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- Improvement of cardiac ventricular function by magnesium treatment in diabetic rat heart
- Diabesity': interlinking treatments to improve outcomes in diabetes and obesity

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From the Editor's Desk

This issue covers a range of topics, from stress hyperglycaemia in an acute coronary syndrome (ACS) setting, the effects of magnesium on cardiac contractility, and diabesity, to the effect of weight loss on diabetes and the diabetogenic associations of statins.

Yao *et al.* (page 42) examined the associations between initial hyperglycaemia in the setting of ACS and various cardiovascular outcomes in a study in Abidjan, Ivory Coast, and show similar adverse associations to those seen in other studies.[1] Stress hyperglycaemia also has an adverse association with acute stroke outcomes,[2] and may be a marker of wider vascular dysfunction and consequent poorer prognosis.

Aboalgasm and colleagues (page 48) studied the beneficial effects of magnesium in rat cardiac contractility. Approximately 10% of hospitalised patients have hypomagnesaemia.[3] Magnesium is involved in over 300 known enzymatic reactions, involving muscle, nerve and heart, and administration can improve vascular tone, cardiac output and afterload. It can also improve blood pressure[4] and insulin metabolism.[5] Perhaps wider clinical trials may show great fundamental benefit for magnesium supplementation in human health.

Dr Lombard discusses diabesity (page 56), especially focused on drug causes and the rational use of drugs to reduce weight. At a population level, governments need to assist with health education (the promotion of healthy diet and exercise regimens) and regulation of adverse dietary content of foods, especially of so-called 'junk food', otherwise we will continue to see the spiralling consequences of diabetes, hypertension and cardiac disease.[6]

Two articles from *Medical Brief* look at the effect of modest weight loss on diabetes in the results of the Norfolk Diabetes Prevention Study (page 63), and at the association between statins and the increased risk of type 2 diabetes (page 64). Statins have an undoubted beneficial effect on cardiac health, so risks and benefits have to be weighed up when prescribing statins. Patients also need to be counselled about these considerations. New cholesterol-lowering drugs, such as the PCSK9 inhibitors, may provide an alternative to statins and we eagerly await more robust and detailed studies involving this new class of drugs.

This year, 2020, has been a difficult year for global health due to the COVID-19 pandemic and we thank all our healthcare workers for their dedication and selflessness during this period.

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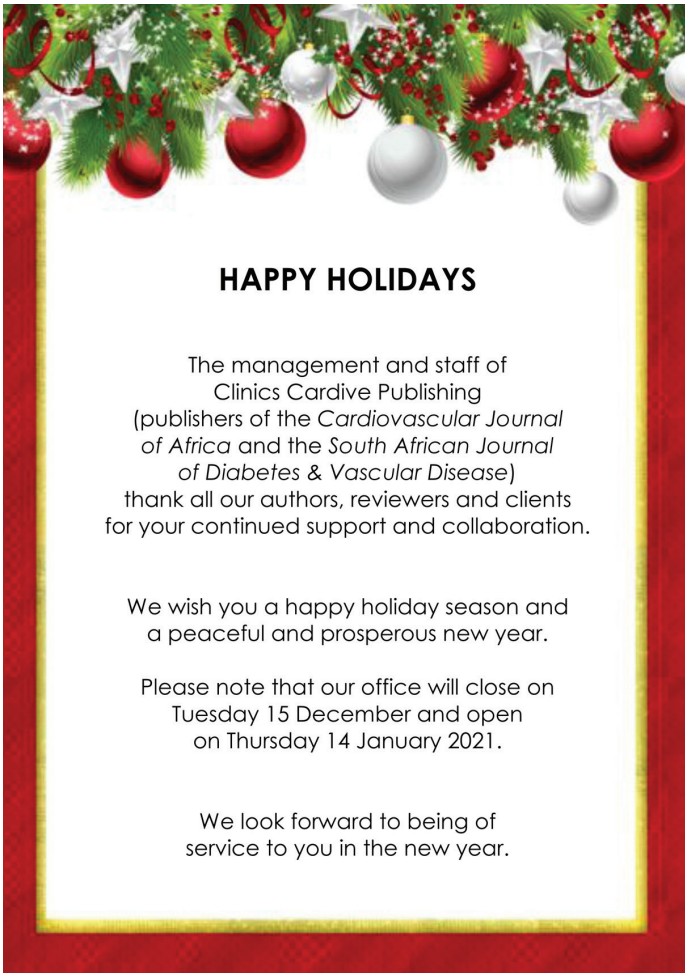

Prognostic value of admission hyperglycaemia in black Africans with acute coronary syndromes: a cross-sectional study

HERMANN YAO, ARNAUD EKOU, THIERRY NIAMKEY, CAMILLE TOURÉ, CHARLES GUENANCIA, ISABELLE KOUAMÉ, CHRISTELLE GBASSI, CHRISTOPHE KONIN, ROLAND N'GUETTA

Abstract

Aim: **The aim of the study was to determine the relationship between acute hyperglycaemia and in-hospital mortality in black Africans with acute coronary syndromes (ACS).**

Methods: **From January 2002 to December 2017, 1 168 patients aged ≥ 18 years old, including 332 patients with diabetes (28.4%), consecutively presented to the intensive care unit of the Abidjan Heart Institute for ACS. Baseline data and outcomes were compared in patients with and without hyperglycaemia at admission (> 140 mg/dl; 7.8 mmol/l). Predictors for death were determined by multivariate logistic regression.**

Results: **The prevalence of admission hyperglycaemia was 40.6%. It was higher in patients with diabetes (55.3%). In multivariate logistic regression, acute hyperglycaemia (hazard ratio = 2.33; 1.44–3.77; $p < 0.001$), heart failure (HR = 2.22; 1.38–3.56; $p = 0.001$), reduced left ventricular ejection fraction (HR = 6.41; 3.72–11.03; $p < 0.001$, sustained ventricular tachycardia or ventricular fibrillation (HR = 3.43; 1.37–8.62; $p = 0.008$) and cardiogenic shock (HR = 8.82; 4.38–17.76; $p < 0.001$) were predictive factors associated with in-hospital death. In sub-group analysis according to the history of diabetes, hyperglycaemia at admission was a predictor for death only in patients without diabetes (HR = 3.12; 1.72–5.68; $p < 0.001$).**

Conclusion: **In ACS patients and particularly those without a history of diabetes, admission acute hyperglycaemia was a potentially threatening condition. Appropriate management, follow up and screening for glucose metabolism disorders should be implemented in these patients.**

Keywords: hyperglycaemia, diabetes, acute coronary syndrome, sub-Saharan Africa

Studies in the West have shown that elevation of blood glucose is a common condition during the early phase of acute coronary syndrome (ACS), even in the absence of a history of diabetes mellitus (DM).[1-3] There is no uniform definition at present, but the 140 mg/dl (7.8 mmol/l) threshold has often been considered.[4] The prevalence of acute hyperglycaemia > 140 mg/dl ranged from 39 to 58%.[1,2,5]

In addition to established prognostic factors (left ventricular systolic dysfunction, heart failure, ventricular arrhythmias),[6] acute elevation of blood glucose level was associated with an increase in in-hospital stay, and 30-day and long-term mortality rate, and there is evidence that the risk of mortality is higher in patients without a history of DM.[7-10] There is a linear relationship between acute glycaemic levels and outcomes.[2,7] Pathophysiological mechanisms are uncertain, but acute hyperglycaemia may be an epiphenomenon of the stress response, or the trigger of complex underlying mechanisms, leading to severe complications and poor outcomes.[4,5]

In sub-Saharan Africa, data on ACS are scarce,[11,12] particularly on the prevalence and outcomes of patients with acute hyperglycaemia. The aim of this study was to assess the prognostic value of hyperglycaemia at admission in ACS patients in our practice.

Methods

Our study was carried out at the Abidjan Heart Institute (Ivory Coast). We conducted a cross-sectional, observational study between 1 January 2002 and 31 December 2017, including patients aged ≥ 18 years who presented to the intensive care unit (ICU) of Abidjan Heart Institute for ACS. These patients were divided into two groups according to their blood glucose level at admission: admission hyperglycaemia (AH) (blood glucose > 140 mg/dl; 7.8 mmol/l) and absence of admission hyperglycaemia (NAH) (blood glucose ≤ 140 mg/dl).[4] The blood glucose level considered was the first venous plasma glucose level obtained at admission or within the first 24 hours, and before any glucose-lowering therapy was given during hospitalisation.

The exclusion criteria were: ACS patients with incomplete medical records or who declined to participate in the study, patients with suspected ACS in whom the clinical course and explorations had excluded the diagnosis of ACS, and patients transferred to another department outside the Abidjan Heart Institute during their hospitalisation.

Consent was obtained from each patient participating in this study. Based on our selection criteria, 1 168 patients were included in our study.

Data were collected using a standardised survey form. The parameters investigated were: (1) socio-demographic data (age, gender) as well as clinical data (cardiovascular risk factors and history, clinical presentation); (2) ECG (diagnosis of ACS)

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and cardiac ultrasound data [left ventricular ejection fraction (LVEF) < 40% or ≥ 40%]; (3) biological data: troponin Ic and cardiac enzymes, (4) coronary angiography findings: number of epicardial vessels affected (one-, two- and three-vessel disease), (5) management: dual antiplatelet therapy (DAPT), percutaneous coronary intervention (PCI), and (6) in-hospital evolution: atrial fibrillation, sustained ventricular tachycardia/ ventricular fibrillation, cardiogenic shock, death.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, measured three times during hospitalisation or treatment of previously diagnosed hypertension. DM was defined according to the American Diabetes Association13 as one of the following criteria: glycated haemoglobin ≥ 6.5%, fasting plasma glucose ≥ 1.26 g/l (6.99 mmol/l) on two occasions, two-hour plasma glucose ≥ 2 g/l (11.1 mmol/l) after 75-g oral glucose tolerance test (OGTT), random plasma glucose ≥ 2 g/l (11.1 mmol/l), or patients on glucose-lowering therapy on admission. Active smoking was defined as current or interrupted smoking for less than three years.

Dyslipidaemia was defined as total cholesterol concentration > 2.40 g/l (6.22 mmol/l) and/or high-density lipoprotein (HDL) cholesterol < 0.40 g/l (1.04 mmol/l) in males and < 0.50 g/l (1.3 mmol/l) in females and/or low-density lipoprotein (LDL) cholesterol > 1.60 g/l (4.14 mmol/l), or triglyceride levels > 1.5 g/l (1.70 mmol/l). Familial history of coronary artery disease (CAD) was defined as the occurrence of a myocardial infarction or sudden death: before the age of 55 years in the father or in a firstdegree male relative; and before the age of 65 years in the mother or in a first-degree female relative. Symptom–admission delay was the time between the onset of symptoms and admission to the Abidjan Heart Institute.

ST-segment elevation myocardial infarction (STEMI) was defined as the presence of symptoms or signs of myocardial ischaemia, persistent ST-segment elevation or newly diagnosed bundle branch block, and an increase in cardiac biomarkers beyond the 99th percentile.[6] Non-ST-elevation ACS (NSTEACS) was defined as the presence of symptoms or signs of myocardial ischaemia, absence of persistent ST-segment elevation, and elevation (non-Q-wave myocardial infarction) or no elevation (unstable angina) of cardiac biomarkers beyond the 99th percentile.[14] Left ventricular systolic dysfunction was defined for a LVEF < 40%.[15]

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical data are presented as numbers and proportions. Statistical comparisons between groups used the Student's *t*-test or Mann–Whitney test for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables. A receiver operating characteristics (ROC) curve was performed to determine the admission glycaemic threshold level predictive of death in our population.

Univariate and multivariate backward stepwise logistic regressions were used to assess predictors of in-hospital death, with an inclusion threshold of $p < 0.20$ in the multivariate analysis. The candidate variables considered were selected according to available data in the literature. The Wald (or Fisher) test was used to assess the significance of hazard ratio (HR) and their 95% confidence interval (95% CI). We defined statistical significance using a two-sided *p*-value < 0.05. We used RStudio statistical software version 1.1.383 (Boston, MA, USA).

Results

Table 1 summarises the patients' general characteristics and outcomes according to blood glucose status at admission. Among the 1 168 patients included in our study, 474 had AH, with a prevalence of 40.6%. The average age of our study population was 56.0 ± 11.6 years (range 21–91). Patients in the AH group were significantly older than those in the NAH group (57.9 ± 11.0 vs 54.7 ± 11.8 years, $p < 0.001$). Patients over 60 years old frequently had acute hyperglycaemia (40.7 vs 31.7%, $p = 0.001$). The male gender was predominant (80.7%) with a ratio of male to female of 4.2. Patients in the NAH group were more likely to be female, with no significant difference (Table 1). According to cardiovascular risk factors and history, AH patients had significant increases in hypertension ($p < 0.001$) and DM ($p < 0.001$). Smoking was frequently reported in the NAH group ($p = 0.002$).

The median symptom–admission delay was 19 hours (5–48). There was no difference concerning blood glucose levels at admission ($p = 0.37$). Heart failure often occurred in AH patients (35.4 vs 20.7%, $p < 0.001$). AH patients presented with increased blood pressure and heart rate. In AH patients, peaks in troponin Ic ($p = 0.004$), creatine phosphokinase (CPK) ($p < 0.001$) and creatine kinase-MB (CK-MB) levels ($p < 0.001$) were higher. Coronary angiography was performed in 564 patients (48.3%). Although there was no significant difference ($p = 0.51$), three-vessel disease was more common in AH patients (Table 1). Two hundred and twenty patients underwent PCI (18.8%). Dual antiplatelet therapy (aspirin + clopidogrel) was given to 782 patients (67.0%). No differences were reported between the groups.

Over the study period, 800 STEMI patients out of 1 138 (68.5%) were admitted to ICU. Thrombolysis was performed in 93 patients, in most of the cases with Alteplase (77/93, 82.8%). PCI procedures started on 27 April 2010. One hundred and fifty-one STEMI patients underwent PCI.

Cardiogenic shock occurred significantly in patients with acute hyperglycaemia ($p < 0.002$). Atrial fibrillation and severe ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) were more frequent in the AH group, without significant difference. Overall in-hospital mortality rate was 9.1% (106/1168). It was higher in AH patients (15.2%, $p < 0.001$) (Table 1).

In multivariate analysis, heart failure (HR = 2.22; 1.38–3.56; $p = 0.001$), LVEF < 40% (HR = 6.41; 3.72–11.03; $p < 0.001$), acute hyperglycaemia (HR = 2.33; 1.44–3.77; $p < 0.001$), sustained ventricular tachycardia or ventricular fibrillation (HR = 3.43; 1.37–8.62; $p = 0.008$) and cardiogenic shock (HR = 8.82; 4.38–17.76; $p < 0.001$) were the risk factors associated with in-hospital death. PCI (HR = 0.35; 0.16–0.79; $p = 0.01$) and dyslipidaemia (HR = 0.48; 0.27–0.84; $p = 0.01$) were identified as protective factors (Tables 2, 3).

The sub-group analyses according to the history of DM emphasised cardiogenic shock (HR = 23.75; 7.60–74.27; $p < 0.001$ and HR = 9.05; 3.66–22.33; $p < 0.001$, respectively) in both AH and NAH populations as risk factors (Tables 4, 5). In patients without a history of DM, only hyperglycaemia was associated with in-hospital death (HR = 3.12; 1.72–5.68; $p < 0.001$) (Table 5).

We carried out a second analysis over two periods: 2002–2010 and 2011–2017. Admission hyperglycaemia was a predictive factor only from 2011–2017 (HR = 2.57; 1.52–4.32). (Tables 6, 7).

The blood glucose threshold of 151 mg/dl (8.38 mmol/l) was the one with the best sensitivity and specificity (area under the

curve = 0.636; sensitivity 61%, specificity 67%; $p < 0.001$) (Fig. 1). Considering the value of 140 mg/dl (7.8 mmol/l), we found similar sensitivity and specificity (sensitivity 62%, specificity 60%).

Discussion

Whereas estimation of the prevalence of DM in ACS patients is known in sub-Saharan Africa, ranging from 25 to 41%,[11,16] to our knowledge this is the first study reporting the prevalence of blood glucose levels at admission and their prognostic value on in-hospital mortality in our practice. The prevalence of admission hyperglycaemia (40.6%) was higher than the prevalence of DM (28.4%). This high rate of acute hyperglycaemia is consistent with available data in the literature in wealthy countries, where the prevalence of hyperglycaemia > 140 mg/dl (7.8 mmol/l) ranges from 39 to 58%.[1,2,5] However, the blood glucose cut-off point differs across studies, and it has been reported that up to 71% of ACS patients had acute hyperglycaemia.[3]

The prognostic impact of hyperglycaemia on admission in patients hospitalised for ACS has been established in numerous studies.[7-10] The Cooperative Cardiovascular Project[7] is the most important registry (n = 141 680) that evaluated the relationship between mortality rate and admission blood glucose after ACS. Mortality at 30 days and one year evolved linearly with blood glucose levels at admission (≤ 110, 110–140, 140–170, 170–240 and ≥ 240 mg/dl) (6.11, 6.11–7.8, 7.8–9.44, 9.44–13.32 and ≥ 13.32 mmol/l). As in our study, the risk of mortality was higher in patients without a history of DM.[7]

In a recent meta-analysis including 214 219 patients, admission hyperglycaemia significantly increased hospital mortality rate (HR = 3.62; $p < 0.0001$), and this impact persisted at 30 days (HR = 4.81, $p < 0.0001$) and long term up to 108 months (HR = 2.02, $p < 0.0001$).[3] In STEMI patients who underwent primary PCI, hyperglycaemia was associated with a higher rate of complications and mortality, including the risk of recurrence of myocardial infarction and heart failure.[17]

Table 1. Patient characteristics according to glycaemia status at admission

Characteristics	AH n = 474	NAH n = 694	p-value
Age (years), m ± SD	57.9 ± 11.0	54.7 ± 11.8	< 0.001
Age > 60 years	193 (40.7)	220 (31.7)	0.001
Female gender	42 (19.8)	94 (15.1)	0.10
Hypertension	312 (65.8)	377 (54.3)	< 0.001
Diabete mellitus	262 (55.3)	70 (10.1)	< 0.001
Active smoking	113 (23.8)	222 (32.0)	0.002
Dyslipidaemia	149 (31.4)	216 (31.1)	0.91
Familial history of CAD	27 (5.7)	44 (6.3)	0.65
History of MI	42 (8.9)	58 (8.4)	0.76
History of stroke	24 (5.1)	23 (3.3)	0.13
Admission delay (hours), m (IQR)	15 (5–52)	20 (5–48)	0.37
Systolic BP (mmHg), m ± SD	148.8 ± 34.3	143.5 ± 29.1	0.01
Diastolic BP (mmHg), m ± SD	92.1 ± 21.2	88.1 ± 19.0	< 0.001
Heart rate (bpm), m ± SD	89.4 ± 20.9	81.8 ± 18.8	< 0.001
Congestive heart failure	168 (35.4)	144 (20.7)	< 0.001
LVEF < 40%	210 (44.3)	198 (28.5)	< 0.001
ECG findings 0.005			
Anterior ACS	274 (57.8)	321 (63.6)	
Inferior ACS	169 (35.7)	315 (45.4)	
Lateral ACS	31 (6.5)	58 (8.4)	
Troponine Ic peak (µg/l), m (IQR)	13.1 (5.2–30.0)	4.9 (1.4–15.0)	0.004
CPK peak (UI/l), m (IQR)	1083 (436–2680)	714 (245–1900)	< 0.001
CKMB peak (UI/l), m (IQR)	91 (40–242)	65 (26–171)	< 0.001
STEMI	369 (77.8)	431 (62.1)	< 0.001
Atrial fibrillation	16 (3.4)	22 (3.2)	0.84
SVT/VF	18 (3.8)	25 (3.6)	0.86
Cardiogenic shock	31 (6.5)	20 (2.9)	0.002
PCI	81 (17.1)	139 (20.1)	0.21
DAPT	455 (65.6)	327 (69.0)	0.22
Death	72 (15.2)	34 (4.9)	< 0.001
Length of stay (days), m ± SD	9.0 ± 5.9	8.4 ± 5.3	0.03
Severity of CAD	n = 144	n = 420	0.51
Non significant CAD	23 (16.0)	59 (14.0)	
1-vessel CAD	48 (34.0)	162 (38.6)	
2-vessel CAD	44 (30.6)	135 (32.1)	
3-vessel CAD	28 (19.4)	64 (15.2)	

Data are in n (%), means ± standard deviation or median (interquartile range). AH: admission hyperglycaemia. NAH: absence of admission hyperglycaemia. CAD: coronary artery disease. BP: blood pressure. MI: myocardial infarction. LVEF: left ventricular ejection fraction. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. DAPT: dual antiplatelet therapy. PCI: percutaneous coronary intervention.

Table 2. Predictors of in-hospital death. Univariate analysis

Predictors	Alive at discharge (n = 1062)	Death during hospitalization (n = 106)	HR	95% CI	p-value
Age > 60 years	361 (34.0)	52 (49.1)	1.87	1.25–2.79	0.002
Female gender	195 (18.4)	30 (28.3)	1.75	1.12–2.75	0.01
Hypertension	619 (58.3)	70 (66.0)	1.39	0.91–2.12	0.12
Diabete mellitus	288 (27.1)	44 (41.5)	1.91	1.27–2.87	0.002
Active smoking	313 (29.5)	22 (20.8)	0.63	0.38–1.02	0.06
Dyslipidaemia	342 (32.2)	23 (21.7)	0.58	0.36–0.94	0.03
History of MI	92 (8.7)	8 (7.5)	0.86	0.40–1.82	0.69
Admission delay (hours), m (IQR)	18 (5–48)	25 (6–72)	–	–	0.02
Congestive heart failure	249 (23.4)	63 (59.4)	4.78	3.17–7.23	< 0.001
LVEF < 40%	322 (30.3)	86 (81.1)	9.88	5.97–16.36	< 0.001
Anterior ACS	527 (49.6)	68 (64.2)	1.82	1.20–2.75	0.004
Admission hyperglycaemia	402 (37.9)	72 (67.9)	3.48	2.27–5.32	< 0.001
STEMI	707 (66.6)	93 (87.7)	3.59	1.98–6.51	0.01
Atrial fibrillation	35 (3.3)	3 (2.8)	0.85	0.26–2.83	0.54
SVT/VF	33 (3.1)	10 (9.4)	3.24	1.55–6.79	< 0.001
Cardiogenic shock	23 (2.2)	28 (26.4)	16.22	8.92–29.48	< 0.001
DAPT	716 (67.4)	66 (62.3)	0.80	0.53–1.21	0.28
PCI	212 (20.0)	8 (7.5)	0.32	0.16–0.68	0.002

Data are in n (%) or median (interquartile range). HR: hazard ratio. 95% CI: 95% confidence interval. MI: myocardial infarction. LVEF: left ventricular ejection fraction. ACS: acute coronary syndrome. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation.
DAPT: dual antiplatelet therapy. PCI: percutaneous coronary intervention

Table 3. Predictors of in-hospital death. Multivariate analysis

	Initial model			Final model		
Predictors	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age > 60 years	1.60	0.95–2.70	0.07			
Female gender	0.84	0.47–1.51	0.57			
Hypertension	0.88	0.51–1.52	0.65			
Diabetes mellitus	1.50	0.85–2.64	0.15			
Active smoking	0.53	0.27–1.05	0.57			
Dyslipidaemia	0.58	0.32–1.05	0.07	0.48	0.27–0.84	0.01
Admission delay (hours), m (IQR)	1.00	0.99–1.01	0.18			
Congestive heart failure	2.25	1.34–3.75	0.002	2.22	1.38–3.56	0.001
LVEF < 40%	6.02	3.37–10.77	< 0.001	6.41	3.72–11.03	< 0.001
Anterior ACS	1.35	0.78–2.35	0.28			
Admission hyperglycaemia	1.76	1.00–3.09	0.05	2.33	1.44–3.77	< 0.001
STEMI	1.75	0.83–3.69	0.14			
SVT/VF	3.97	1.47–10.74	0.007	3.43	1.37–8.62	0.008
Cardiogenic shock	12.32	5.71–26.58	< 0.001	8.82	4.38–17.76	< 0.001
PCI	0.32	0.13–0.80	0.02	0.35	0.16–0.79	0.01

HR: hazard ratio. 95% CI: 95% confidence interval. MI: myocardial infarction. LVEF: left ventricular ejection fraction. ACS: acute coronary syndrome. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. PCI: percutaneous coronary intervention.

In patients without a history of DM, raised blood glucose may correspond to a pre-diabetic state unmasked under a stressful, acute post-ACS phase. In the GAMI trial, OGTT was systematically performed in the follow up of 181 patients with acute myocardial infarction, no history of DM and an admission blood glucose level < 11.0 mmol/l. This study found 67% of new cases of DM and impaired glucose intolerance (IGT).[18]

The potential mechanisms involved with acute hyperglycaemia are still poorly understood, but some hypotheses have been suggested.[4,5] Hyperglycaemia may be a cause or 'marker' of catecholaminergic stress in the post-ACS phase, particularly in relation to the extent of the infarction and the relative alteration of LVEF.[19] Evidence of a reduced mortality rate after lowering blood glucose levels on insulin therapy argues against blood glucose as a simple epiphenomenon of the stress state.[20] Hyperglycaemia is associated with insulin resistance, increased levels of free fatty acids,[21] marked inflammatory response, and endothelial and microvascular dysfunction, leading to myocardial cell vulnerability, ischaemia and hypoxia.[22,23] This may explain why in our study, patients with blood glucose > 140 mg/dl (7.8 mmol/l) had higher peaks of troponin Ic and cardiac enzymes. Recently, a new concept, glycaemic variability, has been described in a few studies. In patients with acute myocardial infarction, glycaemic variability was associated with the severity of CAD[24] and death.[25]

Patients with acute hyperglycaemia and without a history of

Table 4. Predictors of in–hospital death in patients with diabetes. Multivariate analysis.

	Initial model			Final model		
Predictors	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Dyslipidaemia	0.78	0.28–2.16	0.63			
Congestive heart failure	6.43	2.12–19.54	0.04	5.74	2.68–12.30	< 0.001
LVEF < 40%	1.12	0.42–3.00	0.83			
STEMI	1.40	0.36–5.36	0.63			
SVT/VF	15.11	1.88–121.20	0.01	10.09	1.41–72.27	0.02
Cardiogenic shock	29.24	6.83–125.11	< 0.001	23.75	7.60–74.27	< 0.001
DAPT	0.80	0.26–2.41	0.69			
PCI	1.07	0.29–3.89	0.92			

m (IQR): median (interquartile range). HR: hazard ratio. 95% CI: 95% confidence interval. LVEF: left ventricular ejection fraction. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. DAPT: dual antiplatelet therapy. PCI: percutaneous coronary intervention.

Table 5. Predictors of in-hospital death in patients without diabetes. Multivariate analysis

	Initial model			Final model		
Predictors	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age > 60 years	2.39	1.27–4.49	0.007	2.46	1.35–4.49	0.003
Female gender	0.77	0.37–1.6	0.48			
Hypertension	1.17	0.60–2.25	0.65			
Dyslipidaemia	0.53	0.24–1.16	0.11			
History of MI	0.15	0.02–1.32	0.09			
Congestive heart failure	1.44	0.76–2.74	0.27			
LVEF < 40%	8.71	4.05–18.70	0.15	10.18	4.93–21.00	< 0.001
Anterior ACS	1.53	0.78–3.01	0.22			
Admission hyperglycaemia	2.65	1.41–4.99	0.002	3.12	1.72–5.68	< 0.001
STEMI	1.34	0.54–3.30	0.99			
SVT/VF	3.59	1.21–10.64	0.021			
Cardiogenic shock	7.33	2.81–19.08	< 0.001	9.05	3.66–22.33	< 0.001
PCI	0.27	0.09–0.83	0.022	0.29	0.10–0.86	0.02

HR: hazard ratio. 95% CI: 95% confidence interval. MI: myocardial infarction.
ACS: acute coronary syndrome. LVEF: left ventricular ejection fraction. ACS: acute coronary syndrome. STEMI: ST-segment elevation myocardial infarction. SVT/VF: sustained ventricular tachycardia/ventricular fibrillation. PCI: percutaneous coronary intervention.

Table 6. Predictors of in-hospital death from 2002–2010. Multivariate analysis.

Predictors	**HR**	**95% CI**	***p*-value**
Diabetes mellitus	4.79	1.86–12.36	0.001
Congestive heart failure	4.51	1.74–11.70	0.001
Cardiogenic shock	6.10	1.61–23.05	0.008

HR: hazard ratio. 95% CI: 95% confidence interval.

Table 7. Predictors of in-hospital death from 2011–2017. Multivariate analysis.

Predictors	**HR**	**95% CI**	***p*-value**
Admission hyperglycaemia	2.57	1.52–4.32	< 0.001
Congestive heart failure	3.40	2.05–5.64	< 0.001
Cardiogenic shock	14.41	6.82–30.42	< 0.001

HR: hazard ratio. 95% CI: 95% confidence interval.

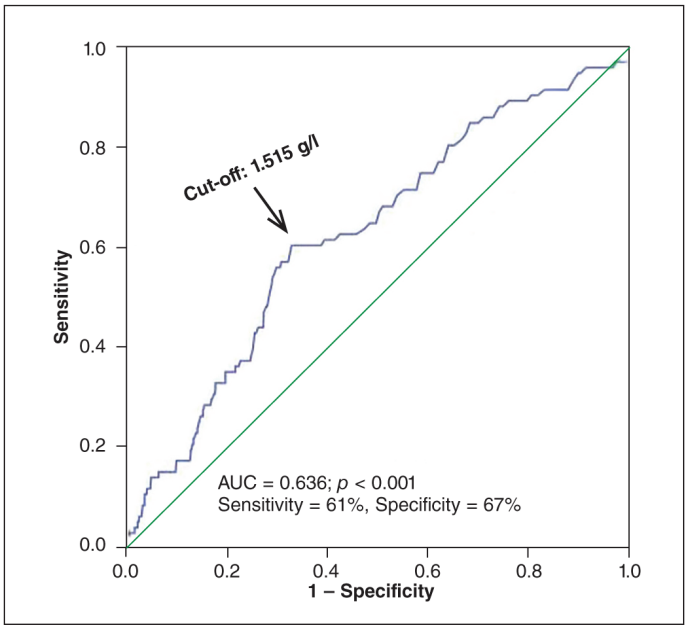

Fig. 1. ROC curve showing glycaemia cut-off value predictive for in-hospital death.

DM should undergo close follow up and screening for glucose metabolism disorders.[18] Current recommendations emphasise the use of OGTT and glycated haemoglobin as screening tests.[26] In a study conducted in South Africa among patients with CAD, the rate of IGT measured by OGTT was 30% higher than the rate of DM (20%).[27] This study included a small sample of patients, but highlights the need for screening of glucose metabolism disorders in patients with CAD in our practice.

The other predictors for in-hospital death identified in our study (age, heart failure, left ventricular dysfunction, sustained ventricular tachycardia/ventricular fibrillation) are powerful prognostic factors in ACS patients, consistent with studies in developed countries.[6] Dyslipidaemia appeared to be a protective factor, and this observation has already been reported.[28] It is mainly the influence of previous lipid-lowering drugs in patients with high cardiovascular risk that would have a beneficial effect on mortality rate.[28] Previous treatments in our study were not specified.

PCI was a protective factor in our series but remarkably, only in patients without a history of DM in sub-group analyses. First, the low rate of PCI in our patients with ACS[29] is a potential bias. Second, CAD patients with DM frequently have multi-vessel coronary heart disease (28.9%) and complex lesions (39.7%),[30] as in studies conducted in developed countries.[31] Coronary artery bypass graft surgery is often the technique of choice for complete revascularisation in patients with DM,[32] but is of limited practice in sub-Saharan Africa. Finally, DM patients are often high-risk patients in whom an earlier invasive strategy should be implemented. However, the excessive admission delays[11] determine the low rate of PCI, which would weaken its beneficial effect.

Limitations

Our study has some limitations. Incomplete medical records did not allow us to make a thorough analysis. Glycated haemoglobin was not available for all patients and was not included in our analysis, nor was the evolution of blood glucose levels during hospitalisation. The influence of previous treatments (antidiabetic drugs, statins) and glucose-lowering treatments given during hospitalisation (particularly insulin infusion) have not been specified. Finally, the low rate of coronary angiography did not make it possible to assess the link between blood glucose levels and the severity of CAD.

Conclusion

This study, carried out in a sub-Saharan African population, shows that in the acute phase of ACS, admission blood glucose has a powerful prognostic value on mortality rate, in accordance with studies conducted in the West. In association with conventional treatment of ACS, adequate control of blood glucose is an important treatment target, especially in non-diabetic patients. Routine screening for glucose metabolism disorders and follow up after ACS must be implemented, as recommended.[26] It would be interesting to determine the rate of IGT and DM in ACS patients without a history of DM in the post-discharge phase, and assess the long-term impact of glucose-lowering therapy on morbidity and mortality rates.

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Improvement of cardiac ventricular function by magnesium treatment in chronic streptozotocin-induced diabetic rat heart

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Abstract

Objective: **Chronic diabetes mellitus is associated with detrimental cardiovascular complications and electrolyte imbalances such as hypomagnesaemia. We investigated the effect of magnesium (Mg^{2+}) on cardiac function and the possible role of histological and electrical alterations in chronic, streptozotocin-induced diabetic rats.**

Methods: **Wistar rats were treated once intraperitoneally with streptozotocin or citrate, and then daily with $MgSO_4$ or saline for four weeks. Cardiac contractile and electrocardiographic parameters were measured on Langendorff-perfused hearts. Other hearts were histologically stained or immunoblotted for the mitochondrial ATP synthase (ATP5A).**

Results: **In diabetic hearts, Mg^{2+} prevented a diabetes-induced decrease in left ventricular developed pressure and improved contractility indices, as well as attenuated the reduction in heart rate and prolongation of QT interval, but not the QT interval corrected for heart rate (QTc). Histologically, there were neither differences in cardiomyocyte width nor interstitial collagen. The expression of ATP5A was not different among the treatment groups.**

Conclusion: **Mg^{2+} supplementation improved cardiac contractile activity in chronic diabetic hearts via mechanisms unrelated to electrocardiographic or histologically detectable myocardial alterations.**

Keywords: magnesium, cardiac, diabetes, ventricular function, streptozotocin

Cardiovascular complications are a major cause of mortality in diabetes mellitus.[1] These complications are a result of the pathological remodelling processes in the heart and blood vessels that are induced by metabolic derangements in diabetes, such as hyperglycaemia, dyslipidaemia, acid–base imbalances and electrolyte disturbances.[2-4] The resultant diabetic cardiomyopathy and coronary artery disease predispose the heart to cardiac contractile dysfunction, ischaemic heart disease and dysrhythmias. In addition, the macrovascular and microvascular angiopathies in diabetes induce target-organ damage in other tissues, such as the brain, kidneys and eyes.[5] Therefore, diabetes mellitus has been proposed to be a cardiovascular disease,[6] and the modulation of pathological cardiovascular remodelling could represent one aspect of diabetic treatment. However, the mechanisms of remodelling are not fully understood.

Hypomagnesaemia is a common and detrimental type of electrolyte disturbance in diabetes, especially in chronic, poorly controlled diabetes.[7,8] In diabetic patients, hypomagnesaemia is associated with cardiovascular conditions such as atherosclerosis,[9] coronary artery disease,[10] and arrhythmias.[11] However, although magnesium (Mg^{2+}) has been shown to modulate insulin receptors and to improve metabolic control in diabetic rats,[12] the role of Mg^{2+} in cardiovascular pathological remodelling remains unclear.

An area of difficulty in determining the role of Mg^{2+} at tissue level is that Mg^{2+} tissue deficits are not readily detectable, given that Mg^{2+} is largely an intracellular ion, binds to cellular components, and has relatively slow shifts across the cell membrane.[13] Furthermore, clinical hypomagnesaemia is indicative of decreased ionised Mg^{2+} in serum and may not necessarily reflect cellular deficits or the degree of imbalance between extracellular and intracellular concentrations. These issues suggest that a possible way to offset the occurrence of subtle, but detrimental Mg^{2+} tissue deficits and imbalances that may be induced by pathological stress conditions such as diabetes would be to prevent subclinical intracellular Mg^{2+} deficiency through Mg^{2+} supplementation.

We previously showed that Mg^{2+} supplementation improved cardiac ventricular compliance and cardiac autonomic function in the early stages of diabetes in rats,[14] but the long-term efficacy of Mg^{2+} in chronic diabetes and the underlying mechanisms remain unknown. In this study, we investigated the long-term effect of Mg^{2+} treatment on cardiac ventricular dysfunction in chronic diabetes and explored the possible role of electrical and myocardial histological alterations.

Methods

The study was approved by the Faculty of Health Sciences Animal Research Ethics Committee of the University of Cape Town (AEC Protocol 014-014). All procedures on animals were performed in compliance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, National Academy Press, 2011). Adult male Wistar rats (~ 275 g) were used in this study. Rats were housed under standardised conditions (12-hour light/dark cycle and temperature of ~ 23°C) and had free access to rat chow and drinking water.

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Unless stated otherwise, drugs and chemicals were obtained from Sigma-Aldrich (SA). Streptozotocin (STZ) was used to induce a moderate form of diabetes mellitus, as previously described.[14] Rats were fasted of food (but not water) for six hours to improve the uptake of STZ before being injected intraperitoneally (i.p.) with STZ (50 mg/kg). The STZ was freshly dissolved in 0.1 M citrate buffer (pH 4.5) before administration.

Blood glucose was measured from tail vein blood samples obtained at similar times of the day using a glucometer (Accu-Chek, Roche, SA).[14] Rats with a random blood glucose concentration ≥ 15 mmol/l were considered diabetic.

Magnesium was administered as $MgSO_4$ (270 mg/kg, i.p.) dissolved in normal saline.[15,16] The i.p. route was chosen for Mg^{2+} to achieve more reliable uptake compared to oral administration in water or food where the uptake may vary in diabetes due to polydipsia and polyphagia.

The rats were randomly divided into four treatment groups, and each rat was identified by a unique label on the tail. The control group was injected i.p. with a single dose of citrate buffer on the first day, and with saline i.p. once daily for 28 consecutive days. The STZ group was injected i.p. with a single dose of STZ 50 mg/kg on the first day, and with saline i.p. once daily for 28 days. The STZ + Mg^{2+} group was injected i.p. with a single dose of STZ 50 mg/kg on the first day, and with $MgSO_4$ 270 mg/kg i.p. once daily for 28 days. The Mg^{2+} group was injected i.p. with a single dose of citrate buffer on the first day, and with $MgSO_4$ 270 mg/kg i.p. once daily for 28 days.

Rat hearts were surgically removed under anaesthesia to euthanise the rats, as previously described.[16] Briefly, rats were anticoagulated with heparin (500 IU/kg, i.p.) and anaesthetised with sodium pentobarbital (70 mg/kg, i.p., Vetserv, SA). Upon loss of the pedal withdrawal reflexes, the hearts were excised via a thoracotomy incision and placed in cold (4°C), filtered (7-µm pore Whatman filter paper, Sigma-Aldrich, SA), modified Krebs-Henseleit (KH) solution containing (in mmol/l): 118.5 NaCl, 4.7 KCl, 25 $NaHCO_3$, 1.2 $MgSO_4$, 1.8 $CaCl_2$, 1.2 KH_2PO_4 and 11 glucose (pH 7.4). $CaCl_2$ was added after the optimisation of pH to prevent precipitation of calcium with phosphate. Some hearts were used for cardiac perfusion studies, whereas the others were either histologically analysed or snap-frozen in liquid nitrogen and stored at –80°C for Western blot analysis.

For perfusion studies, the hearts were retrogradely perfused with K-H solution through an aortic cannula on a constantpressure (74 mmHg) Langendorff apparatus. To ensure optimal cardiac tissue viability, the time lapse between excision of the heart and commencement of perfusion was limited to three minutes. The K-H solution was gassed with carbogen (95% O_2 and 5% CO_2) and was maintained at 37°C. The coronary flow rate was measured by collecting coronary effluent over time and was normalised to heart weight. Blood samples used for Mg^{2+} assays were collected at the time of removal of the heart and centrifuged at 15 000 g (Beckman microfuge, USA) to obtain plasma, which was frozen until further analysis.

Electrocardiographic (ECG) and haemodynamic parameters were measured using the PowerLab data-acquisition system and LabChart Pro 7 software (ADInstruments, Australia), as previously described.[16] ECG was recorded using apex-to-base electrodes via a transducer (ML136) and was analysed using the LabChart Pro ECG module (ADInstruments, Australia). The QT interval, corrected for heart rate (QTc) was calculated using Bazett's formula. Left ventricular (LV) pressure was measured using a water-filled, intraventricular balloon connected to a pressure transducer (MLT1199) and amplifier (ML221, ADInstruments, Australia).

The hearts were stabilised for 20 minutes and the LV end-diastolic pressure (LVEDP) was set at 5–10 mmHg. The LabChart 7 Pro blood pressure module (ADInstruments, Australia) was used to analyse haemodynamic data and to derive the maximal rate of pressure increase ($+dP/dt_{max}$), the maximal rate of pressure decline ($–dP/dt_{max}$), contractility index and the time constant of ventricular relaxation *(tau)*. The LV developed pressure (LVDP) was calculated as the difference between LV peak systolic pressure and LVEDP.

Transverse sections of cardiac ventricular tissue were stained with either haematoxylin and eosin (H&E) or Masson's trichrome, as previously described.[16] Histological images were taken using a charge-coupled device camera (Zeiss AxioCam, Germany) attached to an optical microscope (Zeiss AxioSkop, Germany). The cardiomyocyte width on H&E images was analysed using ImageJ software (NIH, USA). The average width of five cells on each of four sections of the heart was calculated for each heart. The degree of interstitial and perivascular fibrosis on Masson's trichrome images was semi-quantitatively scored, as done previously,[16] based on a scoring system described by Buwa *et al*.[17] as follows: none (–), mild (+), moderate (++), and severe (+++).

Frozen LV tissues were homogenised on ice by sonication in a modified radioimmunoprecipitation assay buffer (50 mM Tris-HCl, 150 mM NaCl, 1% Triton X-100, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulphate, pH 7.4) containing a protease/phosphatase inhibitor cocktail (Thermo Scientific, USA). Protein concentrations were quantified (Pierce protein assay kit, Thermo Scientific, USA) and protein samples (40 µg) were loaded and electrophoresed on 12% sodium dodecyl sulphate-polyacrylamide gels (Mini-Protean Tetra Cell, BioRad, SA) and transferred to isopropanol-soaked polyvinylidene fluoride membranes (Trans-Blot Turbo, Bio-Rad, SA).

The membranes were blocked with 5% bovine serum albumin (BSA) in 0.1% Tween20 phosphate-buffered saline (PBS-T) for one hour at room temperature, and incubated with anti-ATP5A mouse antibody (1:5000, #136178, Santa Cruz Biotechnology, USA) in 5% BSA in PBS-T overnight at 4°C. The primary antibody was excluded in the negative control in order to rule out non-specific binding of the secondary antibody. The membranes were washed with PBST and incubated with horseradish peroxidase-conjugated secondary antibody (1:10000, #170-6516, Bio-Rad, SA) in 5% BSA in PBS-T for two hours at room temperature.

The membranes were then washed with PBS-T, incubated with enhanced chemiluminescence substrate (Bio-Rad, SA) and exposed to X-ray film in the dark room. The membranes were stripped, blocked and re-probed with anti-β-actin rabbit antibody (1:10000, #16039, Abcam, USA) and goat anti-rabbit secondary antibody (1:10 000, #6721, Abcam, USA). The bands on films were analysed using ImageJ software (NIH, USA) and were normalised to those of the housekeeping protein β-actin.

The Mg^{2+} concentration was measured in the plasma samples prepared at exsanguination, 18–24 hours after the final dose of $MgSO_4$ had been administered. Ionised Mg^{2+} concentration was measured using automated spectrophotometric and potentiometric analyses (Beckman AU Chemistry Analyzer, PathCare, SA).[14]

Statistical analysis

Data are expressed as mean and standard error of the mean (SEM) or as box plots and the mean, and *n* indicates the number

of replicates. Statistical analysis was conducted using Statistica 13. Differences among multiple groups for data with normal distribution (Kolmogorov–Smirnov and Shapiro–Wilk normality tests) were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's *post hoc* test. For data without normal distribution, a Kruskal–Wallis test was conducted, followed by Dunn's post hoc test. A two-tailed p value ≤ 0.05 was considered statistically significant.

Results

In vivo treatment with STZ significantly increased the blood glucose concentration and decreased the rat body weight (Fig. 1), starting from the first week after treatment ($p < 0.05$, STZ vs control for each parameter). Overall, treatment with Mg^{2+} did not prevent STZ-induced hyperglycaemia ($p > 0.05$, STZ + Mg^{2+} vs STZ), except for the transient dips in blood glucose concentration observed in the first and third weeks (Fig. 1A). Mg^{2+} also did not prevent the STZ-induced loss of body weight ($p > 0.05$, STZ + Mg^{2+} vs STZ; Fig. 1B). Mg^{2+} treatment alone had no significant effect on blood glucose concentration or on body weight ($p > 0.05$, Mg^{2+} vs control for each parameter).

STZ induced a significant decrease in the LVDP ($p < 0.05$, STZ vs control), and this STZ-induced hypotensive effect was prevented by Mg^{2+} treatment ($p = 0.03$, STZ + Mg^{2+} vs STZ; Fig. 2A). Mg^{2+} treatment on its own had no significant effect on LVDP ($p > 0.05$, Mg^{2+} vs control; Fig. 2A). STZ-treated hearts also exhibited significant reductions in the indices of LV contraction (+dP/dt_{max}) and relaxation (–dP/dt_{max}) as well as in the overall contractility index ($p < 0.05$, STZ vs control for each parameter; Fig. 2B–D). Among these changes, Mg^{2+} treatment reversed the STZ-induced reduction of +dP/dt_{ma}x and contractility index ($p < 0.05$, STZ + Mg^{2+} vs STZ for each parameter; Fig. 2B, C). Mg^{2+} treatment alone had no detrimental effect on +dP/dt_{max}, –dP/dt_{max}, or the contractility index ($p > 0.05$, Mg^{2+} vs control; Fig. 2B–D).

In addition, there were no significant differences in coronary flow rate or in the ratio of heart weight to body weight among the different treatment groups (Fig. 2E, F). There were also no significant differences in the diastolic time constant of ventricular relaxation *(tau)* among the groups (*tau*: 0.043 ± 0.065 s for control, 0.073 ± 0.030 s for STZ, 0.064 ± 0.023 s for STZ +Mg^{2+}, 0.080 ± 0.033 s for Mg^{2+}; values are mean ± SEM, $p > 0.05$, $n = 6$ per group).

Representative ECG traces recorded on isolated hearts (Fig. 3) showed typical apex-to-base electrical waveforms that resembled lead II tracing on a surface ECG recording. Qualitatively, the traces highlight a reduction in the heart rate of STZ-treated hearts (Fig. 3B) compared to controls (Fig. 3A), but without noticeable alterations of the ECG waveform patterns. Summary data of ECG parameters (Table 1) show that STZ significantly decreased the heart rate and prolonged the QT interval ($p < 0.01$ vs control for each parameter), and both these STZ effects could be prevented by Mg^{2+} treatment. Mg^{2+} treatment alone had no significant effect on heart rate or QT interval. There were no significant differences in the R-, S- or T-wave amplitudes and QRS and QTc intervals among the treatment groups.

Representative images of ventricular slices stained with either H&E or Masson's trichrome are shown in Fig. 4. The H&E images showed normal cardiomyocyte structural outlines, separated by extracellular spaces that were relatively free of cellular components or other infiltrates (Fig. 4A). There were also no apparent distortions in the arrangement of the myofibrils. There were no significant

Table 1. Electrocardiogram parameters

Parameters	Control	STZ	STZ+Mg	Mg
Heart rate (bpm)	233 ± 8	178 ± 14*	218 ± 8#	234 ± 13
R-wave amplitude (mV)	5.22 ± 0.79	5.67 ± 1.31	6.24 ± 1.17	6.22 ± 0.85
S-wave amplitude (mV)	1.75 ± 0.27	2.13 ± 0.63	2.35 ± 0.73	0.40 ± 1.38
T-wave amplitude (mV)	2.12 ± 0.53	2.56 ± 0.67	2.73 ± 0.95	1.76 ± 0.46
QRS interval (s)	0.020 ± 0.003	0.024 ± 0.002	0.026 ± 0.006	0.024 ± 0.003
QT interval (s)	0.062 ± 0.002	0.079 ± 0.009*	0.065 ± 0.005#	0.064 ± 0.006
QTc (s)	0.124 ± 0.006	0.137 ± 0.016	0.119 ± 0.007	0.121 ± 0.009

QTc represents QT interval corrected for heart rate. Values are mean ± standard error of the mean; $n = 7$–11 per group; *$p < 0.05$ vs control; #$p < 0.05$ vs STZ.

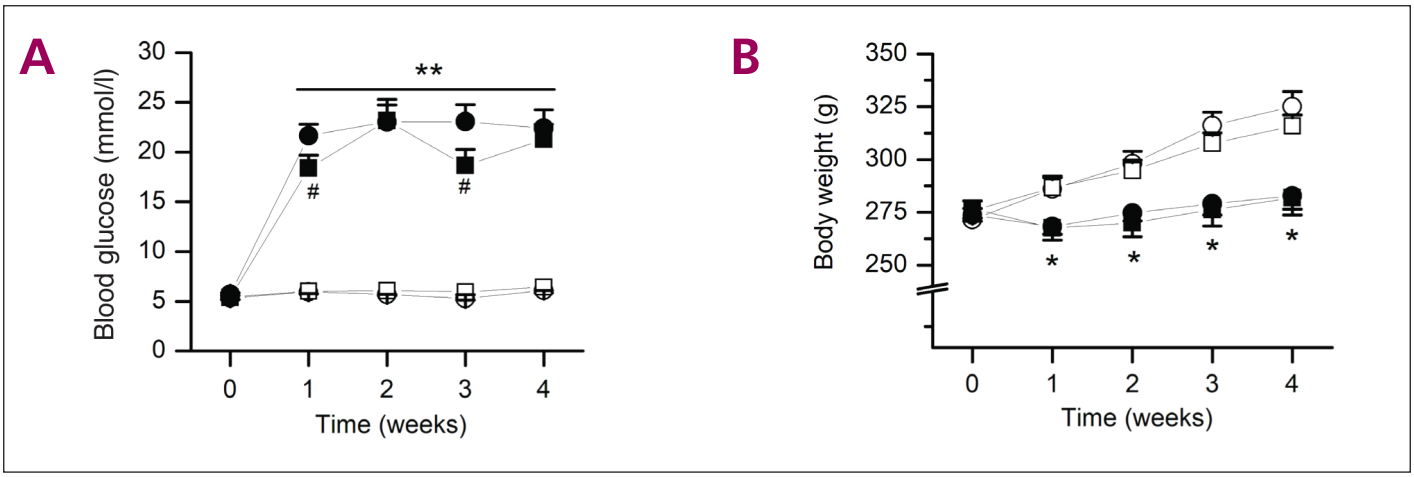

Fig. 1. General parameters. A: Random blood glucose concentration. B: Rat body weight. The parameters were measured weekly in different treatment groups of rats [○, control; ●, streptozotocin (STZ); ■, STZ + Mg^{2}+; ❑, Mg^{2}+]. Values are mean ± standard error of the mean; $n = 12$–15 per group; *$p < 0.05$, **$p < 0.01$ versus control; #$p < 0.05$ versus STZ.

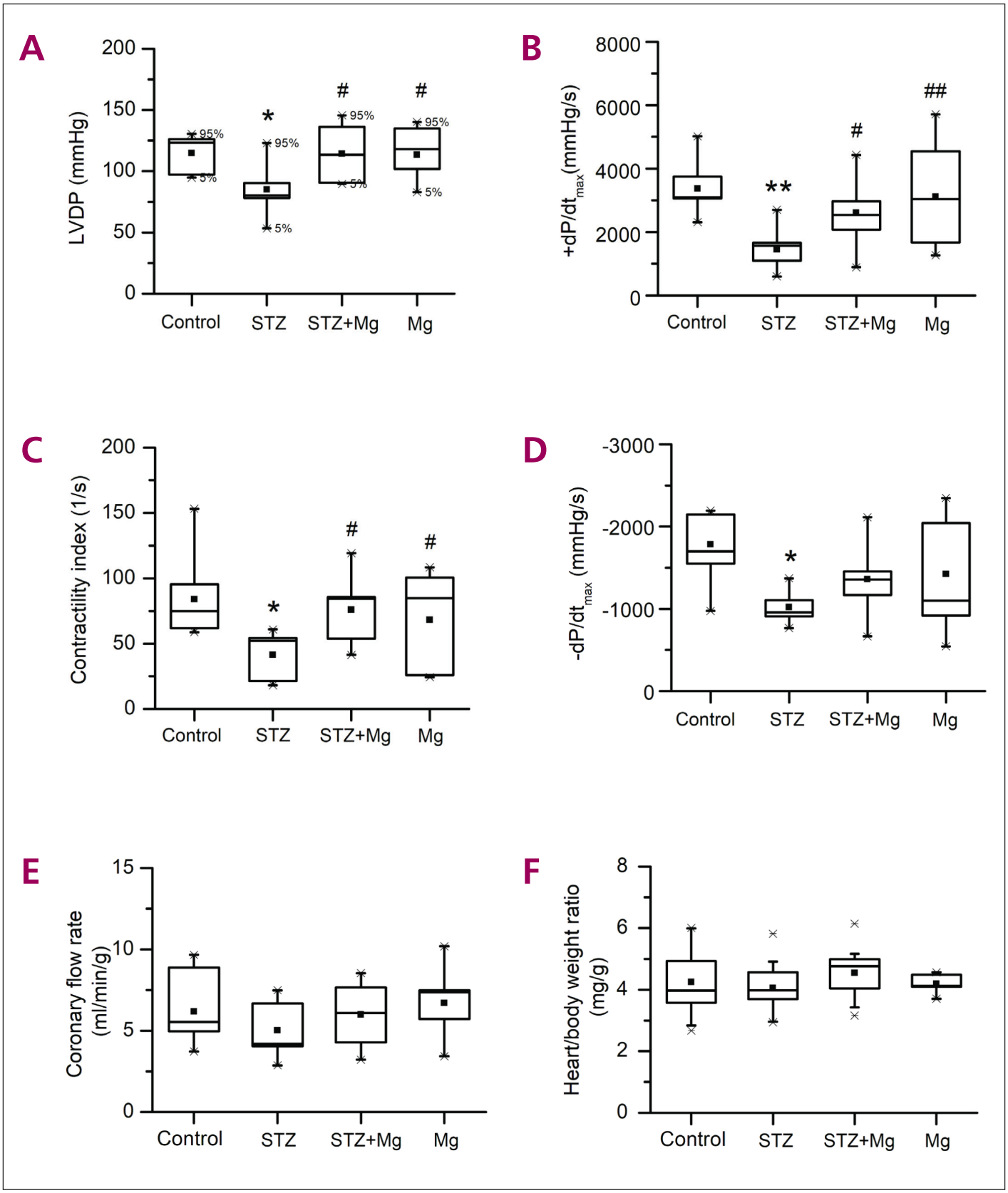

Fig. 2. Effects of treatments on haemodynamic parameters. A: Left ventricular (LV) developed pressure (LVDP). B: Maximal rate of LV pressure increase (+dP/dt$_{max}$). C: Contractility index. D: Maximal rate of LV pressure decline (–dP/dt$_{max}$). E: Coronary flow rate, normalised to heart weight. F: Heart weight to body weight ratio. Data are shown as box plots and the mean (■); n = 6–9 per group; $^{*}p < 0.05$, $^{**}p < 0.01$ versus control; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ versus STZ.

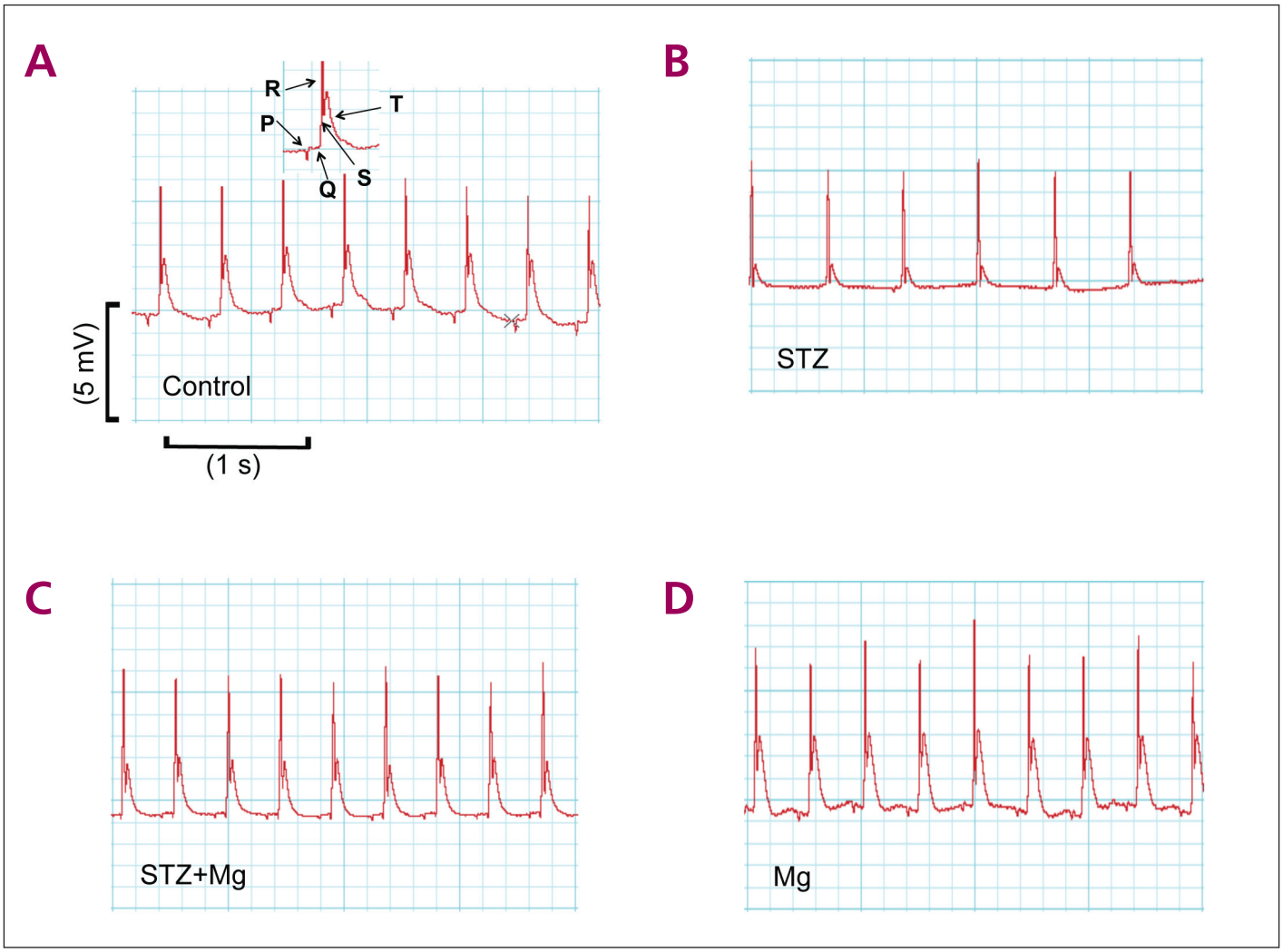

Fig. 3. Electrocardiographic (ECG) traces. A–D: Representative ECG traces recorded from different isolated hearts during Langendorff perfusion. Inset in (A) shows labels of the ECG waves. Notice that the S and T waves in the rat heart are contiguous.

differences in cardiomyocyte width among the treatment groups ($p > 0.05$; Fig. 4C). The Masson's trichrome images showed no differences in the interstitial or perivascular fibrosis score among the treatment groups (Fig. 4B, D).

To explore the role of cardiac metabolic stress, Western blot analysis was performed for the mitochondrial ATP synthase (ATP5A), a key component of the mitochondrial respiratory function. Representative images on Western blot films (Fig. 5A) showed bands of ATP5A and β-actin proteins in the ventricles of different hearts. Semi-quantitatively, there were no significant differences in the expression of ATP5A among the treatment groups (Fig. 5B).

There were no significant differences in the plasma Mg^{2+} concentration among the groups (concentration of ionised Mg^{2+}: 0.89 ± 0.01 mmol/l for control, 0.94 ± 0.05 mmol/l for STZ, 0.85 ± 0.04 mmol/l for STZ +Mg^{2+}, 0.83 ± 0.01 mmol/l for Mg^{2+}; values are mean ± SEM, $p > 0.05$, $n = 8$ per group).

Discussion

The onset and severity of cardiovascular complications in poorly controlled diabetes mellitus are time-dependent entities. In this study, we showed that Mg^{2+} treatment induced long-term improvements in LV contractile function and stabilised heart rate in chronic diabetic rats.

Our results indicated the presence of diabetes-induced ventricular systolic dysfunction in chronic diabetes, as was evidenced by the reduction in LVDP, $+dP/dt_{max}$ and the contractility index in diabetic hearts. These findings are consistent with the systolic dysfunction reported in chronic type 1 diabetes patients[18] and in STZ-induced diabetic rats.[19-21] However, the results are in contrast to the lack of systolic impairment that we previously observed in the acute diabetes disease model,[14] where only diastolic dysfunction was observed, suggesting a time-dependent progression of diabetic cardiac complications.[20]

In the present study, except for the unaltered time constant of relaxation *(tau)*, diastolic dysfunction was not further evaluated since the LVEDP had to be pre-set to a fixed value in order to measure LVDP. Nonetheless, in this study, the systolic dysfunction in diabetes was reversed by Mg^{2+} treatment. Recently, Mg^{2+} was also shown to improve diastolic function and mitochondrial activity in fat-fed chronic diabetic mice.[22] Given that diabetic diastolic

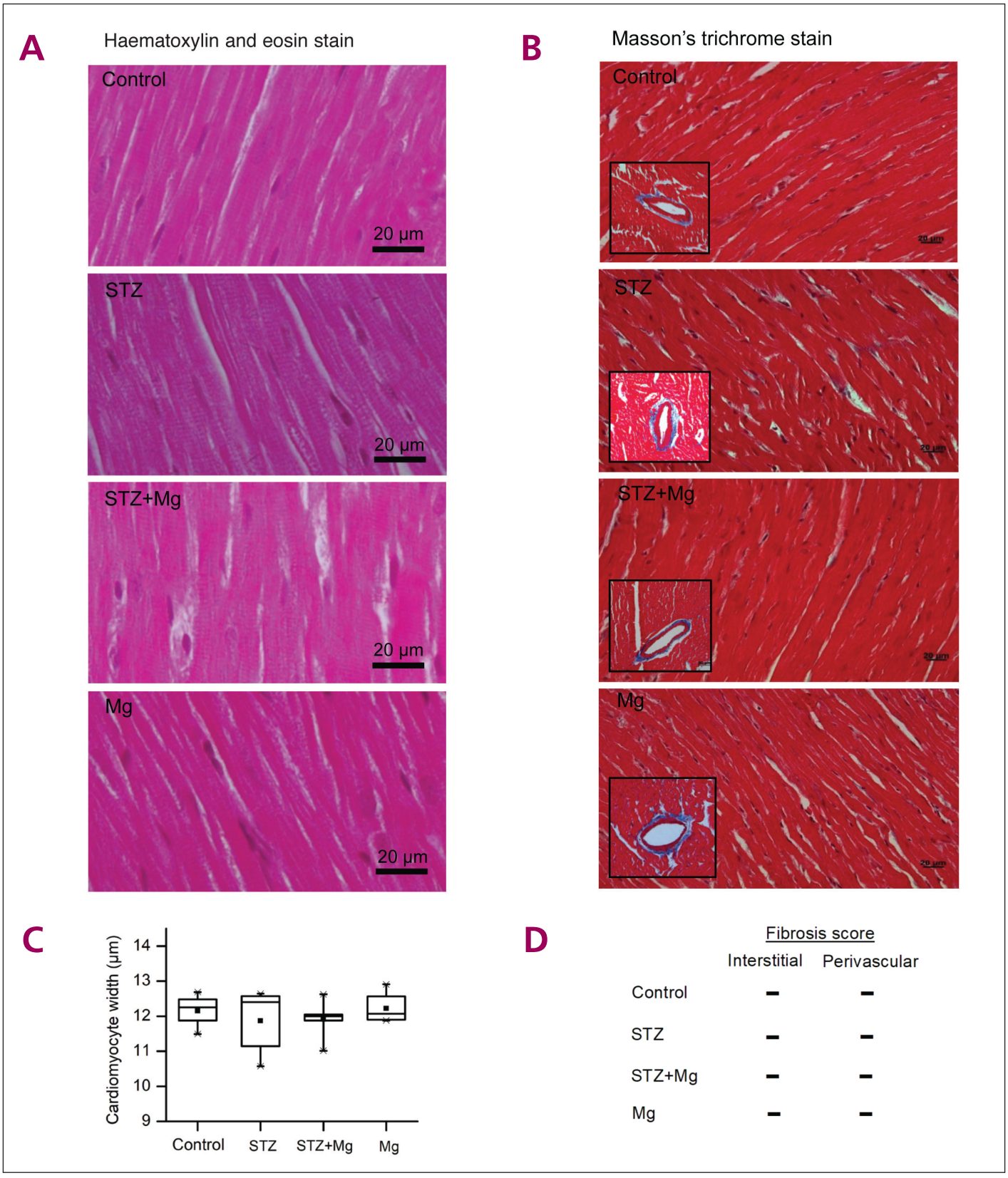

Fig. 4. Histological analyses of ventricular tissue. A: Representative images of different ventricular tissue sections stained with haematoxylin and eosin (H&E). Scale bar = 20 µm (× 40 magnification). B: Representative images of different ventricular tissue sections stained with Masson's trichrome. Insets: Images of perivascular tissue. Scale bar = 20 µm (× 40 magnification). C: Summary data of ventricular cardiomyocyte width. D: Arbitrary score of the degree of interstitial and perivascular **fibrosis: –,** none; +, mild. Data are shown as box plots and the mean (■); *n* = 6 per group.

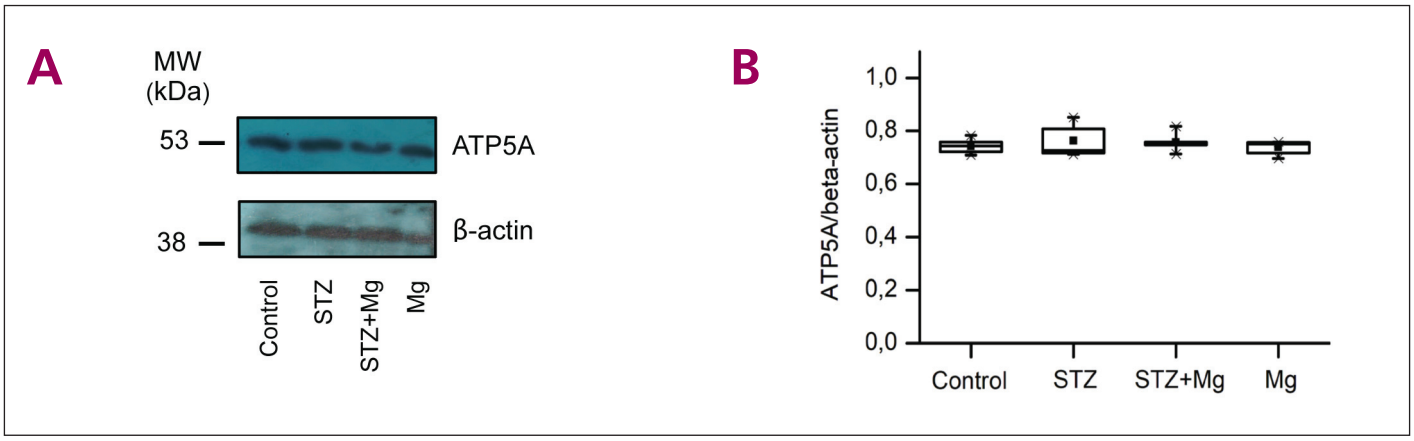

Fig. 5. Western blot analysis of mitochondrial ATP5A protein. A: Representative Western blot film images of ATP5A and the corresponding β-actin in ventricular tissue of different hearts. B: Summary data of the fold-expression of ATP5A, normalised to that of β-actin. Data are shown as box plots and the mean (■); *n* = 3 per group.

dysfunction is known to precede systolic impairment in type 1 diabetic patients[18] and in STZ-induced diabetic rats,[19,20] and that diastolic dysfunction is a common cause of systolic heart failure in diabetes,[23] the improvement of systolic activity by Mg^{2+} observed in our study could be secondary to the diastolic modulation observed in the acute diabetes disease model.[14]

In the present study, there were no detectable cardiac morphological changes to account for the contractile dysfunction induced by diabetes. The gross heart weight was unaltered, and histologically, there was neither a change in cardiomyocyte size nor interstitial fibrosis. In addition, there was no significant coronary perivascular fibrosis or cellular infiltrates that would have been expected to impair coronary perfusion, a finding that was also consistent with the lack of change in coronary flow rate observed in this study.

These findings are in agreement with those in other studies on chronic STZ-induced diabetic rats in which the cardiac dysfunction was not accompanied by histological evidence of cardiac cellular hypertrophy or fibrosis.[20] In contrast, other studies in chronic STZ-induced diabetic rats showed that there was cardiac dysfunction together with histological evidence of cardiomyocyte hypertrophy and fibrosis.[24] These histological differences are likely to be related to the duration of diabetes, given that in diabetic patients, the deposition of collagen in cardiac tissue only becomes more prominent in the later stages of heart failure when there is a low ejection fraction.[25]

In our study, there were no significant cardiac histological changes to account for the effect of Mg^{2+}. Taken together, the lack of histological alterations in our study supports the concept that the nature of diabetic ventricular dysfunction and the effect of Mg^{2+} were functional, rather than structural.

The STZ-induced decrease in heart rate observed in the present study and its prevention by Mg^{2+} were consistent with our previous findings in the acute-diabetes model where the relative bradycardia was also observed *in vivo*.[14] The bradycardia in STZ-induced diabetic rats has also been reported in other studies,[20,26] and has been attributed to cardiac autonomic synaptic degradation,[26] but the basis of the bradycardia in our study remains unclear. In this study, the bradycardia seemed to be unrelated to the modulation of cardiac electrical activity since there were no significant changes in ECG waves. The prolongation of the QT interval in diabetes was probably related to changes in heart rate because the QT interval, corrected for the heart rate (QTc), was not significantly different among the treatment groups. Taken together, the occurrence of bradycardia both *in vivo* and *ex vivo* and its prevention by Mg^{2+} suggest that these effects were intrinsic to the heart.

Despite the improvements in cardiac function by Mg^{2+}, there were no significant differences in the cardiac expression of ATP5A, a cardiac biomarker that could have accounted for the Mg^{2+} effects at a molecular level. Mg^{2+} is a key co-factor of several co-enzymes that may alter the cardiac metabolic status, it also contributes to cellular energetics via its coupling with ATP to form MgATP,[13] and it may therefore alter mitochondrial function. However, in our study, there were no changes in the metabolic indices, as was indicated by the mitochondrial metabolic component ATP5A. Therefore, further molecular studies such as those evaluating aspects of mitochondrial fusion/ fission are required to elucidate the role of Mg^{2+} at the cardiac cellular level.

Limitations of this study include the use of an artificial, STZ-induced diabetic model, in which the Mg^{2+} effects may not be readily translatable to the natural disease. However, the STZ-induced diabetic rat model is known to mimic diabetic complications in humans.[21] We also previously showed the value of this disease model in that, apart from mimicking type 1 diabetes, it also exhibited features of type 2 diabetes, such as dyslipidaemia.[14] Also, the clinical relevance of the Mg^{2+} dose used in this study remains unclear, given that that the dose (270 mg/kg) is higher than that used via the oral route in human supplementation, and is only comparable to the loading intravenous/intramuscular dose used in eclampsia (~ 230 mg/kg).[27] Nonetheless, the peak increases at 3.5 hours of ~ 0.7 mmol/l, achievable under our experimental conditions,[15] are still within the therapeutic ranges of other clinical conditions.[27] Finally, since the experiments were performed at cardiac tissue level, the presence of an intracellular Mg^{2+} deficit cannot be excluded, and therefore requires further investigations at a cellular level.

Conclusion

The results of this study show that Mg^{2+} improved cardiac contractile function and stabilised heart rate in the STZ-induced chronic diabetes rat model, without preventing metabolic derangements

such as hyperglycaemia. The mechanisms underlying the attenuation of cardiac dysfunction in chronic diabetes mellitus by Mg^{2+} were unrelated to electrocardiographically or histologically detectable changes, but the exact pathways involved require further investigation.

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'Diabesity': interlinking treatments to improve outcomes in diabetes and obesity

Learning objectives

You will learn:

- 'Diabesity' is a term used to describe the pathophysiological interlink between obesity and type 2 diabetes mellitus, both of which are characterised by insulin resistance and insulin deficiency.
- Significant benefits of weight loss have been observed in type 2 diabetes mellitus prevention and treatment.
- Rational use of antidiabetic medications is imperative to optimise long-term management of diabesity, balancing optimal glycaemic control with the most appropriate diabesity management regimen.

Introduction

Over recent decades obesity has emerged as the largest chronic health concern globally, with major driving factors being the consumption of high-calorie, high-carbohydrate and high-fat foods and a shift towards a sedentary lifestyle. Moreover, the incidence of severe obesity [i.e. a body mass index (BMI) > 40 kg/m^2] is increasing rapidly and carries an especially elevated mortality risk. Obesity is associated with more than 45 co-morbidities and is known to be the primary risk factor for cardiovascular disease, type 2 diabetes mellitus (T2DM), hypertension, coronary heart disease and certain types of cancer. Obesity is also a cause of diverse psychological problems and various physical disabilities, including a significantly increased risk of developing an arthritic condition. In the context of the COVID-19 pandemic, obesity and diabetes are associated with more severe outcomes of the disease and markedly increased mortality. The infection itself may precipitate acute metabolic complications through direct negative effects on pancreatic β-cell function.[1-4]

It is important for the clinician to recognise the cycle of insulin resistance and obesity, whereby each gives rise to the other and can result in more severe obesity and T2DM. The term 'diabesity' describes the pathophysiological interlink between obesity and diabetes, as both metabolic disorders are characterised by insulin resistance and insulin deficiency. There is a tendency towards decreased treatment success in diabetes whenever weight gain is observed, and weight reduction is considered a key therapeutic goal in the treatment of T2DM. This raises the question of whether weight management and diabetes should be targeted with combined treatment strategies.[1,5,6]

Diabesity is the pandemic that will stay with us long after COVID-19 has passed. Of the South African adult population, 20% are diabetic or pre-diabetic, and half of these remain undiagnosed. This will place an enormous burden on our health system in the coming decade. To improve long-term metabolic control, Dr Lombard confidently favours diabetic treatments that contribute to weight loss or that are at least weight neutral.

From obesity to diabetes

Obesity causes sustained elevation of free fatty acid plasma levels, both in the basal state and following glucose load; this is a major contributing factor to insulin resistance and ultimately the development of diabetes (Fig. 1). Hyperglycaemia and compensatory hyperinsulinaemia associated with insulin resistance and glucose intolerance lead to pathological glycation of circulating proteins and the formation of advanced glycation end-products. This progression ultimately leads to pancreatic β-cell secretory failure and apoptosis.[6] See page 61 for further information on these inflammatory pathways.

What is the importance of body fat distribution?

A high proportion of body fat is regularly seen in people with a BMI > 30 kg/m^2, but this is also observed in one-third of people with normal weight and can usually be identified using waist circumference measurements (women > 80 cm, men > 94 cm).

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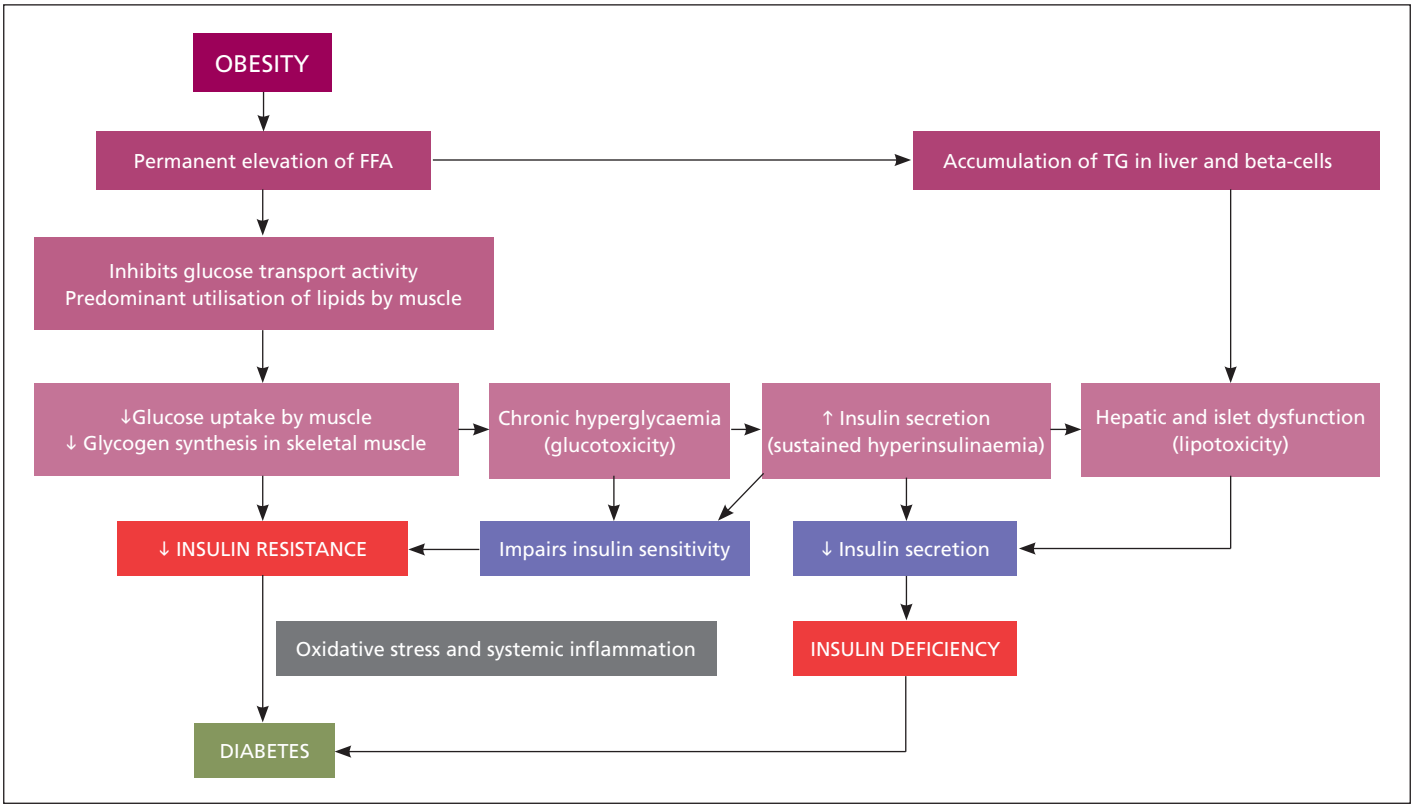

Fig. 1. Pathways from obesity to diabetes.[6]

Independent of the population-specific BMI thresholds determining overweight and obesity, visceral fat distribution has been found to elevate the risk of mortality.[1]

What are the benefits of weight loss in diabetes prevention and therapy?

The progression of T2DM can be arrested and often reversed in the first five years after diagnosis by significantly reducing body weight (≥ 10%); the metabolic dysregulation and inflammatory processes that predispose to T2DM can frequently be corrected.[5]

The Finnish Diabetes Prevention Study[7] showed that in pre-diabetic individuals, intensive dietary and exercise programmes decreased the overall risk of diabetes by 58% (Fig. 2). Similarly, the Diabetes Prevention Program[8] showed that moderate weight loss with lifestyle intervention in an obese population with impaired glucose tolerance could reduce the incidence of diabetes by 58%, whereas metformin alone reduced diabetes incidence by only 31% (Fig. 3).

The American Cancer Society's Cancer Prevention Study I indicated that intentional weight loss of 10 kg in those with T2DM reduced total mortality by approximately 25%. Other clinical trials have demonstrated that a loss of 5–10% of body weight in diabetes patients demonstrates beneficial effects at one year (Table 1).[9-12]

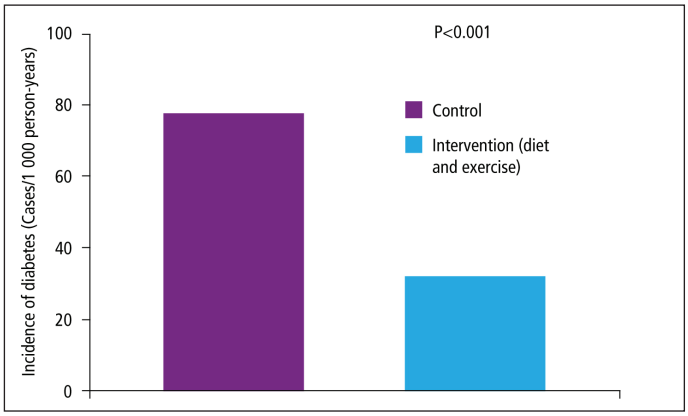

Fig. 2. Finnish Diabetes Prevention Study: intensive dietary and exercise intervention decreases overall risk of diabetes.

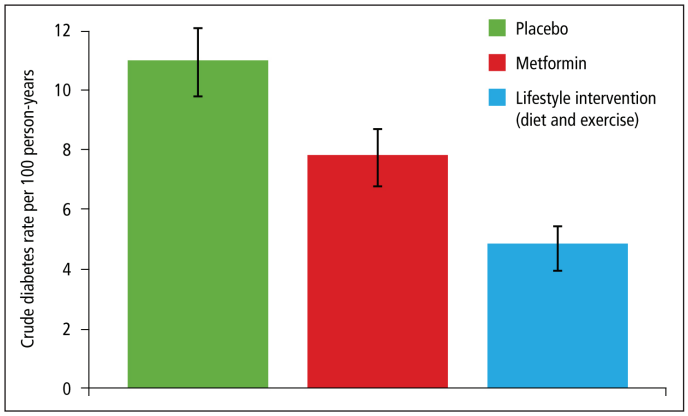

Fig. 3. Diabetes Prevention Programme: lifestyle modification is superior to metformin for the prevention of T2DM.

Table 1. Benefits of weight loss in diabetes patients

- Improves overall fitness
- Reduces HbA_{1c} levels
- Improves cardiovascular disease risk factors
- Decreases the use of antihyperglycaemic, antihypertensive and lipid-lowering agents
- Reduces symptoms of depression
- Reduces severity of, or promotes remission of, symptoms of obstructive sleep apnoea.

In many ways the treatments for diabetes are similar to those for addressing obesity. The treatment of obesity always entails reduction of body weight through lifestyle interventions, pharmaceutical interventions or metabolic surgery. Canada is the only country to publish clinical guidelines for the management of obesity as a chronic disease.

The available treatments for diabetes are variable and based on the type of diabetes with which an individual has been diagnosed. Important factors that need to be considered include a person's lifestyle habits, diet and their medicine choices.[1,13,14]

What is the role of lifestyle in management of weight and diabetes?

Patients' understanding of the role of diet and exercise in preventing and managing diabetes is critical to long-term health status change. Any recommended lifestyle changes should be specific to the patient; patients that participate in lifestyle reconciliation decision-making have a much greater ability to lose weight. However, the reality is that intensive lifestyle interventions are difficult to achieve and maintain over a long period of time.[1,13]

Exercise

The effects of physical activity in improving a patient's metabolic profile are unequivocal. Studies have consistently shown improved glycaemic control, lipid profile, cardiovascular fitness and antioxidant status, along with reduced inflammatory markers, adiposity and atherogenic progression, thereby confirming that physical activity is an evidence-based treatment modality to combat diabesity.[6] Exercising more than three times per week, averaging 150 minutes of physical activity every week, should entail a combination of aerobic exercise with twice-weekly strength training. Aside from obviously strengthening muscle and bone and improving lean mass, strength training also improves insulin sensitivity and can lower blood glucose. There is an additive effect on weight loss when exercise is combined with an energy-restricted diet.[1,13]

Diet and nutrition

Nutritional therapy is practical and useful for improving glycaemic control and metabolism. An energy-restricted diet can be achieved either by a low-fat, low-carbohydrate diet, or the Mediterranean-style diet, which is characterised by beneficial metabolic effects. However, it is not the diet type that determines the success of weight loss, but rather sustained adherence to the diet of choice. Ideally, a broad spectrum of different diet options should be available to best match the patient's individual food preferences, lifestyle and medical conditions.

Clinical focus with Dr Lombard

Top tips for motivating patients to adopt a better lifestyle

Dr Lombard points out that from his clinical experience, the following strategies or interventions work best:

- Motivating patients to lose weight, especially poorly controlled overweight diabetics, is more achievable when they understand the serious implications of their condition. If diagnosed with T2DM at 50 years of age, lifespan is likely to be reduced by 10 years; if diagnosed before the age of 40 years, the individual is unlikely to reach retirement age
- A weight loss of at least 10 kg or 10% of body weight is not easy to achieve and sustain; the addition of anti-obesity drugs is useful, although they are not reimbursed by South African medical aids. Options include orlistat, topiramate, liraglutide and phentermine. Phentermine can only be used short term as it has significant risks; the prescriber should be aware of its indications and contraindications
- Consultation with a motivated and dedicated dietitian can be of great help; a team effort and regular follow up are necessary
- Ensure that other medications are not contributing to weight gain
- Choose diabetic medications that contribute to weight loss.

Pharmacotherapy in diabetes: what are the options for combined obesity and diabetes treatment?

Effective treatment of obesity should simultaneously improve body weight, body composition and glycaemic control. Although metabolic surgery is the best treatment option for patients with diabesity, most patients can only be managed with antidiabetic medications because metabolic surgery is invasive, unacceptable to many patients and expensive, currently around R180 000.

Antidiabetic agents may affect diabesity outcomes because of their effects on body weight and other metabolic parameters. Consequently, rational use of antidiabetic medications is imperative to optimise long-term management of diabesity. The focus of a suitable antidiabetic treatment for obese/overweight patients should at the very least be the prevention of additional weight gain. Glucose-lowering agents that support weight reduction or are weight neutral should be the first choice after the obligatory metformin therapy.[1,15]

Metformin

Although metformin is generally considered weight-neutral, weight loss ranging from 0.6 to 2.9 kg has been shown in multiple studies with HbA_{1c} reduction of ≥ 1%, especially when coupled with lifestyle interventions. Antidiabesity effects arise from inhibition of hepatic gluconeogenesis, improvement of muscle insulin sensitivity and the agent's appetite-suppressing effect. Metformin treatment in combination with lifestyle modifications has shown improvements in polycystic ovary syndrome (PCOS), gestational diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) and cancer, all of which are health problems directly or indirectly linked to diabesity.[5,15]

GLP-1 RAs

The glucagon-like peptide-1 receptor agonists (GLP-1 RAs) can lead to weight loss by decreasing appetite, delaying gastric emptying and enhancing satiety. Collectively, these effects result in a significant improvement in diabesity, with protective effects on the heart,

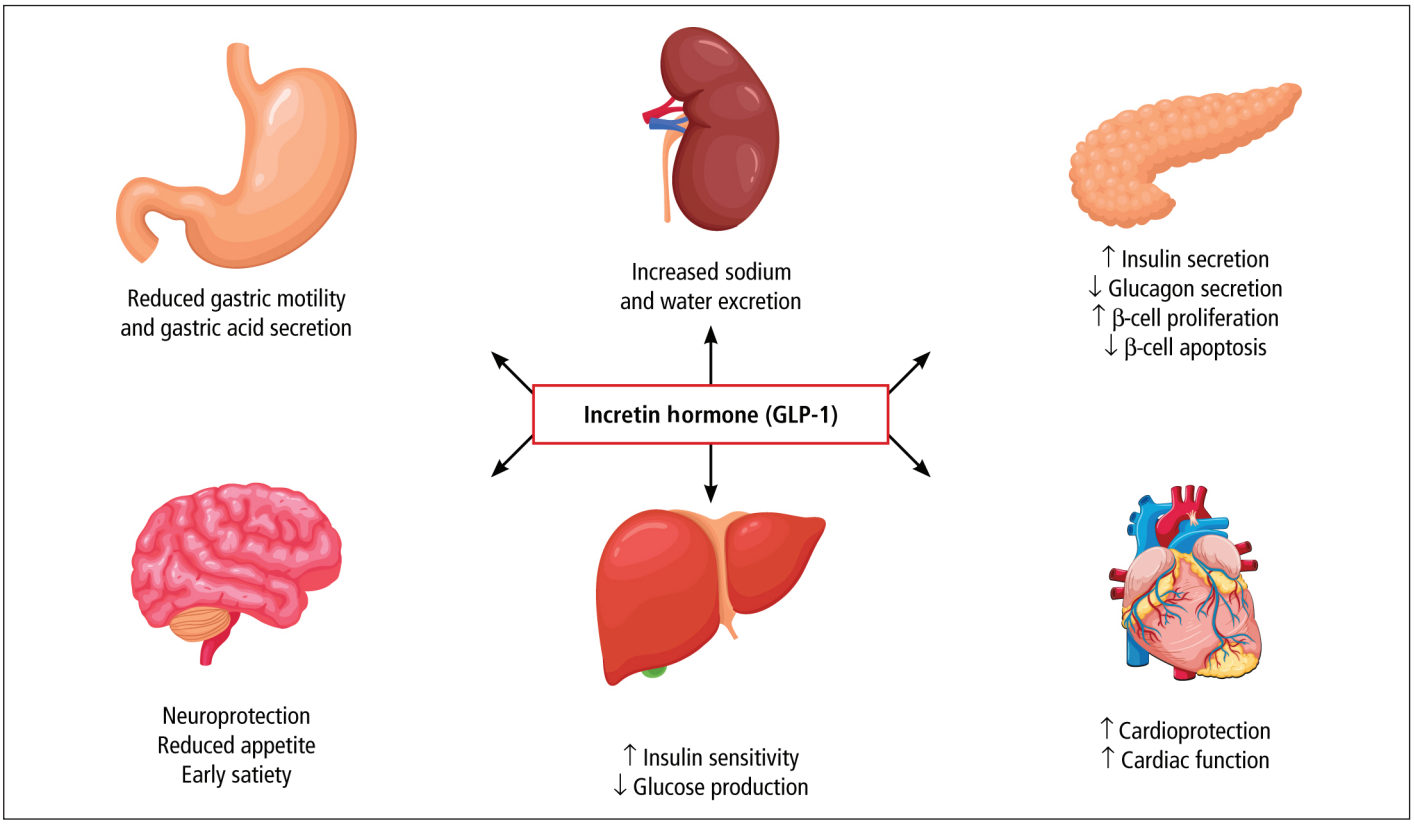

Fig. 4. The physiological roles of GLP-1 and therapeutic benefits of GLP-1 RAs.[15]

kidneys and liver (Fig. 4). Variations in weight loss potential are seen among individual GLP-1 RAs and in different patient groups. Liraglutide is the most potent and best researched for weight loss in the GLP-1 class, with a 3-mg daily dose found to be beneficial as an anti-obesity treatment in patients without diabetes (Table 2).[5,15,16]

Are all GLP-1 RAs equal with regard to weight loss?

A recent comparison of dulaglutide and liraglutide in the AWARD-6 study showed a statistically significantly greater weight loss with liraglutide (Fig. 5), with a difference of 700 g in six months.[17] However, once-weekly dulaglutide has similar glucose-lowering efficacy as the 1.8-mg liraglutide dose and good cardiovascular outcomes. Treatment with exenatide has been associated with only a modest weight loss (2.49 ± 0.66 kg) in a cohort of obese non-diabetic women.[18] Exenatide has not shown any cardiovascular benefit.

The SUSTAIN-7 trial, a head-to-head comparison between semaglutide and dulaglutide as add-on to metformin, demonstrated significantly greater weight loss at 40 weeks with semaglutide. As T2DM and lifestyle factors are the usual consequences of obesity, clinicians should consider this treatment option in very obese subjects not willing or able to undergo metabolic surgery.[19]

Table 2. Anti-obesity treatments: liraglutide and weight management[16]

- Individuals without T2DM, BMI > 30 kg/m² or > 27 kg/m² in the presence of treated or untreated dyslipidaemia or hypertension.
- 3.0 mg liraglutide injected subcutaneously vs placebo; all subjects received counselling on lifestyle modification.
- At 56 weeks, the liraglutide group had lost a mean of 8.4 ± 7.3 kg of body weight and the placebo group had lost a mean of 2.8 ± 6.5 kg.
- Of patients in the liraglutide group, 63.2% lost at least 5% of their body weight compared with 27.1% in the placebo group ($p < 0.001$); 33.1 and 10.6%, respectively, lost more than 10% of their body weight ($p < 0.001$).
- Liraglutide treatment was associated with reductions in cardiometabolic risk factors, including waist circumference, blood pressure and inflammatory markers, along with modest improvements in fasting lipid levels.

SGLT-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) reduce glucose reabsorption by the kidneys, leading to increased urinary glucose excretion. This may result in weight loss via direct caloric loss in the form of glycosuria, as well as improved glucose control.[5] Major adverse effects reported are urinary tract and genital fungal infections (from increased glucose excretion through the kidney) that may lead to discontinuation of the drugs.[15] A beneficial class effect is renoprotection – a more than 40% reduction of renal disease, renal failure, renal replacement therapy and worsening renal function on average. There is also significant benefit in heart failure, with hospitalisation reduced by nearly 40%. Empagliflozin data show a lowering of cardiovascular mortality by an impressive 38% (relative risk reduction) in patients with established cardiovascular disease.

DPP-4 inhibitors

DPP-4 inhibitors are weight neutral. While use of dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, linagliptin, saxagliptin,

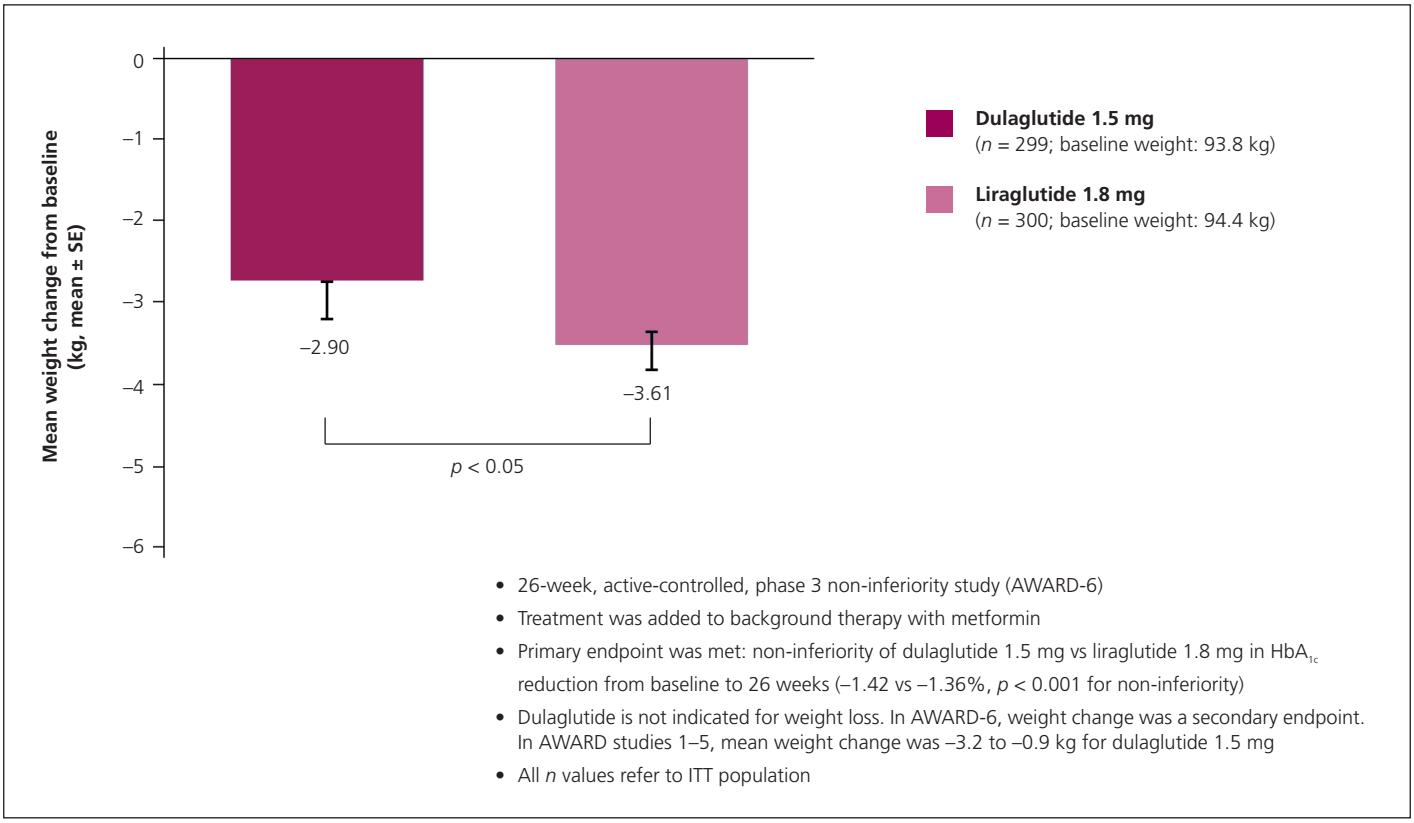

Fig. 5. AWARD-6: Liraglutide is superior to dulaglutide for weight loss.

sitagliptin, vildagliptin) have a low risk of hypoglycaemia and have been associated with improved glycaemic control, insulin secretion and β-cell function, they are considered to be weight neutral or associated with minimal changes in weight. They are very safe drugs, seldom give rise to side effects and are ideal for use in the elderly or those patients at high risk of hypoglycaemia. DPP-4 inhibitors are generally neutral from a cardiovascular point of view, but some should not be used in patients with heart failure.

Thiazolidinediones

The thiazolidinediones are associated with weight gain, making pioglitazone less favourable for patients with diabesity. However, pioglitazone improves NAFLD, although its use is associated with increased risk of heart failure, urinary bladder cancer, secondary osteoporosis and fractures.[15] Thiazolidinediones can be useful in patients with extreme insulin resistance and have demonstrated good stroke prevention data in the IRIS study.

Insulin

Because it is an anabolic hormone, insulin causes weight gain through inhibition of protein catabolism, stimulation of lipogenesis, slowing of basal metabolism and increasing the accumulation of fat. Increase in body weight and fat mass is strongly associated with the intensity of the insulin regimen, as well as worsening of diabesity. Insulin in high doses, as often used in obese diabetics, can cause massive weight gain. Yet insulin and sulphonylureas (gliclazide, glimepiride, glipizide, glyburide) are frequently used early in the management of T2DM. Gliclazide is the only sulphonylurea recommended by the Society for Endocrinology, Metabolism and Diabetes of South Africa and is associated with minimal weight gain.

For patients with obesity and T2DM requiring insulin therapy, the Endocrine Society Clinical Practice Guideline recommends concomitantly prescribing at least one weight-loss promoting medication (e.g. metformin, GLP-1 RAs or pramlintide) to mitigate associated weight gain from insulin use.[5,15]

With all the new agents available, especially the weight-friendly GLP-1 RAs and SGLT-2 inhibitors, these drugs should be optimised before insulin is considered. Insulin should only be used if no other options are left.[4]

Clinical focus with Dr Lombard

Multidrug treatment for glycaemic control: keeping weight top of mind

Drugs with prognostic (survival) benefits should be used first. It is interesting to note that the only classes that have prognostic benefits are also those medications that contribute to weight loss – metformin, SGLT-2 inhibitors and GLP-1 RAs. Variations in drug efficacy within classes imply that the right choices need to be made for each patient – 'the art of medicine'. Dr Lombard observes how very unfortunate it is that medical funders usually do not see the point of individualised management, and these drugs are often poorly reimbursed. They would rather pay for the complications than pay to prevent them. Fixed combinations are entering the market and will offer many more excellent choices, with very robust published data to support their use.

Most patients with T2DM require more than one antidiabetic

agent for glycaemic control at some point on their diabetes journey. In these cases, rational drug combinations with the least potential for worsening diabesity and with maximum benefits in preventing its complications, such as cardiovascular disorders and renal disease, should be chosen when devising the appropriate management strategy. In patients without contraindications (advanced liver and kidney diseases) and drug intolerance, metformin remains the first-line agent for medical management of diabesity. Add second-line agents for glycaemic control depending on the degree of hyperglycaemia, choosing an agent with the least propensity for weight gain.[15]

Summary of interventions

- Addition of insulin to metformin is the best approach for rapid reversal of severe hyperglycaemia and glucotoxicity. However, every attempt should be made to switch from insulin to another antidiabetic agent with weight-loss potential or that is weight neutral once glycaemic control is achieved.
- Although addition of sulphonylureas to metformin worsens diabesity because of the weight-gain potential, this combination is economical and effective in controlling hyperglycaemia and therefore still preferred by many funders.
- Because of the weight-loss potential and beneficial effects on an adverse lipid profile, the combination of GLP-1 RAs with metformin is potentially a very promising regimen for patients with diabesity.
- Combination therapy with metformin and a SGLT-2 inhibitor is encouraging for medical management of diabesity, showing reduction in body weight and improvement of β-cell function.
- Because of weight neutrality and different mechanisms of action, a combination of a DPP-4 inhibitor and metformin is promising in the early management of diabesity in patients reluctant to use injections or intolerant of GLP-1 RAs; a fixed combination should be considered early on.
- Addition of pioglitazone to metformin raises concerns about the management of diabesity, although it may be an appropriate choice among patients with NAFLD and PCOS.

Clinical focus with Dr Lombard

And do not forget about other medications

Many medicines tend to increase body weight (Table 3). In general, net weight gain varies between individuals and from drug to drug. Take time to distinguish between weight gain related to a specific treatment and weight gain that is due to other factors, such as a poor diet or lack of exercise.[1,20]

It is important to note significant co-morbid association between diabesity and neuropsychiatric disease, particularly depression. Importantly, not only is the prevalence of mood disorders elevated in patients with T2DM, but depressed patients are also more prone to develop diabetes. Similarly, there is an association between mood disorders and obesity. Some antidepressants, antipsychotics and anti-epileptic medications lead to an increased appetite, whereas other medicines such as β-blockers slowly induce weight gain over time due to associated fatigue and thus lower patient activity levels. Importantly, treatment of obesity improves depressive symptoms in patients with mood disorder; and patients being treated for depressive symptoms show improved weight loss and weight management.[20,21]

Table 3. Different drug types and their observed trends in weight gain[1]

Drug class	Weight effect
Antidepressant agents	
Tricyclic antidepressants	
Amitriptyline, nortriptyline	+/–
MAO inhibitors	
Phenelzine, tranylcypromine	+++
Moclobemide	0/–
SSRI	
Citalopram, fluoxetine, paroxetine, sertraline	+/–
SNRI	
Duloxetine, venlafaxine, milnacipran	0/–
Others	
Bupropion	0/–
Mirtazapine	++
Lithium	+++
Antipsychotic agents	
Clozapine	+++
Olanzapine	+++
Risperidone	++
Quetiapine	++
Aripiprazole	0/+
Ziprasidone	0/+
Haloperidol	+++
Pherphenazine	+/–
Anti-epileptics	
Valproic acid	++ to +++
Carbamazepine	+ to ++(+)
Gabapentin	+ to +++
Steroid hormones	
Oral corticosteroids (prednisone)	+ to ++(+)
Hormone therapy – contraception (DMPA)	+ to ++
Miscellaneous agents	
Beta-adrenergic blockers (propanolol, metoprolol, atenolol)	+ to ++

+++ significant, ++ moderate, + slight weight gain; 0/+ slightly increasing effect; +/– inconsistent data; 0/– minimal to no weight reduction; – – moderate; – – – significant weight loss.

From obesity to diabetes

When diet-derived fat intake is increased, fat storage occurs within and around other tissues and organs including the liver, skeletal muscle and β-cells, which under normal conditions do not store lipids. This in turn results in excessive mitochondrial production of toxic reactive lipid species that cause organ-specific oxidative damage and cellular dysfunction, leading progressively to the development of insulin resistance, impaired glucose metabolism and finally to diabetes. The accumulation of toxic metabolites within the β-cells in particular affects insulin secretion and enhances β-cell apoptosis.[6]

Obesity-associated inflammation may be due to increased circulatory pro-inflammatory cytokines, decreased anti inflammatory cytokines, reactive oxygen species, increased lipids, free fatty acids, endoplasmic reticulum stress, mitochondrial dysfunction and activation of diverse signalling cascades. In the initial stages, inflammatory responses are triggered by a pro-inflammatory imbalance in the brain and adipose tissue, leading to dysregulated insulin and leptin sensitivity. Over time, ectopic lipids accumulate in the muscle, liver and blood vessels, leading to activated tissue leukocytes, organ-specific diseases and exacerbated systemic insulin resistance. Obesity also induces inflammation via lipopolysaccharide-related endotoxaemia involving gut microbiota. Inflammation is characterised by an upsurge of T-lymphocytes and macrophages secreting pro-inflammatory cytokines that act to perpetuate systemic inflammation and induce insulin resistance. Increasing evidence suggests that chronic low-grade inflammation in adipose tissue affects the pathogenesis of diabetes in obese patients.[6]

Key learnings

- Insulin resistance and obesity each give rise to the other, potentially resulting in more severe obesity and T2DM.
- Weight reduction is considered a key therapeutic goal in the treatment of T2DM, demonstrating numerous beneficial health effects.
- Metabolic surgery is the best treatment option for patients with diabesity, although most patients can only be managed with combined lifestyle interventions and antidiabetic medications.
- Of the available antidiabetic medications, GLP-1 RAs are associated with the greatest weight loss, with variation among individual GLP-1 RAs and in different patient groups.
- The thiazolidinediones, insulin and sulphonylureas are associated with weight gain.
- Medications for treatment of other conditions may increase body weight.

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A few kilograms' weight loss nearly halves the risk of diabetes: large UK clinical trial

Losing a few kilograms in weight almost halves people's risk of developing type 2 diabetes, according to a large-scale research study led by the Norfolk and Norwich University Hospital and the University of East Anglia, published in *J Am Med Assoc Internal Medicine*. The study shows how providing support to help people with pre-diabetes make small changes to their lifestyle, diet and physical activity can almost halve the risk of developing type 2 diabetes.

The findings come from the Norfolk Diabetes Prevention Study (NDPS), the largest diabetes-prevention research study in the world in the last 30 years. The NDPS clinical trial ran over eight years and involved more than 1 000 people with pre-diabetes at high risk of developing type 2 diabetes.

The study found that support to make modest lifestyle changes, including losing two to three kilograms of weight and increased physical activity over two years, reduced the risk of type 2 diabetes by 40 to 47% for those categorised as having pre-diabetes. There are about eight million people with pre-diabetes in the UK and 4.5 million have already developed type 2 diabetes.

The NDPS, funded by £2.5m from the National Institute for Health Research (NIHR), and NIHR CRN Eastern, was led by the Norfolk and Norwich University Hospital (NNUH) and University of East Anglia (UEA), together with colleagues from Ipswich Hospital, and the universities of Birmingham and Exeter. The research trial tested a simple lifestyle intervention, which helped people make small, achievable lifestyle changes that led to a modest weight loss, and increases in physical activity.

Importantly these changes were sustained for at least two years and the weight lost was not put back on. These findings are important as they show that a 'real-world' lifestyle programme really can make a difference in helping people reduce their risk of type 2 (adult-onset) diabetes.

Prof Mike Sampson, NDPS chief investigator and consultant in diabetes at NNUH, said: 'We are delighted with the results of this trial, as until now no one was very sure if a real-world lifestyle programme prevented type 2 diabetes in the pre-diabetes population we studied, as there have been no clinical trials that had shown this.

'We have now shown a significant effect in type 2 diabetes prevention, and we can be very optimistic that even a modest weight loss, and an increase in physical activity, in real-world programmes like this have a big effect on the risk of getting type 2 diabetes.

'This is really great news for the eight million people in the UK with a pre-diabetes diagnosis. The results of this trial show that diabetes prevention is possible in the same pre-diabetes populations being treated in the NHS national diabetes prevention programme. 'This is important to know, as the clinical methods for diagnosing diabetes and pre-diabetes have changed a lot in recent years.'

The Norfolk Diabetes Prevention Study ran between 2011 and 2018 and worked with 135 GP practices in the east of England, and found 144 000 people who were at risk of developing type 2 diabetes. In screening sites across the east of England, 13 000 of these people then took a fasting glucose and glycosylated haemoglobin (HbA_{1c}) blood test to detect pre-diabetes.

More than 1 000 people with pre-diabetes were then entered into a randomised, controlled trial, testing a pragmatic real-world lifestyle intervention, compared to a control group, with average follow up of just over two years. Earlier studies have used quite intense and expensive research interventions in different groups of pre-diabetes participants, but this is the first time a real-world group-delivered intervention has been shown to reduce the risk of type 2 diabetes.

NDPS also asked lay members of the public who had type 2 diabetes themselves to help support participants with pre-diabetes in the trial, but for this particular population, this did not further reduce the risk of getting type 2 diabetes.

NDPS co-investigator Prof Bachman, from Norwich Medical School, is part of UEA's Norwich Institute of Healthy Ageing, a new research centre investigating how we can live longer, healthier and more satisfying lives.

He said: 'The NDPS intervention was delivered in groups, which was far less expensive than individual-focused interventions that have previously shown to be effective under optimal conditions. For every 11 people who received the NDPS intervention, one person was prevented from getting type 2 diabetes, which is a real breakthrough.'

Prof Colin Greaves from the University of Birmingham, who jointly led the development of the NDPS intervention, said: 'If you have been diagnosed with pre-diabetes, this approach offers a way to take a different direction in your life – to get off the path to type 2 diabetes and onto the road to a healthier future.'

Dr Jane Smith, NDPS collaborator from the University of Exeter, said: 'Type 2 diabetes is a huge health challenge globally. NDPS is an incredibly positive story for individuals and healthcare systems, and underlines the importance of providing national diabetes-prevention programmes, which can use our research findings.'

Prof Jonathan Valabhji, national clinical director for diabetes and obesity for NHS England, said: 'This study with similar referral criteria and a similar intensive lifestyle intervention to the NHS Diabetes Prevention Programme has surpassed expectations in preventing type 2 diabetes. This is hugely encouraging for the NHS Diabetes Prevention Programme, and what participants might expect to achieve in the longer term.'

Dr Elizabeth Robertson, director of research at Diabetes UK, said: 'We welcome this new research showing that a group-based support programme can help people at high risk of developing type 2 diabetes reduce their risk. This trial again highlights how achieving modest weight loss through diet and physical activity changes can lead to huge benefits for people at high risk of developing type 2 diabetes. Type 2 diabetes is a serious condition, but with the right help, many cases can be prevented or delayed.'

'Diabetes UK's "Know Your Risk" tool helps people to determine their risk and take steps to reduce it, including by self-referring on to NHS England's Diabetes Prevention Programme in their local area.'

Source: *Medical Brief* 2020

Statins linked to doubled risk of type 2 diabetes

A study of thousands of patients' health records found that those who were prescribed cholesterol-lowering statins had at least double the risk of developing type 2 diabetes. The detailed analysis of health records and other data from patients in a private insurance plan in the Midwest provides a real-world picture of how efforts to reduce heart disease may be contributing to another major medical concern, said Victoria Zigmont, who led the study as a graduate student in public health at The Ohio State University.

Statins are a class of drugs that can lower cholesterol and blood pressure, reducing the risk of heart attack and stroke. More than a quarter of middle-aged adults use a cholesterol-lowering drug, according to recent federal estimates.

Researchers found that statin users had more than double the risk of a diabetes diagnosis compared to those who didn't take the drugs. Those who took the cholesterol-lowering drugs for more than two years had more than three times the risk of diabetes.

'The fact that increased duration of statin use was associated with an increased risk of diabetes – something we call a dose-dependent relationship – makes us think that this is likely a causal relationship, Zigmont said.

'That said, statins are very effective in preventing heart attacks and strokes. I would never recommend that people stop taking the statin they've been prescribed based on this study, but it should open up further discussions about diabetes prevention and patient and provider awareness of the issue.'

Researchers also found that statin users were 6.5% more likely to have a troublingly high HbA_{1c} value – a routine blood test for diabetes that estimates average blood sugar over several months.

The study included 4 683 men and women who did not have diabetes, were candidates for statins based on heart disease risk and had not yet taken the drugs at the start of the study. About 16% of the group – 755 patients – were eventually prescribed statins during the study period, which ran from 2011 until 2014. Participants' average age was 46 years.

Randall Harris, a study co-author and professor of medicine and public health at Ohio State, said that the results suggest that individuals taking statins should be followed closely to detect changes in glucose metabolism and should receive special guidance on diet and exercise for prevention.

Although statins have clear benefits in appropriate patients, scientists and clinicians should further explore the impact of statins on human metabolism, in particular the interaction between lipid and carbohydrate metabolism, said co-author Steven Clinton, a professor of medicine and member of Ohio State's Comprehensive Cancer Centre.

'In addition, researchers conducting large prospective cohort studies should be considering how statins impact on human health overall. They should consider both risks and benefits, not just the disease that is being treated by the specific drug,' Clinton said.

The study was done retrospectively, meaning that the researchers looked back at existing records from a group of patients to determine if there were any possible connections between statin prescriptions and diabetes. Previous research has suggested a connection, but this study design allowed for a glimpse at what is happening naturally in the clinical setting, rather than what happens in a prospective trial that randomly assigns some people to statins and some people to placebo, said Zigmont, who is now an assistant professor at Southern Connecticut State University.

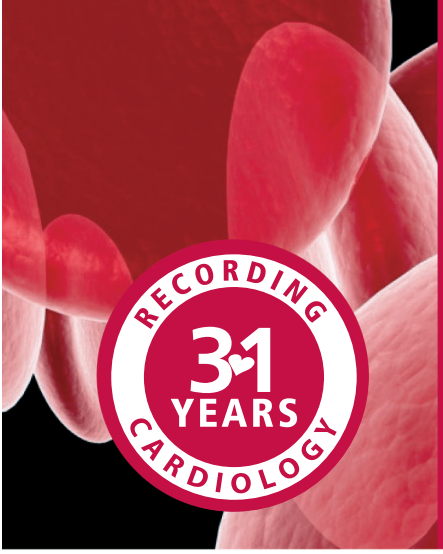
The study was enriched by the availability of a variety of details on the study population, including data from biometric screenings and a health survey that asked about education, health behaviours and ethnicity, Zigmont said. She also had access to medical claims data and pharmacy claims data.

Zigmont was careful to take a wide variety of confounding factors into account in an effort to better determine if the statins were likely to have caused the diabetes, she said. Those included gender, age, ethnicity, educational level, cholesterol and triglyceride readings, body mass index, waist circumference and the number of visits to the doctor. Programmes that help patients improve their fitness and diets could be considered and discussed when doctors are prescribing statins, so that patients can be proactive about diabetes prevention, she said.

It would also be helpful for future research to better determine which statins and which doses might lead to the greatest risk, Zigmont said. Her study didn't allow for an analysis based on different types of statins.

Limitations of the research include the fact that the majority of statin users were white, and that the research team had no way of knowing how closely patients adhered to their doctors' prescriptions. There also was no way of determining who was at elevated risk of diabetes at the study's onset, Zigmont says.

Source: *Medical Brief* 2019



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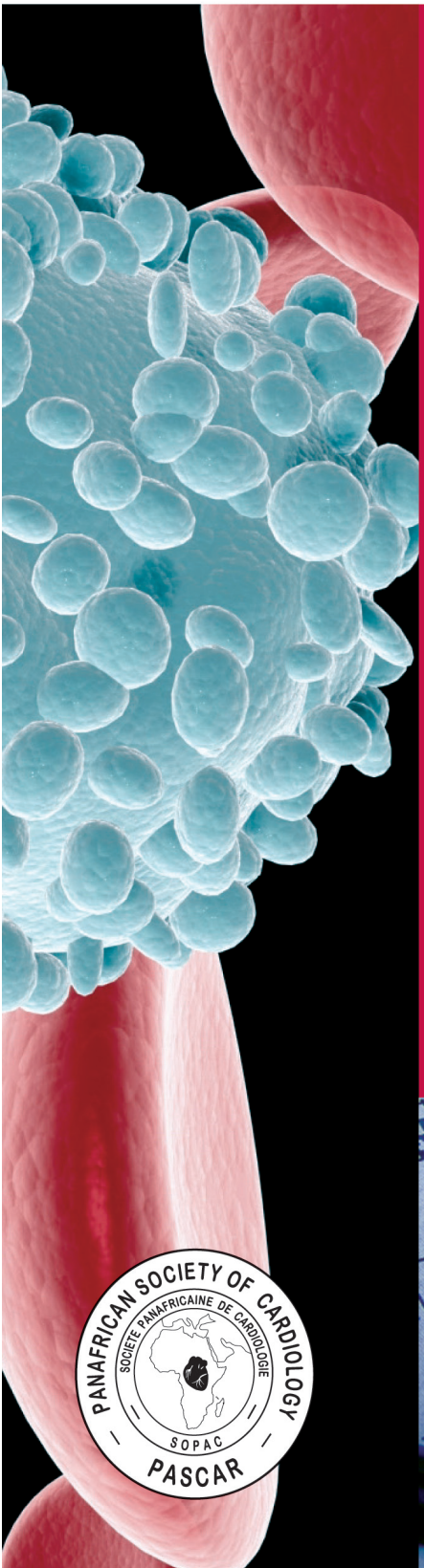

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