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Differential Temperature Evolution for Insulin Delivery Monitoring in Type 1 Diabetic Patients before and after Kidney-Pancreas Transplantation

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Abstract

Continuous differential measure of the body temperature gradient (Dt = deep – superficial temperatures) and the use of its evolution for adequate insulin delivery monitoring was successfully tested in experiments and ICU patients (PDT-2014). The aim of the present study was to extend the method and the use of the Apparatus for Diabetes Diagnosis – Complex for Insulin Therapy (ADD-CIT) device to diabetic patients with severe glucose metabolism disturbances before and after pancreas-kidney transplantation. 134 investigations were provided on 108 informed and consenting informed patients (17- 61 years, DM-1, terminal nephropathy, haemodialysis, and no previous transplantation treatment: 38 before and 70 after pancreas-kidney transplantation). Blood glucose and Dt evolution were specially analysed. Results: before transplantation, ADD-CIT treatment (applied when traditionally performed insulin therapy was no more efficient) has allowed some patient condition improvement unless radical treatment could be realized (mean glucose level decrease from 17.2±5.18 to 9.72± 5.2mmole/l within 4 hours). After transplantation, the programmed insulin pump was frequently deactivated, corroborating surgery success (stable mean glucose level 6.7±3 mmole/l and Dt during 3 hour observation, normalization of kidney and pancreatic function indices). Only 23 CIT sessions (14 patients) were provided which ever corresponded to transplant failure. Postsurgery Dt values were generally decreased with frequent negative ciphers that may be explained by the operation trauma influence. So, in spite of the absence of control patients without ADD-CIT treatment (ethically uncomfortable), the "energetic" feedback for insulin therapy of critical diabetic patients seems "not worse", interesting and opening perspectives.

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Abbreviations

ADD-CIT - Apparatus for Diabetes Diagnosis – Complex for Insulin Therapy, BW – Body weight, °C – Centigrade degree, DM – Diabetes mellitus, DM 0 – no diabetes known, DM 1 – type I diabetes, DM 2 – type 2 diabetes, Dt – Difference of temperatures between core and subcutaneous layer of the body, ICU – Intensive Care Unit, K-P Tx – Combined kidney and pancreas transplantation, mg/dl – milligram/decilitre, mmole/l – milli moles per litre, Tc or Ti – Core or internal temperature, TCKI - Terminal chronic kidney insufficiency, Ts – Superficial temperature

Introduction

In spite of intensive investigations and recent engineering proposals including so-called artificial pancreas, aiming at reducing the risk of hypoglycaemia episodes and yo-yo phenomenon during insulin therapy in Diabetes Mellitus patients, the problem remains recurrent [1-7]. In all the cases the only criterion of efficacy used is the blood or subcutaneous glucose determination. By the way, as several authors had noted, blood glucose level is not in phase with the energetic needs of the body, so the correction is started a little late and may be extreme [8-9]. Direct measure of the energetic of the organism which is insured for 70% by glucose utilization [10], could be realized by basal metabolism evaluation, and would better reflect the organism needs in insulin and glucose. But presently the procedure is no longer performed and not feasible in current clinics conditions. Indirect representation of the energetic balance evolution could be more timely reflected by the evolution of the difference between the body core temperature and the temperature of the body superficial layers, that we have called Dt = Tc – Ts [11]. The concept was developed and a device was elaborated, called "Apparatus for Diabetes Diagnosis – Complex for Insulin Therapy (ADD-CIT) [12-14]. They were successfully tested at different occasions and recently in a group of critical ICU patients with major glucose metabolism disorders [15-18]. The aim of this present work is the report and the analysis of the results of extending the ADD-CIT use in critical diabetic patients before and after kidney-pancreas transplantation.

We report here the results obtained when ADD-CIT was used in critical DM 1 patients before and after kidney-pancreas transplantation.

Material and Methods

The ADD-CIT device was described in previous work [15, 18]. The device schema and the session design are presented in figure 1a and figure 1b.

Shortly, the rectal catheter, enclosed into a thin, hermetic, waterproof and disposable polyethylene membrane, has a 4mm diameter, two temperature sensors at 4.5 cm from each other. The inner sensor being at the top of the catheter is placed at the level of the deep haemorrhoidal venous plexus and registers the core temperature (Tc) reflecting thermogenesis. The lower sensor is situated just above

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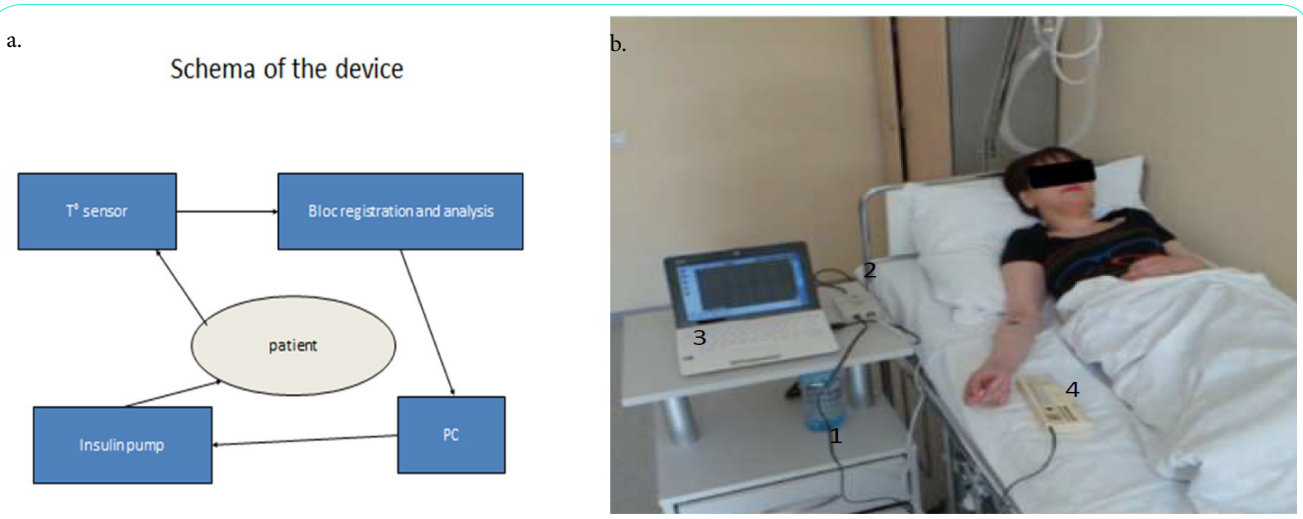


Figure1: a. Schema of the ADD-CIT device, b. Patient during an ADD-CIT session. 1. Catheter with temperature sensors, 2. Temperature data analyzer, 3. Computer programming the insulin pump on the basis of Dt evolution, 4. Insulin pump.

the external anal sphincter and reflects the superficial temperature (Ts) of the subcutaneous para-rectal fat. The catheter is fixed in place thanks to an enlargement of its external layer in form of an 8 mm diameter globe. The sensors data are cabled to an analyser which calculates Dt and the information is delivered to a computer. The evolution of Dt is considered for the elaboration of a program which is transmitted by the computer to an insulin pump adapted in consequence. Insulin – Aktrapid® or Humulin®, that is of rapid action, diluted to 20 or 40 UI/ml, is delivered through a short (<20 cm) catheter to the patient venous access to avoid insulin adsorption and degradation. Insulin delivery might be operator programmed (30 impulses/min usually during 30 minutes at the session beginning while sensors adapt) or automatized according to Dt values evolution. 1 impulse of the pump represents from 0.0003 to 0.001 UI depending on the insulin pre dilution. The program regulated the number of impulses/min. A visual control of the Dt, Tc and Ts values in °C, of insulin delivery impulses number is ensured through the computer. In case of low glycaemia or sudden decrease of Dt, 20% glucose was added in the perfusion.

So during an ADD-CIT session, insulin delivery depended only on Dt continuous evolution, glycaemia being determined every hour for information (and control).

From 2001 to 2016, 108 patients with diabetes mellitus (keyword 2) type 1 (DM 1) and 13 healthy persons (control) have participated to the study, after informed consent. In several cases sessions were repeated one or more times at different moments, so 134 sessions were performed in DM 1 patients and 13 in healthy persons (Table 1). Seven patients were investigated before and after their operation. One healthy patient has performed 10 minute physical exercise (gymnastics) in the middle of its session.

Criteria of inclusion were:

- Severe DM 1 with terminal kidney chronic insufficiency requiring haemodialysis, no efficacy of traditional treatment (blood glucose level higher 11.1mmole/l during 24 hours), necessity to optimize the patient's condition before kidney-pancreas transplantation (K-P Tx),
- Request of the endocrinologist or the surgeon to control the patient after transplantation,
- Age > 16 years
- Sex male or female
- BW > 40 kg
- Gravidity < 3 months

Criteria of exclusion were:

- rectal ulcerations,
- severe haemorrhoid inflammation,
- concomitant acute severe pathology (gangrene, sepsis, infarct))
- Absence of patient's consent,
- Age < 16 years,
- Gravidity > 3 months.

The investigations were performed in a hospital (ICU) room (VN Sklifosovski Institute of Emergencies, Moscow, Russia) in maximally standardized conditions: hospital room with an ambient temperature of 2I±1°C (in order to avoid temperature variation bias), under the control and responsibility of an intensive care physician. After receiving the patient's own informed consent or his family's, the responsible physician mildly introduced the catheter with the sensors into the rectum at a depth of 6.5 cm (mark on the catheter).

Series	Number of patients / sessions	Sex M/F	Age (years) M±SD (Max, min)	BW (kg) M±SD (Max, min)	Height (cm) M±SD (Max, min)
Control: healthy persons	10 /13	4/6	35.15 ± 8.3 (23-50)	62 ± 11 (60-110)	171.9 ± 9.89 (160-185)
Terminal CD1	108/134				
Before transplantation	38/49	16/22	32.9 ± 9.5 (21-61)	60 ± 9.98 (43-83)	164 ± 7.9 (151-182)
After transplantation	70/85				
Successful (ADD only)	56/62	30/26	36.8 ± 6.9 (21-55)	21-55) 58.5 ± 8.6 (41-83)	166 ± 7 (150-181)
Unsuccessful (ADD+CIT)	14/23	8/6	36.1 ± 6.1 (16-60)	61.4 ± 8.8 (46-71)	166.3 ± 5.5 (158-174)

Table 1: Characteristics of involved persons in the present retrospective test study.
Max: the highest value; Min: the lowest value

The intravenous insulin injection line was connected to the patient's perfusion system (Figure 1b). Usually patients did not receive any food except standard hospital meal in conscious patients when session duration exceeded 4 hours.

At the end of the session, rectal catheter was carefully taken out the organism and pump delivering insulin removed. When necessary, further insulin treatment was provided by usual methods under endocrinologist supervision.

Usually, the session duration varied from 2 to 5 hours, depending on the rapidity of the patient's condition improvement. Sometimes it lasted up to 6-10 hours, though previous observations have shown that more prolonged sessions are useless [18]. The session could be interrupted in the case of emergency procedures, defecation or anal discomfort (the last was not observed in this trial). The criteria to end a session were the objective fall of blood glucose to a level < 11.1mmole/l and/or a Dt >0.05°C with subjective improvement of the patient's condition.

Investigations

Evaluation of the capillary or arterial glycaemia was performed hourly by strip method (One Touch, USA) and controlled every 3 hours by arterial glucometer ("Glucose and lactate Analyser", Eco Basic United, Moscow).

Glycaemia was considered as normal if included between 3.88 and 7.7mmole/l (70 and 140 mg/dl), increased but acceptable between 7.71 and 11.1mmole/dl (141 and 200 mg/dl), moderately high between 11.11 and 15.0 (200 and 270 mg/l); high between 15.1 and 20.0mmole/l (270 and 360 mg/dl); very high between 20.1 and 25.0 (360 and 450 mg/dl); threatening high > 25.1 (> 450 mg/dl). The highest glycaemia observed was 33.1 mmole/l (600 mg/dl).

On the basis of previous works, Dt < 0.05 and > 0.2°C was considered as abnormal.

1. Dt at hour 0, i.e. at the moment of introducing the rectal catheter, could not be registered because a 30 min time is necessary for adaptation of thermic sensors to organism conditions. So initial Dt value considered in the graphics is the measure made after the first hour, corresponding to the glycaemia at hour 1.

2. Though insulin delivery (number of the pump impulses) was registered every minute, in this study only the total amount of insulin delivered during the session was taken into account and the quantity per Kg BW calculated. The dose delivered every hour was not calculated and will be the topic of further studies.

The patients underwent the usual in ICU clinic investigations (evaluation of kidney, pancreatic and liver functions, hematologic and coagulation tests, ECG, blood pressure monitoring). We observed them just before and during the ADD-CIT procedure, after what they returned to ICU responsibility or were transferred into other units. Late observation was rarely provided by our teams.

Results are presented as Average or Mean ± Standard Deviation (M± SD) calculation and Td against Tst Student criterion was used for determination of liability (p).

Our investigations were allowed by the Health Ministry of Russian Federation.

Results

The results of our investigation are summarized on table 2.

Control series performed on 10 healthy persons (13 sessions) has shown, that mean blood glucose levels varied during the 6 hour observation between 3.98 and 5.89 mmole/l ± 0.5 – 1.2 mmole/l (Figure 2a). Mean Dt values were situated between 0.20°C at the beginning of the registration and 0.05 °C 3 hours late . Trends to Dt decrease during the session end was noted, but Dt was never <0 in usual situation. In a fasting person 3 last measures after 3 hours indicated a weak negative value. In case of intense physical exercise without external nutritional supply, Dt has quickly fallen and remained < 0 during the whole exercise period (Figure 2b).

Before transplantation of a kidney-pancreas complex, ADD-CIT treatment applied to 38 DM1 patients with terminal chronic kidney insufficiency (TCKI), severe multi organ functional failure, has allowed to decrease significantly blood glucose levels from 17.2±5.18 to 11.6±7.29 mmole/l that is 32.5 % of the initial value within the first 3 hours and 43.5 % after the 4th*. Dt in these patients was generally < 0 (table 2, Figure 3a). Only 2 patients have had no benefit from the session, their glycaemia remaining very high (> 20 mmole/l) after 6 and 8 hour session. The number of hypoglycaemic episodes was low (4 out of more than 200 measures), their intensity was weak, (exactly: 2.9; 3.25; 3.35 and 3.52 mmole/l) and duration less than 1 hour: they were corrected at the next observation delay and not followed by hyperglycaemia (Figure 3b).

The amount of insulin delivered during sessions has varied from 8 to 140 IU, the dose/kg BW – from 0.29 to 1.69 UI - but some sessions have prolonged up to 9 hours. In most of the cases the improvement of the patient's general condition after the sessions was stable enough unless radical surgery could be realized.

After transplantation, the patients could be divided into 2 groups according to the issue of the operation and the results of investigations (Table 2). In the first group (56 patients, 62 sessions), the programmed insulin pump was deactivated, corroborating surgery success, and mean glucose level (6.7±3mM/l) was stable during 3-4 hour observation (Figure 4a). Dt was also stable in each patient, but its values were individual and varied considerably from one patient to another, being often low even < 0, especially when the investigations were provided in the early post operation period (1-15 days). The 23 CIT sessions provided in 14 patients of the second group corresponded to graft failures. In these cases, application of ADD-CIT treatment has allowed normalization of glycaemia within 2-4 hours (Figure 4b), except 2 cases when glycaemia remained high (13.9 and 18.9mmole/l). Hypoglycaemia was not observed. The amount of insulin delivered during the sessions varied between 8 and 60 IU, the dose/kg BW – from 0.18 to 0.87 UI. Later the patients went back to traditional treatment.

During the study, a device failure during session was noted twice, when the pump function has stopped. The insulin delivery was immediately continued according to standard schedule under ADD control.

*If we considered only the cases when ADD-CIT sessions were productive, the average glycaemia decrease was even more important and reached 47,6±24.1% after 3 hours, 49.3±24.13% after 4 hours of the ADD-CIT session.

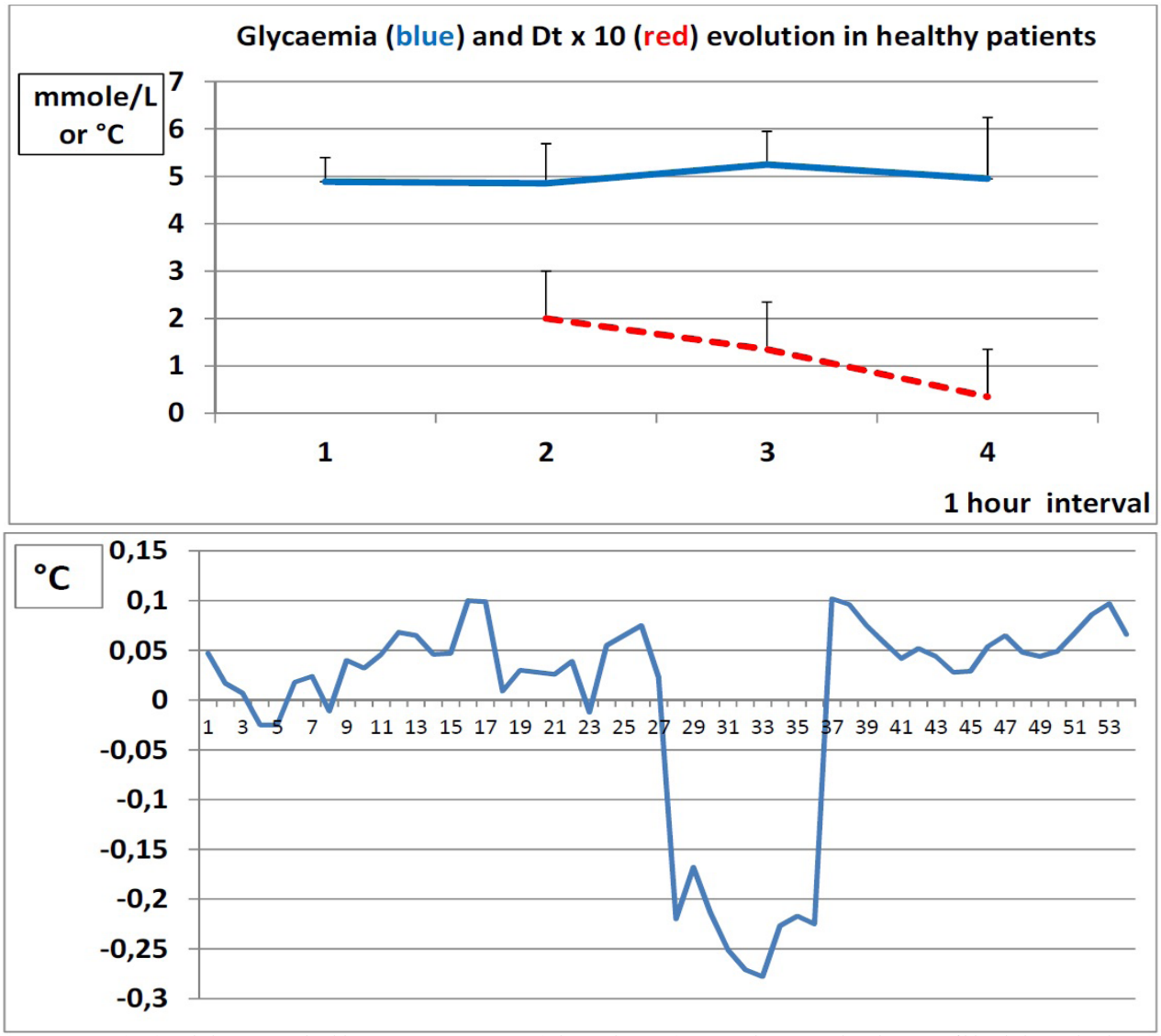
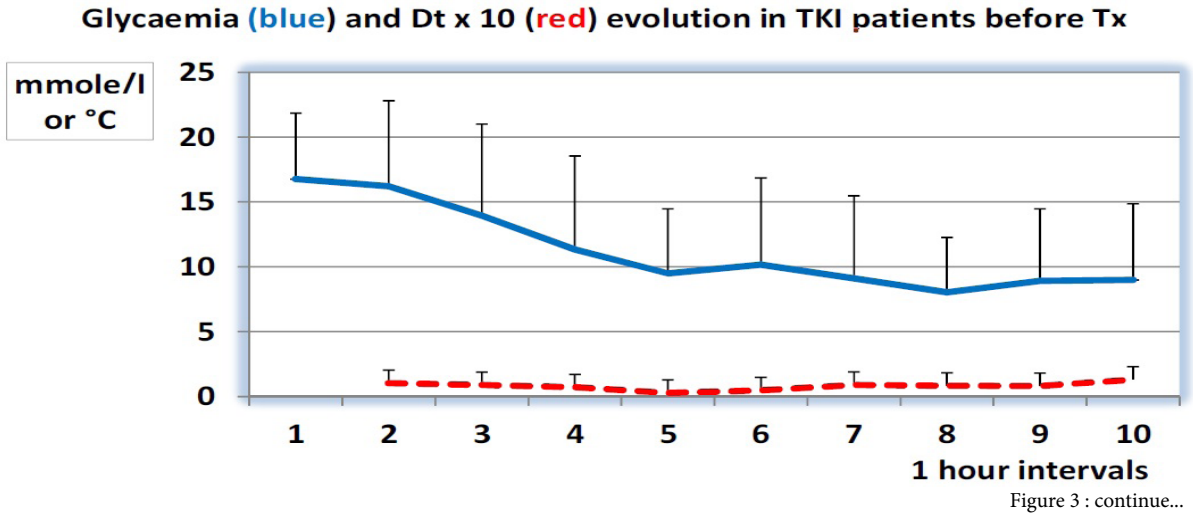


Figure 2: A. Dt (x10) and glycaemia in healthy persons ADD session (6 hours duration). No insulin required. A decrease of blood glucose level (M±SD) and of Dt (x 10) (M±SD) is observed, probably due to lack of food supply. B. Dt registration in 32 years male: during min 25 to 35 – intense physical exercise and fall of Dt values. (Ordinate: mmole/l or °C, abscissa – 1 hour intervals).



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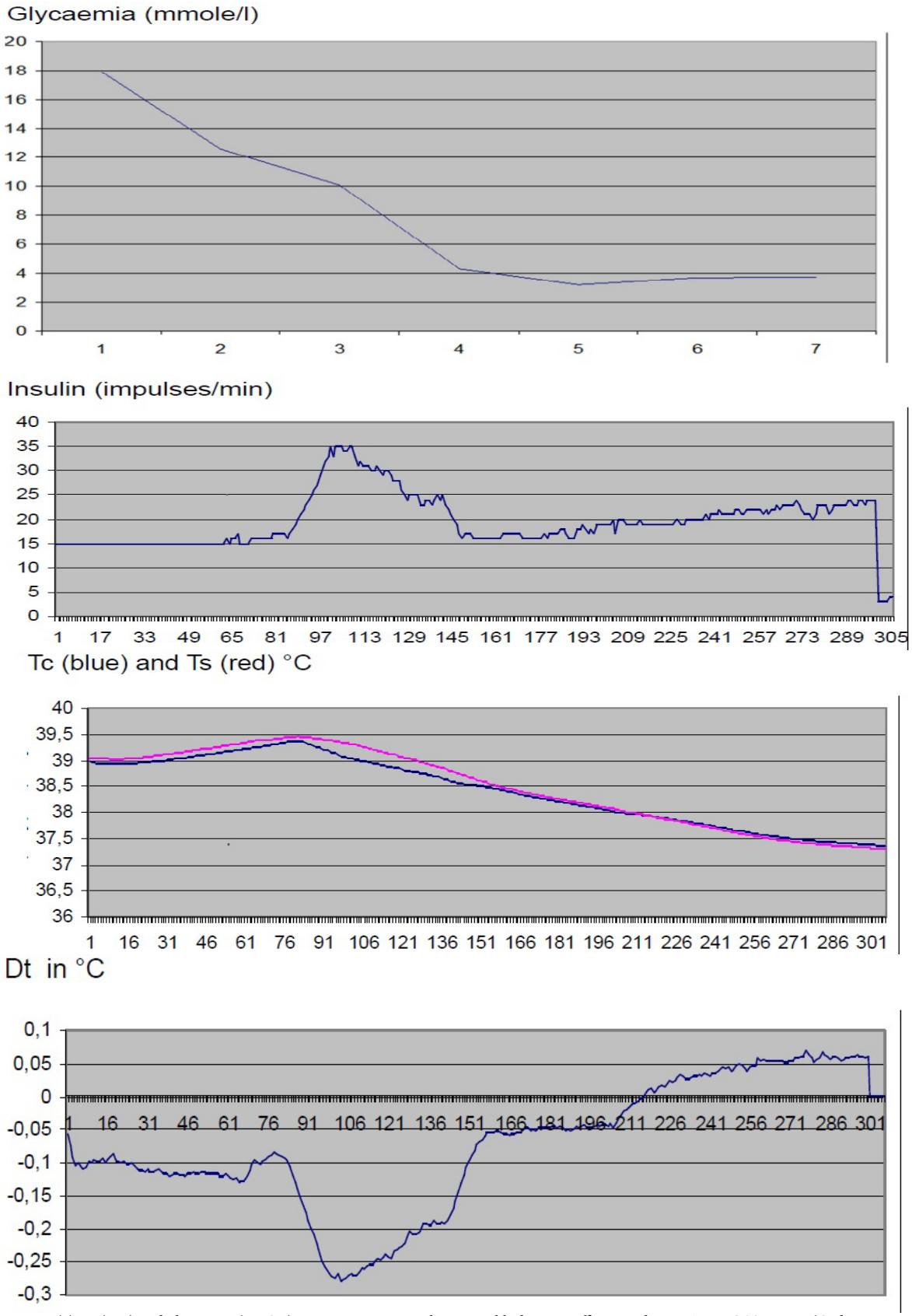

Figure 3: (a) Dt (x10) and glycaemia (M±SD) in DM1 patients with terminal kidney insufficiency during ADD-CIT session (Ordinates: mmole/l or °C, abscissa – 1 hour intervals). (b). Blood glucose and Dt (x 10) in DM1 terminal Kidney insufficiency patient Z (female 24 years) before K-P Tx transplantation (ordinate – mmole/l or °C; abscissa – hour intervals).

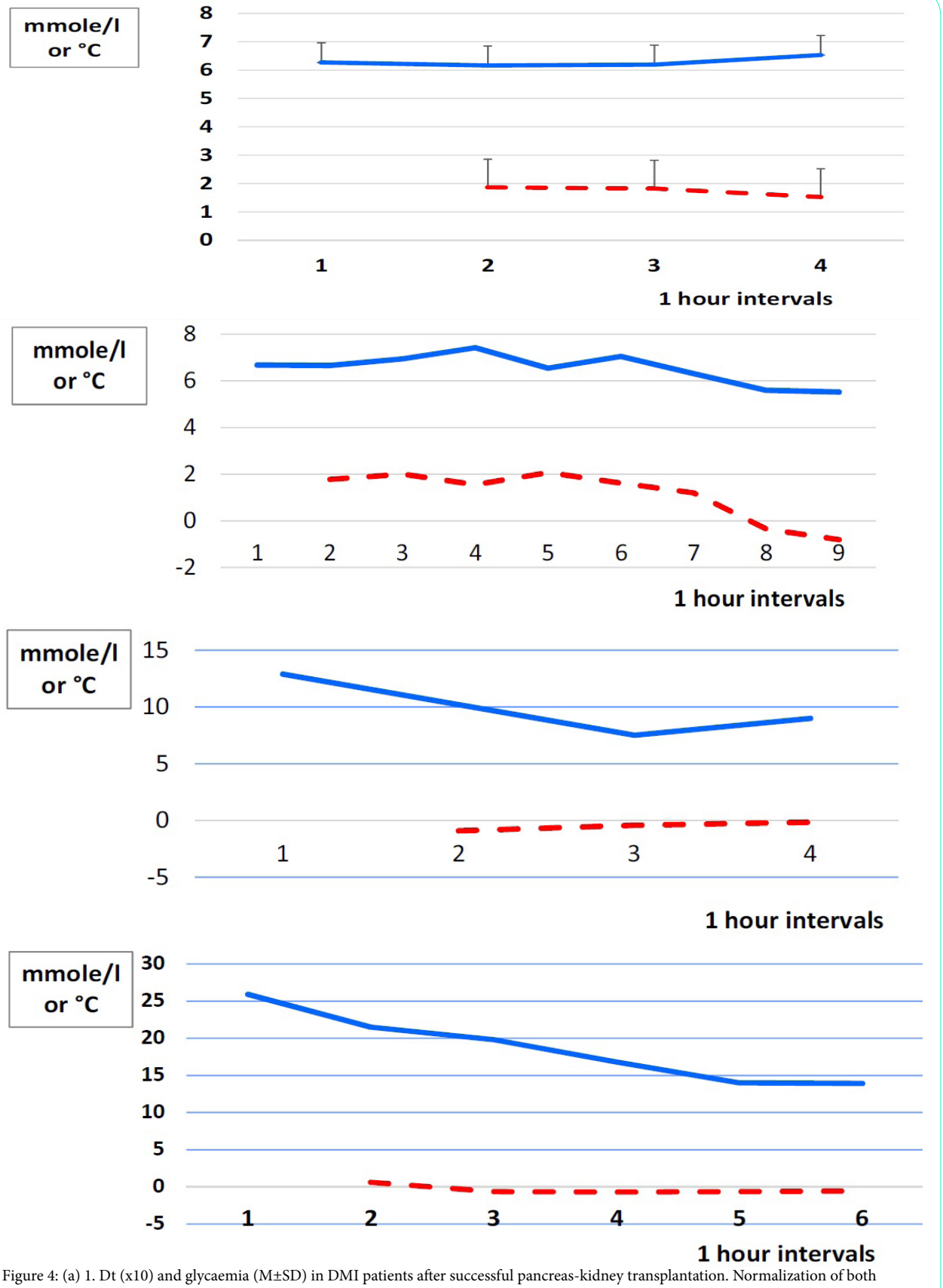

Figure 4: (a) 1. Dt (x10) and glycaemia (M±SD) in DMI patients after successful pancreas-kidney transplantation. Normalization of both indices, no need for insulin injection. 2. Case report of a patient with normalized blood glucose and Dt evolution. (b) Glycaemia and Dt in some patients with unsuccessful kidney pancreas transplantation (Ordinate - mmole/l or °C, abscissa – 1 hour intervals.)

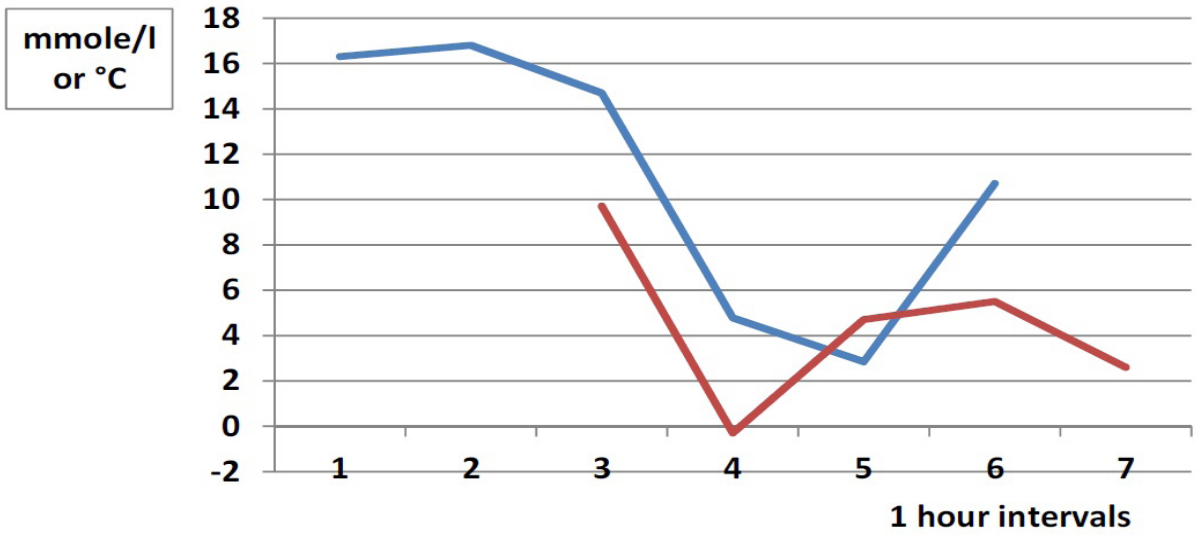

Figure 5: Example of the predictive signification of Dt decrease for hypoglycemia prevention or early correction (Ordinate - mmole/l or °C, abscissa – 1 hour intervals).

Diagnosis and number of investigations (N)	Initial Blood Glucose (mmole/l, M±SD)	Blood Glucose (mmole/l, M±SD) after 3 h (decrease relatively to initial value)	Blood glucose (mmole/l, M±SD) after 4 h (decrease relatively to initial value)	Number of hypoglycaemia events	Insulin dose required by session: minimal – maximal (IU/kg BW)
DM1+TCKI before P-KTx (49)	17.2±5.8	11.6±9.41 (32.5 %)	9.72±5.2 * (43.5 %)	4	0.29 – 1.69
DM1+TCKI after P-KTx: group 1 (62)	6,0±2.0	6.18±1.22 (ns)	6.79 ±1.16 (ns)	0	No insulin required
DM1+TCKI after P-KTx: group 2 (23)	16.05±4.96	10.53±5.07 * (34.4%)	not investigated	0	0.18 – 0.87
Control (healthy) (13)	4.86±0.50	4.05±1.29 (16.6%)	3.98 ±0.61 (19%)	2	No insulin required

Table 2: Results of the investigations.
*p<0.05 - is calculated for the mean values of the glycaemia after 3 or 4 hour session comparatively to initial ones.

Discussion

In severe decompensated and complicated DM 1, when traditional methods were failing, the use of ADD-CIT was efficient: mean glycaemia fall of 32.5% within 3 hours and if considering only cases when ADD-CIT use was successful the glycaemia fall represented 47.6%, very rare hypoglycaemia episodes (4 before transplantation, 0 after K-P Tx), no yoyo phenomenon .This has allowed bridging the patients until transplantation. The fact that the main results of the sessions were obtained during the first 4 hours (figure 3 and figure 4) confirms our previous observations [18]. It may be mainly explained by the negative influence of many hour immobilization especially if the patient was conscious. The amount of insulin necessary by one session does not seem to differ significantly from usual doses traditionally required in similar situations and depended mainly on initial glycaemia level. But it would be interesting and useful to calculate for each patient the dose required at each hour of the session, its evolution and correlation with other factors, as far as insulin delivery is supposed to be more adequately linked with the organism needs. This requires particular conditions of session providing and would be the aim of further investigations.

Another limit of this work is, indeed, the absence of control randomized series, not provided because ethically not comfortable. This has diminished the possibility to compare "energetic" feedback and ADD-CIT to other methods and devices of DM1 treatment. And we know that considerable success were obtained especially in artificial pancreas, which has provided a long lasting permanent insulin administration by programmed pumps, able to prevent predicted or exactly calculated probable night hypoglycaemia /19, 20 /. Prevention of hypoglycaemia events is also important for the patient mental condition /21, 22/. Nevertheless the problem of yo-yo and hypoglycaemia has not been completely resolved yet.

One of the reasons might consist in the use of blood level measure as unique reference criterion. Some authors has pointed /8, 9 /, and we have confirmed (figure 3, figure 4) that glycaemia is about 1 hour late relatively to the real needs of the organism. That means: when hypoglycaemia is detected, the tissue starvation for glucose has been existing during about 1 hour. Dt seems better adjusted as shown in figure 5. The explanation may be that Dt evolution reflects the combustion process, whereas glycaemia shows the combustible amount left. It is not quite resolved in our study: at the end of sessions glycaemia fall was sometimes critical. We have observed that especially

when sessions, prolonged more than 4 hour, Dt often decreased whereas glycaemia levels remained stable. At this moment glucose injection allowed to correct the situation. Then a question arises: is it possible to link glucose infusion directly with Dt evolution too and to program glucose delivery in the same way it is realized for insulin? Moreover, if Dt values correspond to a certain energetic level, the determination of their evolution may be an indicator of the patient glucose metabolism disorders. This was confirmed by the investigation of the patients before and after transplantation: Dt abnormal values (decreased or increased, /14/) and especially their trends were in correlation with clinical decompensating. Negative values of Dt were present in a significant part of the patients after successful K-P Tx, whereas their laboratory indices including blood insulin and glucose were apparently normalized: has this phenomenon to be considered as an alarm sign? The observation may be explained by surgical trauma consequences, immune depression treatment influence, or reflects the persistence of the graft micro injuries, as suggest some authors /23/, and deserves further attention. Dt negative values also occurred in healthy patients, but only in case of starvation or intensive physical exercise (figure 2b, [18]). We have also to remark that negative values of Dt may be not only the consequence of Tc fall following glucose metabolism decrease due to reduced insulin production, as in DM 1. It may be also caused by Ts elevation*. Interesting that in the first evaluations of DM 2 patients Dt seemed to be increased (see [14], that is a challenge.

The question whether variations of the external (ambient or local) or internal (fever, antipyretic drugs use) temperature may influence Dt of a patient deserves special investigations. Previous partly published our experiments [24] have shown that warming or cooling the whole body or a part of it can cause Dt variations either by increasing Ts and decreasing Tc or decreasing Ts and increasing Tc, and that such effect varies during the observation time, depending on the organism capacities of reaction. In order to avoid this possible bias in this study the conditions of session providing were maximally standardized: controlled ambient temperature, patient laying in a bed under light cover, standard perfusion, and standard feeding in case of long lasting sessions, no antipyretic drugs administration. We have also to remind that the proposed feedback is not based on an evaluation of absolute temperatures but on the evaluation of the variations of their difference which is supposed to reflect a functional process : glucose metabolism. At last it is necessary to note that presently ADD-CIT is applicable only to acute situations in ICU, not in the case of chronic treatment. Thus is it possible to consider adaptation of "energetic feedback" to insulin pumps?.

So ADD-CIT device seems to be worthwhile further investigations directed to its use extend to any other situations of hyperglycaemia even in DM 0 patients, as well as for chronic DM 1 and DM 2 insulin requiring patients treatment. It might be also used as a tool for the study of diabetic patient energetic peculiarities.

Conclusion

The body temperature gradient evolution (Dt) or "energetic" feedback constitutes a new complementary approach to the monitoring of insulin therapy of DM patients. Applied in ADD-CIT device for critical diabetic patients treatment, it seems to be at least "not worse" than presently proposed sophisticated methods and devices: it has allowed acceptable hyperglycaemia decrease within 2-4 hours, reduction of hypoglycaemia episodes, in quantity as well as in intensity, and avoiding yo-yo phenomena.

Up to now ADD-CIT use has been applied only to ICU patients during a limited session time. Sessions may be repeated but permanent use is not possible in the present version of the device ADD-CIT. Nevertheless adaptation of the "energetic" feedback concept to insulin pumps might be considered.

The diagnostic value of Dt levels and their evolution seems to be confirmed by their corresponding to the results of the patient's other clinical investigations, as well as by observations in healthy persons. It might be a diagnostic sign of glucose (or more generally, energetic) metabolism impairment, that might be worthwhile further studies.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

V.N.Novikov: design, acquisition of data, analysis and interpretation of data, involvement in drafting and critically reviewing the manuscript.
Iu. Anissimov; acquisition of data, analysis and interpretation of data, participation to the
drafting and reviewing the manuscript.
I.Dmitriev: acquisition of data, analysis and interpretation of data, participation to the
drafting and reviewing the manuscript.
V.Coulic: design, analysis and interpretation of data, involvement in drafting and critically
reviewing the manuscript for important intellectual content.

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