Clinical and metabolic parameters associated with time in ranges and glucose variability in patients with type 2 diabetes treated with insulin

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Background and aim:

• **Continuous glucose monitoring (CGM) provides an excellent opportunity for in-depth assessment of glycemic control and glucose variability (GV) in diabetic subjects.**

• **The aim of our study was to determine the clinical and metabolic parameters associated with non-targeted time in range (TIR) increased GV in patients with type 2 diabetes (T2D) treated with insulin.**

Materials and Methods:

• **One hundred and thirty six insulin-treated patients with T2Dwere included. Real-time or blinded CGM was performed using Medtronic CGM devices.**

• **The TIR and Mean Amplitude of Glucose Excursion (MAGE) were estimated.**

• **The advance glycation end-products (AGEs) levels were measured in blood serum by ELISA.**

CLINICAL AND LABORATORY CHARACTERISTICS OF T2D PATIENTS DEPENDING ON TIR

Parameter	TIR ≥70% (n = 27)	TIR <70% (n = 109)	P
Sex, m/f	9/18	40/69	0.74
Age, years	64 (56; 71)	63 (60; 68)	0.53
BMI, kg/m²	33.7 (29.7; 37.5)	32.2 (29.1; 38.6)	0.71
Diabetes duration, yrs	16 (13; 19)	16 (10; 21)	0.9
Duration of insulin therapy, yrs	6 (2; 10)	7 (4; 11)	0.14
Daily insulin dose, IU/kg	0.6 (0.4; 0.7)	0.6 (0.43; 0.8)	0.3
HbA1c, %	9.8 (9.0; 11.7)	8.4 (7.9; 9.3)	0.0002

Parameter	TIR ≥70% (n = 27)	TIR <70% (n = 109)	P
Triglycerides, mmol/L	2.68 (1.35; 3.91)	1.91 (1.36; 2.59)	0.03
Total cholesterol, mmol /L	5.4 (3.8; 5.9)	4.7 (4.1; 5.7)	0.3
LDL-cholesterol, mmol /L	2.9 (2.0; 3.7)	3.0 (2.4; 3.7)	0.68
Uric acid, µmol / L	305 (269; 384)	335 (257; 401)	0.63
UACR, mg/mmol	21.3 (2.3; 111.9)	9.4 (2; 35.8)	0.11
Urinary protein excretion, mg/day	200 (100; 410)	98 (60; 200)	0.01
eGFR, ml/min/1.73m² (CKD-EPI)	65 (47; 79)	67 (56; 82)	0.33

- Based on CGM results, 27 patients had TIR values ≥70%.
- Patients with non-targeted TIR (>70%) had higher levels of HbA1c, triglycerides and urinary protein excretion. Urinary albumin-to-creatinine ratio (UACR) tended to be higher in patients with non-targeted TIR.
- There were no significant differences in sex distribution, age, BMI, diabetes duration, cholesterol and uric acid levels, and estimated glomerular filtration rate (eGFR) between the groups.

- At the second step, we matched the clinical and laboratory parameters in observed patients depending on MAGE.
Patients with MAGE >4.5 mmol/L demonstrated lower levels of triglycerides and uric acid as compared to those with MAGE <4.5 mmol/l.

CLINICAL AND LABORATORY CHARACTERISTICS OF T2D PATIENTS DEPENDING ON MAGE

Parameter	MAGE >4.5 ммol/L (n=57)	MAGE <4.5 mmol/L (n=79)	P
Sex, m/f	20/37	29/50	0.87
Age, years	63 (61; 68)	63 (59; 68)	0.83
BMI, kg/m²	32 (28.8; 36.1)	33.9 (29.4; 39.6)	0.13
Diabetes duration, years	14 (9; 20)	17 (11; 20)	0.46
Duration of insulin therapy, years	5 (3; 10)	8 (4; 11)	0.12
Daily insulin dose, IU/kg	0.6 (0.4; 0.8)	0.6 (0.45; 0.8)	0.61
HbA1c, %	9.0 (8.3; 9.9)	8.3 (7.7; 9.7)	0.05

Parameter	MAGE >4.5 ммol/L (n=57)	MAGE <4.5 mmol/L (n=79)	P
Triglycerides, mmol/L	1.75 (1.16; 2.44)	2.25 (1.67; 2.99)	0.001
Total cholesterol, mmol /L	4.83 (4.07; 5.52)	4.8 (4.08;5.86)	0.82
LDL-cholesterol, mmol /L	3.01 (2.34; 3.61)	2.98 (2.23; 3.68)	0.83
Uric acid, µmol / L	304 (243; 362)	368 (269; 431)	0.002
UACR, mg/mmoL	1.4 (0.6; 5.5)	2.6 (0.7; 13.1)	0.13
Urinary protein excretion, mg/day	120 (60; 210)	100 (60; 300)	0.76
eGFR, ml/min/1.73m² (CKD-EPI)	69 (55.8; 82.0)	64.6 (54; 79)	0.47

• **Diabetic patients had increased serum levels of AGEs compared to non-diabetic subjects (p=0.04). No relations were found between AGEs and TIRs. Patients with higher MAGE demonstrated increased levels of AGEs.**

CGM-DERIVED GV PARAMETERS IN T2D PATIENTS DEPENDING ON MAGE VALUES

Parameter	MAGE >4.5 ммоl/l (n=57)	MAGE <4.5 mmol/l (n=79)	P
Mean glucose, mmol/l	8.91 (8.18; 10.15)	7.96 (6.79; 8.9)	<0.001
TIR, %	47.1 (30.4; 54.7)	67.4 (45.2; 80.5)	<0.001
TAR, %	50.1 (41.5; 66.1)	30.1 (14.4; 51.2)	<0.001
TBR, %	1.18 (0.0; 4.8)	0.46 (0.0; 3.9)	0.2
SD, mmol/l	2.6 (2.39; 3.08)	1.79 (1.4; 2.1)	<0.001
MAGE, mmol/l	5.57 (5.05; 6.45)	3.65 (3.14; 4.04)	<0.001

Parameter	MAGE >4.5 ммоl/l (n=57)	MAGE <4.5 mmol/l (n=79)	P
CONGA, mmol/l	7.38 (6.6; 8.68)	6.6 (5.7; 7.6)	0.0002
LI, a.u.	3.54 (2.8; 4.3)	1.48 (1.09; 2.07)	<0.001
HBGI, a.u.	7.6 (6.0; 11.9)	3.54 (2.7; 5.8)	<0.001
LBGI, a.u.	1.32 (0.47; 1.82)	0.69 (0.23; 1.3)	0.02
MAG, mmol/l/h	1.9 (1.46; 2.3)	1.35 (1.18; 1.58)	0.001

TIR, Time In Range; TAR, Time Above Range; TBR, Time Below Range; SD, Standard Deviation; MAGE, Mean Amplitude of Glucose Excursions; CONGA, 2-hour Continuous Overlapping Net Glycemic Action; LI, Lability Index; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index; MAG, Mean Absolute Glucose.

Conclusion: In T2D subjects, non-targeted TIR is associated with hypertriglyceridemia and proteinuria, meantime, increased MAGE is related to lower serum levels of triglycerides and uric acid and higher levels of AGEs.