



CO-ADMINISTRATION OF METFORMIN AND INTRANASAL INSULIN MORE EFFECTIVELY RESTORES THE METABOLIC AND HORMONAL PARAMETERS IN DIABETIC RATS IN COMPARISON WITH MONOTHERAPY

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Introduction

Metformin, a first-line drug for type 2 diabetes mellitus (DM2), restores metabolic and hormonal parameters by acting on both peripheral tissues and the central nervous system. Intranasally administered insulin (INI), which enters the brain directly, normalizes insulin signaling in the hypothalamus and other brain regions, impaired in DM2, and thereby improves the central regulation of metabolism, eating behavior and the endocrine system. We have suggested that co-administration of metformin and INI will enhance their restorative effects in DM2.

Objective

To carry out a comparative study of the restorative effects of separate and combined 4-week treatment of male DM2 rats with metformin and INI on glucose sensitivity and the plasma levels of insulin, leptin, glucagon-like peptide-1 (GLP-1), thyroid hormones and testosterone.

Methods and Materials

The study was conducted on Wistar male rats (n=30) divided into five groups, control (n = 6, Group C), diabetic (n = 6, Group D), intranasal insulin-treated diabetic rats (0,5 IU/rat) (n=6, Group Ins), metformin-treated diabetic rats (100 mg/kg) (n=6, Group M), and diabetic animals with combined treatment (n=6, Group Ins+M).

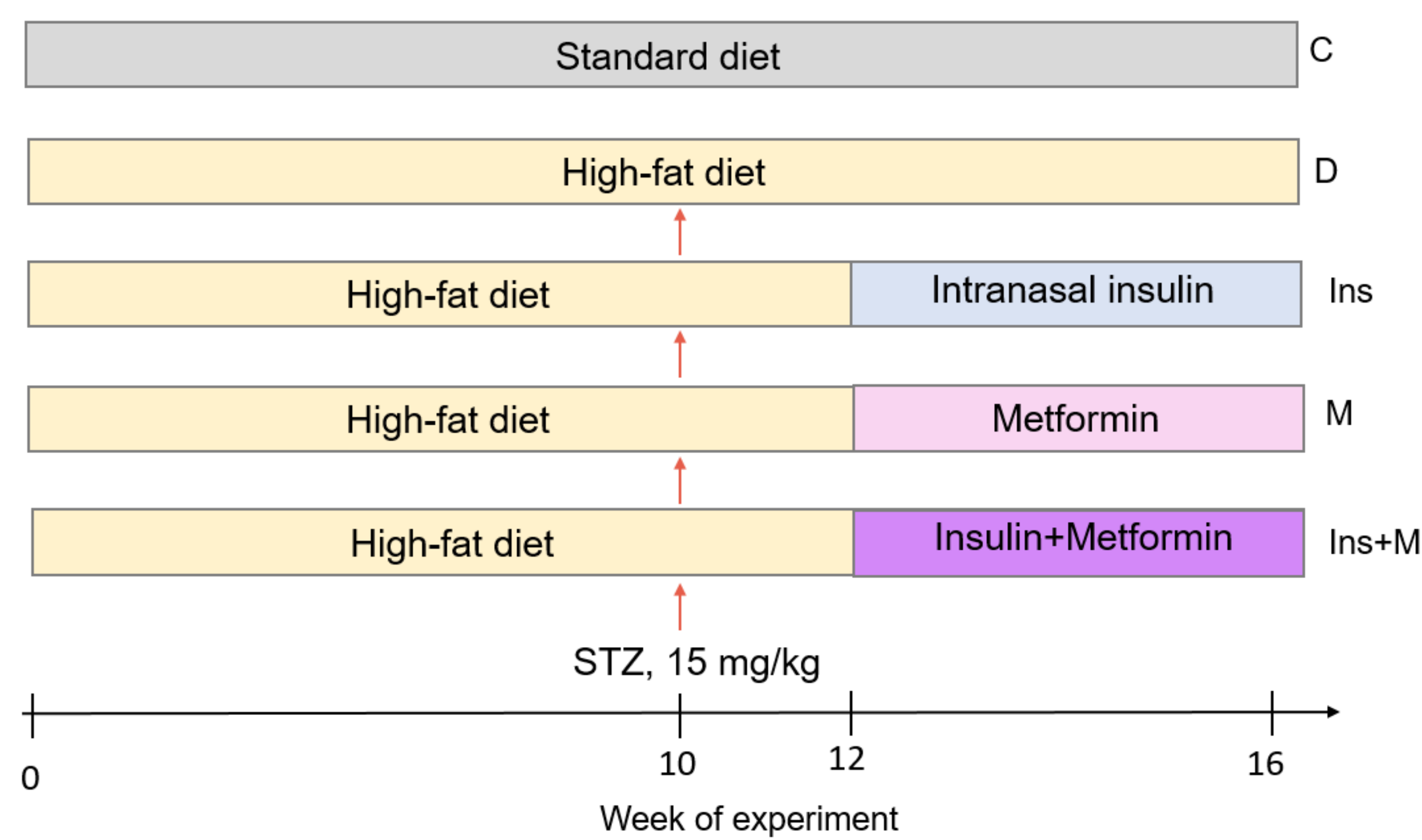


Figure 1. The design of HFD/low-dose STZ model of DM2 and the treatment of rats with metformin, intranasally administered insulin and combined treatment.

- OGTT test was performed before the administration of STZ and at the end of experiment.
- Blood samples were obtained from the tail vein. The blood levels of glucose, insulin, leptin, GLP-1, tT4, tT3, fT3, fT4, and testosterone were measured using ELISA kits.
- The statistical analyses were performed using the software IBM SPSS Statistics 23.0.0.0 ("IBM", New York, NY, USA).

Results

Figure 2. Glucose levels during OGTT in the studied groups at the end of experiment.

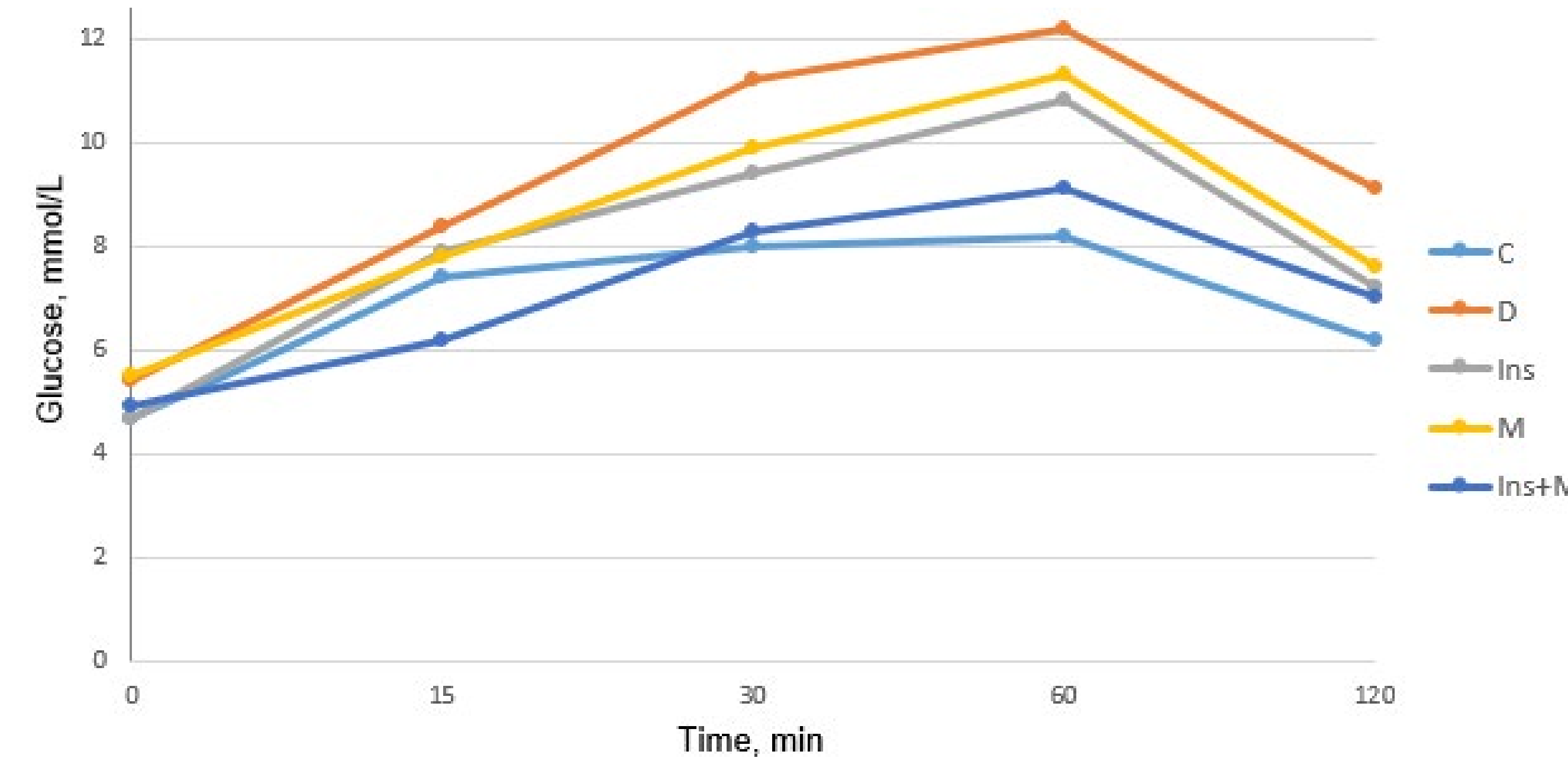
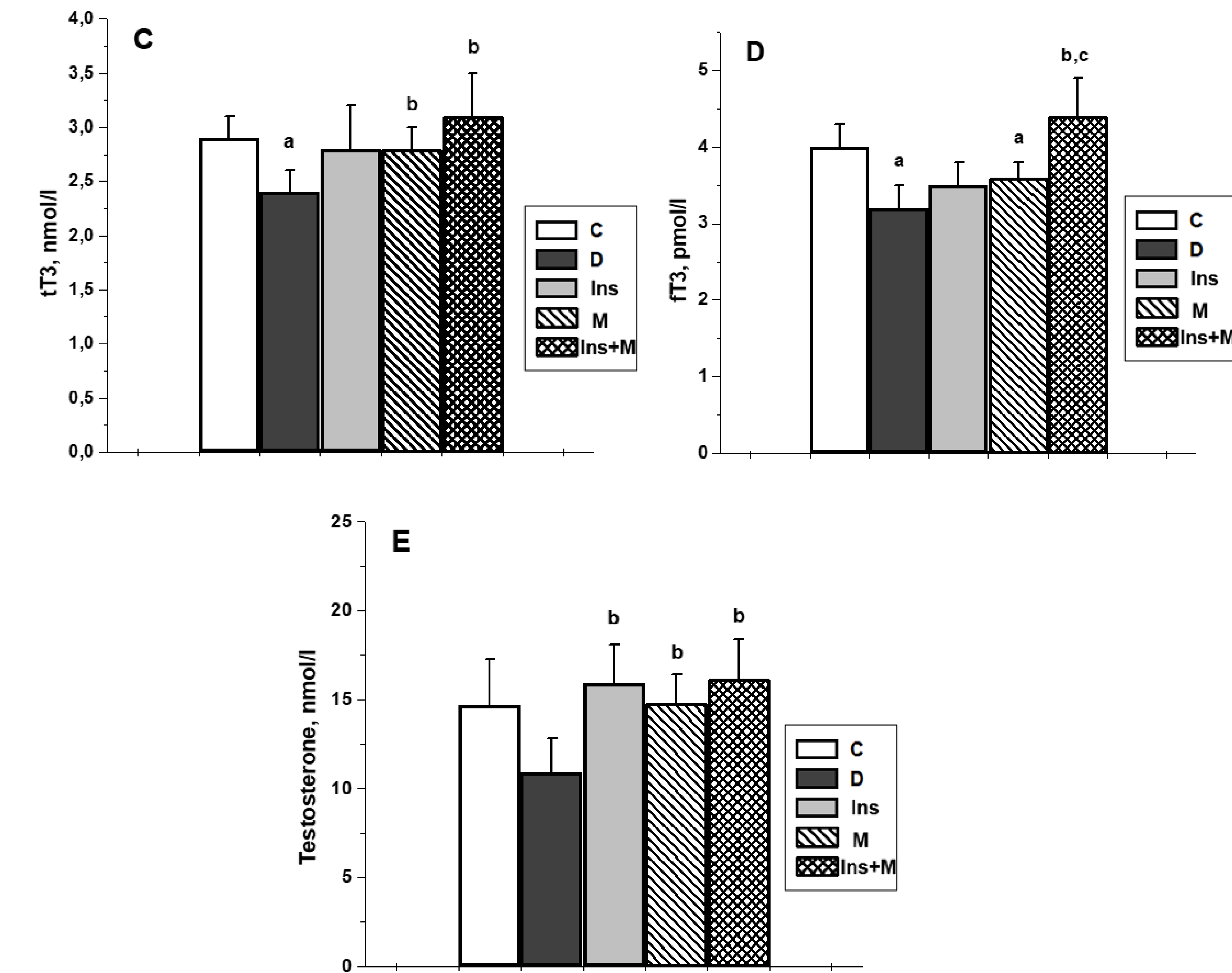
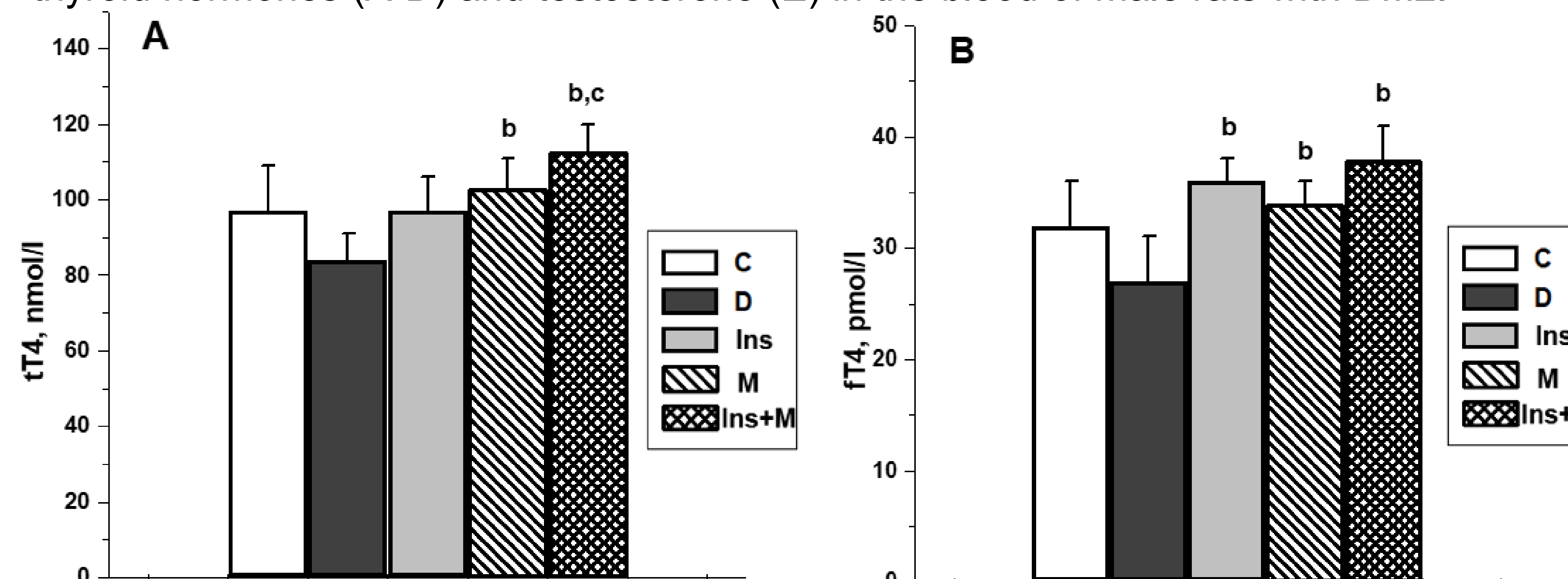


Table 1. Basal and glucose-stimulated plasma levels of insulin, leptin, and GLP-1 in OGTT in the studied groups at the end of experiment.

	Insulin, ng/ml		Leptin, pg/ml		GLP-1, pg/ml	
	0'	60'	0'	120'	0'	15'
C	0.57±0.05	1,86±0.11	3.73±0.23	5.54±0.48	22.71±2.07	45.18±2.71
D	0.87±0.14*	2.57±0.71	6.00±0.67*	10.66±0.45*	39.30±3.61*	40.69±2.93
Ins	0.70±0.07	2.39±0.49	5.43±0.27*	9.69±0.47*	31.48±4.53	55.37±4.62#
M	0.76±0.08*	1.78±0.15	4.45±0.20*#	7.07±0.46*#	33.13±3.76*	68.97±7.47*#
Ins+M	0.65±0.09	1.66±0.27	4.01±0.24#	6.10±0.26#	33.53±2.89*	59.04±2.50*#

The difference between C and D (*), and between D and treated groups (#) is significant at P < 0.05. M ± SEM.

Figure 3. The effect of metformin and intranasally administered insulin on the levels of thyroid hormones (A-D) and testosterone (E) in the blood of male rats with DM2.



a - differences between control and diabetic groups are statistically significant at p < 0.05; b - the differences between the D group and the diabetic treatment groups are statistically significant at p < 0.05; c - the differences between the DM and DMI groups are statistically significant at p < 0.05. Data are presented as M ± SD, n = 6.

Conclusions

The treatment of diabetic rats with a combination of metformin and intranasal insulin had a normalizing effect on metabolism and thyroid hormones, hyperinsulinemia and hyperleptinemia, glucose-stimulated levels of glucagon-like peptide-1, and led to restoration of testosterone production.

The data indicate that the combination of metformin plus intranasally administered insulin is promising for normalizing metabolic and hormonal disturbances in DM2.