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Clinical Evaluation of Decision Support System for Insulin-Dose Adjustment in IDDM

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Objective: We developed a wallet-sized learning memory decision support system that helps patients with insulin-dependent diabetes mellitus adjust their insulin dosages. Research Design and Methods: To determine the efficacy of the support system, we designed a randomized clinical trial with patients participating in a program in a diabetes education center. Patients were assigned to two groups of 21 patients each. All patients performed self-monitoring of blood glucose (SMBG) and were treated with multiple daily injections of insulin. Each of the patients was examined over a 32-day period. The basic educational program, i.e., practical advice in SMBG, diet, and exercise under homelike conditions, was identical in both groups. The only difference was that the first group used the computer for adjusting the insulin dose, whereas the second group received recommendations from the education team. Results: The baseline HbA_1 levels (9.8 ± 1.6 vs. 9.9 ± 1.6%) of both groups did not differ significantly. Mean blood glucose over the last 2 wk of the study was higher ($P < 0.01$) in the second group (8.4 ± 1.4 vs. 9.2 ± 2.0 mM); the frequencies of hypoglycemic episodes were not different (1.7 vs. 2.3%). Conclusions: Metabolic control and safety were comparable in both groups. Thus, patients may benefit from such a system at home where no support by diabetes educators is available. *Diabetes Care* 14:875–80, 1991

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Various sets of computerized algorithms (1–9) have been applied as therapeutic guidelines in the self-monitoring of blood glucose (SMBG; 10) in insulin-dependent diabetes mellitus (IDDM). Essentially, these algorithms intend to imitate the decision-making process of experienced diabetes educators. However, it seems that a considerable analytic effort, by means of the control theory (11,12) and mathematical modeling (13), is necessary to come close to the quality of human empirical decision making.

In this study, we compared two groups of patients participating in an educational program for intensified insulin therapy in a diabetes education center. Basically, the program was identical in both groups. However, the patients received different decision support in adjusting their insulin dose. The personal explanations by an education team in one group were substituted by the use of a decision-support system called *learning memory* in the other. We hypothesized that metabolic control and safety would be comparable in both programs.

RESEARCH DESIGN AND METHODS

The input variables included the actual blood glucose, observed hypoglycemic episodes, estimated carbohydrate content, physical activity (score 0–5), and time of day and date taken from a hardware clock. The output variables were the basal insulin dose (NPH injection) and the regular insulin dose (regular injection), which were recommended by the system.

The concept of the system is based on algorithms designed to control the blood glucose in a near-normoglycemic range (see Appendix 1) and on a statistical

glucose-insulin model (see Appendix 2). The model determines insulin requirements for extra carbohydrates and physical activity in the individual patient. The applied control algorithms were derived from Skyler et al.'s algorithms (14,15). For the design of a control system, these algorithms have been modified according to the principles of engineering optimum control theory (11,12). The complete sets of algorithms have been tested in >10,000 simulated situations with a metabolic simulator before testing them in patients (17).

Data input and output were based on a planning-learning concept. Each of the four intervals (morning, afternoon, evening, night) consisted of a planning phase in the beginning and a learning phase at the end. In the planning phase, actual blood glucose, planned carbohydrate intake, and planned physical exercise for the next 4–6 h were estimated prospectively and entered into the learning memory system. In the learning phase at the end of the interval, the patient entered the resulting blood glucose. The patient may have improved the system's recommendations by identifying implausible values (e.g., if the resulting blood glucose has been influenced by factors like sauna or alcohol). Implausible values can be excluded from learning. Based on the data recorded during planning and learning phases, the system addressed the following questions: *1*) How should the insulin dose be adjusted to keep blood glucose in a near-normoglycemic target range? and 2) Are insulin supplements necessary in this individual to compensate for the effect of carbohydrates and physical activity? The learning memory system condenses the information of all recorded data and recommends an insulin dose range (e.g., regular 7–9 U) in the subsequent planning phase. The final decision (e.g., regular 7 U) is left to the patient.

We designed a hardware prototype of the learning memory system especially for diabetes management (20). Technical data consisted of 128 kbytes ROM, 128 kbytes RAM, a two-line display, three keys (increment, decrement, return) for simple ergonomic handling, real-time hardware clock, and data interface RS 232.

TABLE 1
Patient criteria

Selection
Insulin-dependent diabetes mellitus (clinical symptoms and fasting C-peptide ≤0.17 nM)
Age ≥18 and ≤60 yr at randomization
Exclusion
Acute illness
Chronic diseases that complicate diabetes treatment
History of coronary heart disease
Creatinine ≥130 μM
Self-monitoring of blood glucose impossible (vision or psychological problems)
Hemoglobinopathy or hemolytic anemia
Endocrine disorders other than corrected primary hypothyroidism or uncomplicated menstrual disorders
Willful removal of the microchip from device

TABLE 2
Characteristics of patients at randomization

	Experimental	Control
Patients	21	21
M/F	11/10	8/13
Conventional treatment/multiple daily injections	5/16	6/15
Age at onset of diabetes (yr)	20.3 ± 9.9	20.7 ± 11.6
Age (yr)	31.9 ± 9.1	34.9 ± 10.9
Creatinine (μM)	85.2 ± 9.2	82.0 ± 9.2
Body mass index (kg/m^2)	23.7 ± 3.9	22.7 ± 2.1
Insulin dose/body weight (U/kg)	0.63 ± 0.14	0.65 ± 0.13
Baseline HbA_1 (%)	9.8 ± 1.6	9.9 ± 1.6

Values are means ± SD.

The study population consisted of patients with IDDM from the Helbachtal Diabetes Education Centre (21). The study was performed in accordance with the principles of the Declaration of Helsinki. Each patient gave his written informed consent (22).

Before starting education in the diabetes center, patients were investigated according to selection criteria (Table 1). Patients without exclusion criteria were randomly assigned to an experimental or control group (Table 1). Because patients entered the study consecutively, block randomization was not possible. At randomization, ~25% of the patients in each group used conventional treatment with two daily injections of mixed insulin. The others were on a multiple daily injection regimen. Table 2 shows the baseline features of the patients at randomization, and no significant differences existed between the groups.

We selected a sample size of $n = 2 \times 20$ to have sufficient power of the test for detecting a difference in mean blood glucose of 0.6 mM between the two groups (α-error <0.05 and β-error <0.2 in a 2-tailed test). Fifty patients entered the study. Four patients from the experimental group were excluded according to the criteria (2 patients removed the microchip and 2 patients developed acute infectious disease). To avoid imbalance between the two groups, four patients from the control groups were excluded randomly.

Each patient was examined over a 32-day period. The basic educational program, i.e., practical advice in SMBG, diet, and exercise (swimming, hiking) under homelike conditions, was identical in both groups. The insulin-dose adjustment in the control group was supported by the educational team only, whereas the experimental group exclusively received support from the learning memory system. The experimental group received a 1-h technical instruction course on how to use the learning memory system. Data input of one learning and one planning phase required ~2 min. The experimental group did not participate in the daily consultations with the educational team, whereas the control group did (15 min · day^{-1} · patient^{-1}). The experimental group had the opportunity to discuss every problem,

except insulin-dose adjustments, with the physicians and nurses on the team. They had to determine their insulin dosage by themselves, supported only by the learning memory system. The control group patients were instucted according to the algorithms of Skyler et al. (14,15). During the study, all patients in both groups were treated with multiple daily injections; i.e., one injection of short-acting insulin with the main meals and long-acting insulin (NPH) in the morning, evening, or at bedtime. The patients were told to measure blood glucose at least four times a day before breakfast, lunch, dinner, and at bedtime.

Daily blood glucose monitoring was peformed by all patients with commercial solid-phase reagent strips (Haemogluco Test 20–800, Boehringer Mannheim, Mannheim, Germany) referenced two times a day by laboratory staff with measurements by glucose oxidase method (23). HbA_1 was determined at the beginning and end of treatment by high-performance liquid chromatography (5.4–7.6%, between-run SD 0.07%, coefficient of variation 1%; 24). Body mass index was recorded at the beginning and end of the treatment. M value (25) and mean amplitude of glycemic excursions (MAGE) (26) were calculated by an evaluation program (27,28), and mean blood glucose and hypoglycemic frequency were determined on the basis of SMBG in the first (first 14 days) and second (last 14 days) phases. The hypoglycemic frequency is described as the number of blood glucose values ≤3.3 mM per total number of blood glucose values during the first and second phases. In the case of low blood glucose (≤3.3 mM), only one measurement is counted within an interval of ±2 h.

Statistical analysis. Data are means ± SD. Significant differences were determined between the two groups by unpaired *t* test and within each group with Student's paired *t* test. Because normal distribution was not assumed in hypoglycemic frequency, the *U* test was applied.

TABLE 3
Parameters of metabolic control, hypoglycemic frequency, insulin requirements, and frequency of self-monitoring at baseline and at end in experimental and control groups

	Experimental	Control
Metabolic control		
Baseline HbA_1 (%)	9.8 ± 1.6	9.9 ± 1.6
End HbA_1 (%)	9.0 ± 1.2*	9.2 ± 1.2*
Mean blood glucose (mM)†	8.2 ± 1.8	8.5 ± 1.8
Mean blood glucose (mM)‡	8.4 ± 1.4§	9.2 ± 2.0‖
Day-to-day standard deviation (mM)†	2.8 ± 0.9	2.9 ± 0.8
Day-to-day standard deviation (mM)‡	2.6 ± 0.8¶	2.8 ± 0.9
M value‡	22.3 ± 11.1§	28.7 ± 17.9
Mean amplitude of glycemic excursions (mM)‡	7.1 ± 1.4¶	8.1 ± 2.0
Proportion of blood glucose ≥11.1 mM (%)†	17.2 ± 12.5	22.5 ± 15.2
Proportion of blood glucose ≥11.1 mM (%)‡	16.8 ± 0.7§	28.0 ± 15.1
Hypoglycemia		
Proportion of blood glucose ≤3.3 mM (%)†	3.3	3.7
Proportion of blood glucose ≤3.3 mM (%)‡	1.7**	2.3
Insulin requirement		
Baseline insulin dose/body weight (U/kg)	0.63 ± 0.14	0.65 ± 0.13
End insulin dose/body weight (U/kg)	0.57 ± 0.15**	0.64 ± 0.20
Baseline body mass index (kg/m^2)	23.7 ± 3.9	22.7 ± 2.1
End body mass index (kg/m^2)	23.4 ± 3.4	22.4 ± 1.9
Self-monitoring of blood glucose		
Frequency (day^{-1})	5.5 ± 0.8	5.7 ± 0.9

Values are means ± SD. Phase 1, first 14 days; phase 2, last 14 days.
*$P < 0.001$, ‖$P < 0.01$, **$P < 0.05$, vs. phase 1.
†Phase 1.
‡Phase 2.
§$P < 0.01$, ¶$P < 0.05$, vs. control group.

RESULTS

The baseline HbA_1 levels of the experimental and control groups did not differ significantly (Table 3). A reduction ($P < 0.001$) in HbA_1 was observed after the 32-day treatment period in each group. Mean blood glucose of the first 14 days was not different (experimental vs. control, 8.2 vs. 8.5 mM), and the hypoglycemic frequency (3.3 vs. 3.7%) was comparable.

Comparing the first with the second phase, a reduction ($P < 0.05$) of the hypoglycemic frequency from 3.3 to 1.7% was observed in the experimental group, whereas the mean blood glucose remained unchanged. In the control group, the hypoglycemic frequency decreased from 3.7 to 2.3% but at the cost of an increase ($P < 0.01$) of mean blood glucose in the second phase. M value ($P < 0.01$) and MAGE ($P < 0.05$) were lower in the experimental group during the second phase. Severe hypoglycemia with neurological symptoms or ketoacidosis was not observed in any group.

The insulin requirements per body weight were not significantly different at randomization (0.63 vs. 0.65 U/kg). The insulin requirements decreased ($P < 0.01$) in the experimental group (0.57 U/kg) and remained unchanged in the control group (0.64 U/kg). There was no significant difference in body mass index at randomization or during treatment in both groups.

The differences between the dose injected by the patient and the mean of the dosage interval recommended by the system followed a distribution with a standard deviation of 0.8 U regular insulin/injection (0.1 U NPH/injection) during the first phase and 0.5 U regular insulin/injection (0.1 U NPH/injection) during the second phase of the study. Because the width of the suggested

dosage interval is ±1 U of insulin (i.e., 2 U), most recorded dosages are found to be within this interval.

The parameters of the glucose-insulin model were updated every week during the study and tested for validity in a model-fit test by the means of F statistics (29). The coefficient of correlation (r) was transformed into an F distributed test parameter (see Appendix 2). If this test parameter was 15 ($P < 0.01$) in the validation test, the adapted model parameters were introduced into the continuing feedback process. In 18 of 21 patients, model validation was significant at $P < 0.01$.

CONCLUSIONS

This study compared the safety and metabolic control of two training programs for the adjustment of insulin dosages. Parameters of glycemic control, i.e., mean blood glucose, M value, MAGE, and hypoglycemic frequency, of the group supported by the learning memory system were of at least equal quality to the group advised by the educational team. The duration of a study comparing human decision support with that of a computer is limited by the necessity of providing continuous support by diabetes educators. Although we are aware of the short-term nature of this study, we conclude that patients may receive support in adjusting their insulin dose by means of such a system at home where there is no education team. For many patients who were given their basic education in a hospital or in an education center, it is difficult to apply their acquired knowledge under the conditions of everyday life. The learning memory system may be a representative teacher in such situations but should not take the place of any basic educational program or consultations with the doctor.

The internal data processing of the learning memory system is based on mathematical modeling of the glucose response, which depends on insulin, carbohydrate intake, physical activity, and time. Glucose metabolic models are used in the physiological sciences (13,30,31) to quantitatively describe internal inaccessible metabolic parameters and to predict glucose responses in a certain individual. A glucose model may be inverted for clinical application such that it predicts an insulin dose to aim at a defined near-normoglycemic target. Some authors designed models for closed-loop infusion systems, whereas this study describes the application of a glucose model in intensified insulin therapy (32–36). With SMBG as a data base, the model may also identify a valid parametric description of a patient's metabolic reactions and may improve the control of his/her blood glucose in a feedback process. Because most models are based on data from glucose tolerance tests or homeostatic measurements in clamp technique, it has not been demonstrated previously that a valid model identification based on SMBG is possible. This means that records in diabetes self-management contain enough information to perform valid mathematical modeling.

The model can be used to estimate the supplemental insulin that is necessary to compensate the actual blood glucose, extra carbohydrates, and physical exercise in the individual patient. The learning memory system can be used to determine the supplemental requirements of insulin in special situations. Thus, it may be a helpful tool for the patient when planning meals and exercise in advance.

Several algorithms have been developed to control blood glucose, many of them coded for computer application (1–9,14,15,37,38). The idea of the learning memory concept is to combine the computer data processing with the human skills of decision making. The learning memory system condenses the information of several stored data and prepares the final patient's decision on how to adjust the insulin dose. Patients remain active and self-reliant in this program. In the planning-learning concept, patients may learn from the didactic structure of the stored information to distinguish between prospective and retrospective dose adjustments. A self-organizing mutual learning and training process between the patient and the system may be interpreted as cooperative learning (39). Thus, the system is not an alternative technical controller of blood glucose that replaces the patient, but more a catalyzer of the learning process on how to administer insulin.

Physicians and patients do not accept computer support in general. Therefore, psychosocial aspects, knowledge about diabetes self-management, and the doctor's and patient's technological interest should be considered carefully before such a system is applied.

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APPENDIX 1: CONTROL ALGORITHMS

Insulin (INS)-dose adjustments are described by an INS controller on a day-to-day basis. The difference in INS dose on 2 successive days is a function of the difference between the actual blood glucose (BG) and the reference input (RI; eq. 1). The product of the three gain factors, μ_i, modifies the insulin response on the basis of (n) preceding blood glucose values.

$$\Delta\text{INS} = K_1(\text{BG} - \text{RI}) \prod_{i=1}^{3} \mu_i$$

$$K_1 = \text{const}(1/\text{mM}) \qquad (1)$$

The quality criterion (ϵ) defines quantitatively to which degree BG values reach the near-normoglycemic target (Eq. 2). Comparable with the definition of the M value, Eq. 2 expresses the asymmetric valuation of hypo- and hyperglycemic values.

$$\epsilon = K_2 \sum_{i=t-1}^{t-n} \left| ln \left(\frac{BG(t)}{RI} \right) \right|$$
$$K_2 = \text{const} \quad (2)$$

The actual gain factors μ_i in eq. 1 are functions of the quality criterion ϵ. The nonlinear gain factor (Eq. 3) μ_1 describes the different insulin responses to hypo- or hyperglycemic inputs, respectively. The response to hypoglycemia is amplified ($\mu_1 > 1$), whereas it is damped ($\mu_1 < 1$) as a reaction to hyperglycemia.

$$\mu_1 = 1 + \epsilon \times [K_3(e^{K_1(BG-RI)} + k_3 - 1)^{-1} - 1]$$
$$K_3 = \text{const} \quad (3)$$

The artifact damping factor μ_2 represents a differential control element (Eq. 4). A significant difference in two successive blood glucose values results in a diminished control action.

$$\mu_2 = e^{-K_4[BG(t) - BG(t-1)]^2}$$
$$K_4 = \text{const}(1/\text{mM}^2) \quad (4)$$

The stability gain factor μ_3 is proportional to the quality criterion ϵ (Eq. 5). In periods of good control, the stability factor functions as a damping factor to maintain stability.

$$\mu_3 = K_5 \cdot \epsilon$$
$$K_5 = \text{const} \quad (5)$$

The RI depends on the threshold for symptomatic hypoglycemia (H; Eq. 6). BG values are marked by the patient in the case of symptomatic hypoglycemia. All BG values $\geq$H have a statistical probability of <0.20 of being marked.

$$RI = K_6 + 0.5(H - K_6)[\text{sign}(H - K_6) + 1]$$
$$K_6 = \text{const(mM)} \quad (6)$$

The system warns if hypo- or hyperglycemia are expected on the basis of previous calculations. The system also warns if insufficient BG decline is observed after repeated increases of insulin dosages (16).

APPENDIX 2: MODEL

The statistical model is based on the method of multiple correlation. Thus, it has noncompartmental structure and describes the process by the vector equation (v_1, date; v_2, actual blood glucose; v_3, carbohydrate content; v_4, physical activity; v_5, basal insulin [NPH]; v_6, regular insulin; y, resulting blood glucose after 4–6 h)

$$y(j) = v(j)^T c$$
$$1 \leq j \leq n \quad (7)$$

where n is the number of observations, with the characteristic vector

$$v(j)^T = [1 v_1(j) \ldots v_p(j)] \quad (8)$$

and the parameter vector

$$c = [c_0 c_1 \ldots c_p]^T \quad (9)$$

The initial parameter (p) vector has been defined on the basis of data from literature (18,19). The modeling was performed once a week on the basis of the data that have been recorded during the previous 3 wk. Each new parameter vector is validated by a model-fit test by means of F statistics. Validation of the model is performed by the transformation of the coefficient of correlation (r) into an F distributed test parameter (Eq. 10). If this test parameter is >15 ($P < 0.01$), the process identification is assumed to be valid.

$$F = \frac{r^2(n - p - 1)}{(1 - r^2)p} \quad (10)$$

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