

Electronic Supplementary Material (ESM)

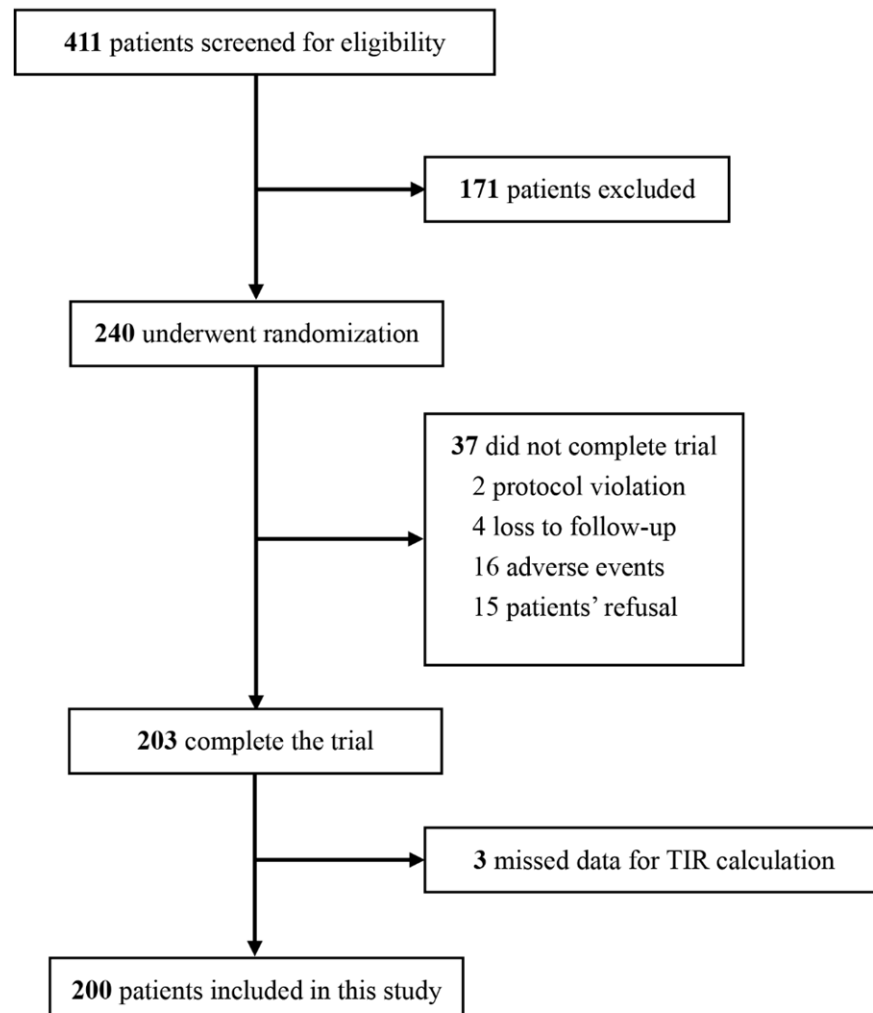
Association of time in range with endothelial injury in patients with type 2 diabetes treated with exenatide

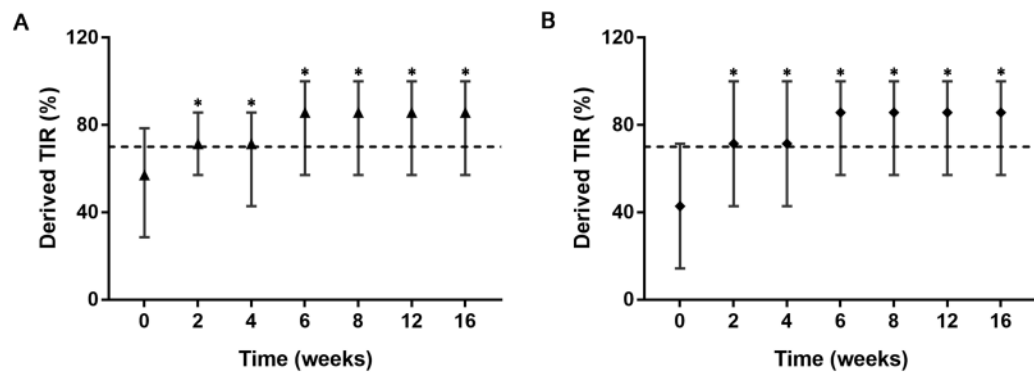
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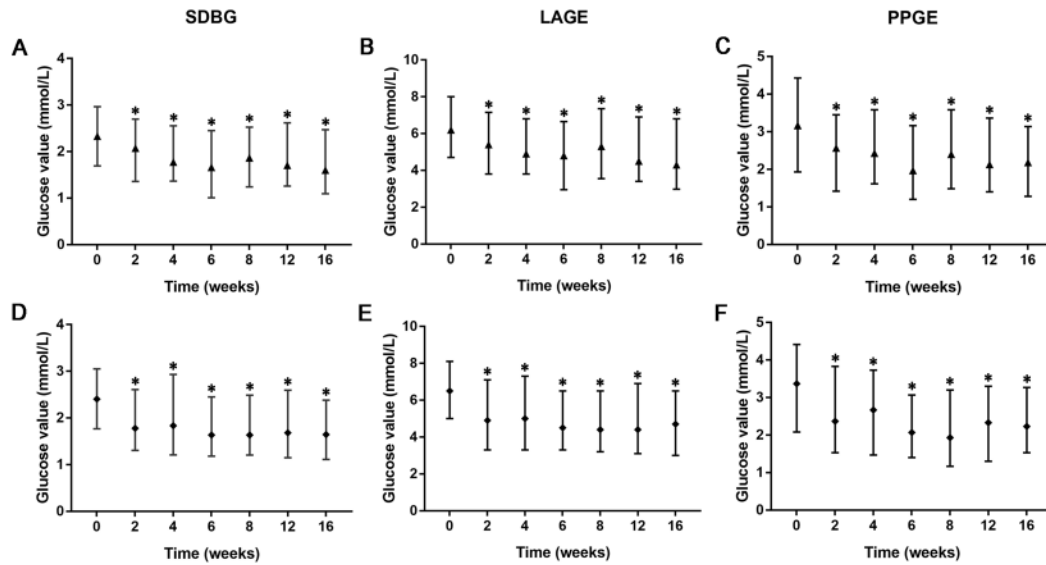
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Supplementary figure 1. The flow diagram of patient inclusion.





Supplementary figure 2. The changes in derived TIR value from baseline during the exenatide treatment in patients with and without the evaluation of endothelial injury markers. A: Subgroup of patients with the evaluation of endothelial injury markers. B: Subgroup of patients without the evaluation of endothelial injury markers. Data are presented as median (interquartile range). * $P < 0.05$ vs. baseline. *TIR* time in range



Supplementary figure 3. The changes in the parameters of glycemic variability from baseline during the exenatide treatment in patients with and without the evaluation of endothelial injury markers. A–C: Subgroup of patients with the evaluation of endothelial injury markers. D–F: Subgroup of patients without the evaluation of endothelial injury markers. Data are presented as median (interquartile range). * $P < 0.05$ vs. baseline. *SDBG* standard deviation of blood glucose, *LAGE* largest amplitude of glycemic excursions, *PPGE* postprandial glucose excursions

Supplementary table 1. Baseline clinical characteristics in patients with and without the evaluation of endothelial injury markers.

Parameters	Patients with endothelial injury markers (n=93)	Patients without endothelial injury markers (n=107)	<i>t</i> / <i>Z</i> / <i>X</i> ² value	<i>P</i> value
Age, years	49.5 ± 9.52	49.8 ± 10.1	−0.271	0.786
Sex–male	55 (59.1)	64 (59.8)	−0.009	0.100
Duration of diabetes, years	4.42 (2.29, 8.17)	5.08 (2.42, 9.34)	0.692	0.489
Background therapies			−3.241	0.198
Metformin	46 (49.5)	43 (40.2)		
Insulin secretagogues	10 (10.7)	8 (7.5)		
Both	37 (39.8)	56 (52.3)		
Body weight, kg	79.3 ± 16.2	80.1 ± 14.0	−0.404	0.687
Body mass index, kg/m ²	28.1 ± 4.13	28.7 ± 4.16	−1.039	0.300
Systolic blood pressure, mmHg	124.5 ± 11.0	128.4 ± 14.1	−2.140	0.034
Diastolic blood pressure, mmHg	77.8 ± 8.23	79.9 ± 8.21	−1.848	0.066
Fasting blood glucose, mmol/L	9.46 ± 1.88	9.33 ± 1.73	0.480	0.632
Postprandial 2 h blood glucose, mmol/L	16.3 ± 3.60	16.1 ± 3.36	0.519	0.604
Glycated hemoglobin A1c, %	8.23 ± 0.87	8.16 ± 0.92	0.567	0.571
Glycated hemoglobin A1c, mmol/mol	66.5 ± 9.52	65.6 ± 10.1	0.567	0.571
Total cholesterol, mmol/L	5.02 ± 1.00	4.73 ± 0.92	0.274	0.784
Low-density lipoprotein cholesterol, mmol/L	3.11 ± 0.85	2.81 ± 0.86	2.188	0.030
High-density lipoprotein cholesterol, mmol/L	1.28 ± 0.36	1.23 ± 0.40	0.864	0.389
Triglycerides, mmol/L	1.62 (1.21, 2.40)	1.65 (1.20, 2.68)	0.065	0.948
Uric acid, µmol/L	307.8 ± 85.0	328.0 ± 89.1	−1.635	0.104
Alanine aminotransferase, U/L	23.8 (15.5, 42.0)	24.3 (17.0, 39.0)	0.059	0.953
Aspartate aminotransferase, U/L	25.0 (20.0, 32.0)	23.0 (17.5, 32.2)	0.780	0.435
Alkaline phosphatase, U/L	68.6 (57.0, 82.0)	69.0 (58.5, 86.0)	0.498	0.618
Creatinine, µmol/L	65.3 ± 15.9	63.5 ± 13.5	0.845	0.399
Blood urea nitrogen, mmol/L	4.85 ± 1.29	4.97 ± 1.31	−0.644	0.520
Derived TIR, %	57.1 (28.6, 78.6)	42.9 (14.3, 71.4)	−1.338	0.181
SDBG, mmol/L	2.33 (1.69, 2.97)	2.40 (1.76, 3.05)	−0.746	0.456
LAGE, mmol/L	6.20 (4.70, 8.00)	6.45 (5.00, 8.10)	−0.683	0.495
PPGE, mmol/L	3.17 (1.93, 4.43)	3.33 (2.05, 4.43)	−0.271	0.786

Data are presented as number (%), mean ± SD or median (interquartile range), as appropriate. *TIR* time in range, *SDBG* standard deviation of blood glucose, *LAGE* largest amplitude of glycemic excursions, *PPGE* postprandial glucose excursions

Supplementary table 2. Clinical characteristics before and after treatment with exenatide for 16 weeks in patients with TIR > 70% and TIR ≤ 70% who were included for the evaluation of endothelial injury markers.

Parameters	TIR > 70% (n =65)		t/Z value	P value	TIR ≤ 70% (n = 28)		t/Z value	P value
	Baseline	After treatment			Baseline	After treatment		
Age, years	48.7 ± 10.0				51.2 ± 8.12			
Sex–male	38 (58.5)				17 (60.7)			
Duration of diabetes, years	5.36 ± 4.20				7.21 ± 5.35			
Background therapies								
Metformin	34 (52.3)				12 (42.9)			
Insulin secretagogues	3 (4.6)				7 (25.0)			
Both	28 (43.1)				9 (32.1)			
Body weight, kg	80.3 ± 15.3	77.6 ± 14.5	8.058	<0.001	77.0 ± 18.1	76.6 ± 18.4	0.299	0.767
Body mass index, kg/m ²	28.5 ± 4.09	27.5 ± 3.86	8.205	<0.001	27.3 ± 4.15	27.1 ± 4.19	0.383	0.705
Systolic blood pressure, mmHg	125.1 ± 11.2	125.4 ± 13.0	−0.153	0.879	123.2 ± 10.7	122.3 ± 10.6	0.424	0.675
Diastolic blood pressure, mmHg	77.4 ± 7.98	76.7 ± 7.25	0.699	0.487	78.6 ± 8.90	74.3 ± 7.23	2.783	0.010
Fasting blood glucose, mmol/L	9.23 ± 1.79	7.44 ± 1.58	6.963	<0.001	9.98 ± 2.00	9.44 ± 2.25	1.183	0.247
Postprandial 2 h blood glucose, mmol/L	16.1 ± 3.62	12.4 ± 3.58	6.590	<0.001	16.8 ± 3.55	15.5 ± 4.15	1.531	0.137
Glycated hemoglobin A1c, %	8.08 ± 0.82	6.67 ± 0.77	11.237	<0.001	8.58 ± 0.92	8.04 ± 0.75	2.896	0.007
Glycated hemoglobin A1c, mmol/mol	64.8 ± 8.91	49.9 ± 8.40	11.237	<0.001	70.2 ± 10.0	64.4 ± 8.20	2.896	0.007
Total cholesterol, mmol/L	4.98 ± 1.00	4.89 ± 0.88	0.301	0.764	5.14 ± 1.03	4.96 ± 1.05	1.021	0.316
Low-density lipoprotein cholesterol, mmol/L	3.08 ± 0.87	3.11 ± 0.77	−1.106	0.273	3.17 ± 0.82	2.94 ± 0.81	1.113	0.275
High-density lipoprotein cholesterol, mmol/L	1.26 ± 0.34	1.24 ± 0.32	0.672	0.504	1.32 ± 0.39	1.30 ± 0.36	0.316	0.755
Triglycerides, mmol/L	1.58 (1.30, 2.75)	1.58 (1.23, 1.11)	−0.595	0.552	1.63 (0.92, 1.36)	1.61 (1.20, 2.36)	−0.171	0.864
Uric acid, μmol/L	315.1 ± 76.6	326.5 ± 79.0	−1.092	0.279	290.6 ± 101.2	302.9 ± 79.7	−1.017	0.318
Alanine aminotransferase, U/L	23.0 (14.9, 40.5)	24.2 (16.3, 35.6)	−1.736	0.083	26.0 (16.0, 42.0)	27.6 (15.0, 54.2)	−1.033	0.301
Aspartate aminotransferase, U/L	25.0 (19.0, 31.7)	23.9 (18.4, 28.4)	−0.014	0.989	26.2 (20.3, 35.3)	27.3 (19.1, 41.5)	−2.084	0.037
Alkaline phosphatase, U/L	66.2 (53.9, 84.0)	64.5 (54.6, 18.2)	−1.356	0.175	72.0 (60.5, 82.3)	74.0 (60.3, 82.5)	−0.529	0.597
Creatinine, μmol/L	65.3 ± 15.7	65.8 ± 15.9	−0.701	0.486	65.2 ± 16.8	65.8 ± 15.9	−0.102	0.919
Blood urea nitrogen, mmol/L	4.73 ± 1.27	4.71 ± 1.28	0.066	0.947	5.12 ± 1.32	4.71 ± 1.28	0.978	0.337
SDBG, mmol/L	2.07 (1.59, 2.62)	1.26 (0.89, 1.69)	−5.374	<0.001	2.97 (2.19, 3.61)	2.82 (2.18, 3.00)	−0.553	0.581
LAGE, mmol/L	5.50 (4.30, 7.10)	3.60 (2.40, 5.20)	−4.932	<0.001	8.35 (5.75, 10.9)	7.20 (6.00, 8.90)	−0.961	0.336
PPGE, mmol/L	2.77 (1.67, 3.80)	1.80 (1.10, 2.50)	−4.631	<0.001	3.87 (3.01, 5.68)	3.57 (3.03, 4.13)	−1.225	0.220
vWF, mIU/mL	1166.2 (848.1, 1335.5)	907.4 (674.3, 1335.1)	−3.432	0.001	1245.8 (1022.0, 1812.6)	1168.2 (802.2, 1455.3)	−2.619	0.009
sEPCR, ng/mL	96.9 (48.5, 150.9)	74.5 (32.8, 122.5)	−2.734	0.006	108.7 (39.8, 137.1)	107.5 (26.4, 135.7)	−0.501	0.616

Data are presented as number (%), mean $\pm$ SD or median (interquartile range), as appropriate. *TIR* time in range, *SDBG* standard deviation of blood glucose, *LAGE* largest amplitude of glycemic excursions, *PPGE* postprandial glucose excursions, *vWF* von Willebrand factor, *sEPCR* soluble endothelial cell protein C receptor

Supplementary table 3. List of independent ethics committees/institutional review boards in our study

Site No.	Investigator name	Independent Ethics Committee/Institutional Review Board name
01	Prof. Tianpei Hong	Ethics Committee of Peking University Third Hospital
02	Prof. Lixin Guo	Ethics Committee of Beijing Hospital
03	Prof. Quanmin Li	Ethics Committee of PLA Rocket Force Characteristic Medical Center
04	Prof. Liyong Zhong	Ethics Committee of Beijing Tiantan Hospital
05	Prof. JinKui Yang	Ethics Committee of Beijing Tongren Hospital
06	Prof. Jing Yang	Ethics Committee of Shanxi Medical University
07	Prof. Yongyi Gao	Medical Ethics Committee of Hainan General Hospital