Optimization of Diabetes Type 1 and Type 2 Treatment
Using New Algorithms and Technologies for Education
and Disease Monitoring:
DiabetesFIT® for Comprehensive Chronic Care

PhD Thesis
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October 2014
Declaration of originality

‘I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.’

In October 2014

Confidentiality Statement

This Doctor Thesis, entitled

“Optimization of Diabetes Type 1 and Type 2 Treatment Using New Algorithms and Technologies for Education and Disease Monitoring: DiabetesFIT® for Comprehensive Chronic Care”

by Kinga Howorka, Univ.-Prof., Dr.med., MBA, MPH, Acad. Hospital Manager, MSc Gender Med

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Acknowledgments

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My deep gratitude goes to my patients who throughout decades brought me to this work. The development of DiabetesFIT® system and related media results of approximately 40 000 patient years experience of authors’ commitment to the maximal enhancement of patients’ therapeutic competence. In this task my patients have been main initiators of the induced changes in the routine of diabetes treatment.

Public health today is evolving a world full of people with chronic diseases. There is no way to skip the necessity of therapeutic patient competence. This Thesis summarizes authors’ inventions and experiences in enhancing patient skills for chronic treatment of diabetes and related diseases.

Vienna, October 2014

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<th>Acronym</th>
<th>Description</th>
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<tr>
<td>4S</td>
<td>Scandinavian Simvastatin Survival Study</td>
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<tr>
<td>ABPM</td>
<td>Ambulatory blood pressure monitoring</td>
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<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
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<td>ATII (ARB)</td>
<td>Angiotensin II receptor blocker, sartans</td>
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<td>BGAT</td>
<td>Blood glucose awareness training</td>
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<td>BMI</td>
<td>Body Mass Index ([\text{kg/m}^2])</td>
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<td>BP</td>
<td>Blood pressure</td>
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<td>CAN</td>
<td>Cardiovascular autonomic neuropathy</td>
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<td>Chol</td>
<td>Cholesterol</td>
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<tr>
<td>CSII</td>
<td>Continuous subcutaneous insulin infusion, insulin pump</td>
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<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
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<tr>
<td>Diab</td>
<td>Diabetes (tables)</td>
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<tr>
<td>EBM</td>
<td>Evidence-based medicine</td>
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<td>ED</td>
<td>Erectile dysfunction</td>
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<td>EEG</td>
<td>Electroencephalogram</td>
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<td>ESRD</td>
<td>End-stage renal disease</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>FIT</td>
<td>Functional Insulin Treatment</td>
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<tr>
<td>FQSD</td>
<td>Forum Qualitätssicherung Diabetes</td>
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<tr>
<td>H</td>
<td>Hypoglycaemia, iatrogenic</td>
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<tr>
<td>HbA1c (Rel)</td>
<td>(Relative) haemoglobin A1c (100%=reference mean)</td>
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<tr>
<td>HCP</td>
<td>Health care professional</td>
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<td>HDL</td>
<td>High density lipoprotein</td>
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<tr>
<td>HOMA</td>
<td>Homeostasis model assessment (of insulin resistance)</td>
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<td>HRV</td>
<td>Heart rate variability</td>
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<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
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<td>IGT</td>
<td>Impaired glucose tolerance</td>
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<td>ISO</td>
<td>International Standardization Organization</td>
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<td>LDL</td>
<td>Low density lipoprotein</td>
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<td>LF</td>
<td>Low-frequency (band, HRV)</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<td>NCEP</td>
<td>National Cholesterol Education Program</td>
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<tr>
<td>NHANES III</td>
<td>Third National Health and Nutrition Examination Survey</td>
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<tr>
<td>NLP</td>
<td>Neuro-linguistic programming</td>
</tr>
<tr>
<td>PSA of HRV</td>
<td>Power Spectral Analysis of heartr rate variability</td>
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<tr>
<td>RR or BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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<tr>
<td>VLCD</td>
<td>Very-low calorie diet</td>
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<tr>
<td>VLDL</td>
<td>Very-low density lipoprotein</td>
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Summary

Previous decades and controlled randomized trials on treatment efficacy and safety in type 1 (DCCT, 1993) and in type 2 (UKPDS, 1999) have shown that more efficient treatment significantly reduces the risk of late complications in diabetes (micro- and macroangiopathy). Later on, consecutive investigations (EDIC, 2003) demonstrated that additional lowering of blood lipids and blood pressure further improved the outcomes. Glucocentric view of the treatment has been replaced with a multifactorial one. Therefore, the treatment intensification with the goal of improved intermediate outcomes (HbA1c, blood pressure and blood lipids) became an unquestionable goal in treatment of type 1 and type 2 diabetes. In practical terms, to include the patient himself in the treatment process appears as the most important factor in closing the loop while using new technologies for blood glucose self-monitoring and insulin delivery (multiple injections and insulin pumps). Simple algorithms for insulin delivery became thus absolutely necessary to allow the patient for improved quality of life while using the algorithms based on insulin production rate of healthy man (Functional Insulin Treatment, FIT, Howorka 1984, 1987ff). But from purely glucocentric focus we have to move to a multifaceted comprehensive approach, as lowering of blood lipids and blood pressure in diabetes remains very important. A high efficacy model of ambulatory care has been developed by the author in the last decades on the medical university of Vienna. There was a strong impact of clinical experiences from the outpatient medical Czech as well as Austrian offices within an informal co-operation.

Aims: The goals of the Thesis include therefore a comprehensive integration of own and international investigations focused on development of contents for a modular structured patient education as well as assessment of its efficacy among others in terms of benchmarking outcomes. The final goal is to provide an overview of related print media for method dissemination developed within the last 25 years.

Methods: (a) Analytical Part: Inventions and investigations on algorithms for Functional Insulin Treatment FIT considering prandial, correctional and basal requirements based on insulin production rate of healthy man, and on insulin requirement and glycemic outcomes, while using various insulin analogs, pumps and continuous glucose monitoring, including assessment of proneness to severe hypoglycaemia and options for reversibility of autonomic neuropathy.  
(b) Synthetical Part: Invention of a modular patient education system DiabetesFIT® including among others modules Diabetes basics, FIT, Pregnancy and diabetes, Hypoglycemia prevention, Hypertension and ESRD prevention, Hyperlipidaemia, Metabolic syndrome Slim n FIT, and Updates. The assessment of its efficacy using benchmarking outcomes from a common database of
FQSD (Forum Quality Assurance in Diabetes) for German and Austrian centres. Seven largest German and seven Austrian diabetes centres have been selected (voluntary participation for benchmarking purposes, total of 16403 ambulatory patients (all/type 1/type 2; x+sd): n=16403/2335/13114. We achieved consistently the best positions for relative HbA1c (type 1: 130%, type 2 diabetes: 120%, reference mean=100%)., the lowest systolic (123+17 mmHg) and diastolic BP (72+10 mmHg), total (191+33 mg/dl) and LDL cholesterol (99+28 mg/dl) in both diabetes types (p<0.001 vs. the rest of the cohort) despite the longest diabetes duration in our patients. We have normalized outcomes of diabetic pregnancies in terms of LGA, SGA, gestation duration and disappearance of postnatal hypoglycaemia.

**Results:** As a result of a consistent diabetes translation research, media for dissemination of modular structured education within DiabetesFIT® have been developed: 9th German editions of a monograph for patients ("Insulinabhängig?...,” Kirchheim Publishers, Mainz, with translations into Czech: "Pichate si insulin?...“ and English ("Diabetes? Insulin-dependent?") and four editions for health care professionals “Funktionelle Insulintherapie” Springer Publishers Berlin with translations into Polish, Hungarian, English in the US have been achieved. A Chinese edition is planned for the academic year 2014/15. The modular system for transfer of patient competence has been successfully spread to HCP within multiple international FIT Seminars for physicians.

**Conclusion:** Translation of comprehensive secondary and tertiary diabetes prevention by means of therapeutic education lead to continuous active creation of a world where the chronically ill often wants to belong. We hope for the impact on the health care systems, so that patients get these services reimbursed all over in the EU.
1. Introduction


In the last three decades, our goal was to develop an efficient model of comprehensive, integrated care, ready for replication and easily applicable in outpatient care setting. The presented Thesis covers the subject of treatment optimization for both, type 1 and type 2 diabetes based mainly on outpatient care and focusing on secondary and tertiary prevention while providing the patient with the maximal treatment competence. Today, as defined in Wikipedia, Integrated care is also known as “integrated health, coordinated care, comprehensive care, seamless care and transmural care – (...which is) a worldwide trend in health care reforms and new organizational arrangements focusing on more coordinated and integrated forms of care provision. Integrated care may be seen as a response to the fragmented delivery of health and social services being an acknowledged problem in many health systems.” Integrated care covers a complex and comprehensive field and there are many different approaches to and definitions of the concept. WHO gives the following definition: *Integrated care is a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion. Integration is a means to improve services in relation to access, quality, user satisfaction and efficiency*.

Central concepts of the integrated care literature distinguish between different ways and degrees of working together and three central terms in this respect are autonomy, co-ordination and integration. While autonomy refers to the one end of a continuum with least co-operation, integration (the combination of parts into a working whole by overlapping services) refers to the end with most co-operation and co-ordination (the relation of parts) to a point in between. Distinction is also made between horizontal integration (linking similar levels of care, e.g. multiprofessional teams /in our case e.g. cooperation between eye specialists, nephrologists, diabetologists/) and vertical integration (linking different levels of care, e.g. primary, secondary and tertiary care).

The purpourse of modular education model was to provide an optimum care in the sense of mainly horizontal integration with only little degree of vertical integration (inclusion of general practitioners for continuous care and university tertiary care for end stage renal diseases). International models of integrated care includes among others Kaiser Permanente, US Dept of Veterans Affairs and Mayo Clinic (*Wikipedia, “Integrated Care”,* download on 2. Aug. 2014)
The concept of comprehensive care becomes more important in historical context. Until the middle of the past century the acute medicine represented the majority of all medical care. In the recent decades however, it became clear that in the developed industrial world the needs for treatment of chronic diseases will determine the total costs of health care. Thus, the prevention of late complications and/or “secondary” diseases is the utmost necessity.

In the case of diabetes mellitus with its late complications and associated diseases (central obesity, hypertension and hyperlipidemia), the focus was – and sometimes even now still is – on the treatment of acute complications such as ketoacidotic coma or severe hypoglycemia and in case of type 2 diabetes often on late complications like neuropathy associated ulcerations (diabetic foot) or on myocardial infarction, resulting from insufficient treatment. For decades, the necessity of active involvement of the patient into the therapy process was neither recognized nor induced. Although irrational, this “traditional” focus in the treatment was justified by patient non-compliance, his ignorance and unwillingness to stick to the physician’s recommendations.

The very early proponents of patient active involvement in the treatment were Joslin (Joslin 1924) and Stolte (Berger 2000). However, they have been misunderstood, and their patient-oriented solutions not accepted. Finally, in the 1980’s medical communities in Switzerland, in Germany and in Austria had accepted the active patient role in the treatment (Assal et al, 1985, Mühlhauser, Bruckner, Howorka et al, 1987). The author of this thesis developed functional insulin treatment targeting on normoglycemia and flexibility. In this sense, it has been shown in the recent decade only, that the quality of treatment can also be defined by patient involvement in the treatment process. It has been recognized that this can only be achieved by thorough and structured patient education. Group education became a solution of choice due to its social, psychological and economical advantages (Howorka et al, 1994, Int J Clin Pharm Therap, and Thesis Hospital Management). The establishment of group training programs is costly and has far-reaching structural effects in the area of health care. In this way the time since the publication of the most relevant diabetes-related multicenter study, the Diabetes Complication and Control Trial (DCCT Research Group 1993), together with the recognition of relevance of structured education, became the most decisive turning point from the traditional, end-stage and acute-complication-related treatment towards -- hopefully -- definitive establishment of chronic care oriented on primary, secondary and tertiary prevention, patient involvement, and structured therapeutic education. Patients have been deliberated from the passive role as object of physician’s rigid prescriptions and changed to active partners and accepted contributors to the every day treatment (Howorka 1987). Despite of the fact of seemingly general acceptance of this active patient role (Brown 1990), as the unsolved problem remained the lack of “homogeneity” of patient needs in rehabilitation and education. The targets and contents of structured education for individuals with insulin-dependent diabetes (type 1 diabetes) for youngsters in puberty are very different from those ones for overweight
1.2. Gender aspects of secondary and tertiary prevention in diabetes

1.2.1. Known gender differences in coping with diabetes

Previous investigations of Enzlin et al. in 2002 have focused already on gender differences in coping mechanisms in type 1 diabetes. Authors evaluated gender related variables in the psychological adjustment to diabetes as well as the relation between such adjustment and metabolic control in patients with type 1 diabetes (Enzlin et al. in 2002). “The 280 adult patients attending the outpatient diabetes clinic of the university hospital in Leuven, Belgium, completed psychological self-rating questionnaires evaluating coping, depression, marital satisfaction, cognitive and emotional adjustment to diabetes where metabolic control was assessed by HbA1c-values. This study documented that men used significantly more active coping, less avoiding, less social support seeking and less depressive coping. Despite these active coping mechanisms in men, their glycaemic control was not significantly better than in women. In contrast, women reported in this study more depressive symptomatology than men did and more women were depressed. Significant gender differences were also found in psychological adjustment to diabetes. The psychological factors negatively related with the psychological adjustment to diabetes in men and women are depressive coping and depressive symptoms. The study on described coping mechanisms however give only insufficient information on the resulting gender specific disease-related quality of life and treatment satisfaction. These target variables have been investigated in our study” (Enzlin et al. in 2002).

Another study on a similar subject targeting coping mechanisms in type 2 diabetes (Kacerovsky et al 2009) has shown that “women employed more active strategies for coping with diabetes, including religion (p=0.0001), active coping (p=0.048) and distraction (p=0.007). Women reported lower satisfaction with social support (p=0.034), but not more depression than men” (Kacerovsky et al 2009). This study contradicts to some degree the findings of Enzlin, but the patient cohort was different.
1.2.2. Sex and gender differences in diabetes: Vascular complications and treatment

A recent review of Franconi et al. (2012) has indicated, “how diabetes mellitus and cardiovascular diseases act ‘as two sides of the same coin’: diabetes is recognized as an important risk factor for cardiovascular disease while patients with ischemic cardiovascular diseases often have diabetes or pre-diabetes” (Franconi et al., 2012). Franconi indicated, that “as firstly shown by Framingham study, diabetic women have an increased cardiovascular risk some 3.5 fold higher than non diabetic women, against an increase of "only" 2.1 fold found in male subjects” (Franconi et al. 2012, and among others Lee et al., 2000, Kanaya et al. 2002, Standl et al. 1995).

Considering the impact of sexual hormones on glucose homeostasis, the insulin resistance related molecular pathways suggest a gender specificity mechanism in the development of complications of diabetes leading to the unmet need of gender therapeutic approaches. This has also been seen in other diabetic complications such as renal diseases, which seems to progress at a faster rate in women compared with males and females benefit less from treatment than do men. Interestingly, none of the trials done so far are primarily designed to assess sex and gender differences in the benefit from a specific intervention strategy, usually de facto excluding fertile women from experimentation. The inclusion of gender issues in design of future studies has already been repeatedly requested (Kautzky-Willer et al, 2009). As discussed, in many necessary interventions, women receive their necessary therapy much later and to the less intensive degree. Franconi et al. 2011 finalizes with a call to “provide a more base evidenced medicine for women and to reach equity between men and women, asking for gender epidemiological reports, and for preclinical and clinical research becoming mandatory to evaluate the impact of gender on the outcomes” (Franconi et al. 2011). The Italian group asks therefore for improving gender awareness and competency in the health care system. As these differences in the DCCT/EDIC studies have been only sparingly published, we have investigated these disparities thoroughly.

Functional insulin treatment FIT discriminating between prandial, basal and correctional use of insulin was shown to improve glycaemic control, treatment satisfaction and enhance perceived control over diabetes. In our own investigation, on gender differences in intermediary outcomes as well as late complications we were able to demonstrate that men with diabetes are more prone to severe hypoglycaemia, they reach specialised care later and are much more subjectively impaired apparently due to real (late complications) and gender induced disadvantages in their social roles due to a chronic disease (Howorka 2012, Thesis MSc Gender Med).
1.3. **Our own inventions: algorithms of functional insulin treatment**

To assure a transfer of the methodology of functional insulin treatment to other centres various approaches have been developed, validated, and implemented. They include:

1. Development of algorithms derived from insulin production of healthy men *(Howorka et al. 1984, WiKliWo)*

2. Development of nomograms based on clinical data of patients under conventional treatment who have been switched to FIT. These nomograms were a part of an academic thesis at the Technical University of Vienna under supervision of Prof. Rudolf Dutter. These nomograms are reduced to the most relevant parameters which are individuals’ mean daily insulin requirement as well as resulting mean daily blood glucose. The nomograms are a relevant part of the manual for physicians translated into four languages, *K. Howorka, Springer Publisher*, see Results.

3. Development of formulas based on daily insulin requirement for correctional basal and prandial insulin need. These formulas have been published and are a part of patient manual, translated into two languages, *K. Howorka, Kirchheim Publishers Mainz.*

4. Together with the development of nomograms, a software for initial algorithms for FIT has been developed (part of the mentioned Thesis in point 2.)

1.4. **Biomedical engineering and its development in assessment of late complications of diabetes mellitus: hypoglycaemia unawareness and heart rate variability**

The basic investigations have been performed 1986-2000 on the phenomenon of “hyperglycemia cluster” *(Howorka et al. 1986, Diabetologia)*. Severe hypoglycemia hits only a minority of patients (approx. 12-20% of people with insulin dependent diabetes but these individuals contribute to almost 90% of all severe hypoglycemic episodes). These findings have been confirmed among others by *DCCT 1993* and *EDIC 1999*. Severe hypoglycemia in type 1 diabetes only seldom results in death, however, if associated with concomitant autonomic neuropathy, the probability of deadly outcome is increased. While investigating the phenomenon of hypoglycemia cluster, we started to routinely measure and quantify the impairment of autonomous nervous system with spectral analysis of heart rate variability. It could be found that the reduction of parasympathetic function is one of the early signs in incipient cardiac autonomic neuropathy. In the following decades we have been investigating methods for potential reversibility of autonomic function in impaired autonomic balance in diabetes. Measures like food restriction/fasting, endurance training, and guided breathing had a strong impact and allow a restoration of impaired autonomic function.
1.5. Own vision and patient-therapist relationship strategy: Empowering through competent patient leadership

The implementation of routine “empowerment” in the 80s resulted in a “revolution” in the treatment of chronic diseases such as diabetes. In our context that was facilitated through several factors:

- The establishment of routinely used indicators for quality of glycemic control ($HbA1c$, assessing the glycemic control within the time period of about 6 weeks before the blood sampling; and fructosamine, two weeks),
- First cross sectional assessments of such indicators within different patient subgroups. The author’s own investigations (Howorka-Czerwenka et al, 1983, Derfler, Howorka et al, 1986) showed that solely 4% the diabetic patients in the rural area and up to 30% of those cared for by an university diabetes outpatient department reached the therapy goal of the near normalization of the $HbA1c$,
- Systematic assessment of intermediate treatment outcomes: Establishment of a specific computerized data acquisition system for routine assessment of quality indicators (Howorka-Czerwenka et al, 1983), mainly those related to outcome quality like the degree of late complications, including retinopathy, nephropathy, coronary heart disease, macroangiopathy and neuropathy (Howorka-Czerwenka 1983),
- The step-by-step definition of the most important contents and rehabilitation methods (Howorka 1987, Springer Publishers Berlin) including mathematical description of algorithms for insulin replacement (Howorka-Czerwenka 1984A, §10-report, WiKliWo),
- Recognition of the patient’s inability to stick to rigid and unpractical, non-flexible “rules” set by physicians and the patient’s right for self determination in everyday life. Indicators of quality of life (Bradley et al, 1994) have been introduced for routine measurements and use. That made a comparison among treatments and/or centers potentially possible,
- The inpatient treatment of individuals with chronic diseases lost its relevance due to economic and infrastructural difficulties inhibiting patient learning of self-treatment. It became clear that hospitalization is neither necessary nor practical for structured patient group education (Howorka 1987, Grillmayr, Howorka et al, 1989). Thus, secondary and tertiary prevention in diabetes become feasible in an exclusively outpatient setting.

In the context of FIT education, we have been able to perform a randomized clinical trial quantifying individual’s health locus of control and treatment of diabetes, see Methods (Howorka et al. 2000 J Psychosom Res).
The combination of these outcomes in terms of measurable change of health locus of control in combination with favorable metabolic outcomes was most important for further optimization of modular system of structured education. Our goal was to increase individual’s action scope in chronic treatment. As patient is responsible for 99.99% of therapeutic decisions in every day life, we become committed to the transfer of therapeutic competence to the end user to a maximum degree.

1.6. Quality assurance and best practice experience

Although not without controversies, eventually it has been summarized after International Diabetes Federation (IDF) and World Health Organization (WHO) through the European IDDM Policy Group in 1993 (European IDDM Policy Group 1993) where the most important resource for diabetes care has been identified in the patient him/herself. In the Declaration of St Vincent in 1989 (http://www.show.scot.nhs.uk/crag/topics/diabetes/vincent.htm, WHO 1990, WHO 1992, European IDDM Policy Group 1993) it has been eventually recommended to develop, initialize and evaluate comprehensive programs for control of diabetes and prevention of diabetes late complications. Since these recommendations have been published, systematic assessment of indicators of process-, structure- and outcome quality has become inevitable necessity. In the mentioned document from 1989 it has been clearly stated that diabetes is a model for prevention and self care. Several years after the Declaration however, reports released displaying an almost comparable situation as before the St Vincent for many of targets set (Piwernetz et al, 1993). Thus, the recommendations from the year 1989 remained still valid.

In Vienna, and typically for the rest of the world, hospitals have been established exclusively for acute, traditional care. Behavioral modification and learning in general required the opposite: an adequate setting for learning prevention of acute and late complications with groups of patients. Resources to create such setting were lacking within the clinics (Grillmayr, Howorka et al, 1989). In this context, a Research Group Functional Rehabilitation emerged from a theoretical Institute of the medical Faculty in Vienna (Institute of Biomedical Engineering and Physics, later on Ctr for medical Physics and Biomedical Engineering). Scientific focus was put on development and application of technical aids indispensable for appropriate rehabilitation. To assure adequate chronic care, author’s outpatient office serves for clinical activities such as research and care. After the certification which was an eventual coronation for construction of a quality management system, the group became a registered association „International Research Group Functional Rehabilitation and Group Education“.

We have improved quality in following dimension:

1. **Outcome quality** relates to the change of the total state of health of the patient, either during the hospitalization or through ambulatory interventions. Such status change in case of diabetes can be
assessed by indicators of metabolic/glycemic control (e.g., HbA1c) or late complications rate (e.g., incidence of retinopathy), or with other indicators of psychic, psychosomatic or social wellbeing.

2. **The process quality** deals with the course of treatment-related procedures. It describes the adequacy, relevance and timing of the medical, nursing and infrastructural management. The course of treatment will be judged in relation to the performance and to the degree of goal accomplishment. Indicators of process quality describe the treatment and care processes as well as the management.

3. **The structure or resources quality** has reference to the availability and preparedness of the personnel and the operations-related goods. In case of structured education and rehabilitation of chronic diseases, indicators of structured quality could include development of media for patients and therapists, as well as establishment of various modules of structured education. (*Howorka 2006*)

"Best practice"

Since the end of the last century “best practice” – criteria has been defined. “What’s best practice? Copy with pride”. These criteria include (Source: www.olev.de/b/b-p-kriterien.htm) (*Keehley et al, 1996*)

- Successful over time
- Quantifiable results
- Innovative
- Recognized positive outcome
- Repeatable or replicable with limited modifications
- Has certain importance
- Not linked to unique situations which makes it transferable to other organizations

In the USA had the criterion of “best practice” as the outcome of benchmarking processes very often consequences for policymaker. In Austria, this is only seldom the case up to now…

Our goal is to develop a valid and replicable model for effective rehabilitation, treatment and involve,ent of the end user in the treatment to a maximum degree. As it will be shown further, this approach contributes to the best achievable results. The implementation of the Quality Management system was of paramount importance in 1997.
Figure 1.1 The structure of the Research Group Functional Rehabilitation and Group Education.

Who is the client?

While the research and education are often a part of universitary activities, the clinical care became the main task within the extrauniversitary specialized clinical outpatient office. The quality management system and ISO-conformity was reached for all three main interrelated processes (research, education, rehabilitation). The “clients“ of the research group are mentioned (modified after Res.Group Funct.Rehab. & Gr. Educ., Quality Mgmt Handb. 2004 and Howorka, Thesis MBA 2007).

*a multicomponent organizational solution was chosen to assure political stability and operational flexibility*
1.7. Aim of the thesis in the context of epidemiological data

The first Austrian diabetes report was prepared in 2004 (Rieder et al, 2004, Dorner et al, 2006). In combination with other sources, it can be assumed that the diabetes prevalence and incidence, as well as diabetes-related mortality, are increasing (in the report, however, the mortality “seemingly decreased due to the fact that neither coronary heart disease nor stroke were not coded as complications of diabetes”). Details about the outcome will follow in this chapter, strategies for primary, secondary and tertiary prevention of type 2 diabetes and subsequent diseases have been stated. It has been stated that “Austrian policymakers and politicians have reacted promptly and positively”.

**Recommendations were (Dorner et al 2006):**

**Professional level**

- Standards for care of diabetes patients with cardiovascular disease need to be developed, implemented and monitored. This process should be assisted with practical guidelines.
- Patients at high risk should be identified as soon as possible so that active treatment including lifestyle modification can be initiated at an early stage. Patients need to be involved actively in the management of their care.
- Health care professionals need to be engaged in this process and adequately trained.
- The creation of a network of care across health care providers should be promoted.

**National level**

- The economic impact of cardiovascular disease and diabetes on the active population needs to be recognized.
- Sufficient funding must be provided, particularly for
  - empowerment of patients to ensure that they receive appropriate education and risk-reduction treatment
  - appropriate training of health care providers
  - research at the national level.
- Standards of care provided for patients with diabetes and cardiovascular disease should be monitored according to available guidelines.
- Cross-governmental initiatives to improve lifestyle, including nutrition, physical activity, environment and education should be implemented.
European level

• EU-wide standards of care should be set and reflected by national guidelines with consistent targets to reduce morbidity and mortality.
• Equitable access to care should be ensured across the EU.
• The immediate and long-term impact of the implementation of programs of care should be monitored.
• The initiatives of national governments, industry, NGOs and health care professionals to provide opportunities for healthy living should be optimized.
• Research in the field of diabetes and its complications should be funded from Framework Programs.

Finally the experts have defined the following priorities:

• The combined impact of diabetes and cardiovascular disease on the individual patient, health services and economy needs to be recognized and addressed.
• Equitable access to appropriate management and care of diabetes, cardiovascular disease and associated risk factors must be provided to all patients.
• The implementation of available European management guidelines for diabetes and cardiovascular disease needs to be supported at the national level.
• Immediate and long term outcomes following the implementation of improved programs of care need to be monitored.
• Funding of European research in diabetes and its complications needs to be enhanced.”

EU diabetes strategy

At EU level there is a need for an EU diabetes strategy to include

• an EU Council Recommendation on diabetes prevention, early detection and management
• a permanent EU Forum for exchange of best practice and
• a collection of comparative data on common measurement criteria.

The question was what really causes the low treatment efficacy of secondary and tertiary prevention of diabetes. According to Narayan et al, 2000, “The failure to use efficacious treatments as recommended is often caused by a breakdown at the patient, health care provider, and system levels, and the process of ameliorating these problems is fraught with difficulty”.

In order to solve the discrepancy between the therapy target for millions and the present state of facts, the translation research emerged (Narayan et al, 2000)

It strives to translate science into clinical and public health practices and it attempts to measure and/or present a variety of real world attributes of interventions shown to be efficacious in idealized settings.
These attributes include

1. public health impact (i.e., extent of spread and equity),
2. effectiveness (i.e., influence on process outcomes and sustainability),
3. efficiency (value under conditions of limited resources),
4. transferability (i.e., issues concerning applications in other diverse settings and situations).

It was stated by Narayan et al., 2000 that “…many more major translation research initiatives […] are needed to suggest steps toward optimal population care for diseases like diabetes”.

Aim of the thesis

The thesis summarizes the basic investigation (analytical part) as well as own inventions and (synthetical part) for improvement of diabetes care in the sense of diabetes translation research. The analysis of internationally used measures for quality improvement in comprehensive diabetes prevention, as well as the author’s own experience, have shown that the traditional therapy forms based on inpatient care focusing on emergency treatment are not able to achieve the accepted goal of secondary and tertiary prevention of late complications in a chronic disease. As a result, the developed rehabilitation model includes modular education and care for outpatients with chronic diseases such as diabetes, hypertension, hyperlipidemia, often based on central obesity.

Description the multi-component system for health promotion based on therapeutic education and proof of its efficacy in metabolic syndrome and diabetes remain the key component for providing an applicable model for routine practice. It will contribute to future optimization and dissemination of DiabetesFIT®. The ultimate goal is to present specifically designed media for enhancement of therapeutic competence in chronic diseases a potential impact on policy maker will be considered.
2. Methods, analytical part: Basic investigations and inventions as a background for educational contents

2.1. New technologies: Insulin analogs, continuous glucose monitoring and insulin pumps

The introduction of biotechnology with development of short acting and delayed acting insulin preparations at the end of last century was one of the milestones toward spreading insulin treatment and making it readily available in western world. In general, for functional insulin treatment the delayed acting preparations have been not necessarily that advantageous as the short acting ones. The author of this thesis was involved in several multi-centre and/or investigator initiated trials related to the introduction of insulin analogues.

**Figure 2.1 Choices of insulin preparations**

(modified after Howorka, “Diabetes? Insulin-dependent?... 2011, Kirchheim Publishers Mainz). Knowledge of insulin pharmacokinetics and pharmacodynamics is an essential prerequisite for designing appropriate insulin treatment.)
2.1.1. Algorithms of Functional Insulin Treatment: Mathematical model for transfer of FIT, nomograms, IT solutions for promoting of therapeutic switch to FIT

Algorithms for functional insulin treatment have been derived from insulin production rate of healthy man.

Figure 2.2 Algorithms for functional insulin treatment

Modified after Howorka et al. 1984 and Howorka et al. 1990. and are based on insulin production rate of healthy probands (Waldhäusl et al 1979)

Moreover, based on empirical data, nomograms for transfer to FIT have been developed with Institute of Statistics and Probability Theory (Professor R. Dutter), Technical University Vienna. The following tables were devised on the basis of statistical analysis of data from 158 FIT-patients.

The baseline data from each patient – weight, height, HbA1c, ketonuria, urine glucose, mean blood glucose (MBG), daily insulin requirement, diet (in carbohydrate choices per day) have been acquired during three days before the switch to FIT) i.e. under conventional or intensified treatment). They were then related to the individually optimised algorithms from the end of the training programme (MBG 118±21 by means of stepwise regression in order to generate the nomogram) (Egger, 1986, Thesis). For simplification, the baseline data were reduced to the two statistically most relevant parameters: the total daily insulin dose (in IU/d) and the daily MBG (10-12 measurements/day including postprandial values). The original calculation of the initial algorithms for FIT was based on all of the parameters mentioned above and is available as a CD. The basal delayed acting insulin is divided into two approximately equal
portions and administered twice daily. When NPH or detemir insulins are used for the basal dose, the evening dose should be administered late, just before going to bed, and never before the evening meal. For “combined” basal rate with insulin Lantus® in the morning and shorter delayed acting insulin at bedtime (insulin NPH or detemir, and for CSII, the total basal dose per 24 hrs) given in the nomogram should be reduced by approx. 10%.

Figure 2.3 Nomograms for generating the initial algorithms for FIT

Appendix 3: Nomogramm for Generating the Initial Algorithms for FIT

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Fig. A 3.1e. Delta BG: Amount that blood glucose is lowered by 1 U of regular insulin. This value should be increased (i.e., a greater drop should be assumed) in situations that have a high risk of hypoglycemia (for example, at the beginning of FIT) and for patients with characteristics that increase the risk of severe hypoglycemia.

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Fig. A 3.1f. Delta BG: Amount that blood glucose is raised by 1 carbohydrate unit (12 g CHO = 50 kcal from carbohydrates).
### Appendix 3: Nomogram for Generating the Initial Algorithms for FIT

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Fig. A 3.1a.* Amount of basal long-acting insulin per day.

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Fig. A 3.1b. Component of regular insulin in the morning basal dose.

* With high daily insulin requirements it is advisable to use also an evening regular insulin as an integrated basal component to keep the dose for delayed acting insulin as low as possible.
2.1.2. Treatment satisfaction with short acting analogs: insulin lispro. Considerations for FIT Algorithms

Early in the 1990s insulin analogues have been introduced to the market.

We have investigated the impact of the switch from regular to a short acting insulin lispro by means of a randomised, controlled, cross-over study (Howorka et al., Quality of Life Research 2000). The treatment satisfaction has been evaluated with newly developed instruments (DTSQ extended for FIT together with Prof. Clare Bradley, initial instrument included only first 6 questions).
The psychometrics of the newly developed instrument showed a satisfactory data. The study has shown consistently a significant increase of treatment satisfaction in all categories dealing with correctional and prandial insulin delivery clearly showing advantages of short acting insulin analogues for functional insulin treatment.

In summary (Howorka et al 2000), “… even a small improvement in satisfaction with treatment for a chronic disease can be valuable. In parallel, glycaemic control improved with lispro (e.g., HbA1c p=0.023). Improved satisfaction with treatment was even more apparent with DTSQ(C) (Change version of DTSQ) than DTSQ(S) in patients who at baseline were at or near ceiling for treatment satisfaction.“ (Howorka et al 2000)

Figure 2

Figure 2.4 Increase of treatment satisfaction in classical DTSQ in cross-over study (Howorka et al 2000)
Furthermore, as evaluated in 1998 (Howorka et al. 1998, Diabetes Nutrition Metab), the switch to short acting analogues had impact on algorithms for FIT: “Our aim was to investigate the necessity and degree of dosage adaptation to pre-defined criteria during ambulatory transfer from regular insulin to insulin lispro under functional insulin treatment (FIT), discriminating between prandial, basal and correctional use of insulin and emphasizing flexibility. Open label prospective observation study with within subject
comparison vs. baseline. 63 insulin-dependent diabetic patients who routinely make acute corrections of hyperglycaemic blood glucose levels, have been transferred to insulin lispro and were evaluated after 2 and 11 weeks of observation period with insulin lispro. Basal insulin including either human insulin ultralente in the morning and either NPH (62% of cases) or lente type insulin late before bed rest (22%), twice daily ultralente (13%) or twice daily lente (3%) was suitable for insulin lispro. The necessary algorithm adaptation was of minor degree: increase of delayed-acting insulin before bed rest by 0.3 U (p=0.04), decrease of morning basal short-acting component by 0.3 U (p=0.008), no change in prandial insulin requirements, decrease of algorithm for expected blood glucose lowering per 1 unit of short-acting insulin by 0.1 mmol/l (p=0.004) and decrease of postprandial target for hyperglycaemia correction by 0.2 mmol/l (p=0.008). Transfer to insulin lispro induced in FIT educated patients a lowering of mean blood glucose by 0.4 mmol/l (p=0.004), of mean postprandial blood glucose by 1.4 mmol/l (p<0.001) and of HbA1c (p=0.04). No episodes of severe hypoglycaemia were recorded after transfer to insulin lispro. FIT allows safe ambulatory transfer to insulin lispro, a slight decrease in short-acting insulin in the morning is recommendable.

<table>
<thead>
<tr>
<th>Algoritms/Investigations</th>
<th>1: regular</th>
<th>2: lispro, 2wk</th>
<th>3: lispro, 11wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal delayed-act. ins. morning U</td>
<td>10.8±3.9</td>
<td>11.3±4.30.02</td>
<td>11.0±3.90.46</td>
</tr>
<tr>
<td>Morning short-acting component U</td>
<td>2.3±1.9</td>
<td>2.2±1.90.10</td>
<td>2.1±1.80.208</td>
</tr>
<tr>
<td>Delayed-acting late evening U</td>
<td>10.8±4.4</td>
<td>11.2±4.80.15</td>
<td>11.1±4.30.04</td>
</tr>
<tr>
<td>Prandial insulin/50 kcal CHO U</td>
<td>1.8±0.7</td>
<td>1.7±0.60.51</td>
<td>1.7±0.70.48</td>
</tr>
<tr>
<td>Correction insulin: Delta BG/1U↓mmol/l</td>
<td>-2.4±0.6</td>
<td>-2.4±0.70.53</td>
<td>-2.3±0.60.204</td>
</tr>
<tr>
<td>Target for corr., premeal BG mmol/l</td>
<td>5.7±0.4</td>
<td>5.7±0.40.57</td>
<td>5.7±0.40.38</td>
</tr>
<tr>
<td>Target for corr., after meal mmol/l</td>
<td>9.0±0.6</td>
<td>8.9±0.80.40</td>
<td>8.8±0.80.006</td>
</tr>
</tbody>
</table>

Table 2-1 Change of FIT algorithms during switch to insulin lispro

(Howorka et al 1998, DNM)

Functional insulin treatment allows safe ambulatory transfer to lispro without a relevant change in insulin dosage algorithms. A slight decrease in the morning dose of short-acting insulin is recommendable.

The target point for postprandial correction of hyperglycaemia and the algorithm for blood glucose correction per 1 unit (Delta BG, i.e. lowering of blood glucose by 1 unit of short-acting insulin) were used more „sharply“/aggressively; despite that, the transfer to lispro was associated with lowering of frequency of hypoglycaemic blood glucose values.
2.1.3. Insulin glargine: Computerized generation of sensor modal days

The development of delayed acting insulin analogues seems to improve basal insulin replacement without insulin pumps. With the implementation of continuous glucose monitoring, an objective measurement assessment of glycemic control was possible in addition to assessment of patient treatment satisfaction. Insulin glargine is a very long acting insulin analogue which initially was promised to the patients to be sufficient with only one daily injection. We have participated in a multinational study designed for comparison of insulin glargine injected either before breakfast or before evening meal or before bed-time. We added an assessment with continuous (non-real time) glucose monitoring in the sense of an investigator-initiated trial where we have been measuring also treatment satisfaction. The main target parameter was early fasting glucose: as expected, the highest values have been recorded with pre-breakfast injection indicating insulin waning in the morning hours.

Moreover, it became clear that with “Viennese habits” of larger evening meals, a pre-dinner administration was more advantageous than a bed-time application. The pre-dinner application prevented a post-prandial spike of glucose on the one hand and, apparently due to maximal insulin concentration upon awakening, best morning control of dawn phenomenon was achieved on the other.

![Figure 2.6 Insulin Glargine: Comparison of early morning glucose values with different injection timepoints of insulin glargine (Howorka et al 2003)](image)
Due to the analysis of various insulin application timepoints, since the publication of the results of this investigator-initiated trial, in patients who have chosen only once daily application of insulin glargine, we recommend the pre-dinner time-point as probably the most advantageous option.

Figure 2.8 Glargine: Comparison of hourly circadian sensor modal days for pre-breakfast and bedtime insulin administration (Howorka et al 2003)
2.1.4. CSII versus injections for functional insulin treatment: crosssectional and controlled studies

Continuous subcutaneous insulin infusion (CSII) in type 1 diabetes results usually in moderate improvement of glycemic control and diabetes-related quality of life (Pickup Meta-analysis 2002, Hoogma et al.2006). Such improvement is dependent on diabetes education provided and is inversely related to the initial glycemic control on pre-pump treatment. The impact of structured patient education received was only inconsistently taken into account and to a limited degree. Around 10 – 20 % of our FIT patients (functional insulin treatment, discriminating between prandial, correctional and basal insulin use, (Howorka et al. 1984, 2008) routinely choose CSII, often hoping on more stability in their glycemic control. The acceptance of various models of pumps varied a bit over last decades, with new models becoming eventually small enough for long term acceptance and sophisticated enough even to enhance some “insight” interaction and device-induced cohesive consumer and/or self-help communication settings all over the world. Diabetologists controversies on pro and con in CSII continue to somehow confuse patients even more so that sometimes industrial interests can finally be best represented (Pickup and Shade 2006).

In Austria, insulin-pumps as technical rehabilitation aids are easily covered from specific sources of health insurance, even including a hospitalization of 21 days in contrast to structured outpatient group education for type 1 diabetes. which currently has to be covered by patients themselves.

Our aim was to compare treatment efficacy assessed with intermediate outcomes in FIT educated patients with long term type 1 diabetes who later on have chosen CSII vs. those who have chosen multiple daily injections, MDI by means of a crossectional study comparing the intermediate treatment outcomes (HbA1c), (Pumprla et al. 2008). This investigation has shown that in contrast to previous findings, CSII was equally effective as MDI therapy indicating that education has the main impact on glycemic outcomes. As the comparisons between CSII and MDI remained controversial, a specific retrospective case-controlled study was initiated. Two matched controls (matched for gender, diabetes duration and the degree of initial late complications have been chosen for each patient with CSII after a FIT education. Long-term data have been extracted and evaluated in time slices of one year each. Furthermore, we evaluated the impact of such freely chosen treatment strategy (CSII vs. MDI) on parameters of quality of life, treatment satisfaction and subjective perception of empowerment.

In summary, both investigations provided evidence that continuous subcutaneous insulin infusion in self-selected individuals provides comparable results to MDI in terms of glycemic control as well as treatment satisfaction.
Figure 2.9 Results of a cross-sectional study CSII vs MDI after FIT (Pumprla et al. 2008)

**Cross-sectional Study: Continuous Subcutaneous Insulin Infusion or Multiple Daily Injections for Functional Insulin Treatment in Type 1 Diabetes?**

**Background and Aim**

Continuous subcutaneous insulin infusion (CSII) in type 1 diabetes results usually in moderate improvement of glycaemic control and diabetes-related quality of life which is dependent on diabetes education provided and inversely related to the initial glycaemic control on pre-pump treatment.

Our aim was to investigate motifs and characteristics of FIT (functional insulin treatment) -educated patients with type 1 diabetes who later on have chosen CSII vs. those who have chosen multiple daily injections (MDI including insulin glargine).

Furthermore, we evaluated the impact of such freely chosen treatment strategy (CSII or MDI) on parameters of metabolic control, quality of life and treatment satisfaction.

**Methods**

Cross-sectional study comparing the outcomes in FIT-educated patients using either CSII vs MDI including glargine for FIT discriminating between prandial, correctional or basal insulin.

Structured outpatient FIT UPDATE module (educational weekend specifically developed for FIT patients) including detailed information on insulin pumps and pens was used for the invitation to participate in the study.

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>MDI</th>
<th>CSII</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>111</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age [yrs]</td>
<td>49±4±14.8</td>
<td>44.0±11.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Gender [m/f] [%]</td>
<td>49/62 (69%)</td>
<td>7/18 (55%)</td>
<td>0.21</td>
</tr>
<tr>
<td>BMI</td>
<td>24.4±9</td>
<td>24.4±7.7</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes duration [yrs]</td>
<td>22.8±12.6</td>
<td>22.1±8.3</td>
<td>0.81</td>
</tr>
<tr>
<td>FIT duration [yrs]</td>
<td>11.4±6.7</td>
<td>12±7.3</td>
<td>0.56</td>
</tr>
</tbody>
</table>

**Results**

Differences found for reported number of daily blood glucose self-measurements (CSII: 5.4±0.9 vs MDI: 5.1±0.8, p=0.01), perceived dietary flexibility (p=0.03), DTSQ for FIT item 4 for convenience (p=0.04) and item 13 for basal insulin satisfaction (borderline, p=0.06) but not for HbA1c (7.1±0.9 vs 7.3±1.0%, p=0.4), neither for frequency of daily dosage adjustment (p=0.3), treatment satisfaction total score (Bradley s et al. DTSQ extended for FIT: 90±20 vs 86±20, p=0.2) and its subscores (DTSQ classic total score, p=0.4, subscores predictability p=0.6, hypoglycaemia proneness p=0.2, basal insulin p=0.1, correctional insulin p=0.3, prandial insulin p=0.5) nor for diabetes-specific quality of life (Bradley s ADDQoL), and subscores (all p>0.3: for working life, family life, friendship, sex, physical appearance, things to do, holidays and travel, self-confidence, society reaction, future, finances and dependence), with tendency towards significance for subscore in motivation showing higher motivation in pump patients (p=0.1) and enjoyment of food (p=0.07).

**Conclusion**

Functional insulin use with in average more than 6 daily injections results in FIT-educated patients in similar outcomes independently of the mode of insulin delivery. Pump treatment is associated with slightly more “motivation” for treatment.
Figure 2.10 Results of a retrospective case-controlled study CSII vs MDI after FIT

**AIM**

- To compare treatment outcomes in FIT educated patients with type 1 diabetes who later on have chosen CSII vs. those who have chosen multiple daily injections, MDI by a mean of a retrospective case-controlled study.
- To evaluate the impact of such freely chosen treatment strategy (CSII vs. MDI) on parameters of quality of life, treatment satisfaction and subjective perception of empowerment.

**METHODS**

- Retrospective case-controlled study where for each CSII patient two MDI controls using FIT have been used, matched for diabetes duration, FIT duration, associated diseases at time point of FIT training and if possible, gender.
- Selected from participants of an annual outpatient FIT update (educational weekend specifically developed for FIT patients) who were also in treatment of the diabetes outpatient office working specifically with diabetes patient education.
- The impact of diabetes was measured with ADDQoL (Bradley, 1999), DTSQ extended for FIT State version (Howorka and Bradley, 2000) and DES (Andersson, 2003) and with a specifically developed ranking scale for advantages and disadvantages of pumps and/or injections.

**PATIENTS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CSII</th>
<th>MDI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>30</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Age [yrs]</td>
<td>45.2±12.2</td>
<td>44.6±13.0</td>
<td>0.83</td>
</tr>
<tr>
<td>Gender [m/f]</td>
<td>7/23</td>
<td>20/40</td>
<td>0.33</td>
</tr>
<tr>
<td>Diabetes duration [yrs]</td>
<td>24.2±13.3</td>
<td>23.4±10.2</td>
<td>0.78</td>
</tr>
<tr>
<td>FIT duration [yrs]</td>
<td>13.0±6.4</td>
<td>14.0±5.9</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**OUTCOMES**

The outcomes are represented by graphs showing the comparison between CSII and MDI treatments. The graphs illustrate the reduction in glycemic control, improvement in quality of life, and better overall satisfaction with the treatment Regimes.

**CONCLUSIONS**

- No significant differences were found between outcomes of CSII and MDI in FIT educated patients beyond an initial HbA1c improvement of 6-12 months.
- Functional insulin use with in average more than 6 daily injections results in FIT-educated patients in similar outcomes independently of the mode of insulin delivery.
2.1.5. Continuous glucose sensing: clinical experiences

Initially, continuous glucose monitoring did not provide any option for the patient for an immediate correction of neither hyper nor hypoglycemia. This kind of glucose monitoring was used for retrospective analysis as already shown in the study comparing various injection time points for insulin glargine (Howorka et al. 2003). In this way the so-called “sensor modal day” has been created, a glucose profile resulting from hourly means of individual glucose values, useful for comparison of treatment regimens.

Figure 2.11 Computation of sensor modal days on consecutive days in the same individual (Howorka et al. 2003)

The introduction of real-time glucose monitoring was a further step for improving treatment efficacy with functional insulin treatment. The implementation of a routine use of continuous glucose sensing and excellent experiences with the CGMS DexCom Seven Plus® allows to prevent severe hypoglycemia in patients with history of unconsciousness and thus of repeated episodes of severe hypoglycemia requiring external help: With real time-sensor an MBG of 182mg/dl could be achieved.

Figure 2.12 An example of a real time glucose control in a patient with increased risk of sever hypoglycaemia and attention deficit disorder.
2.2. Investigations on iatrogenic hypoglycemia

2.2.1. Hypoglycemia cluster phenomenon

Frequency of severe hypoglycemia events in type 1 diabetes is not equally distributed. Only twelve to twenty percent of type 1 diabetic patients experience confusion or lack of consciousness due to hypoglycemia, but they tend to display severe hypoglycemia repeatedly. This phenomenon has been called hypoglycemia cluster phenomenon (Howorka et al, 1986) and confirmed thereafter (White et al, 1983; DCCT, 1991).

![Diagram showing H4/Year distribution](image-url)

**Figure 2.13** H Cluster Phenomenon. The risk of severe hypoglycemia is not normally distributed in a sample of patients with type 1 diabetes. H4/year means frequency of severe hypoglycemia per patient year. Modified after Howorka 1986.

Clinical classification of hypoglycemia (modified after Howorka et al, 1986) is done according to the degree of acute impairment of cerebral function:

(H1) Minor hypoglycemia: symptoms of hypoglycemia with blood glucose values under 70 mg/dl or accidental blood glucose values free of symptoms under 60 mg/dl. No noticeable limitation of abilities.

(H2) Medium-serious hypoglycemia: loss of rational reasoning. Patient is physically present but mentally "absent" (lowering of vigilance level).
(H3) Serious hypoglycemia: loss of consciousness. Need of external help.

(H4) Serious hypoglycemia requiring medical intervention: loss of consciousness treated with glucagon or intravenously with glucose.

To prevent severe hypoglycemia, several detailed investigations dealing with phenomenon of early vigilance decrease in patients with hypoglycaemia unawareness have been performed (Howorka et al. 1996, Howorka et al. 2000).

2.2.2. Early vigilance decrease during insulin induced hypoglycemia in hypoglycemia unawareness

To elucidate neurophysiological characteristics in hypoglycaemia unawareness we investigated the relationship between electroencephalography (EEG) parameters of vigilance and awareness of various symptom categories early in response to hypoglycaemia in intensively treated diabetic patients with different degrees of hypoglycaemia unawareness (Howorka et al. 1996, Psychoneuroendocrinology).

Hypoglycaemia (venous plasma glucose below 2.2 mmol/l) was induced with an intravenous insulin bolus in 7 patients with insulin-dependent diabetes mellitus (IDDM) with a history of hypoglycaemia unawareness and repeated severe hypoglycaemia, as well as in a group of 7 IDDM patients with good awareness of hypoglycaemia. Both groups were comparable in age, treatment strategy, glycaemic control and level of late complications. Basic cognitive performance and other symptom categories were estimated serially during a period of two hours following the insulin bolus. A vigilance-controlled EEG was recorded continuously; its automatic analysis included the evaluation of vigilance indices. In the baseline prehypoglycaemic state, hypoglycaemia unaware patients showed higher initial vigilance (p=0.05) than the aware group. Unaware patients reported during hypoglycaemia fewer neurogenic (p=0.002, mainly cholinergic, p=0.009) hypoglycaemia symptoms and developed an impairment in cognitive performance over time (p=0.002). EEG analysis indicated a more rapid decrease in vigilance after the hypoglycaemic stimulus for unaware patients than for aware patients. The lowering of plasma glucose to 3.06-3.89 mmol/l already induced a significant increase in delta and theta as well as a decrease in alpha relative power only in the unaware group. Differences between groups as refers to the degree of deceleration were most pronounced early during only slight hypoglycaemia and topographically spread over central and parietal brain regions. Further lowering of plasma glucose induced an even more pronounced, abrupt increase in slow waves in unaware patients at higher plasma glucose levels than in hypoglycaemia aware subjects (for delta waves at 2.41±0.16 vs 1.96±0.1 mmol/l, p=0.04). This preceded the worsening of cognitive performance during hypoglycaemia in unaware patients by 19±3 minutes. Hypoglycaemia unawareness associated with previous unconsciousness is associated with - and may be the result of - an early hypoglycaemia-
induced reduction in vigilance and an early EEG deceleration, which seems to be a teleologically effective measure for delaying eventual cerebral energy failure in hypoglycaemia.

The investigation has been performed on patients with similar diabetes duration, glycemic control and status of late complications. The history of severe hypoglycemia with unconsciousness was the most important feature distinguishing between both patient groups.

Vigilance has been defined as "readiness to adapt the appropriate behavior in a given situation, finding outward expression through the quality and quantity of the behavior occurring in response to a given (internal and external) stimulus situation" (Hermann & Schärer, 1987; Koella, 1982). Vigilance describes the behaviour of watching for and responding to irregular critical signals under monotonous conditions whereby sustained attention is essential for signal detection (perception). The vigilance level can be assessed precisely by various vigilance indices using a computerized EEG evaluation. During our investigation with induction of hypoglycaemia (no clamp methodology, bolus injection), the vigilance level was controlled by verbal commands, assessment of symptoms and tests of cognitive performance. If signs of drowsiness appeared in the EEG, acoustic stimuli were used for vigilance control (Anderer et al., 1992). The following parameters (Hermann & Schärer, 1986; Matejcek, 1982) were used for assessment of vigilance: Alpha slow wave index (one of the most important indices of vigilance) (ASI at Pz), computing the ratio of the alpha power to delta and theta power, and the Index of Alpha Anteriorization (IAA), computing the ratio of alpha power at the frontal lead to alpha power at occipital lead and absolute delta power. In "Results" (see figures) IAA is presented for the dominant, left hemisphere. High ASI and low IAA as well as low slow wave power usually are indicating high vigilance level. A basal EEG was recorded for 3 min before the insulin bolus; after the bolus the EEG was recorded continuously for 120 min (Howorka et al 1996).

To summarise, “hypoglycaemia unawareness associated with previous unconsciousness is associated with - and may be the result of - an early hypoglycaemia-induced reduction in vigilance and an early EEG deceleration, which seems to be a teleologically effective measure for delaying eventual cerebral energy failure in hypoglycaemia". (Howorka et al 1996).
Figure 2.14 Cognitive function and symptoms during hypoglycemia

Patients with history of severe hypoglycaemia display a dramatic decrease of cognitive function without symptoms, while patients without hypoglycemia unawareness display dramatic symptoms without any derangement of cognitive function (Howorka et al. 1996)
Fig. 2.15 Dramatic increase of slow delta waves and other indices of vigilance in patients with history of severe hypoglycaemia (Howorka et al. 1996).

Figure 2.15 Dramatic increase of slow delta waves and other indices of vigilance

In patients with history of severe hypoglycaemia (Howorka et al. 1996).
Figure 2.16 Alpha slow wave index topography decreases in patients with hypoglycaemia unawareness

Fig. 4. Alpha slow wave index topography. (a) (upper panel) Topographic distribution of ASI (bird’s view: nose in front) before (plasma glucose > 3.89 mmol/l) as well as after induction of hypoglycaemia in plasma glucose categories 3.06–3.89, 2.22–3.06 and 1.39–2.22 mmol/l (as in Table II). To allow comparison, ASI scale is set from 0.9 to 5.8 for all eight maps. (b) Differences of ASI during hypoglycaemia compared with prehypoglycaemic basal values. Descriptive significance probability maps based on paired samples t-test are shown. Hot colours represent significant increases, cold colours significant decreases (t > 1.94, p < .1; t > 2.45, p < .05; t > 3.71, p < .001) as compared with baseline prehypoglycaemic values. (c) Differences between hypoglycaemia induced changes of ASI in patients with and without hypoglycaemia unawareness. Descriptive significance probability maps based on a t-test for independent samples are shown. Hot colours represent significant increases, cold colours significant decreases (t > 1.78, p < .1; t > 2.18, p < .05; t > 3.05, p < .01) in patients with hypoglycaemia unawareness compared with patients without hypoglycaemia unawareness.
2.2.3. EEG mapping in euglycemia: decreased vigilance in unawareness

In type I diabetic patients with history of recurrent severe hypoglycaemia, a more rapid decrease in vigilance (slowing of brain function) during hypoglycaemia in comparison to patients without history of such events was found. In our next investigation (Howorka et al 2000, Psychoneuroendocrinology), our aims were (1) to study EEG parameters of vigilance in non-hypoglycaemic state in representative groups of Type I diabetic patients with and without previous recurrent severe hypoglycaemia and (2) to compare them with non-diabetic controls. A vigilance-controlled EEG mapping (10-20 system, significance probability maps) was performed in a non-hypoglycaemic state (blood glucose 4.0-10.0 mmol/l) in a group of 13 Type I diabetic patients with a history of recurrent severe hypoglycaemia and compared to that of 14 Type I diabetic patients without history of severe hypoglycaemia, matched for HbA1c, age and gender, and to age- and gender-matched non-diabetic controls. When compared to non-diabetic controls, hypoglycaemia patients demonstrated a reduction in absolute power in beta band (13-35 Hz) and slowing of centroid frequencies of beta and total frequency bands (1.3-35 Hz) (up to p<0.01), whereas patients without history of severe hypoglycaemia showed only a borderline reduction of absolute power in delta (1.3-3.5 Hz) band. Deceleration in hypoglycaemia patients versus those without recurrent hypoglycaemia was most remarkable (p<0.01) in centroid frequency of total frequency band. Patients with history of recurrent severe hypoglycaemia demonstrated in non-hypoglycaemic state significantly reduced vigilance when compared to the group without hypoglycaemia history and to the controls, as well. Lower vigilance may be at least in part responsible for impaired hypoglycaemia perception in these patients, but, as it resembles EEG patterns seen in pathologic ageing, it might also represent a consequence of recurrent episodes of severe hypoglycaemia.

In summary, patients with history of recurrent severe hypoglycaemia demonstrated in non-hypoglycaemic state significantly reduced vigilance when compared to the group without hypoglycaemia history and to the controls, as well. (Howorka et al. 2000, Psychoneuro-endocrinology)
Figure 2.17 Patient group comparison. Both cohorts have been carefully matched

In this investigation (Howorka et al, 2000, Psychoneuroendocrinology), diminished vigilance was already shown even in euglycemic state. Patients have been very carefully matched for glycaemic control and late complications including autonomic neuropathy.

Descriptive significance probability maps based on two-tailed two sample t-test (bird’s eye view, nose at the top, white dots indicate electrode positions) depict intergroup differences in 13 absolute (ABS.) power measures (upper part of the figure, a), 12 relative (REL.) power measures (middle part of the figure, b) and 11 dominant frequency and centroid measures (lower part of the figure, c) (D=delta, T=theta, DT=combined delta and theta, A=alpha, B=beta, C=centroid, CD=centroid deviation, CT=centroid of total frequency band /1.3-35 Hz/, HZ DF=dominant alpha frequency, C DT=centroid of delta and theta). Hot colours represent significant increases, cold colours significant decreases (t>1.71: p<0.1; t>2.06: p<0.05; t>2.8: p<0.01)

Figure 2.18 Absolute and relative power topography in vigilance-controlled EEG

Differences between IDDM patients with history of severe hypoglycaemia and normal controls (n=2x13), in absolute, relative, and dominant frequency centroid measures, eyes closed (next page).
IDDM PATIENTS WITH HISTORY OF SEVERE HYPOGLYCAEMIA VS. NORMAL CONTROLS (N: 2x13)

Fig. 1. Absolute and relative power topography in vigilance-controlled EEG, eyes closed. Differences between IDDM patients with history of severe hypoglycaemia and normal controls (n = 2 ×13). Descriptive significance probability maps based on two-tailed two sample t-test (bird’s eye view, nose at the top, white dots indicate electrode positions) depict intergroup differences in 13 absolute (ABS) power measures (upper part of the figure, a), 12 relative (REL) power measures (middle part of the figure, b) and 11 dominant frequency and centroid measures (lower part of the figure, c) (D, delta; T, theta; DT, combined delta and theta; A, alpha; B, beta; C, centroid; CD, centroid deviation; CT, centroid of total frequency band 1.3–35 Hz; DF, dominant frequency, C DT, centroid of delta and theta). Hot colours represent significant increases, cold colours significant decreases (t > 1.71: p < .1; t > 2.06: P < .05; t > 2.8: P < .01)
2.2.4. Weak relationship between perceived symptoms and autonomic changes

To assess the relationship between symptom perception and neurophysiological characteristics in hypoglycaemia unawareness, we investigated the awareness of symptoms, objective changes of autonomic function, and counter-regulatory neuroendocrine responses to hypoglycaemia in intensively treated Type I (insulin-dependent) diabetic patients with different degrees of hypoglycaemia unawareness. (Howorka et al. 1998, Acta Diabetol). Hypoglycaemia (venous plasma glucose below 2.2 mmol/l) was induced with intravenous insulin bolus in subjects with a history of repeated severe hypoglycaemia and hypoglycaemia unawareness (n=10) and in a comparable group with good awareness of hypoglycaemia (n=8). Autonomic symptoms, selected parameters of autonomic function and counter-regulatory hormones were assessed serially. Although hypoglycaemia was more pronounced in unaware patients (1.6 vs. 2.0 mmol/l, p=0.05), their induced adrenaline response was markedly impaired (delta adrenaline: 1.25±1.10 vs. 2.55±1.46 nmol/l, p=0.05). Astonishingly, differences between both patient groups in course of autonomic function changes did not reach the level of significance (p=0.35 to 0.92), although hypoglycaemia unaware group reported markedly fewer autonomic symptoms, both neurogenic (p=0.001) and neuroglycopenic (p=0.04) as compared with the hypoglycaemia aware group. (Howorka et al. 1998, Acta Diabetol)

![Figure 2.19](image-url)
Figure 2.20 Changes in different symptom scores during hypoglycaemia in patients with (solid symbols) and without hypoglycaemia unawareness (Howorka et al. 1998, Acta Diabetol)

In summary, this study indicates that in hypoglycaemia unawareness even extensive changes in autonomic function are not sufficient for perception of hypoglycaemia and confirms that the central nervous system plays an important role in the awareness of hypoglycaemia. (Howorka et al. 1998, Acta Diabetol)
2.3. **Short-term spectral analysis of heart rate variability**

2.3.1. **Review of methodology**

Heart rate variability is an easy to assess parameter. We have developed a standardized approach with orthostatic load *(Howorka et al 2013, J DiabCompl)* which successfully replaced conventional assessment of Total Ewing Score *(Pumprla et al. 2002, Int J Cardiology)*.

2.3.2. **Method improvement and optimal parameters for HRV assessment**

Our aim was to select those parameters of heart rate variability (HRV) within its short-term power spectral analysis (PSA), which have a capability similar to that of the standard Ewing battery of cardiovascular function tests in determining different degrees of cardiovascular autonomic neuropathy (CAN) in diabetes and to compare the usefulness of both methods for diagnostic purposes in the everyday routine. Commonly used standard battery of cardiovascular autonomic function tests evaluated as total Ewing score as well as short-term PSA of HRV were used in 119 diabetic patients (age: 52.7±9.8, diabetes duration: 22.2±12.7 years). From this cohort, patients were selected according to the total Ewing score by matching for age, gender, BMI and diabetes type for 3 groups, each of 17 patients, with no CAN (total Ewing score 0-0.5), with early involvement (score 1.0-2.5) and with definite or severe CAN (score 3.0-5.0). Short-term PSA of HRV performed in three positions (supine1 - standing - supine2) included frequency-domain and time-domain parameters of HRV. Cumulative spectral power of total frequency band (0.06-0.50 Hz) and spectral power of low-frequency band (0.06-0.15 Hz) during both supine positions proved to be the most selective and discriminating among all patient groups in inter-group comparison and in analysis of discriminance. The correlation between the total Ewing score and the cumulative spectral power of total frequency band was \( r = -0.87 \) (p<0.001). 83.2% of cases classified by short-term PSA of HRV using the variables selected by analysis of discriminance were congruent with the classification by the total Ewing score alone. Time expenditure for the performance of each examination was 31±10 min for Ewing test battery vs. 14±2 min for short-term PSA of HRV (p<0.001). *(Howorka et al., 1998, J Autonomous Nervous System)*
Figure 2.22 Relationship between the Total Ewing score and cumulative spectral power of total frequency band in the whole unslected diabetic cohort (n=119). (Howorka et al., 1998, J Autonomous Nervous System)

In summary, the latter method showed similar diagnostic value concerning the CAN as the classical Ewing standard battery of cardiovascular function tests, although its application proved to be shorter, less stressful and more independent from patient co-operation. Cumulative spectral power of total frequency band (LFHF cumpower) can be used for overall description of the degree of cardiac denervation in diabetes while using short-term PSA of HRV. (Howorka et al., 1998, J Autonomous Nervous System)

2.3.3. Reversibility of CAN?

With the methodology of routine assessment of autonomous neuropathy with spectral analysis of heart rate variability, the question emerged, whether cardiac autonomic neuropathy is reversible and/or the total power of HRV can be increased. The author of this thesis initiated several investigations to provide the definite answer to these questions: yes. The HRV can be increased with endurance training, fasting, and with guided breathing.

2.3.3.1 Exercise

Our objective was to investigate effects of a regularly performed endurance training on heart rate variability in diabetic patients with different degrees of cardiovascular autonomic neuropathy (CAN, Howorka et al. 1997, Cardiovascular Research). Bicycle ergometer training (12 weeks, 2x30 min./week, with 65% of maximal performance) was performed by 22 insulin requiring diabetic patients (age: 49,5±8,7 years, diabetes duration: 18,6±10,6 years, BMI: 25,1±3,4 kg/m²), i.e. by 8 subjects with no CAN, 8 with early CAN and by 6 patients with definite/severe CAN. A standard battery of cardiovascular reflex tests was used for grading of CAN, a short-term spectral analysis of heart rate variability for follow-up monitoring of training-induced influences. While the training-free interval induced no changes in spectral indices, the 12-weeks training period increased
the cumulative spectral power of total frequency band (p=0.04) but to a different extent (p=0.039) in different degrees of neuropathy. In patients with no CAN the spectral power in high-frequency (HF) band /0.15-0.50 Hz/ increased from 6.2±0.3 to 6.6±0.4 ln [ms²]; p=0.016, and in low-frequency (LF) band /0.06-0.15 Hz/ from 7.1±0.1 to 7.6±0.3 ln [ms²]; p=0.08, which resulted in increase of total spectral power /0.06-0.50 Hz/ from 7.5±0.1 to 8.0±0.3 ln [ms²]; p=0.05. Patients with early form of CAN showed an increase of spectral power in HF (5.1±0.2 to 5.8±0.1 ln [ms²]; p=0.05) and LF bands (5.6±0.1 to 6.3±0.1 ln [ms²]; p=0.008), resulting in increase of total power from 6.1±0.1 to 6.6±0.1 ln [ms²]; p=0.04, whereas those with definite/severe CAN showed after the training period no changes. Training improved fitness in the whole patient cohort. The increased autonomic tone as assessed by spectral indices disappeared after a training withdrawal period of 6 weeks. (Howorka et al. 1997, Cardiovascular Research)

Figure 2.23 HRV: Influence of regularly performed physical training and training withdrawal period

on spectral indices of HRV in groups of diabetic patients with various degrees of CAN: cumulative spectral power of total frequency band (upper panel), cumulative spectral power of total frequency band (upper panel), cumulative spectral power in low-frequency band (middle panel) and in high-frequency band (lowest panel). (Howorka et al. 1997, Cardiovascular Research)

In summary, in diabetic patients with no or early CAN the regularly performed endurance training increased the heart rate variability due to improved sympathetic and parasympathetic supply, whereas in subjects with definite/severe CAN no effect on heart rate variability could be demonstrated after this kind of training. (Howorka et al. 1997, Cardiovascular Research)
2.3.3.2 Fasting

Effects of fasting on the cardiovascular system in diabetes are not sufficiently described. We assessed possible influence of fasting periods exceeding 13 hrs on heart rate variability (HRV) as compared to a short postprandial period in diabetic patients and controls (Howorka et al. 1997, Diab. Nutr. Metab.). Short-term spectral analysis of HRV was used either in a common postprandial/postabsorptive state (interval since the last meal 146±11 min) or during the fasting day (interval 1072±22 min) in 56 diabetic patients with different degrees of cardiovascular autonomic neuropathy and in 15 non-diabetic control persons comparable in age, body mass index and gender. Fasting resulted in diabetic patients with all degrees of cardiovascular autonomic neuropathy (including its definite form) in an increase of cumulative spectral power of total frequency band from 7.4±0.2 to 7.9±0.2 ln [ms²], p<0.001, of low-frequency band from 6.6±0.2 to 6.9±0.2 ln [ms²], p=0.004, and of high-frequency band from 6.5±0.2 to 7.3±0.2 ln [ms²], p<0.001, and in an increase of parameters of time-domain analysis (p<0.001) as well. In contrast, non diabetic control group displayed only a non-significant increase of HRV (p=0.19). (Howorka et al. 1997, Diab. Nutr. Metab.)

In summary, we conclude that fasting increases HRV in diabetic patients, mainly due to an increase of vagal tone. In any interpretation of short-term spectral analysis of HRV the interval since the last meal should be considered. We proposed a standardisation of this interval. (Howorka et al. 1997, Diab. Nutr. Metab.)
2.3.3.3 Proof of concept: Prolongation of expiration with Resperate ®, impact on HRV?

Our aim was to investigate medium-term effects of device-guided breathing on blood pressure (BP) and its capacity to improve the cardiovascular autonomic balance in hypertensive diabetic patients (Howorka et al. 2013). This feasibility study was conceived as a proof-of-concept trial under real life conditions for justification of further investigations.

A randomized, controlled study (RCT) of the effects of device-guided slow breathing on top of usual care against usual care alone (including non-pharmacological and pharmacological treatment). The intervention included 12-min sessions of guided breathing performed daily for 8 weeks. Treatment effects were assessed with ambulatory blood pressure monitoring (24 h ABPM) and with spectral analysis of short-term heart rate variability (HRV) obtained during standardized modified orthostatic load. Thirty-two subjects with diabetes and antihypertensive therapy were randomly assigned to both study groups.

After 8 weeks of guided breathing, significant reductions were demonstrated in 24 h systolic BP (x ± SEM: 126.1 ± 3.0 vs 123.2 ± 2.7 mm Hg, p = 0.01), and in 24 h pulse pressure (PP, 53.6 ± 2.6 vs. 51.3 ± 2.5 mm Hg, p = 0.01), whereas no significant impact in the control group was shown. The differences in treatment effects (delta mm Hg, RESPeRATE® vs control) were significant only for PP (−2.3 ± 0.8 vs + 0.2 ± 1.2 mm Hg, p < 0.05). Strong baseline dependence of treatment effects (delta systolic BP) was observed (p < 0.01). Guided breathing showed a stronger treatment effect in terms of an increase in HRV, predominantly in low frequency band (p < 0.03 vs. usual care). (Howorka et al., 2013, Autonomic Neuroscience).

In summary, even in well controlled hypertensive diabetic patients, guided breathing induced relevant effects on BP and HRV, finding which should be investigated further.
2.4. Investigations on gender aspects of secondary and tertiary prevention in diabetes

Functional insulin treatment FIT discriminating between prandial, basal and correctional use of insulin was shown to improve glycaemic control, treatment satisfaction and enhance perceived control over diabetes. Gender differences have never been sufficiently investigated up to now in respect to treatment outcomes. As women prevail (61%) in all modules of our structured education, our aim was to investigate gender differences in treatment outcomes, treatment satisfaction and quality of life (Howorka et al. 2012, and Thesis MSC Gender).

Patients with type 1 diabetes (n=652, males: 279, females: 373, age: 47.6±15.6, diabetes duration: 21.9±3.2, FIT duration: 12.1±7.1 yrs) and or functional insulin treatment undergoing annual diabetes education refreshment weekend FIT-UPDATE have been investigated. Their diabetes-associated treatment satisfaction and quality of life as well as and diabetes-related state of knowledge have been measured using questionnaires (including those of C. Bradley´s and K. Howorka Diabetes Treatment Satisfaction Questionnaire, DTSQ Extended for FIT, and C. Bradley’s ADDQoL, Audit of Diabetes-Dependent Quality of Life).

No differences have been found for: HbA1c (7.3±1.1, p=0.71), number of daily injections (6.4±1.3, p=0.60) and blood-glucose self-measurements (5.2±1.1, p=0.22) diabetes knowledge (initial correct mark score 75±10, p=0.43). For microvascular complications, more men than women displayed differences.
2.4.1. **Reported frequency of hypoglycemia**

Correspondingly to the impairment of treatment satisfaction, men reported much higher frequency of severe hypoglycemia of all categories (H3, episodes with unconsciousness within the last 5 years, p=0.013; H4, glucose iv and/or glucagon within the last 5 years, p=0.002) whereas females displayed a higher, but not statistically significantly different frequency of moderate symptomatic hypoglycemia (episodes per month, p=0.084)

![Reported Frequency of Hypoglycemia](image.png)

**Figure 2.26 Gender differences in reported frequency (means) of hypoglycemia**

Relevant gender differences for absolute number of H4 (episodes with glucose iv and/or glucagon) within the last 5 years, for average annual number of reported unconsciousness in total diabetes duration and for relative average annual number of reported severe hypoglycemia H4 (episodes with glucose iv and/or glucagon) per year of total diabetes duration (p= 0.002, p=0.001, p=0.003 respectively, questions 36, 37/24, 38/24 respectively, questionnaire page 7, appendix). (Howorka 2012, Master Thesis for MSc. Gender Medicine)
2.4.2. Assessment of diabetes specific quality of life with ADDQoL
(Audit of Diabetes Dependent Quality of Life)

The impact of diabetes on quality of life was assessed using the ADDQoL questionnaire. The general wellbeing of both genders was despite of diabetes very good. However, the impairment caused by diabetes in general wellbeing was significantly stronger for men than for women (p<0.002). The impact of diabetes remained consistently negative in the areas of working life (p=0.02), family life (p=0.05), and even in the area of friendship and social life (p=0.02). Men however were much more severely impaired in the area of sexual life than women (p<0.0001). Interestingly, women felt somewhat more impaired by diabetes when it came to “things to do physically” (p=0.04). The average weighted impact score (AWI) of all eighteen areas, was not statistically different between men and women (-1.53±1.53 in men vs -1.44±1.42, p=0.43) (Howorka 2012, Master Thesis for MSc. Gender Medicine).

In summary, the most profound impairment in quality of life in males was in area of sexuality and seems to be related to erectile dysfunction. For the first time much stronger hypoglycaemia proneness in men was revealed. It can be probably related to gender differences in central nervous system function. Other differences found seem to mirror stereotypes of social roles whereas in the context of a chronic, incurable illness, female preserving tendency fits more the “restitutio ad optimum” and seems more appropriate in comparison to the (male and less flexible) tendency to the (in diabetes currently unachievable) “restitutio ad integrum”. (Howorka 2012, Master Thesis for MSc. Gender Medicine).

2.5. Investigations on fat reduction technologies: radiofrequency, cold-induced thermogenesis, injection lipolysis and patient education

With time, as an addendum to the structured education, our focus turned to various supportive measures for fat tissue and weight reduction. Our clinical experiences with injection lipolysis, cold-induced thermogenesis, as well as with monopolar radiofrequency have brought positive results. (Howorka et al 2014, WiKliWo). Treatment effects after cold induced thermogenesis have been borderline significant (Howorka et al 2014 WiKliWo), whereas radiofrequency seemed to be even more effective (Pumprla et al 2014, unpublished). All these methods are not used instead but as an addendum to lifestyle modification.
Figure 2.27 Cold induced thermogenesis: SlimVest® effects after 8 weeks.

Significant effects on total body fat and superficial fat as assessed with caliper around the spina iliaca anterior. Modified after Howorka et al 2014, in press, WiKliWo

3. Methods, synthetical part: Invention of structured patient education and modular integrated care

3.1. General remarks and historical development

Historically, structured diabetes education was essential since activities of JP Assal and the Genova Model has been eagerly overtaken by the Dusseldorf Group of M Berger in early eighties of the last century. The FIT model first published in 1984 was successfully inhaled in to the Duesseldorf Model albeit under the name of Intensified Insulin Treatment education. Although initially implemented by Skyler (1979: “Algorithms for Insulin Adjustment for Patients who Monitor Blood Glucose”), his contribution was also not appropriately appreciated in Germany.

For the designing of the modular education system, the author of the thesis visited several centers (Joslin, Boston, Düsseldorf, Prof. Berger, Prof. J.P. Assal, Genf) in the eighties. 1982-4 algorithms for functional insulin treatment have been developed (Howorka et al 1983, WikliWschr, and Howorka et al, 1990 based on insulin production rate of healthy man (Waldhäusl et al. 1979) and correction algorithms have been adapted from Bernstein (Bernstein 1981, The Glucograph Method). Our optimal outcomes of structured education have been reported (Mühlhauser, Howorka et al 1986, Diabetologia) and modular education systems implemented 1984-1990. In 1997, ISO 9001 conformity has been achieved for areas: research, education, and clinical care.

The core competence of our ISO-9001 certified (Howorka et al, 1998, Biomedizinische Technik) research group Functional rehabilitation and group education, lies in structured outpatient modular education for self-management of chronic diseases clustered in metabolic syndrome, under the vision of patient’s empowerment for “competent patient leadership” in treatment (Howorka et al, 1999, 2000, 2001). Our research group offers altogether ten educational modules, seven of them the
eight focusing on individual component of metabolic syndrome and/or diabetes, while FIT-Update (and recently also Type 2 Update) is a refreshing weekend education that updates patients – participants of previous education – on new information and empowers for further self-responsibility in their treatment (Howorka et al, 1994). In 2006 we started two new educational initiatives, “Type-2 Update” designed specifically as a refreshment module for patients with metabolic syndrome, and “Pump’n’eve”, for initiation of CSII in FIT patients: no statistical outcome data for these modules are available yet.

**Figure 3.1 Participation of chronically ill in individual educational modules as offered by our research group; evaluation covers time period of around 15 years (modified after Howorka et al 2007)**

The figure displays participation of our patients in the educational modules in percentage of evaluated sample of 1020 patients in treatment of outpatient office.

The time- and logistics structure of modules for therapeutic patient group education is usually a result of various factors like patient needs (verbally expressed and/or estimated by the physician or counselors), relevance for public health, availability of HCP for course delivery, predefined development direction, reimbursement options, industrial co-operations and pure experience of HCP s. At present, time requirements are estimated as follows:

- Basic Diabetes Training 10 hrs
- FIT-Training 28 hrs
- FIT-Update 12 hrs: an educational weekend
Module rehabilitation process comprises not only various modules according to patient needs, but also— if considered as a process—following phases (Howorka et al, 1990 Comp Methods Programs in Biomed)…

In general, phases of rehabilitation comprise following steps:

- **Phase 0**: Individual information on treatment standards. This includes the explanation of treatment goals and prognosis. Motivation for cooperation with physician. Important part is the assessment of patient treatment goals in his/her present social context.

- **Phase I**: Basic structured group education. Learning achieving the goals set. Recognizing limitations of conventional treatment. Important: Inducing a wish to self-treat through increasing the level of treatment competence and radius.

- **Phase II**: Making effective treatment feasible. In classical case taking part in FIT program with insulin games, practical experiments, and special situations. Inducing a competent treatment leadership. Important: change of interaction rules: physician in coaching function.

- **Phase III**: Improving partnership. Updates and shift of focus to associated diseases and complications. Focus on tertiary prevention. Patient leadership reinforced. Physician remains a coach.

The system of modular structured outpatient education is offered to health care providers and to medical students as a part of graduate university education (Howorka et al, 1992), as well.

### 3.2. Functional insulin treatment after the basic diabetes course

FIT is an independent use of insulin by the patient either for fasting or for eating or for correction of hyperglycemia. Necessary methods are: patient education, self BG monitoring and multiple injections or CSII (insulin pump). An individual preparation, a structured basic group education and a structured FIT training seem to be necessary to achieve optimal results. The mentioned components require about 30-40 hours of structured individual and group education.
Individual outpatient preparation for phase I and phase II

(For about 70% of our clients this is part of their initial one-on-one consultation.) Last outpatient visit: preparation of the patient for structured basic diabetes education and the one-on-one FIT-Program (modified after Howorka et al 2009, Curricula DiabetesFIT®)

Methods and contents (selected)

- Possible strategies of insulin-therapy: multi-component- vs. functional therapy.
- Technique of blood glucose measurement, urine glucose and ketone measurement techniques (recent ketonuria? - test now).
- Interpretation of self-monitoring results and definition of individual preliminary treatment targets.
- Record-keeping (FIT protocol version with younger patients and with patients already clearly FIT motivated).

Basic diabetes training

Background and didactic goals (see Howorka et al. 2009, Schulungscurricula DiabetesFIT®)

Training is offered to all insulin requiring patients.

Didactic Goals:

1. To improve the ability to self-adapt insulin doses under intensified insulin therapy.
2. To avoid acute complications and minimize long-term complications.
3. To form a partnership with medical and training staff that provides a solid base for communication and further therapy.

Undesirable effects; ‘Counter goals’:

Doing without medical supervision in the future and without individual consultations.

Specific contents of the Basic Diabetes Education-Program (see Howorka et al. 2009, Schulungscurricula DiabetesFIT®)

FIT Training course

Background and didactic goals (Howorka et al. 2009)

Our training program is open to all who wish to get control over their diabetes to improve their quality of life by improving their independence from scheduled food-intake. Avoidance of medical supervision

We try to reach these goals by educating the patients by a set of structured group modules, explaining the theory and using insulin games for experiments. Special situations (assumptive situations for the future) are used to exercise practical applicability of theoretical knowledge.

FIT Program: Contents

- How much insulin (and which) if I don’t eat?
• How much (and how) if I eat?
• How can I correct high blood sugar?
• How (and when) to change FIT rules?
• The modules do not consist exclusively of lectures alone, but also of supervised practical experiments…

**FIT Program: Methods are “Insulin games” and “special situations”**

- Fasting
- Eating (feast)
- Renal threshold for glucose

Different periods and situations where behavior is influenced by diabetes are discussed in order for the patients to understand and adapt their diabetes treatment to their lifestyle… and not the other way around. This is why we discuss not only special situations in “… as if…”-discussions…:
- e.g. pregnancy planning..., pregnancy..., hospital admission...

**Generation of “Initial Algorithms of Insulin Dosage” derived from insulin production rate of healthy man (alternatively: nomograms, or formulas…)** is not that relevant as the so called secondary adjustment of insulin dosage (=algorithm change). The well educated patient can so adjust his dosage to his needs.

**Secondary Adjustment of Insulin Dosage**

- …is based on daily net result (daily balance and MBG)
- In the case of an average blood glucose above the desired target level, the prandial or basal dosage should be **increased** (in the first step around 10-20%), similarly it should be **reduced** with increased hypoglycemic incidents or MBG are below the desired target
- Criteria for basal: “Stability, fasting values, ratio…“

The FIT education allows flexible lifestyle without scheduled food intake, and immediate control of hyperglycemia in a more self-responsible and self-controlled patient.

**Longitudinal results of the FIT program**

**Assessment of patient empowerment as induced by the FIT training**

Empowerment can be measured in terms of health locus of control *(Bradley et al, 1996)*. External control means that the individual is controlled by external powers, such as the physician or “chance”. E.g. patient feels that he/she cannot control blood glucose since it fluctuates due to unknown reasons. Internal control means that patient feels “empowered” and able to exercise control over blood glucose values. He/she can lower or increase them deliberately at wish. We have evaluated the outcomes of FIT on parameters on health locus of control, health beliefs and glycemic control.
Figure 3.2 Long-term Study 2: Effects of FIT on HLC

Significant effects (p for intraindividual comparison; baseline values: light bars; final assessment: dark bars) are demonstrated for "Medical Control" made up by "Treatment" and "Doctor Control". Impact of FIT an HLC (38+20 months after the training) on "Perceived Control over Diabetes" (percent of maximal possible score) assessed by subscale scores (upper panel) and composite scale scores (lower panel) (Howorka et al, 2000)

FIT has been evaluated in context of comparison with patients from primary care in Tirol, Austria, without intensified treatment and without FIT education, carried out in Vienna in the years up to 1988. The outcomes are presented in the figure above. At the end point of the observation (at that time at this institution no FIT updates were performed) the statistical difference between groups disappeared (p=0.1) However, statistical differences were given in retinopathy and nephropathy prevalence in those patients. (Fasching et al, 1994)
Figure 3.3 Long-term Study 2: Effects of Functional Insulin Treatment on "Diabetes Specific Health Beliefs".

Significant influences (p for intraindividual comparison; baseline values: light bars; final assessment: dark bars) on perceived "Cost-Effectiveness of Treatment" (="Benefits" - "Barriers"), on perceived "Barriers to Treatment", and "Vulnerability" are demonstrated. Maximal possible score (=100%) for subscales is given in parentheses, (38+20 months after the training) (Howorka et al, 2000)

Figure 3.4 Longitudinal changes in postprandial blood glucose and HbA1c in IDDM treated by either intensive (IIT) or conventional (CIT) insulin therapy over a > 4.5 years period

(IIT vs. CIT; analysis of variance for repeated measures) (Fasching et al., 1994).
3.3. FIT UPDATE

This module has been designed as “educational weekend" for periodical motivation and enhancement in diabetes management-related knowledge in patients previously taught in FIT.

Many intervention studies on intensification of diabetes self management show timely restricted benefits (Norris et al., 2001, 2002). They confirm clinical experience, that in parallel to increasing time period after an educational intervention the positive effect on glycemic control usually deteriorates (DCCT Research Group 1991). Thus, the primary goal was to reinforce individual motivation for self-treatment, enhance model learning in chronic treatment through interaction with other participants in small groups as well as to establish a routine for updating knowledge of patients concerning their pharmacotherapy and technical aids (Norris et al., 2002).

The target participants were insulin-treated patients who had previously already been trained in FIT. This module is the only one, where the treatment initiation on a one-to-one basis is not explicit mandatory, since an arbitrary non-recurring, “first and final” adjustment of individual pharmacotherapy is not designed as a primary goal of this module. Historically, this intervention became the most crucial for patients living far from us and this seen only seldom (Fasching et al., 1994).

Module FIT-Update: Goals

- To maintain patients’ long-term capability for optimal self-treatment
- To update & refresh applicable diabetes-related knowledge
- To enhance motivation

Methods and structure

A weekend seminar FIT-Update consists of a structured, additional outpatient training (offered annually) including plenary lectures (audience up to 100 patients) and small groups.

Methods used:

- teaching conversation,
- analysis of case reports of patient records,
- interactional learning
- exchange of experience in plenum and in small groups.

Module FIT-Update: Pilot assessment

The Module FIT Update have been evaluated in a prospective pilot study measuring an increase of diabetes management related knowledge (Howorka et al., 1994) in the first patient samples taking part in
the educational module during the first years of its application. Patients: n=348 participants of five consecutive annual FIT-UPDATE seminars 1989-1992 (age: 40±15 years, diabetes duration: 15±10 years, type 1 diabetes: 90 %, relevant late complication of diabetes: 31%) taking part 35±28 months after a structured training in functional insulin treatment (FIT = functionally separate use of insulin for basal, prandial and correctional purposes) in the module FIT Update.

Methods of module evaluation (Howorka et al 1994)

Diabetes-management related knowledge and its increase was assessed with a newly developed FIT-knowledge questionnaire (psychometrics):

- **Reliability:** Test-retest reliability: 0.74, test internal consistency (Alpha): 0.80, item-total correlation: 0.2-0.6, maximum likelihood solution: 0.30-0.85
- **Validity:** sufficient correlation with HbA1c

Effect on patients' motivation for self-treatment and record keeping of blood glucose self-monitoring has been assessed by means of a questionnaire in a subgroup of 142 patients.

Longitudinal FIT Update evaluations

The module FIT Update had a relevant impact on diabetes management related knowledge and patient motivation to treatment. The mentioned methods of evaluation showed an increase of knowledge in all investigated knowledge categories (correct mark score increased by 7-13 %, p=0,0003-0,0001) and a correlation between HbA1c and the state of knowledge in the beginning of the seminar (r=-0,39, p=0,0001). Two months after the FIT-UPDATE seminar, its effect on patients' motivation for self-treatment have been recorded by means of a questionnaire in a subgroup of 142 patients. The enhancement of motivation caused by FIT-UPDATE has been confirmed by 64 % of them and was associated with an increase of self-monitoring and keeping of patients' self-monitoring records including daily balance of insulin consumption (p=0,0001).

A weekend seminar FIT-UPDATE makes possible to improve a rehabilitation status of a large number of patients. Such seminar is efficient in terms of costs and time and may be realized with only a few diabetes counselors. The effectiveness of this new training model is caused in part by the increase of management-related knowledge and enhancement of motivation for treatment. Another advantage of such educational event as also to assure specialized intermittent care to those patients who would never became recipients of a such sophisticated education as living e.g. far away from specialized centers. Ambulatory individual care specifically designed for those only coming every two to three years was therefore offered the day after the seminar to patients from Tirol or northern Italy.
3.4. Pregnancy & birth preparation module

Background information

Module Pregnancy and Delivery in Diabetes is Offered to Women Planning Pregnancy or Already Pregnant Patients

The main risks of diabetic pregnancy remained increased malformation rate, prematurity and macrosomia/disproportionate growth which all are three to six times increased if compared with background population (von Kries et al, 1997, Häusler et al, 1996).

Goals

- Elimination of diabetes-related complications of late pregnancy
- Optimal self-treatment during late pregnancy, delivery and post-partum period
- Harmonisation of the whole period of intensive treatment during pregnancy
- Co-operation of the patient: from receiver of information to informed decision-maker

The outcome of the use of FIT and pregnancy modules was summarized in our paper in Diabetic Medicine 2001 and recognized later on for the best pregnancy outcomes in diabetes: We have fully eliminated the classical complications of diabetic pregnancy like macrosomia, postnatal hypoglycaemia

Methods: (Howorka et al, 2001).

1. Prospective use of modular outpatient group education and FIT based on separate insulin dosages for fasting, eating or correcting hyperglycemia in 76 consecutive pregnancies (in 20 cases after conception) of 57 patients with pregestational diabetes (IDDM in 70 of index pregnancies)

2. Retrospective comparison of the pregnancy outcome of FIT-educated diabetic women with outcome of (a) historical controls, (b) non-diabetic case-controlled cohort matched for parity, age, place and date of delivery) and (c) with the population-based pregnancy outcome, i.e. with a cohort of all living born neonates delivered in Austria (n=1,342,838) in the corresponding time period (1985-1999). Peripartal data of patients with pregestational diabetes treated with functional insulin treatment ("FIT cases") and controls. (Howorka et al, 2001).

Results: Prospective Study (Howorka et al, 2001).

- Mean HbA1c of 11.3±18% of mean value (=100%) of non-diabetic, non-pregnant population and mean self-monitored blood glucose of 5.6±0.7 mmol/l was achieved throughout all diabetic pregnancies.
- Severe hypoglycemia occurred in 16 pregnancies (21%).
• The gestational age at delivery was 39.0 (Q1 38.5, Q3 40) weeks with an average birth weight of 3305±496 (1950-4450) g.
• One case of respiratory distress was observed.
• Hypoglycemia was recorded in only 6 newborns (8%).
• Malformations were found in two infants whose mothers booked for diabetes education only after conception.

Comparison with pregnancy outcome of non-diabetic controls matched for parity and age (birth weight 3305±433 g, p=0.68) and with that of population-based cohort (birth weight 3286±540 g, p=0.5-0.9 for different groups of parity and age) demonstrated a full normalization of pregnancy outcome. (Howorka et al, 2001).

Conclusions:
Modular outpatient group education for Functional Insulin Treatment adapted for pregnancy prior to conception normalizes pregnancy outcome in diabetes. (Howorka et al, 2001).

Figure 3.5 Daily insulin requirement (x+SEM) during the pregnancy in functionally treated patients with pregestational diabetes.
A slight decrease in insulin consumption at the end of 1st trimester (28) drops not below the baseline level (Howorka et al, 2001, DiabMedicine).

Figure 3.6 Structured outpatient group education modules adapted for pregnancy (next page): (Howorka et al, 2001, DiabMedicine)
<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>A measure of long-term glucose control</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>Measures blood glucose level before a meal</td>
</tr>
<tr>
<td>Random plasma glucose (mmol/L)</td>
<td>Measures blood glucose level 2 hours after a meal</td>
</tr>
<tr>
<td>2-hour postprandial glucose (mmol/L)</td>
<td>Measures blood glucose level 2 hours after a meal</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>Measures body weight in relation to height</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>Measures the circumference of the waist</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>Measures the pressure of blood against the walls of arteries</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>Measures the pressure of blood between heartbeats</td>
</tr>
</tbody>
</table>

**Table 1:** Key parameters for diabetes management.
Figure 3.7 Mean blood glucose of the week (x+SD) during pregnancy in diabetic patients with FIT
(values of the first 9 weeks explicitly display data of preconceptionally educated patients only): The decrease of MBG in pregnancy weeks 5-6 can be interpreted as a motivation effect of positive pregnancy test in the context of information on organogenesis in the "Preconceptional Training" (a subunit of FIT Training); in week 29 this may be an effect of "Pregnancy and Birth Preparation" educational module (Howorka et al, 2001, DiabMedicine).

Figure 3.8 Course of HbA1c during pregnancy
(x+SEM, mean HbA1c for the reference non-pregnant, non-diabetic population=100%)
in patients where FIT has been started before (continuous line) and only after conception (dashed line; first visit in 11+3 week; *p=0.028 vs. HbA1c of preconceptionally FIT educated patients, after the 15th week of pregnancy no statistical difference between patient groups). Two cases of major malformations (10%) were found in the latter group of 20 infants of mothers with only postconceptional FIT education (Howorka et al, 2001, DiabMedicine).
Even comparing of the outcomes with that of “background population” showed that our results were similar to that of non-diabetic women. One of the major goals of Vincent declaration has been thus fully achieved.

<table>
<thead>
<tr>
<th>Gestational age at delivery (weeks)</th>
<th>FIT cases</th>
<th>Non-diabetic controls</th>
<th>Population cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean delivery rate</td>
<td>25.0%</td>
<td>22.7%</td>
<td>13.5%*</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3304.6 ± 496.2</td>
<td>3305.3 ± 432.7</td>
<td>3286.6 ± 540.4†</td>
</tr>
<tr>
<td>n &gt; 90th weight percentile</td>
<td>4 (5.3%)</td>
<td>16 (11.2%)</td>
<td>134 299 (10% &gt; 3900 g)‡</td>
</tr>
<tr>
<td>Biochemical hypoglycaemia (&lt; 1.7 mmol/l) in newborn</td>
<td>6 (8.0%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>n major malformations, rate (%)</td>
<td>2 (2.6)%§</td>
<td>3 (2.1)</td>
<td>8997 (0.67)%§</td>
</tr>
<tr>
<td>Fetal death/perinatal mortality (%)</td>
<td>1 (1.3)%§</td>
<td>3 (2.1)</td>
<td>52.56 (0.4)%**</td>
</tr>
</tbody>
</table>

*Data on mode of delivery available only for the last 4 years (for a subcohort of 344 241 newborns); significant difference vs. FIT cases, P < 0.01.
†No statistical differences vs. FIT cases in four groups according to age and parity of the mother (P = 0.5–0.9).
‡Data available in hecogram (100 g) only.
§Malformations occurred exclusively in the group of patients not trained in FIT until after conception.
¶Based on ‘mother-and-child passport’ (Maternity Care Programme), low degree of ascertainment, underreporting should be suspected for ICD-9: 740–757, 759, multiple congenital anomalies not specified. Other sources with higher degree of ascertainment [26] report higher malformation rate (prevalence 2.88%) of major malformations in Austria.
**Includes exclusively stillbirths. NA, Data not available.

Figure 3.9 Pregnancy outcome of patients with pregestational diabetes treated with functional insulin treatment (‘FIT cases’), of matched non-diabetic controls, and of population-based cohort of all Austrian births delivered in the respective time period, n = 1342 993 new-borns (Howorka et al, 2001).

### 3.5. Hypoglycemia module

One of the hypoglycemia aspects relevant to public health are the driving mishaps: Only minor hypoglycemia is of no relevance for traffic due to high frequency of driving mishaps in type 1 in contrary to type 2 diabetes (Cox et al, 2003).

**Pathophysiology**

Approx. 20% of insulin-dependent diabetic patients experience repeated severe hypoglycemia with unconsciousness. History of repeated hypoglycemia has a high predictive value for severe hypoglycemic events in the future. Previous studies (Howorka et al, 1996) shown that these patients had a specific EEG pattern (rapid decrease of vigilance, EEG deceleration during hypoglycemia). We have demonstrated, that these patients display characteristic patterns of vigilance. Vigilance describes readiness to adapt behavior appropriately to a given situation. In particular, it describes the behavior of watching for and responding to irregular critical signals under monotonous conditions. Patients with history of repeated severe hypoglycemia demonstrated in non-hypoglycemic state significantly reduced vigilance when compared to the group without history of severe hypoglycemia and to the control group, as well.
These EEG patterns in hypoglycemia patients are similar to those seen in attention deficit syndrome. Indeed, in a recent study (Howorka et al, 2007) we could confirm that patients with history of repeated severe hypoglycemia displayed some degree of attention deficit, not necessarily fulfilling all DSMIV criteria. Their indices for hyperkinetic, or impulsive or inattentive behavior was different as in patients without severe hypoglycemia problems. This very recently described interrelationship between hypoglycemia unawareness/history of unconsciousness and ADS underlines its relevance for public health (Cox et al, 2003). It seems that driving mishaps are much more common in patients with type 1 diabetes as in type 2.

**Structure**

Module: Hypoglycemia prevention in hypoglycemia unawareness is offered to all patients with history of severe hypoglycemia with unconsciousness or confusion. Its organizational structure included two 3-hours units, together with some practical exercises as “homework”. Practical exercises have high similarity with the program of Cox et al (1994 and 2001) although it does not require that many units (time expenditure) due to the fact that patients after the FIT training already have much more experience with blood glucose self-monitoring (including error grid analysis, while self-estimating current blood glucose value, BGAT).

**Goals of hypoglycemia prevention module**

- Improvement of hypoglycemia awareness
- Reduction of hypoglycemic episodes
- Decrease of severe hypoglycemia rate

**Methods**

- Choice of higher glycemic targets
- Cognitive understanding of the pathophysiology of hypoglycemia unawareness
- Training of hypoglycemia awareness

**Characteristics of patients at risk for severe hypoglycemia (modified from Howorka, 2001)**

- History of severe hypoglycemia with unconsciousness
- Inattentiveness, perfectionism, unrealistic glycemic goals
- Diabetes of long duration
- Low body mass index (underweight)
- Erratic insulin absorption kinetics due to lipohypertrophy and/or lipatrophy
- Renal insufficiency
Characteristics of situations that increase the risk of hypoglycemia

- Overfatigue
- Alcohol consumption
- Restriction of food intake/lower hepatic glucose production
- 1st and 2nd trimester of pregnancy
- Use of betablockers
- Use of sympathomimetics
- State after methyphenidate and/or coffee consumption
- Failure to self-monitor
- “Blind” corrections of unverified hyperglycemia (!)
- Consumption of foods with unknown carbohydrate content (sweets)
- Physical activity without corresponding changes in carbohydrate and/or insulin dose
- Inadequate patient education: errors in primary or secondary adaptation of insulin dosage; incorrect algorithms, e.g., basal rate too high (allows eating without rise in BG)
- Inappropriate counseling from physician or trainer (e.g., target value too low, etc.)

Longitudinal and cross-sectional efficacy data

We tested the efficacy of the shortened version of this blood-glucose awareness training (BGAT, Cox et al, 1994, 2001: BGAT, 2003) training reduced to two units as mentioned above. The reduction of hypoglycemic episodes was very pronounced and significant in intraindividual comparisons (case studies, data not shown). In periodical cross-sectional investigations, the reached incidence I hypoglycemia H4 was $<0.07$ patient/year which is with mean HbA1c values reach 119% (type 1 diabetes, n=140) or 123% (type 2 diabetes insulin requiring, n=31) of upper reference limit (=100%) very low when compared with usual frequency.

3.6. Hypertension and nephropathy prevention

As it is well known from practical therapeutic experience with patients requiring chronic pharmacological treatment, the adherence to agents such as antihypertensives, lipid-lowering drugs, as well as oral antidiabetic agents, is very low (Poluzzi et al, 2006). To improve it, structured group education helps.

Concerning the program structure, it should be mentioned that the first unit focused on non-pharmacological measures of blood pressure lowering (see Hypertension Training Unit I). Although not considered in the last decades, but already well established measure for controlling blood pressure became endurance and resistance training (Fagard, 2006).
The effects of hypertension and nephropathy prevention training have been evaluated in form of a pilot study and a long term follow up:

**Participants**
- Training is offered to all diabetic patients with constantly increased microalbuminuria and/or increased blood pressure values

**Structure**
- Three units of about 3 hours approximately one week apart

**Contents**
- Pathophysiology in diabetes, therapeutic targets for blood pressure
- Possible non-pharmacological and pharmacotherapeutic measures
- Pharmacotherapy including pregnancy and in lactation
- Teratogenicity of the ACE-inhibitors; alternative therapy in pregnancy

**Short-term results**

Short term results have been investigated for assessment of intervention effects on blood pressure self-monitoring, changes in self-monitored values, use of non-pharmacological measures and adherence to pharmacotherapy (*Heydarian and Howorka et al, 1990, Pumprla et al, 1994*).

In summary, the short-term outcomes of hypertension training were highly beneficial for the participants. The weakness of the study is no control group although at the timepoint of trial the evidence for improvement in prognosis with intensified blood pressure treatment in diabetes was already overwhelming. The main reason for the choice of structured group education was its applicability in larger number of patients. Thus, this kind of intervention can itself be understood as a part of diabetes translation research.

---

**Figure 3.10 Rates of persistence and coverage of new patients**

(diamonds, persistence; bars, coverage) (*Poluzzi et al, 2006*)
The long-term outcomes of hypertension training have been thoroughly evaluated (Ibrahim Amir 2012, Pumprla 2007). Our evaluation confirmed its public health relevance.

**Long term outcomes of hypertension module**

The efficacy of the hypertension educational module has been thoroughly investigated. In a prospective manner 394 patients (179 men, 45.4%) have been included, educated in the last two decades. It effectively postpones ESRD.

![Demography of hypertension module participant sample](image)

The patients had type 1 diabetes (n = 189, 48%), type 2 diabetes (n = 181, 46%) of which 119 had insulin treatment (30% of all) and 24 patients (6%) had no diabetes. (Amir, I. 2012)

**Table 3-1 Patient characteristics at the entry**

<table>
<thead>
<tr>
<th>All patients</th>
<th>Mean.</th>
<th>St.dev</th>
<th>Median</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR.sys(mmHg)</td>
<td>139.38</td>
<td>18.16</td>
<td>137.00</td>
<td>393</td>
</tr>
<tr>
<td>RR.diast(mmHg)</td>
<td>80.83</td>
<td>8.88</td>
<td>79.73</td>
<td>393</td>
</tr>
<tr>
<td>HbA1c(%)</td>
<td>7.18</td>
<td>1.14</td>
<td>7.20</td>
<td>390</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.85</td>
<td>15.32</td>
<td>78.25</td>
<td>393</td>
</tr>
<tr>
<td>Height(cm)</td>
<td>170.17</td>
<td>9.49</td>
<td>170.00</td>
<td>356</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.17</td>
<td>16.67</td>
<td>66.00</td>
<td>394</td>
</tr>
</tbody>
</table>
Table 3-2 Blood pressure, systolic and diastolic, mmHg.

Mean differences vs. initial values before hypertension module (paired t-test)

<table>
<thead>
<tr>
<th>Year after intervention</th>
<th>systolisch</th>
<th>p-value</th>
<th>diastolisch</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-5.89</td>
<td>0.000</td>
<td>-3.01</td>
<td>0.000</td>
</tr>
<tr>
<td>1</td>
<td>-6.25</td>
<td>0.000</td>
<td>-3.14</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>-6.79</td>
<td>0.000</td>
<td>-3.62</td>
<td>0.000</td>
</tr>
<tr>
<td>3</td>
<td>-5.90</td>
<td>0.000</td>
<td>-3.88</td>
<td>0.000</td>
</tr>
<tr>
<td>4</td>
<td>-6.37</td>
<td>0.000</td>
<td>-4.18</td>
<td>0.000</td>
</tr>
<tr>
<td>5</td>
<td>-6.35</td>
<td>0.000</td>
<td>-4.93</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Figure 3.12 Annual mean systolic casual blood pressure after hypertension education.

Time point “0” corresponds to hypertension module. 394 patients, bold line represents mean values (mean difference after 5 years 7 mmHg) (*Amir, I. 2012*)

The impact of hypertension education was most relevant in the subcohort of 95 patients with microalbuminuria:

Figure 3.13 Median (Q1, Q3) microalbuminuria in 95 patients with initially elevated values (p<0.0001, 27 vs 15 mg/dl) (*Amir, I. 2012*)
Economic impact of hypertension education has been evaluated by the means of simulation with PROSIT model (free ware, Pumprla, 2008)

Figure 3.14 The economic impact of hypertension education is huge.

In modelling using a PROSIT model, this module results in postponing the end stage renal disease ESRD and retinopathy (modified after Pumprla 2008, Thesis MBA). Hypertension training results in delivering gain of QUALYs
3.7. Slim´n´FIT module

Behavioral interventions in obesity have not been shown to be the most effective in the long term treatment. In patients with diabetes, the usual “simple” rules for reducing the “intake” of calories while increasing the daily amount of exercise seem not to work at all. The reason for such classical failure of behavioral approaches for obese people with diabetes are numerous, and only partially understood. As presented in several reviews, in the contrary to surgical procedures which allow a weight reduction in the vicinity of 15-20 kg in long-term outcomes, the behavioral measures usually reach only a weight reduction of 1kg in obese people with diabetes. However, it seems that they help to prevent further increase in body weight. In several cases, however, a successful weight reduction and decrease of insulin resistence (HOMA) can be reached. Reversal of IGT is possible with behaviour modification alone.

For formulation of behavioral goals, neurolinguistic programming a “Goal model” was chosen (Grinder, Bandler 1976) (see Howorka et al. 2009, Schulungscurricula DiabetesFIT®)

Goal Model: NEUROLINGUISTIC PROGRAMMING

- positive formulation (new added behavior)
- Under own control (self-initiated and continued)
- Coupling with internal states & conditions
- Behavior precisely described in context
- In harmony with individual ‘life ecology’

“Cognitive” interventions in obesity (4-8 units), program contents

- Metabolic syndrome X - pathophysiology
- Metabolic consequences of weight reduction, treatment adaptation
- Behavioral changes in eating habits
- Necessary physical exercise: win in obesity; fasting with exercise
- Physiology of being “fed-up”; fiber-rich products
- Hunger emergency handbook
- Fat in food and weight maintenance
- Social consequences of being slim and healthy
- Associated risk factors: hyperlipidemia, hypertension, diabetes

The method summarizes contemporary experience with behavioral approaches to weight reduction in obesity, the knowledge on pharmacotherapy adaptation while reducing food intake and recent insides from solution focus (deShazer, 1989) and neurolinguistic programming (Bandler et al 1986).
Slim’n’FIT program effect on weight and HDL cholesterol in n=91(x+SEM) up to 602±461 days after the intervention (Howorka, 2007), and this effect lasts for about two years.

The educational module slim’n’FIT integrates the clinical experience with “Special low calory days” (inserting occasional “vegetable and fruit” day), a practice already recommended in early 1900’s by Carl v Noorden, fasting and very-low calory diets (VLCD) as modified forms of fasting as well as an overall reduction in food intake in form of a fat reduced conventional low calory diet. The presented module is also useful as a primary prevention strategy (compare the high proportion of non-diabetic patients participating in this module) as already requested (Tuomilehto et al, 2001, CDC 2004, Dorner et al, 2006, Toth 2007).

### 3.8. Hyperlipidemia module

Pharmacotherapeutical interventions in hyperlipidemia have already been evaluated according to the principles of evidence-based medicine (4S, 1994, Nissen et al, 2005). In renewed rules of ATP IV it has been declared that diabetes mellitus is a coronary artery disease risk equivalent (ACC/AHA Guideline: Stone NJ et al. 2013). Therefore, modified guidelines for therapy goals are applicable now to people with impaired glucose tolerance and/or diabetes. The most strict guidelines changes are valid for the new targets of LDL cholesterol. On the other hand it was already known from the Framingham Study that low HDL values signal an independent risk factor for coronary artery disease (Gordon et al, 1977). Cv outcomes have been shown to be a linear function for both, secondary and primary cardiovascular prevention as well.

As hyperlipidemia is very common in metabolic syndrome and diabetes, we decided to develop an appropriate educational intervention to reduce the educational expenditure and increase efficiency while dealing with big numbers of people with diabetes and metabolic syndrome. In the presented hyperlipidemia educational module we adapted the recommendations of ATP III, as would later be adapted in ATPIV (ACC/AHA Guideline: Stone NJ et al. 2013).

**Educational goals and outcome criteria,** (see Howorka et al. 2009, Schulungscurricula DiabetesFIT®, Kirchheim Publishers 2009).

Main clinical goals of the hyperlipidemia module were:

- Translating the interrelationship between hyperlipidemia and other components of metabolic syndrome, atherosclerosis and life expectancy
- Lowering of blood lipids by nutritional change (as part of improvement of cardiovascular risk profile by behavioral change)
- Therapeutic competence and adherence to pharmacological treatment if necessary

Explicit unwanted outcomes:

- Pharmacotherapy *instead of* nutritional change
Methods and structure

The hyperlipidemia module consists of individual outpatient educational preparation (one-to-one setting with the therapist), and of two units of structured group education (each about 3 hours), approximately eight weeks apart.

Ambulatory individual preparation has the aim of inducing initial nutritional/behavioral changes as they are addressed more intensively during the first structured group education unit. Moreover, the patient laboratory results (total cholesterol, HDL, LDL cholesterol) in the context of other patient cardiovascular risk factors are discussed so that an appropriate grading of hyperlipidemia within the individual patient clinical profile can be done.

Contents (2 units)

The focus of the first group unit includes non-pharmacological measures ie. mainly dietary and lifestyle modification and that of the second group educational unit is put on pharmacological measures according to recommendations of NCEP/ATP III.

Main areas of contents of both units are:

- Causes and risk factors of atherosclerosis
- Physiology of lipid metabolism, lipid target values, specifically for diabetes
- Dietary treatment
- Pharmacological modalities including statin associated risks, fibrates, Omega 3 FFA

Longitudinal study: long-term outcomes

Hyperlipidemia educational model was applied in 79 patients with metabolic syndrome and/or diabetes mellitus (type 1: 48%, type 2: 40%, no diabetes: 12%). Observation period was 52±20 months. The pharmacotherapy was necessary in long-term in 52% of patients, remaining group received lifestyle and nutritional counseling including instruction on regular physical training.

More detailed discussion of the hyperlipidemia group unit and its outcomes is outlined elsewhere (Pumprla, 2007). Fifteen percent of all our patients participated in the hyperlipidemia training module up to now. The longitudinal and cross sectional investigation confirmed its efficacy. The comparison with other centers is very favorable, see chapter on cross-sectional analysis with FQSD data.
4. Quality Assurance and Benchmarking Outcomes

Figure 4.1 Process-based quality management system. (Quality Management Handbook and Howorka et al., 1998, Biomedizinische Technik) System is designed for continuous improvement through inclusion of patient wishes and competence.
Our superior outcomes can be linked to our quality management system which allows continuous improvement (Quality Management Handbook, short version, *Howorka et al 1998 Biomedizinische Technik* 43). We implemented a Quality Management System in 1997 to assure covering of Patient’s needs and wishes and to improve our quality of research.

The patient educational media got more and more importance in parallel to the increase of the quality in treatment of chronic diseases.

**Integration of components into a modular system of rehabilitation**

The implementation and continuous availability of following components of structured group education was decisive for the development of a modular rehabilitation system as a whole, see modules, see *Howorka et al. Curricula DiabetesFIT® 2009*:

- basic diabetes training,
- training in functional insulin treatment (FIT, *Howorka 1987*),
- slim’n’FIT module against central obesity & metabolic syndrome (*Howorka et al., 1997*),
- hypertension and nephropathy prevention (*Howorka 1990, Pumplra et al, 1994*),
- FIT-update (*Howorka et al, 1994*),
- pregnancy and delivery in diabetes (*Howorka et al, 2001*),
- hyperlipidemia module (*Howorka et al, 1999*).

**International Benchmarking** is used where partners are sought from other countries because best practitioners are located elsewhere in the world and/or there are too few benchmarking partners within the same country to produce valid results. Globalization and advances in information technology are increasing opportunities for international projects.

In 1982 a computerized data acquisition system for supervision of diabetes outpatient chronic care has been developed by the author of this thesis, described and the first cross-sectional studies have been performed (*Howorka et al, 1983, Waldhäusl, Howorka et al, 1985, Derfler et al, 1986*). An insufficient glycemic control was found in vast majority of diabetic patients. In this way, first comparisons of different treatment approaches could be done in larger patient cohorts (*Waldhäusl, Howorka et al, 1985, Derfler et al, 1986*). The preliminary experiences with common data acquisition were the basics for the development of FQSD (“Forum Qualitätssicherung Diabetes”, [www.fqsd.org](http://www.fqsd.org)) in Germany and Austria. This forum for quality assurance in diabetes consolidates the efforts of diabetes educators and physicians from various levels of diabetes care (university departments, general hospitals, small hospitals with and without outpatient departments, centers for
inpatient rehabilitation and education, specialist diabetes outpatient offices, and general practitioners. In Austria, FQSD became a registered association on July 1, 2001 under the name “Verein Forum Qualitätssicherung in der Diabetologie Österreich”. In Germany, the FQSD acts in form of the civil code partnership (“Gesellschaft nach Bürgerlichem Recht”). Usually it provides open access to quality data for the participants, and democratic principles: the same rights for all participants.

The author’s research group for functional rehabilitation and group education has been involved in common data acquisition virtually since the beginning of the activity of FQSD. Benchmarking was an accepted “side-effect” of common data gathering. This allowed the center comparison for benchmarking purposes: our outpatient office, after the implementation of the quality management system and ISO 9001 conformity is represented in Figure 4.2 and Figure 4.3 as “Center No 4”.

**Process and outcome quality in diabetes care in Austria and Germany**

The goal of this evaluation is to present selected process and outcome quality indicators (performance and internationally benchmarking) in diabetes treatment and in this way to compare the performance of 14 centers in Austria and Germany. The data analysis includes 29063 individuals with diabetes mellitus. Out of them, n=16543 have been investigated in the time period from January 1st 2002 until July 31st 2004, and n=12520 from August 1st 2004 until May 31st, 2007. Within this patient cohort, 14.5% had type 1 diabetes and 79.8% of them type 2 diabetes.

**Selection Criteria**

For the investigation seven centers from Austria (1-7) and seven centers from Germany (8-14) have been selected. These centers cared mainly for adult diabetic patient population including type 1 as well as type 2 diabetes, focusing on chronic ambulatory care for patients with diabetes and associated diseases, with the biggest available numbers of individuals assessed via number of basic information sheets (BIS, describing an annual clinical investigation to be performed in each patient), who were registered and taking part on either German or Austrian FQSD voluntary investigation for assessment of quality indicators. The goal of FQSD as tool for benchmarking was known to all participants.
Figure 4.2 Relative HbA1c.

Time periods – Initial: Jan 1st, 2002 -- Jul 31st, 2004 (n=16543), and Follow-up: Aug 1st, 2004 -- May 31st, 2007 (n=12520). Reference mean = 100%. (From Howorka 2007, MPH)

Figure 7: LDL cholesterol - during initial time period for type 1 ($F_{13,1683} = 8.45, P < 0.001$) and type 2 ($F_{13,1683} = 8.45, P < 0.001$) and during follow-up period for type 1 ($F_{12,1210} = 8.52, P < 0.001$) and type ($F_{13,6388} = 21.65, P < 0.001$).

Figure 4.3 LDL cholesterol.

The presented data analysis of selected indicators of process and outcome quality represents probably only the top of the benchmarking iceberg. Centers have been included according to numbers of submitted BIS representing the number of patients. One can assume that centers selected are those not only with the highest patient numbers but also with the highest impact on standards of care. We are fully aware of all methodological limitations of such analyses based on voluntary participation. However, we believe that the best results demonstrated in our case (No 4) are related to the operational infrastructure (modular outpatient education) and the respective quality management system. Taking into consideration that the vast majority of included almost 17,000 individuals will eventually die due to cardiovascular event, we believe that aggressive and effective influencing of each single risk factor can postpone such death. The presented results and advantages concerning glycemic, blood pressure, and blood lipids control should be linked in our case to continuous availability of specific interventions such as antihypertensive training, hyperlipidemia training and slim’n’fit module, module against central obesity and preparing to the long-term treatment of metabolic syndrome. These results illustrates the “best rehabilitation practice” of our system.
5. Outcome/Results: Comprehensive DiabetesFIT® System, development of print media and dissemination

5.1. Curricula DiabetesFIT®

The “structuring” the group education means differentiation of the education process with respect to the educational goals, contents and methods under consideration of the time distribution of the process into several subunits. This is a "conditio sine qua non" necessary for keeping a constant education quality and reproducibility of the educational results. The structuring of a training entity is also absolutely required, if several different persons act as teachers consecutively in the education process. Since the training of chronically ill for self-treatment is not based exclusively on "purely cognitive" interventions, but it rather needs congruence with a process-wise “mastering” of the illness. Therefore, an appropriate construction of the educational process becomes necessary. Moreover, in the background of a specific training, diagnostic measures have to be performed; so that the coordination with the educational process is thus only possible within a structured procedure.

So clear the necessity of the structuring of the education process is, so seldom the problems or difficulties resulting from the structuring are addressed: The more detailed structuring of the process, the less room remains for the flexible adjustment of the education to the needs of individual group members. According to our experience, the repetitive education during consecutive educational events with identical training contents can only be accepted by the teaching personnel, if a notable part of the education process is lead in "charismatic" way, with full flexibility and -- so to speak -- with a dramatic “touch”.

In order to allow such flexible and individual, patients and teacher oriented performance, the educational subunits must be clearly defined with easily verifiable operational goals. The mentioned problems, that result from a structuring of the educational process, could be solved best with phase-wise and modular education structure. Moreover, it should be stressed, that an optimal rehabilitation process is a result of an appropriate mixture between group and individual interventions.
An essential instrument for structuring the education process is a "didactic curriculum". As such, a didactic curriculum includes for each unit predefined

- educational goals,
- educational contents,
- methods,
- educational materials.

The educational performance, however, is to be chosen by the teacher: the methods therefore, are as little standardized as possible to allow a maximal flexibility to all members of educational team involved. The educational curricula Diabetes FIT® have been published by Kirchheim-Publishers Mainz and are available via AMAZON.

The so-called curricula for teaching personnel have been implemented in German and English versions for

- basic diabetes training,
- functional insulin treatment,
- hypertension training,
- obesity and metabolic syndrome “slim-date” module,
- hyperlipidemia training,
- hypoglycemia prevention module,
• pregnancy and delivery in diabetes module,
• FIT-update module.

The curricula have been copyrighted by the authors in Kirchheim publishers Mainz and have been used as models for more differentiated education as a part of a comprehensive diabetes care in specialized physician’s offices as well as rehabilitation centers. The curricula represent a part of SOPs and they are a component of quality management handbook.


Development of media for education of physicians

In 1987 a book Functional Insulin Treatment (Howorka 1987) was released by Springer Berlin, focusing on the teaching methodology and content transfer to the patient within the setting of group teaching. Until now, seven editions appeared in four languages (German, English, Hungarian, Polish), illustrating high interest for this monograph which can also be understood as a proof of its value.

Figure 5.2 Multilingual editions of Functional Insulin Treatment, Springer Publishers, Berlin.

Monographs for patient education: Diabetes? Insulin dependent?...

The most important decisive step in the quality improvement of therapy and education is therefore definition of recommended written materials for the patients. Since the 20-minute or even 1-hour individual counseling in no case can replace neither the group education or individual activity of the patient, it proved itself to work with a "list of the recommended literature for the patient". On this list, according to individual educational need of the particular patient, corresponding positions are then marked. The proposed "list of the recommended literature for the patient" in abbreviated form has been published in patient book “Insulin-dependent?...” *(Howorka 1987, 9th edition 2011)*.

![Monograph “Insulin-dependent?...”](image)

*Figure 5.3 Monograph “Insulin-dependent?...”


As far as the educational contents are concerned, an important model for patient materials for the German speaking countries has been proposed in the 80’s by the team around Michael Berger and
Viktor Jörgens, University of Dusseldorf. The contents of their educational approach has been derived from a training program in Geneva (Assal et al, 1985). The “Dusseldorf educational model” addresses patients with relatively low basic diabetes-related knowledge. For this group of patients, the mentioned position of Jörgens and team fully cover the educational needs. For the Viennese team, therefore, it was unnecessary to write and develop a new book.

The book "Insulin-dependent?..." (Howorka 1987, 9th edition 2011) was developed for the more advanced stage of the rehabilitation process. This book was the basics for future modular training system. It provided a definition of contents for more advanced education and allowed to delimit them from that of the "basic" Düsseldorf education program. The book "Insulin-dependent?..." received 1989 the award of the city of Vienna. Up to now, nine editions in three languages appeared which fact is in practical terms the best proof of its value. The Chinese edition is planned for the academic year 2014/15.

A czech edition exists based on the 7th german edition, also published by Kirchheim-Verlag Mainz. In 2011 two English editions of “Insulin-dependent?...” appeared on the US-market and are available via AMAZON.
Hyperlipidemia book for patients

The hyperlipidemia educational entity was initially introduced in 1998. After several years of experience an appropriate monograph (“The dangerous fat”, *Grillmayr and Howorka, 2002*) focusing on nutritional and pharmacotherapeutical measures against high blood lipids was released as a standard educational material for patients. The book focuses on the nutritional therapy of hyperlipidaemia and explains the pharmacotherapeutic procedure in case of insufficient dietary treatment. As diabetes represents an equivalent of the coronary artery disease, statins remains very important. Preliminary experiences have shown an improvement of treatment adherence. As shown in international benchmarking results (*Howorka, MPH Thesis 2007*) we have consistently achieved best outcomes in terms of LDL cholesterol, total cholesterol in both, type 1 and type 2 diabetes. It can be assumed that both, hyperlipidemia educational module as well as the monography for hyperlipidemia have contributed to such best outcomes internationally.

Figure 5.5 Monograph dietary and pharmacologic treatment of hyperlipidaemia

“The Dangerous Fat” (Fett muss nicht schaden) initial edition 2002, Krenn Publishers, Vienna
Future resources for patient training: Lay media in preparation

While in the 90’s the publication of basic books for education in diabetes was a decisive step forwards toward improvement of the quality of the training, in the recent years it became clear that new audiovisual media should help in a further differentiation of the educational process. Accordingly, still outstanding are patient materials and books on therapy of central overweight, metabolic syndrome, hypoglycemia prevention, pregnancy and delivery in diabetes or "update" in functional insulin treatment with focus on the therapy of the microvascular late complications.

5.4. Graduate university education

Until 1986, there were at the medical faculty no lectures dedicated specifically to the patient education. Also the present medical curriculum on the Medical University Vienna gives quite low priority to structured patient education. The author’s teaching appointments at the Medical University Vienna is obviously the only one related to this important area.

At present, multiple, usually at least five universitary teaching appointments related to individual and structured group education are given to the author of the thesis:

- “Diabetes self-treatment”, relates to treatment and education of type 1 diabetes, mainly with functional insulin treatment,
- “Hypertension/nephropathy prevention training”, relates to hypertension education module and thus to the treatment of hypertension and nephropathy prevention in diabetes,
- “Obesity/metabolic syndrome and behavioral modification” relates to the educational “slim-date” module, and to pharmacological and behavioral treatment of type 2 diabetes and associated diseases,
- The increase of knowledge of medical students has been quantified and was investigated within a project of a medical diploma thesis together with Cand. med. Stockinger in 2014.
Fig. 5.4.1 Increase of knowledge in medical students (modified after Stockinger 2014), n= 199, p<0.001 in all knowledge categories.

Modified after Stockinger, 2014 (in press), Supervisor: K. Howorka

5.5. Postgraduate education

International seminars for physicians and educators

A two-stage workshop model for health care providers has been developed to cover functional insulin therapy and other modules of structured patient education for self-treatment in chronic diseases. Functional insulin treatment (FIT, separate insulin dosages for fasting, eating or correcting hyperglycemia) allows a “normal” life now in insulin-dependent diabetes.

In order to secure its transfer and dissemination, we worked out seminars on FIT for health care providers (HCP). So far, 10 seminars in German (6 in Germany and 4 in Austria: 496 participants) and 4 seminars in English (USA: 78 participants) were held.
Table 5-1 International FIT-Seminars

<table>
<thead>
<tr>
<th>FIT-Seminars in German</th>
<th>FIT-Seminars in English</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987, n=60, Baden</td>
<td>2000, n=20, University of Vienna</td>
</tr>
<tr>
<td>1988, n=47, Rehabilitation Center Aflenz, A</td>
<td>2000, n=22, University of Miami (in abbreviated form as 3-day-seminar)</td>
</tr>
<tr>
<td>1989, n=50, Rehabilitation Center Aflenz, A</td>
<td>1996, n=51, Rehabilitation Center Aflenz, A</td>
</tr>
<tr>
<td>1990, n=52, Privatklinik Dr. Schindelbeck, Herrsching, D</td>
<td>1991, n=41, Privatklinik Dr. Schindelbeck, Herrsching, D</td>
</tr>
<tr>
<td>1991, n=41, Privatklinik Dr. Schindelbeck, Herrsching, D</td>
<td>1992, n=47, Diabetesklinik Bad Nauheim, D</td>
</tr>
<tr>
<td>1996, n=51, Rehabilitation Center Aflenz, A</td>
<td>1999, n=65, Privatklinik Dr. Schindelbeck, Herrsching, D</td>
</tr>
<tr>
<td>2000, n=22, University of Miami (in abbreviated form as 3-day-seminar)</td>
<td>2001, n=16, St. Paul/Minneapolis</td>
</tr>
<tr>
<td>2005, n=4+18, Minneapolis/Miami (in abbreviated form as 3-day-seminar)</td>
<td>2009, n=35, Vienna, post EASD congress Seminar</td>
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</table>

In the USA, FIT-Foundation has been founded to support the dissemination of modular outpatient education in the USA (www.fitusa.org). Further information on the research group and current programs can be found on the web, as well (www.diabetesfit.org, www.diabetes-austria.com).

In total, 10 nationalities were represented. In accordance with their postgraduate education scheme, in the German FIT seminars 57% of participants were physicians while 39% of attendee’s participants were physicians in the English FIT seminars in the USA.

In these seminars, know-how and capabilities necessary for implementation of an out-patient, structured, modular patient education system were presented. Lectures, problem-oriented learning (PBL), participation in patients’ classes (“second stage” approach, “live-class”), simulation of counseling work with patients, solution-oriented group work and interviews with patients with diabetes experienced in FIT have been used as main didactic methods.

Assessments of increase in knowledge and of quality of didactic process were performed using questionnaires (mostly multiple-choice questions) at the beginning and at the end of the seminars. Psychometric features of the instruments were high content validity and acceptable reliability.
Participants’ state of knowledge (correct mark score) increased from 57.7±18.1 to 78.5±11.5. Details: There was a significant increase in knowledge in 100% of the questions regarding guidelines for adaptation of insulin dosage (rank variance analysis, p<0.02-0.0001; the percentage of correctly answering participants rose by 19-60%). However, due to high initial score, only a minority of the psychological questions at the seminar end could be answered significantly better. Seventy-nine % of the participants were able to set up FIT insulin dosage algorithms correctly at the end of the seminar (vs. 11% at the beginning). 96% judged the whole seminar to be “good” to “excellent”.

The integration of educational routine with patients was particularly appreciated. The educational and therapeutic efficacy of FIT seminar participants could be evaluated in a subgroup of their patients, showing the net improvement of outcome quality indicators similar to that achieved by originator team: values of 129-130% of relative HbA1c target (100% corresponds to the mean of the reference range in non-diabetic population), compare also chapter on benchmarking and outcome quality indicators achieved by the Research Group Functional Rehabilitation and Group Education.

The designed seminars for HCP on Functional Insulin Treatment are effective for didactical transfer of methods and translation of “patient competent leadership” into chronic therapy. In a “microformat” this concept has been implemented for 20 years in teaching at the Medical University Vienna (for students of medicine, nutritional sciences, sports medicine, pedagogics, psychology and nursery scientists, compare chapter on universitary teaching appointment, see 5.4 Graduate university education: Universitary teaching appointment).

The quite often superlative reviews concerning the international seminars resulted from the integration of the “second stage”, i.e. patient structured education live into the theoretical scheme of the physicians workshop (Howorka et al, 2002). In such a way physicians and educators were able to follow the whole psychological change process during the rehabilitation: from the early stage of just passive following the physicians prescription on diet and fixed insulin dosage to the conscious, active, enthusiastic and competent patient leadership with much better glycemic control and virtually free diet in insulin dependent diabetes.
6. Discussion

In the last two decades our aim was to involve the patient to a maximum degree in the chronic treatment prevention and care. This goal required the development and implementation of “integrated care approach”.

According to Wikipedia, integrated care “also known as integrated health, coordinated care, comprehensive care, seamless care or transmural care – is a worldwide trend in health care reforms and new organizational arrangements focusing on more coordinated and integrated forms of care provision. Integrated care may be seen as a response to the fragmented delivery of health and social services being an acknowledged problem in many health systems.

Integrated care covers a complex and comprehensive field and there are many different approaches to and definitions of the concept. Integrated care is a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion. Integration is a means to improve services in relation to access, quality, user satisfaction and efficiency.

The concept of integrated care seems particularly important to service provision to the elderly, as elderly patients often are chronically ill and subjects to co-morbidities and thus in special need of continuous care. As shown in “Results” our aim was to assure the competent patient involvement in the sense of integrated care.

Chronic diseases impose a large public health burden. Although basic and clinical research has provided efficacious treatments, the quality of care for people with diabetes remains suboptimal (Vinicor et al., 1994). Narayan et al 2000 explored the reasons why the existence of efficacious treatments has not reduced the burden of diabetes. He explores extensive availability of proven treatments, and the inadequate implementation of such treatments. He then argues that efficacy or mechanism research, which is aimed at understanding the causes of disease and the efficacy (proof under ideal conditions) of treatments, cannot ameliorate the burden of chronic disease without more concomitant translation research to change and improve clinical practice at the population level. People with diabetes have two to four times the risk of cardiovascular disease and are at increased risk of neuropathy, dental disease, and complications of pregnancy (Vinicor et al., 1994). In addition, the total annual costs attributable to diabetes require integrated care and translation research including identification of “best practice” activities.
Figure 6.1 Translation research in the context of other models of research.

The development of integrated care approach based on patient education relates to translation research (Narayan et al 2000).

As already mentioned in the introduction, with the method of competitive benchmarking and cross-sectional comparison of the biggest centres in Austria and Germany, we have proven to fulfill the “best practice” criteria defined (Keehley, 1996):

- To be successful over time, produce quantifiable results
- Innovative
- Recognized positive outcome
- Replicable with limited modifications, has general importance and not linked to unique situations which makes it transferable to other organizations.

“**To be successful over time, produce quantifiable results**”

We have shown the best outcomes concerning glycemic control for decades; the benchmarking over two consecutive two-year periods from 2002 to 2004 and from 2005 to 2007. A recent comparison reveals similar results. Moreover, the best or the almost best positions have been achieved in many most diabetes relevant outcomes including blood lipids, blood pressure and in process quality outcomes.

“**Innovative**”

The development of functional insulin treatment has been provided in 1983 (Howorka et al. 1983 and 1984) on an internal medicine ward on the medical university in Vienna and a constant
availability of training was given thereafter since 1988 due to cooperation with the Institute of Biomedical Engineering in Vienna in an outpatient office/surgery in private practice in an exclusively ambulatory setting. The modules for FIT, FIT-Update, pregnancy/delivery/breastfeeding in diabetes, hyperlipidemia, slim’n’fit have all been invented virtually de novo without any comparable educational modules. The module hypertension/nephropathy prevention in diabetes have been overtaken in about 50% from the analog module model as developed by Mühlhauser and Sawicki (1986, 1988, 1995). The part on ACE inhibitors and ARBs (sartans) as well as the remaining part of pharmacotherapy was invented de novo. At present a combined therapy with ACE inhibitors and ARBs is recommended in people with micro-vascular complications and proteinuria, if a sufficient blood pressure reduction with ACE inhibitors alone or in combination with diuretics can not be reached to a sufficient degree (Mogensen et al, 1999, 2000; Rossing et al, 2003, Strippoli et al, 2004).

The hyperlipidemia and type2 update modules are completely innovative (Howorka, Schulungscurricula Diabetes FIT®, 2009) and in course of evaluation.

“Recognized positive outcomes”
If recognition could be measured by the amount of “stolen educational stuff” (despite its copyrights), this fact could count for “recognized positive outcomes”. Simplified FIT-model as “Basis-bolus” is already used in many places throughout Europe and the US, most often as insulin Lantus-based regiment; an abbreviated FIT-like education is implemented in many places, mainly by physicians, previously participating in FIT seminars for HCP.

”Replicable with limited modifications, has general importance and not linked to unique situations which makes it transferable to other organizations”
In a small number of participants using the FIT-method, the similar outcome was replicated. This has been assessed within the multicenter translation study carried out with volunteering participants of international seminars for physicians in Austria and Germany. The main inhibitor in method translation is the lack of reimbursement for quality-assured outcome-secured therapeutic patient education.

In the US, after American seminars for therapists on modular education and FIT the method has been used under the name “MYD” for “Mastering Your Diabetes” at the University of Miami (Howorka and Meneghini et al, 2006), whereas in Switzerland it was used even under our original name FIT, while delivering similar outcomes (Pavlicek et al, 2006.).
While discussing the options for improving the current situation in the sense of translation research (compare the articles by Vinicor, 1994 and Narayan et al, 2000), barriers and enhancements on the level of patients, physicians and of the system should be discussed, as follows for the specific Austrian situation (modified after Howorka, 2007). For patients the most important is quality of life whereas HCP seem to be motivated for systemic change if there is a financial gratification.

As diabetes epidemic continues to increase (Engelgau et al, 2004), adequate measures for primary (Tuomilehto, 2000, CDC 2004), secondary and tertiary prevention are necessary. As already repeatedly stated also by others, if diabetes prevention should really go beyond the primary prevention, the key for success for better implementation of known treatments and end-user competence in chronic treatment would be the policy for reimbursement of structured patient education (Narayan et al, 2004, Colagiuri et al, 2006). Reimbursed measures of treatment will be chosen as the first choice and would modify a common practice...Therefore, reimbursement is the skeleton key to behavior modification of physicians (prescriptions, diagnostics, treatment choices).

To summarize, DiabetesFIT® dissemination appears quite successful. Up to now, 14 FIT (Functional Insulin Therapy) international seminars for health care providers have been performed in German (Germany, Austria) and English (USA) and some 100,000 copies of physician’s and/or patients manual in five languages have been sold. The developed print media had their historical role in spreading of patient’s competence. It is fascinating to look forward toward the Chinese translation of the patient manual…

7. Conclusions

This Doctoral Thesis comprises the evidence that structured educational programmes (Howorka et al, 2009, Curricula DiabetesFIT®, Kirchheim Publishers Mainz) have created a basis for effective secondary and tertiary prevention and treatment of both type 1 and type 2 diabetes mellitus. In this way, the development of adequate strategies, printmedia and an active, challenging and partnership approach of health care providers and insurance companies appears to be both, possible and necessary (see numerous respective publications in 8 Bibliography) to effectively translate our academic experience into every day practice.
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