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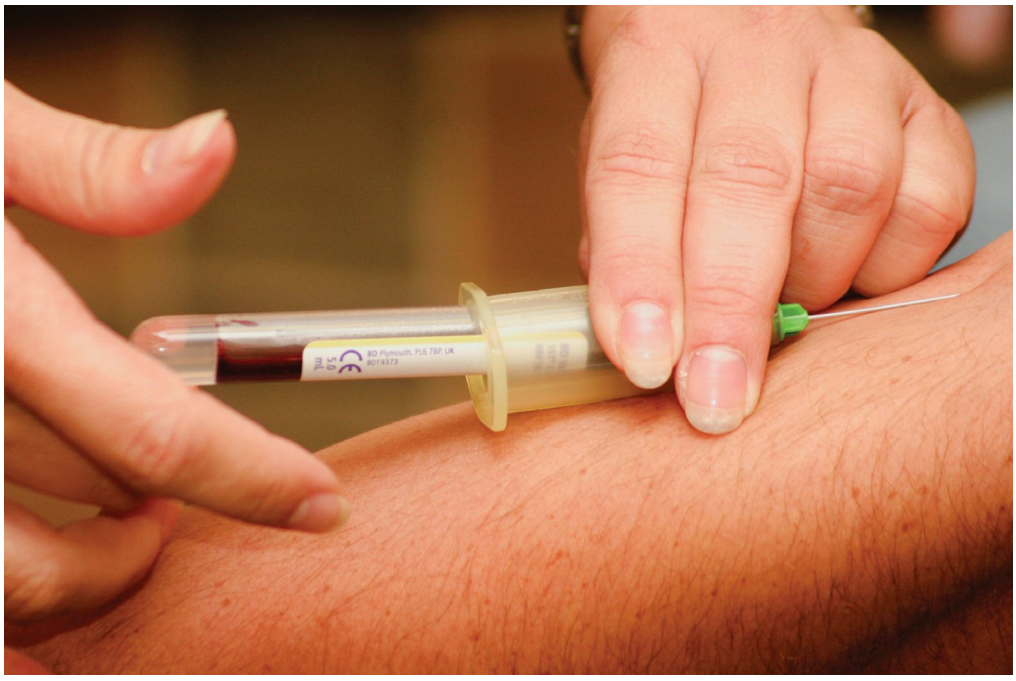

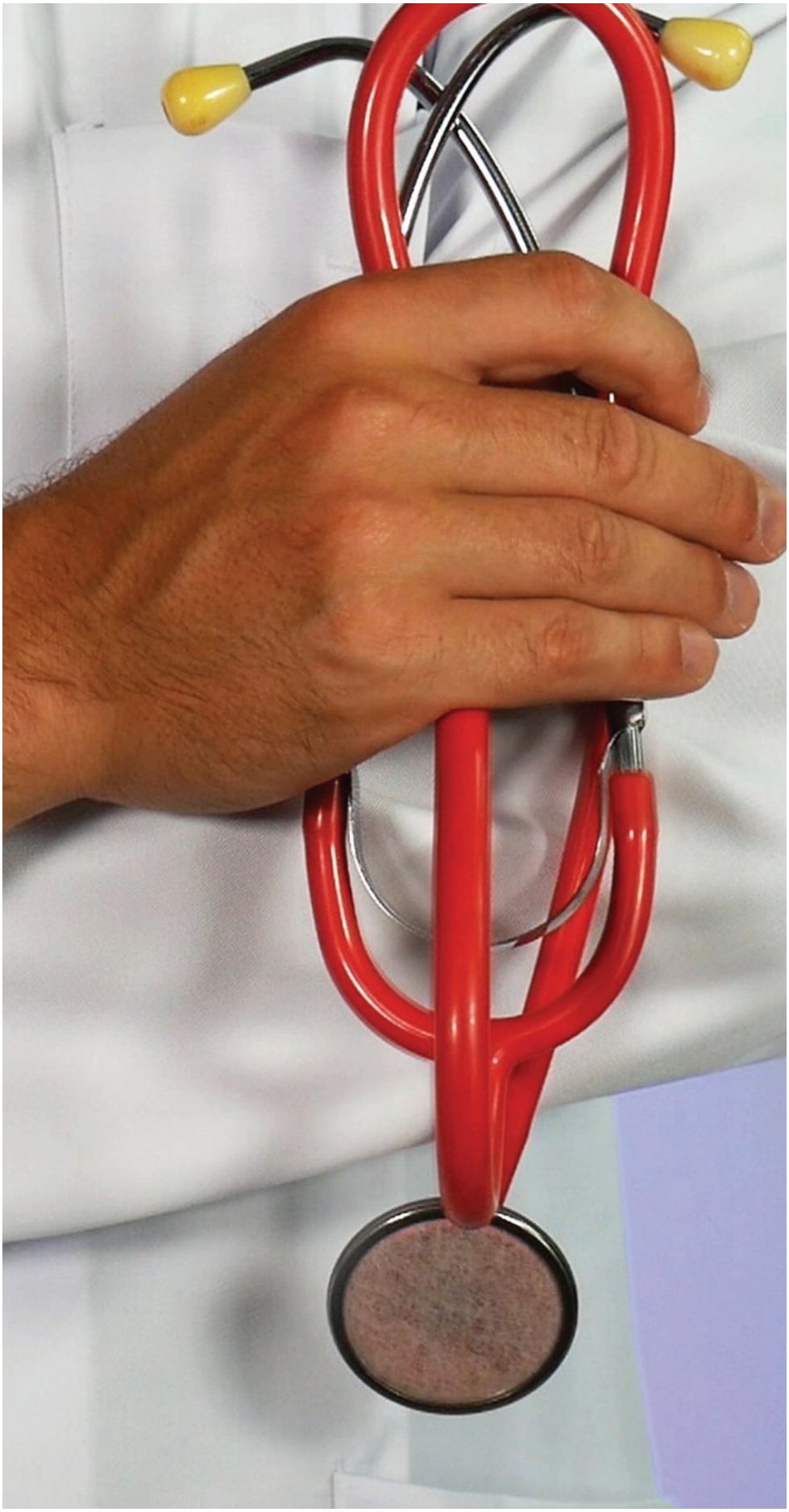

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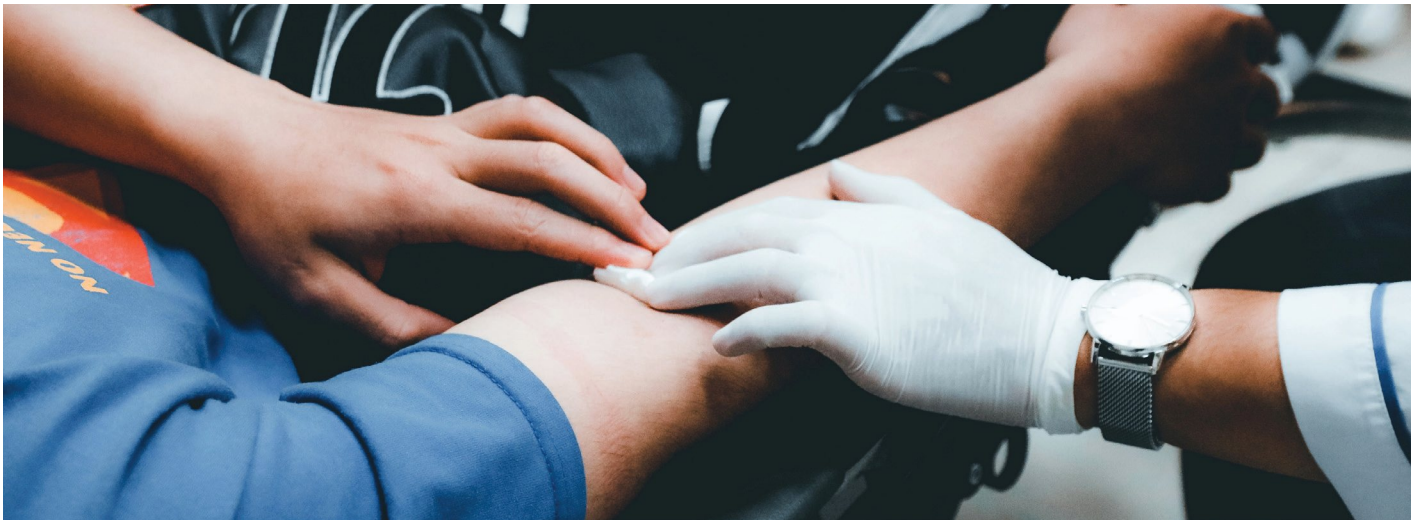

From the Editor's Desk

Ferreira and colleagues (page) examined bradycardia in the setting of diabetic ketoacidosis (DKA). They focused on the entity of atrial standstill. The emphasis is on rapid diagnosis and management. The usefulness of early ECG testing assists with the diagnosis of arrythmia, the possible underlying metabolic cause and possible underlying myocardial ischaemia. A number of arrythmias are described in DKA, including bradycardia, atrial fibrillation, supraventricular tachycardia and ventricular tachycardia.[1]

Phiri and co-workers (page) researched gestational diabetes mellitus in Blantyre, Malawi. They examined the associated factors and also compared the World Health Organisation (WHO) criteria to the more stringent International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria. They compared private and public health facilities as well.

The WHO and Malawian Ministry of Health did a general survey in 2009 in Malawi of non-communicable diseases and found a prevalence of diabetes of 5.6% in a group of patients from 25 to 64 years old. This is lower than in developed countries. However, hypertension was found in about a third of this group and 95% of these were undiagnosed. Phiri *et al.* found a hypertension prevalence of 3–4%, although their patients were mainly in their third trimester. A full hypertension survey in pregnant patients, in all trimesters and across different age ranges, would also be important to do.

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Prevalence of gestational diabetes mellitus in urban women in Blantyre, Malawi: a cross sectional study evaluating diagnostic criteria and traditional risk factors

TAMARA J PHIRI, MARIANNE KASIYA, THERESA J ALLAIN

Abstract

Background: **Gestational diabetes mellitus (GDM) is associated with maternal and neonatal complications. The application of appropriate diagnostic criteria is essential. There is a paucity of GDM prevalence data for African countries, including Malawi.**

Objectives: **This study aimed to establish the prevalence of GDM in Blantyre, Malawi and assess the implications of applying different cut-off points for diagnosis as defined by WHO criteria and the recently established International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria. It evaluated the relevance of internationally defined risk factors for GDM and compared the risk factors and prevalence between women accessing antenatal care in private hospitals to those accessing antenatal care at government hospitals. Patients at private hospitals are generally of a higher socio-economic status, have better access to care and are more likely to have a sedentary lifestyle and Westernised diet.**

Methods: **In this cross-sectional study, 2 274 consecutive women presenting at five antenatal clinic sites in Blantyre were screened for GDM, employing a random blood glucose (RBG) test. Of these, 250 women were randomly selected for an oral glucose tolerance test (OGTT). Logistic regression was used to quantify the association between various exposure variables and prevalence of GDM. Characteristics of patients attending government and private antenatal clinics were compared.**

Results: **The study population was predominantly urban, with a mean age of 25 years (range 14–43) with 66% being in the third trimester. The mean RBG level was 5.1 mmol/l (range 2.4–10.6) and overall prevalence of GDM based on the OGTT was 1.6 and 24% using the WHO and IADPSG criteria, respectively. GDM, diagnosed using WHO criteria, was associated with older maternal age, high parity, and attendance at government antenatal clinics but not with mid upper-arm circumference, a positive family history of diabetes mellitus (DM) or previous poor neonatal outcome. There was no correlation between RBG level and GDM diagnosed on the OGGT.**

Conclusions: **The prevalence of GDM in Blantyre using WHO criteria was low in the predominantly young population that was screened. A much higher proportion had GDM based on the IADPSG criteria and these may warrant long-term follow up. GDM was not associated with some previously described risk factors for GDM, suggesting a different risk-factor profile compared to the high-income countries.**

Keywords: gestational diabetes mellitus, diabetes mellitus, non-communicable diseases, pregnancy, sub-Saharan Africa, Malawi

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Background

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1] It is associated with an increased risk of pre-eclampsia, macrosomia and risk of the mother developing type 2 diabetes mellitus after pregnancy. Infants born to mothers with GDM are at an increased risk of birth trauma and neonatal metabolic complications, including hypoglycaemia, hypocalcaemia and hyperbilirubinaemia.[2,3] Risk factors for GDM in developed countries include advanced maternal age, obesity and a family history of diabetes mellitus (DM).[4]

Few studies have been done in Africa on the prevalence of GDM. A 2013 systematic review on the prevalence of GDM in Africa found data for only six of the 54 African countries.[5] The review included 14 studies and estimated the average prevalence of GDM in Africa at 5% (range 0–14). While some studies in the review screened women with risk factors for GDM only, others screened all women regardless of risk factors. The study populations were predominantly rural and GDM was associated with macrosomia, maternal age over 30 years and prior history of diabetes mellitus.

Comparisons between the African studies are limited by heterogeneity of the study populations, small sample sizes and variable diagnostic criteria used. In seven African studies over the past three decades, using the WHO criteria, the prevalence was reported as 3.8% in South Africa (1989),[6] 0% in Tanzania (1990),[7] 11% in Nigeria (1997),[8] 3.7% in Ethiopia (1997),[9] 1.7% in Nigeria,[10] 3.8% in South Africa (2007),[11] and 14% in Nigeria (2012).[12] Among studies using WHO criteria, however, some used the 1985 diagnostic criteria while others used the 1999 diagnostic criteria.

In Malawi, the nationwide WHO STEPwise Approach to Surveillance (STEPS) survey in 2009 found that 5.6% of adult Malawians had DM, the majority of which was undiagnosed.[13] There are no studies on the prevalence of GDM in Malawi.

There has been a universal lack of consensus on screening and diagnosis of GDM with regard to the impact of screening on

outcomes, appropriate individuals to screen, optimal screening time, the appropriate screening tool and appropriate diagnostic criteria. This has resulted in several revisions of diagnostic criteria by various groups.

There are two large studies that have influenced the interpretation of diagnostic criteria. The 2005 Australian Carbohydrate Intolerance Study in Pregnancy (ACHOIS)[14] demonstrated that mild forms of hyperglycaemia, below those diagnostic of GDM, were associated with poor perinatal outcomes. The 2008 Hyperglycaemia and Pregnancy Outcomes (HAPO) study[15] showed a linear association between maternal hyperglycaemia and adverse events, including macrosomia, pre-eclampsia, caesarean section rates and neonatal hypoglycaemia with no clear cut-off above which these adverse events occurred.

Following the HAPO study, the IADPSG recommended new criteria for the diagnosis of GDM with a fasting plasma glucose cut-off level much lower than the WHO criteria.[16] This has resulted in up to a three-fold increase in the proportion of women diagnosed as having GDM using the IADPSG criteria compared to WHO criteria. There is varied opinion as to whether IADPSG criteria universally translate into improved outcomes, particularly when applied to a population that is different from that in the HAPO study.[16-19]

Some guidelines favour selective screening of women with known risk factors for GDM in order to avoid unnecessary screening of low-risk women. Whether the traditional risk factors, as described in studies in high-income countries, are applicable to and predict GDM in sub-Saharan Africa has not been explored.

Establishing a risk-factor profile for women with GDM to be prioritised for screening is essential, particularly in a low-resource setting such as Malawi where routine screening of all pregnant women is not feasible. Random blood glucose (RBG), fasting blood glucose and the 50-g oral glucose tolerance (OGTT) tests have all been used in studies as screening tests.[20] Finger-prick RBG, although inferior to formal laboratory glucose tests, is a feasible screening option in Malawi where the majority of the population has limited access to formal blood glucose tests.

This study aimed to establish the prevalence and risk factors for GDM among urban women in Blantyre, compare the differences in prevalence using the different cut-offs defined in the WHO and IADPSG criteria, and assess if the prevalence would differ in women seen at government antenatal clinics (ANCs) compared to those attending private ANCs.

Methods

Blantyre is the main commercial city in southern Malawi, with an estimated population of 1.1 million.[21] Queen Elizabeth Central Hospital (QECH) is the main government tertiary referral centre. Chilomoni and Limbe health centres are government primary-care facilities in Blantyre with an average ANC attendance of 100 women per day. Mwaiwathu and Blantyre Adventist hospitals are the two main private hospitals in Blantyre.

In this cross-sectional study, consecutive women presenting at any gestational age to QECH, Chilomoni and Limbe ANCs between 1 June and 30 September 2012 and at Mwaiwathu and Blantyre Adventist hospital private ANCs between February and April 2013 were asked to participate in the study. Recruitment was restricted to women of Malawian origin residing in Blantyre during the study period.

Ethical approval for the study was obtained from the Malawi College of Medicine Research and Ethics Committee (reference number P02 12 1170). Each participant provided written consent. For participants who could not read or write, the consent form was read out to them by a research assistant and the participant gave verbal consent and put her fingerprint on the consent form to acknowledge her voluntary participation in the study. The consent form was available in English and the vernacular and had been approved by the College of Medicine Research and Ethics Committee prior to commencement of the study.

Consenting women had a capillary RBG test done at the clinic site with a finger-prick test and a SDCheck® glucometer (SD Standard Diagnostics Inc, Hagal-dong, Korea). A sub-sample of 200 women from the government ANCs and 50 women from the private ANCs were randomly selected for an OGTT by selecting every fifth woman who was recruited. Gestational age was calculated from the last normal menstrual period.

For RBG, a sample size of 614 was initially calculated in order to detect hyperglycaemia at an estimated prevalence of 2–3% (suggested by local Blantyre obstetricians from observation) but the sample size was subsequently increased after detecting a high proportion of normal RBGs when recruitment began. Furthermore, the test could easily be administered to large numbers of women attending the facilities within a short period of time. The sample size of 250 for OGTTs was limited by available resources to perform OGTTs.

All OGTTs were done at QECH laboratory and plasma glucose level was determined using an automatic analyzer (KeyLab BPC BioSed®, Rome, Italy). OGTTs were done following the 1999 WHO guidelines, with each participant having a fasting plasma glucose test done and then being given 75 g of anhydrous glucose dissolved in 200 ml of water to drink. Plasma glucose level was re-checked two hours after taking the glucose solution.

Using the WHO criteria,[22] GDM was defined as a fasting plasma glucose of 7.0 mmol/l or a two-hour plasma glucose of 11.1 mmol/l. Using the modified IADPSG criteria,[15] GDM was defined as a fasting plasma glucose of ≥ 5.1 mmol/l or two-hour plasma glucose of 8.5 mmol/l.[16]

Blood pressure (BP), weight, height and mid upper-arm circumference (MUAC) were recorded on recruitment. BP was measured with an Omron® digital BP machine (Omron Healthcare Worldwide, Kyoto, Japan). Weight was measured using a digital scale. Where previously documented in the woman's health records, the pre-pregnancy weight was noted. The majority of the women did not have a documented pre-pregnancy weight or height and pre-pregnancy body mass index (BMI) could not be calculated. MUAC was used to assess nutritional status as a single BMI in pregnancy is not an accurate measure because of the additional weight gain from pregnancy.[23,24]

Patients diagnosed with GDM or hypertension were referred to the QECH, Mwaiwathu and Blantyre Adventist specialist diabetes clinics for follow up and management.

Statistical analysis

Means and percentages were used to explore the distribution of risk factors between government and private ANCs. The relationship between GDM prevalence and risk factors was first explored through univariate analyses. The *t*-test comparing women with GDM to those without GDM was used to assess if any of the continuous risk factors were associated with prevalence. To

adjust for possible simultaneous confounding of the risk factors, a multivariate logistic regression was fitted.

The stepwise model selection method was employed to come up with the final model, which included the following risk factors: type of hospital, age, parity, MUAC and history of macrosomia for the WHO criteria. Similarly, a multivariate linear regression was used to assess the relationship between RBG and the risk factors. The final selected model included hospital type, BMI and history of macrosomia.

SAS software version 9.3 (SAS Institute, North Carolina State University) was used for analysis and all inferences were made at the 0.05 significance level.

Results

All participants were recruited from urban Blantyre. Fig. 1 shows a flow chart of participants recruited in the study.

The study population was predominantly young with an average age of 25.8 years (25th, 50th and 75th percentiles: 22, 25 and 30, respectively). Six per cent of the women were above 35 years of age, 66.4% were in the third trimester and 24% were between 24 and 28 weeks' gestational age. Table 1 compares the demographic characteristics of women in government and private ANCs.

Women at government-funded facilities were younger, of higher parity and gravidity, had a lower pregnancy BMI and were more likely to be HIV positive. Based on MUAC, 9% of the women were overweight (MUAC 28–31 cm) and 1% were obese (MUAC ≥ 32 cm). There was no difference in the average MUAC between government and private ANCs. When the BMI in pregnancy was calculated, half of the women had a normal BMI (average BMI 26 kg/m^2; 50th percentile 25).

Three per cent of the women had hypertension, but this was not explored further to determine whether this was pre-eclampsia or pre-existing hypertension. Eleven per cent of the women had HIV and of these, 61% had documented records of being on anti-retroviral therapy.

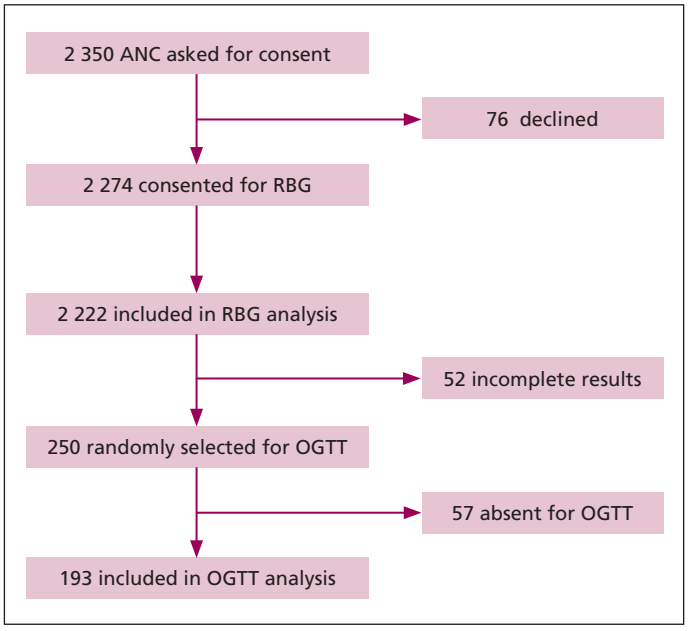

Fig. 1. Recruitment of participants. RBG, random blood glucose; OGTT, oral glucose tolerance test.

Table 1. Comparison of demographic characteristics between government and private ANCs

Characteristics	Government ANCs (*n* = 2044)	Private ANCs (*n* = 178)	*p*-value
Age (years), mean ± SD	25.8 ± 0.25	29.4 ± 0.6	< 0.0001
Gestational age (weeks), mean ± SD	26.9 ± 0.36	27.6 ± 3.2	0.68
Parity, mean ± SD	1.2 ± 0.05	0.76 ± 0.13	< 0.0001
Gravidity, mean ± SD	2.5 ± 0.05	2 ± 0.12	< 0.0001
BMI in pregnancy, mean ± SD	26.2 ± 0.3	27.7 ± 0.8	0.0003
MUAC (cm), mean ± SD	23.7 ± 0.15	23.5 ± 0.6	0.3646
Hypertension, *n* (%)	97 (4.7)	6 (3.3)	0.6574
HIV, *n* (%)	205 (10.0)	15 (8.4)	0.01
DM family history, *n* (%)	15 (0.7)	43 (24.1)	0.1573
Previous miscarriage, *n* (%)	361 (17.6)	41 (23.0)	0.308

ANC, antenatal clinic; BMI, body mass index; MUAC, mid upper-arm circumference; DM, diabetes mellitus.

Tables 2 and 3 show RBG and OGTT results. Only three women (0.1%) had an RBG level above 11.1 mmol/l. Twelve women (0.5%) were hypoglycaemic. There was a significant association between RBG level and attending government ANCs and BMI.

Based on the OGTTs, the overall prevalence of GDM was 1.6% (*n* = 5) and 24.8% (*n* = 65) by WHO and IADPSG criteria, respectively. The simple kappa coefficient was calculated to

Table 2. Risk factors associated with increasing RBG levels

Variable	Parameter estimate	Standard error	*t*-value	*p*-value
Government ANC	–15.50589	4.763	–3.26	0.0013
BMI	1.09278	0.37628	2.90	0.0041
Macrosomia	–22.14294	12.98251	–1.71	0.0898

RBG, random blood glucose; ANC, antenatal clinic; BMI, body mass index.

Table 3. Comparison of RBG and fasting glucose levels and GDM prevalence by OGTTs in government and private ANCs

Variable	Government ANCs	Private ANCs	Overall	OR (95% CI)
RBG (g/dl), mean ± SD	94.4 ± 20	107 ± 24	94 ± 21	
Fasting glucose (g/dl), mean ± SD	84 ± 16	70 ± 16	81 ± 19	
2-h glucose (g/dl), mean ± SD	84 ± 18	86 ± 53	84 ± 17	
GDM (WHO), % (95% CI)	1.4 (0.04–5.5)	0.04 (0–1)	1.6 (0.3–4)	3.5 (0.08–8.1)*
GDM (IADPSG), % (95% CI)	31.7 (24.6–39.8)	7.8 (3–19.1)	24.8 (19–32)	5.5 (1.9–16)*

*GDM prevalence odds ratio for government ANCs vs private ANCs.
RBG, random blood glucose; ANC, antenatal clinic; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

Table 4. Risk factors associated with GDM by WHO criteria

Parameter	df	Estimate	Standard error	Wald chi-square	*p*-value
Government ANCs	1	2.0860	0.5959	12.2527	0.0005
Age	1	0.0973	0.0424	5.2690	0.0217
Parity	1	0.6160	0.2353	6.8541	0.0088
MUAC	1	–0.0744	0.0533	1.9534	0.1622
Previous macrosomia	1	–1.8416	0.9789	3.5391	0.059

df, degrees of freedom, ANC, antenatal clinic; GDM, gestational diabetes mellitus; MUAC, mid upper-arm circumference.

determine correlation between GDM diagnosed by the WHO and GDM diagnosed by IADPSG criteria, and it was found to be 0.597 (a coefficient of zero being no correlation and a coefficient of one being a strong correlation).

Table 4 shows risk factors associated with GDM. Five per cent of the women reported having previously had macrosomic babies (birth weight > 4 kg). This could not be confirmed as the majority did not have written records of birth weights from previous pregnancies and their responses were based on recall. Seven per cent reported having first-degree relatives with diabetes and 19% reported having had miscarriages or stillbirths in previous pregnancies.

Attending government ANCs, age and parity were associated with having GDM ($p < 0.05$). The risk of having GDM was higher in government compared to private ANCs and this increased with age and parity. A family history of diabetes mellitus, previous miscarriage/stillbirth, BMI, being HIV positive and having hypertension were not associated with GDM ($p > 0.05$).

Seventy-one per cent of the women diagnosed with GDM were lost to follow up post-delivery and complete outcome data were available for only 18 women. There were four miscarriages, four women who had a caesarean section and two babies with macrosomia. Data on follow up for diabetes at six weeks postpartum in particular were missing as this was collected telephonically and some of the women could not be reached.

Discussion

This study showed that the prevalence of gestational diabetes mellitus in Blantyre was low. It also showed a wide discrepancy in the prevalence when IADPSG criteria were used compared to WHO criteria, with a 12-fold increase in the prevalence when the IADPSG criteria were used. To our knowledge, this is the first description of the prevalence of gestational diabetes in the Malawian population.

The HAPO study, with an average BMI of 27 kg/m^2 among its participants, showed a direct correlation between obesity and poor outcomes.[15] Our study population, however, being largely young with few obese women (1% based on MUAC), was different from that described in other studies of risk factors for GDM.

In the nationwide WHO STEPS survey,[13] the prevalence of overweight and obesity among Malawian women was 16 and 2%, respectively. The age of the women screened was 25–64 years, but the majority of the women screened were young, as 46% of the women were between the ages of 25 and 34 years. Our GDM study similarly screened a young population of women and the prevalence of overweight and obesity was 9 and 1%, respectively. From both studies, obesity appears to be rare among Malawian women.

In another 2007 study of 620 patients attending the adult diabetes clinic at QECH, the average BMI in type 2 DM patients was 28.7 kg/m^2.[25] These observations suggest that obesity may not be the main driver for the DM epidemic in Malawi and that other factors such as genetics, low birth weight and stunting may play a larger role.

Advanced maternal age, high parity and attending government ANCs were associated with GDM, the older women being more likely to have high parity than the younger, consistent with traditional risk factors for GDM. Other known risk factors for GDM, such as a family history of DM, a history of macrosomia, previous miscarriages or stillbirths, or MUAC were not associated with GDM.

As observed in the STEPS survey, the majority of DM in the population is undiagnosed; as such a negative family history of DM may in part be a reflection of this. The overall picture however highlights the fact that risk factors for developing GDM may be population specific and there may be genetic variability inherent in the population to explain such differences. This raises a need

for exploring population-specific risk factors other than those stated in the WHO guidelines or those from high-income countries.

Women attending private hospitals are generally perceived as having a higher socio-economic status and more likely to adopt a diet rich in refined foods and a sedentary lifestyle than their counterparts. By including private ANCs, we anticipated showing that this group would tend to be more obese and have a higher risk of developing GDM. Our findings though were contrary to this expectation as there was no difference in terms of nutritional status between women from government facilities and those from private hospitals. Furthermore, women at private ANCs were less likely to have GDM than those in government hospitals.

Dietary differences between the two groups were not explored in particular but it appears that the risk that may be conferred by sedentary habits or a Westernised diet may be balanced by better health-seeking behaviour and ready access to screening and diagnostic services in private hospitals.

RBG measurements were largely normal as only three women had RBG levels > 11.1 mmol/l and 75% of the study population had an RBG level below 5.5 mmol/l. Other than the RBG test being an insensitive screening tool, it was also observed on random questioning that many of the women at the health centres had not eaten for some time before the measurement, particularly those who had to leave their homes early in the morning to attend the clinic on time. Their results may reflect a fasting rather than RBG level and may explain the large proportion of women with normal RBG levels. There was no correlation between RBG level and GDM diagnosed by OGTT or risk factors for GDM. The RBG test may therefore not be a sensitive screening tool or used as a proxy for OGTTs in this population.

The prevalence of GDM of 1.6% using WHO criteria was lower than that described in other African studies using the 1999 WHO diagnostic criteria (8.8% in South Africa and 13.9% in Nigeria),[11,12] but comparable with what was expected by local obstetricians who estimated prevalence between 2 and 3% among women attending ANCs (B Makanani pers commun). GDM was rare, even among those with traditional risk factors for GDM, suggesting there may be a unique environmental or genetic influence on risk factors for GDM in this population.

Using IADPSG criteria, the prevalence of GDM was 12 times higher compared to WHO criteria and, interestingly, showed a higher prevalence in government ANCs compared to private ANCs.

We anticipated finding a higher prevalence of GDM using IADPSG criteria compared to WHO criteria, as has been described in other studies. There are no other published studies from African populations for comparison. Many studies have compared prevalence using the two criteria, with some finding the two to be comparable.[19] The decision to change the criteria depends on performing careful cost analysis and weighing the risk–benefit ratio, particularly in a population that is different from the HAPO population.[17,18,26] In a low-income setting, priority should probably be placed on treating those diagnosed with GDM based on WHO criteria.

There was a large loss to follow up among the women diagnosed with GDM, which precludes definitive conclusions on outcome. The causes of the four miscarriages among the women diagnosed with GDM were not explored further.

Limitations

The study had several limitations. The study population, being urban, may have been unrepresentative as it excluded older women in rural settings likely to have risk factors for GDM. Older and multiparous women are less likely to attend formal ANCs. Family history of DM was likely under-reported as most DM in Malawi is undiagnosed. Loss to follow up precluded making meaningful conclusions on outcomes on the already small population of women diagnosed with GDM. Digital instruments used for measuring anthropometric and biochemical data, including glucometers, BP machines and the weight scale, although readily accessible for use in the practical sense, are not always standardised and may be inappropriately calibrated, which could affect quality and reproducibility of data collected.

Being descriptive, definite causal relationships cannot be established. A larger prospective study with OGTTs performed on all women, exploring risk factors for GDM and comparing outcomes between the WHO and IADPSG criteria would reflect better on the usefulness of diagnosing GDM in this population.

Conclusion

Using the WHO criteria, GDM was relatively uncommon in women in Blantyre presenting to ANCs, even among those with traditional risk factors for GDM. This low prevalence has been demonstrated in other sub-Saharan countries and we anticipated that the prevalence would be similar in the Malawian population in general. The implication of the higher prevalence found when the IADPSG criteria were used remains to be explored.

Increasing age, parity and being at government hospitals were associated with GDM in this population. Alternative risk factors other than the traditional known risk factors need to be explored. Maintaining optimal weight should be encouraged as this is the single modifiable risk factor for GDM that was identified in this study. Should screening for GDM be performed, the RBG test is not a sensitive screening tool and risk factor-based screening may be more feasible and cost effective.

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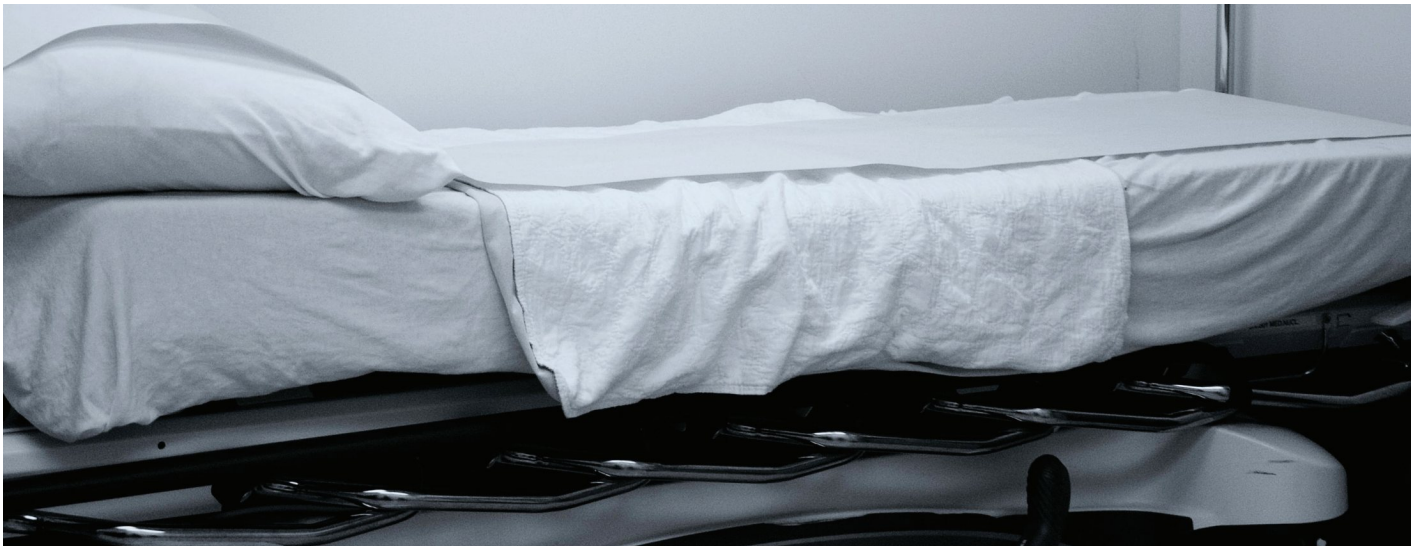

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Severe bradycardia caused by diabetic ketoacidosis

JOÃO FERREIRA, JOÃO MARTINS, LINO GONÇALVES

Abstract

Atrial standstill is an uncommon but serious clinical entity that is often unrecognised in the clinical setting. Its diagnosis and treatment should be swift as malignant arrhythmias and thromboembolic complications can arise. We present a 79-year-old man brought to our emergency department with acute confusion, heart failure and severe bradycardia in the context of diabetic ketoacidosis, and discuss the diagnosis and management of this arrhythmic condition.

Keywords: atrial standstill, electrocardiogram, transthoracic echocardiogram, emergency, bradycardia, diabetic ketoacidosis, medical educatione

Case report

A 79-year-old man with a history of hypertension, type 2 diabetes mellitus and known poor therapeutic compliance was brought to our emergency department with acute confusion. A physical examination revealed normal blood pressure (144/65 mmHg), a heart rate of 30 beats/min and tachypnoea on ambient air with normal peripheral oxygen saturation (95%). Lung auscultation showed bilateral basal crackles with concomitant jugular venous distention.

Arterial blood gas analysis showed partially compensated metabolic acidosis (pH 7.312, Pa_{CO_2} 21.5 mmHg and HCO_3 10.6 mmol/l), severe hyperkalaemia (7.89 mmol/l), high serum lactate level (2.5 mmol/l) and hyperglycaemia (849 mg/dl; 47.12 mmol/l). High-sensitivity cardiac troponin was negative (27.9 ng/l). Blood tests also showed acute kidney injury (serum creatinine 3.89 mg/dl).

The initial electrocardiogram (ECG) revealed no discernible P waves with a slightly irregular bradycardic junctional rhythm (Fig. 1A). Bedside transthoracic echocardiography revealed a preserved left ventricular ejection fraction, moderate mitral regurgitation, mild left atrial enlargement and confirmed absent atrial contraction as there were no A waves on transmitral pulsed-wave Doppler flow (Fig. 2). These findings were suggestive of atrial standstill (AS).

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The patient was quickly started on calcium gluconate, furosemide, inhaled salbutamol, intravenous saline and insulin perfusion, restoring normal glycaemic levels. While the metabolic and electrolyte changes were being corrected, and because he had a supra-hissian escape rhythm, the patient was put on isoproterenol infusion in order to treat acute heart failure, mainly caused by new severe bradycardia. The patient successfully returned to sinus rhythm 82 minutes after the first ECG (Fig. 1B).

After the emergency presentation, the patient was hospitalised in the endocrinology ward, where treatment was continued and antidiabetic drugs were optimised. He was discharged symptom free and referred for a cardiology and endocrinology consultation, where he has been followed up with good glycaemic control and no further rhythm disturbances.

Discussion

AS was first described in 1946 by Chavez *et al.,*[1] and is characterised by the complete absence of electrical and mechanical atrial activity. Therefore, the most common ECG pattern associated with this entity is the absence of atrial depolarisation with bradycardic regular junctional or ventricular escape rhythm[2,3] (Fig. 1A). Recognising this ECG pattern is important because secondary causes must be excluded, avoiding unnecessary interventions and non-priority therapies.[4]

AS is usually transient, occurring with digitalis or quinidine intoxication, hypoxia, hyperkalaemia or myocardial infarction. Persistent AS is rare, being reported in association with some types of muscular dystrophies, cardiomyopathies, valvular diseases, congenital heart diseases, Ebstein's anomaly, amyloidosis, acute myocarditis, following open cardiac surgery or after longstanding atrial fibrillation.[4] In this specific case, as the patient did not present any other major causes of AS, severe hyperkalaemia was most likely responsible for the transient AS.

The mainstay of diagnosis of this entity is an electrophysiological study, capable of proving the bilateral absence of atrial electrical activation, and transthoracic echocardiography, through spectral Doppler, showing lack of atrial contraction by the absence of an A wave in transmitral or transtricuspid flow, the absence of atrial contraction in tissue Doppler imaging or the absence of telediastolic mitral valve opening.[5] Also, the lack of an A wave during jugular venous pulse when jugular distension is present, a sign nowadays rarely searched for, is also proof of absent atrial contraction. However, in the emergency setting, a rapid approach to this patient is needed, and diagnosis must be confirmed with ECG, jugular venous pulse observation and transthoracic echocardiography, tools readily available in the majority of emergency departments.

AS can be a serious condition as the loss of active atrial contraction and profound bradycardia can lead to markedly decreased cardiac output. Cardiac arrest can also occur, not only because the escape mechanism can be unstable but also because the bradycardia can be extreme, and pause-related ventricular arrhythmias such as polymorphic ventricular tachycardia can arise.[6] Moreover, blood stasis, originating with no atrial activity, can cause

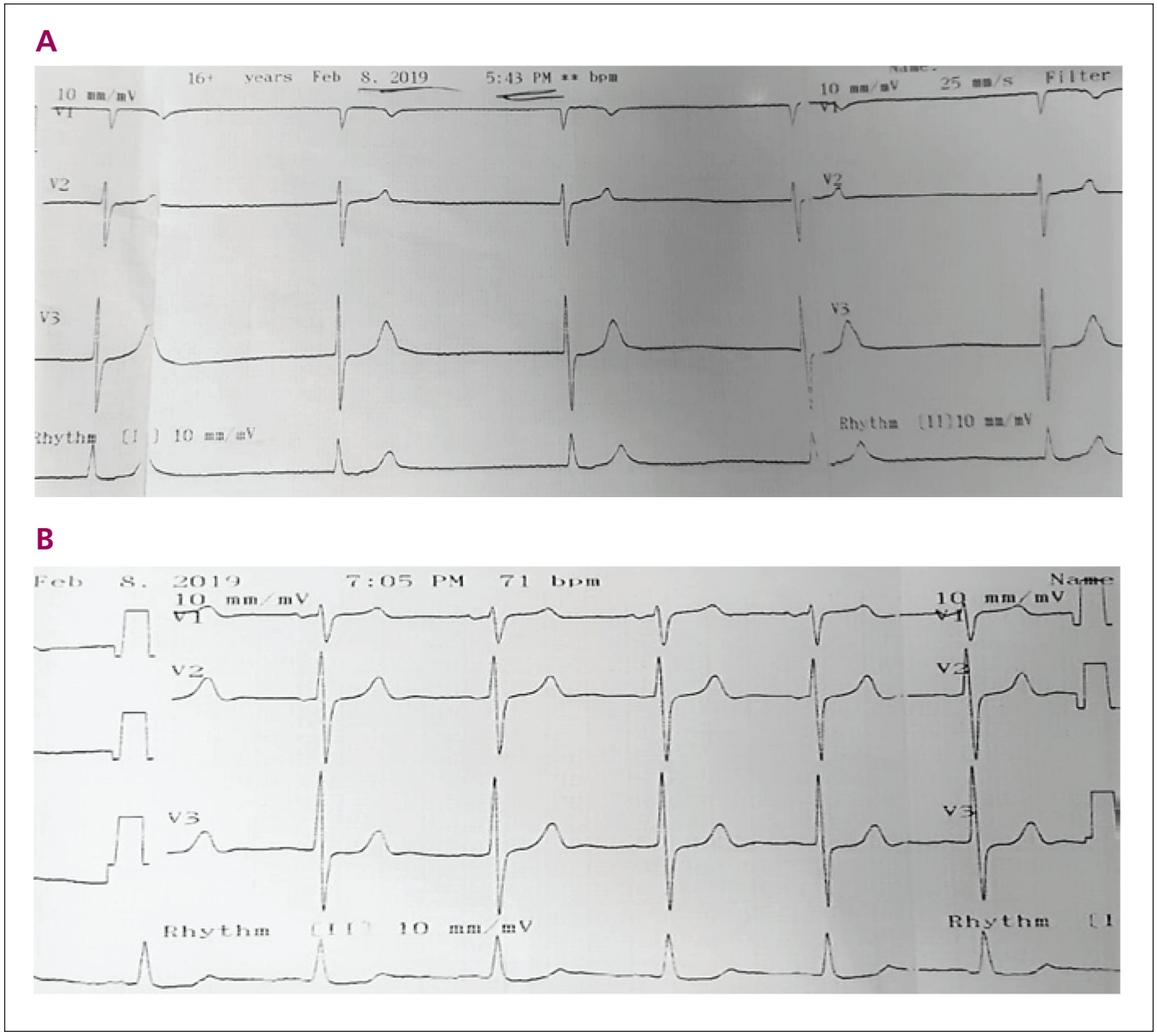

Fig. 1. A: Initial ECG showing slightly irregular junctional rhythm and absence of atrial electrical activity. **B:** ECG showing sinus rhythm after metabolic and electrolyte correction.

thromboembolic events, as would happen with other arrhythmias such as atrial fibrillation.[2,6]

Treatment of AS depends on clinical consequences and the underlying cause. If the patient shows important signs of heart failure, treatment with diuretics and vasodilators is indicated, as well as positive chronotropic drug infusion, such as isoproterenol, for a limited time as a supportive measure while the underlying condition that gave rise to the AS is corrected.

Temporary transvenous pacing should be deferred and only used as a last resort if chronotropic drugs are insufficient, in cases of a high-degree atrioventricular block without escape rhythm, and for pacing in cases of pause-related ventricular arrhythmias.

Temporary transcutaneous pacing should be avoided, as pacing provided by patches and an external defibrillator does not provide reliable ventricular stimulation and should only be used under strict monitoring when no other option is available.[7]

Conclusion

Severe hyperkalaemia in the context of acute kidney injury was the most likely cause of AS in this case. We highlight three learning points: (1) AS is an uncommon but potentially hazardous condition, which can present as a complication of diabetic ketoacidosis; (2) diagnosis of AS can be made with readily available tools in any emergency room, such as ECG and echocardiography; (3)

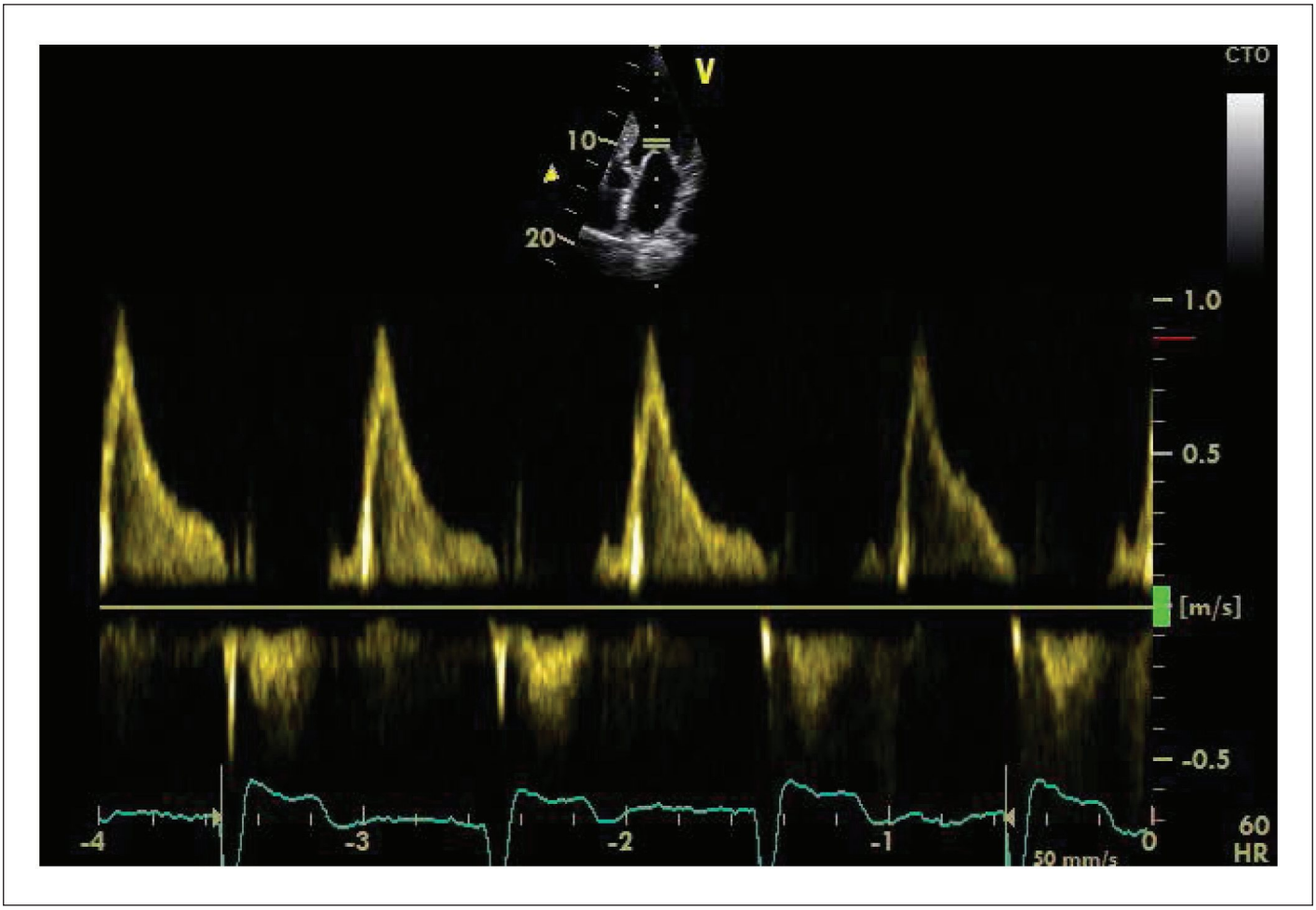

Fig. 2. Transmitral pulsed-wave Doppler imaging after isoproterenol infusion, showing the absence of A waves.

treatment should be prompt and depends on the aetiology of AS, resorting to transvenous pacing only in refractory cases, as AS is usually transient.

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Drug Trends

Dairy-rich diet linked to lower risk of diabetes and cardiovascular disease

Eating at least two daily servings of dairy is linked to lower risks of diabetes and high blood pressure, as well as the cluster of factors that heighten cardiovascular disease risk (the metabolic syndrome), finds a large international study, led by Dr Andrew Mente at the Population Health Research Institute, Hamilton Health Sciences and McMaster University. The observed associations were strongest for full-fat dairy products, the findings indicated.

Previously published research has suggested that higher dairy intake is associated with a lower risk of diabetes, high blood pressure and the metabolic syndrome. But these studies have tended to focus on North America and Europe to the exclusion of other regions of the world.

To see whether these associations might also be found in a broader range of countries, the researchers drew on people taking part in the Prospective Urban Rural Epidemiology (PURE) study. Participants were all aged between 35 and 70 years and came from 21 countries: Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, Palestine, Pakistan, Philippines, Poland, South Africa, Saudi Arabia, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe.

Usual dietary intake over the previous 12 months was assessed by means of food frequency questionnaires. Dairy products included milk, yogurt, yogurt drinks, cheese and dishes prepared with dairy products, and were classified as full or low fat (1–2%).

Butter and cream were assessed separately as these are not commonly eaten in some of the countries studied.

Information on personal medical history, use of prescription medicines, educational attainment, smoking and measurements of weight, height, waist circumference, blood pressure and fasting blood glucose level were also collected.

Data on all five components of the metabolic syndrome were available for nearly 113 000 people: blood pressure above 130/85 mm Hg, waist circumference above 80 cm, low levels of (beneficial) high-density lipoprotein cholesterol (< 1–1.3 mmol/l), blood fats (triglycerides) of > 1.7 mmol/dl, and fasting blood glucose of 5.5 mmol/l or more.

Average daily total dairy consumption was 179 g, with full fat accounting for around double the amount of low fat: 124.5+ versus 65 g.

Some 46 667 people had the metabolic syndrome, defined as having at least three of the five components. Total dairy and full-fat dairy but not low-fat dairy were associated with a lower prevalence of most components of the metabolic syndrome, with the size of the association greatest in those countries with normally low dairy intakes. At least two servings a day of total dairy were associated with a 24% lower risk of the metabolic syndrome, rising to 28% for full-fat dairy alone, compared with no daily dairy intake.

The health of nearly 190 000 participants was tracked for an average of nine years, during which time 13 640 people developed high blood pressure and 5 351 developed diabetes.

At least two servings a day of total dairy was associated with an 11–12% lower risk of both conditions, rising to a 13–14% lower risk for three daily servings. The associations were stronger for full-fat than they were for low-fat dairy.

This is an observational study, and as such can't establish cause. Food frequency questionnaires are also subject to recall, and changes in the metabolic syndrome were not measured over time, all of which may have influenced the findings.

Nevertheless, the researchers suggest: 'If our findings are confirmed in sufficiently large and long-term trials, then increasing dairy consumption may represent a feasible and low-cost approach to reducing (the metabolic syndrome), hypertension, diabetes and ultimately cardiovascular disease events worldwide.'

Source: MedicalBrief 2020

Diabetes powerfully associated with CHD in women: Women's Health study

Diabetes and insulin resistance, in addition to hypertension, obesity and smoking, appeared to be the strongest risk factors for premature onset of coronary heart disease (CHD), found an analysis from the large, decades-long Women's Health study.

While deaths related to heart disease have declined among older people, studies suggest that death rates among younger patients have remained stagnant or increased slightly. To understand what factors put younger individuals at higher risk of premature CHD, researchers from Brigham and Women's Hospital and the Mayo Clinic analysed more than 50 risk factors in 28 024 women who participated in the study.

Notably, women under 55 years with type 2 diabetes had a 10-fold greater risk of having CHD over the next two decades, with lipoprotein insulin resistance (LPIR) proving to be a strong, predictive biomarker as well.

'We're going to see, unfortunately, younger and younger people having heart attacks,' said corresponding author Dr Samia Mora, of the Brigham's Centre for Lipid Metabolomics in the Division of Preventive Medicine and an associate professor at Harvard Medical School. 'When a younger individual has a cardiovascular event, it will affect their quality of life going forward, their productivity, and their contribution to society.'

'Prevention is better than cure, and many risk factors for heart disease are preventable. This study shows the impact that lifestyle has on heart health in women of all ages, and younger women in particular,' said Dr Sagar Dugani, a hospital internal medicine practitioner at Mayo Clinic in Rochester, Minnesota. Dugani is the co-first author of the study.

The researchers analysed approximately 50 biomarkers associated with cardiovascular health. Commonly used metrics such as low-density lipoprotein (LDL) cholesterol (or 'bad' cholesterol) and haemoglobin A_{1c} (a measure of blood sugar levels) had much weaker associations with CHD onset in women younger than 55 years than LPIR, a newer metric for insulin resistance. LPIR uses a weighted combination of six lipoprotein measures and is analysed through specialised laboratory testing. Whereas LDL cholesterol was only associated with a 40% increase in risk of CHD onset in women under 55 years, LPIR demonstrated a six-fold (600%) increase.

'In otherwise healthy women, insulin resistance, type 2 diabetes, and its sister diagnosis, the metabolic syndrome, were major contributors to premature coronary events,' said Mora. 'Women under 55 who have obesity had about a four-fold increased risk for coronary events, as did women in that age group who smoked or had hypertension. Physical inactivity and family history are all part of the picture as well.'

The researchers acknowledged the study is limited in its generalisability – beyond its focus on women, who have been shown to have worse outcomes after premature cardiac events than men – its participants were over 95% white. According to Mora, findings could be even more dramatic in ethnic and racial groups that have a greater prevalence of the metabolic syndrome, insulin resistance and diabetes, among other risk factors.

'Diabetes is mostly preventable, but it's a systems-wide problem, and we urgently need further research into new strategies to address it,' Mora said. 'These could be innovative lifestyle-based strategies, like community efforts, greater public health efforts, ways to medically target metabolic pathways, or new surgical approaches.'

With the prevalence of diabetes and its associated risk factors increasing dramatically, and affecting more women than men, the researchers emphasise the urgency of developing effective interventions.

'We need new strategies to improve outcomes in these younger individuals and address the risk of diabetes, because we're only seeing the beginning of this epidemic now,' said Mora.

Source: MedicalBrief 2021

CVD the leading cause of death in patients with type 2 diabetes

Cardiovascular disease was the leading cause of death among the over 16 000 patients with type 2 diabetes (T2DM) who were enrolled in the SAVOR-TIMI 53 trial. Two-thirds (66.3%) of all 798 deaths after a median 2.1 years of follow up were caused by one of five cardiovascular (CV) conditions, with sudden cardiac death accounting for the largest share (30.1%) of the total, Dr Ilaria Cavallari, and associates at the University Campus Bio-Medico of Rome, Italy said.

Most common among the non-CV causes was malignancy at 13.9% of all deaths in a T2DM population at high/very high risk for CV disease (*n* = 16 492), followed by infection (9.3%), the members of the TIMI Study Group noted.

After variables independently associated with overall mortality were identified, a sub-distribution of competing risks was constructed using a competing-risk analysis based on the proportional hazards model, they explained.

Prior heart failure was the clinical variable most associated with CV death and could, along with older age, worse glycaemic control, prior CV events, peripheral artery disease and kidney complications, 'identify a subgroup of T2DM patients at high risk of mortality who are likely to achieve the greatest benefit from aggressive management of modifiable risk factors and newer glucose-lowering agents,' the investigators wrote.

It was a pair of laboratory measurements, however, that had the largest sub-distribution hazard ratios. 'Interestingly, the magnitude of associations of abnormal N-terminal pro-B-type natriuretic peptide (sHR, 2.82) and high-sensitivity troponin T (sHR, 2.46) measured in a stable population were greater than clinical variables in the prediction of all causes of death,' Cavallari and associates said.

Source: J Am Coll Cardiol 2021

Patients with type 2 diabetes
should expect more after metformin

REALISE THE POTENTIAL

NEW Ozempic®

The once-weekly treatment unifying superior efficacy and CV benefits[1-5]

SUPERIOR GLYCAEMIC CONTROL[1-4*]

HbA_{1c} reduction of –1.8% with Ozempic® 1 mg vs –1.4% with Dulaglutide 1.5 mg[3]

SUPERIOR AND SUSTAINED WEIGHT LOSS[1-4*]

More than double the weight loss vs Dulaglutide[3] (–6.5 kg with Ozempic® 1 mg vs –3.0 kg with Dulaglutide 1.5 mg)

PROVEN CV BENEFITS[1,5†]

26% CV risk reduction[1,3‡] (Primary composite outcome of CV death, nonfatal MI or nonfatal stroke)

For adults with type 2 diabetes and established CVD,
the 2019 ADA/EASD consensus report update and the 2021 ADA Standards of Medical Care in Diabetes recommend GLP-1 RA therapy with proven CV benefit.[6,7]

CV=cardiovascular; MI=myocardial infarction; CVD=cardiovascular disease; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; GLP-1 RA=glucagon-like peptide-1 receptor agonist.
*Results apply to Ozempic® across SUSTAIN trials, which included placebo, sitagliptin and dulaglutide.[1-4]
†In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal MI or nonfatal stroke) versus placebo in patients with type 2 diabetes with established CVD.[5]

Abbreviated Professional Information

Scheduling status: S4 **Name of the medicine:** OZEMPIC®. **Qualitative and quantitative composition:** Semaglutide 1, 34 mg/ml. **Therapeutic indication:** Ozempic® is indicated: for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, as combination therapy with oral anti-diabetic medicines (metformin, thiazoledinediones, sulphonylurea), basal insulin with or without metformin and pre-mix insulin, to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. **Posology and method of administration:** Ozempic® starting dose is 0,25 mg once weekly. After 4 weeks, the dose should be increased to 0,5 mg once weekly. After at least 4 weeks with a dose of 0,5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. Ozempic® is to be administered once weekly at any time of the day, with or without meals. Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Ozempic® should not be administered intravenously or intramuscularly. The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 2 days (>48 hours). **Contraindications:** Hypersensitivity to semaglutide or to any of the excipients, a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), pregnancy and lactation. **Special warnings and precautions for use:** Ozempic® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Ozempic® is not a substitute for insulin. Acute pancreatitis has been observed with the use of Ozempic®. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Ozempic® should be discontinued; if confirmed, Ozempic® should not be restarted. Patients treated with Ozempic® in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with Ozempic®. Risk of Thyroid C-cell Tumours: Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist have been reported in the post marketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans. **Interaction with other medicines and other forms of interaction:** In vitro studies have shown very low potential for Ozempic® to inhibit or induce CYP enzymes and to inhibit drug transporters. The delay of gastric emptying with Ozempic® may influence the absorption of concomitantly administered oral medicines. The potential effect of Ozempic® on the absorption of co-administered oral medicines was studied in trials at Ozempic® 1 mg steady state exposure. **Fertility, pregnancy and lactation:** Ozempic® is contraindicated during pregnancy and lactation. **Undesirable effects:** The most frequently reported adverse reactions with Ozempic® in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. Adverse reactions by system organ class and absolute frequencies identified in all phase 3a trials listed here as Very common (≥1/10): Hypoglycaemia when used with insulin or sulfonylurea, nausea, diarrhoea; Common (≥1/100 to <1/10): Hypoglycaemia when used with other OADs, decreased appetite, dizziness, diabetic retinopathy complications, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastrooesophageal reflux disease, eructation, flatulence, cholelithiasis, fatigue, increased lipase, increased amylase, weight decreased; Uncommon (≥1/1,000 to <1/100): hypersensitivity, dysgeusia, increased heart rate, injection site reactions; Rare (≥1/10,000 to <1/1,000): anaphylactic reaction. **Overdose:** There is no specific antidote for overdose with Ozempic®. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long halflife of Ozempic® of approximately 1 week. **Reg. No.:** 53/21.13/0497. For full prescribing information, refer to the Professional Information approved by the Regulatory Authority.

References: 1. Rodbard HW, Lingvay I, Reed J, *et al.* Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *J Clin Endocrinol Metab.* 2018;103(6)(suppl 1):1-28. 2. Ahrén B, Masmiquel L, Kumar H, *et al.* Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol* 2017;5(5):341-354. 3. Pratley RE, Aroda VR, Lingvay I, *et al.* Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018;6(4):275-286. 4. Capehorn MS, Catarig A-M, Furberg JK, *et al.* Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1 – 3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 2020;46(2):100-109. 5. Marso SP, Bain SC, Consoli A, *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-1844. 6. Buse JB, Wexler DJ, Tsapas A, *et al.* 2019 Update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020;43:487-493. 7. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*, 2021;44(1):S1-S232.

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