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Study protocol

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Randomised prospective study for the effect of therapy on residual beta cell function in type-1 diabetes mellitus [ISRCTN70703138]

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Abstract

Background: Newly diagnosed insulin-dependent diabetes mellitus is characterised by a temporary recovery of endogeneous insulin ("remission") after the beginning of medical treatment with subcutaneous insulin injections. Although most diabetologists think, that insulin reserve is related to reduced occurrence of diabetic long-term complications, such as eye, nerve and kidney disease, there is only one prospective controlled clinical study (the DCCT) addressing this question, however as secondary hypothesis.

Methods/Design: Therefore, we composed a trial consisting of two cohorts with two therapeutic options within each cohort (conventional versus intensive therapy) and a three-year follow-up. In one group the patients are randomly assigned to the treatment regimes to test the statistical alternative hypothesis if variable insulin dosage is superior to fixed insulin injection in preserving insulin reserve measured by C-peptide in serum. Another group includes patients who prefer one of the two therapies, decline randomisation, but consent to follow-up. Apart from the determination of insulin reserve as a biological parameter a second primary endpoint was defined as 'therapeutic failure' according to the criteria of the European Association for the Study of Diabetes. Patients pass a training program to help them self-manage diabetes. A standardised protocol is being set up to minimize centre effects and bias of health care providers. Potential patient dependent bias will be investigated by questionnaires measuring psychic coping processes of people with diabetes. Management of visit dates is directly navigated by the database. Automated visit-reminders are mailed to patients and caregivers to optimise the number of visits on schedule. Data quality is regularly monitored and centres are informed on the results of continuous data management.

Background

Complications of diabetes

The incidence and the risk of type-1 diabetes differs between populations with highest rates reported for Finland (> 30 cases per year and 100,000 inhabitants), and minimal rates for developing countries (< 2). The incidence rates in central Europe vary between 5.2 and 12.1. A census from the early 80's reported 7.4 cases per year and 100,000 for Germany [1]. It has long been expected that the level and duration of high blood glucose (hyperglycemia) is strongly associated with a variety of microvascular complications, such as eye, kidney, and nerve disease.

The Diabetes Control and Complications Trial (DCCT), a randomised trial included a total of 1,441 patients with type-1 diabetes and was published in 1993. The DCCT for the first time provided unequivocal evidence that, in fact, lower blood glucose concentrations delay the onset of diabetic complications [2]. Subjects chosen for the primary prevention cohort had had diabetes for 1–5 years with no evidence of eye disease or initial kidney disease. The biological parameters used in this study have become important for studies on patients with type-1 diabetes, in general. Glycemic control was assessed with glycosylated hemoglobin (GHb). GHb is widely used in diabetes studies to describe the mean blood glucose level over a period of 4–6 weeks. Eye disease is diagnosed by fundus examination, and nerve disease is assessed by testing the vibration threshold of the foot. Measurement of albumine in the urine is a screening method to detect diabetic kidney disease at an early stage.

Residual Beta Cell Function

A few months after the initiation of insulin therapy endogeneous insulin production recovers. Disease remission is characterised by a significant reduction of therapeutic insulin, sometimes patients are even completely "off insulin". Although insulin therapy has been practiced by physicians for decades, it is hypothesized that only modern insulin therapy has the potential to maintain a significant insulin reserve over a longer period of time mainly by reducing the glucotoxic effect on the pancreatic cells.

Treatment with immunosuppressive drugs to protect insulin producing cells from the immune attack showed that initial improvement did not last longer compared to insulin injection alone. These studies used plasma C-peptide concentration for the measurement of insulin reserve because it is secreted in equimolar amounts with endogeneous insulin. The C-peptide radioimmunoassay did not crossreact with injected insulin circulating in the blood stream. It was also found that adult-onset patients with type-1 diabetes have a longer period of residual insulin secretion than children [3].

Recently, intrinsic biological acitivity of C-peptide was described after years of general belief, that it is not biologically active [4].

A subgroup of 303 participants of the DCCT trial who were diagnosed for diabetes less than five years from baseline had a positive endogeneous insulin response. These patients were reported to have a lower value of mean blood glucose as GHb and also a 50% reduced risk for progression of eye disease [5].

It was also observed that hypoglycemia (low blood glucose concentration) – a typical side effect of the subcutaneous injection of insulin – occurred less frequently in patients with residual C-Peptide [6].

Conventional and Intensive Insulin Therapy

The majority of patients face a challenge when the goal is optimal regulation of blood glucose. Indeed, only 5% of patients in the DCCT, a carefully selected and closely monitored group, maintained glycosylated hemoglobin levels in the normal, nondiabetic range through the whole trial. Optimal diabetes care is a behavioral, psychosocial and motivational challenge for caregivers and patients. Therefore, the term "intensive" insulin therapy describes a comprehensive approach to the goal of optimal glycemia. In principle, different educational strategies have been developed to teach patients how to increase the number of insulin injections and frequency of testing. The "intensive" strategy also includes a systematic approach to quantifying food and matching insulin to food intake, and education that enables patients to change aspects of the regimen for varying circumstances. By contrast, "conventional" therapy is a less complex and demanding regimen concerning the performance of several unpleasant tasks: injections (not more than three per day), testing, dietary modifications, and exercise routines.

Hypoglycemia is the principal adverse effect of intensive diabetes management. Fear of hypoglycemia is an important determinant of patients' personal goals for glycemic control. In the DCCT, intensively managed patients had three times as many episodes of severe hypoglycemia as their conventionally treated peers.

In Germany, intensive insulin therapy has become standard in the past 10 years, 8 out of 10 subjects with long standing insulin-dependent diabetes practice this kind of therapy [7]. Most care providers feel, that intensive therapy should be implemented from the first day of diagnosis, because they have the impression that quality of life of the patient is superior compared to conventional therapy.

A pilot trial conducted at our department on 49 adult type-1 diabetic patients with persisting insulin reserve and

randomised for either intensive or conventional therapy resulted in reduced prevalence of peripheral neuropathy in the intensively treated group [8].

Rationale

Although C-peptide was measured in some patients of the DCCT we must express our concerns on the validity of these data, since insulin reserve was not the main objective of the DCCT. A bulk of uncontrolled trials in the past 20 years has implicated that residual C-peptide was beneficial for the prevention of diabetes related vascular disease. This is an important reason for the conduction of this trial. Further, intensive insulin therapy was thought to be the optimal way for glucose control in type-1 diabetes, however only a minority of patients comply with all the elements necessary for optimal control over a time period of several years. Therefore we think that our trial will help to settle the question whether preservation of residual insulin/C-peptide facilitates stabile glucose levels. Moreover, intensive insulin therapy is considered optimal for all patients, however a major obstacle is the increased incidence of severe hypoglycemia. We had observed in the pilot trial that patients with residual insulin on intensive therapy had no episode of severe hypoglycemia (defined as the need of intravenous injection of glucose).

Since 1998 we planned a prospective randomised trial to document the advantage of intensive insulin therapy in the preservation of insulin reserve and also the protection from complications by residual insulin in type-1 diabetes. This would require a large sample size, which could only be realized by a multicenter trial. Furthermore, such a study would have to recognize aspects of self-management, life quality, training, psychosocial factors, and coping strategies of the patient.

To begin with we performed a telephone survey in twenty clinical diabetes centers in Germany. It became clear that the access of a sufficient number of patients to such a trial would require the collaboration of several centres and years of cooperative data collection.

Aims and objectives

The DCCT landmark study for the treatment of insulin dependent diabetes demonstrated that reduction of hyperglycemia was associated with prevention of microvascular complications. But there still remained several open issues [9].

Will intensive therapy delay the breakdown of patients' own remaining insulin output in contrast to conventional therapy?

Will intensive therapy improve glucose control and delay or prevent the development of long-term complications?

Which factors determine the preservation of C-peptide concentration when diabetes proceeds with time?

Design

The NeuDia Trial is a national multicenter open controlled randomised study. Four clinic-based diabetes centres in Germany participate in the recruitment process. The protocol was approved by the responsible institutional review boards. Each recruited subject has to sign an informed consent form. Patients give their consent to randomisation and/or collection of data depending if they enter randomisation or the observational follow-up.

Intervention

Interventional cohorts will be instructed to practice basis-bolus (intensive) insulin therapy. This therapy includes frequent injections at meal times with variable doses of short-acting insulins, estimation of carbohydrate content of the meals, self-dosage of insulins, self-management of insulin requirement. The participating centres have agreed on the detailed algorithms of this intervention.

Control (conventional) groups will apply not more than three insulin injections per day without making allowance for different meal sizes or flexible insulin dosage adaptions apart from ambient blood glucose.

Study population, inclusion and exclusion criteria

Subjects are recruited from diabetic patients diagnosed with type-1 diabetes not more than three months ago. Type-1 diabetes is defined by more than one elevated blood glucose (concentration >11.1 mmol/l), and the medical decision to prescribe insulin within three months after diagnosis. The frequency of antibodies indicating an autoimmune process is expected to be less than 50% in adult type-1 diabetes [10,11]. Therefore the presence of diabetes related antibodies may support diagnosis but will be not mandatory for incusion.

Inclusion criteria

- Men or women aged 18–40 years at diagnosis
- Established Type-1 Diabetes diagnosed up to three months ago
- Consent to participate in a diabetes training programme
- Informed consent before enrollment

Exclusion criteria

- History of neuropathy, nephropathy, and retinopathy of other than diabetes related origin

- Negative C-peptide level at diagnosis
- History of psychiatric disease or drug or alc ohol abuse
- Treatment with oral antidiabetic medication
- Subject unlikely to comply with the protocol (e.g. inability or unwillingness to participate adequate training or to complete diaries appropriately) or to understand the nature and the scope of the study

Subsequent eligible patients and their status concerning the study are recorded. Additionally, the number of those patients refusing data collection are recorded in each centre.

Compliance of patients after inclusion

A patient is considered non-compliant when he/she:

- misses more than two visits without contacting the study centre

- moves and does not provide a new address or phone number

- Wants to change therapy due to personal reasons

Primary endpoints and hypotheses

Our overall objectives formulated above made it necessary to define two primary endpoints:

As we are interested in the preservation of C-peptide concentration under both therapies, one primary endpoint of interest is the 'change of C-peptide concentration' between baseline and three years follow-up ($\Delta_{\text{C-Peptide}}$ = C-peptide$_{\text{prae}}$ - c-peptide$_{\text{post}}$). The other primary endpoint of interest is 'failure'. of therapy. 'Failure' is a dichotomous variable and defined as follows:

- The occurrence of an GHb value greater than 6,7 % (upper 2-SD limit of central laboratory) twice in succession.
- Decrease of fasting C-peptide to a value less or equal 0.15 nmol/l or stimulated C-peptide to a value less or equal 0.3 nmol/l diagnosed twice in succession.
- The occurrence of albumine in collected urine, i. e. an excretion rate greater than 21 μg/min once.
- The diagnosis of neuropathy or retinopathy, examined in 1-year intervals.

'Failure' is stated if at least one of these items will occur.

The main question will be analysed in form of confirmatory hypothesis testing. H_0 and H_1, are defined for the two primary endpoints as follows:

Primary endpoint 'change of C-peptide'

As the level of C-peptide under three years of therapy may depend on baseline values, these must be taken into account as one of the covariates in the analysis. The two factors of interest are 'therapy' and the 'willingness of patients to take part' in such a clinical study. According to our question the interaction hypothesis is the one of interest.

So the nullhypothesis is as follows:

$\mathbf{H_0}$: Under consideration of baseline data, the willingness of patients has no influence on the difference of C-peptide levels between patients under intensive therapy and conventional therapy. That means there is no interaction between both factors.

Against the alternative

$\mathbf{H_1}$: Under consideration of baseline data the difference of C-peptide levels between patients under intensive therapy and conventional therapy depends on the willingness of the patients to take part in such a clinical study

Primary endpoint 'failure' of the therapy

$\mathbf{H_0}$: Intensive insulin therapy has a failure rate greater or equal to the conventional therapy

$P(\text{failure} \mid \text{ICT}) \geq P(\text{failure} \mid \text{CT})$

$\mathbf{H_1}$: The failure rate of intensive therapy is less than the rate of conventional therapy.

$P(\text{failure} \mid \text{ICT}) < P(\text{failure} \mid \text{CT})$

Both hypotheses are formulated as a one-sided statistical question.

Secondary endpoints and hypotheses

Apart from the main hypotheses we will investigate several secondary questions in form of explorative data analysis.

One point of interest is the effect of conventional vs. intensive insulin therapy on the incidence of severe hypoglycemia. In this regard we want to know the effect of C-peptide at diagnosis on the incidence of severe hypoglycemia and on the trend of glycosylated hemoglobin within three years of observation. Hypoglycemia will be

retrieved according to the Working Group on Structured Diabetes Therapy [7].

We will test the influence of the "change of C-peptide concentration" on the occurrence of diabetic complications at the end of the observation time, such as the concentration of albumin in urine. In case of a beneficial effect of C-peptide, we will then evaluate the influence of body weight at diagnosis as well as change of body weight under therapy on the progress of C-peptide concentration.

Analysis of the primary endpoints

We are interested in the probability of 'failure' under the different therapies. As 'failure' is a dichotomous variable, the results of the study will be analysed by means of logistic regression measures. The independent variable of interest (exposure variable) is therapy with the two expressions ICT and CT. As explained before, we have to take into account, that the effect of therapy may be modified by the patients' willingness to participate in a clinical study. Therefore 'willingness' and the interaction term 'therapy * willingness' is a part of the model. Variables observed at baseline like GHb and C-peptide and scores describing patient's psychical situation are confounders of the model.

As we assume, that 'the change of C-peptide' depends on the baseline values, the influence of the therapy will be evaluated by analysis of covariance in consideration of patients' agreement to take part in a clinical study. That means the two factors of interest are 'therapy' and 'willingness'. For our approach the interaction hypothesis is the important one. As the assumption of the normal distribution of C-peptide is questionable for the analysis the non-parametric analogue will be used.

Level of significance

As described we defined two primary endpoints in the study protocol. It seems to be adequate to choose alpha = 0.05 as the familywise error rate. To take into account the arising multiple comparison problem we perform the Bonferroni-Procedure for the final evaluation of each primary variable in order to control the familywise error rate.

Analysis Set

The statistical analysis of the two primary endpoints will be calculated based on the full analysis set to prevent from an overoptimistic estimate. In order to take into account, that drop outs (see definition non compliers) could falsify the estimation of the primary endpoint 'failure' sensitivity analysis will be done. For the second primary endpoint 'change of C-peptide' the method 'last observation carried forward' will be used.

Patients who change their therapy will be analysed as randomised. Furthermore, different frequencies of 'therapy change' in the therapeutic cohorts must be taken into account. It is expected that 'therapy change' will be rare in the intensive group compared to the conventional group. Under this assumption and the additional assumption that the drop out rate in the intensive therapy group will be lower than in the conventional group missing values will be controlled for by carrying the last value forward. This procedure will be applied to all non-compliant patients, i.e. drop outs and therapy changers, regarding the second primary endpoint 'change of C-peptide'. All other variables defining one of the secondary endpoints will be analysed in an explorative way.

Calculation of sample size

The study consists of a variable recruiting period and a three-year follow-up. An eligible patient will be observed three years at least. Because of the long-term observation, we expect a constantly increasing number of drop outs during follow-up caused by non-compliance. We estimate an overall drop out rate of about 10 %. As mentioned before two primary parameters, failure rate and change of C-peptide-level, will be analysed. According to the results of the pilot study we assume, that conventional therapy causes a failure-rate of 0.3, that means P(failure 1 CT) = 0.3. From a clinical point of view it is desirable to reduce this failure-rate to at least 0.15 in the intensive therapy in contrast to the conventional therapy, that means P(failure 2 CT) = 0.15. With a type I error of $\alpha = 0.025$ and a power of 80 % we have to recruit at least 132 patients in each therapeutic group.

From the clinical point of view it will also be desirable to reduce 'the decline in the C-peptide-level', the second primary parameter, from the expected 0.75 nmol/l in the conventional therapy to 0.5 nmol/l under intensive therapy. In a pilot study we estimated a common standard deviation of the C-peptide-level of 0.52. With a type I error of $\alpha = 0.025$ and a power of 80% in order to fulfil conditions for these parameters we have to recruit 82 patients in each therapy group. With a 10% drop out rate we have to recruit at least 91 patients for each group.

Because of a familywise evaluation of both primary endpoints the result of the primary parameter 'failure rate' was taken as a basis, i. e. 132 patients per therapy arm have to be recruited including the drop-out rate.

Randomisation procedure

The assignment to one of the therapy arms is made by the study center at Giessen. Patients and diabetes professionals are both informed on the result of the randomisation. From the medical point of view variables, which have to be similarly distributed in the therapy arms are 'age of the

Table 1: Possible values for the defined variables used.

Variable	C-peptide nmol/l	age years	BMI kg/m2
Interval 1	< 0.3	18 ≤ age < 30	< 21 kg/m^2
Interval 2	≥ 0.3	30 ≤ age ≤ 40	≥ 21 kg/m2

patients', 'C-peptide' and 'body mass index' (BMI). As it is expected that a single study center recruits a relatively small number of patients, we randomise on the basis of a 'minimisation' procedure with defined variables. The possible values of the variables are divided into two intervals according to the table 1:

Efficacy Data

Clinical Data

Overall examination of the patients will include all the items of the St. Vincent Declaration data collection form [12]. This includes foot examination with palpation of pulses and screening sensation loss with the Rydel-Seiffer-Tuning fork as described by Liniger et al [13]. A sensational loss of < 6/8 will be denominated „neuropathy". Handling of the tuning fork and symptom questionnaire are described by the Foot Working Group of the Deutsche Diabetesgesellschaft http://www.ag-fuss-ddg.de.

Retinopathy is diagnosed by ophthalmologists according to a standardized procedure [14] used previously in a population based study in the city of Wolfsburg, Germany on more than 2,800 diabetic patients [15].

Central Laboratory Data

The main parameters are determined at the central study laboratory of Giessen. Glycated hemoglobin is measured by high-performance liquid chromatography at baseline and every six months after inclusion into the study [16]. C-peptide is measured using a highly specific two-site monoclonal antibody immunoradiometric assay and blood glucose by the hexokinase method.

Concentration of urine albumine is not determined in a centralized fashion. Therefore, a cross-validation procedure was introduced. Frozen urine samples are sent to each of the participant's laboratories once a year. Between- and within-laboratory means, standard deviations, and coefficients of variation are calculated as factors of variability.

Data Quality Management

A relational database was developed to facilitate data entry and control data quality. Predefined members of the study group review the data base at various intervals throughout the study. They assess completeness and validity of data and safety aspects. They make sure that queries generated by the data bank are responded and corrections are entered into the data bank.

An important issue is coordinating the patient visits coming from all over Germany. Not only have the patients to be reminded of their visits but also the centres need to know when each patient is due for a visit. Therefore, both, centre and patient, have to be informed to ensure that the patient admits to the centre. Therefore, a module combined with the database was created to establish a mailing system for the patient visits. This system

- calculates dates of the next visits for all patients,

- automatically prints a letter to all patients due for a visit within one month's time

- prints a monthly reminder for the centres listing those patients with visits due the next three months.

Another issue in every clinical study is the achievement of optimal data quality with reasonable expense. We tried to solve this problem by a high level of automation and a flexible deployment of study-staff. Examples for these automated processes are lists of patient schedules for all participating centres sent at regular intervals, inventory of visit-reminders for patients, randomisation of patients, and basic data plausibility control.

Continuous safety and quality review (Source data verification)

Data safety and quality are monitored in predefined intervals. Study report files are regularly sent to the study centre where they are reviewed for inconsistent or missing data. When data from the report files are entered into the data base they are automatically checked for plausibility in relation to the last data set of the same patient. Finally, new data are balanced with the patient files at the occasion of the monitoring visits. If one of these steps yields missing or false data a query is prepared and sent back by fax or mail to the individual center. Corrected data are also sent back by mail or collected at the monitoring visit.

Centre performance

A periodical newsletter is sent to the centres containing data on centre performance. This letter contains, for instance, the following rates

- recruitment rate (number of recruited patients per year compared to the estimated number of patients per year)

- time for incoming data and available source data compared to required data).

- dropout rate (dropouts compared to the total patient number per centre)

Elements of flexible staff management

An important element is the adaptation of study related qualifications of the medical and biometrical team to changing requirements in the course of the study. Since the principal investigator is also responsible for patients himself he will combine the study protocol with personal medical practice and communicate his experiences to the other investigators.

Visits

Another serious problem is the change of address in long-term studies. Therefore, we developed a form for patients planning to move in the next few months. The patient will be asked to fill in their new address.

We have found out that minimal interference of study visits with occupational or private life of the patients is a major factor for adherence to arrangements made by physicians and diabetes educators with the patients. By definition age at inclusion is 18 to 40 years, i.e. most of the patients are expected to be engaged in an occupation. This is especially important for patients with diabetes related problems at work.

We also arrange visits at weekends or in the evenings when patients are not obliged to leave their working place during the week. Patients are called by phone or cellular-phone in the evening in case they have not made an appointment up to four weeks following the automated reminding letter was sent off. The medical staff is informed about exceptional visit dates and will be present when the patient enters the centre. Investigators are supported in organising the visits for a given patient.

Handling of Bias

Health care providers' preference

For the reasons described in the introduction health care providers in Germany are expected to consider intensive therapy to be optimal from the first day of diagnosis due to the results of the DCCT trial. In addition, professionals tend to have their own attitudes concerning the appropriate therapy for a given patient [17], which may be different from the patient' s attitude.

To harmonize therapeutic regimes we invited representatives of the study centres to discuss details in which way either intensive or conventional therapy was performed in their own clinical setting. After meeting twice the therapeutic regimes were defined in the study protocol. At the meetings the examiners were requested to inform their patients such that no therapy was superior to the other at diagnosis of diabetes even if they personally would prefer the intensive therapy because of delay of complications after many years of diabetes duration.

Patient Preference

Patients are responsible for their insulin therapy involving individual social surroundings. Patients' success of treatment and quality of glucose management is often related to the attitude towards disease.

As the manifestation of the disease is a very profound event for the patients, they might easily be influenced by a lot of factors for example by the attitudes of their diabetologists towards therapy, by other patients with diabetes in a later stage of the disease, as well as the support offered by family and friends. Very sensitive in this state of the disease, they might be guessing what therapy the health care professional would prefer, even if he tries to be neutral. Therefore we expect that not every patient of the possible study population will agree to the restricting feature of an experimental clinical study nor to the randomisation into one of the two therapy regimes. On the contrary, we even expect a selection bias. Further we assume, that especially younger or self-confident diabetic patients would prefer a more complicated regime in order to reach more freedom concerning the flexibility of working hours and career prospects, the selection of food and drinks, leisure time activities and so on. So there is reason to doubt, that this group would give their consent to take part in such a study. Those patients are likely to insist on the intensive insulin therapy possibly developing a more generous attitude towards their disease not being anxious to fail in handling the more complicated therapy regime.

On the other hand the first manifestation of diabetes could make the patients insecure, the diagnosis of diabetes sometimes causes psychical crisis. For such patients a fixed therapy regime could be helpful. These and many other facts can influence the patient' s consent to take part in clinical trials and therefore cause a selection bias [18].

Zelen was the first who took into account bias caused by patient' s preference or disagreement with randomisation results [19]. The methods developed by him to handle this bias cannot be chosen in our situation.

In this study there will be no comparison between a standard and an experimental therapy, but a comparison between two common therapies, which appliances depends on the patient' s and his caregiver' s preferences. As mentioned before in addition both therapies have specific demands on the patient himself and his management of his everyday life. Therefore we believe, that a lot of patients will not consent to participation in such a clinical trial.

Patient-related bias

Theoretically, to demonstrate the superiority of one of both therapies the conduction of an observational study alone would not be sufficient, since effects of 'therapy' and 'patients' preferences' would be mixed. Therefore, randomisation is essential. On the other hand, patients who agree on randomised participation may not be representative due to selection bias. In order to estimate such a potential bias, the observational cohort was introduced into the study. If different outcomes in the observational and the controlled randomised cohort will result, we will estimate the impact of the confounding factor 'patients' preferences' and therewith control for a possible selection bias. In a multifactorial analysis we look for interactions of the two therapies and the factor 'consent: yes/no'. If we do not find evidence of interaction we will search for a global effect of the factor 'consent' alone.

By additionally introducing the observational study, we actually analyse four subgroups: the randomised cohort with the two therapies according to randomisation procedure and the observational cohorts also consisting of the two therapeutic groups, intensive or conventional therapy, respectively.

Centre effects

In agreement with the centres we established a training curriculum, so that patients are trained almost identically concerning knowledge and didactic methods.

All eligible patients receive a basic diabetes training with defined topics independent from the kind of therapy. During this initial training patients are informed about the study and asked to give their consent. To decrease centre-related effects a curriculum was developed for both therapy arms synchronized in content, methods and time. Basic training is followed by a more thorough training programme according to the demands of the therapy. We will also check the level of patients' knowledge treated in the different centres and therapies. That is why we chose a validated test (DWT Typ-1-Test) as control instrument to measure the theoretical knowledge conveyed by diabetes education [20-22].

There are more psychological factors influencing the outcome of diabetes therapy, for example the patients' attitude towards disease, his/her individual coping strategies, or family support. Therefore, we will integrate a psychological assessment reflecting therapy contentment [23], attitude of patients towards their disease, and how they cope with the requirements of insulin therapy. The questionnaire consists of 45 diabetes-specific items evaluated on nearly 2,000 individuals with type 1 or type 2 diabetes including eight scales (values of Cronbach's alpha 0.69–0.81) and a re-test reliability of 0.63 [24]. This questionnaire will be repeated every six months during the course of the study. We expect to learn more about individual motives for the confounding factor 'patient preferences'.

Development of standard operating procedures for patient training courses

Multicenter clinical trials on the effect of non-pharmacologic intervention in diabetic patients are rare and often lack standardized procedures. Even in the DCCT trial no effort was undertaken to standardize patient education between the centres. A reason for this situation is that the implementation of evaluated curricula in an individual training center depends on the specific local conditions, such as adequate rooms, number of personel, qualification of personel, cooperations with other medical facilities, etc.

Training is undoubtedly one of the most important elements of therapy of newly diagnosed patients and therefore we organized two consensus conferences inviting doctors and diabetes educators of the participating centres to find a common guideline concerning patient training. This guideline was added to the treatment protocol as an amendment.

In short, every patient is instructed how to inject mixed insulin preparations and how to monitor blood glucose in the first week after diagnosis. After randomisation a training course with 20 lessons of 45 min each will be offered for each patient. Education goals and methods were defined by the study consensus meetings in accordance with the guidelines of the German and European Diabetes Societies [21]. Only registered diabetes educators are allowed to train the study patients.

Appendix

Listing of Participating Clinical Centers

T. Linn, R. Bretzel, University Hospital Centre, Giessen

W. Spuck, A. Hof, Rotes Kreuz Krankenhaus, Kassel

M. Dietlein, Hospital Haunstetten, Augsburg

C. Jaursch-Hanke, B. Piepkorn, Deutsche Klinik für Diagnostik, Wiesbaden

Data-monitoring team

Markus Mann, University Hospital Centre, Giessen

Marion Mann, Statistics Workgroup, Institute for Medical Informatics, Giessen

Rolf H. Boedeker, Statistics Workgroup, Institute for Medical Informatics, Giessen

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