 (25/46)*	50 (14/28)	53 (16/30)	52 (82/157)
Not knowing if the mood or feeling you are experiencing are related to your blood glucose	47 (22/47)	54 (25/46)*	61 (17/28)*	53 (16/30)	53 (83/157)
Feeling constantly burned out by the constant effort to manage diabetes	51 (24/47)	37 (17/46)	54 (15/28)	63 (19/30)*	49 (77/157)
Not accepting diabetes	45 (21/47)	37 (17/46)	50 (14/28)	43 (13/30)	41 (64/157)
Coping with complications of diabetes	38 (17/47)	39 (18/46)	21 (6/28)	60 (18/30)*	40 (62/157)
Feeling angry when you think about living with diabetes	40 (19/47)	30 (14/46)	39 (11/28)	50 (15/30)	39 (61/157)
Feeling overwhelmed by your diabetes regimen	19 (9/47)	28 (13/46)	11 (3/28)	27 (8/30)	22 (34/157)
Treatment-related problems					
Not having clear and concrete treatment goals for your diabetes care	38 (18/47)	37 (17/46)	36 (10/28)	63 (19/30)*	41 (65/157)
Feeling unsatisfied with your diabetes physician	34 (16/47)	46 (21/46)	61 (17/28)*	33 (10/30)	41 (65/157)
Feeling discouraged with your diabetes regimens	36 (17/47)	39 (18/46)	46 (13/28)	43 (13/30)	40 (62/157)
Food-related problems					
Feeling constantly concerned about food	45 (21/47)	44 (20/46)	32 (9/28)	43 (13/30)	42 (66/157)
Feelings of deprivation regarding food and meals	34 (16/47)	44 (20/46)	32 (9/28)	50 (15/30)	40 (63/157)
Uncomfortable interactions around diabetes with family/friends (e.g. other people telling you what to eat)	38 (18/47)	35 (16/46)	3 (11/28)	40 (12/30)	37 (58/157)
Social support-related problems					
Feeling that friends/family are not supportive of diabetes-management efforts	55 (26/47)*	41 (19/46)	64 (18/28)*	40 (12/30)	48 (75/157)
Feeling alone with diabetes	40 (19/47)	44 (20/46)	43 (12/28)	37 (11/30)	40 (63/157)

#Total PAID ranges from 0–80 on a scale (0–1) 'not a problem', (2) 'a little problem' and (3–4) 'serious problem.
*Very high areas concerning diabetes-specific distress in Zambian patients.

these items. Cronbach's alpha was 0.90 (lambda 2 = 0.90).

The internal consistency of the total PAID, as indicated by Cronbach's alpha, was 0.88 (lambda 2 = 0.89), and for the 16 items, PAID alpha was 0.90 (lambda 2 = 0.90). For subjects with T1DM, Cronbach's alpha was 0.89 (lambda 2 = 0.90), while for subjects with T2DM, Cronbach's alpha was 0.86 (lambda 2 = 0.88). Inspections of the item total correlations revealed that 15 out of 20 items were worthy of retention. The greatest increase in alpha resulted from deleting the following items; 'coping with complications' (0.06), 'feeling constantly concerned about food' (0.17), 'deprivation regarding food and meals' (0.23), 'feeling overwhelmed by diabetes regimens' (0.24) and 'not having a clear and concrete goal for diabetes' (0.33). Removal of these items increased the alpha by only 0.03 (0.91). Cronbach's alpha for HFS was 0.80 and lambda 2 = 0.81, for the SCI, alpha was 0.71 and lambda 2 = 0.74, and for the MDI, alpha was 0.79 and lambda 2 = 0.80.

Table 3 shows that regardless of the type of diabetes, 'worry about low blood sugar reactions' was most endorsed as a serious problem (i.e. a score of 3 or 4, 'a problem' or 'a serious problem') among T2DM patients and in all patients (62 and 61%, respectively). Overall, 60% of the patients (T1DM and T2DM) endorsed 'the feeling that diabetes was taking up too much of their mental and physical energy' and was a serious problem.

Women with T2DM scored higher (54 ± 21, 95% CI: 46–61) than men or women with T1DM (49.0 ± 24.0, 95% CI: 41.8–56.0; 49.5 ± 23.0, 95% CI: 42.6–56.40), respectively. Men with T2DM scored higher (51 ± 22, 95% CI: 43–60) than men (49 ± 24, 95% CI: 42–56) and women (50 ± 23, 95% CI: 43–60) with T1DM, and these differences were significant (see Table 4).

Concurrent validity of the PAID scale was evaluated by assessing the correlations between the PAID and age, body mass index, socio-economic status, fear of hypoglycaemia, depression and diabetes self-care. Table 5 shows the correlation between the PAID and other variables of interest. There was a moderately significant correlation between the PAID with the diabetes self-care [r (157) = –0.30], fear of hypoglycaemia [r (157) = 0.35] and depression [r (157) = 0.39] scores. However, there was no significant correlation between the PAID and age [r (157) = 0.12], socio-economic status [r (156) = –0.01] and body mass index [r (157) = –0.14].

Table 6 shows a stepwise multiple regression model that examined the relationship of six variables with the total PAID score. In the first step, demographic variables were entered as control variables; no significant associations were found with diabetes distress. In the second step, clinical variables (body mass index, depression, diabetes self-care and fear of hypoglycaemia) were entered. These variables were positively associated with total PAID scores, except for body mass index, which was negatively associated with diabetes distress. The strongest predictor of diabetes-specific distress was fear for hypoglycaemia (beta = 0.29), followed by depression (beta = 0.27), and perceived diabetes self-care was the third most significant predictor of diabetes-specific distress (beta = 0.25). The predictor variables explained 32% ($p < 0.01$) of total variance of the PAID.

Study 2

As a further study of the adequacy of the PAID in the Zambian context, we conducted a qualitative study, addressing the adequacy of the instrument's instructions, items and response scale. We used cognitive interviews to assess the adequacy, comprehensibility and cultural appropriateness.[34]

Eight patients (three adolescents and five adults) participated in the study. These cognitive interviews focused on the 20 items of the PAID. Patients were asked to provide verbal feedback on each item regarding (1) response categories, (2) clarity, (3) the respondent's knowledge about the specific topics that were enquired, and recall of experiences and sensitivity of the items and overall impression of the content (see Table 7).

All interviews were conducted in English and were audio-recorded and verbatim transcribed. Interviews lasted between 30 and 45 minutes. Table 8 shows examples of questions asked during the cognitive interview. Of the eight patients who were interviewed, only one had completed the PAID scale earlier during the research project.

Verbatim transcriptions were first read through several times in order to get familiar with the data. After establishing familiarity with the data, each question response was analysed and comments were assigned to each response, based on the cognitive theory model by Tourangeau.[35] The model consists of four processes: (1) comprehension of the question (question intent and meaning of terms), (2) retrieval from memory of relevant information (recallability of information and recall strategy – recalling each one individually versus estimation strategy), (3) decision process (motivation – devotion of mental effort to answer question and sensitivity of question or indication of social desirability), and (4) response process, which involves matching responses to scale categories.

Results

In general, most of our patients could understand the majority of the items (16/20 = 80% of the items). The following items were

Table 4. PAID mean scores on items and sub-dimensions for the males and females subjects with type 1 and type 2 diabetes

	Type 1 diabetes		Type 2 diabetes	
Sub-dimension	**Males (*n* = 47) Mean ± SD (95% CI)**	**Females (*n* = 46) Mean ± SD (95% CI)**	**Males (*n* = 28) Mean ± SD (95% CI)**	**Females (*n* = 30) Mean ± SD (95% CI)**
Diabetes-related emotional problems	30.9 ± 15.3 (26.4–34.5)	30.0 ± 13.8 (26.9–35.6)	31.6 ± 14.1 (26.1–37.1)	34.3 ± 13.9 (29.0–31.5)
Feeling that diabetes is taking up too much mental and physical energy	3.1 ± 2.1 (2.5–3.8)	2.8 ± 2.1 (2.3–3.4)	3.3 ± 2.3 (2.5–4.1)	3.9 ± 1.8 (3.1–4.5)
Not knowing if the mood or feeling you are experiencing are related to your blood glucose	2.6 ± 2.1 (2.0–3.3)	2.9 ± 2.1 (2.3–3.5)	3.5 ± 2.0 (2.6–4.1)	3.3 ± 2.0 (2.5–4.0)
Feeling guilt/anxious when you get off track with your diabetes management	3.3 ± 1.9 (2.8–3.9)	2.5 ± 2.1 (1.9–3.1)	3.6 ± 1.9 (2.9–4.3)	3.3 ± 2.0 (2.5–4.0)
Feeling constantly burned out by the constant effort to manage diabetes	2.9 ± 2.1 (2.3–3.5)	2.4 ± 2.3 (1.8–3.0)	3.0 ± 2.1 (2.1–3.8)	3.3 ± 1.9 (2.5–3.9)
Coping with complications of diabetes	1.9 ± 2.1 (1.3–2.5)	2.1 ± 2.1 (1.5–2.8)	1.4 ± 2.0 (0.6–2.1)	3.1 ± 2.1 (2.3–3.9)
Feeling depressed when you think about living with diabetes	2.8 ± 2.3 (2.1–3.8)	3.1 ± 2.0 (2.5–3.8)	3.0 ± 2.1 (2.1–3.9)	3.0 ± 2.0 (2.3–3.8)
Worry about low blood sugar reactions	3.1 ± 2.0 (2.5–3.8)	3.0 ± 2.0 (2.5–3.6)	3.3 ± 2.1 (2.4–4.1)	3.1 ± 2.0 (2.4–3.9)
Feeling scared when you think about living with diabetes	2.6 ± 2.3 (2.0–3.3)	2.9 ± 2.1 (2.3–3.5)	2.6 ± 2.1 (1.8–3.5)	2.9 ± 2.3 (2.0–3.6)
Feeling angry when you think about living with diabetes	2.3 ± 2.3 (1.6–2.9)	1.9 ± 2.1 (1.3–2.5)	2.3 ± 2.4 (1.3–3.1)	2.8 ± 2.1 (1.9–3.6)
Feeling overwhelmed by your diabetes regimen	1.3 ± 1.8 (0.8–1.8)	1.9 ± 1.8 (1.4–2.4)	0.8 ± 1.6 (0.1–1.4)	1.9 ± 2.0 (1.3–2.6)
Worrying about the future and possibility of serious complications	3.0 ± 2.1 (2.4–3.8)	3.4 ± 2.0 (2.8–3.9)	3.6 ± 2.0 (2.9–4.4)	2.6 ± 2.3 (1.8–3.4)
Not accepting diabetes	2.5 ± 2.3 (1.8–3.1)	2.1 ± 2.1 (1.5–2.8)	2.6 ± 2.5 (1.6–3.5)	2.3 ± 2.4 (1.3–3.1)
Treatment-related problems	**6.6 ± 4.4 (5.3–7.9)**	**7.1 ± 4.9 (5.6–5.5)**	**8.0 ± 4.5 (6.3–9.8)**	**7.6 ± 4.1 (6.1–9.3)**
Not having clear and concrete treatment goals for your diabetes care	2.4 ± 2.0 (1.8–2.9)	2.3 ± 2.1 (1.8–2.9)	2.0 ± 2.3 (1.3–2.9)	3.1 ± 2.1 (2.4–3.9)
Feeling discouraged with your diabetes regimens	2.5 ± 2.1 (1.6–2.9)	2.3 ± 2.1 (1.6–2.9)	2.8 ± 2.1 (1.9–3.5)	2.5 ± 2.3 (1.8–3.4)
Feeling unsatisfied with your diabetes physician	2.0 ± 1.1 (1.4–2.6)	2.6 ± 25 (1.9–3.3)	3.3 ± 2.5 (2.4–4.1)	2.0 ± 2.1 (1.1–2.8)
Food-related problems	**6.4 ± 4.5 (5.0–7.6)**	**6.8 ± 4.3 (5.5–8.0)**	**6.1 ± 4.3 (4.4–7.8)**	**7.3 ± 5.3 (5.3–9.3)**
Feelings of deprivation regarding food and meals	2.0 ± 2.1 (1.4–2.5)	2.3 ± 2.3 (1.6–2.9)	2.0 ± 2.3 (1.1–2.9)	2.8 ± 2.3 (1.9–36)
Feeling constantly concerned about food	2.3 ± 2.3 (1.6–2.9)	2.4 ± 2.1 (1.8–3.0)	1.9 ± 2.3 (1.0–2.6)	2.4 ± 2.4 (2.6–3.3)
Uncomfortable interactions around diabetes with family/friends (e.g. other people telling you what to eat)	2.1 ± 2.0 (1.5–2.8)	2.1 ± 2.1 (1.5–2.6)	2.5 ± 2.5 (1.4–3.1)	2.1 ± 2.1 (1.4–2.9)
Social support-related problems	**5.1 ± 4.0 (4.0–6.4)**	**4.6 ± 3.9 (3.5–5.9)**	**5.6 ± 4.0 (4.0–7.1)**	**4.4 ± 3.0 (3.4–5.5)**
Feeling that friends/family are not supportive of diabetes management efforts	2.9 ± 2.5 (2.5–3.6)	2.4 ± 2.3 (1.6–3.0)	3.4 ± 2.1 (2.5–4.3)	2.3 ± 2.1 (2.6–3.2)
Feeling alone with diabetes	2.3 ± 2.1 (1.6–2.9)	2.3 ± 2.3 (1.6–3.0)	2.3 ± 2.3 (1.4–3.1)	2.1 ± 2.1 (1.4–3.0)
PAID 20-item scale	**40.3 ± 34**	**49.0 ± 24.0 (41.8–56.0)**	**49.5 ± 23.0 (42.6–56.40)**	**51.4 ± 2 1.9 (42.8–59.9)**	**53.5 ± 20.9 (45.8–61.4)**
Total PAID, 16 items	**33.8 ± 27.2**				

Transformed from 0–4 scale (0–80) to a scale 0–5 (0–100) by multiplying the results by 1.25.

Table 5. Correlations between the total PAID, the four PAID factors (based on previous research) and other variables of interest

	Diabetes self-care	Fear for hypoglycaemia	Age	SES¶	BMI	MDI#
PAID total	0.30**	0.35**	0.12	0.00	–0.14	0.39**

**$p \leq 0.01$, *$p \leq 0.05$; ¶Socio-economic status; #Major depression inventory total score.

problematic to understand for some patients: 'feeling constantly burned out by constant effort to manage diabetes' and 'not having a clear and concrete goal for managing diabetes care'.

Some adolescents and adults had challenges with specific words in the items although they were able to deduce the meaning of the entire question. The words and concepts that the patients found challenging were 'overwhelmed', 'regimens', 'unsatisfied', 'burnout', 'physicians' and 'concrete goal'. The patients were also able to suggest some replacements to the words they initially had challenges with to include 'treatment plan' for 'regimens', 'unhappy' or 'happy' for 'unsatisfied', 'doctor' for 'physicians'. In some cases it was difficult to recall occurrences of certain events evoked by the questions such as when patients were angry, guilty or anxious and uncomfortable. These challenges were mostly noted among young people. Table 8 outlines common problems that were identified, as indicated above.

Discussion

The aim of this study was to examine the latent structure, reliability and validity of the PAID among individuals with type 1 or 2 diabetes in Zambia. The results of our study strongly support a one-factor solution of the Zambian translation of the PAID, although four items 'concerned with complications', 'feelings of deprivation regarding food', 'coping with complications' and 'feeling overwhelmed by diabetes' had factor loadings less than 0.30. These low loadings may result from the fact that all our subjects were out-patients without any serious complications. It remains unclear why the item 'concerned about food' had a low loading considering that initial interviews by the first author with the patients showed that it was a major concern.[17]

Our data rejected the two-factor model found in Iceland by Sigurdardottir and Benediktsson,[6] the three-factor model found in Sweden by Amsberg and colleagues,[7] and the four-factor model found in the USA/the Netherlands.[18,19] A one-factor model was also found in the USA/the Netherlands.[18]

Originally, the PAID was conceptualised as a unidimensional scale;[2] therefore, our one-factor structure using all 20 items remains plausible. Moreover, in studies among Chinese,[20] Dutch and USA[18] individuals with diabetes, the one-factor solution was also supported. The Zambian translation of the PAID showed high internal consistency with Cronbach's alpha and lambda, which has recently been recommended in the literature because it shows the least amount of bias.[36] Consequently, a total of at least 16 items from the EFA results seems useful for clinical assessment to detect diabetes-related distress and suggest psychological help to Zambian patients with such distress, with possibly some word changes, as suggested by the cognitive interview study.

Our study also found that most patients endorsed, 'worrying about low blood sugar reactions', 'feeling that diabetes is taking up too much mental and physical energy', 'feeling guilty/anxious when you get off track with your diabetes management', 'worrying about future and possible serious complications' and 'feeling depressed when you think about living with diabetes' as the most bothersome diabetes-specific problems, which is consistent with findings by Sigurdardottir and Benediktsson.[6] 'Worrying about the future and possible complications', and 'feeling guilty when you get off track with your diabetes management' were also found to be the most commonly endorsed by Snoek and associates.[18]

It was not surprising that our patients endorsed these items, considering that the mean score for fear for hypoglycaemic episode was relatively high (58 ± 12) and the diabetes self-care score was below average (48 ± 9). Moreover, having a hypoglycaemic episode in Zambia might be more stressful, as medical care is less available, compared to Europe or the USA. Furthermore, all the participants

Table 6. Stepwise multiple regression analyses predicting PAID by demographic and clinical characteristics in 157 patients with T1DM and T2DM

Models	Beta	*t*	*p*-value
Model 1: demographic characteristics			
Age	0.122	1.286	ns
Being T2DM	0.029	0.313	ns
Being female	0.011	0.138	ns
Socio-economic status	0.005	0.054	ns
$R^2 = 0.020$			
Adj $R^2 = -0.007$			
$p \geq 0.005$			
Model 2: clinical characteristics			
Body mass index	–0.107	–1.348	ns
Depression (MDI)	0.268	3.122	***
Fear for hypoglycaemia	0.289	3.456	***
Diabetes self-care	0.252	3.249	***
$R^2 = 0.335$			
Adj $R^2 = 0.315$			
$p \leq 0.001$***			

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 7. Cognitive interview questions

Warm up question/instruction clarity
Tell me what this introduction is telling you?
Comprehension (question intent and meaning of term)
Can you tell me in your own words what this question was asking?
What does the [word/term] mean to you as it has been used in this question?
Tell me what you were thinking when I asked about [topic]?
Assumption
How well does this question apply to you?
Can you tell me more about that?
Knowledge/memory
How much would you say you know about [topic]?
How much though would you say you have given to this?
How easy or difficult is it to remember [event]?
You said [answer]. How sure are you about that?
How did you come up with that answer?
Sensitivity/social desirability
Is it ok to talk about this diabetes problem area or is it uncomfortable?
The question uses the [word/term]. Does that sound ok or would you choose something different?
Specific and general probes
Why do you think that [topic] is the most serious diabetes problem?
How did you arrive at that answer?
Was it easy or hard to answer?
I noticed that you hesitated. Tell me what you were thinking?

Table 8. Item total correlations of 20 PAID items

Items	Scale mean if deleted	Scale variance if deleted	Corrected item total correlation	Cronbach alpha if item deleted
1. Worrying about future and possible complications	37.83	307.10	0.62	0.87
2. Feeling guilty or anxious when getting off track with your diabetes management	37.83	312.85	0.56	0.87
3. Feeling scared when you think about living with diabetes	38.12	304.65	0.65	0.87
4. Feeling discouraged with diabetes regimens	38.41	305.26	0.65	0.87
5. Worrying about low blood sugar	37.74	317.27	0.47	0.87
6. Feeling constantly burned out by constant effort to manage diabetes	38.08	306.18	0.64	0.87
7. Not knowing if mood/feelings experiencing are related to your blood glucose	37.98	311.06	0.56	0.87
8. Coping with complications of diabetes	38.54	339.95	0.06	0.89
9. Feeling diabetes is taking up too much of your mental and physical energy	37.70	311.74	0.56	0.87
10. Feeling constantly concerned about food	38.50	332.56	0.17	0.88
11. Feeling depressed when thinking about living with diabetes	37.94	305.58	0.65	0.87
12. Feeling angry when you think about living with diabetes	38.50	309.53	0.55	0.87
13. Feeling overwhelmed by your diabetes regimens	39.10	332.15	0.24	0.88
14. Feeling alone with diabetes	38.33	311.81	0.53	0.87
15. Feeling deprived regarding food	38.47	328.89	0.23	0.88
16. Not having a clear and concrete goal for your diabetes care	38.37	323.66	0.33	0.88
17. Uncomfortable interactions around diabetes with friends/family	38.61	313.51	0.52	0.87
18. Not accepting diabetes	38.51	308.00	0.55	0.87
19. Feeling that family/friends are not supportive of diabetes management effort	38.20	306.06	0.60	0.87
20. Feeling unsatisfied with your diabetes physician	38.44	314.39	0.48	0.87

with T1DM were on insulin injection therapy, which has been shown to be physically and mentally challenging. Patients are required to buy their own strips for blood glucose testing, which are often unaffordable for most patients. Generally, diabetes patients get off track with diabetes management and care, which can cause a sense of guilt and anxiety.

The mean value for the 16 items of the PAID was 33.8 ± 27.2 (it would be 40.3 ± 33 in the case of 20 items) suggesting that the Zambian participants experienced high levels of diabetes-specific emotional distress. In the Icelandic participants (T1DM only) the mean value for the PAID was 28 ± 18, in Swedish participants (T1DM only) it was 27 ± 18, in the Dutch, 24 ± 19, and in USA participants, it was 31 ± 23. The results suggest that living with diabetes in Zambia is perceived as much more stressful compared to Western Europe and the USA, and that it imposes many demands on the patients, which may exacerbate diabetes-specific emotional distress.

These differences in levels of diabetes-specific emotional distress may reflect differences in access to physical and mental healthcare, and costs associated with diabetes management. Another explanation could be cultural differences in the experience of psychological problems. Graue and colleagues also speculated that differences in diabetes-specific emotional distress across countries may be due to cultural differences in the explanation of psychological problems.[24] Most importantly, definitions and attributes of depression are dominated by Western cultural assumptions, which may not reflect the conceptualisation and treatment of depression in Zambia. To the best of our knowledge diabetes patients in Zambia are not given any psychosocial help. Moreover about 48% of our participants indicated that family/friends were not supportive of diabetes management efforts.

In our study, the PAID scores were positively associated with fear for hypoglycaemia and depression, and negatively associated with diabetes self-care. Equally, PAID scores were predicted by the patients' depression levels, diabetes self-care and fear of hypoglycaemia. This was expected, as the literature has shown associations between body mass index, socio-economic status, glycaemic control and self-care with depression.[37-41]

Overall, the cognitive interviews demonstrate that our respondents were able to comprehend the scale items and to link them to the scale category. Four items ('feeling constantly burned out by constant effort to manage diabetes', 'not having a clear and concrete goal for managing diabetes care', 'coping with complications of diabetes' and 'feeling diabetes was taking up too much of your mental and physical energy', were not well comprehended by five respondents. The difficulties were beyond word difficulties or vague concepts, but were the comprehension of the question intent. Although some of the respondents had difficulties with the meaning of some words/terms (e.g. anxious, physician, concrete goals), overall they were able to comprehend the intent of the questions, with the exception of a few questions.

Of the main items that influenced the missing values figure, 'feeling constantly burned out by constant effort to manage diabetes' and 'feeling diabetes is taking up too much of your mental and physical energy' were also items that patients found difficult to comprehend. Patients also had problems with the meaning of the word 'overwhelmed' in the item 'feeling overwhelmed by your diabetes management'. It is possible that patients were uncomfortable answering the items 'feeling constantly concerned with food' and 'not accepting diabetes', hence leaving them unanswered by some patients.

Implementing the feedback from respondents on some changes to key words could improve the strength of the items. In addition, including items covering patients' worries on adapting in future roles such as marriage and work, costs associated with medicine and worries on discrimination would enrich the Zambian version of the PAID.

This study is the first to validate an African version of the PAID. The sample in this study was drawn from three provinces in Zambia, including adolescents and adults with type 1 and 2 diabetes mellitus, making the sample heterogeneous and generalisable

within the urban Zambian context. Secondly, we were able to demonstrate that participants did not employ response style bias, instead respondents were able to map responses based on the categories given in the survey and were able to comprehend the question intent.

However, the study is not without limitations. First, the sample size was relatively small and drawn from urban settings only. Second, due to the small sample size, we could not conduct a confirmatory factor analysis, which would have enabled a more rigorous comparison of different factor solutions. Therefore, future studies should work with a larger sample size and subject the Zambian version of the PAID to confirmatory factor analysis. Third, we cannot rule out the influence of social desirability in the manner participants responded to the scale. In social research, participants tend to respond to survey questions in a manner that will be viewed favourably by others.[42]

Conclusion

This study revealed good internal consistency, reliability and validity of the PAID among patients with type 1 and 2 diabetes mellitus in Zambia. Moreover, the majority of our patients demonstrated that they were able to comprehend most questions well and match their responses to the scale categories, although some items may need to be rewritten. The measure has satisfactory psychometric properties to assess individual levels of diabetes-specific distress, which qualifies it for diagnostic and clinical use, although some items may need to be clarified and simplified to enhance its comprehensibility. We found a single-factor solution to be the best approximation of the data. The existence of a single factor implies that the participants did not make a distinction between clusters of domains or complaints. Rather, diabetes seems to work as a global stressor that comes with multiple complaints.

To our knowledge, the findings in the current study are the first to highlight the use of the PAID in Zambian patients with diabetes. The study also demonstrated that diabetes-specific emotional distress is very high in Zambian patients compared to patients with diabetes in Western Europe or the USA. These results show that there should be strong pressure to further improve the quality of medical treatment of Zambian people with diabetes, and it would be particularly helpful to educate the families.

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Diabetes is often overlooked after a myocardial infarction

At least 10% of people who have a myocardial infarction (MI) may also have undiagnosed diabetes. Yet many doctors fail to look for diabetes in these patients, a recent study has found.

Dr Suzanne Arnold, assistant professor at Saint Luke's Mid-America Heart Institute and the University of Missouri in Kansas City, and her team studied data from 2 854 patients who experienced an MI and had never been diagnosed with type 2 diabetes. The study tested the patients' HbA_{1c} levels.

It revealed that doctors often failed to recognise and begin treating diabetes in patients who have experienced MIs with no prior history of diabetes, even when the patient tested positive for diabetes. The researchers found that 287 or 10.1% of the patients who experienced MIs tested positive for diabetes. Out of the 287 patients who tested positive for diabetes, less than one-third received education or medication when discharged from hospital.

According to the results, doctors failed to recognise diabetes in 198 or 69% of the previously undiagnosed patients. The researchers noted that when a patient's HbA_{1c} test results were checked while they were being treated for their MI, there was a 17-fold greater chance that the diabetes would be diagnosed.

In a press release, Dr Arnold stated, 'Diagnosing diabetes in patients who have had a heart attack is important because of the role diabetes plays in heart disease. By recognising and treating diabetes early, we may be able to prevent additional cardiovascular complications through diet, weight loss and lifestyle changes, in addition to taking medications. Another important reason to diagnose diabetes at the time of heart attack is that it can guide the treatments for the patient's coronary artery disease.'

According to Dr Arnold and her team, two in three patients with diabetes die from heart-related conditions. Patients with diabetes experience a significantly higher risk for MI. The authors concluded that people who have an MI should ask for a diabetes test if they present with other risk factors such as being overweight, having high blood pressure or a family history of diabetes.

This study was presented on 3 June at the American Heart Association's Quality of Care and Outcomes Research Scientific Sessions 2014.

http://www.diabetesincontrol.com/articles/diabetes-news/16453-diabetes-often-times-overlooked-after-heart-attack.

The metabolic syndrome among newly diagnosed non-diabetic hypertensive Nigerians: prevalence and clinical correlates

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Abstract

Background: **Hypertension is the commonest cardiovascular risk factor worldwide. Clustering of cardiovascular risk factors has been noted to increase the risk of developing type 2 diabetes mellitus and cardiovascular diseases. There are few reports on the prevalence of the metabolic syndrome among hypertensives African subjects.**

Methods: **One hundred and forty newly diagnosed hypertensive subjects and 70 apparently healthy controls were recruited consecutively for this study. Demographic and clinical parameters were assessed using a pretested data-collection form. Fasting blood glucose and fasting serum lipid levels were determined. The metabolic syndrome was defined according to NCEP ATP III. Statistical analysis was performed using SPSS 16.0. Intergroup comparisons were done using *t*-test and chi-squared tests, as appropriate.**

Results: **The hypertensive and control subjects were similar in age (55.14 ± 10.83 years vs 54.67 ± 10.89 years, $p = 0.8$) and gender distribution [females 75 (53.6%) vs males 37 (52.9%), $p = 0.3$]. The metabolic syndrome was diagnosed in 44 (31.4%) of the hypertensive subjects and 11 (15.7%) of the controls. Systolic blood pressure, body mass index and prevalence of left ventricular hypertrophy were higher among subjects with the metabolic syndrome than in those without it. Prevalence of the metabolic syndrome increased with age and was more common among female subjects.**

Conclusion: **This study shows that prevalence of the metabolic syndrome was high among newly diagnosed hypertensive subjects in Osogbo, Nigeria. It was, however, lower than that described among many Caucasian populations. Presence of the metabolic syndrome in hypertensive Nigerian subjects was closely related to and influenced by demographic and clinical factors.**

Keywords: metabolic syndrome, prevalence hypertension, Nigeria, diabetes, impaired glucose tolerance

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Introduction

Systemic hypertension affects about one billion people and accounts for about 7.1 million deaths per year worldwide.[1] It is the commonest non-communicable disease in Nigeria, with prevalence rates, according to published studies, ranging from seven to 20%.[2-4] Hypertension is commonly associated with many other cardiovascular risk factors, such as obesity, dyslipidaemia impaired glucose tolerance (or hyperglycaemia) and hyperuricaemia.[5-9]

The metabolic syndrome is defined as a clustering of components that reflects the expanding waistlines of the world's populations. Although there are different criteria for the definition of the metabolic syndrome, as recommended by the various working groups, the core components of the syndrome, which include increased waist circumference, impaired glucose tolerance, dyslipidaemia and hypertension, are commonly required by the various groups for diagnosis.[10]

Prevalence of the metabolic syndrome varies in different populations and is influenced by race, gender, differing socio-economic status, work-related activities and cultural views on body fat.[10] Reported prevalence rates in different countries vary between two and 66.9%.[10] Reports also show that prevalence of the metabolic syndrome is increasing to epidemic proportions, not only in the USA and other developed countries but also in developing nations.[10]

The clustering of cardiovascular risk factors is associated with increased risk of the development of cardiovascular diseases (CVD), such as coronary heart disease (CHD) and stroke, as well as an increase in all-cause mortality. The metabolic syndrome has been shown to predict the development of diabetes. Various studies have indicated that the presence of multiple risk factors confers greater risk than a single factor.[11-16]

In the Kuopio Ischaemic Heart Disease Risk Factor study, Finnish men without CVD were followed up for approximately 11 years and those with the metabolic syndrome were three to four times more likely to die of CHD, 2.6 to three times more likely to die of CVD and twice as likely to die from all causes.[12] The age-adjusted relative risks for CVD and CHD in men with the metabolic syndrome were 2.88 and 2.54, respectively, and 2.55 and 1.54 in women, respectively, using the Framingham database.[13] Information on the prevalence of the metabolic syndrome among Nigerian hypertensive subjects is scarce.

Methods

The metabolic syndrome was defined in this study as the presence of three or more of five cardiovascular risk factors in the patients, according to the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III). These include fasting plasma glucose concentration > 6.1 mmol/l, fasting plasma triglyceride level > 150 mg/dl (1.7 mmol/l), fasting plasma high-density

lipoprotein cholesterol (HDL-C) level for men < 1.04 mmol/l, fasting plasma HDL-C for women < 1.29 mmol/l, blood pressure ≥ 130/85 mmHg and waist circumference for men > 102 cm and for women > 88 cm.[17]

This was a cross sectional study; 140 newly diagnosed non-diabetic hypertensive subjects and 70 normotensive controls were recruited consecutively from the cardiology clinic of LAUTECH Teaching Hospital, Osogbo, Nigeria. The control subjects were patients' relatives and hospital staff who voluntarily gave their consent to participate in the study. The hypertensive subjects and controls were well matched in age and gender distribution.

Hypertension was diagnosed as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg taken twice after at least five minutes of rest at the clinic, according to standardised criteria. Subjects with mild hypertension were asked to return after two weeks for confirmation. Those with moderate and severe hypertension (JNC 7 stage 2) were recruited for the study immediately. Patients with chronic kidney disease, known diabetics, clinical evidence suggestive of CHD and pregnant patients were excluded from the study.

Clinical and demographic data were taken using a structured data form. Laboratory analyses performed included fasting plasma glucose concentrations, urinalysis, ultrasound, and fasting serum plasma lipid, electrolyte, urea and creatinine levels. All subjects had 12-lead resting electrocardiography.

Patients and controls were recruited after an informed consent. Ethical approval was obtained for the study from the ethics board of LAUTECH Teaching Hospital, Osogbo, Nigeria.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences 16.0. Quantitative variables are summarised as means ± standard deviation while qualitative data are summarised using proportions and percentages. Inter-group comparison was done using the *t*-test and chi-squared test as appropriate; $p < 0.05$ was taken as statistically significant.

Results

One hundred and forty hypertensive subjects and 70 controls were recruited for this study. The mean age of the patients and controls were 55.14 ± 10.83 years (age range 23–82 years) and 54.67 ± 10.89 years (age range 35–75 years), respectively. There was no statistically significant difference between the mean ages of the subjects and controls ($p > 0.05$).

Table 1. Clinical and demographic parameters of the study participants

Parameters	Hypertensives ($n = 140$)	Controls ($n = 70$)	*p*-value
Age (years)	55.14 ± 10.83	54.67 ± 10.89	> 0.05
#Female gender, *n* (%)	75 (53.6)	37(52.9)	> 0.05
#Family history of DM	5	7	> 0.05
Mean WC (cm)			
Male	92.5 ± 13.4	84.0 ± 7.3	< 0.005*
Female	94.3 ± 11.5	84.6 ± 10.7	< 0.005*
Mean HC (cm)	100.15 ± 11.63	92.79 ± 9.92	> 0.05
Mean WHR	0.94 ± 0.082	0.91 ± 0.054	> 0.05
Mean BMI (kg/m^2)	26.89 ± 5.31	23.86 ± 3.46	> 0.05
Mean SBP (mmHg)	147.18 ± 26.47	115.06 ± 13.11	< 0.005*
Mean DBP (mmHg)	89.25 ± 17.04	70.96 ± 9.67	< 0.005*
Mean PP (mmHg)	57.93 ± 24.38	44.75 ± 10.25	< 0.005*

DM, diabetes mellitus; WC, waist circumference; HC, hip circumference; WHR, waist–hip ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. *Statistically significant.

Table 2. Biochemical parameters of the study population

Parameter	Hypertensives ($n = 140$)	Controls ($n = 70$)	*p*-value
Mean sodium (mmol/l)	135.9± 4.7	133.7 ± 2.4	> 0.05
Mean potassium (mmol/l)	3.8 ± 0.5	3.1 ± 0.4	< 0.05*
Mean urea (mmol/l)	5.8 ± 2.2	3.2 ± 1.7	> 0.05
Mean creatinine (µmol/l)	84.2 ± 12.6	68.4 ± 10.8	> 0.05
Mean FBS (mmol/l)	5.6 ± 1.9	4.0 ± 1.3	< 0.005*
Mean LDL-C (mmol/l)	2.49 ± 1.41	2.35 ± 0.63	> 0.05
Mean HDL-C (mmol/l)	1.06 ± 0.36	1.29 ± 0.46	< 0.05*
Mean TG (mmol/l)	1.33 ± 0.59	1.18 ± 0.41	> 0.05
Mean TC (mmol/l)	4.84 ± 1.69	4.23 ± 1.29	> 0.05

FBS, fasting blood sugar; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol. *Statistically significant.

The demographic and clinical parameters of the study participants are as shown in Table 1. When compared with control subjects, the hypertensive subjects had a higher mean systolic blood pressure (147.18 ± 26.47 vs 115.06 ± 13.11 mmHg, $p < 0.005$), diastolic blood pressure (89.25 ± 17.04 vs 70.96 ± 9.67 mmHg, $p < 0.005$), pulse pressure (57.93 ± 24.38 vs 44.75 ± 10.25 mmHg) and fasting plasma glucose level (5.6 ± 1.9 vs 4.0 ± 1.3 mmol/l, $p < 0.005$), although the mean fasting plasma glucose levels were both within normal limits. Also, the waist circumference of the hypertensive subjects was significantly higher compared with the controls (93.89 ± 11.96 vs 83.82 ± 9.0 cm, $p < 0.05$).

Table 2 shows the biochemical profile of the study population. The hypertensive subjects had significantly higher mean fasting plasma glucose levels (5.6 ± 1.9 vs 4.0 ± 1.3 mmol/l, $p < 0.05$). The lipid profile analysis of the study population is also as shown in Table 2. Hypertensive subjects had a significantly lower HDL-C compared to control subjects (1.06 ± 0.36 vs 1.29 ± 0.46 mmol/l, $p < 0.05$). Although mean total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels were higher among the hypertensive subjects than the controls, they were not statistically significantly different.

Hypertensive subjects with the metabolic syndrome were older and were more likely to be female than those without the metabolic syndrome. They also had a higher body mass index, systolic blood pressure, fasting plasma glucose level and increased prevalence of left ventricular hypertrophy, as shown in Table 3.

As seen in Table 4, hypertension combined with obesity and low HDL-C level was the commonest pattern of combination of cardiovascular risk factors among the hypertensive subjects, followed by a combination of hypertension, obesity and impaired glucose tolerance.

Discussion

The frequency of occurrence of the metabolic syndrome in this study was 31.4% in the hypertensive subjects compared to 15.7% in the control group. A similar report by Okpechi *et al*.[18] among black hypertensives in South Africa documented a frequency of occurrence of 33.5%. Therefore, about a third of newly diagnosed

Table 3. Clinical characteristics of hypertensive subjects with and without the metabolic syndrome

Parameter	Hypertensives with MetS (*n* = 44)	Hypertensives without MetS (*n* = 96)	*p*-value
Age (years)	57.22 ± 9.65	53.52 ± 10.58	< 0.05*
Gender, *n* (%)	38 (27.1)	39 (27.9)	< 0.05*
Mean BMI (kg/m^2)	30.15 ± 5.27	24.14 ± 4.10	< 0.005*
Mean SBP (mmHg)	141.36 ± 23.66	130.16 ± 29.50	< 0.05*
Mean DBP (mmHg)	86.17 ± 18.19	80.97 ± 17.54	> 0.05
Hypertensives with LVH	39 (70.9 %)	56 (65.9 %)	< 0.05*
Mean QTc (msec)	0.42 ± 0.03	0.41 ± 0.03	< 0.05*
FBS (mmol/l)	4.7 ±1.6	5.6 ± 1.2	< 0.05*

MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy. *Statistically significant.

subjects with hypertension already have at least two other major cardiovascular risk factors, and are already at increased risk of developing cardiovascular events. It is also more likely that many other cardiovascular risk factors may soon appear in these patients as time goes on.[6,10] Therefore, newly diagnosed subjects with hypertension should be adequately screened for other cardiovascular risk factors so as to reduce the burden of cardiovascular disease in the population.

The prevalence of the metabolic syndrome among hypertensive subjects in our study was however lower than that reported among Caucasians. A report from Spain shows that 52% of a hypertensive cohort fulfilled the NCEP ATP III criteria for diagnosing the metabolic syndrome.[19] Some authors have linked race with the frequency of occurrence of the metabolic syndrome and suggested that African blacks are at lower risk than whites and Indians.[20]

It has been suggested that black Africans have lower serum lipoprotein and apolipoprotein levels than their Caucasian counterparts.[21] Blacks have also been reported to have a lower blood total cholesterol level when compared to whites and a comparably higher level of HDL-C, especially among females. This was thought to be due to the dietary pattern among blacks, which is particularly related to low dietary fat intake, especially among Nigerians.[21] This and possible genetic reasons may be responsible for the difference in frequency of occurrence of cardiovascular risk factor clustering among black and Caucasian subjects.[10,22]

Hypertension has been closely associated with many other cardiovascular risk factors. This clustering increases the risk of cardiovascular events for these groups of patients.[22-24] A possible reason for the increased frequency of clustering of cardiovascular risk factors among hypertensive subjects has been suggested to be due to similar pathogenic pathways underlying the clustered risk factors.[25,26] These include insulin resistance, hyperinsulinaemia, inflammation and hyperadrenergic state.

Table 4. Pattern of combination of risk factors among subjects with the metabolic syndrome

Combination of risk factors	Number (%)
Hypertension + obesity + low HDL-C	29 (20.7)
Hypertension + obesity + IFG	5 (3.6)
Hypertension + obesity + hypertriglyceridaemia	3 (2.1)
Hypertension + low HDL-C + hypertriglyceridaemia	2 (1.4)
Hypertension + low HDL-C + IFG	2 (1.4)
Hypertension + hypertriglyceridaemia + IFG	1 (0.7)
Hypertension + hypertriglyceridaemia + IFG	1 (0.7)
Hypertension + obesity + low HDL-C + hypertriglyceridaemia + IFG	1 (0.7)

HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose.

Hypertensive subjects with the metabolic syndrome were significantly older than their counterparts without the metabolic syndrome. There were more female than male hypertensives with the metabolic syndrome. Several studies have documented increased prevalence as age increases, and more so among females.[27-31] However, reports are not consistent as other reviews have found marginal increase in prevalence among males.[27] These gender-related differences may be due to differing work-related activities, and cultural views on body fat and work-related activities. The increasing prevalence of the metabolic syndrome may not be implausible, since many of its components increase in prevalence with age.

Hypertensives with the metabolic syndrome seem to have a greater degree of target-organ damage, as indicated by increased prevalence of left ventricular hypertrophy and cardiomegaly. Left ventricular hypertrophy is an important pointer to cardiovascular risk and morbidity. Apart from this, hypertensive subjects with the metabolic syndrome also had a higher QTc interval, body mass index and systolic blood pressure than those without the metabolic syndrome. QTc prolongation is a non-invasive marker for the development of arrhythmias and sudden cardiac death.

The combination of hypertension, obesity and low HDL-C levels was the commonest pattern among hypertensive subjects with the metabolic syndrome, followed by the combination of hypertension, obesity and impaired fasting plasma glucose levels. Hypertensives with the metabolic syndrome had higher fasting plasma glucose levels than those without the metabolic syndrome. Impaired fasting plasma glucose levels have been associated with an increased likelihood of developing diabetes mellitus. These hypertensive subjects therefore require intensive cardiovascular evaluation and care to reverse the increased tendency towards the development of diabetes and cardiovascular diseases.

As Africa undergoes an epidemiological transition, the inevitable increase in prevalence of the metabolic syndrome would have important implications with regard to the potential rise in the incidence of ischaemic heart disease and diabetes. Available evidence suggests that the prevalence of cardiovascular disease among Nigerians is increasing.[32-34] Therefore it is important to identify high-risk individuals for target therapy to reduce the overall cardiovascular disease prevalence.

Conclusion

This study shows that prevalence of the metabolic syndrome among newly diagnosed hypertensive subjects is high and is influenced by demographic and clinical factors such as age, gender, systolic blood pressure and body mass index. These observations raise major clinical and public health concerns, which include an inevitable increase in the prevalence of cardiovascular diseases due to the increasing frequency of hypertension and other cardiovascular risk factors in the population.

The cost of management of cardiovascular disease is enormous, which imposes a serious economic burden, especially on developing countries. As urbanisation and westernisation increase, the clustering

of cardiovascular risk factors is likely to be more widespread due to the expected increase in the prevalence of high blood pressure. The potential economic impact would be huge, therefore measures for lifestyle modification, which have the potential to reduce incidence of cardiovascular disease, arising from the epidemic of obesity and the metabolic syndrome, need to be reinforced.

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Study of the effect of altitude on the measurement of glycated haemoglobin using point-of-care instruments

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Abstract

We measured the glycated haemoglobin (HbA_{1c}) levels of a total of 24 non-diabetic volunteers and diabetic patients using a point-of-care (POC) analyser in three Cameroonian cities at different altitudes. Although 12 to 25% of duplicates had more than 0.5% (8 mmol/mol) difference across the sites, HbA_{1c} values correlated significantly (r = 0.89–0.96). Further calibration studies against gold-standard measures are warranted.

Keywords: glycated haemoglobin, altitude, diabetes

Introduction

HbA_{1c} concentration is used for the appropriate diagnosis and management of diabetes,[1,2] but the standard way of measurement requires an expensive and time-consuming ion-exchange, high-performance liquid chromatography (HPLC) technology. Point-of-care (POC) instruments represent a cheaper alternative to determine HbA_{1c} levels in five to 10 minutes. They can be used by non-laboratory staff to tailor a patient's care and educational messages to HbA_{1c} values and clinical findings in a one-stop-shop approach.[3,4] Their potential shortcomings include cases of haemoglobinopathy or some environmentally linked limitations.[5,6]

While operating temperature and humidity are easily controlled, altitude cannot be standardised for operation. We investigated the performance of one of the most commonly used POC HbA_{1c} instruments in African clinical settings, situated at varying altitudes.

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Methods

In this cross-sectional study, HbA_{1c} concentrations were measured in three cities of Cameroon in blood samples simultaneously collected from the same individuals. The study settings were Douala (13-m altitude), Yaounde (650-m altitude), and Bamenda (1 600-m altitude).

The study was approved by the National Ethics Committee of Cameroon. All participants gave their informed consent.

The study participants were 24 volunteers distributed in four groups: six non-diabetic (healthy) volunteers [no clinical symptoms, fasting glycaemia < 1.26 g/dl (6.99 mmol/l) and HbA_{1c} levels < 6.6% (< 49 mmol/mol)], six patients with diabetes with HbA_{1c} levels < 6.6% (< 49 mmol/mol), six patients with HbA_{1c} levels at 6.6–8.0% (49–64 mmol/mol) and six patients with HbA_{1c} levels > 8.0% (> 64 mmol/mol).

All patients had to have had diabetes for at least one year, with stable treatment and HbA_{1c} values over at least three months preceding the study defined by HbA_{1c} variation < 1% between two measurements. Exclusion criteria included any haemoglobinopathy, recent malaria, haematological disorder or any other acute medical condition in the preceding month, total haemoglobin level > 11 g/dl, and creatinine clearance < 60 ml/min.

Volunteers were invited, and after informed consent, we conducted an interview, clinical examination and biochemical investigations for the ascertainment of eligibility. Collections of venous blood in eligible participants were all done the same day from an antecubital vein in four EDTA tubes stored in refrigerated containers for all three assays.

The blood samples collected on the same day for each participant were immediately transported by car to the target settings in a refrigerated container. The room temperature was standardised for all study sites at 25°C, and humidity was maintained between 45 and 60%.

HbA_{1c} measurements were performed using the In2it POC device (Bio-Rad laboratories, Deeside, UK), which was calibrated prior to the study, with all reagents from the same lot (072T128). The same operator performed the assays in each of the settings within 48 hours of blood collection. All manipulations were done following the operating procedure of the manufacturer in order to reduce the variability of the measurements.

Statistical analysis

Using SPSS 17.0, data were analysed and expressed as mean ± standard deviation. Comparisons across the groups were done using analysis of variance, and associations were verified by Spearman's correlation. Agreement between methods was assessed using Bland and Altman plots of the difference against the means of the two methods.

Results

Participants were 12 males and 12 females, aged 54 ± 15 years. Their mean body mass index was 28.9 ± 5.8 kg/m^2, mean systolic and diastolic blood pressures were 128 ± 18 and 77 ± 8 mmHg, respectively, and mean haemoglobin was 13.4 ± 1.8 g/dl. The duration of diabetes in all patients was 10 ± 6 years with a pre-inclusion HbA_{1c} value of 7.8 ± 2.3%.

Overall, there was no statistically significant difference between mean HbA_{1c} measurements across the sites (Table 1). The correlation between measurements varied from $r = 0.89$, $p < 0.001$ between the 650-m/1 600-m altitudes, $r = 0.92$, $p < 0.001$ between the 13-m/650-m altitudes, to $r = 0.96$, $p < 0.001$ between 13-m/1 600-m altitudes. The coefficient of variation (CV) was 3.4% for the 650-m/13-m duplicates, 5.1% for 1 600-m/13-m duplicates and 3.2% for 1 600-m/650-m duplicates.

The mean differences expressed as estimates (95% CI) in percentages between measurements at two different sites were –0.04 (–1.05–0.97%), +0.14 (0.95–1.24%) and +0.13 (–0.45–0.70%), respectively, between the 650-m/13-m (Fig. 1A), 1 600-m/650-m (Fig. 1B), and 1 600-m/13-m altitudes (Fig. 1C).

The HbA_{1c} differences were > 0.5% (8 mmol/mol) in 3/24 (12%) between the 1 600-m/13-m measurements, 4/24 (17%) between the 650-m/13-m measurements and in 6/24 (25%) between the 1 600-m/650-m measurements. In only one case associated with more than one percentage difference across sites was a patient with one of the readings at 4.2% (22 mmol/mol) in one site, which normally would have prompted a second check. We did not find any differences in the percentage variation of HbA_{1c} levels at the low ($n = 12$), medium ($n = 6$) and high ($n = 6$) values for the different study sites, namely 650-m/13-m ($p = 0.453$), 1 600-m/650-m ($p = 0.111$) and 1 600-m/13-m altitudes ($p = 0.344$).

Table 1. Comparison of mean HbA_{1c} levels by group across the sites

Study group	Point-of-care In2it analyser			
	Douala (13 m)	Yaounde (650 m)	Bamenda (1 600 m)	*p*-value
Healthy controls Patients with diabetes	5.0 ± 0.6	5.4 ± 0.3	5.6 ± 0.5	0.15
HbA_{1c} < 6.5% (< 49 mmol/mol)	5.9 ± 0.6	5.7 ± 0.6	5.9 ± 0.4	0.29
HbA_{1c} 6.5–8.0% (49–64 mmol/mol)	8.1 ± 3.0	7.9 ± 3.1	8.0 ± 3.0	0.66
HbA_{1c} > 8.0% (> 64 mmol/mol)	8.4 ± 1.8	8.5 ± 1.7	9.0 ± 2.2	0.84
All study participants	6.8 ± 2.2	6.9 ± 2.2	7.1 ± 2.3	0.31

Discussion

This study indicates that the POC analyser showed no significant differences across Cameroonian sites located at altitudes varying from 13 to 1 600 m (≤ 0.5% in 75% of comparisons). Although measurements were not repeated in each site to reflect clinical practice, our results suggest a test reliability of the In2it POC instrument below 1 600 m.

Interestingly, previous studies in which the device calibration was performed with HPLC, had suggested satisfactory external validity.[7] This was however not investigated in our study and therefore represents a major limitation with the sample size.

However, considering our findings and the cut-off value of 3.5% of CV for optimal performance between laboratories (between study sites in our case), one could say that although no significant difference was observed between HbA_{1c} levels at the three altitudes, the POC apparatus had a relatively high variability between 13 and 1 600 m.[8] As expected, this variability was higher in low and normal HbA_{1c} levels (not shown).

In this regard, the use of the POC HbA_{1c} analyser could be more indicated for the monitoring of patients with a view to comparing

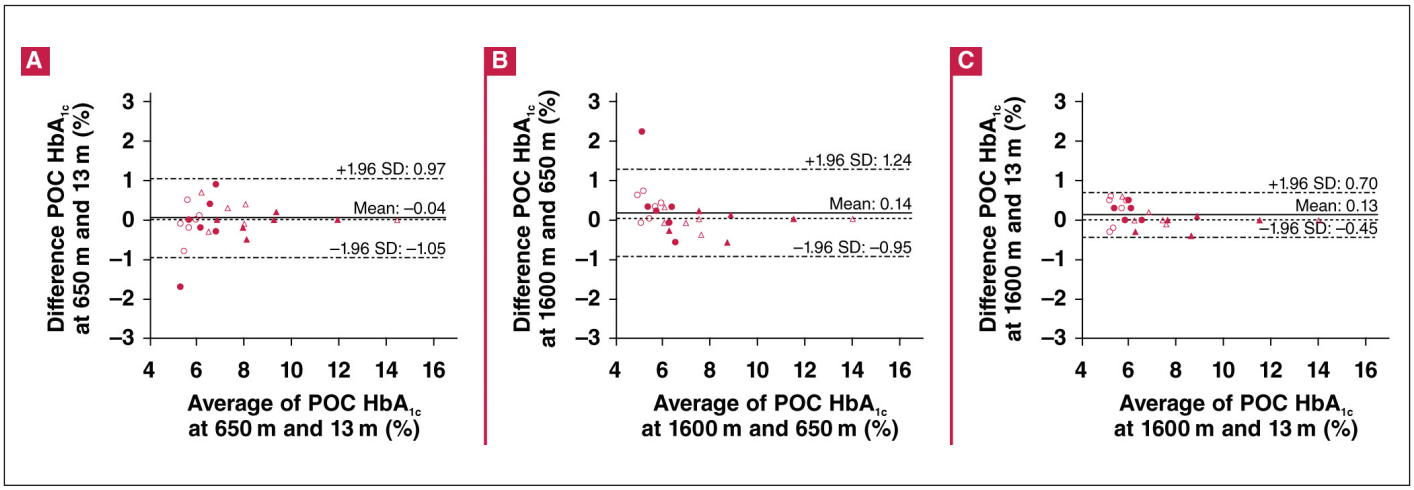

Figure 1. Plots of the differences against averages of POC HbA_{1c} levels at 13-m and 650-m altitudes (A), 1 600-m and 650-m altitudes (B), and a1 600-m and 13-m altitudes (C), with mean difference (bias) and 95% agreement limits.

before- and after-treatment glucose control, especially in the lower values, even in the absence of calibration with an HPLC machine.

Consistent with our results, a recent study of HbA_{1c} variations in Chinese populations living at different altitudes did not find meaningful variations in the HbA_{1c} levels and the estimated average glucose levels of patients living in different sites.[9]

However, on the one hand, Ju *et al*.[9] in their study used the immunoturbidimetric method for the measurement of HbA_{1c} levels (also without validation against the gold standard for HbA_{1c} measurement), while we used a baronate affinity chromatography to separate glycated from non-glycated haemoglobin for photometry.[4,9] On the other hand, we sought to evaluate the possible effect of altitude on the accuracy of a POC HbA_{1c} analyser in patients with diabetes, while they aimed to evaluate whether altitude could modify the glycation of HbA_{1c}.

In our study, we observed that 12–25% of duplicates had more than a 0.5% (8 mmol/mol) difference across the sites. The performance of POC apparatus in general and the In2it in particular has (independent of altitude) been assessed before. These investigations constituted a body of evidence showing the need for improvement in the performance of devices for optimal care.[10-12]

The recent performance of these devices has given promising results. This also was the case where the In2it apparatus is concerned, despite the between-batch variability of results, which still needs to be addressed.[7,13] To circumvent this in our study, we used reagents from the same lot number at all study sites. However, in daily clinical practice, this could indeed be a concern for patients' follow up.

With the generalisation of HbA_{1c} use, especially in developing countries that have limited access to an HPLC and have a wide variety of physical environments, it is important to know which parameters should be taken into account when validating POC HbA_{1c} devices, which are commonly presented as the adequate alternative to estimate glycaemic control of patients.

Conclusion

Our results reinforce the need for calibration of POC instruments against the HPLC in each setting used, to ensure validity of the readings. We did not find any significant differences when measuring HbA_{1c} levels at different altitudes on the same samples. However this requires validation with further studies, using larger sample sizes and addressing situations with higher proportions of patients with haematological disorders.

Acknowledgements

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Short-term outcomes after hospital discharge in patients admitted with heart failure in Abeokuta, Nigeria: data from the Abeokuta Heart Failure Registry

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Abstract

Background: **Compared to other regions of the world, there is a paucity of data on the short-term outcome of acute heart failure (AHF) in Africa's most populous country, Nigeria. We examined the six-month outcomes (including case fatality) in 285 of 309 AHF subjects admitted with HF to a tertiary hospital in Abeokuta, Nigeria.**

Methods: **The study cohort of 285 subjects comprised 150 men (52.6%) and 135 women (47.4%) with a mean age of 56.3 ± 15.6 years and the majority in NYHA class III (75%).**

Results: **There were a number of differences according to the subject's gender; men being older and more likely to present with hypertensive heart disease (with greater left ventricular mass) while also have greater systolic dysfunction. Mean length of stay was 10.5 ± 5.9 days. Mean follow up was 205 days, with 23 deaths and 20 lost to follow up. At 30 days, 4.2% (95% CI: 2.4–7.3%) had died and by 180 days this had increased to 7.5% (95% CI: 4.7–11.2%); with those subjects with pericardial disease demonstrating the highest initial mortality rate. Over the same period, 13.9% of the cohort was re-admitted at least once.**

Conclusions: **The characteristics of this AHF cohort in Nigeria were different from those reported in high-income countries. Cases were relatively younger and presented with non-ischaemic aetiological risk factors for HF, especially hypertensive heart disease. Moreover, mortality and re-admission rates were relatively lower, suggesting region-specific strategies are required to improve health outcomes.**

Keywords: heart failure, mortality, outcome, Abeokuta, Nigeria

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Introduction

Heart failure (HF) has emerged as a global epidemic in at-risk populations, including those living in high-income countries and, as recently described, in low- to middle-income regions of the world, such as sub-Saharan Africa.[1-4] While there are well-established HF registries to capture both the characteristics and health outcomes among those hospitalised with AHF in Europe,[5,6] North America,[7,8] and the Asia–Pacific region,[3,9,10] there are few reports from sub-Saharan Africa.[11] This includes Nigeria (the most populous country in the region), where HF has emerged as a potentially large public health problem.[1]

Although there have been many therapeutic gains in the management of chronic HF,[12] leading to improved overall survival rates,[13] there has been very little parallel success (pending further evaluation of the recently reported RELAX trial[14] with regard to AHF). This is particularly important when one considers the high proportion of patients who still require hospitalisation for acute HF, and associated high levels of in-patient case fatality and poor short- to medium-term health outcomes.

Given the paucity of data describing health outcomes in unselected patients hospitalised with AHF in Nigeria (and indeed the wider sub-Saharan Africa), we examined short- (30 days) to medium-term outcomes (180 days) in consecutive subjects with AHF recruited into the Abeokuta HF registry over a period of six months. Standardised data collected via the registry were used to both describe the baseline characteristics of the cohort and identify correlates of mortality during the six-month follow up.

Methods

The Abeokuta HF registry was a hospital-based, single-centre, prospective, observational study that consecutively recruited 285 subjects with de novo AHF and 24 cases of decompensated HF (acute-on-chronic HF), all admitted during the period 1 January 2009 to 31 December 2010. The 24 cases of decompensated HF were excluded from the final analysis.

The main objective of the registry was to characterise the current profile of HF in the community. It was also aimed at determining the mode of care as well as intra-hospital and six-month outcomes.

Clinical information relating to the socio-demography, medical history, signs and symptoms, medications, results of laboratory investigations, including 12-lead ECG and echocardiography, were collected. A standardised case report form was used for data collection. Home addresses and telephone contacts of the subjects as well as their next of kin were also recorded.

Subjects were weighed without shoes and in light clothing using a standard beam balance. An anthropometric plane was used for height measurement to the nearest centimetre. Body mass index (BMI) was calculated using the standard formula. Blood pressure measurements were done according to international guidelines,[15] with the use of a mercury sphygmomanometer (Accousson, London).

We defined anaemia as haematocrit of less than 10 g/dl. The modification of diet in renal disease (MDRD) formula was used for the estimation of glomerular filtration rate (GFR).[16] An estimated GFR (eGFR) of less than 60 ml/min/1.73 m^2 was the criterion used for defining renal dysfunction.[4]

A clinical diagnosis of HF was based on the Framingham criteria.[17] Using the recent guidelines of the European Society of Cardiology,[18] subjects were categorised into de novo presentation, as well as recurrent presentation of typically decompensated HF (i.e. acute-on-chronic HF).

Standard 12-lead resting ECGs were recorded for each patient using a Schiller ECG machine (Schiller AG, Switzerland). All the 12-lead resting ECGs were performed by trained nurses/technicians and analysed by a reviewer who was blinded to the clinical data of the patients.

Echocardiography was performed on the subjects with the use of an Aloka SSD – 4000 echocardiography (Aloka Co Ltd, Tokyo, Japan). Standard views and two-dimensional guided M-mode measurements were obtained according to international guidelines. Aortic root and left atrial diameter, left ventricular (LV) internal dimensions and wall thicknesses were obtained according to the American Society of Echocardiography (ASE) criteria. Measurements were obtained in up to three cycles and averaged. One experienced cardiologist (OSO) performed all the procedures.

In our laboratory, the intra-observer concordance correlation coefficient and measurement errors have been reported.[19] The Devereux and Recheck formula was used for LV mass calculation.[20] Increased relative wall thickness (RWT) was defined as RWT > 0.43.[21]

Impaired LV systolic function was defined as LV ejection fraction of < 50%. Transmitral flow velocities, deceleration time and isovolumic relation time were obtained using standard methods.[22] Tissue Doppler imaging (TDI) was applied only to identify true pseudo-normalised filling pattern.

The cohort was prospectively followed up for six months. The mean follow-up period was 205 days. Subjects were contacted via clinic visits or telephone calls at one month, three months and six months. Follow-up data included their wellbeing, medications, history of rehospitalisation and deaths (from next of kin). In addition to patient or relative telephone interviews, where necessary, referring physicians were contacted for additional information. Fig. 1 is a flow chart showing the recruitment and follow up of the study cohort.

Table 1. Demographic and clinical profile characteristics of the cohort.

Variable	All (*n* = 285)	Men (*n* = 150)	Women (*n* = 135)	*p*-value
Socio-demographic variables				
Age (years)	60.0 ± 13.2	57.0 (13.6)	55.6 (17.3)	0.382
Age > 60 years (%)	46.3	48.7	43.7	0.425
No education	98 (34.4)	39 (26.0)	59 (43.7)	0.028
Married (%)	156 (67.8)	92 (73.0)	64 (61.0)	0.014
Unemployed	7 (2.3)	1 (0.6)	6 (4.2)	0.007
Urban residence	216 (75.8)	113 (75.3)	103 (76.5)	0.389
Risk factors and co-morbidities				
Never smoked cigarettes	233 (81.8)	103 (68.7)	103 (96.3)	< 0.001
Current alcohol use	17 (6.0)	14 (9.3)	3 (2.2)	< 0.001
Diabetes mellitus	37 (13.0)	19 (12.7)	18 (13.3)	0.735
Hypertension	232 (81.4)	128 (85.3)	134 (77)	0.103
COPD	20 (7.0)	11 (7.3)	9 (6.7)	0.923
Family history of heart disease	25 (8.8)	9 (6.0)	16 (11.9)	0.240
Clinical/laboratory parameters				
NYHA class				
Class II	24 (8.4)	16 (10.7)	8 (5.9)	0.212
Class III	215 (75.4)	107 (71.3)	108 (80.0)	
Class IV	46 (16.1)	27 (18.0)	19 (14.1)	
BMI (kg/m^2)	25.2 ± 5.7	24.1 (5.0)	23.7 (5.5)	0.527
Systolic BP (mmHg)	131.9 ± 25.1	137.9 (30.0)	133.3 (27.9)	0.253
Diastolic BP (mmHg)	85.4 ± 15.9	89.0 (19.6)	85.3 (17.1)	0.156
Pulse pressure (mmHg)	46.5 ± 15.7	49.0 (19.0)	47.7 (16.6)	0.527
Respiratory rate (cycles/min)	30.2 ± 6.5	28.5 ± 6.4	27.9 ± 6.7	0.541
Pulse rate (bpm)	95.9 ± 16.7	96.2 ± 18.2	96.3 ± 17.8	0.527
Packed cell volume (%)	35.9 ± 7.8	37.5 ± 7.2	36.8 ± 7.7	0.541
Total white blood cell count (×109 cells/l)	6.4 ± 2.9	7.3 ± 3.7	7.4 ± 3.8	0.933
Serum sodium (mmol/l)	136.5 ± 6.4	135.9 ± 6.7	136.3 ± 6.1	0.134
Serum potassium (mmol/l)	3.7 ± 0.8	3.7 ± 0.8	3.6 ± 0.8	0.461
Total cholesterol (mg/dl)	162.5 ± 53.3	157.7 ± 84.0	181.2 ± 64.6	0.213
Serum glucose (mg/dl)	111.7 ± 53.2	115.6 ± 50.6	114.0 ± 58.5	0.845
Serum urea (mg/dl)*	38.5 ± 30.0	50.5 ± 51.4	36.1 ± 29.7	0.020
Serum creatinine (mg/dl)*	1.8 ± 0.4	1.7 ± 2.5	1.2 ± 1.4	0.093

COPD = chronic obstructive pulmonary disease.

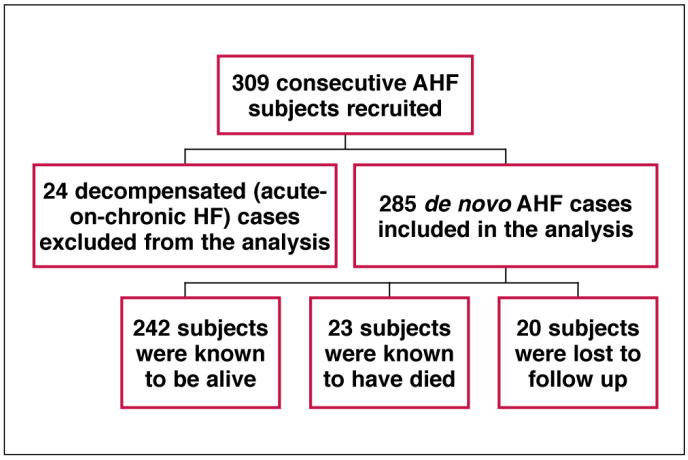

Figure 1. Flow chart showing the recruitment of the subjects.

We examined (1) length of hospital stay (LoS), (2) Survival status on discharge (dead or alive), (3) short-term case fatality/re-admission (30 days), (4) medium-term case fatality (within 180 days), (5) rehospitalisation status (within 180 days), and (6) event-free survival from re-admission or death.

The study was reviewed and approved by the institution's ethics review board. All the subjects gave informed consent and the study was carried out in accordance with the Declaration of Helsinki.[23]

Statistical analysis

Data were entered into EpiData software. The EpiData association (att. Jens Lauritsen, Enghavevej 34, DK5230 Odense M, Denmark) was used for data entry, while SPSS version 15 and Stata version 11.1 were used for data cleaning and analysis. Continuous variables are presented as means and standard deviations (SDs), or medians with their 25th and 75th percentiles when the distribution of the data did not follow Gaussian distribution.

Categorical variables are displayed as frequencies and proportions. Group comparison was done with the Student's *t*-test, and chi-square statistics was used for comparison of categorical variables. Survival function estimates were performed using the Kaplan–Meier method and the difference was tested using the log-rank test. The follow up was censored at six months post admission.

Predictors of survival were determined using univariate regression analyses. Thereafter multiple logistic regression analysis was performed to identify independent predictors of survivals ($p < 0.1$ used for selection of variables).

Results are expressed as odds ratio (OR) with their 95% confidence intervals (95% CI). Odds ratios that were significantly greater than 1.00 implied that subject with that attribute had higher risks of death compared to subjects who did not. A *p*-value of < 0.05 was taken as significant.

Table 2. Aetiology of HF and discharge medications in the 285 subjects.

Variable	All (*n* = 285)	Men (*n* = 150)	Women (*n* = 135)
Aetiology of HF, *n* (%)			
Hypertension	216 (75.8)	119 (79.3)	97 (71.9)
Dilated cardiomyopathy	24 (8.4)	16 (10.7)	8 (5.9)
Cor pulmonale	16 (5.6)	9 (6.0)	7 (5.2)
Pericardial diseases	9 (3.2)	1 (0.7)	8 (5.9)
Rheumatic heart disease	7 (2.5)	4 (2.7)	3 (2.2)
Peripartum cardiomyopathy	6 (2.1)	0 (0.0)	6 (4.4)
Thyroid heart disease	3 (1.1)	0 (0.6)	3 (2.2)
Ischaemic heart disease	1 (0.4)	1 (0.7)	0 (0.0)
Adult congenital heart disease	1 (0.4)	0 (0.0)	1 (0.7)
Endomyocardial fibrosis	2 (6.7)	0 (0.0)	2 (0.7)
Type of heart failure			
Systolic heart failure (%)	66.4	71.4	60.9
Heart failure with normal EF (%)	33.6	28.6	39.1
Medications, n (%)			
Loop diuretics	249 (87.4)	132 (88.0)	117 (86.7)
Digoxin	219 (76.8)	114 (76.0)	105 (77.8)
ACE inhibitors/ARBs	281 (98.6)	148 (98.7)	133 (98.5)
Beta-blockers	56 (19.6)	35 (23.3)	21 (15.6)
Spironolactone	247 (86.7)	133 (87.3)	116 (85.9)
Hydrallazine–isosorbide	33 (11.7)	19 (12.9)	14 (10.4)
Amiodarone	5 (1.8)	4 (2.7)	1 (0.7)

Results

Overall, there were 150 men (52.6%) and 135 (47.4%) women (Table 1). The mean age was 56.3 ± 15.6 years (57.0 ± 13.6 and 55.4 ± 17.6 years for men and women, respectively) with 46% aged ≥ 60 years. Around one-third had no formal education, two-thirds were married and most (75.8%) were urban residents. The majority of the subjects were in NHYA class III (75.4%).

The women were more likely not to have had formal education (43.7 vs 26.0%, $p = 0.029$), more likely not to be a smoker (96.3 vs 68.7%, $p < 0.001$), and less likely to be a current alcohol user (2.2 vs 9.3%, $p < 0.001$). Alternatively, men had higher rates of hypertension (85.3 vs 77.0%) and chronic obstructive pulmonary disease (COPD) (7.3 vs 6.7%).

Table 2 shows the laboratory profile, aetiological risk factors and discharge medications. Serum urea and creatinine concentrations were significantly higher in men than women.

Except for peripartum cardiomyopathy (PPCM), the aetiological risk factors were similar in men and women. Hypertensive heart disease was found in 75.8% of patients, dilated cardiomyopathy in 8.4%, cor-pulmonale in 5.6%, pericardial diseases in 3.2% and rheumatic heart disease in 2.5%. PPCM, thyroid heart disease, coronary artery disease and endomyocardial fibrosis were found in 2.1, 1.1, 0.4, 0.4 and 0.7% of patients, respectively.

The discharge medications were similar in men and women except for beta-blockers, which were prescribed more in men.

Table 3 depicts the 12-lead ECG and echocardiographic

Table 3. Twelve-lead ECG and echocardiographic profile according to gender.

Variable	All (*n* = 285)	Men (*n* = 150)	Women (*n* = 135)	*p*-value
Ventricular rate (bpm)	96.3 ± 22.5	94.3 ± 17.3	101.3 ± 21.8	0.110
QRS duration (ms)	116.0 ± 26.2	117.1 ± 24.5	107.8 ± 41.1	0.213
QT interval (ms)	350.7 ± 30.6	374.3 ± 35.0	348.8 ± 45.5	0.006
Corrected QT (ms)	442.0 ± 20.9	462.2 ± 38.2	447.6 ± 36.2	0.085
Atrial fibrillation (%)	13.3	16.7	9.6	0.337
Aortic root diameter (cm)	3.2 ± 0.6	3.26 ± 0.58	2.84 ± 0.38	< 0.001
Left atrial diameter (cm)	5.9 ± 0.8	4.75 ± 0.89	4.50 ± 0.85	0.176
Left atrial area (cm^2)	30.15 ± 9.91	28.8 ± 9.0	24.7 ± 6.3	0.010
IVSD (cm)	1.18 ± 0.28	1.33 ± 0.39	1.23 ± 0.32	0.393
LVPWd (cm)	1.38 ± 0.35	1.19 ± 0.39	1.10 ± 0.35	0.116
LVIDd (cm)	5.52 ± 0.97	5.81 ± 1.61	5.16 ± 1.45	0.353
LVIDs (cm)	4.51 ± 1.57	4.80 ± 1.63	4.16 ± 1.43	0.001
Fractional shortening (%)	14.5 ± 2.97	17.77 ± 13.10	19.80 ± 12.21	0.060
Ejection fraction (%)	36.8 ± 6.53	40.57 ± 23.61	45.12 ± 20.11	0.007
E/A ratio	2.11 ± 1.55	2.14 ± 1.47	1.90 ± 1.25	0.199
DT (ms)	145.8 ± 59.2	144.2 ± 58.3	147.9 ± 60.5	0.480
IVRT (ms)	111.0 ± 34.3	114.9 ± 35.8	106.1 ± 32.1	0.127
LV mass (absolute)	449.0 ± 217.5	561.7 ± 106.6	233.0 ± 54.24	0.026
LV mass (indexed)	274.1 ± 117.5	336.4 ± 46.6	160.9 ± 16.1	0.016
Mitral regurgitation (%)	19.6	18.7	20.7	0.894
Tricuspid regurgitation (%)	15.1	12.7	17.8	0.459

IVSD = interventricular septal wall thickness in diastole, LVPWd = left ventricular posterior wall thickness in diastole, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, DT = deceleration time, IVRT = isovolumic relaxation time.

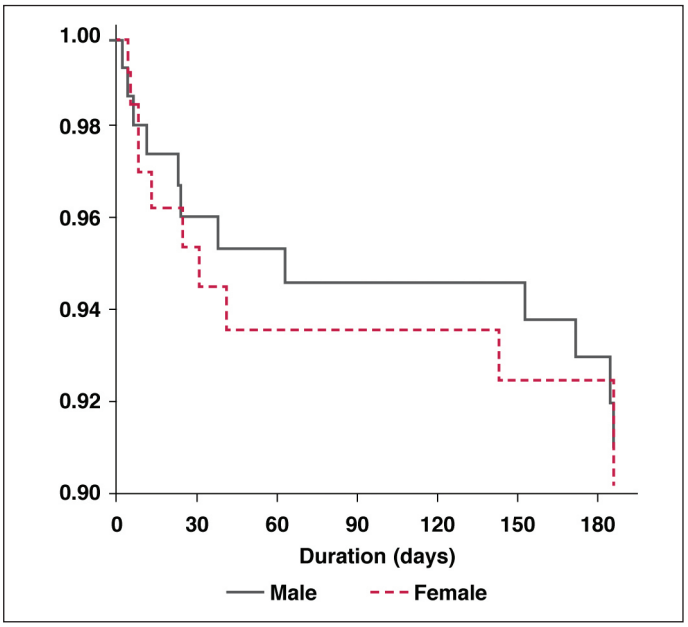

Figure 2. Kaplan–Meier survival curve for males and females.

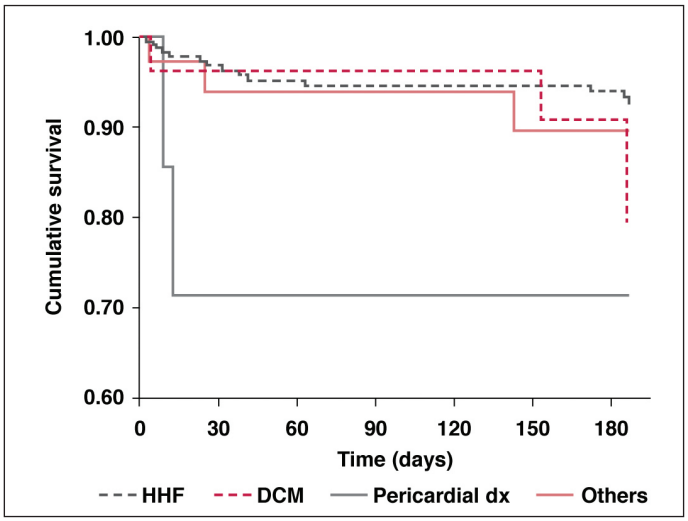

Figure 3. Kaplan–Meier survival curve for the different aetiological risk factors.

parameters according to gender. Men had significantly higher mean absolute QT intervals (374 ± 35.0 vs 348 ± 45.5 ms, p = 0.006), left atrial area (28.8 ± 8.8 vs 25.0 ± 6.4 cm^2, p = 0.010), LV internal dimension in systole, as well as absolute and indexed LV mass (p = 0.001, 0.026 and 0.016, respectively). On the other, hand women had significantly higher ejection fractions (45.1 ± 20.1 vs 40.6 ± 23.6, p = 0.007).

The mean length of hospital stay was 10.5 ± 5.9 days, (11.0 ± 5.4 and 10.0 ± 6.3 days for women and men, respectively). Mortality rate at 30 days was 4.2% (95% CI: 2.4–7.3) for the whole cohort. It

Table 4. Clinical and demographic predictors of outcome on univariate analysis (six-month survival).

Variable	All (n = 285)	Alive (258)	Dead (23)	OR	95% CI
Age (years)	57.3 ± 15.4	57.4 ± 14.0	57.2 ± 19.1	0.99	0.96–1.01
Female gender (%)	52.6	54.5	50	1.14	0.48–2.70
No education (%)	33.3	32.8	30.0	0.77	0.26–2.28
Not married (single) (%)	67.8	69.6	52.9	1.51	0.56–4.07
Body mass index	24.0 ± 5.4	23.7 ± 4.9	23.4 ± 3.6	0.97	0.87–1.08
Non-smoker (%)	81.8	82.3	85.0	1.51	0.43–5.34
Alcohol use (%)	6.0	5.6	5.0	0.79	0.32–1.95
Presence of diabetes (%)	13.0	13.1	10.0	0.65	0.14–2.92
Respiratory rate (bpm)	28.3 ± 6.2	28.0 ± 6.6	29.2 ± 5.3	1.02	0.96–1.08
Heart rate (bpm)	95.5 ± 17.1	95.0 ± 17.4	100.5 ± 15.9	1.00	0.97–1.03
Systolic blood pressure (mmHg)	136.1 ± 29.4	137.3 ± 27.7	122.5 ± 20.0	0.98	0.96–6.99
Diastolic blood pressure (mmHg)	87.1 ± 29.4	88.6 ± 18.7	80.0 ± 13.4	0.98	0.95–1.00
Pulse pressure > 30 mmHg (%)	3.3	2.1	5.0	0.42	0.16–1.10
NYHA (III and IV) (%)	91.5	90.4	95.0	4.03	1.53–10.65
Serum sodium (mmol/l)	136.9 ± 4.6	136.0 ± 6.4	137.2 ± 7.4	1.03	0.96–1.11
Serum potassium (mmol/l)	3.7 ± 0.5	3.6 ± 0.7	4.0 ± 1.0	1.64	0.72–3.75
Blood glucose (mg/dl)	112.3 ± 56.0	117.0 ± 58.5	111.8 ± 58.5	1.00	0.99–1.01
(mmol/l)	(6.23 ± 3.11)	(6.49 ± 3.25)	(6.20 ± 3.25)		
Packed cell volume (%)	41.0 ± 7.6	37.6 ± 7.0	32.2 ± 8.4	0.92	0.86–0.97
Total white blood cell count	6.8 ± 3.1	6.9 ± 3.4	9.2 ± 5.1	1.13	1.02–1.25
Serum creatinine (mg/dl)	0.8 ± 0.3	1.2 ± 1.0	2.1 ± 2.5	1.38	1.04–1.83
(µmol/l)	(70.72 ± 26.52)	(106.08 ± 88.40)	(185.64 ± 221.00)		
QRS duration (ms)	107.1 ± 9.4	110.3 ± 29.5	110.9 ± 32.2	1.01	0.99–1.03
Corrected QT (ms)	439.4 ± 40.9	449.3 ± 34.4	457.3 ± 34.6	1.01	0.99–1.04
Atrial fibrillation (%)	13.3	14.6	20.0	1.14	0.36–3.55
E/A ratio	2.2 ± 1.0	2.1 ± 1.3	2.7 ± 1.6	1.40	0.99–1.97
Left atrial area (cm^2)	26.2 ± 6.7	26.8 ± 7.5	34.2 ± 12.1	1.11	1.01–1.21
Left atrial diameter (cm)	4.8 ± 0.9	4.6 ± 0.9	5.0 ± 1.1	1.56	0.94–2.60
LVID (cm)	5.47 ± 1.55	5.6 ± 1.5	5.7 ± 1.2	1.11	0.74–1.67
HF with systolic dysfunction	66.4	67.5	70.6	0.66	0.27–1.59
MR (yes) (%)	19.6	20.2%	25.0	1.34	0.50–3.60
TR (yes) (%)	15.1	13.1%	35.0	2.64	1.00–6.95

LVID = left ventricular internal diameter, MR = mitral regurgitation, TR = tricuspid regurgitation.

was 3.9% (95% CI: 1.7–8.5%) and 4.5% (95% CI: 2.1–9.3%) for men and women, respectively. At 180 days, the mortality rate was 7.3% (95% CI: 4.7–11.2%). This was 7.1% (95% CI: 3.8–12.7%) and 7.5% (95% CI: 3.9–14.0%) for men and women respectively.

Patients with pericardial diseases had the highest early mortality rate. Hypertensive HF subjects had the best survival rates (Figs 1, 2, 3). At 180 days, 13.9% of the subjects were rehospitalised at least once (14.6% for women and 13.3% for men).

Table 4 shows the univariate correlates of survival in the cohort. Mortality was associated with female gender, being single, HF with normal ejection fraction, lower blood pressure, higher heart and respiratory rates, higher body temperature, anaemia, high creatinine levels and higher total white blood cell counts. Other factors included higher QRS duration and corrected QT interval, larger left atrial diameter and area, higher NYHA class and presence of tricuspid and mitral regurgitation. In a multiple regression analysis for predictors of mortality at 180 days, none of these variables reached statistical significance.

Discussion

This is the first detailed study of the clinical profile and short- or medium-term outcome of AHF cases in southern Nigeria. Similar to our earlier observation,[24] AHF in our community predominantly affects younger and middle-aged individuals who are in the prime of their lives. Hypertensive heart disease and other non-ischaemic aetiology contribute to over 90% of the cases.

The majority of our subjects presented with de novo acute HF. Our findings with the use of some disease-modifying agents such as angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), aldosterone antagonists (except for beta-blockers and hydralazine–isosorbide combination) are remarkably similar to findings in many other parts of the world.[6,8] Mortality rates in the short and medium term are relatively low, and higher in women than men.

Our findings of relatively young age at presentation for AHF is similar to reports from many parts of Africa.[1,4,25] AHF patients on the continent are about 20 years younger than similar patients in high-income countries.[6-9] This implies that HF afflicts our population in their productive years, with attendant economic loss to the society and greater disability-adjusted life years.

The comparable or even lower short- or medium-term mortality rate of HF in our cohort compared to findings in high-income countries is an important observation from this study.[7,8] Mortality rates in our study were 4.2% (95% CI: 2.4–7.3%) and 7.3% (95% CI: 14.7–11.2%) at 30 days and 180 days, respectively.

Unlike findings in high-income countries,[26,27] we noted that age was not associated with poorer outcome in our cohorts. Our finding of a better prognosis in obese individuals is similar to that of other researchers.[27,28] In the Framingham study, high BMI was associated with a better prognosis (HR for mortality per one SD: 0.88, 95% CI: 0.75–1.04 for men, and 0.86, 95% CI: 0.72–1.03 for women). This may also be consistent with the 'obesity paradox' in HF.[29-31] Underweight in HF patients may be indicative of cardiac cachexia, and progression of HF and poor prognosis.

Lower blood pressure or pulse pressure was associated with a poorer outcome. This may reflect advanced HF and decreased stroke volume. This has been noted in previous studies.[26,32]

It is now well known that impaired renal function is an important predictor of all-cause mortality in HF.[33-35] This is similar to the observation in our study. Patients with renal impairment often develop cardio-renal syndrome, which is caused by low cardiac output. These patients often develop multiple alterations at the vascular level, leading to endothelial dysfunction, coagulation abnormalities, insulin resistance, hyperhomocystinaemia and activation of the sympathetic nervous system, as well as the renin–angiotensin and aldosterone system. They are prone to unstable HF and susceptible to high catecholamine levels. Furthermore HF patients with renal dysfunction are also less likely to receive proven medications for HF.

Hyponatraemia and hypokalaemia were associated with a better prognosis in our study. This is contrary to most reports from the Western world, although in a Polish study, Biegus *et al*.[8] reported that hypokalaemia was associated with a better outcome. This may be related to better response to diuretics in the survivors, leading to the electrolyte derangement. It may also be speculated that sodium may play a lesser role in the pathophysiology of HF in our setting.

We also observed that left atrial size, left atrial area, left ventricular size, higher E/A ratio and presence of mitral and tricuspid regurgitation were associated with poorer outcomes. This has been well recognised by earlier studies.[7,9] Left atrial or ventricular size reflects left atrial or ventricular pressure and volume overload, and the severity and duration of increases in LV filling in response to cardiac functionl abnormality associated with HF.[36]

A plausible reason for the younger age at presentation for HF in our study and many parts of Africa may be related to the aetiology of the condition, which are conditions that present in young and middle age (for example rheumatic heart disease and cardiomyopathies). In addition, hypertension and related target-organ damage present at a younger age in Africans and people of African descent.

The dominance of de novo presentation of HF in our cohort may be related to poorer long-term outcome of HF in our setting, that is, few people are living with chronic HF. Another reason may be because of poor or inadequate health education. Most often patients do not keep to one health facility when they have chronic illnesses such as HF. They often move from one facility to another (including alternative healthcare facilities) seeking a cure.

The relatively low mortality rate in our cohort may be related to the fact that the study was conducted in a cardiology unit and may not reflect what happens in a general medical ward or in private practice in the country. The clinical characteristics of our patients may also be explanatory. Our subjects were younger compared to the typical patients with HF in the Western world, who are generally elderly.

The average length of hospital stay was longer in our setting (9 days) compared to 6.1 days in the USA[28] and nine days in Europe.[7] However it was shorter than the 21 days reported from Japan.[37] It is possible that longer stay in hospital affords patients the opportunity to recover well and get used to medications for HF. HF outcome is generally better in Japanese patients compared to other high-income countries.[7,8,10]

Furthermore it is also possible that the aetiology of HF in our cohort could have affected the outcome. Hypertension is predominantly the major risk factor for HF in our cohort. Ischaemic heart disease is relatively uncommon. It is well known that mortality rates from coronary artery disease (CAD) are generally worse than in those with non-ischaemic heart disease. Mitchell *et*

al.[38] reported a total mortality rate of 30% at three years in the placebo group of ischaemic HF patients compared to a rate of 15% in the non-ischaemic HF group.

The poorer outcome of women in our study may be because the women were less educated and more likely to be unemployed and dependent than the men, and may not be able to pay for HF medications. Clinic follow up may also be poorer in the women.

The finding of low frequency of use of some disease-modifying drugs in our cohort is an opportunity for future intervention in HF management in our environment. This is because studies have shown that ACE inhibitors,[39] ARBs,[40] and beta-blockers[12] can improve survival in patients with HF. Furthermore, the African-American Heart Failure trial has shown the efficacy of the hydrallazine–isosorbide combination in the treatment of HF in blacks.[13]

The main aetiological factors for HF in our cohort were non-ischaemic in origin, with hypertensive heart disease being responsible for over 75% of cases. It may be reasonable to suggest that applying guidelines derived from clinical trials in the Western world, where most HF is ischaemic in origin, may be inappropriate in our population.

Limitations

Our study was a single-centre, hospital-based study conducted in a cardiology unit and therefore may not have captured all the patients with heart failure in the city during the study period, although many referrals were received from surrounding hospitals and clinics during the period due to the awareness that was created of the study. The findings of the study may not be extrapolated to the general population or the situation in other Nigerian hospitals. A national HF registry is needed, as has been done in many other countries.

The use of the Framingham criteria as a screening tool may have missed some patients, especially the elderly with HF, as the criteria are not sensitive in this population.

Due to cost consideration, our subjects did not have NT-proBNP levels done as this has not become a routine practice in the country. NT-proBNP has been shown to be a strong predictor of prognosis in HF.[41] Other prognostic variables, such as exercise capacity (VO_2 and six-minute walk) were also not assessed in our patients.

Some of our patients were lost to follow up and this may have affected the survival information in this study. However the rate of attrition was similar to that in other follow-up studies.[8,42] This was complicated by the fact that there is no effective national death registry in the country. We also could not ascertain the exact cause of death for patients who died outside the hospital environment.

Conclusions

The characteristics of the HF population in Nigeria is different from similar populations in high-income countries. Our patients are about 20 years younger and have non-ischaemic aetiological risk factors for HF, especially hypertensive heart disease. Short- or medium-term outcome is relatively lower than (or comparable to) findings from high-income countries and have some similar prognostic factors, such as renal function, anaemia, body mass index, blood pressure parameters, as well as ECG and echocardiographic variables. There is a need for a national HF registry in the country to better understand the characteristics, management and outcome of HF in the different regions of the country.

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Prevalence and determinants of hypertension and associated cardiovascular risk factors: data from a population-based, cross-sectional survey in Saint Louis, Senegal

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Abstract

Background: **The incidence of cardiovascular disease is growing worldwide and this is of major public health concern. In sub-Saharan Africa, there is a lack of epidemiological data on the prevalence and distribution of risk factors of cardiovascular disease. This study aimed at assessing the prevalence of hypertension and other cardiovascular risk factors among an urban Senegalese population.**

Methods: **Using an adaptation of the WHO STEPwise approach to chronic disease risk-factor surveillance, we conducted a population-based, cross-sectional survey from 3 to 30 May 2010 on 1 424 participants aged over 15 years. Socio-demographic and behavioural risk factors were collected in step 1. Physical anthropometric measurements and blood pressure were documented in step 2. Blood tests (cholesterol, fasting blood glucose, and creatinine levels) were carried out in step 3.**

Results: **The prevalence of hypertension was 46% (95% CI: 43.4–48%), with a higher prevalence in females (47.9%) than males (41.7%) ($p = 0.015$), and 50% of these hypertensive were previously undiagnosed. Mean age was 53.6 years (SD: 15.8). In known cases of hypertension, the average length of its evolution was 6 years 9 months (range 1 month to 60 years). Hypertension was significantly associated with age ($p = 0.001$), socio-professional category ($p = 0.003$), dyslipidaemia ($p < 0.001$), obesity ($p < 0.001$), physical inactivity ($p < 0.001$), diabetes ($p < 0.001$) and stroke ($p < 0.001$).**

Conclusion: **We found a high prevalence of hypertension and other cardiovascular risk factors in this population. There is need of a specific programme for the management and prevention of cardiovascular disease in this population.**

Keywords: hypertension, cardiovascular, Africa, risk factors, Senegal

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Introduction

Hypertension (HTN) remains a major public health concern worldwide and particularly in sub-Saharan Africa.[1-3] The overall prevalence of HTN worldwide is estimated to be 30% and the attributable mortality is ~30%. Lawes *et al*. reported that overall, about 80% of the attributable burden occurred in low- and middle-income economies, and over half occurred in people aged 45–69 years.[4]

In sub-Saharan Africa, the prevalence of HTN is estimated to vary between 15 and 33%.[1] HTN is usually associated with other cardiovascular risk factors such as diabetes, dyslipidaemia and obesity.[5] In Senegal, there is a lack of population-based epidemiological data on HTN and cardiovascular risk factors. Our study aimed at assessing the prevalence and deteminants of HTN and associated cardiovascular risk factors among an urban population in Senegal (Saint Louis).

Methods

This study was a population-based, cross-sectional survey conducted in the city of Saint Louis (north Senegal, 250 km from the capital Dakar). It population is 190 000 inhabitants (2008 estimate) and the number of subjects over 15 years is estimated at 110 000.

Data were collected in three steps;[6] step 1 comprised using a questionnaire to collect demographic and lifestyle data; step 2 involved measurements of height, weight, blood pressure, waist and hip circumference; and step 3 included laboratory (biochemistry) investigations. Data presented in this publication are related only to hypertension.

A list of the districts in the city was used for sampling. Each district was divided into squares and each square was subdivided into concessions (a group of households). A list of all concessions was obtained from the regional statistics office. This list was used as a sampling frame for the random selection of squares.

In each square, concessions to be visited were randomly selected and inside the concession, a household was also randomly selected. In each household, all the persons matching the selection criteria

were invited to participate in the study. One hundred and twenty households were randomly selected, giving a total of 1 424 participants; 32 sets of data were not been analysed because of missing biological and/or clinical data.

Eligible criteria were age ≥ 15 years and being a resident of Saint Louis. Formal written consent was obtained. Non-consenting patients and pregnant women were not included.

Participants were involved in the survey for one day. Those with abnormal physical or laboratory findings were counselled and referred to the regional hospital as defined by the National Health reference system. Interviews, body measurements and laboratory tests were performed by nurses and clinical officers.

The survey questionnaire consisted of socio-demographic (age, gender, education, marital status), lifestyle (fruit and legumes consumption, exposure to tobacco and alcohol, and physical activity) variables, and medical and health history.

Physical body measurements included blood pressure (BP), height, weight, and waist circumference. Blood pressure measurements were taken using an electronic digital blood pressure machine (OMRON® M6). Three BP measurements were performed on both arms, in a seated position, legs uncrossed, after a five- to 10-minute rest. The highest BP value was recorded.

Waist circumference was measured in centimeters using a tape measure, and the measurement was made at the mid-axillary line, midway between the last rib and the superior iliac crest. Height was measured with the participant standing upright against a wall on which a height mark was made. Weight measurements were taken on a pre-calibrated weighing scale (Seca 750). Participants were weighed dressed in light clothing and barefoot.

Blood samples were analysed in a single laboratory using an automate Reflotron-Plus®. Cholesterol [total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)], triglyceride, fasting blood glucose, uric acid and creatinine levels were analysed.

Hypertension was defined as a systolic BP ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg, or a documented medical history of antihypertensive treatment.[7] Obesity was defined as body mass index (BMI) ≥ 30.0 kg/m², and overweight by a BMI > 25 but < 30 kg/m².

Diabetes mellitus was defined as two fasting blood glucose levels > 1.26 g/l and/or a documented medical history of diabetes or diabetes treatment. The threshold for normal values were < 2g/l for total cholesterol, < 1.6 g/l for LDL cholesterol, > 0.4 g/l for HDL cholesterol, and < 1.5 g/l for fasting triglycerides.

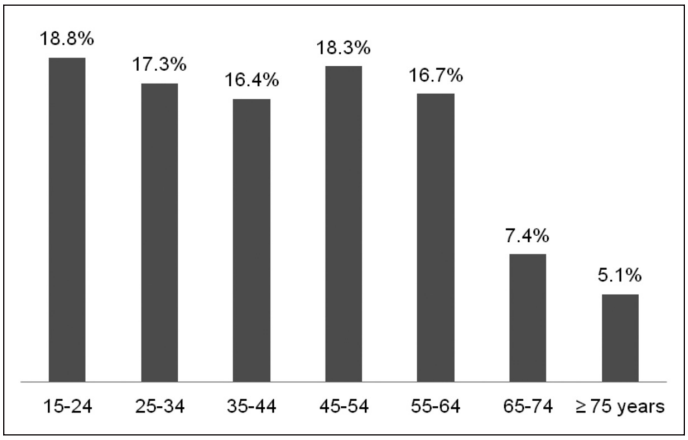

Figure 1. Distribution of study population by age (n = 1424).

Table 1. Characteristics of the study population (n = 1 424)

	Female	Male	Total	p
Sample size	983	441	1424	
Age (years), mean (SD)	44.2 (17.2)	41.7 (18.9)	43.4 (7.8)	0.016
Weight (kg), mean (SD)	71.7 (17.9)	67.6 (13.6)	70.5 (16.7)	< 0.001
Height (cm), mean (SD)	163.3 (8.3)	174.9 (8.5)	166 (9.9)	< 0.001
Waist circumference (cm), mean (SD)	87.4 (16.5)	81.2 (46.8)	84.6 (15.9)	0.0003
Systolic BP (mmHg), mean (SD)	131.1 (28.7)	131.9 (22.3)	131.2 (27.8)	0.893
Diastolic BP (mmHg), mean (SD)	86.7 (24.5)	82.4 (22.4)	85.4 (22.4)	0.0001
BMI (kg/m²), mean (SD)	27 (7.2)	22.1 (16.2)	25.5 (6.7)	< 0.001

SD: standard deviation

Physical inactivity was defined as the absence of daily physical activity or the presence of physical activity lasting less at 150 minutes per week. Abdominal obesity was defined according to NCEP, with a waist circumference greater than 102 cm in men and 88 cm in women.

Ethics committee approval to undertake the survey was in accordance with national and local regulations. Written, signed consent was obtained for each of the patients included. The study was conducted in accordance with the Helsinki II Declaration.

Statistical analysis

Data recorded in the standard questionnaire were double checked by external monitor and double-entered using Epi Data software. Entered data were cleaned and analysed by an experienced biostatistician using Epi info version 3.5.1 software.

Binary variables were described by their proportion and continuous variables by means and standard deviation (SD). Pearson and Yates (when appropriate) chi-square test were used for the comparison of qualitative variables and Student's t-test for the comparison of quantitative variables between groups. A logistic regression model was built with variables associated with hypertension. Age and gender were forced into the final model. The results were statistically significant if $p < 0.05$.

Results

We recruited 1 424 participants (983 female, 69%). Mean age was 43.4 years (SD: 17.8), (range 15–96 years); 70.8% were < 55 years and 87.5% were < 65 years. Fig. 1 shows the distribution of the population by age. Table 1 shows the characteristics of the

Table 2. Prevalence of cardiovascular risk factors in the studied population (n = 1 424)

Risk factors	Prevalence, % (95% CI)
Hypertension	46 (43.4–48.6)
Abdominal obesity	33.2 (30.8–35.7)
Obesity (BMI > 30 kg/m²)	23 (18.1–28.2)
Tobacco smokers	5.8 (4.7–7.2)
Physical inactivity	44.4 (40.2–49)
Diabetes	10.4 (8.9–12.1)
Raised cholesterol (> 2 g/l) (> 5 mmol/l)	36.3 (33.8–38.9)
Raised LDL cholesterol (> 1.6 g/l) (> 4.14 mmol/l)	20.6 (18.5–22.8)
Low value of HDL cholesterol	41.9 (39.4–44.5)
Metabolic syndrome	15.8 (14–17.8)

BMI: body mass index, CI: confidence interval.

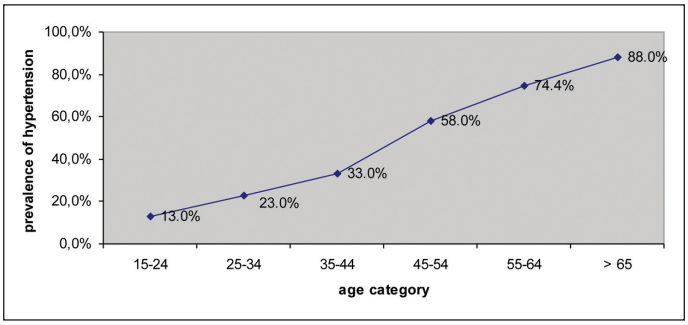

Figure 2. Prevalence of hypertension by age (n = 655).

enrolled population and Table 2 shows the prevalence of various cardiovascular risk factors.

Six hundred and fifty-five participants had HTN, giving a prevalence of 46.0% (95% confidence interval: 43.4–48.6%). Among these 655 cases, 327 (50%) were previously undiagnosed. HTN was more frequent in females [47.9% (44.8–51.1%)] than in males [41.7% (37.1–46.5%), p = 0.015, OR = 1.29 (1.02–1.62)]. The mean age was significantly higher in the hypertensive participants (53.6, SD: 15.8 years) than in non-hypertensive participants (34.7 years, SD: 14.5, $p < 0.001$). The prevalence of HTN increased with age (p = 0.001) (Fig. 2). Mean duration of HTN was 6.9 years (range: 1 month – 60 years).

Among HTN participants, mean systolic BP was 136 mmHg and mean diastolic BP 88 mmHg. Grade 1 HTN was more frequent (48%) than grade II (25%) and grade III (27%). HTN tended to be more frequent in participants who had primary school level education (42.1%) than in those who had higher levels of education (28.4%, p = 0.18). Table 3 shows the distribution of hypertension according to socio-professional category. There was a statistically significant relationship between hypertension and the different socio-professional categories, except for self-employed, privately employed and voluntary participants (p = 0.0031).

Diabetes was detected in 16.5% (13.8–19.6%) of the participants with HTN and in 5.2% (3.8–7.1%) of participants without HTN [p = 0.023, OR = 0.32 (0.21–0.47)]. Moreover, HTN was more frequent in participants with diabetes [73% (65.1–79.9%)] than in those without diabetes [43% (40.1–45.6%), $p < 0.0001$, OR = 3.59 (2.46–5.25)].

Other risk factors associated with HTN were dyslipidaemia in 71.1% (67.5–74.6%) of participants with HTN versus 59% (55.5–62.5%) in non-HTN participants ($p < 0.001$), physical inactivity [48.5% (43.9–52.1%) vs 40.2% (36.3–44.5%), $p < 0.001$] and abdominal obesity [47.3% (43.5–51.2%) vs 21.2% (18.4–24.3%), $p < 0.001$].

HTN was more frequent in the case of a past history of smoking (50.8%) (41.8–59.7%) than in passive exposure (44.8%) (40.9–48.8%) and cigarette users (33.7%) (23.7–44.9%). A medical history of stroke was more frequent in participants with HTN (2.7%) (1.7–4.4%) compared with those without HTN (0.5%) (0.2–1.4%) ($p < 0.001$). HTN was correlated with the creatinine level ($p < 0.05$) (Fig. 3). The mean clearance rate of creatinine gradually decreased with the duration of hypertension (Fig. 4) (p = 0.26).

Table 3. Prevalence of hypertension in socio-professional category

	Number	Hypertension (%)	*p*
Official	71	36.6	1
Private	72	25	0.13
Self employed	496	48.2	0.06
Volunteer	9	22.2	0.39
Housewife	528	50.9	0.023
Student	130	10	< 0.001
Unemployed	35	57.1	0.045
Retired	83	81.9	< 0.001

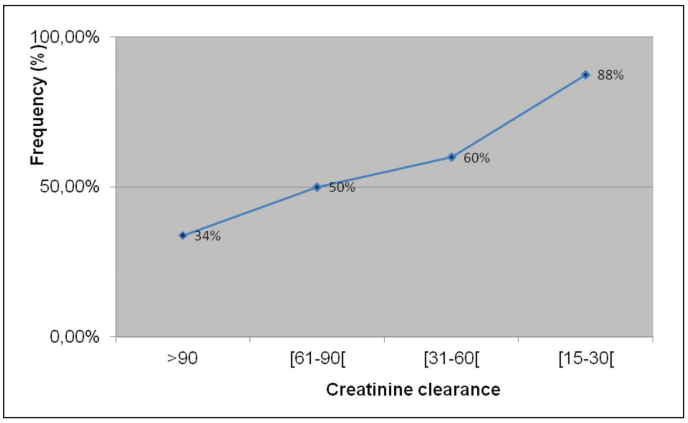

Figure 3. Prevalence of hypertension by creatinine clearance rate (n = 655).

Discussion

In order to gather data on the frequency of HTN and associated risk factors in urban Saint Louis residents, we carried out a population-based, cross-sectional survey with a methodology closed to the WHO STEPwise approach. We found a significant increase in the prevalence of HTN.

A previous study performed in the same region in 1970 found a prevalence of 4.9% in a rural population, whereas the prevalence was 7% in an urban population. Even though the methodology (HTN if BP ≥ 160/95 mmHg) in this study was not similar to ours, our results suggest a significant increase in the prevalence of HTN since 1970.[8] Moreover, Kane *et al*. in 1995 found a prevalence of 20.2% with a methodology very similar to ours.[5] In the sub-Saharan African region, two studies have reported a median prevalence of 28%, with a regional variation ranging from 15 to 38.6%.[1,9] Changes in lifestyle may be the major factor leading to this increasing prevalence of HTN and other cardiovascular risk factors.[9-11]

While we have not found significant associations between HTN and level of education, it should be noted that previous studies

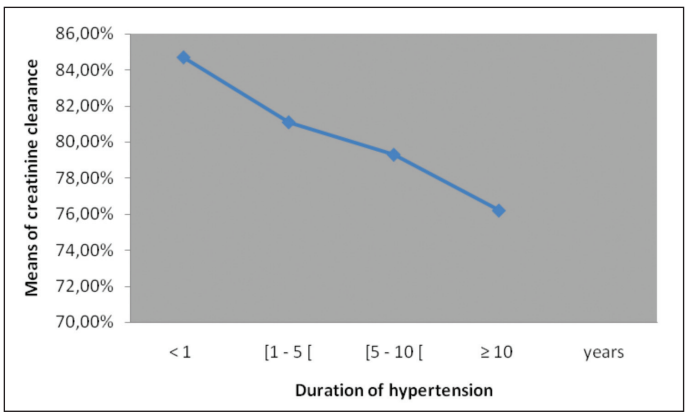

Figure 4: Means of creatinine clearance by duration of hypertension

found such an association. The ENNS trial found than HTN was twice as frequent in people with a primary level of education than in those who had secondary or postgraduate levels of education. This difference was higher in women: the risk of HTN was four-fold higher in less-educated women than in those with higher levels of education.[2] The same observation was made in Brazzaville, Congo.[9]

The association between HTN and low socio-econonomic conditions is well described in studies conducted in low-income countries. The lower the socio-economic income, the higher is the probability of having HTN.[12,13]

In our population sample, women were more represented than men. This could have been related to the observation that women were more likely to be at home at the time the study team came around than men, who were involved in economic activities outside the home. Additionally, men were more inclined to decline participation in the survey. This observation was noticed by other authors in this kind of population-based survey.[14]

We found a predominance of HTN in women. This observation was previously reported in the CONSTANT trial in Guadeloupe (37.3 vs 33%) and Tunisia (36 vs 25%).[12,13] This is in contradiction with the predominance of HTN found in males, reported in many epidemiological surveys.[2,14] Some authors have suggested that women are protected from HTN up to menopause.

In our study, obesity and inactivity were significantly more frequent in women than men, and females were older than males. This could explain the predominance of HTN in the women. We also noted a significantly higher diastolic blood pressure in women than in men, for which we did not find an explanation, except that the women may have had more risk factors.

Regarding other risk factors, we found that age correlated with the prevalence of HTN. This was previously noted in Algeria and France.[9,15] Obesity accounted for 11 to 25% of HTN and prevention studies have reported that a decrease of 1 kg of body weight led to a decrease of 1.1/0.9 mmHg in BP.[16-18] The meta-analysis of Whelton (54 randomised clinical trials) reported a decrease of 3.8/2.9 mmHg in people with regular aerobic physical activity; the highest decrease was found in hypertensive subjects (4.9/3.7 mmHg).[17]

Obesity and physical inactivity are known to be risk factors for the onset of diabetes, HTN and other cardiovascular diseases. The review of Sowers showed that HTN was twice as frequent in patients with diabetes than in those with normal glycaemia. Additionally, Sowers reported an increase in the risk of diabetes in HTN patients compared to non-hypertensives.[17] Dussol found that HTN was present in 80% of type 2 diabetes patients.[19]

We noticed a lower prevalence of HTN in participants who reported tobacco smoking. Nebie *et al*. reported a prevalence of 23% of HTN in smokers.[20] The association between tobacco usage and HTN is still controversial and a possible confounding effect of both alcohol usage and overweight is being assumed.[21] The association of HTN with other cardiovascular risk factors contributes to increase the global cardiovascular risk of patients.

The results showed a higher prevalence of hypertension with worsening creatinine clearance rates. This was probably a consequence of hypertension, as shown by the decrease in creatinine clearance rate with the duration of hypertension.

Conclusion

This population-based survey is the first performed in Senegal. It was intended to serve as a baseline situation for other surveys locally or at a national level. We found a high prevalence of hypertension associated with other cardiovascular risk factors such as diabetes, obesity, inactivity and dyslipidaemia. The majority of participants were not aware of their condition.

Nationwide surveys are needed to better assess the burden of cardiovascular disease in this population. This will help authorities to formulate and implement adequate strategies to control hypertension and the emerging epidemic of non-communicable diseases.

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The prevalence and distribution of non-communicable diseases and their risk factors in Kasese district, Uganda

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Abstract

Background: **To date there has been no population-based survey of the major risk factors for non-communicable diseases (NCD) in Uganda. Hospital-based data from urban centres report an increasing burden of NCDs in Uganda. Our population-based survey aimed to describe the prevalence of risk factors for NCDs in a rural Ugandan district.**

Methods: **The survey was conducted using the WHO STEPwise approach to surveillance of non-communicable diseases (STEPS) methodology. Participants (*n* = 611) were residents of the Kasese district selected in a one-step, complete survey of a rural district. Standardised international protocols were used to record history of disease, and measure behavioural risk factors (smoking, alcohol consumption, fruit and vegetable consumption, physical activity), physical characteristics [weight, height, waist and hip circumferences, blood pressure (BP)], fasting blood glucose (BG) and total cholesterol (TC) levels. Data were analysed using simple descriptive analysis.**

Results: **In this sample, the prevalence of hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) was 22.1% for men and 20.5% for women. Fifteen per cent of men and 16.8% of women were overweight [body mass index (BMI) ≥ 25 kg/m^2] and 4.9% of men and 9.0% of women were obese (BMI ≥ 30 kg/m^2). Nine per cent of participants were diabetic, 7.2% ate five or more combined servings of fruit per day while only 1.2% ate five or more combined servings of vegetables per day. Fifty-one per cent of the population were physically inactive and 9.6% were daily smokers. Thirty-one per cent of females had fasting blood sugar levels (FBS) ≥ 6.1 mmol/l while 10% of males had FBS > 6.1 mmol/l.**

Conclusion: **This study presents evidence on the magnitude of NCDs, their risk factors and gender distribution in a rural population in Uganda, a poor country in east-central Africa. These data, when combined with urban population data, could be useful in the formulation and advocacy of NCD policy and plans of action in Uganda.**

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Keywords: non-communicable diseases, WHO STEPS, smoking, obesity, physical activity

Introduction

Non-communicable diseases (NCDs) are currently responsible for 35% of all deaths in low- and middle-income countries,[1] and this alarming figure is predicted to rise in the near future. The World Health Organisation projects that the burden of disease due to NCDs will increase rapidly in the years ahead. From a projected total of 58 million deaths from all causes in 2005, it was estimated that NCDs would account for 35 million deaths, which was double the number of deaths from all communicable diseases (including HIV/AIDS, tuberculosis and malaria), maternal and perinatal conditions and nutritional deficiencies combined.[1]

This epidemiological transition in global health from infectious diseases to NCDs is posing not only a threat to the health of those affected but also places an enormous burden on the health systems of nations, particularly those of the least-developed countries, as they must now address a double burden of acute and chronic diseases amidst scarce resources.[2-4] Furthermore, this epidemiological transition is adversely impacting on socio-economic development of nations, as NCDs tend to be more prevalent in young working class people.[2] As a more sophisticated workforce becomes a highly valued and harder-to-replace economic investment, the increasing prevalence of NCD risk factors in developing countries, particularly sub-Saharan Africa (SSA), becomes a real threat to economic progress, adversely impacting on all the previous gains made in combating HIV, malaria, tuberculosis and other infectious diseases.[5]

In Uganda, while acute infectious communicable diseases still contribute the major (75%) disease burden, with malaria, acute respiratory infections and HIV/AIDS among the top 10 causes of illness and death,[6] the burden of NCDs is increasingly posing a threat of dual epidemics of communicable and non-communicable diseases. The International Diabetes Federation put estimates of incidence of diabetes mellitus in Uganda at 50 000 affected individuals in the year 2003, and projected a 10-fold increase in the cases of diabetes by 2025 if no interventions are initiated.[7] Estimates suggest that as many as 8% of people living in Kampala may have type 2 diabetes (T2D),[8] while deaths attributed to NCDs in Uganda were estimated at 31 700 in 2002.[9]

Estimates of age-standardised mortality from NCDs suggest that countries in SSA, including Uganda, might have a more than three-fold higher mortality rate than several European countries, including the UK.[9] However, these estimates are based on limited data and statistical models derived from child mortality rates and cause-specific rates from external sources. Several publications have highlighted the need for local high-quality epidemiological data on the burden of NCDs and their risk factors, particularly in SSA where such data are scarce.[10,11-14]

To date, there has been no systematic population-based study on NCD risk factors conducted in Uganda. Accordingly, between

December 2011 and February 2012, we conducted a cross-sectional survey using the WHO NCD STEPS survey tools to determine the magnitude of NCDs and their risk factors in Kasese district, Uganda to serve as a pilot study for the nationwide survey of NCD risk factors.

Methods

Ethical approval was granted by the Uganda National Council for Science and Technology's Human Research and Ethics Committee, and the President's Office Research Secretariat. Written informed consent was obtained before participants were enrolled in the study, using the WHO NCD STEPS survey consent form.

This study was a community population-based, cross-sectional survey designed according to a WHO STEPwise approach to chronic disease risk-factor surveillance.[15] Data were collected in three steps; step 1 used a questionnaire to collect demographic and lifestyle data; step 2 involved measurements of height, weight, blood pressure (BP), waist and hip circumference; and step 3 used laboratory (biochemistry) investigations.

Kasese district is divided into two counties, Bukonzuo (10 sub-counties) and Busongora (12 sub-counties). One sub-county was selected from each county. Bugoye sub-county from Busongora is predominantly rural, whereas Mpondwe sub-county from Bukonzuo is peri-urban. The two sub-counties selected are the most populous in each county. Both sub-counties comprise 14 parishes, 61 villages with a total of 11 986 households. Using the cluster sampling method, seven households were randomly selected from each village. Finally, at least one adult in the selected households was invited to participate. Where a household had no consenting adults, the neighbouring household was approached.

The survey was conducted using the WHO recommended STEPwise approach.[16] Step 1, the survey questionnaire, was administered by the field staff. It consisted of core (age, gender, education in years, current exposure to tobacco and alcohol, diet and physical activity), expanded (rural/urban setting, occupation, average household income) and optional (marital status, medical and health history, past history of smoking and alcohol consumption) variables. The medical and health history component included questions on medication, cigarette use, diabetes mellitus and hypertension.

Step 2 involved physical body measurements, including BP, height, weight, and waist and hip circumference measurements. BP measurements were taken using battery-powered digital BP machines (Omron M3-I). The participant was asked to sit on the chair and rest quietly for 15 minutes with his/her legs uncrossed. The left arm of the participant was then placed on the table with the palm facing upward. Three readings, three to five minutes apart, were then taken on the left arm. During the analysis the average of the last two readings was the final BP reading used.

Height was measured with the participant standing upright against a wall on which a height mark was made. Measurements were taken with the participant barefoot, standing with the back against the wall and head in the Frankfort position, with heels together. The participant was asked to stretch to the fullest. After being appropriately positioned, the participant was asked to exhale and a mark was made with a white chalk to mark the height. The height was then measured to the nearest 0.1 cm from the mark to the floor using a tape measure.

Weight measurements were taken on a pre-calibrated weighing scale (Seca scale). Participants were weighed dressed in light clothing and barefoot. Measurements were taken to the nearest 0.1 kg.

Step 3 involved laboratory tests. Consenting participants were asked not to consume any food, only water from after supper that day until the survey team collected the blood samples the next day (eight-hour fast). People converged at the agreed place in their community. Those who had complied with the overnight fast were eligible for finger-prick blood sample collection. Total cholesterol (TC) and triglyceride (TG) levels were measured using Reflotron-Plus machines manufactured by Roche. Fasting blood glucose (FBG) level was measured on two machines, the Accu-Chek Active glucometer from Roche and the Soft-Style glucometer from Chem-labs.

Hypertension was defined as a diastolic BP of 90 mmHg or more, or a systolic BP of 140 mmHg or more, or currently on medication for hypertension (documented in the health booklet). Diastolic BP ≥ 110 mmHg or systolic ≥ 180 mmHg was considered to be severe hypertension. Raised fasting blood glucose was defined as a blood glucose level ≥ 7.0 mmol/l or currently on medication for diabetes mellitus (documented in the health booklet). Raised total cholesterol was defined as cholesterol level ≥ 5.0 mmol/l. Overweight was defined as body mass index (BMI) ≥ 25.0 kg/m^2 and obesity as BMI ≥ 30.0 kg/m^2.

Excessive or harmful use of alcohol was defined as the consumption of five or more for men, four or more for women, standard units per day for three or more days per week. Physical activity was measured using questions on four different aspects: physical activity at the workplace, physical activity during recreation time, physical activity while travelling, and physical resting time. A heavy smoker is, according to the recommendations of the World

Table 1. Characteristics of the study participants

	Total	Male		Female	
		n	%	*n*	%
Gender*	528	297	45.5	231	54.5
Age (years)					
25–34	179	98	34.0	81	35.1
35–44	118	63	21.9	55	23.9
45–54	104	57	19.9	47	20.2
55–64	57	36	12.8	21	9.3
> 64	60	33	11.5	27	11.5
Education					
None	112	41	14.1	71	30.9
Primary school	243	129	45.1	114	49.7
Secondary school (O level)	113	82	28.3	31	13.5
Secondary school (A level)	27	18	6.4	9	3.9
University/college	23	17	6.1	6	2.0
Occupation					
Peasant	326	159	55.6	167	72.2
Trader	20	11	3.7	9	3.9
Teacher	28	22	7.4	6	2.5
Housewife/homemaker	10	0	0	10	4.49
Other	80	66	23.3	14	6.2
None	54	29	10.1	25	10.7
Marital status					
Married	411	244	84.9	167	71.9
Separated	38	17	6.1	21	9.3
Widowed	39	8	2.4	31	13.5
Never married	30	18	6.7	12	5.3

*Percentage is by column for gender only. The rest of the variables are by rows.

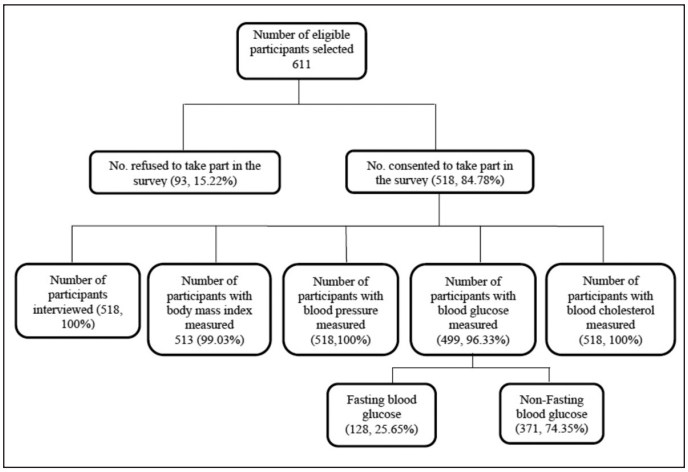


Figure 1. Flow diagram.

Health Organisation (WHO), a smoker with a daily consumption of more than 20 cigarettes.

Statistical analysis

Data were collected manually using case record forms (CRFs), captured into epi-data and later transferred to STATA version 10 for analysis. Values are expressed as percentages of total respondents. Simple bivariate analysis was used to analyse the data. Priority was given to practical benefit and clinical significance in interpreting statistically significant data. Statistical significance was set at $p < 0.05$.

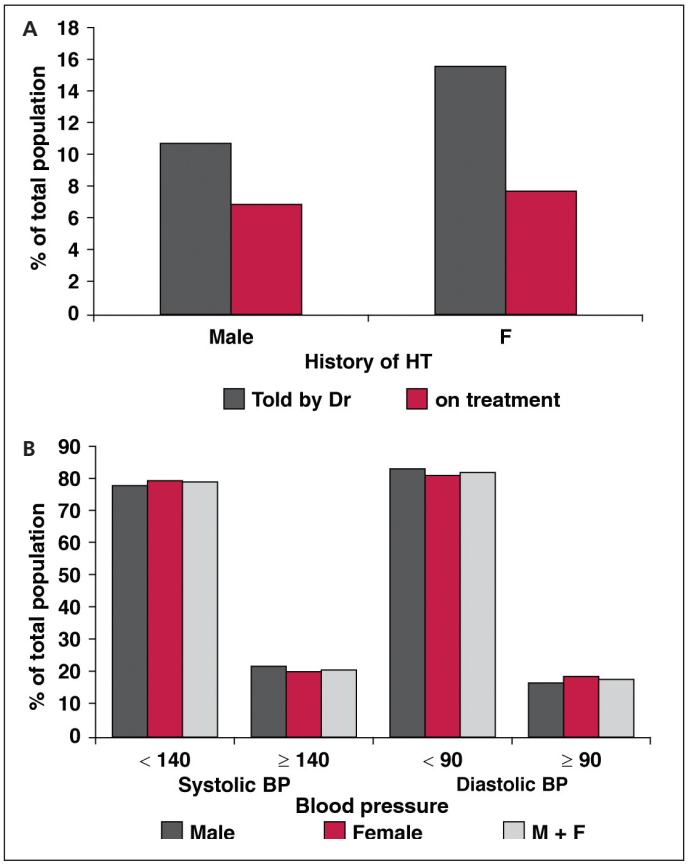


Figure 2A. History of hypertension (HT) and treatment status; 11% of males knew of their hypertension, 7% were on treatment; 16% of females knew of their hypertension, 8% were on treatment.

Figure 2B. Systolic and diastolic BP; 21% of the population had SBP ≥ 140 mmHg; 18% of the population had DBP of ≥ 90 mmHg.

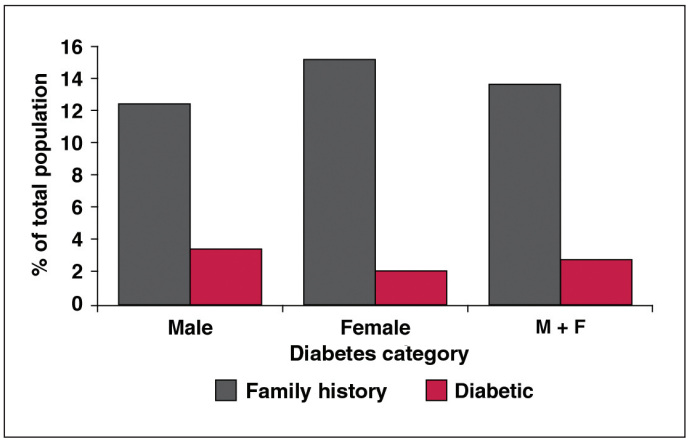


Figure 3. Family history of DM and on treatment for DM; 13.9% of the total study population had a family history of DM; 2.9% were diabetic.

Results

A total of 611 eligible adults were selected and approached to participate in the survey. Of these, 93 (15.22%) refused while 518 (84.87%) consented to take part in the survey. Of the 518 participants who took part, 56% were female and 29% had no formal education, while 41% had primary school education. BP, and fasting blood sugar and total cholesterol levels were measured in 100, 25.7 and 27.8%, respectively of the 518 participants (Fig. 1, Table 1).

Sixteen per cent of females and 11% of males were told by the doctor that they had hypertension, while only 8% of females and 7% of males with diagnosed hypertension were currently on medication for hypertension (Fig. 2). Twenty per cent of females had SBP ≥ 140 mmHg and 20% had DBP ≥ 90 mmHg; while 22%

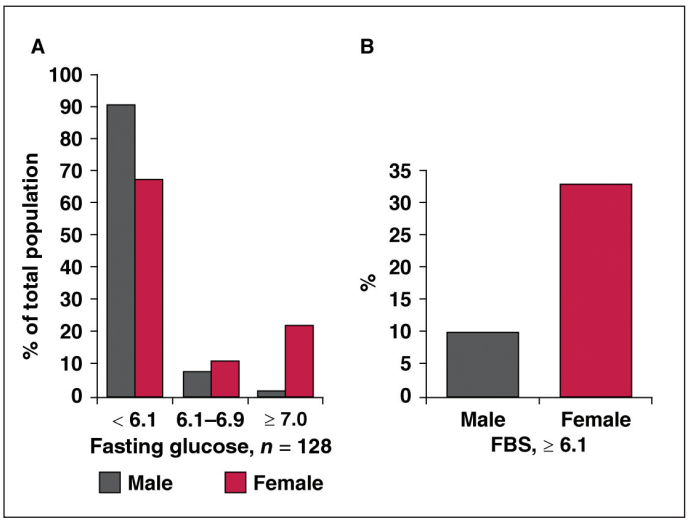
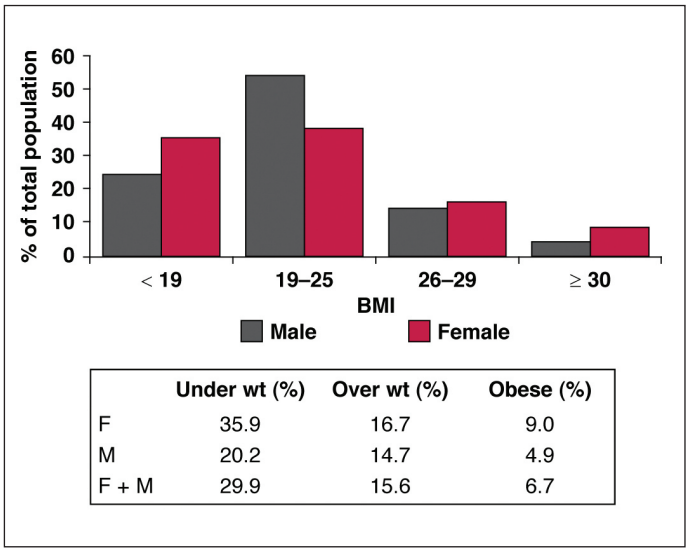


Figure 4. Fasting blood sugar (FBS). A) 19% had FBS 6.1–6.9; 9% ≥ 7.0 mmol/l. B) 31% female FBS ≥ 6.1, 10% Male ≥ 6.1 mmol/l.



	Under wt (%)	Over wt (%)	Obese (%)
F	35.9	16.7	9.0
M	20.2	14.7	4.9
F + M	29.9	15.6	6.7

Figure 5. Body mass index; 29.9% were underweight, 15.6% were overweight, and 6.7% were obese.

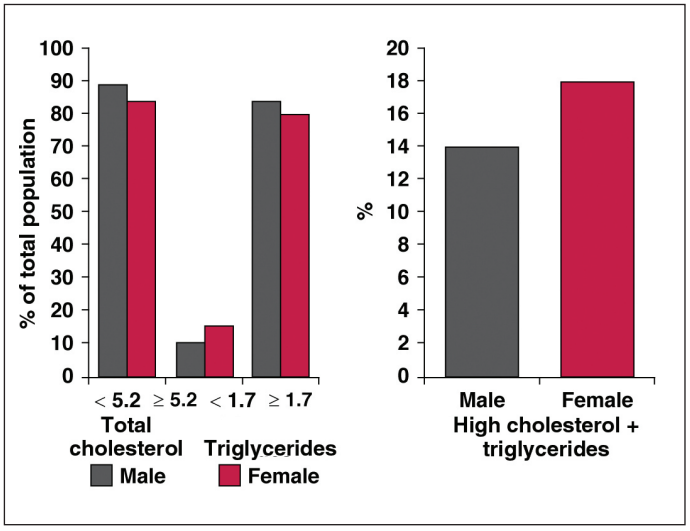


Figure 6. Cholesterol and triglycerides; 14% of males had elevated lipids, 18% of females had elevated lipids.

of males had SBP ≥ 140 mmHg and 17% had DBP ≥ 90 mmHg (Fig. 3). There was no statistical difference between the genders (SBP, $p = 0.758$; DBP, $p = 0.503$).

Ten per cent of males had fasting blood sugar levels > 6.0 mmol/l compared to 33% of females, while 12.5% of male had a positive family history of diabetes mellitus (DM) and 3.5% were on treatment for DM. Sixteen per cent of females had a positive family history of DM and 2.2% were on treatment for DM (Figs 4, 5).

The prevalence of underweight, overweight and obesity were more frequent in women than men (35.9 vs 20.2%, 16.7 vs 14.7% and 9.0 vs 4.9%) (Fig. 6). Raised total cholesterol was more frequent in women than men (16 vs 11%). Ten per cent of the population had elevated total cholesterol levels while 21% had elevated triglyceride levels (Fig. 7). Nine per cent of males and 5.7% females ate five or more servings of fruit per day; 1.2% of males and 1.1% of females ate five or more servings of vegetables per day.

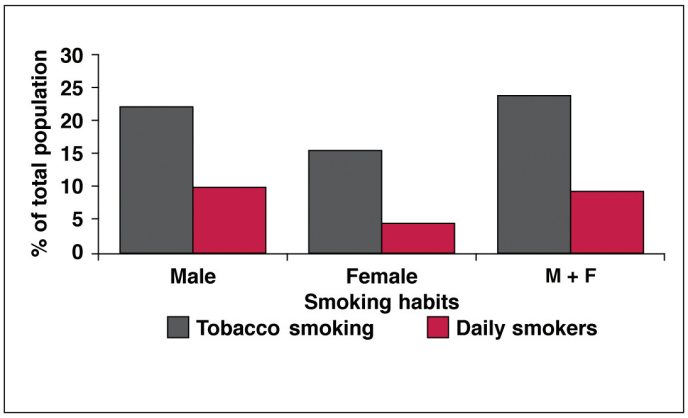


Figure 7. Smoking habits; 24% had a history of smoking; 9.6% were daily smokers (average number of cigarettes per day was six for males and three for females).

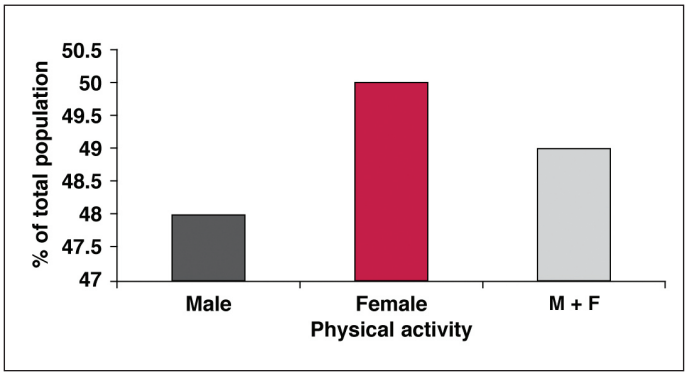


Figure 8. Physical activity; 51% of the population was physically inactive.

Tobacco smoking, alcohol drinking (any amount) and excessive alcohol drinking were more common in men than women (22.5 vs 15.5%, 23.9 vs 10.3%, 4.1 vs 1.2%, respectively). There was no significant difference between the genders with regard to physical activity (52% male, 50% female, $p = 0.703$) (Figs 8–10).

Discussion

This is the first population-based survey using internationally standardised protocols to report the prevalence of risk factors for NCDs in the Kasese district of Uganda. This study demonstrated that chronic non-communicable diseases and their risk factors constitute a public health problem in the Kasese district, with at least one in five men smoking tobacco, one in five with hypertension, one in 10 with a positive family history of DM, one in five being pre-diabetic and therefore a candidate for the metabolic syndrome, and one in five overweight/obese.

The first major finding of this study was the high prevalence of hypertension, both self-reported and point-measured BP during the survey. The majority of people with hypertension did not know they had this medical problem, which is consistent with findings from other studies in sub-Saharan Africa.[17] Hypertension is the leading cause of stroke in Africa. A further finding that only 3.7% were on treatment reflects the low level of knowledge of the dangers of untreated hypertension in the population. A striking finding was that there was no difference in the prevalence of hypertension between the genders.

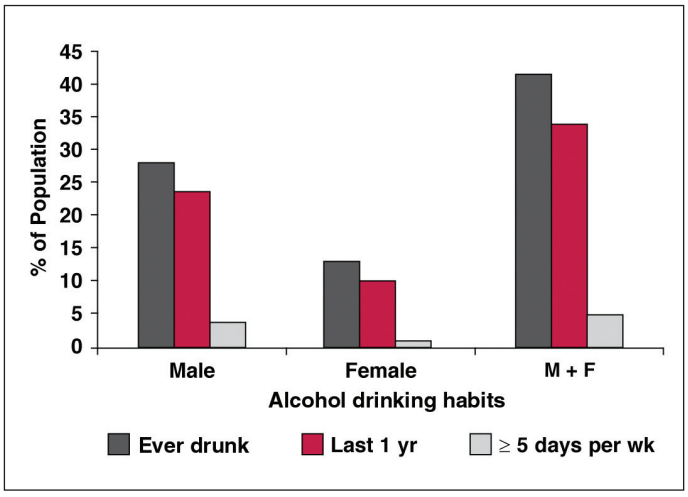


Figure 9. Alcohol consumption; 41.6% had ever drunk alcohol in life; 34.1% drank in past 12 months; 5.3% of active drinkers ≥ 5 days/wk – (average number of drinks per day was 3 for men and 2 for women)

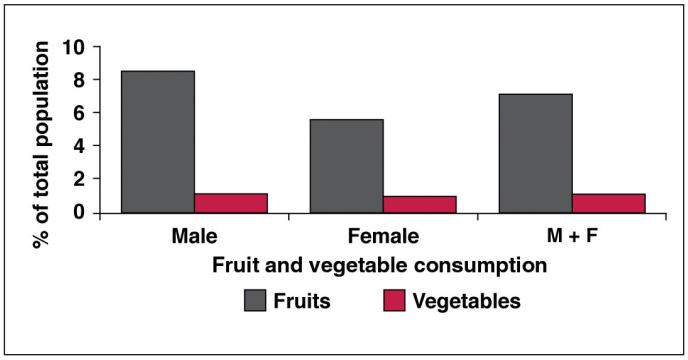


Figure 10. Fruit and vegetable intake; 7.2% of total population ate ≥ 5 servings of fruits per week; 1.2% of total population ate ≥ 5 servings of vegetables per week

Factors not measured in this survey, and which may explain the observed risk among women, were hormonal status, saturated fat consumption and salt intake. Also, further studies should be done to document the proportion of those on treatment whose BP is under control, as well as the presence of hypertensive heart disease among those with hypertension.

The second major finding was that the risk profile of this predominantly rural population of Kasese was markedly different from that reported previously for the urban and peri-urban settings.[10-12] The prevalence of raised blood glucose levels (defined as capillary whole BG of at least 6.1 mmol/l) in 31% of females and 10% of males, DM (13.9% had a family history of DM, 2.9% were diabetic), raised BMI (15.6% were overweight, 6.7% were obese), and tobacco smoking (24% had history of smoking with 9.6% heavy smokers) were markedly higher than previously speculated. The level of physical activity was surprisingly lower than expected in this predominantly hilly area, although different definitions of physical activity could have led to this response. These findings support the need for regular screening of individuals for NCDs and their risk factors.

There was a high prevalence of underweight people (29.9%). When taken together with the observed rates of DM and glucose intolerance, questions arise with regard to the possibility of a connection between under-nutrition and DM.

In general, this study highlights the need to undertake population-based studies in all districts in the country to quantify the magnitude of NCDs at a national level. It is evident that there is variation among ethnic groups and locations, as various factors contribute to the development of disease and other factors contribute to the perpetuation of diseases.

In order to institute a cost-effective intervention, the specific factors at play in a given population must be identified. It may not be appropriate to generalise these findings to refer to the Karamoja population. These results though are useful in guiding intervention and preventative measures for the Kasese population, and should be well received by policy makers in the local government of Kasese, as well as the ministry headquarters. For example, vegetables and fruits are grown in large quantities in Kasese, but consumption is low. Most are sold to the cities. The population is not aware of the benefits to their health of eating fruit and vegetables. Mass education to encourage increased consumption of fruits and vegetables will benefit the population.

A key strength of this study was the use of a representative sample, with analysis taking into account the complex survey design. The relatively high response level minimises the likelihood of selection bias, and the range of factors that were measured should be a good reflection of those factors in the Kasese population. The use of WHO standardised protocols, intensive training of data-collection staff, pre-study testing of procedures, and the close supervision of staff during data collection all highlight the attention that was paid to minimising avoidable sources of measurement error.

Limitations of this study need to be borne in mind. The STEPS methodology is designed to provide standardised information on key modifiable risk factors that can be measured in population-based surveys without resorting to high-technology instruments. It is not designed to measure total energy intake, dietary fat, dietary sodium, body fatness or physical activity by objective methods, such as accelerometry and pedometry. Information on these factors would have provided a more comprehensive picture of the relationships we studied. In addition, these cross-sectional data do not allow age-related differences in BP, blood glucose and total cholesterol levels to be attributed to ageing, independent of cohort effects. Assessment of risk factors by age group as well as fasting blood sugar level for different BMIs would have provided more insight. Finally, due to lack of power, we were not able to assess the relationship between underweight and diabetes.

Conclusion

This study provides the first NCD risk-factor profile of people in the Kasese district, Uganda, using internationally standardised methodology. Our findings for this predominantly rural sample provide evidence for health policy-makers as well as district authorities on lifestyle problems in the population studied. The burden of more diseases is to be expected if an effective prevention strategy is not undertaken.

Although even short-term educational programmes have been shown to be effective in improving lifestyle, a durable education strategy and cost-saving policies supported by sustained large-scale media education and school-based educational programmes could be the starting point for a possible national programme on

controlling NCDs in Uganda. A national NCD risk-factor survey should however be undertaken to avoid biased generalisation of results, as Kasese is not a representative population of Uganda.

Acknowledgements

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A novel treatment for type 2 diabetes patients

Previous reports suggest that the kallikrein-kinin system (KKS) could be involved in insulin sensitisation and glucose homeostasis. The KKS consists of serine protease tissue kallikrein-1 (KLK-1), kinogens, bradykinin (BK) and lys-bradykinin. BK has been shown to increase insulin sensitivity and glucose uptake in rat models; however, the role of KLK-1 is not well known.

KLK-1 is a 'ubiquitous 238 amino acid glycoprotein [that] exists as a heterogeneous mixture of glycoforms due to variable glycosylation at three potential sites', according to a study published recently in *PLoS One*. In pre-clinical studies, KLK-1 has been shown to significantly decrease blood pressure, and insulin, glucose, plasma triglyceride and cholesterol levels. However, these benefits of KLK-1 were not characterised in terms of dose, glycoform profile or activity.

To further investigate the characteristics and benefits of KLK-1 for type 2 diabetes, Kolodka and colleagues designed a pre-clinical study involving DM199, a recombinant human tissue kallikrein-1 protein (rhKLK-1). In this study, DM199 was produced from Chinese hamster ovary cells. Its specific activity was measured *in vitro* by cleavage of the substrate D-Val-Leu-Arg-7 amido-4-trifluoromethyl coumarin, and compared to the activity of porcine kininogenase standard acquired from the National Institute for Biological Standards and Control. After the purification process, DM199 was injected into obese rats and mice for fasting blood glucose and oral glucose tolerance tests.

The results from hyperinsulinaemic–euglycaemic clamp studies indicated that DM199 helped increase glucose infusion rates and glucose disposal in non-diabetic rats. In obese db/db mice, a single dose of 360 µg/kg of DM199 could significantly reduce fasting blood glucose (FBG) and post-prandial glucose levels. In Zucker diabetic fatty (ZDF) rats, sub-acute dosing of DM199 for seven days also increased fasting insulin levels significantly. After the sub-acute dosing period, FBG levels in ZDF rats remained lower than controls during the wash-out period.

According to the authors, the low FBG levels observed in the rats after medium and high doses of DM199 may have been due to a protective effect on beta-cell function or the stimulation effect on insulin secretion. Based on the results of this study, DM199 could be a potential novel therapy for type 2 diabetes patients due to its anti-hyperglycaemic effect.

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Prevalence of the metabolic syndrome in people of Asian Indian origin: outcomes by definitions

M DAS, S PAL, A GHOSH

Abstract

Background: **The prevalence of the metabolic syndrome (MS) is high among south Asian Indians. In order to better comprehend the MS, its definition and modifications require region-specific cut-off values and common minimum criteria for people of Indian origin.**

Methods: **To define the MS, the criteria as defined in the National Cholesterol Education Program (NCEP): expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) (ATP III 2001), followed by the modified ATP III of 2005 were used, along with a modified version specific to the people of south Asian origin (ATP III SAS, 2009).**

Results: **The three definitions showed differences in prevalence of the MS among the adult Asian Indians. According to the criteria of NCEP ATP III 2001, the prevalence was found to be 32.3%. Using the modified ATP III 2005, the prevalence was 48.3%, and for south Asian-specific (SAS) ATP III, it was 31.4%. For all three definitions, females had a considerably higher prevalence of the MS than males. It was also observed that that a large number of individuals were misclassified due to lack of common minimum criteria.**

Conclusion: **In order to curb the growing threat of the MS, and to aid clinical management among people of Indian origin, a more comprehensive definition of the MS is urgently required.**

Keywords: obesity, metabolic syndrome, CVD, diabetes, Asian Indians

Introduction

People of Indian origin are ethnically a particularly vulnerable group from the standpoint of metabolic abnormalities. Throughout the Asia–Pacific region, there are differences in the prevalence of obesity and metabolic disturbances. South Asians (e.g. Indians) have a more centralised distribution of body fat and a markedly higher mean waist–hip ratio (WHR) for a given level of body mass index (BMI) compared to Europeans. In Asian populations, morbidity and mortality is occurring in people with lower BMI and smaller waist circumference (WC). Therefore they tend to accumulate intra-abdominal fat without developing generalised obesity.[1,2]

The metabolic syndrome (MS), which can be defined as the constellation of cardiovascular disease (CVD) risk factors, is one of the growing public health burdens in the Asia–Pacific region, although the populations are no more overweight than Europeans and Americans.[1] The MS is a phenotype and therefore is used to identify subjects with a high risk, based on easily measurable biological variables. However, it lacks some critical variables, which are population specific, in order to better predict the population's risk. It therefore needs further validation among Asian Indians.[3,4]

The present work was an attempt to study the prevalence of the MS using different definitions of the MS in people of Indian origin.

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Methods

The cross-sectional study comprised 350 adult Asian Indians (≥ 30 years) (184 males and 166 females) living in and around Calcutta, India. Written consent was obtained from all participants. The institutional ethical committee of the Human Genetic Engineering Research Center (HGERC), Calcutta, India approved the study. Written consent from participants was also obtained prior to actual commencement of the study.

Anthropometric measures, namely height, weight and waist circumference were obtained using standard techniques.[5] BMI (kg/m^2) was computed accordingly.

Left arm systolic (SBP) and diastolic (DBP) blood pressure measurements were taken twice using a sphygmomanometer and stethoscope and were averaged for the analyses. A third measurement was taken only when the difference between the two measurements was ≥ 5 mmHg. Prior medical records for blood pressure were also taken into consideration.

A fasting blood sample (~7 ml) was collected from each subject for the determination of metabolic profiles. All subjects maintained an overnight fast of approximately 12 hours prior to blood collection. The serum was separated by centrifugation within two hours of collection. Determination of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol and fasting blood glucose (FBG) levels was carried out on the separated serum using a semi-autoanalyser. Low-density lipoprotein (LDL) cholesterol was then calculated using the standard formula:

LDL = TC – (HDL + TG/5).

All biochemical parameters were analysed at the HGERC and were measured in mmol/l.

Definition of the metabolic syndrome

To define the metabolic syndrome, the criteria as set out in the National Cholesterol Education Program (NCEP): expert panel on

Table 1. Descriptive statistics of the study population (n = 350)

	Male (n = 184)		Female (n = 166)		Total (n = 350)	
Variables	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)**	54.04	12.40	48.48	11.57	51.40	12.31
BMI (kg/m²)	22.37	4.09	23.20	4.37	22.76	4.24
WC (cm)	89.81	10.04	88.90	9.69	89.38	9.87
SBP (mmHg)	132.97	24.02	137.21	24.52	134.98	24.31
DBP (mmHg)	82.22	11.41	83.48	10.55	82.82	11.01
TC (mmol/l)*	2.23	0.31	2.24	0.26	2.27	0.29
TG (mmol/l)	1.61	0.30	1.57	0.25	1.59	0.28
HDL (mmol/l)	1.13	0.12	1.13	0.11	1.13	0.12
LDL (mmol/l)	3.39	0.70	3.25	0.59	3.32	0.65
VLDL (mmol/l)	0.32	0.006	0.31	0.005	0.31	0.005
FBG (mmol/l)**	5.17	1.30	4.92	0.93	5.05	1.15

BMI = body mass index; WC = waist circumference; WHR = waist–hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; TG = triglyceride; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; FBG = fasting blood glucose.
Significant gender difference at *$p < 0.05$; **$p < 0.01$.

detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) (ATP III, 2001),[6] followed by the ATP III as modified in 2005,[7] were used, plus the modified version specific to the people of south Asian origin (ATP III SAS 2009).[8-10] These criteria were as follows:

- waist circumference: male > 90 cm; female > 80 cm
- triglycerides: ≥ 2.25 mmol/l
- HDL: male < 1.03 mmol/l; female < 1.28 mmol/l
- blood pressure: SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg
- fasting blood glucose: ≥ 5.56 mmol/l.

Statistical analyses

Parameters were expressed as mean and standard deviation (SD), separately for males and females in the study population. The prevalence (%) of the MS and its confounding factors were calculated using standard cut-off values. All statistical analyses were performed using SPSS (PC + version 10.0).

Results

The mean and standard deviation by gender of obesity values, lipid profiles and blood pressure is presented in Table 1. It was observed that males had significantly ($p < 0.05$) higher mean total cholesterol and fasting blood glucose values ($p < 0.05$) than females.

Table 2. Prevalence (%) of metabolic syndrome phenotypes by definitions

Factors	ATP III 2001	ATP III 2005	SAS 2009
WC	30.9	61.1	61.1
TG	39.7	39.7	2.3
HDL	50.9	50.9	50.9
BP	63.7	63.7	63.7
FBG	10.0	21.7	21.7
Metabolic syndrome (%)	32.3	48.3	31.4

SAS = South Asian specific.

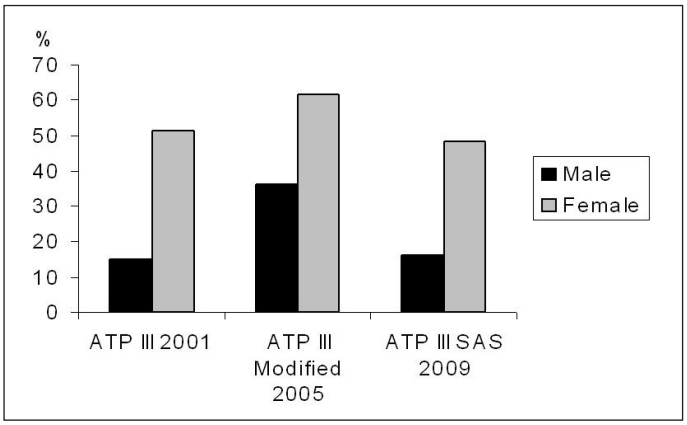

Fig. 1. Prevalence of the metabolic syndrome by definitions and gender.

The difference in prevalence of the MS according to the three definitions is presented in Table 2. Using the original ATP III (2001) definition, the overall prevalence of the MS in the study was found to be 32.3%. However, according to the ATP III modified criteria (2005), the prevalence was found to be 48.3% among the participants. When the south Asian-specific cut-off values were taken into consideration, the prevalence was found to be 31.4%.

Out of five confounding factors, the three factors playing a crucial role were high abdominal obesity (61.1%), low HDL cholesterol (50.9%) and high blood pressure (63.7%). It was also observed that for all three definitions (NCEP ATP III 2001, ATP III modified 2005, and ATP III SAS 2009), female participants had a considerably higher prevalence of the MS compared to male subjects (Fig. 1).

Discussion

It was observed that the prevalence of the MS was different, depending on the three definitions used. Moreover, the prevalence of elevated triglyceride levels (hypertriglyceridaemia), which is a distinctive feature of people of Indian origin, varied considerably in the study population owing to the use of the south Asian-specific cut-off value for elevated triglycerides. The marked difference in the overall prevalence of the MS from the ATP III (2005) definition to the SAS (2009) definition (48.3 vs 31.4%) was due to the use of the south Asian-specific cut-off values for WC and triglyceride levels. Importantly, whether the modified ATP III (2005) or the revised SAS (2009) definition is used, a large number of individuals are likely to be misclassified due to lack of a common minimum criterion required to better comprehend the problem of the MS among Asian Indians.

Several other studies have shown such discrepancies, not only in the Indian population but also in other Asian countries, such as China and Iran. In a study from India,[10] the World Health Organisation (WHO), ATP III and IDF criteria of the MS identified a differential prevalence of the MS in the study population. The WHO criteria identified a greater number of coronary artery disease (CAD) subjects in males, but not in females.[10]

Studies pertaining to Asian Indians revealed that the ATP III criteria identified a significantly higher proportion of people with the MS compared with the WHO criteria.[11,12] It was mentioned that lower cut-off values of WC and BMI to define the MS might be critical for the accurate assessment of the MS among

Asian Indians. Moreover, inclusion of BMI and making WC a non-obligatory criterion, more cases of the MS were detected. However, for Asian Indians, making WC a mandatory variable to define the MS would lead to non-inclusion of many patients who would otherwise be diagnosed as having the MS according to the modified NCEP ATP III definition.

A study from China also revealed that in subjects with established type 2 diabetes, the International Diabetes Federation (IDF) definition of the MS failed to identify a subgroup of patients who had the highest risk for CHD, whereas the ATP III definition predicted an increased risk of CHD in the same cohort.[13] In a study in an adult Iranian population, the IDF definition of the MS was found to have a good correlation with the ATP III definition but a lower correlation with the WHO definition.[14]

It is therefore reasonable to argue that to use the presence of the MS as a more sensitive guideline, factors such as family history of cardiovascular disease, lack of physical activity, abuse of alcohol, cigarette smoking and tobacco chewing, along with region-specific cut-off values are required to better comprehend the MS in people of Indian origin. There is an urgent need to develop a comprehensive risk profile for Asian Indians. Moreover, owing to ethnic and cultural heterogeneity in people of Indian origin, studies incorporating those subjects living in the Indian subcontinent, as well as migrants elsewhere in the world are required before making any statement about the definition of the MS in people of Indian origin.

Conclusion

The major limitation of the present investigation was that the study was performed on a relatively small sample size and therefore is not representative of the Asian Indian population. Because of considerable ethnic and cultural heterogeneity in the Asian Indian population, it is imperative to study other ethnic groups to see whether the observed trend also exists there. Results from such studies could be used to define the metabolic syndrome in the Asian Indian population. Moreover, investigations should also be initiated in the Indian diaspora worldwide to elucidate whether migrant Asian Indians show similar trends to those of sedentes in India or to native populations of their respective counties. Such studies would generate valuable information on the clinical management of the metabolic syndrome.

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Diagnostic and prognostic values of B-type natriuretic peptides (BNP) and N-terminal fragment brain natriuretic peptides (NT-pro-BNP)

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B-type natriuretic peptide (BNP) is a member of a four-natriuretic peptide family that shares a common 17-peptide ring structure. The N-terminal fragment (NT-pro-BNP) is biologically inert, but both are secreted in the plasma in equimolar quantities and both have been evaluated for use in the management of congestive heart failure. BNP and NT-pro-BNP are frequently used in the diagnosis of congestive heart failure and the distinction between patients with dyspnoea of cardiac or pulmonary origin. Values of NT-pro-BNP are affected by age or the presence of one or several co-morbidities such as chronic renal failure, type 2 diabetes, and acute coronary syndrome. 'Normal' values of these peptides also vary depending on the type of test used. The performance characteristics of these tests vary depending on the patients on whom they are used and the manufacturer. For this reason, the determination of reference values for this peptide represents such a challenge.

Keywords: natriuretic peptides, prognostic values, NT-pro-BNP

Introduction

BNP was initially discovered in the porcine brain, but the largest concentrations are found in the heart. It is a peptide with 32 amino acids, synthesised in the ventricles as a response to stretching of the myocytes and/or pressure overload. It is released as an active hormone and as an inactive N-terminal fragment (NT-pro-BNP).[1]

Once released in the blood flow, BNP has numerous physiological actions, their net effect being to reduce pre- and post-load. Specifically, BNP produces a decreased vascular tonus by relaxing the smooth muscles, leading to a decrease in post-load. In addition, it induces a movement of fluid into the interstitial space, thus leading to a decrease in pre-load.

BNP reduces the proliferation of fibroblasts and smooth muscle cells, sympathetic nervous activity, water and salt retention, release of the antidiuresis hormone, and synthesis of aldosterone and its release from the adrenal glands. In the kidneys, BNP increases glomerular filtration rate and renal blood flow by increasing the outgoing arterial tonus and decreasing the ingoing one. In addition it decreases the release of renin and the reabsorption of sodium, leading to diuresis and natriuresis.[2]

The N-terminal fragment of BNP is derived from proteolysis of pro-BNP, which is composed of 108 amino acids. It consists of 76 amino acids and has recently caused great interest, due to its possible role in monitoring heart failure and distinguishing acute coronary syndromes. Its effects on diuresis and natriuresis in patients with congestive heart failure represent a compensatory mechanism for stress on the myocytes, which leads to ventricular dysfunction.[1]

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Diagnostic and prognostic value of BNP and NT-pro-BNP

Serum levels of natriuretic peptides are important, not just as indicators of numerous cardiovascular deficiencies but also as markers of their severity.[1] For patients with acute coronary syndromes, the determination of BNP levels offers predictive information on the apportioning of risk, in the absence of elevation in the S-T interval. In addition, BNP and NT-pro-BNP have prognostic signification for acute pulmonary embolism.[1]

The diagnostic value was recently confirmed by Coutance *et al*.[3] Even if high levels of BNP demonstrate a high sensitivity for detecting patients with risk of sudden death, the specificity of this neurohormone is decreased. A diverse analysis between mortality and levels of BNP was recently conducted by Nunez and his team, which demonstrated a positive linear correlation between the risk of death and BNP level.[4]

With regard to the prognostic value of NT-pro-BNP for chronic heart failure, the Val-HeFT study (Valsartan Heart Failure Trial) demonstrated the positive nature of advanced heart failure. Moreover, BNP concentrations appeared significantly increased in patients with dilated cardiomyopathy and cardiovascular disease in NYHA classes III or IV, but it could not predict mortality or the requirement for a heart transplant.[1]

Variability of BNP

Despite the evidence that BNP is secreted in ventricular overload states, there is an individual and inter-individual variation in both healthy subjects and those with stable chronic heart failure, which makes the interpretation of BNP levels difficult. Multiple studies have shown that only changes in BNP level larger than approximately 113 to 130% and changes in NT-pro-BNP larger than 90 to 98% can be considered to have exceeded individual, inter-individual and analytical variations.[2]

There are several reasons for these variations. In healthy subjects, BNP level is connected to gender and age; its levels increase with age and are higher in women than in men. Despite increases with age, BNP and NT-pro-BNP proved effective in excluding congestive heart failure in an elderly population that presented with acute

dyspnoea. Race also plays a role, with a higher variability being seen in African-Americans than Caucasians.[2] Studies conducted in Africa found reference values higher than those recommended by the manufacturer.[5] A recent study showed that the reference value for NT-pro-BNP depends on age over 50 years.[6] Another study containing nonagenarian patients reported a link between values of NT-pro-BNP and echocardiographic anomalies.[7]

Levels of BNP are lower for obese patients compared to non-obese. In addition, it was observed that genetics plays a role in the variability of BNP levels. Along with age, gender, genetics and body mass index, there are other physiological reasons for the variability of BNP.

Renal function also affects levels of BNP, significantly increased levels being recorded for those with renal dysfunction. Patients on haemodialysis showed significant rhythmic oscillations in BNP levels, compared to healthy subjects.[2] In the Breathing Not Properly study, BNP predictors from 'the grey area' in the absence of heart failure included age, atrial fibrillation, lower body mass index and anaemia.[2]

The lack of a single set of normal values due to different idiopathic levels and the available commercial kits can lead to confusion in clinical application. While some researchers claim that values above 100 pg/ml indicate heart failure, others suggest a value above 200 pg/ml. The ADHERE study, which included over 48 000 patients, indicated as prognosticators of mortality values over 430 pg/ml.[8] In all cited conditions, a careful clinical examination, accompanied by an echocardiographic examination that evaluates the systolic–diastolic function, should be complementary to BNP analysis for diagnostic strategy and implementation of treatment.[9]

Heart failure

Chronic heart failure is an illness that is appearing with increasing frequency, especially in elderly patients. Nevertheless, classification is often difficult due to non-specific symptoms and the lack of a 'gold standard' protocol for a correct diagnosis.[9] The European guidelines from 2008 highlight the role of natriuretic peptides as potential markers of heart failure.[9]

Measurement of plasma concentrations of BNP has proved to be a very efficient screening technique for the identification of patients with various heart diseases, regardless of aetiology and the degree of systolic dysfunction of the left ventricle, which has the potential to develop into manifested heart failure and has a high risk of producing a cardiovascular event. Recently, the Food and Drug Administration approved NT-pro-BNP for the evaluation of the prognosis of patients with congestive heart failure and acute coronary syndromes. Determination of BNP level was also approved for risk segregation in acute coronary syndromes.[10]

Multiple studies have confirmed the efficiency of the determination of BNP concentrations in the plasma of patients with acute dyspnoea. The Breathing Not Properly study is an example, in which 1 586 patients participated.[9] In addition, studies such as Val-HeFT[11,12] and COPERNICUS[13] indicated that chronic treatment with beta-blockers and blockers of the renin–angiotensin–aldosterone system leads to a reduction in levels of natriuretic peptides in the plasma and improved the prognosis, which is possibly a reflection of the improvement in cardiac function secondary to treatment.[2]

Together with its role in acute decompensated heart failure, levels of BNP are also high for diastolic dysfunction. Increased BNP levels can be found with isolated diastolic dysfunction, hypertrophic cardiomyopathy, or associated with systolic dysfunction. Echo-cardiographic parameters correlated with BNP levels include mass index of the left ventricle, its end-diastolic volume and isometric relaxation time. The further the stage of diastolic dysfunction the higher the levels of BNP.[2]

Other heart diseases

As with congestive heart failure, BNP level has a prognostic value for acute coronary syndromes. BNP is additive with, and independent of, the increases in troponin I for these syndromes.[2]

A sub-study of Breathing Not Properly showed that plasma levels of BNP were high for patients with atrial fibrillation that was not diagnosed with congestive heart failure, but its levels were not different in the presence of heart failure.[2] In addition, levels of BNP were high with heart valve diseases and aortic stenosis, and were linearly related to the symptoms. Moreover, levels over 190 pg/ml foresaw a negative evolution, suggesting that BNP can be used for identification of subgroups of patients that would benefit from a replacement of the aortic valve. In addition, BNP level was increased with aortic insufficiency.[2]

For patients with mitral insufficiency, an increased BNP level was correlated with mortality and the onset of congestive heart failure, regardless of the degree of regurgitation present on echocardiography, suggesting that BNP is a reflection of its atrial and ventricular consequences.[2] Finally, it was proven that NT-pro-BNP was correlated with symptoms and echocardiographic severity of mitral stenosis.[2] In addition, the levels of BNP were increased in patients with pulmonary embolism and pulmonary hypertension.[2]

In unstable angina, NT-pro-BNP represents an effective marker of the damage produced by cardiac ischaemia. The severity of the coronary disease is shown by an increase in the levels of NT-pro-BNP. In addition, in the case of acute coronary syndromes, NT-pro-BNP had an immuno-modulating role and offered important information for the prognosis of patients.[1]

Castro *et al*.[14] divided 87 patients with non-ST-segment elevation acute coronary syndrome into two groups: 37 (42.5%) with unstable angina and 50 (57.5%) with non-ST-segment elevation myocardial infarction. Left ventricular ejection fraction above 40% was found in 86.2% of the total sample. Serum levels of NT-proBNP were higher in patients with non-ST-segment elevation myocardial infarction than in those with unstable angina ($p < 0.001$).[14]

Increased levels of NT-pro-BNP were associated with increases in troponin I (rs = 0.425, $p < 0.001$), peak CK-MB (rs = 0.458, $p< 0.001$) and low left ventricular ejection fraction (rs = –0.345, $p= 0.002$); no correlation was found with the TIMI risk score (rs = 0.082, $p = 0.44$). Multivariate analysis revealed that left ventricular ejection fraction and troponin I levels were independently correlated with NT-pro-BNP levels ($p = 0.017$ and $p = 0.002$, respectively).[14]

Renal failure

Renal failure complicates congestive heart failure so often that many have suggested a 'cardio–renal' syndrome, which influences survival, duration of hospitalisation and re-admission ratio.[2] A sub-study of PRIDE[15] showed a reduction in the sensitivity and specificity of NT-pro-BNP in the diagnosis of heart failure for persons with renal failure, and also showed that its concentration tends to be more affected by renal dysfunction than BNP levels.[2] The levels of BNP are known to be significantly increased for patients on haemodialysis, and they are known to decrease after dialysis.[2]

In another study that involved 72 patients on haemodialysis, NT-pro-BNP level was not associated with heart failure, but was dependent on factors associated with an increase in post-load.[16] An association between increased levels of NT-pro-BNP and chronic renal failure was also demonstrated in patients without left ventricular dysfunction.[17,18]

Diabetes mellitus

In a study on 371 patients with heart failure, 81 of whom had diabetes, the levels of 10 neurohormones from the plasma (adrenaline, noradrenaline, dopamine, aldosterone, renin, endothelin, ANP, NT-pro-ANP, BNP and NT-pro-BNP) were measured. All patients were also part of the PRIME-II study that investigated the effects of ibopamine on the causes of mortality in patients with moderate or severe heart failure.[19]

Most of the neurohormones were similar between the two groups, but patients with diabetes had higher values of BNP and NT-pro-BNP. The patients were monitored for five years, and during this time, 195 died, of whom 51 had diabetes. For patients with diabetes, noradrenaline, ANP, NT-pro-ANP, BNP and NT-pro-BNP levels were significantly higher than in those who did not survive. Therefore BNP and NT-pro-BNP proved the strongest predictors of outcome for both groups of patients.[19]

The most likely explanation for the increase in BNP and NT-pro-BNP levels in these patients with diabetes was the presence of diastolic dysfunction.[19] Another study showed normal values of NT-pro-BNP for women with gestational type 2 diabetes mellitus, and lower values for those with insulin-dependent gestational diabetes.[20]

Cirrhotic cardiomyopathy

Cirrhotic cardiomyopathy is an under-diagnosed condition. This is most likely due to the fact that there is no single diagnostic test to identify these patients.[21]

Numerous recent studies demonstrated that patients with hepatic cirrhosis had increased plasma concentrations of BNP and NT-pro-BNP, representing markers of early ventricular dysfunction. Henriksen *et al*.[22] showed that these markers were correlated with the severity of hepatic cirrhosis, and with heart dysfunction. BNP could therefore have prognostic value with regard to the evolution of cirrhosis. In addition NT-pro-BNP represents a useful marker to demonstrate the existence of diastolic dysfunction of the left ventricle caused by a chronic hepatic disease.[23]

A study conducted on 153 patients subjected to a liver transplant determined their BNP levels post-transplant and on days 1 and 7. It was observed that a BNP level higher than 391 pg/ml immediately after the liver transplant appeared to be an early marker for heart dysfunction related to the cirrhosis.[24]

Conclusion

In patients with dyspnoea, overlapping or even conflicting history, physical and radiographic findings often hinder the differentiation between cardiac and non-cardiac aetiology. The primary value of BNP and NT-pro-BNP testing in the emergency department is its diagnostic value in the differential diagnosis of acute dyspnoea and possible congestive heart failure.

Levels of natriuretic peptides may also assist the emergency physician in appropriately triaging the patient with congestive heart failure.[25] Studies have shown that measurements of BNP or NT-pro-BNP in the emergency department can be used to establish the diagnosis of congestive heart failure when clinical presentation is ambiguous or when confounding co-morbidities are present.[25]

After multiple studies, the conclusion was reached that levels of BNP < 100 pg/ml and > 500 pg/ml have a positive and negative predictive value, respectively, of 90% for the diagnosis of congestive heart failure for patients presenting with acute dyspnoea. For values between 100 and 500 pg/ml, the physicians must consider underlying left ventricular dysfunction, the effects of renal failure, or right ventricular dysfunction secondary to chronic pulmonary disease or acute pulmonary embolism.[25]

The recommended thresholds of less than 100 pg/ml to rule out heart failure and more than 500 pg/ml to rule in heart failure have been estimated to have the following likelihood ratios (LRs): LR-negative = 0.13 and LR-positive = 8.1. These different cut-off values create an intermediate range of 100–500 pg/ml with an LR-positive of only 1.9 pg/ml. Therefore, an intermediate BNP result alone cannot be used to rule in or rule out heart failure.[25]

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Effects of intensive glycaemic control on ischaemic heart disease

How can three landmark trials of intensive versus standard glucose-lowering strategies, ADVANCE, ACCORD and VADT, raise more questions than they answer? This was the conundrum a recent *post hoc* analysis of the studies looked to address.

None of the three studies met their primary objective of reducing cardiovascular events, despite achieving significantly lower HbA_{1c} levels. In the ACCORD study, the data-monitoring committee prematurely stopped the intensive-strategy arm due to an excess rate of cardiovascular death. These results flew squarely in the face of conventional wisdom that lowering HbA_{1c} to 'normal' levels would improve cardiovascular outcomes, similar to the clearly proven benefit of reducing microvascular complica-tions. Each trial has subsequently published numerous analyses that have tried, mostly unsuccessfully, to explain why mortality in particular did not decrease, or in the case of ACCORD, even increased, with a more intensive glycaemic strategy.

What is interesting is that across these studies, there does appear to be a consistent signal that improved glycaemic management may reduce coronary artery events. This observation was first noted over a decade ago in the UKPDS study, in which more intense glycaemic control reduced the rate of myocardial infarction (MI).

The ACCORD investigators now report a consistent reduction of about 15 to 20% in non-fatal MI, unstable angina and coronary revascularisation in the intensive-therapy arm. The benefit became more apparent during the longer follow-up period, suggesting a legacy effect. Interestingly, when controlling for achieved HbA_{1c} level, the benefit was attenuated, which implies that better glycaemic control may be causal in reducing ischaemic events.

It is important to remember that this was a *post hoc* analysis and still could not reconcile the higher rates of death in the intensive-strategy arm. But it raises the possibility that there may be strategies that can both safely lower glucose and reduce cardiovascular events. How you improve glycaemic control may be as important as the actual HbA_{1c} target level. The score of ongoing cardiovascular outcome trials of novel antihyperglycaemic agents will likely provide further insight into this clinical dilemma.

The researchers assessed 10 251 adults aged 40 to 79 years with established type 2 diabetes, mean HbA_{1c} concentration of 67 mmol/ml (8.3%) and risk factors for ischaemic heart disease, enrolled in the ACCORD trial. Participants were assigned to intensive or standard therapy [target HbA_{1c} level < 42 or 53–63 mmol/ml (< 6.0% or 7.0–7.9%), respectively]. They assessed fatal or non-fatal MI, coronary revascularisation, unstable angina and new angina during active treatment (mean 3.7 years) plus a further mean of 1.2 years.

Raised glucose concentration was a modifiable risk factor for ischaemic heart disease in middle-aged people with type 2 diabetes and other cardiovascular risk factors. MI was less frequent in the intensive- than in the standard-therapy group during active treatment (HR 0.80, 95% CI: 0.67–0.96; $p = 0.015$) and overall (HR 0.84, 95% CI: 0.72–0.97; $p = 0.02$). Findings were similar for combined MI, coronary revascularisation and unstable angina (active treatment HR 0.89, 95% CI: 0.79–0.99, overall HR 0.87; 95% CI: 0.79–0.96), and for coronary revascularisation alone (HR 0.84, 95% CI: 0.75–0.94) and unstable angina alone (HR 0.81, 95% CI: 0.67–0.97) during full follow up. With lowest achieved HbA_{1c} concentrations included as a time-dependent covariate, all hazards became non-significant.

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Drug Trends in Diabetes

Hypoglycaemia in type 2 diabetes increases the risk of cardiovascular events

In type 2 diabetes, careful control of blood glucose can help prevent or delay micro- and macrovascular complications. Initially this may be adequately achieved with lifestyle changes and oral medication, but because of the progressive nature of diabetes, characterised by gradual decline in β-cell function and density, most patients will eventually require insulin to achieve glycaemic goals.[1] The benefits of control achieved early in the disease remain for many years, despite it becoming more difficult to maintain target glucose levels.[2]

Hypoglycaemia limits effective diabetes management

A common limitation in achieving glucose targets however, both with oral therapies and especially as one intensifies insulin therapy, is hypoglycaemia.[3] Hypoglycaemia not only has a negative impact on the wellbeing of the patient in the short and long term, it is also an important factor underlying clinical inertia. This describes both a reluctance by clinicians to intensify therapy in patients who are insufficiently controlled on current therapies and a decreased motivation in patients to adhere to prescribed therapies.[3]

Hypoglycaemia becomes more common with duration of therapy

Although hypoglycaemia is infrequent in early type 2 diabetes, the duration of diabetes, loss of the glucagon response to hypoglycaemia, and duration of insulin therapy cause the incidence to begin to increase, approaching that of hypoglycaemia in type 1 diabetes. Mild hypoglycaemic events are even more common, but less reported. One prospective study reported that patients with type 2 diabetes were experiencing more than 16 mild hypoglycaemic episodes per year![4]

Nocturnal hypoglycaemia is especially common. Asymptomatic hypoglycaemia may be identified with continuous glucose monitoring in around 50% of patients with type 2 diabetes, and the majority of episodes (74%) occur at night.[5] Nocturnal hypoglycaemia may be suspected in patients who report morning headache, poor quality of sleep, vivid dreams or nightmares and profuse sweating in bed. Restlessness during sleep may disturb the partner.[6]

Hypoglycaemia worsens an already increased risk of CVD

Patients with type 2 diabetes are at increased risk of cardiovascular disease (CVD). However, results of long-term studies of intensive glucose-lowering for CVD prevention have been disappointing. Tighter glycaemic control appears to be no more effective than standard glucose reductions in reducing the risk of CVD mortality among high-risk individuals.

One hypothesis that might help to explain these observations is the occurrence of severe hypoglycaemic episodes with intensive therapy. It has been suggested that severe hypoglycaemia is associated with a significantly increased risk of adverse vascular events and CVD mortality.[7]

There are various mechanisms that link hypoglycaemia to increased risk of myocardial ischaemia, acute thrombotic events and accelerated atherosclerosis, especially in an individual who is already at high risk of CVD. Hypoglycaemia induces a number of adverse acute haemodynamic changes, including tachycardia, systolic hypertension, elevated cardiac output and myocardial oxygen demand, and increases the risk of potentially fatal cardiac arrhythmias. It is also associated with pro-thrombotic and pro-inflammatory effects, such as increased neutrophil and platelet activation, increased levels of factor VII, C-reactive protein, vascular endothelial growth factor (VEGF) and inflammatory mediators, and reduced vasodilatation consequent to endothelial dysfunction.[7]

Clinical implications of treatment-related hypoglycaemia

From a clinical perspective, while it is important to achieve adequate glycaemic control, it is also desirable to avoid hypoglycaemia, especially in patients who are at high risk for CVD.[7] Patients who are especially at risk include those with:[3]

- older age
- longer duration of diabetes
- concomitant medication
- renal dysfunction
- hypoglycaemia unawareness
- cognitive dysfunction
- peripheral neuropathy
- intense glucose-lowering strategy.

Patients and relatives require education on the symptoms of and risk factors for hypoglycaemia, and appropriate management, should it occur.[3] Where appropriate, it would be prudent to consider therapies with a lower propensity to hypoglycaemia. Where insulin is required, it needs to be titrated carefully.

New insulins provide solutions to better diabetes management

Modern insulins carry a lower risk of hypoglycaemia than older insulins.[3] Furthermore, progress in insulin therapy continues, allowing improved glycaemic control with fewer injections and less chance of hypoglycaemia, especially at night.[8] Leading these developments, Novo Nordisk aims to make better diabetes outcomes available to all patients because achieving target glycaemic control should not be at the expense of adverse outcomes, which can be a direct result of therapy.

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Patient information leaflet

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Keep and Copy Series

WOMEN WITH DIABETES FACE SPECIFIC CHALLENGES

Diabetes is a condition in which the blood glucose (sugar) level remains too high. This has disastrous effects on health, damaging nerves and blood vessels and causing alterations in mood and wellbeing. Although some people develop diabetes at a young age, more commonly it arises later in life, especially in people with an unhealthy diet, who put on weight and do not get sufficient physical activity.[1,2]

WOMEN WITH DIABETES ARE AT INCREASED RISK OF HEART DISEASE

Due to the oestrogen in their bodies, premenopausal women without diabetes have a risk of having a heart attack or a stroke (cardiovascular disease) that is considerably lower than that in men of the same age. However, with diabetes, that protection is lost, placing women at a devastatingly increased risk of cardiovascular disease and death in comparison with their peers.[2]

RELATIONSHIPS CAN SUFFER: TALKING IS THE KEY

Significantly more women with diabetes refrain from sexual activity and are dissatisfied with their sex life than those without. Usually this means that they just don't seem to feel in the mood for sex. And this can cause problems in relationships, which can be compounded even more when her partner does not understand the condition, or is fearful of somehow hurting her because she has diabetes.[2] In fact, when men don't understand, just her having diabetes can sometimes put the relationship in jeopardy.[2]

Of course, all of these problems might cause a woman to feel depressed. But depression can also arise directly from the changes in glucose levels, so it can be a particular problem for women with diabetes.[2] Regretfully, many of these concerns are so private that women do not feel comfortable talking about them. But they can be easily managed with some education and the right professional care!

DIABETES CAN ARISE DURING PREGNANCY

For some women, diabetes may be a problem during pregnancy when hormonal changes, which normally encourage growth of the baby, cause the mother's blood glucose level to rise.[2] The first signs of this 'gestational diabetes' may be similar to those of severe diabetes – being thirsty all of the time, passing a lot of urine and losing weight despite being pregnant.[2]

Gestational diabetes is a serious condition that increases the chance of the mother needing a caesarean section, and may cause other health risks for both mum and baby into the future. Both mother and baby have an increased chance of developing type 2 diabetes later in life, especially if they are overweight and do not get enough physical activity.

If gestational diabetes is recognised early and properly treated, all of these risks are significantly reduced.[2] Insulin is usually recommended and, as long as blood glucose levels remain normal, injections can usually be stopped as soon as the baby is born.[2]

LEARNING ABOUT DIABETES CAN PROTECT THE WHOLE FAMILY

Anyone can develop diabetes. Looking out for the symptoms means that you are prepared if

you notice them in yourself or your family. Diabetes can be treated, and when it is recognised early on, and by adopting a healthy lifestyle, the chances of developing the devastating problems associated with uncontrolled diabetes are a lot smaller. Life with diabetes can be normal.

- Worldwide, there are almost 200 million women with diabetes.[1]
- One in two adults with diabetes are undiagnosed.[1]
- People with diabetes are two to four times more likely to develop cardiovascular disease than people without diabetes.[2]
- Cardiovascular disease is the most common cause of death in men and women with diabetes.[2]
- Thirty to 40% of women with diabetes have problems with sexual function.[2]
- Women are twice as likely as men to suffer from depression.[2]
- Gestational diabetes tends to occur from the 24th week of pregnancy, and it may be necessary to be screened for diabetes at this time.[1]

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Increased platelet activation leads to cardiovascular risk in adolescents with type 2 diabetes

Adolescents with type 2 diabetes are at risk of atherosclerosis and cardiovascular disease early on in life. There are well-established data that diabetes, platelet hyperactivity and cardiovascular disease (CVD) are causes of mortality in adults with type 1 and type 2 diabetes.

The purpose of a pilot study by Israels *et al*., published in *Diabetes Care* on 4 June 2014, was to establish whether the same connection was present in adolescents as in adults relative to non-diabetic control subjects. The study examined the expression of the surface and soluble platelet activation markers.

In vivo platelet activation was compared in four different groups of adolescents aged 12 to 18 years. These groups comprised type 1 diabetics (n = 15), type 2 diabetics (n = 15), control subjects with normal body mass index (n = 14) and control subjects who were obese/overweight (n = 13). Type 1 and 2 diabetes were classified according to Canadian Diabetes Association criteria.

Subjects with Prader–Willi syndrome or hypothyroidism, those who abused alcohol or drugs, had congenital CVD, were pregnant, and/or who used glucocorticoids, lipid-lowering agents or platelet-inhibitory agents were all excluded from this study.

Measurements of platelet surface and soluble activation markers were performed using the FACSCalibur flow cytometer. Results were shown as percentage of platelets expressing CD62P and CD63 platelet surface antigen as well as PAC-1 monoclonal antibodies.

Results showed that there were significantly higher platelet activation markers in adolescent type 2 diabetics when compared with either the obese or normal control group ($p < 0.05$). There was a small difference in platelet activation between adolescent type 1 diabetics and the two control groups, although the pattern leaned towards an increase in activation markers for type 1 diabetics. There were no differences in platelet activation markers between the non-diabetic groups.

The study showed that *in vivo* platelet activation was increased in adolescent type 2 diabetics, which can be a potential cause of atherosclerosis, thrombosis and other cardiovascular diseases in early adulthood. Although it was a small study, it raises awareness of the fact that a more aggressive approach should be undertaken when modifying therapeutic interventions for type 2 diabetes in adolescents.

http://www.diabetesincontrol.com/articles/diabetes-news/16447-increased-platelet-activation-leads-to-cv-risk-in-adolescents-with-type-2-diabetes

Patient information leaflet

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Keep and Copy Series

BE A MAN: GET YOUR HEALTH CHECKED!

Erectile dysfunction, relationship problems, depression, heart attack; in that order. Not very attractive? If you were told this was your future, what would you do? If you were told that you could prevent it, now what would you do?

'I definitely would have done whatever I could to have stopped that from happening to me', says 53-year-old Sam. 'Looking back, there were so many signs that things were going wrong. I didn't feel right for ages – years, maybe. And it all started when I began to put on a little weight. Not a lot at first – just a bit of a tyre around my waist. It was uncomfortable, but I didn't do anything about it, because all my friends were putting on weight and I thought it was normal for men our age. Even when I was told I had type 2 diabetes I didn't really pay much attention. I ate the same things. I didn't exercise. I left my health up to an occasional handful of tablets and six-monthly visits to the doctor.'

'It's ironic that it took a heart attack to wake me up. Now I exercise, I watch what I eat and drink, I have lost weight and I feel better. But, because of problems remaining after my heart attack, I can't do all the things I used to. And I really do regret not doing something about it when I had the chance!'

Type 2 diabetes is one of the largest global health emergencies of the 21st century.[1] Worldwide, it is a leading cause of cardiovascular disease (heart attacks and stroke), blindness, kidney failure and lower-limb amputation, and a major cause of death.[1] It affects up to 4.5 million South Africans, more than half of whom are unaware that they have it, and the majority of whom will be dead before the age of 60.[1]

Primarily caused by an unhealthy diet, lack of physical activity and excess body weight, type 2 diabetes occurs when the body stops making enough insulin, or does not respond properly to the insulin it has.[1] This deficiency of effective insulin causes glucose (sugar) to accumulate in the blood stream, rather than entering the cells, where it would normally provide energy. The sustained abnormally high blood glucose level causes damage to blood vessels and nerves, resulting in these horrendous health consequences.[1]

Dr Zane Stevens, an endocrinologist in private practice in Cape Town is very concerned that men are not proactive about their health. 'Diseases of lifestyle creep up slowly. Many previously fit, active men get married and, as the years go by, adopt unhealthy lifestyles due to the stresses of work, financial pressures, and trying to get ahead in a career. Health becomes far from a priority.'

'With regard to the diagnosis of diabetes in men, unfortunately many men tend to seek help very late. I think it's partly because, as men, we often feel we are supposed to be invincible and prefer to believe that diabetes or blood pressure problems would never happen to us! Added to this is the fact that diabetes can go unnoticed for many years, as the typical warning symptoms only occur once the glucose rises to extremely high levels. Or even worse, that something has been very wrong with our health is only considered when a devastating complication such as a heart attack has occurred!'

ERECTILE DYSFUNCTION AND DIABETES

In men, one of the first signs that something is wrong in the arteries may be erectile dysfunction

(ED). The chance of having ED increases with longer duration of diabetes, but eventually up to around seven out of 10 men with diabetes will be unable to get or keep an erection.[2,3] For many men, ED is devastating, leading to depression, reduced self-esteem and strained relationships.[4]

Nevertheless, paradoxically, ED itself might be a blessing in disguise. Although that sounds counter-intuitive, ED is an early warning sign that a heart attack could be imminent, affording time to do something about it before it's too late. In fact, men with ED are almost 15 times more likely than those without to suffer a heart attack, and ED has been identified as the most significant predictor of that in comparison to any other conventional cardiovascular risk factor.[2]

'I should have told my doctor, but I was too shy to bring it up', says Sam. 'Looking back, that was silly, because it could have prevented what came next.'

ED, diminished interest in sex and depressed mood are also symptoms of low testosterone level, which occurs twice as commonly in men with diabetes than in those without.[5] And diabetes itself also predisposes to depression.[6] 'The problem is', explains Sam, 'that all of these symptoms overlap, so you don't really connect them to one cause. I put most of them down to me just putting on weight.'

And that's where it starts. In fact, overweight and obesity, together with physical inactivity are the strongest risk factors for type 2 diabetes, and the majority of people with type 2 diabetes are overweight.[6,7] It's a big problem in our country. Approximately 40% of South African men are overweight and fewer than one out of four participates in sufficient exercise! In fact, less than half participate in any physical activity at all![8,9]

'Men have to be told that diabetes is preventable!' exclaims Sam passionately. 'It's not that difficult to make healthier food choices and do a bit of exercise! And get a regular check-up. My doctor told me that if my diabetes had been detected a bit earlier and I had been more conscientious with my treatment, I could have prevented some of the problems that I am facing now.'

DIABETES AND LIFESTYLE

Dr Stevens agrees. 'Remaining balanced is key. Making time for exercise and creating a culture of healthy eating is not only important for ourselves but serves to set an example and ensure the health of our families. Men who have risk factors for diabetes, such as being overweight or having a family history of the condition should consider being screened for it.'

Once diabetes has been diagnosed, careful control of blood glucose levels can help prevent or delay the complications. When control is achieved early on, the benefits remain for many years, despite it becoming more difficult to maintain control of glucose levels.[10] For many men, this merely requires a change in diet, some exercise and sometimes medication. However, because diabetes is a progressive disease, over time, insulin may also be required.[11]

Insulin is the most effective treatment to control blood glucose levels.[12] Despite what many people believe, insulin does not need to be complicated to use and often only needs to be taken once a day.[11] A small price to pay for protecting your future health and lifestyle!

BE PROACTIVE ABOUT YOUR HEALTH AND TREATMENT

'The earlier treatment can be initiated, the better the chances of avoiding diabetes complications', explains Dr Stevens. 'Regular follow up is also key. The name of the game in diabetes management is prevention. By regular screening for complications and intensifying therapy as needed, complications can be minimised.'

You are a man. Some health needs are specific to men. Men are prone to developing a 'boep', which in turn can lead to higher risk of diabetes, cardiovascular disease and low testosterone level. Each one of these presents its own challenges to a healthy future, but all are manageable if they are addressed proactively or, when they do occur, early and before complications start. And the key to a healthy future is awareness of that. But men don't talk about their health, do they? That's not what being a man is all about. Or is it?

Be a man. Speak up. Talk to your doctor about your health before it's too late.

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Drug Trends in Diabetes

Novo Nordisk holds the first new-generation insulin summit to educate doctors on novel developments in diabetes management

Diabetes is a global epidemic

Diabetes is one of the largest global health emergencies of the 21st century.[1] Worldwide, it is a leading cause of cardiovascular disease (heart attacks and stroke), blindness, kidney failure and lower-limb amputation.[1]

The *International Diabetes Federation Atlas* 2015 figures reveal that almost 60 to 80% of patients suffering from diabetes die before the age of 60 in sub-Saharan Africa. Furthermore, diabetes accounts for almost one out of every three deaths among the economically active age group of 30 to 40 years.[1] Consequently, the economic burden of diabetes in terms of healthcare costs and loss of productivity is massive.[1]

According to the International Diabetes Federation, one in every 11 adults worldwide and up to 2.28 million adults in South Africa have diabetes.[1] Furthermore, due to increases in economic development, urbanisation and unhealthy lifestyle choices, these figures are expected to rise dramatically in the future.[1] Over the next 20 years, the current population of some 14.2 million people with diabetes in Africa will increase to over 34 million.[1]

The most common type of diabetes is type 2, which accounts for nine out of 10 cases.[1] Primarily caused by an unhealthy diet, lack of physical activity and excess body weight, type 2 diabetes can progress undiagnosed for years. Around half of all people with type 2 diabetes are unaware that they have it.[1]

Novo Nordisk at the forefront of novel strategies to address diabetes management

Clearly, effective strategies to identify and treat diabetes, better access to medicines, and awareness and education programmes about healthy living to prevent new cases are a healthcare priority. Globally, Novo Nordisk is spearheading this drive, already supplying around half of the world's insulin. Worldwide, about 24 million people with diabetes rely on Novo Nordisk for their daily medication. The company is at the forefront of diabetes research, an attitude that has been instrumental in developing a broad range of diabetes medications and insulins, and award-winning devices since Novo Nordisk was founded in 1923.[2]

Novo Nordisk leads the search for patient-friendly solutions

In type 2 diabetes, careful control of blood glucose levels can help reduce the risk of cardiovascular, kidney, eye and nerve disease. When this control is achieved early on, the benefits remain for many years.[3] Type 2 diabetes is a progressive disease. Although dietary and lifestyle changes may initially be effective in controlling blood glucose levels, ultimately most people will require escalating doses of medication and many will require insulin.[4]

Insulin is the most effective treatment to control blood glucose levels. With appropriate doses, it is possible to achieve target blood glucose level control, depending on what is required for an individual patient. However, in practice, achieving and sustaining these targets is very difficult, because people with diabetes do not always adhere to their treatment regimens and doctors may be overly cautious, so that treatment is not intensified when it needs to be.[5]

Close to 40% of people with diabetes report that daily medication interferes with their ability to live a normal life.[6] This is why Novo Nordisk focuses research on individual solutions and personal needs in order to improve diabetes control and make treatments more efficacious, acceptable and convenient.[2]

New-generation insulin summit

As part of this commitment to seeking solutions and ongoing education, Novo Nordisk South Africa held the first new-generation insulin summit in Cape Town on 14 May. Speaking at the summit, leading local and international diabetes experts shared advances in the understanding of diabetes and its management with over 200 healthcare providers from around the country, who were eager to learn how they could improve the lives of their patients.

Summit session chairperson Prof Brynne Ascot-Evans, head of the Division of Endocrinology and Diabetes at the University of Stellenbosch and Tygerberg Academic Hospital, highlighted the global epidemic of diabetes and its importance to South Africans. Speakers included private physicians, Dr Adri Kok and Dr Tanya Kinvig, who spoke about the challenges faced by both prescribers and patients, with particular emphasis on those posed by insulin therapy. They explained that even with the availability of insulin, it is estimated

Prof Brynne Ascott-Evans, Dr Zane Stevens, Dr Adri Kok

Dr Manash Baruah

that no more than one-quarter of South Africans with diabetes currently achieve and maintain their glucose target levels, even at tertiary care and university-associated hospitals.[7,8] These speakers highlighted the importance of education for both patients and healthcare providers and the need for effective treatments that are easy to administer with a low risk of side effects.

Endocrinologist Dr Zane Stevens and renowned expert in clinical pharmacology, Prof Jacques Snyman, reviewed highlights in the history of insulin and the development of novel molecules that have revolutionised the lives of people with diabetes. These treatments, which are easier to use, require less frequent administration and are less likely to cause serious side effects, such as excessive drops in blood glucose levels (hypoglycaemia) or weight gain, are expected to go at least part of the way in making glucose targets more achievable.

To close the meeting, Dr Manash Baruah, director and consultant endocrinologist at the Excel Centre, Guwahati, India, provided some insight into clinical experience with new diabetes treatments that are expected to be available soon.

Novo Nordisk's ongoing commitment to diabetes care

The new-generation insulin summit forms part of Novo Nordisk's annual education programme for healthcare professionals, in addition to their incretin and diabetes summits. Globally, only a minority of people who receive diabetes care end up achieving the desired health outcomes.[1] This means that millions of people worldwide do not reach their goal of living a life free of diabetes-related complications. Novo Nordisk is committed to reducing this number by providing ongoing education, patient-friendly treatment solutions, and supporting and encouraging patients in effective self-management.

For more information, please contact: Kerrin Tessendorf on (011) 280-6679.
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Gender differences in the control of multiple cardiovascular disease risk factors in type 2 diabetes patients

Adjusted mean diastolic blood pressure levels were found to be significantly higher in women compared to men, but other risk factors were almost the same between genders, according to recent research.

Williams and colleagues conducted a cross-sectional study in which patients were randomly recruited from three primary care clinics in the south-eastern USA and asked to complete a self-report survey yielding data relevant to gender differences in cardiovascular disease (CVD) risk-factor control. The primary outcomes were individual diabetes-related risks, which were defined as not having an HbA_{1c} level < 7%, blood pressure of < 130/80 mmHg, and low-density lipoprotein (LDL) cholesterol level < 100 mg/dl (2.59 mmol/l), and composite control defined as having all three outcomes under control simultaneously.

Of the patients enrolled, 56% were men, 67% were non-Hispanic black, and 78% made less than $35 000 per year. Unadjusted mean systolic blood pressure (134 vs 13 mmHg, p = 0.005) and LDL cholesterol levels [99.7 vs 87.6 mg/dl (2.58 vs 2.27 mmol/l), p < 0.001] were much higher in women than in men; however, after adjusting for relevant confounders, differences in systolic blood pressure and LDL cholesterol levels were not significant. Adjusted mean diastolic blood pressure levels were found to be significantly higher in women compared to men (β = 3.09, 95% CI = 0.56–5.63).

Regarding the gender differences in composite control, the results showed that women had poorer control of multiple CVD risk outcomes than men (β = 2.90, 95% CI = 1.37–6.13). Other primary outcomes were not statistically significantly different, including glycaemic control in both genders.

Limitations of this study included the fact that the cross-sectional study design did not prove causal associations. Also, confounders not controlled for included diabetes knowledge, self-management practices, medication adherence, co-morbidity burden, social support, duration of diabetes, medications used to treat diabetes, and hypertension. In addition, high triglyceride level was an independent risk factor for coronary heart disease, particularly for women.

In conclusion, further study is needed. In the meantime, both genders, but especially women, need to be encouraged to adopt healthy lifestyle habits with a view to modifying their risk factors and achieving better outcomes.

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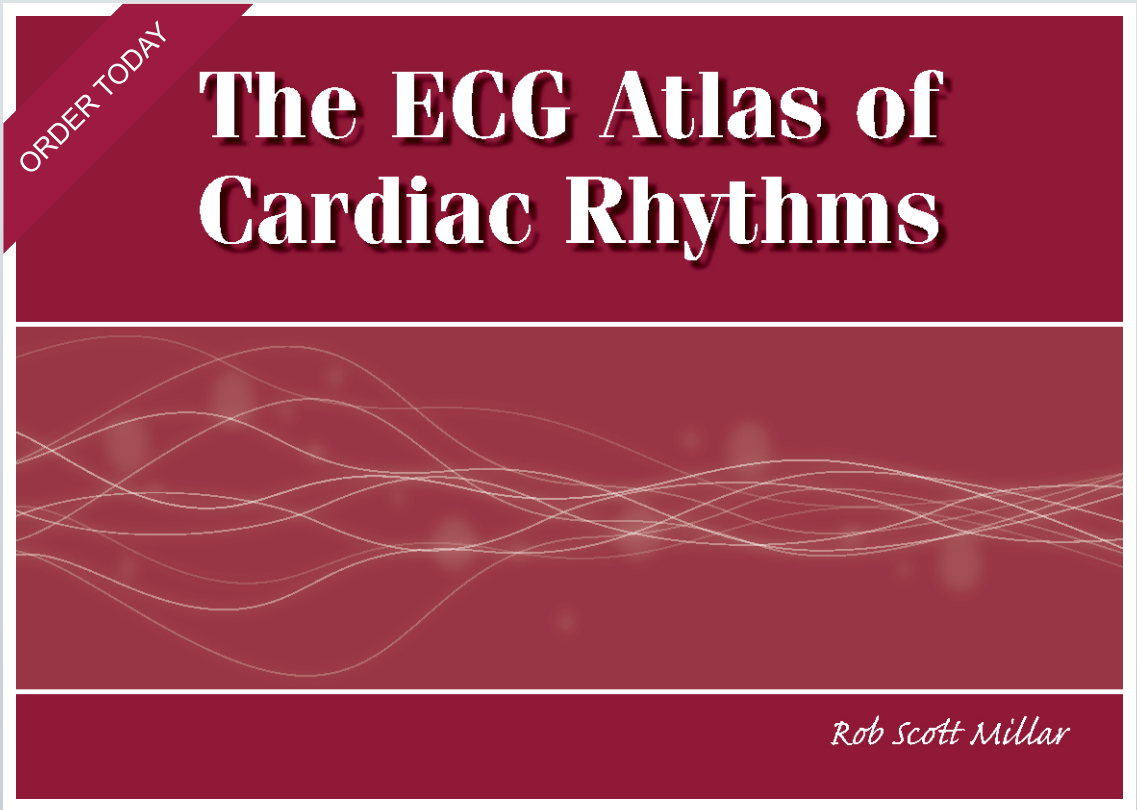

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How can we overcome barriers
to effective glycaemic control in type 2 diabetes?

Diabetes is a global epidemic. Worldwide, it is a leading cause of cardiovascular disease, blindness, kidney failure and lower limb amputation.[1. p8a; 11a; 28a] In SubSaharan Africa, the majority of people with diabetes will die before the age of 60. Furthermore, diabetes accounts for almost one out of every three deaths among the economically active age group of 30 to 40 years.[1 p71a,73]

Diabetes is a global epidemic

1 out of every 3 deaths in 30-40 year olds

Insulin is an effective diabetes treatment

Careful control of blood glucose can help prevent or delay micro- and macrovascular complications of diabetes. Initially this may be adequately achieved with lifestyle changes and oral medication, but because of the progressive nature of diabetes, characterised by gradual decline in ß-cell function and density, most patients will eventually require insulin to achieve glycaemic goals.[2 p72a] Nevertheless, the benefits of control achieved early in the disease remain for many years, despite it becoming more difficult to maintain target glucose levels.[3 p1577a]

Insulin is an effective treatment to control blood glucose. With appropriate doses it is possible to achieve any level of glycaemic control depending on the target set for an individual patient.[4 p197a] However, in practice, achieving and sustaining these targets is very difficult, because patients do not always adhere to their treatment regimen, and doctors may be overly cautious, so that treatment is not intensified when it needs to be.[5 p38a, b]

Patient considerations

Adequate glycaemic control is achieved in no more than about 1 in every 4 patients with diabetes

In fact, a substantial proportion of patients with type 2 diabetes do not achieve internationally recognised glycaemic targets.[5 p38a] Even in some South African specialist clinics, adequate glycaemic control is achieved in no more than about 1 in every 4 patients with diabetes![6 p154a]

Of course, nonadherence to therapy is an important problem associated with chronic diseases. Nevertheless, there are also specific reasons why diabetic patients may be reluctant to initiate or intensify antihyperglycaemic medication. Some of these include feelings of failure about suboptimal glycaemic control, anxiety about hypoglycaemia or weight gain, and fear of injections. Poor education about type 2 diabetes and the importance of treatment can exacerbate nonadherence.[5 p38b]

Nonadherence through anxiety of weight gain fear of injections

In addition to consideration of their patients' concerns, clinicians themselves may have reasons to delay initiation or intensification of insulin therapy in a patient who needs it. This is a worldwide phenomenon, sometimes referred to as 'clinician inertia'.[5,7 5.p38b; 7.p2675a] Causes range from time and resource constraints to underestimation of the patient's needs, and failure to identify and manage comorbidities.

Physicians may be afraid of causing harm and be overly cautious when prescribing so as to avoid weight gain and hypoglycaemia, especially in patients who already have comorbidities.[5,8 5.p39a; 8. p17a] They may be concerned about patient non-compliance, or merely not know how to manage a patient who simply refuses to entertain the thought of escalating treatment.[8 p17-18a] Accordingly, oral therapies are continued for as long as possible, in the hope that patients will implement lifestyle changes.[9 p370]

Physicians overly cautious when prescribing so oral therapies are continued for as long as possible

Physician-related barriers to timely initiation of insulin[8]

- Concerns over patients with comorbidities
- Excess weight gain in already overweight patients
- Concerns about patient non-compliance
- Risk of severe hypoglycaemia/adverse effects on quality of life
- Lack of resources
- Patient refusal

Novo Nordisk seeks to dismantle barriers to insulin prescribing

In response to these complex challenges, Novo Nordisk is leading the way in developing new molecules and delivery devices to change the way people with diabetes, and their healthcare providers, think about insulin. Novo Nordisk understands that if treatment regimens can be made simpler and more comfortable, and concerns over side effects no longer get in the way of efficient glycaemic management, then life with diabetes will be simpler, less scary and of a much better quality than it has ever been before.

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The recommended starting dose of Ryzodeg® is 60 – 70 % of the total daily insulin requirements.
Transfer from other insulin medicinal products: Close glucose monitoring is recommended during transfer and in the following weeks. *Patients with type 2 diabetes:* Patients switching from once-daily basal or premix insulin therapy can be converted unit-to-unit to once-daily Ryzodeg® at the same total insulin dose as the patient's previous total daily insulin dose. Patients switching from more than once-daily basal or premix insulin therapy can be converted unit-to-unit to twice-daily Ryzodeg® at the same total insulin dose as the patient's previous total daily insulin dose. Patients switching from basal/bolus insulin therapy to Ryzodeg® will need to convert their dose based on individual needs. In general, patients are initiated on the same number of basal units. Doses and timing of concomitant antidiabetic treatment may need to be adjusted. Patients with type 1 diabetes: For patients with type 1 diabetes mellitus, the recommended starting dose of Ryzodeg® is 60 – 70 % of the total daily insulin requirements in combination with short-/rapid-acting insulin at the remaining meals followed by individual dosage adjustments. Doses and timing of concurrent short-/rapid-acting insulin products may need to be adjusted. *Flexibility:* Ryzodeg® allows for flexibility in the timing of insulin administration as long as it is dosed with the main meal(s). If a dose of Ryzodeg® is missed, the patient can take the next dose with the next main meal of that day and thereafter resume the usual dosing schedule. Patients should not take an extra dose to make up for a missed dose. Ryzodeg® should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. **Side Effects:** Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1.000 to < 1/100); rare (≥ 1/10.000 to < 1/1.000); very rare (< 1/10.000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Peripheral oedema and rare: Hypersensitivity and urticaria. **Pharmacological classification:** A 21.1 Insulin Preparations **Reg. No.:** 47/21.1/0165

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