MICRO LABS LIMITED

Diabetes Update

Vol. 2 | Issue 33| 2021

Dear Doctor,

Greetings from Micro Labs Limited. We are happy to bring you "DIABETES UPDATE" which contains latest and interesting news in the field of Diabetes and Endocrinology.

- Prediction tool for severe hypoglycaemia and adverse cardiovascular events in DEVOTE, calculated from haemoglobin glycation index and single fasting glucose value
- Randomized clinical trial comparing glycemic excursion minimization (GEM) to weight loss (WL) in the management of type 2 diabetes
- A study on impaired fasting glucose, a risk factor for atrial fibrillation and heart

Prediction tool for severe hypoglycaemia and adverse cardiovascular events in DEVOTE, calculated from haemoglobin glycation index and single fasting glucose value

Despite evidence that some adults have consistently higher or lower HbA1c than their plasma glucose (PG) levels would predict, glycated haemoglobin A1c (HbA1c) is considered the gold standard for measuring and monitoring glycemic management. The factors that cause this variance are unknown, however they are assumed to be biologically determined. The haemoglobin

glycation index (HGI) derives a predicted HbA1c from PG readings using a population-based linear regression equation.

The HGI is calculated by subtracting the expected HbA1c from the observed HbA1c. In both type 1 diabetes (T1D) and type 2 diabetes (T2D), abnormalities in HGI have been shown to predict consequences such as mortality, cardiovascular disease (CVD), hypoglycemia, and microvascular complications. HGI has also been shown in tests to predict the responsiveness to antihyperglycemic medicines. These findings show that HGI may have a role in predicting diabetes outcomes and aiding in the personalization of care.

The aim of this study was to understand if insulin initiation/titration had an effect on HGI, the association between HGI tertile and cardiovascular and hypoglycemic risk, and the relative strengths of HGI and HbA1c in predicting these risks.

People with type 2 diabetes were given insulin degludec or insulin glargine 100 units/mL once a day in DEVOTE, a randomised, double-blind, cardiovascular outcomes experiment. Time to first major adverse cardiovascular event (MACE), which included cardiovascular mortality, myocardial infarction, or stroke, was the primary outcome; severe hypoglycemia was a secondary endpoint. The population data were categorised into HGI tertiles based on the computed HGI values, which were derived using a linear regression equation based on DEVOTE data (HbA1c=0.01313 FPG (mg/dL). Kaplan–Meier curves were used to

compare time to first event distributions; HRs and 95 percent confidence intervals were calculated using Cox regression models comparing risk of major adverse cardiovascular event (MACE) and severe hypoglycemia between tertiles. For the entire cohort and insulin-naive patients, changes in HGI were noted at 12 months following insulin introduction and stabilised by 24 months. Participants with a high HGI had the highest risk of MACE (low vs high, HR: 0.73 (0.61 to 0.87)95 percent CI; moderate vs high, HR: 0.67 (0.56 to 0.81)95 percent CI; p0.0001). There were no significant changes in the risk of severe hypoglycemia between HGI tertiles (p=0.0911). HGI was no longer a significant predictor of MACE after HbA1c was included in the model.

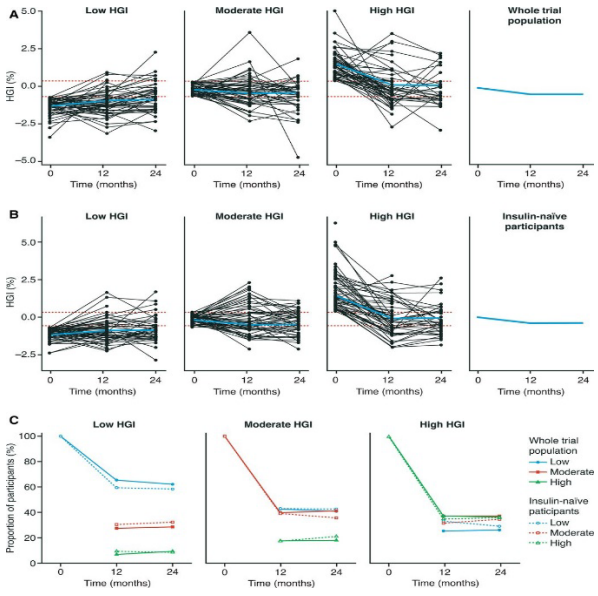

Figure 1: HGI variability over time in the whole trial population and in insulin-naive participants.

	MACE HR (95% CI)

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HGI	
Low vs moderate	1.15(0.92 to 1.44)
High vs moderate	1.22(0.98 to 1.53)
Pvalue for interaction between HGI tertile and outcome	0.1598
HbA1c	
	1.42 (1.15 to 1.76)
<7.5%vs 27.5-<9%	0.99 (0.79 1 to 1.24)
Pvalue for interaction between HGI tertile and outcome	0.0046

Table 1: Time to first occurrence of MACE,adjusted for baseline HGI tertile and HbA_{1c} in the whole trial population

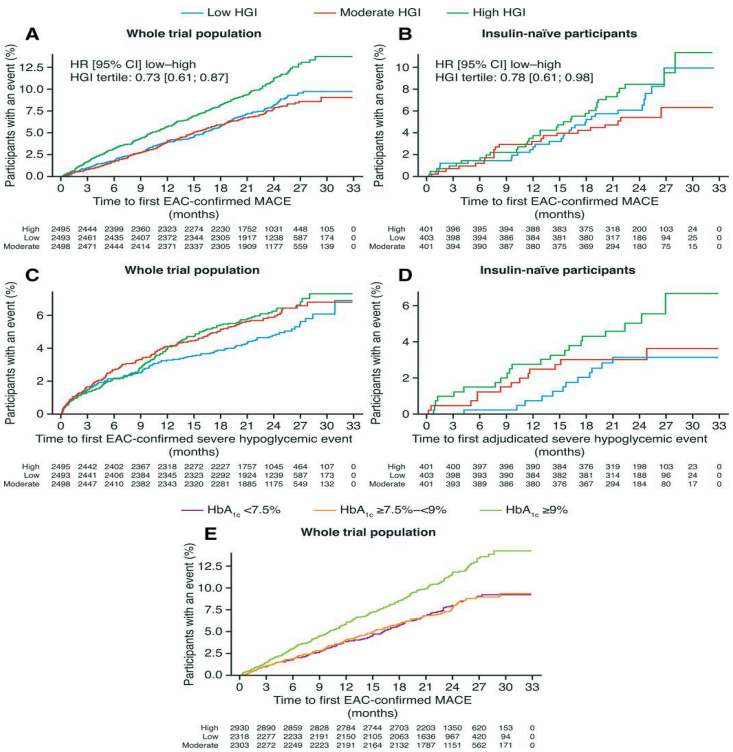

Figure 2: Kaplan–Meier curves for time to first MACE and severe hypoglycemia.

These findings show that HGI fluctuates initially with insulin titration or commencement before stabilising at a population level over a lengthy period of time. In a patient population with advanced diabetes at high risk for cardiovascular events, baseline HGI showed a trend toward association with baseline microvascular disease markers and a significant association with prospective cardiovascular risk; additionally, these findings support the initial findings of ADVANCE that HGI is not a better predictor of cardiovascular outcomes than HbA1c.

Reference: Klein KR, Franek E, Marso S, et al. Hemoglobin glycation index, calculated from a single fasting glucose value, as a prediction tool for severe hypoglycemia and major adverse cardiovascular events in DEVOTE. BMJ Open Diab Res Care 2021;9:e002339

Randomized clinical trial comparing glycemic excursion minimization (GEM) to weight loss (WL) in the management of type 2 diabetes

In contrast to pharmaceutical therapies for type 2 diabetes (T2D), which target a number of pathways, lifestyle interventions that are generally focused on weight loss (WL). Some adults with T2D, however, may not need to reduce weight (about 15%), do not want to lose weight, or are unable to lose weight and keep it off for the duration of their disease. As a result, this study devised a lifestyle intervention paradigm shift that lowers

postnutrient blood glucose (BG) excursions, referred to as glycemic excursion reduction (GEM). GEM lowers BG area under the curve by identifying meal choices that reduce BG rises and physical activities that speed up BG recovery, empowering patients to choose choices that limit BG excursions and consequently HbA1c and cardiovascular risk.

The aim of this study was to present the first long-term follow-up of GEM, testing the hypothesis that GEM will be equivalent to or superior to WL in maintaining its benefits in the primary (HbA1c) and secondary variables (physical, psychological, and behavioural parameters) found improved at a 3-month follow-up, without any maintenance intervention.

A total of 172 people ranged in age from 30 to 80 years old, had T2D for at least ten years, had a HbA1c of 6.8% (51 mmol/mol), and did not use insulin, were included in this study. Participants were randomly assigned to either WL or one of three GEM variants for 6 hours of group therapy. The degree of blood glucose (BG) feedback supplied during treatment varied amongst GEM groups, with no advised feedback, systematic capillary BG feedback before and after nutrition intake and physical activity, and continuous glucose monitoring being the most common. Because there was no difference in pre-post improvement between these GEM groups, they were pooled for the initial and current analyses. 100% and 96 percent of the WL and GEM participants, respectively, completed the 13-month follow-up evaluation after completing the 3-month postassessment.

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		WL			GEM		
Baseline variable	Test	Responders	Non- responders	P value	Responders	Non- responders	P value
Demographic variable		15	21	NA	61	57	NA
Age (years)	t-test	56.9+12.8	59.3=9.5	0.52	58.1=12.3	54.7=10.7	0.11
Education (years)	t-test	15.2+2.9	15.4+2.5	0.84	16.1+3.0	16.1+3.2	0.99
Gender (% female)	x^2	40%	67%	0.11	53%	68%	0.08
Race (% white)	x^2	80%	67%	0.12	82%	72%	0.13
Body mass index (BMI)	t-test	34.4+7.9	35.2+6.6	0.74	33.8+6.3	35.7+5.6	0.09
Psychological variables							
Diabetes empowerment	t-test	29.3=3.7	31.6+3.6	0.09	30.0+4.1	30.0+5.2	0.99
Diabetes distress (emotional)	t-test	2.1+0.9	2.4+1.1	0.43	2.2+1.1	2.6+1.1	0.06
Diabetes distress (regimen)	t-test	2.9+0.9	3.3=1.3	0.34	2.9=1.3	3.2+1.4	0.23
Depression (Patient Health Questionnaire-9)	t-test	5.1+4.6	4.1+4.0	0.51	3.7+4.2	4.8=5.1	0.21
Disease severity							
HbA1c (% and (mmol/mol))	t-test	8.4+1.0 (68.6+11.1)	8.1+1.0 (65.1+10.6)	0.34	8.4=1.5 (68.6+16.3)	8.3=1.2 (67.3=13)	0.62
Medication Effect Score	t-test	1.2+0.8	1.0+0.7	0.39	1.2+0.8	1.1+0.7	0.33
Years with diabetes	t-test	4.8+3.0	6.0+2.0	0.26	5.5+3.1	5.4+3.3	0.87

Table 2: Baseline variables for responders and non-responders in the GEM and WL groups, with contrasts (p value levels)

Within-group comparisons from pre- to post-intervention revealed that WL participants improved their body mass index (BMI) (- 0.9 ± 1.4, p=0.001). HbA1c (- 0.5 ± 1.4, p<0.001), BMI (-1±1, p<0.001), HDL (p<0.001), carbohydrate ingestion reduction (p<0.001), self-monitoring of blood glucose satisfaction (p<0.001) and frequency (p<0.001), diabetes knowledge (p<0.001), diabetes empowerment (p<0.001), and both diabetes distress emotional (p=0.009) and regimen (p=0.001) subscales all improved in GEM participants. With a mean HbA1c reduction of -1.2 percent and -1.5 percent, 42 percent and 52 percent of WL and GEM participants, respectively, were categorised as responders (individuals whose A1c dropped by at least -0.5 percent). Neither WL nor GEM responders differed from non-responders in baseline demographics, psychological or disease severity characteristics. While WL responders could not be anticipated,

post-treatment versus pre-treatment reductions in HbA1c, diabetic medication, and BMI could predict 73 percent of GEM responders.

Variables, GEM	OR	95% CI	P value
HbA1c	2.02	1.32 to 3.08	0.001
Body Mass Index (BMI)	1.58	1.11 to 2.27	0.012
Medication Effect Score (MES)	7.04	1.90 to 26.1	0.003

Table 3: Logistic regression comparing GEM responders to non-responders

While WL's BMI improved with time, GEM's advantages were sustained across a wide variety of physical, behavioural, and psychological factors, which was useful to clinicians and T2D patients. This is especially important for primary care physicians, who are responsible for around 90% of T2D patients.

Reference: Cox DJ, Oser T, Moncrief M, et alLong-term follow-up of a randomized clinical trial comparing glycemic excursion minimization (GEM) to weight loss (WL) in the management of type 2 diabetesBMJ Open Diabetes Research and Care 2021;9:e002403.

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A study on impaired fasting glucose, a risk factor for atrial fibrillation and heart failure

Diabetes mellitus is associated to a higher risk of cardiovascular disease and a shorter lifespan. This elevated risk is already present at the pre-diabetes stage. Heart failure is one of the most serious cardiovascular consequences linked with diabetes, with diabetes raising the risk of heart failure by up to two times when risk factors are well-controlled and significantly greater if risk factors are unmanaged. Diabetes has also been linked to being a risk factor for atrial fibrillation and having a detrimental impact on the disease's prognosis.

This study aimed to understand if there was a link between glucose levels, especially those below the current diabetes diagnostic threshold, and the risk of getting atrial fibrillation and heart failure in people who had never had a heart problem before.

Subjects from the Swedish AMORIS-cohort with fasting glucose from health examinations 1985–1996 and no previous cardiovascular disease (N = 294,057) were monitored for incident atrial fibrillation or heart failure until December 31, 2011. To estimate hazard ratios by glucose categorised groups (normal glucose 3.9–6.0 mmol/L, impaired fasting glucose; 6.1–6.9 mmol/L, undiagnosed diabetes 7.0 mmol/L, and diagnosed diabetes), Cox proportional hazard models with attained age as timescale and adjustments for sex, cholesterol, triglycerides, and socioeconomic status were used.

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	Glucose level	PYR	Events	Adjustment	HR (95% CI)
Atrial fibrillation	Low	147 692	490	Age adj.	0·98 (0·90-1·07)
				Multi adj.	0·98 (0·90-1·07)
	Normal	5 122 588	24 689	Ref.	1·00
	IFG	161 570	1 458	Age adj.	1·23 (1·16-1·29)
				Multi adj.	1·19 (1·13-1·26)
	Undiagnosed DM	78 134	881	Age adj.	1·31 (1·22-1·40)
				Multi adj.	1·23 (1·15-1·32)
	Diagnosed DM	77 314	715	Age adj.	1·37 (1·28-1·48)
				Multi adj.	1·30 (1·21-1·41)
Heart failure	Glucose level	PYR	Events	Adjustment	HR (95% CI)
	Low	148 663	397	Age adj.	0·95 (0·86-1·05)
				Multi adj.	0·99 (0·90-1·09)
	Normal	5 166 911	21 145	Ref.	1·00
	IFG	162 318	1 612	Age adj.	1·57 (1·49-1·65)
				Multi adj.	1·40 (1·33-1·48)
	Undiagnosed DM	76 669	1 406	Age adj.	2·52 (2·38-2·66)
				Multi adj.	2·11 (1·99-2·23)
	Diagnosed DM	75 983	1 044	Age adj.	2·54 (2·39-2·70)
				Multi adj.	2·22 (2·08-2·36)
Combined event	Glucose level	PYR	Events	Adjustment	HR (95% CI)
	Low	146 578	717	Age adj.	0·98 (0·91-1·06)
				Multi adj.	1·00 (0·93-1·08)
	Normal	5 070 759	35 929	Ref.	1·00
	IFG	157 797	2 336	Age adj.	1·37 (1·32-1·43)
				Multi adj.	1·28 (1·23-1·34)
	Undiagnosed DM	74 535	1 745	Age adj.	1·88 (1·80-1·98)
				Multi adj.	1·67 (1·59-1·76)
	Diagnosed DM	74 069	1 356	Age adj.	1·92 (1·82-2·03)
				Multi adj.	1·75 (1·65-1·85)

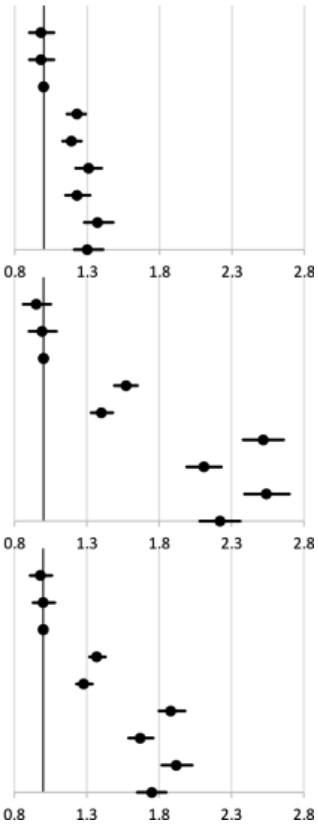

Figure 3: Total events, and hazard ratios (HR) for atrial fibrillation, heart failure and combined event by glucose group.

Over the course of 19.1 years, 28,233 people acquired atrial fibrillation and 25,604 people developed heart failure. Impaired fasting glucose had an HR of 1.19 (95 percent confidence interval 1.13–1.26), undiagnosed diabetes had an HR of 1.23 (1.15–1.32), and diagnosed diabetes had an HR of 1.30 (1.21–1.41). Heart failure figures were 1.40 (1.33–1.48), 2.11 (1.99–2.23), and 2.22 (2.08–2.36), respectively. These relationships were weaker in a subset having BMI data (19%),

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and only those with confirmed diabetes (HR 1.25; 1.02–1.53) remained statistically significant for atrial fibrillation (HR 1.25; 1.02–1.53).

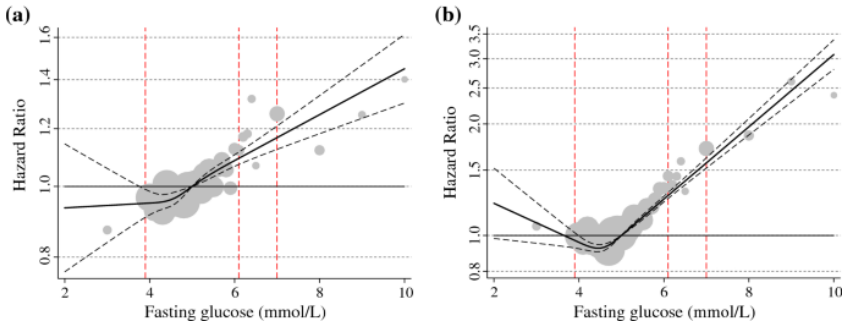

Figure 4: Hazard ratio and 95% confidence limits for A atrial fibrillation (left) and B heart failure (right) by fasting glucose level presented as splines.

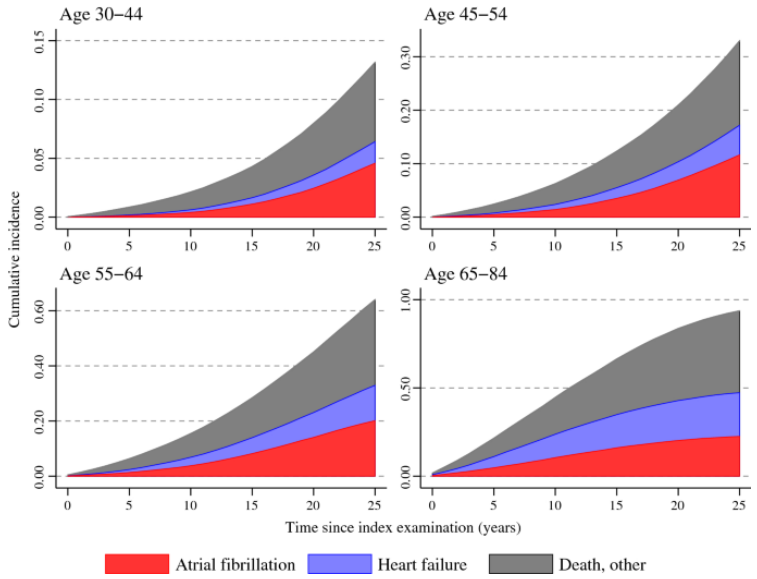

Figure 5: Cumulative incidence of events

Elevated fasting glucose and undiagnosed diabetes are risk factors for the development of atrial fibrillation and heart failure in the future, highlighting the need of early identification of dysglycemia in cardiovascular prophylaxis.

Reference: Lind, V., Hammar, N., Lundman, P. *et al.* Impaired fasting glucose: a risk factor for atrial fibrillation and heart failure. *Cardiovasc Diabetol* **20,** 227 (2021).