

**CHRONOBIOLOGIC APPROACH TO CORRECTION OF DISTURBANCES IN HEMOCOAGULATION CIRCADIAN ORGANIZATION IN DIABETIC NEPHROROPATY**

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**AIM:** to study circadian organization of hemocoagulation and correction its disturbances in diabetic nephropathy by using chronobiologic approach to therapy with trental.

**MATERIAL AND METHODS:** 41 pts with diabetic nephropathy (DN) on the background of insulin dependent diabetes mellitus (IDDM), several form aged 38 years old were divided into three groups. The 1st from 17 pts aged 38,8±2,3 years; the 2nd group of 14 pts from 38 to 42 years old, the 3rd group of 10 pts from 42 to 57 years old were investigated by hemocoagulation variables yvery 4 hours: at 07.00; 11.00; 15.00; 19.00; 23.00; 03.03. There were examined autocoagulation test (ACT), antithrombin III (ATIII), index of thrombin inactivation (IIT), soluted completes of fibrinonomers (SCFM), fibrinogen (F), thrombin time (TT), MNO, fibrinogaze activity (FLA), hemocoagulation of aggregation test (HAT). 15 pts with IDDM without nephropathy aged 28,2±3,2 years old arranged the control group. All pts received adequate insulinotherapy, diet. Before and 16 days after traditional therapy (TT) and chronotherapy (CT) with trental circadian organization were examined too. Besides, insulinotherapy these pts received trental in dosage of 100 mg × 3 times a day in traditional regimen (TT). Trental in a dose of 100 mg once a day was administered in CT – 2 hours before maximum of platelets aggregation.

**RESULTS:** before start therapy with trental there were observed disturbances in chronostructure of hemocoagulation variables, such as hypercoagulation during 24 hours with maximum platelets aggregation, levels of F, SCFM and minimum of FLA, IIT at night. After TT with trental mean values of hemocoagulation during 24h improved with decreasing grad of hypercoagulation by data of plasmic homeostasis were not changed. CT with trental was more effective, than TT on the background of complex therapy. Coagulating potential of blood decreased by data of daily profile in plasmic and platelets hemostats. There were observed more increasing FLA and IIT in CT, than in TT with trental. All these effects were reached by smaller doses of trental, than in TT By 3 times.

Pic.1 Circadian rhythm of hemocoagulation parameters in patients with diabetic nephropathy on the 1st grad before and after chronotherapy with trental

Parameters	MESOR	Amplitude	Acrophase
ACT A, % before therapy	23.30 (22.39-24.22)	5.31 (4.48-6.14)	0.44 (23.58-1.33)
After therapy	18.33 (17.84-18.83)	2.52 (1.54-3.50)	00.47 (23.51-1.37)
MC, % before therapy	100.24 (93.34-8.83)	2.43 (1.33-3.54)	23.44 (22.52-1.59)
After therapy	95.24 (93.45-97.04)	3.8 (1-6.25)	00.54 (23.09-2.07)
T, min before therapy	8.59 (8.35-8.83)	1.45 (1.27-1.63)	12.41 (12.08-13.15)
After therapy	9.65 (9.53-9.78)	0.44 (0.27-0.60)	13.11 (1.42-14.40)
IIT, before therapy	1.87 (1.84-1.90)	0.17 (0.15-0.20)	12.30 (11.15-13.13)
After therapy	2.02 (1.99-2.06)	0.10 (0.07-0.12)	13.11 (12.09-14.47)
ATIII, % before therapy	80.66 (76.60-84.71)	14.51 (11.12-17.89)	12.34 (11.54-13.23)
After therapy	93.32 (89.85-96.78)	9.11 (6.75-11.48)	13.06 (12.07-14.38)
SCFM, before therapy	0.94 (0.95-1.32)	0.31 (0.09-0.53)	01.05 (23.41-2.33)
After therapy	0.21 (0.05-0.04)	0.07	05.23
Fg, g/l before therapy	4.21 (4.10-4.32)	0.45 (0.33-0.58)	13.16 (12.51-13.43)
After therapy	3.33 (3.22-3.45)	0.13 (0.05-0.21)	01.13 (22.57-4.09)
TT, sec. before therapy	17.00 (16.76-17.24)	1.44 (1.26-1.62)	13.16 (12.51-13.43)
After therapy	19.05 (18.41-19.68)	1.05 (0.72-1.38)	12.50 (12.01-13.38)
PI, % before therapy	112.18 (110.60-113.75)	8.48 (7.21-10.47)	00.56 (0.23-1.29)
After therapy	100.08 (97.41-102.74)	5.24 (2.92-7.55)	01.03 (0.01-1.59)
AF, % before therapy	135.95 (131.30-140.60)	13.80 (10.79-16.82)	00.15 (23.25-0.58)
After therapy	112.32 (105.90-118.73)	10.47 (7.92-13.03)	00.05 (22.08-2.50)
FA, min. before therapy	170.64 (165.10-175.82)	20.94 (1.51-5.16)	0.04 (23.26-0.40)
After therapy	130.46 (128.37-152.90)	10.09 (4.34-15.84)	0.23.11 (18.54-1.21)
HAT, 103/ml, % before therapy	110.63 (107.18-114.08)	3.34 (1.51-5.16)	00.15 (23.36-2.42)
After therapy	77.20 (74.35-80.04)	6.67 (4.58-8.76)	20.47 (19.33-22.28)
107/ml, % before therapy	137.63 (131.52-143.73)	12.21 (8.71-15.70)	00.40 (23.60-1.19)
After therapy	84.09 (80.01-88.17)	6.63 (3.47-9.78)	23.38 (19.35-21.55)
IAT, before therapy	1.24 (1.22-1.26)	-----	-----
After therapy	1.118 (1.103-1.132)	0.06 (0.03-0.09)	00.34 (23.05-1.27)

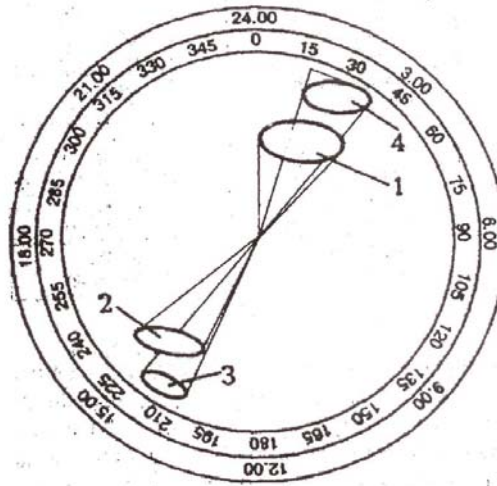
Pic. 2 Circadian rhythm of hemocoagulation parameters in patients with diabetic nephropathy on the 2nd grad before and after chronotherapy with trental

Parameters	MESOR	Amplitude	Acrophase
ACT A, % before therapy	33.499 (25.188-41.81)	-----	-----
After therapy	16.978 (16.363-17.593)	-----	-----
MC, % before therapy	86.774 (81.542-92.006)	-----	-----
After therapy	90.97 (89.32-92.61)	1.80 (0.04-3.55)	13.11 (9.06-19.06)
T, min before therapy	7.345 (6.875-7.815)	-----	-----
After therapy	9.756 (9.675-9.837)	-----	-----
IIT, before therapy	1.69 (1.62-1.77)	0.19 (0.10-0.29)	23.09 (22.08-0.59)
After therapy	2.09 (2.06-2.11)	0.04 (0.01-0.07)	12.52 (10.47-16.19)
ATIII, % before therapy	71.95 (67.94-75.97)	5.51 (3.86-7.16)	12.45 (11.06-14.16)
After therapy	98.53 (96.26-100.81)	4.02 (1.08-6.97)	12.50 (10.51-16.00)
SCFM, before therapy	1.55 (1.48-1.61)	0.56 (0.41-0.71)	22.55 (21.41-0.11)
After therapy	0.19 (0.04-0.37)	0.05	10.01
Fg, g/l before therapy	3.86 (3.35-4.38)	0.61 (0.44-0.78)	22.10 (21.32-23.33)
After therapy	2.84 (12.80-2.87)	0.19 (0.11-0.28)	22.51 (22.07-23.49)
TT, sec. before therapy	16.786 (16.194-17.377)	-----	-----
After therapy	22.29 (22.11-22.47)	1.06 (0.88-1.24)	12.07 (11.25-12.48)
PI, % before therapy	112.92 (106.09-119.74)	7.49 (3.13-11.85)	22.52 (21.42-0.07)
After therapy	85.54 (84.75-86.34)	3.43 (1.96-4.89)	23.51 (22.25-1.12)
AF, % before therapy	105.38 (94.86-115.90)	9.88 (4.94-14.81)	22.57 (21.36-0.03)
After therapy	96.33 (93.30-99.361)	9.67 (7.08-12.26)	21.48 (20.48-22.41)
FA, min. before therapy	138.810 (130.349-147.270)	-----	-----
After therapy	135.22 (131.44-139.00)	4.90 (2.16-7.65)	16.27 (12.32-18.57)
HAT, 103/ml, % before therapy	444.571 (295.340-593.803)	-----	-----
After therapy	82.30 (79.87-84.73)	4.16 (2.61-5.71)	19.36 (17.41-21.39)
I07/ml, % before therapy	610.893 (487.505-734.281)	-----	-----
After therapy	92.69 (89.44-95.64)	4.38 (2.01-6.74)	20.15 (17.45-22.16)
IAT, before therapy	1.52 (1.36-1.68)	0.18 (0.05-0.30)	22.31 (21.21-2.18)
After therapy	1.126 (1.114-1.139)	-----	-----

Pic. 3 CIRCADIAN ORGANIZATION OF HEMOCOAGULATION IN HEALTHY PEOPLE

Parameters	MESOR	Amplitude	Acrophase
ACT A, %	18.433 ± 0.159 (18.059 - 18.808)	2.457 ± 0.364 (1.871 - 3.043)	13.45 (13.18 - 14.12)
MC, %	91.183 ± 0.596 (89.866 - 92.500)	7.012 ± 1.177 (5.118 - 8.905)	14.12 (13.37 - 14.41)
T, min	9.892 ± 0.028 (9.826 - 9.958)	0.306 ± 0.072 (0.191 - 0.422)	00.51 (0.02 - 1.47)
IIT,	2.061 ± 0.006 (.049 - 2.073)	0.087 ± 0.015 (0.063 - 0.110)	01.46 (0.46 - 2.51)
ATIII, %	95.533 ± 0.895 (94.753 - 96.314)	8.235 ± 1.275 (6.185 - 10.286)	02.06 (1.11 - 2.59)
SCFM, units	0.252 ± 0.027 (0.198 - 0.305)	0.229 ± 0.075 (0.109 - 0.305)	12.38 (11.39 - 13.41)
Fg, g/l	2.463 ± 0.014 (2.431 - 2.494)	0.179 ± 0.020 (0.148 - 0.211)	14.19 (13.42 - 14.57)
TT, sec.	24.433 ± 0.088 (24.215 - 24.652)	1.570 ± 0.275 (1.127 - 2.012)	02.00 (1.14 - 2.44)
AF, %	89.867 ± 0.639 (88.450 - 91.284)	8.186 ± 0.987 (6.599 - 9.773)	15.33 (14.54 - 16.20)
FA, min.	137.717 ± 0.592 (136.468 - 138.966)	9.642 ± 1.482 (7.257 - 12.026)	14.44 (14.06 - 15.27)
HAT, 103/ml, %	85.975 ± 0.951 (83.861 - 88.089)	7.888 ± 1.561 (5.377 - 10.399)	13.60 (12.52 - 15.14)
I07/ml, %	95.667 ± 1.561 (92.206 - 99.128)	11.015 ± 1.887 (7.981 - 14.050)	14.04 (13.08 - 15.04)
IAT	1.138 ± 0.005 (1.126 - 1.150)	0.029 ± 0.006 (0.020 - 0.038)	13.57 (12.40 - 15.19)

Pic. 4 Cosinors of circadian organization of hemocoagulation in pts IDDM and healthy people.



1 - FG; 2 – TT in pts with IDDM; 3 – FG; 4 – TT in healthy people.  
Pic. 5 Cosinor of circadian organization of hemocoagulation in IDDM and in healthy.

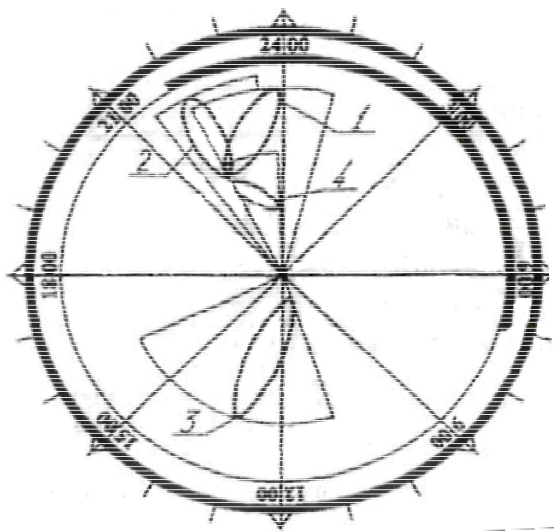


In pts: 1 – A; 2 – MA; 3 – T; In healthy: 4 – A; 5 – MA; 6 – T.  
Pic.6 Cosinor of circadian organization of hemocoagulation in pts with IDDM and in healthy people .



1 – A in 103/ml; 2 – A in 107/ml; 3 – IAT in pts with IDDM; 4 - A in 103/ml; 5 – A in 107/ml;  
6 – IAT in healthy.

Pic. 7 Circadian rhythm of hemocoagulation parameters (cosinor – analysis) in pts with diabetic nephropathy on the 2<sup>nd</sup> grad



1- ИТ; 2- Fg – before therapy; 3- ИТ; 4- Fg – after therapy

**CONCLUSION:** Patients with IDDM and nephropathy 1,2,3 grad severity were revealed hypercoagulation during 24h with its maximum at night. CT with trental is more affective therapy method, than TT and more economic CT led to normalization of circadian organization in hemocoagulation, which was not revealed in TT with trental. In CT trental influence on the more sensitivity phase of platelets aggregation.

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