

# Diagnosis, Treatment and Follow-up of Diabetes mellitus in the Elderly

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## Foreword

*Worldwide an increasing number of people with diabetes are beyond the age of 65 years. For this rapidly growing group of elderly and very old patients with diabetes there is a big demand for information based on randomized controlled trials. In any case, it is clear that evidence-based guidelines targeting younger persons cannot be simply extrapolated to elderly persons without considering their special conditions such as multimorbidity, functional impairment and the need to evaluate their individual goals including life perspective and quality of life.*

*Evidence-based medicine (EBM) is the integration of best research evidence with clinical expertise and patient-oriented values. Thus we distanced ourselves from “eminence-based medicine” and compiled all studies targeting older diabetics in order to present the best evidence-based guideline. Novel is that two leading associations (German Diabetes Association and German Geriatric Society) combined their efforts to make a unique guideline. To our knowledge the first guideline worldwide that unites aspects of diabetology with aspects of clinical geriatric medicine.*

*This guideline documents the wide range of special procedures for the diagnosis, treatment and follow-up of diabetes and its complications with a real focus on older people. It is invaluable to all those involved in the treatment, management and care of older people with diabetes, especially regarding those with functional decline in their activities of daily living.*

*The limitation is that the amount of data available and thus, the basis for evidence-based judgements for elderly patients with diabetes mellitus is still unsatisfactory. In the future, studies on diabetes mellitus and its treatment should always include an adequate number of older diabetics, including also the very old. Furthermore, it is crucial that these types of studies are supplemented with an assessment of the status of the cognitive and affective functions and mobility, which facilitate a description of the patient’s situation.*

*“Add more life To years and not merely years to life” – Treating diabetes in an elderly person who suffers from other diseases and is impaired by geriatric syndromes requires clinical attention, experience and a guideline that collects the evidence we have from studies: The Evidence-based Guideline „Diabetes in The Elderly“.*



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## Methodology for the Preparation and Revision of Guidelines from the German Diabetes Association (DDG)

The scientific and political legitimization of evidence-based consensus guidelines is high [Ollenschläger et al., 2000]. This probably explains the high acceptance of this type of guideline in comparison with others [Cabana et al., 1999; Klazinga et al., 1994]. The EBM strategy for the development of the existing guidelines followed the procedure defined by AHCPR and SIGN (see Table 1).

The methodological approach for the guideline development process attempts to meet the requirements of evidence-based medicine. It is based upon nationally and internationally accepted quality criteria that were defined by the Agency for Health Care Policy and Research [AHCPR, 1992], the Evidence-Based Medicine Working Group [Hayward et al., 1995], the Scottish Intercollegiate Guidelines Network [SIGN, 1999], the German Association of the Scientific Medical Societies [AWMF, 2004] and the German Agency for Quality in Medicine [ÄZQ, 1999]. A detailed description has been published separately ([www.leitlinien.de](http://www.leitlinien.de), [www.aeqz.de](http://www.aeqz.de)).

### Selection of the Experts

For each guideline, the managing committee and the guidelines commission of the DDG have established panels of experts composed of recognised authorities in the relevant fields.

### Literature Search

Dr. B. Richter is responsible for the coordination between the expert panel and the work group in the selection of the literature search terms.

For each project group, a complete search strategy of medium sensitivity is developed for the Ovid-operated MEDLINE database, for example, and later adapted to the Cochrane Library and Embase. If necessary, a supplementary search in other data-bases is conducted. The list of references obtained

from the various databases are checked for duplicates by using a bibliographic programme, sorted according to publication year, and converted into PDF files. The titles and abstracts are sent to the experts per e-mail. Definition of the original papers to be procured for the experts. To guarantee transparency and reproducibility of the literature search, the search strategies and terms are published in the appendix of every guideline.

### Appraisal and Evaluation

Experienced physicians and biometrists classify the studies and analyses of study designs on the basis of their scientific conclusiveness into levels of evidence I-IV as proposed by AHCPR and SIGN (see Table 1). When opinions diverged, the case is discussed and classified by consensus. Evidence is evaluated according to internationally accepted quality criteria (see above). Clinical studies are divided into different levels corresponding to their scientific validity and significance and, additionally, weighted according to their clinical relevance. For example, meta-analyses of randomised controlled clinical studies and randomised controlled studies receive the highest ranking.

The weighting of the final intervention recommendations (screening, prevention, diagnosis, treatment and rehabilitation) with strengths of recommendation A to C is undertaken by clinically experienced experts based on the supporting evidence and clinical relevance.

In areas in which the clinical evidence must be weighted differently from the scientific evidence, the strength of recommendation is determined by interdisciplinary consensus (see Table 2).

Recommendations for which there is insufficient or no external evidence available, but are known to be indispensable from clinical experience, could receive the highest strength of recommendation A.

In contrast, interventions for which levels of evidence Ia or Ib exist, could receive the lowest strength of recommendation if their clinical significance is only marginal. The

necessary transparency is achieved through the linking of both the supporting external evidence and the strength of recommendation to the respective recommendations (see Table 1).

### Preparation Process

After the conclusion of the systematic literature search by the Cochrane Metabolic and Endocrine Disorders Group and peer review by the experts, a draft version of the guidelines is formulated based on the core statement of the documented and evaluated publications.

Levels of Evidence (level)	
<b>Ia</b>	Evidence based on meta-analyses of randomised controlled studies
<b>Ib</b>	Evidence based on at least one randomised controlled study
<b>IIa</b>	Evidence based on at least one well-planned, nonrandomised controlled study
<b>IIb</b>	Evidence based on at least one well-planned, nonrandomised and not controlled clinical study, e.g., cohort study
<b>III</b>	Evidence based on well-planned, nonexperimental, descriptive studies, such as e.g., comparative, correlation, or case-control studies
<b>IV</b>	Evidence based on reports from expert committees or expert opinions and/or clinical experience of recognised authorities

**Table 1:** Published papers are classified into levels of evidence based on their scientific validity [modified according to AHCPR, 1992; SIGN, 1996]

Additionally, internal evidence (unpublished results of studies, experience of experts) from rounds of discussions with competent experts and experts from related disciplines, are integrated into the draft version.

The discussion draft, after checking for practicability and plausibility and revision, is published in the web site of the DDG. Thus, the draft is presented to a wider forum for critical evaluation with a call for active participation in the compilation of the guidelines through the contribution of

comments, supplementary information and suggestions for modifications.

All suggestions received before printing are discussed by the expert group and are taken into consideration commensurate with their relevance. The diabetes guidelines are examined again by the guideline commission and adopted by the managing committee of the DDG.

Each evidence-based diabetes guideline is first published in the journal "Diabetes and Metabolism;" each actualisation is published in the web site of the DDG ([www.deutsche-diabetes-gesellschaft.de](http://www.deutsche-diabetes-gesellschaft.de)).

Strength of Recommendation	Supporting Evidence
A	Level of evidence Ia, Ib or from the clinical point of view first class
B	Level of evidence IIa, IIb, III or from the clinical point of view second class
C	Level of evidence IV or from the clinical point of view third class

**Table 2:** Weighting and recommendation with strengths of recommendation [modified according to AHCPR, 1992; SIGN, 1996]

### Further Development of Guidelines

The existing guidelines are scientifically valid guidelines on the selected priority diseases. Important information: The diabetes guidelines do not include diagrammatic procedural instructions and algorithms. This function is fulfilled by the clinical practise guidelines, which are based on the scientific guidelines and contain all guideline-relevant aspects for practical implementation including algorithms (clinical practise guidelines of the German Diabetes Association, 2001).

Furthermore, a patient version has been drawn up, in which these recommendations are explained in language easily understood by patients and which is available in the internet ([www.diabetes-deutschland.de](http://www.diabetes-deutschland.de)).

### Internationalization of Guidelines

The internationalization of the German guidelines constitutes an important development. This includes consideration of European guidelines within the German guidelines as well as translation of the German versions and their implementation in other European countries and beyond.

In the context of internationalization two German guidelines already have been translated into English, among them "Psychosocial Aspects of Diabetes" and "Diagnosis, Therapy and Longterm Management of Neuropathy Type 1 and Type 2 Diabetes mellitus". A proper and scientifically correct translation was assured by hiring a scientist whose native language is English, by proof reading through experts from the guidelines expert committee and by authorizing the translation through the speaker of the expert committee. Furthermore the guideline "Nutrition and Diabetes mellitus", which has been developed in coordination with the German Diabetes Society (DDG) is already available as an English language European version, has now been translated into German.

The evidence-based guidelines are valid until May 2007. The diabetes guidelines will be updated in a timely manner should new and relevant scientific findings become available.

### Financing of the Guidelines

These guidelines were prepared by the scientific medical association (German Diabetes Association) independent of interest groups.

They are financed with funds from the German Diabetes Society and the National Diabetes Action Forum (Nationales Aktionsforum Diabetes, NAFDM), which is coordinated by the German Diabetes Union (Deutsche Diabetes-Union. A portion of the funds was raised from membership dues and donations and from the fees paid by companies for their exhibits at the annual DDG congress. Additional funds were raised as uncommitted donations to the

DDG from the German Industry Forum for Diabetes (IFD).

All experts worked voluntarily and received no remuneration. Travel and offices expenses were reimbursed according to the directives of the DDG, which are based on prevailing university guidelines.

Duesseldorf and Karlsburg, May 2006

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## 1 Introduction

The goal of this guideline is to present the most important clinical aspects of diabetes mellitus in people over 65 years on the basis of study results and to give practical treatment advice for the care and improving the quality of life of these patients.

The guideline at hand concentrates entirely on the subject "diabetes in the elderly" and deliberately deviates in some technical aspects from existing guidelines of the DDG. This is due, in part, to the age-specific subject that is touched upon in almost all present guidelines of the German Diabetes Association (DDG). Special attention was given to the conformity with other diabetes guidelines; however, in some sections there is also a differentiation between this and previous diabetes guidelines. Furthermore, the current data situation, which in many areas did not allow an indisputable recommendation, requires cautious evaluation of the available knowledge. Important findings from studies in younger people with diabetes mellitus were included when required for comprehension. These findings were not uncritically transferred, extrapolated or applied to older people. The guideline is meant to examine the topic "diabetes in the elderly" coherently and comprehensively and also provide recommendations for areas that are not adequately corroborated through studies.

Diabetes mellitus is the most frequent comorbidity of old age [Harris MI, 1993, level III]. In industrialised nations, such as Germany, every second person with diabetes mellitus (currently ca. 52.2 per cent) is over 65 years old [King H et al., 1998, level III].

Diabetes mellitus is a chronic metabolic disease of global magnitude: the worldwide prevalence was between 147 and 154 million cases in 2000. In the coming years, the proportion of people with diabetes mellitus will dramatically rise due to the demographic development (until 2010, an annual growth of between 5.8 and 7.4 million cases is expected) [Amos AF et al., 1997, level III; King H et al., 1998, level III].

The number of health care service claims for elderly people with diabetes (60 to 74 years old) is two to three times higher than that for the general population of the same age [Damsgaard EM, Froland A et al., 1987, level III].

The cost to the health care system for elderly people with diabetes is two to three times higher than that for elderly nondiabetics. A large part of the costs go into the treatment of diabetic sequelae (e.g. foot ulcers) and into the necessary treatment follow-up [Damsgaard EM, 1990, level III].

Elderly people with diabetes require treatment concepts that differ from that of young people with diabetes due to the sequelae of this metabolic disease (e.g. vascular complications), age-dependent functional deficits, the susceptibility to hypoglycaemia and the necessary inclusion of caretakers and medical attendants [Hendra TJ et al., 1997, level IV].

The complexity of the disease due to the longterm complications necessitates a balanced cooperation between the professional health care providers (e.g. nursing staff, general practitioner, specialist for internal medicine, diabetologist, geriatrician, ophthalmologist, nephrologist, dietician, podiatrist) and family members who participate in the care [Sinclair AJ et al., 1994, level IV].

## 2 The Geriatric Patient

### 2.1 Definition

Geriatric patients are generally older than 65 years old and have disabilities that affect daily life, which mostly develop as a consequence of multimorbidity and that negatively affect the quality of life.

### 2.2 Characteristics of Geriatric Patients

- Increased vulnerability due to physiological age-related changes
- Multimorbidity with multiorgan interactions



- Deficits in several functional areas: at the organ, personal or social levels
- Increased instability in the somatic, cognitive and affective areas, decreased adaptability and limited ability to compensate
- Affective and communicative disturbances
- Atypical symptom presentation, lowered spontaneous recovery, increased need for rehabilitation
- Frequent presence of geriatric syndromes and problems (incontinence, constipation, tendency to fall, chronic wounds, malnutrition, depression, dementia, chronic pain, sleep disorders, polypharmacy)
- Impending loss of independence, development of the need for care
- Often insufficient or incorrectly reacting social support system
- Great variability in the findings
- Increased susceptibility to iatrogenic injuries (e.g. through changed pharmacokinetics)

### 3 Epidemiology – Morbidity and Mortality Risks

#### 3.1 Prevalence

The prevalence of diabetes mellitus in Germany rises with increasing age. Data from the former GDR (1987) show that 14 per cent of the men and 16.2 per cent of the women in the 65 to 69-year old age group have diabetes. The highest rate is attained between the ages of 75 to 79 with 15.6 per cent in men and 20.5 per cent in women (WHO criteria from 1985) [Michaelis D et al., 1987, level III]. With further advancing age, the prevalence of diabetes mellitus continually sinks; the proportion in the over 95-year olds is 5.07 per cent of the men and 6.02 per cent of the women [Janka HU et al., 2000; compare Tab. 1]. More recent data from southern Germany (2000) show a prevalence of diabetes mellitus among the 65 to 69-year olds of 22.2 per cent in the men and 16.4 per cent in the

women. Between the ages of 70 to 74, 23.1 per cent of the men and 17.0 per cent of the women have diabetes mellitus (WHO criteria von 1999). On the average, about half of the cases of diabetes mellitus were previously undetected [Rathmann W et al., 2003].

Unfortunately comparison of the data from 1987 and 2000 is limited due to the different geographical regions and the fact that the WHO criteria for the diagnosis of diabetes mellitus were modified in the interim. However, the continual rise in the prevalence of diabetes, which was particularly pronounced in older people, was already observed in the GDR population from 1960 to 1987 [Michaelis D et al., 1991, level III].

The prevalence of diabetes mellitus in Europe in the over 70-year olds varies with age, sex and country between 5.6 per cent (70 to 73-year old men, Poland) and 56.5 per cent (80 to 89-year old women, Spain) (WHO and ADA criteria) [The Decode Study Group, 2003]. Europeans have a moderate to low prevalence of diabetes mellitus in comparison with other ethnic groups worldwide, as far as the age- and sex-specific prevalence of diabetes mellitus is reported.

The proportion of men in Germany with impaired glucose tolerance is 19.5 per cent in the 65 to 69-year olds and 22.8 per cent in the 70 to 74-year olds. The values for women are 18.7 per cent in the 65 to 69-year olds and 18.9 per cent in the 70 to 74-year olds [Rathmann W et al., 2003]. These values are comparable with results from the USA and Finland [Harris MI et al., 1987, level III; Harris MI, 1990 level III; Hiltunen L et al., 1994, level III].

Cross-sectional and prospective studies have shown that because blood glucose levels after glucose loading increase with age (ca. 0.83 mmol/l per decade) and fasting blood glucose levels increase only 0.06 to 0.11 mmol/l per decade, the frequency of hyperglycaemia after stress increases with age [The Decode Study Group, 1999, level III]. Hence, the prevalence of undiagnosed diabetes mellitus in Europe is un-

derestimated, particularly in the elderly and female populations when only the fasting blood glucose is tested [The Decode Study Group, 2003]. Although between the ages of 40 and 60, more men are affected than women, the relationship reverses itself after age 60 [Hauner H, 1998, level IV; Helmert U et al., 1994].

### 3.2 Morbidity

A differentiated classification of the complication frequency in people with diabetes mellitus is undertaken in the chapters "Complications" and "Geriatric Syndromes". Further details are also found in the evidence-based diabetes guideline "Epidemiology and Course of Diabetes mellitus in Germany" [Janka HU et al., 2000].

### 3.3 Mortality

The relative mortality risk in older people with diabetes mellitus is increased, even when diabetes is first detected at the age of 60 and also even after the age of 75. The cause of death is primarily coronary heart disease and cerebrovascular diseases [Sinclair AJ et al., 1997, level IV].

Insurance statistics from the USA point out that the life expectancy of people who have been diagnosed with diabetes mellitus between the ages of 60 and 70 is five years shorter than in the insured general population [Goodkin G, 1975, level III]. Also in the American NHANES study, the life expectancy of people with diabetes in comparison with nondiabetics in the 55 to 64- and in the 65 to 74-year old age group was about eight years and four years shorter, respectively [Gu K et al., 1998, level III].

An European study showed in an age and sex adjusted evaluation that for persons between 60 and 79 years, there is an increased mortality for those with diabetes mellitus, for those with fasting hyperglycaemia and for those with an isolated incidence of stress hyperglycaemia of 1.9 (95 per cent CI: 1.6 to 2.2), 1.8 (1.5 to 2.3) and 1.6 (1.1 to 2.3), respectively [The Decode Study Group, 1999].

### 3.4 Costs in Germany

The costs for treating diabetes mellitus in Germany lie, depending on the number of concomitant diseases about 1.3 to 4.1-fold higher than for other patients [Liebl A et al., 2001, level III].

In the German arm of the CODE-2 study, the average age of people with type 2 diabetes was 67 years old. Eighty-one per cent of the patients were treated with drugs and 19 per cent were treated exclusively with diet and exercise. Every tenth patient needed nursing care. The total costs were between EUR 3,359 and 4,500 per patient. Fifty per cent of the costs were accounted for by stationary treatment, 13 per cent by outpatient care and 27 per cent by the treatment with drugs [Liebl A et al., 2001, level III; Schwenk S, 2002, level III].

The drug expenses for the 60 to 79-year olds are comparable to that for the 40 to 59-year olds. The expenses for the over 79-year olds is somewhat lower; this applies to all prescribed drugs including oral anti-diabetic agents and insulin, as well as blood glucose test strips [Schwenk S, 2002, level III].

The total costs for people with diabetes mellitus amount to per year and person between EUR 3,359 and 4,500 (DM 9,018) [Liebl A et al., 2001, level III; Schwenk S, 2002, level III].

With EUR 3,538, the sum of the average costs for the 60 to 79-year olds was approximately 20 per cent above that of the 40 to 59-year olds (EUR 2,840) and was comparable with that of the over 79-year olds (EUR 3,436) [Schwenk S, 2002, level III]. Presumably untreated diabetes-related dysfunctions, in particular mental deterioration processes in older people are associated with very high costs [Meerding WJ et al., 1998]. Estimated costs for six months' treatment of depression EUR 1,872 +/- 140 versus EUR 2,622 +/- 413 for untreated cases [Revicki DA et al, 1998]; incontinence EUR 3,565 annually [Wagner TH et al., 1998]; EUR 18,408 for mild, EUR 30,096 for moderate, and EUR 36,132 for severe forms of dementia annually [Leon J et al., 1998]; falls with injury sequelae

EUR 19,440 annually [Rizzo JA et al., 1998].

**Recommendation:**

**Even in elderly people for whom the diagnosis of diabetes mellitus is made after the age of 60, there is a higher mortality rate in comparison with nondiabetics. The costs for elderly people with diabetes (over 60 years) are higher than for younger diabetics (under 60 years old) and are attributable to the more frequent hospital stays in particular. A demonstrative reduction of the therapeutic expenses for diabetes mellitus can probably be achieved only through the prevention or treatment of macrovascular complications, diabetes-associated dysfunctions and geriatric syndromes. (strength of recommendation B / grade of evidence D)**

#### 4 Definition, Classification and Diagnosis of Diabetes mellitus and Impaired Glucose Tolerance in the Elderly

##### 4.1 Definition

Diabetes mellitus is defined as a regulatory dysfunction of metabolism mainly characterised by chronic hyperglycaemia. The underlying cause may be impaired insulin secretion, diminished effectiveness of insulin or also both. Chronic hyperglycaemia leads to diabetes-specific microangiopathy that, in turn, causes sequelae primarily in the eyes, kidneys and nervous system. chronic hyperglycaemia also leads to diabetes-associated macroangiopathy that, in turn, leads to complications primarily in the heart, brain and peripheral arteries.

Detailed definitions of diabetes mellitus type 1 and type 2 are presented in the evidence-based diabetes guideline "Definition, Classification and Diagnosis of Diabetes mellitus" [Kerner et al., 2001].

**The definition of diabetes mellitus on the basis of blood glucose levels is independent of age.**

##### 4.2 Classification

The classification of diabetes mellitus is found in the guideline "Definition, Classification and Diagnosis of Diabetes mellitus" [Kerner et al., 2001].

Type 2 diabetes is the most frequent form of diabetes in elderly people (90 per cent). Type 1a diabetes is diagnosed in 4 to 15 per cent of the older people with a first manifestation of diabetes mellitus and in up to 21 per cent of the insulin-injecting diabetics (late autoimmune diabetes in adults, LADA) [Kilvert A et al., 1986, level IIb; Laakso M et al., 1985, level III]. There is no clinical data that indicate that elderly patients with late-onset autoimmune diabetes, LADA, benefit from a specific therapy [Pozzilli et al., 2001].

**Recommendation:**

**Whether an immunological differentiation between type 1 and type 2 diabetes mellitus in elderly diabetics is useful for the treatment is presently still disputed and cannot be resolved in the existing studies. The possibility of a primary need for insulin should be considered. The development of ketoacidosis is also possible in elderly patients. (strength of recommendation C / grade of evidence D)**

#### 5 Screening and Diagnosis

##### 5.1 Screening of Older People

In 1987 it was already assumed that the prevalence of undiagnosed diabetes in the 65 to 74-year olds in USA (9.4 per cent) was comparable with the prevalence of diagnosed diabetes (9.3 per cent) [Harris MI et al., 1987, level III]. In a patient sampling conducted in 2000 in the region of Augsburg, Germany, over 40 per cent of the 55 to 74-year olds had impaired glucose tolerance or diabetes mellitus. Half of the cases were not previously diagnosed. The HbA<sub>1c</sub> level of patients with recently diagnosed diabetes mellitus was very low, 6.2 per cent; the clinical relevance of this finding is unclear [Rathmann W et al., 2003].

People with undiagnosed diabetes mellitus also have with high probability dyslipidaemia, high blood pressure and are overweight. Moreover, they have a significantly higher risk for coronary heart disease, stroke and peripheral vascular disease in comparison with people who do not have diabetes mellitus [Klein R, 1995, level III].

Nevertheless, the benefit of a population-wide diabetes screening has not been proven [Berger M, 2001]. Outcome studies from England and estimates based on the NHANES data [Lawrence et al., 2001] come to the conclusion that only a screening of high-risk populations is clinically and economically advisable. Score systems based on risk predictors are possibly superior to glucose measurements for predicting diabetes [Lawrence JM et al., 2001; Stern MP et al., 2002].

Predictors for the potential development of diabetes mellitus are, for example, overweight (body mass index [BMI] above 27 kg/m<sup>2</sup>), first degree relatives with diabetes, arterial hypertension (blood pressure above 140/90 mm Hg), dyslipidaemia (HDL below 35 mg/dl or triglyceride above 250 mg/dl), impaired fasting glucose or impaired glucose tolerance.

For middle-aged persons with an impaired glucose tolerance (IGT) but no diabetes, a change in the lifestyle (lifestyle intervention) [Knowler WC et al., 2002, level Ib; Pan XR et al., 1997, level IIa; Tuomilehto J et al., 2001, level IIa] and/or also pharmacological intervention (acarbose, metformin), but with lower success rates [Chiasson JL et al., 2002, level Ib; The Diabetes Prevention Program (DPP), 2002, level IIb], can reduce the frequency of conversion to diabetes mellitus. Study results on older persons are not available.

#### **Recommendation:**

**The benefit of a population-wide diabetes screening has not yet been demonstrated. For existing risk factors for diabetes mellitus (e.g. overweight, first degree relatives with diabetes, hypertension, dyslipidaemia, IGT, IFG) and therapeutic follow-up, testing for dia-**

**betes by means of fasting blood glucose and postprandial blood sugar tests or, if necessary, through a 2-hour blood glucose test should be performed once annually in elderly persons. (strength of recommendation C / grade of evidence D)**

## 5.2 Diagnosis

The new diagnostic criteria of the ADA [American Diabetes Association 2000, level IV] have been used since 1997. The diagnosis is made on the basis of fasting blood glucose level [Kerner W et al., 2001]. These criteria were largely adopted from the diabetes guideline "Definition, Classification and Diagnosis of Diabetes mellitus" [Kerner et al., 2001].

- fasting plasma glucose levels below 110 mg/dl are regarded as normal
- fasting plasma glucose levels of 110 mg/dl or higher are regarded as abnormal fasting glucose; if applicable an oral glucose tolerance test (oGTT) should be performed
- fasting plasma glucose levels of 126 mg/dl or higher are regarded as diabetes mellitus (retesting on the next day is necessary)

There are no separate diagnostic criteria for elderly people with diabetes mellitus.

Glucose tolerance testing has shown that blood glucose level increases between 6 and 15 mg/dl per decade of life, whereas the fasting glucose level increases by only 0.7 mg/dl per decade of life in men and by 2.0 mg/dl in women [Barrett-Conor E, 1980, level III]. In elderly persons, the probability is higher than for younger persons that diabetes mellitus will be detected through the 2-hour blood glucose level as specified in the old WHO criteria from 1985 than by the fasting blood glucose level, which is recommended in the new ADA criteria [Barrett-Conor E, 1980, level III; Wahl PW et al., 1998, level III].

Independent of age, a higher prevalence of diabetes mellitus has been detected through the application of the new ADA criteria

[Decode Study Group 1998, level III; The Decode Study Group, 1999, level III].

**Recommendation:**

**For establishing a diagnosis, the quality-assured determination of fasting plasma glucose is recommended despite its limited sensitivity. In contrast to the guideline “Definition, Classification and Diagnosis of Diabetes mellitus” [Kerner W et al, 2001], performing the oral glucose tolerance test (oGTT) for impaired fasting glucose (IFG) is not routinely recommended due to poor practicability and low retest reliability. If a lifestyle intervention is possible and appears advisable for older persons with suspected diabetes mellitus, an oral glucose tolerance test can be performed in addition to the determination of the fasting blood glucose. (strength of recommendation C / grade of evidence C)**

## 6 Pathogenesis of Diabetes mellitus Type 2 in the Elderly

Complex interactions between genetic variables, day to day habits and age-related changes in the glucose metabolism all play a fundamental role in the pathogenesis of diabetes mellitus type 2 [Meneilly GS et al., 1995, level IV].

Eating habits that include high fat consumption, little exercise or reduced muscle mass favour the development of diabetes mellitus in the elderly [Feskens EJ et al., 1995, level III].

## 7 First Manifestation of Diabetes mellitus in the Elderly

Diabetes mellitus often begins without symptoms or only with unspecific symptoms. Typical symptoms such as polydipsia and polyuria are observed rarely in diabetes mellitus type 2 and in the elderly since the sensation of thirst in older people is reduced and the renal threshold value for glucose may be elevated [Samos LF et al., 1998, level IV].

Hypertension and/or cardiovascular disease has been found in over half of the recently

diagnosed diabetics [Andersson DK et al., 1995, level III].

The first manifestation of diabetes mellitus rarely occurs as a coma caused by hyperosmolarity or ketoacidosis [Small M et al., 1988, level III]. More frequently diabetes mellitus type 2 is diagnosed on the basis of specific diabetic complications [Morley JE et al., 1990, level IV; Samos LF et al., 1998, level IV].

Some rare, but potentially diabetes-specific age symptoms have been described: periarthopathy of the shoulder, neuropathic cachexia, diabetic amyotrophy, diabetic dermopathy and malignant otitis externa [Ellenberg M, 1974; Friedmann NA et al., 1989, level III; Morley et al., 1990, level IV; Samos LF et al., 1998, level IV].

**Recommendation:**

**For all acute diseases and for the occurrence of unspecific diabetes-associated disorders (e.g. for vascular diseases, hypertension, overweight, depression, progressive loss of mental capacity, recurrent urinary tract infections, erectile dysfunction etc), the blood glucose concentration of even nondiabetic elderly patients should be measured and the hyperglycaemia treated. After the acute disease has subsided, the glucose metabolism should again be tested. (strength of recommendation B / grade of evidence C)**

## 8 Blood Glucose Control and Diabetes-Associated, Acute and Chronic Complications

Numerous studies have demonstrated that the high rate of diabetes-specific complications, the mortality rate and the development of geriatric syndromes are correlated with higher blood glucose levels even in the elderly [Andersson DK et al., 1995, level III; Kuusisto J et al., Diabetes 1994, level III; Kuusisto J et al., Stroke 1994, level III; Nathan DM et al., 1986, level III].

In the United Kingdom Prospective Diabetes Study (UKPDS), it was shown in recently diagnosed middle-aged diabetics that by lowering the blood glucose level

(reduction of the HbA<sub>1c</sub> level by 0.9 per cent) over 12 years, the microvascular, but not (in any case not for the long-term) the macrovascular complications or total mortality were significantly decreased [Gadsby R, 1998, level Ib; UK Prospective Diabetes Study (UKPDS) Group, 1998, level Ib].

Based on the results of several studies on collectives of younger people with diabetes in intensive care stations, it is likely that a normoglycaemic blood sugar level is a positive factor in view of complications and mortality from serious acute diseases for even elderly diabetic patients [Malmberg K et al., 1995; van den Berghe G et al., 2001].

Diabetes-associated complications and findings continue to develop even in very old diabetic patients [Konen JC et al., 1996, level III]. A rise in diabetes-specific complications with increasing age is documented for:

- Ischaemic heart diseases
- Stroke
- Peripheral vascular diseases
- Retinopathy [Cohen DL, 1991, level III]

#### **Recommendation:**

**The treatment of older people with diabetes mellitus should be an individualised therapy. The target value for blood glucose level or HbA<sub>1c</sub> level should be discussed with the patient and should be oriented on quality of life, the age, the functional status, the life expectancy and the primary therapeutic goals of the patient. Normally, the desired HbA<sub>1c</sub> level lies below 8 per cent. A stricter control of the blood glucose level should be undertaken when serious acute diseases, diabetes-associated symptoms or influenceable geriatric syndromes are present. The family physician should also be alert for the presence of diabetes-associated complications or concomitant diseases in elderly patients without known diabetes mellitus. If such compli-**

**cations are present, diabetes mellitus should be excluded.**

**(strength of recommendation B / grade of evidence D)**

## **9 Complications, Sequelae and Concomitant Diseases**

### **9.1 Cardiovascular Complications**

The life expectancy of people with diabetes is primarily limited by cardio-vascular complications [Gu K et al., 1998, level III] (see also evidence-based diabetes guideline "Diabetes and the Heart" [Standl E et al., 2002]).

The incidence of cardiovascular diseases is twice as high for elderly patients with diabetes mellitus as that for patients without diabetes mellitus (men 2.1-fold, women 1.8-fold) [Kannel WB, 1997, level IV]. Because cardiovascular outcomes are not significantly reduced by improved blood glucose control alone in younger people with diabetes mellitus [UK Prospective Diabetes Study (UKPDS) Group, 1998, level Ib], it is assumed that this is also true for older diabetics.

The extent of a cardiac insufficiency and mortality can probably be lowered in older patients through strict blood pressure control [UK Prospective Study Group, 1998, level Ib] (further information in chapter 11.4). Lipid-lowering agents presumably reduce the risk cardiovascular outcomes in both diabetic and nondiabetic elderly, independent of the of the chol-esterol level [Shepherd J et al., 2002 level Ib; The Anti-hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), 2002, level Iib].

#### **Recommendation:**

**Cardiovascular risk factors, such as positive family medical histories, overweight, smoking, dyslipidaemia, hypertension, hyperglycaemia should also be identified in elderly patients with diabetes mellitus. (strength of recommendation A / grade of evidence B)**

## 9.2 Cerebrovascular Complications

The incidence of strokes clearly increases with age regardless of the presence of diabetes mellitus [Stegmayr B et al., 1995, level III]. Epidemiological studies have shown a 2 to 3-fold increased incidence for strokes in people with diabetes mellitus of all age groups in comparison with non-diabetics. The age-adjusted relative risk is for men about 2.7 and for women 3.8 [Kannel WB et al., 1979, level III; Stegmayr B et al., 1995, level III]. People with diabetes mellitus of all ages have higher mortality after a stroke in comparison with nondiabetics, more major functional deficits (among others, decreased mental capacity), disabilities and a higher probability of suffering from a second stroke [Mankovsky BN et al., 1996, level IV]. Significant indicators for a stroke in people with diabetes mellitus are:

- elevated fasting and 2-hour blood glucose levels
- elevated HbA<sub>1c</sub> level
- elevated blood pressure
- atrial fibrillation
- duration of diabetes [Kuusisto J et al., Stroke 1994, level III]

Lowering the blood glucose level alone does not lead to the reduction of the incidence of strokes in younger people with diabetes mellitus [UK Prospective Study (UKPDS) Group, 1998, level Ib]; this probably also applies to elderly people.

The reduction of blood pressure, however, presumably lowers the incidence of strokes also in the elderly [UK Prospective Diabetes Study Group, 1998, level Ib].

### **Recommendation:**

**Older people with diabetes mellitus should be examined for the sequelae of high blood pressure and atrial fibrillation. The blood pressure should be stabilised below a maximum of 140/90 mm Hg if it is tolerated by the patients. For primary and secondary prevention, an oral anticoagulant or acetylsalicylic acid (ASA) is recommended for atrial fibrillation after taking into consideration the risks and benefits of both. ASA is**

**also recommended, in addition to conscientious diabetes monitoring, in the early phase of therapy after a stroke. (strength of recommendation A / grade of evidence B)**

## 9.3 Complications of the Eye

Diabetic retinopathy is the most common diabetes-specific eye disease and the most frequently occurring microvascular complication. Diabetic retinopathy occurs in 32.9 per cent of the patients who were at least 70 years old when diabetes was diagnosed and up to four years after the onset of the disease; after 5 to 14 years, the prevalence is 34.8 per cent and after 15 years, 55.6 per cent [Klein R et al., 1984, level III]. The number of patients blinded by diabetic retinopathy in North Rhine doubled from 1978 to 1997 [Bertram B et al., 1997].

The severity of diabetic retinopathy positively correlates with:

- Duration of the disease
- HbA<sub>1c</sub> level
- Diagnosis at a young age
- High systolic blood pressure
- Insulin therapy
- Proteinuria
- Low body weight [Klein R et al., 1984, level III].

It is not an age-related disease [Standl et al., 1997].

Strict blood glucose control helps prevent the development and progression of retinopathy. The incidence of blindness cannot be significantly reduced by strict blood glucose control in people with diabetes mellitus; however, blindness probably occurs later in the course of diabetes mellitus [UK Prospective Diabetes Study (UKPDS) Group, 1998, level Ib].

Strict blood pressure control slows the progression of retinopathy; however, it neither reduces the deterioration of vision nor the number of cases of blindness [UK Prospective Diabetes Study Group, 1998, level Ib]. Still, there are indications that an aggressive diabetes therapy with insulin during the first year can worsen retinopathy

[Tovi J et al., 1998]. Likewise, cataract, age-related macular degeneration and open-angle glaucoma are frequent causes of blindness in older people with diabetes mellitus, whereby it is unlikely that there is a causal connection between glaucoma and diabetes mellitus [Hiller R et al., 1983, level III; Klein R et al., 1992, level III; Klein BE et al., 1994 level III; Tielsch et al., 1995].

#### **Recommendation:**

**The DDG recommends that elderly people with diabetes mellitus should be examined by an ophthalmologist at least once a year and to the same extent as younger patients. Depending upon the examination results and the state of health, the frequency of the examinations can be varied. The examinations should include tests for other frequently occurring eye diseases in elderly people, for example, age-related macular degeneration, glaucoma and cataract and not just diabetic retinopathy. (strength of recommendation B / grade of evidence D)**

#### 9.4 Complications of the Kidney

Twenty-five years after the onset of diabetes, 57 per cent of the persons with type 2 diabetes develop persistent protein-uria [Hasslacher C et al., 1989, level III] (see also the DDG evidence-based diabetes guideline "Diagnosis, Treatment and Follow-up of Diabetic Nephropathy" Hasslacher C et al., 2000).

Before persistent proteinuria is assessed as a complication of diabetes mellitus, other causes should be excluded. Other causes include high blood pressure, cardiac insufficiency, nondiabetic renal diseases and urinary tract infections [Ritz E et al., 1996, level IV]. Proteinuria or albuminuria is not a specific marker for diabetic nephropathy in older people with diabetes mellitus. It could be, among other things, a symptom of generalised vascular damage or renal artery damage, high blood pressure and/or of a treatment with diuretics [Ritz E et al., 1996, level IV]. Intensive glucose control

delays the occurrence and progression of microalbuminuria [UK Prospective Diabetes Study (UKPDS) Group, 1998, level Ib]. Strict blood pressure control reduces the occurrence of albuminuria in younger people with diabetes mellitus [UK Prospective Diabetes Study Group, 1998, level Ib]. This presumably also applies to elderly people with diabetes mellitus.

The benefit of the primary application of AT1 antagonists and ACE inhibitors for the specific treatment of diabetic nephropathy has been demonstrated only in younger people with diabetes mellitus [Heart Outcomes Prevention Evaluation Study Investigators, 2000]; a benefit for older people with diabetes has not been proven.

#### **Recommendation:**

**The benefit of annual testing for albumin excretion in older people with diabetes mellitus has not been verified. Regular examinations for infections of the efferent urinary tract, high blood pressure and clinical signs of cardiac insufficiency (e.g. by determining the hydration status) are of more value to elderly diabetics. Using serum creatinine level as the sole method for evaluating renal function in older people with diabetes mellitus, especially when pharmaceuticals that are eliminated through the kidneys are to be prescribed, is inadequate. Estimating creatinine clearance through the Cockcroft-Gault formula is recommended. (strength of recommendation B / grade of evidence D).**

#### 9.5 Diabetic Foot Syndrome

The most important risk factors for diabetic foot ulcers are sensorimotoric neuropathy, autonomic neuropathy, peripheral arterial vascular disease, decreased joint mobility and increased pressure on the soles of the feet [Plummer S et al., 1996, level III; Young MJ et al., 2001, level IV] (see also the guideline "Diagnosis, Treatment and Follow-up of Diabetic Foot Syndrome" [Morbach S et al., 2004]). A large fraction of elderly diabetics is no longer



able to touch their toes (about 40 per cent) or to inspect the soles of their feet (about 86 per cent) due to age-related restricted movement [Thomson FJ et al., 1992]. One of seven people with diabetes mellitus (average age 64.8 years old) has foot ulcers of which 12.9 per cent are classified as grade 0 and 1.8 per cent in the more advanced grades I and II of the Wagner system [de Sonnaville JJ et al., 1997, level III].

The Association of Statutory Health Insurance Physicians of North Rhine (KV Nordrhein) found that 2 to 3 per cent of the older people with diabetes mellitus had foot ulcerations.

In Germany, diabetes mellitus is the most frequent cause for an amputation in the lower extremities [Bild DE et al., 1989, level IV; Deerochanawong C et al., 1992, level III; Most RS et al., 1983, level III; Siitonen II et al., 1993, level III; Trautner C et al., 1996, level III].

After limb amputations, 50 per cent of the patients die within three years [Palumbo PJ et al., 1985, level IV]. These numbers increase rapidly with advancing age: two years after amputation 50 per cent of the over 70-year olds and one year after amputation over 50 per cent of the 80-year olds have died.

Age-independent studies show that through appropriate multidisciplinary intervention (adapted shoes, foot care, phase-adapted wound treatment, decompression, antibiotic treatment) and educational programmes for employees and patients, the amputation rate can be lowered between 44 and 85 per cent [Assal JP et al., 1985, level IV; Edmonds ME et al., 1986, level III; Larson J et al., 1995, level III].

The goals of the St. Vincent Declaration (Target: 50 per cent reduction in amputations) were not achieved in Germany [Trautner C et al., 2001, level III].

#### **Recommendation:**

**At least every three months, the feet of elderly patients with diabetes mellitus should be examined by a physician. Particular attention should be given to deformities, skin condition, loss of mobility, neuropathy, foot pulse, walking**

**range, infections, ulcerations and appropriately fitting shoes. The patient and family members and, if applicable, the caretaker should be shown how to perform routine foot inspections. It should be checked whether the patient is able to perform adequate foot care independently. (strength of recommendation B / grade of evidence C)**

#### **9.6 Sensorimotoric Polyneuropathy**

Neuropathic symptoms occur in 37 per cent of the older people with diabetes mellitus in comparison with 10 per cent of the nondiabetics (average ages 57.9 and 58.1 years, respectively) [Mayne N, 1965, level III]. The frequency of neuropathic symptoms in type 1 and type 2 diabetics rises with increasing age or length of disease duration: from 5 per cent in the group of the 20 to 29-year olds to 44.2 per cent in the group of the 70 to 79-year olds or 20.8 per cent in people with diabetes for less than five years to 36.8 per cent in those with diabetes for longer than ten years [Cabezas-Cerrato J, 1998; Young MJ et al., 1993, level III] (see also guideline "Diagnosis, Treatment and Follow-up of Sensorimotoric Diabetic Neuropathy" [Haslbeck et al., 2000]).

The following neuropathic symptoms and findings occur in people with diabetes mellitus significantly more often: cold, dry or burning feet, paraesthesia, pain, constipation, numbness, and limited foot and knee reflexes, vibration sensation and proprioception, and impotence in men [Mayne N, 1965, level III].

Peripheral neuropathy is the most important risk factor for non-trauma related amputations [Siitonen OI et al., 1993, level III; Trautner C et al., 1996, level III].

People with diabetes mellitus (average age  $58.1 \pm 17.5$  years) experience pain in the feet (8.1 per cent versus 2.4 per cent) or lower legs (8.8 per cent versus 4.0 per cent) more frequently than the nondiabetic control group (average age  $53.5 \pm 16.2$  years) [Chan AW et al., 1990, level III]. Although the quality of life in diabetics

with painful neuropathy in comparison with diabetics without neuropathy and nondiabetics is significantly lower [Benbow SJ et al., 1998, level III], people with diabetes mellitus and chronic pain are often inadequately treated [Chan AW et al., 1990, level III].

The risk of developing of diabetic neuropathy in older patients can probably not be reduced through intensive blood glucose control [UK Prospective Diabetes Study (UKPDS) Group, 1998, level Ib].

#### **Recommendation:**

**Elderly patients with diabetes mellitus should be tested once a year for diabetic neuropathy. The 10-g monofilament test (Semmes and Weinstein) is the preferred test method. The objective is to determine whether there is symptomatic evidence for neuropathy. If the patients are hindered in their daily life, adequate pain medication must be provided. Appropriate medications include peripherally and centrally acting analgesics and also, if necessary, amitriptyline, carbamazepine and gabapentin. Possible side effects (in particular the danger of falling) and drug interactions as a result of polypharmacy should be considered. (strength of recommendation C / grade of evidence D)**

### 9.7 Cardiac Autonomic Diabetic Neuropathy

Heart rate variability decreases with increasing age. For patients over 70 years old there are no reliable reference ranges for the diagnosis of cardiac autonomic neuropathy [Agelink MW et al., 2001, level III; Mathias CJ, 1999, level IV; Ziegler D et al., 1992, level III].

Gastrointestinal Neuropathy  
Diabetics suffer more often than nondiabetics from diarrhoea or constipation (15.6 per cent), abdominal pain and heartburn (13.5 per cent each), flatulence (12.3 per cent) or loose stools (10.0 per cent) [Bytzer P et al., 2001, level III].

#### **Recommendation:**

**Due to a lack of reference ranges (and possibly also a lower predictive value of the method), a routine examination of elderly diabetics at this time is not advised. (strength of recommendation C / grade of evidence D)**

### 9.8 Gastrointestinal Neuropathy

Forty to seventy-six per cent of the people with diabetes mellitus complain of gastrointestinal problems [Bytzer P et al., 2001, level III; Feldmann M et al., 1983, level III]. These are, however, not always diabetes specific [Enck P et al., 1994, level III; Maleki D et al., 2000, level III]. The quality of life is decreased for diabetics with gastrointestinal symptoms [Talley NJ et al., 2001 level III].

#### **Recommendation:**

**Gastrointestinal symptoms occur frequently in diabetic patients, but are not necessarily specific for diabetes mellitus. For this reason, before diagnosing gastrointestinal neuropathy, other causes for the symptoms must always be excluded. (strength of recommendation C / grade of evidence D)**

## 10 Geriatric Syndromes

### 10.1 Malnutrition

For older nursing home residents, being underweight is a greater problem than being overweight [Rosenthal MJ et al., 1987, level IV].

The nutritional status of older people with diabetes mellitus is worse than that of nondiabetics [Turnbull PJ et al., 2002, level III]. Loss of weight is associated with a higher mortality in elderly diabetics and nondiabetics and is independent of all known covariables [Weddick NM et al., 2002]. In addition to cognitive impairments, limited chewing ability represents an important risk factor for malnutrition and, as a result, also for complications in the treatment of diabetes mellitus in old age. For more than 75 per cent of all persons between the ages of 60 and 90 years,

the teeth of at least one jaw are replaced by a prosthesis, whereby more than 50 per cent of the dental prostheses have considerable functional shortcomings that lead to selective eating habits with unfavourable dietetic consequences.

Hence, there is a significant relationship between the objective nutritional state of older patients and impaired chewing ability, as well as deficiencies in the dental prostheses [Wöstmann B et al., 1999].

#### **Recommendation:**

**The causes for underweight in patients should be clarified and, if possible, corrected (teeth problems, inflammations, inability to go shopping or to cook) and a nutritional plan, if necessary, with the help of a dietician should be prepared. Simple instruments for assessing the causes are available. Limiting the selection of food in elderly and slender diabetics should be avoided. (strength of recommendation C / level of evidence D)**

## 10.2 Status of the Teeth, Chewing Function and Diabetic Periodontitis

In the past, periodontitis in connection with diabetes mellitus has been given little notice neither as a risk factor for diabetes mellitus nor as a predisposition for cardiovascular events [Kohal RJ et al., 2001]. There are indications that diabetes mellitus and periodontal diseases and also stenosing coronary arteriosclerosis, stroke and periodontitis are interlinked [Grossi SG et al., 1994; Joshipura KJ et al., 1996; Loe H, 1993; Oliver RC et al., 1994; Oliver RC et al., 1993; Presson SM et al., 2000].

Various authors describe a close correlation between the severity of diabetogenic nephropathy, retinopathy and even polyneuropathy and the existence of periodontal inflammations [Fowler EB et al., 2001; Karjalainen KM et al., 1994; Martin S et al., 2001; Thorstensson H et al., 1995; Westfeld E et al., 1996]

A reduction of the saliva flow rate (e.g. in poorly stabilised diabetes mellitus) leads to reduced dental prosthesis function [Ghani F et al., 1995; Wöstmann B et al., 1989]

#### **Recommendation:**

**Elderly patients, who are often fitted with dentures that are worn on the oral mucosa, need more frequent dental check-ups, because the coverage of mucous membrane by the dental prosthesis – in particular by manifest diabetes – abets the development of candidiasis. An examination for periodontal diseases should be performed at least once a year.**

### 10.2.1 Enteric and Parenteral Nutrition

The use of conventional nutrition solutions for diabetics in nursing homes is associated with elevated blood glucose levels and increased need for insulin [McMahon MM, 1996].

Adding dietary fibre and exchanging carbohydrates for simple unsaturated fatty acids is associated with lower plasma glucose concentration [Printz H et al., 1997].

An increased proportion of unsaturated fatty acids is correlated to higher HDL, lower triglyceride levels and a lower rate of infections [Craig LD et al., 1998]. Post-operative high blood glucose levels are likewise associated with higher frequencies of infections [Pomposelli JJ et al., 1998]. Low blood glucose levels reduce the morbidity and mortality of diabetics in surgical intensive care units [van den Berghe G et al., 2001]. Blood glucose level fluctuations in diabetics on tube feeding could be due to a gastric emptying disorder [Horowitz M et al., 1996]. Diabetes mellitus is a risk factor for aspiration pneumonia [Terpenning MS et al., 2001].

#### **Recommendation:**

**A feeding tube diet should contain an increased proportion of unsaturated fatty acids and possibly also dietary fibre. There is no evidence for a special benefit from the use of fructose as a substitute for glucose in a feeding tube diet. (strength of recommendation C / grade of evidence D)**

### 10.3 Pressure Ulcers

Decubitus ulcers are a frequent problem in nursing home residents with and without diabetes mellitus (prevalence 8 to 35.7 per cent) [Allman RM et al., 1995, level III; Brandeis GH et al., 1990, level III; Casimiro C et al., 2002, level III; Spector WD et al., 1998, level III].

Diabetes mellitus is an independent risk factor for the development of pressure ulcers in the lower extremities, against which there are contradictory results as to what extent diabetes mellitus is also an independent risk factor for the development of a sacral decubitus ulcer [Allman RM et al., 1995, level III; Berlowitz DR et al., 2001; Brandeis GH et al., 1994, level III; Casimiro C et al., 2002, level III; Maklebust J et al., 1994, level III; Spector WD, 1994, level III; Spector WD et al., 1998, level III; Margolis DJ et al., 2003].

Standardised proven risk factors for pressure ulcers are limited mobility, underweight and faecal incontinence [Brandeis GH et al., 1994, level III; Spector WD et al., 1998, level III].

#### **Recommendation:**

**For diabetics with risk factors for the development of a pressure ulcer, the skin should be regularly inspected and, if necessary, a pressure ulcer prophylaxis or treatment should be initiated. Particular attention should be given to an appropriate food and fluid intake. The use of risk assessment scales for the development of pressure ulcers (e.g. Norton scale, Braden scale) is recommended. (strength of recommendation C / grade of evidence D)**

### 10.4 Mobility and Falls

The majority of all falls in old age have a multifactorial origin [Tinetti ME, 1986]. Many of these factors are associated with diabetes mellitus, such reduced visual acuity, balance disorders, cognitive disorders, depression, overweight, polyneuropathy, polypharmacy etc. It is not clear whether diabetes mellitus is an independent risk

factor for recurring falls [Bueno Cavanillas A et al., 1999; Carpenter CR et al., 2003; Schwartz AV et al., 2002; Wallace C et al., 2002]. Fifty per cent of the elderly people with diabetes mellitus report falls [Conner-Kerr T et al., 2002 level III]. Patients with falls in their previous history usually suffer from limited sensitivity in their lower extremities (100 per cent) and frequently from balance disorders (40 per cent) [Conner-Kerr T et al., 2002 level III; Richardson JK, 2002]. Thirtytwo per cent of the women with diabetes mellitus and fifteen per cent of the men older than 60 years are not able to walk more than 400 meters, climb stairs or do housework [Gregg EW et al., 2000, level III].

There are numerous indications that diabetes mellitus is a risk factor for hip fractures [Forsen L et al., 1999; Ivers RQ et al., 2001; Ottenbacher KJ et al., 2002] and is correlated with a poor perioperative prognosis [Dubey A et al., 2000].

#### **Recommendation:**

**Numerous causes for falls, such as impaired vision, decreased mental capacity, depression, overweight, neuropathy, infections, polyuria / nocturia are associated with diabetes. Therefore, during every examination, the patient should be asked about balance or gait problems and falls within the past six months. Walkers (rollator), hip protectors and also physiotherapy, reviewing medications, or modifications to the living space could be very helpful when there is a tendency to fall and should be considered for patients with serious afferent polyneuropathy, if applicable, also as preventive measures. (strength of recommendation B / grade of evidence D)**

### 10.5 Constipation

Between 10 and 60 per cent of middle-aged diabetics (under 65 years old) have constipation problems [Bytzer P et al., 2001, level III; Enck P et al., 1994, level III; Feldmann M et al., 1983, level III; Maleki D et al., 2000, level III]. The frequency of constipation is age-dependent

for both diabetics and nondiabetics [Enck P et al., 1994, level III] and increases with age. The determination of the colonic transit time with radio-opaque markers can be used as a diagnostic tool. Patients with diabetes mellitus presumably have a slower transit time than those without diabetes [Maleki D et al., 1998, level III; Ron Y et al., 2002, level III].

**Recommendation:**

**Patients with diabetes mellitus should be asked about constipation problems. The following are recommended for therapy: regulation of the bowels, ample intake of liquids (about 1.5 litres per day), exercise (walk for 15 minutes twice daily), lactulose, magnesium sulphate, sodium sulphate, motility and secretion promoting laxatives (bisacodyl, antra-chinone) and macrogol could be prescribed. For pharmacological therapy, macrogol and lactulose seem to have fewer side effects. A therapy with prokinetic drugs (metoclopramide, domperidone) could also be attempted. (strength of recommendation C / grade of evidence D)**

### 10.6 Urinary Incontinence

In women, it is assumed that there is a correlation between diabetes mellitus and urinary incontinence. The latter can occur in combination, concomitantly or independently [Ueda T et al., 2000, level III; Wetle T et al., 1995, level III]. Of the middle-aged people with diabetes mellitus, 53.7 per cent of the women and 10.5 per cent of the men report incontinence [Ueda T et al., 2000, level III].

In elderly people with diabetes mellitus, diabetic cystopathy is associated with a detrusor hyperreflexia or with a decreased or absent contractility of the detrusor in 28 to 55 per cent and in 33 to 43 per cent of the cases, respectively [Kaplan SA et al., 1995, level III; Primus et al., 2002]. Diabetic cystopathy is associated with diabetic neuropathy [Buck AC et al., 1976, level III]. Complete recovery of normal bladder function after diabetic cystopathy is not possible through any of the known meas-

ures. When other urological diseases exist, an autonomic neuropathy with nocturia, dysuria, pollakisuria or incontinence may be present [Ellenberg M, 1980, level III; Kaplan SA et al., 1995, level III; Starer P et al., 1990, level III].

Most persons with incontinence (over 50 per cent) do not seek professional help [Ueda T et al., 2000, level III].

Indwelling urinary catheters are not suitable for the therapy of incontinence due to the frequency of complications. The primary indication for an indwelling urinary catheter is urinary tract dysfunction (more than 50 per cent residual urine based on bladder capacity). An indication for an indwelling urinary catheter for urinary incontinence first exists after the failure, refusal or inapplicability of all other options. The suprapubic catheter drainage should be given priority to male patients in particular

**Recommendation:**

**Elderly people with diabetes mellitus should be asked once annually about the existence of urinary incontinence. An active therapy of incontinence in diabetics is possible. The therapy is functional and should be adapted to the type of incontinence (urge incontinence, stress incontinence, overflow incontinence or reflex incontinence) and based on the recommendations of the International Continence Society (ICS). A therapy based on the exclusive use of absorbent pads should be restricted to immobilised patients. (strength of recommendation C / grade of evidence D)**

### 10.7 Urinary Tract Infections

The prevalence of asymptomatic bacteriuria in women with diabetes mellitus is three times as high as that in nondiabetic women. Many patients with asymptomatic bacteriuria also suffer from urge incontinence.

**Recommendation:**

**There are many different interactions between diabetes mellitus, urinary tract infections and incontinence. (strength of**

**recommendation C / grade of evidence D)****10.8 Faecal Incontinence**

About 22 per cent of elderly diabetics suffer from faecal incontinence [Amaral SS et al., 1997]. Faecal incontinence probably does not generally occur more frequently in diabetics. However, in the Japanese a correlation between diabetes mellitus and faecal incontinence has been demonstrated [Nakanishi N et al., 1997, level III]. The aetiology is usually multifactorial [Sun WM et al., 1996]. Diabetics with faecal incontinence frequently have a pressure reduction (decreased resting tension) of the inner anal sphincter, while the function of the outer is comparable to that in nondiabetics. The dysfunction of the anal sphincter correlates with the duration of the disease [Schiller LR et al., 1982, level III]. An impaired rectal sensitivity could also be a co-trigger for faecal incontinence in diabetics [Aitchison M et al., 1991, level III]. Other pathophysiological factors could include steatorrhoea, diarrhoea, bacteria-caused changes in the intestinal environment, the use of drugs (metformin, acarbose, sorbitol etc) and hyperglycaemia [Verne GN et al., 1998; Füsgen et al., 2003].

**Recommendation:**

**Elderly people with diabetes should be asked about faecal incontinence. The treatment is symptomatic with bulk-forming substances, antidiarrhoeal agents, behavioural training or bio-feedback. A paradoxical diarrhoea caused by faecal impaction or stenosis should be excluded just as malabsorption or endocrine causes. (strength of recommendation C / grade of evidence D)**

**10.9 Impairment of Cognitive Function and Diabetes mellitus**

Various studies have shown that the mental performance, most notably the short-term memory, of older diabetics is impaired

[Perlmutter LC et al., 1984; Reaven GM, et al., 1990; U'Ren RC et al., 1990; Jagusch W et al., 1992; Mooradian AD et al., 1988; Gradmann TJ et al., 1993]. However, other studies did not show a decreased cognitive function in older people with diabetes mellitus [Atiea JA et al., 1995, level III, Mooradian AD et al., 1988, level III, Robertson-Tchabo EA et al., 1986, level III; Rodriguez-Saldana et al., 2002].

Possible risk factors for a reduced cognitive function have been identified as duration of disease, high blood pressure and peripheral neuropathy [Elias PK et al., 1997, level III; Strachan MW et al., 1997, level III]. Diabetes-associated diseases, which could likewise be coupled with a loss of cognitive function, are depression, cerebrovascular diseases, high triglyceride levels and cortical atrophy [Helkala EL et al., 1995, level III; Palumbo PJ et al., 1978, level III; Perlmutter LC et al., 1988, level III; Tun PA et al., 1987, level III]. In particular the combination of stroke and diabetes mellitus shows a high risk for the development of dementia [Haan MN et al., 2003].

Alzheimer's disease is also associated with diabetes mellitus [Leibson CL et al., 1997, level III; Ott A et al., 1999, level III]. Whether intensive diabetic treatment can improve the verbal learning ability in particular is still debated [Areosa SA et al., 2002] and has been shown in only two small studies [Gradman TJ, 1993, level IIa; Meneilly GS et al., 1993, level III]. In a population-based US American study on elderly women with diabetes mellitus, it was shown that the risk for a cognitive decline during antihyperglycaemic therapy with oral antidiabetic agents was renormalized [Logroscino G et al., 2004].

**Recommendation:**

**Elderly people with diabetes should be checked for cognitive impairment once annually. For cognitive dysfunction, causes such as depression, hypothyroidism, vitamin B12 deficiency, hydrocephalus, drug-induced dementia and other forms should be excluded. The possible interactions of depression and**

**dementia especially oblige a diagnosis. Even though it has not been demonstrated without a doubt that a reduction of blood sugar level can prevent dementia, an optimised blood glucose stabilisation is to be strived for to improve cognitive function (in particular the verbal learning ability). (strength of recommendation B / grade of evidence C)**

#### 10.10 Depression and Diabetes mellitus

The prevalence of depression in diabetics is at least three times higher than in the general population [Gavard JA, 1993, level IV]. Also the converse is true: depression is a risk factor for the development of diabetes mellitus [Eaton WW et al., 1996, level III]. Age and chronic diseases result in poorer depression inventory scores [Palinkas LA et al., 1991, level III].

Diabetics with depression have more hospital stays [Rosenthal MJ et al., 1998, level III].

##### **Recommendation:**

**The interaction of diabetes mellitus and depression is well-documented and must also be borne in mind during clinical care. A pharmacotherapy of depression should be considered; the therapeutic effect should be documented. (strength of recommendation C / grade of evidence D)**

#### 10.11 Persistent (Chronic) Pain

Persistent pain (lasting longer than three months) occurs in diabetics significantly more frequently than in nondiabetics (25.2 per cent compared with 15.5 per cent), but is more rarely mentioned. This is particularly true for pain in the lower legs and feet [Chan AW et al., 1990, level III]. Diabetics with pain also have more sleep problems compared with nondiabetics with pain (66 per cent versus 47 per cent) and indicate more extensive limitations in daily activities [Young MJ et al., 1993, level III].

More than 50 per cent of the diabetics over 60 years suffer from peripheral neuropathy. Patients with neuropathy have more

pain and are restricted in terms of their emotional reactions, their energy, their mobility and their sleep. Through this, the quality of life is lower [Benbow SJ et al., 1998, level III]. There are no therapeutic studies for age-specific pain treatment in diabetics. From studies on collectives of younger people with diabetes mellitus and geriatric patients without diabetes mellitus, the following recommendations could be derived.

##### **Recommendation:**

**For persistent pain, a comprehensive assessment of the cause should be made. The treatment of persistent pain in older people with diabetes mellitus is oriented on the same specifications made for middle-aged people without diabetes mellitus and is explained in the guideline "Diagnosis, Treatment and Follow-up of Sensorimotor Diabetic Neuropathy" [Haslbeck M et al., 2000]. Among other things, it should be noted that all non-steroid anti-inflammatory drugs (NSAID), as well as COX-2 inhibitors impair kidney function and, in particular, in combination with ACE inhibitors present a special risk to older diabetics. Due to the increased danger of falling, gabapentin and carbamazepin should be introduced in gradually increasing dosages. (strength of recommendation C / grade of evidence D)**

#### 10.12 Sleep

##### 10.12.1 Hypersomnias

Diabetes and sleep-disordered breathing is found more frequently in overweight patients [Katsumata K et al., 1991]. Diabetics with autonomic neuropathy suffer significantly more often from obstructive sleep-disordered breathing than diabetics without autonomic neuropathy [Ficker JH et al., 1998, level III]. Every fourth diabetic with autonomic neuropathy (26 per cent) has obstructive sleep apnoea.

##### **Recommendation:**

**In especially overweight, older diabetics, arterial hypertension or neuropathy is frequently accompanied by sleep-disordered breathing. The patients should be asked about daytime sleepiness, snoring and nocturnal respiratory arrests (information provided by a third party). For a positive case history, an ambulatory screening test for sleep-disordered breathing (respiratory polygraphy) should be performed. (strength of recommendation B / grade of evidence D)**

## 11 Treatment of Diabetes mellitus in the Elderly

### 11.1 Therapeutic Goals

There are no reviews or randomised studies on the ethical or moral aspects of diabetes treatment of older diabetic people.

In the therapy of older people with diabetes mellitus, numerous factors in the diagnostic and therapeutic considerations must be incorporated. These include, among other things, the quality of life, the life expectancy, the level of education, the socio-economic status, the cognitive and physical abilities, as well as existing and anticipated complications and concomitant disease. Likewise, the individual life perspectives and religious/ethical aspects (the meaning of life) must be included in the decision.

Another important factor is the cooperation of the patient. Regarding compliance, the cognitive, affective and fine motoric disabilities are especially relevant. Side effects from drugs, in particular due to polypharmacy, clearly restrict the spectrum of the pharmacological arsenal. Cost efficiency, the possibilities of patient care and the inclusion of the patient's situation (family members, qualified nursing assistance) all have important roles in a realistic therapeutic plan.

Defined, individual therapeutic goals in place of undifferentiated efforts to reduce only the blood sugar concentration represent a major advance in the care of diabetics and especially of elderly people with

diabetes mellitus. For this reason, precise guidelines for HbA<sub>1c</sub> or blood lipid levels are not very helpful in the therapy. It is the physician's responsibility, while considering the biological age of the patient, the presence of concomitant diseases and symptoms, as well as the social surroundings, to define the individual therapeutic goal and, thus, to determine the individual treatment plan.

Improving and maintaining the quality of life and the general well-being of the patient are the globally and generally accepted therapeutic goals of diabetes treatment. This is achieved, on the one hand, through a strategy that avoids the symptoms of hyperglycaemia and its impact on functional disorders and reduces adverse effects of the therapy, particularly that of drugs, to a minimum and, secondly, through targeted treatment of geriatric syndromes, which are fundamentally responsible for a loss in the quality of life.

Depending upon age, the goals of reducing diabetes-associated complications and concomitant diseases and, if applicable, extending the life expectancy increasingly lose their primary importance.

The extension of the length of life without disability or the "compression of morbidity" in respect to the quality of life also becomes more important with age. This especially applies to geriatric patients with diabetes mellitus.

### 11.2 Non-Pharmacologic Therapy

#### 11.2.1 Exercise

Exercise has a positive effect on the cardiovascular system, on balance and steadiness and on the psychological well-being [Horowitz M et al., 1996; Rosenthal MJ et al., 1987, level IV; van den Berghe G et al., 2001], even though a study showed that regular exercise did not lead to a significant improvement in blood glucose levels in older diabetics [Skarfors ET et al., 1987, level Ib]. Other positive effects such as the reduction of fear, depression and sleeplessness and also improvements in bone



density, osteoarthritis symptoms and mobility were demonstrated.

An intensive exercise programme is not feasible for many older diabetics due to concomitant diseases [Skarfors ET et al., 1987, level Ib]. Concomitant diseases could be a contraindication for increased exercise. Monitoring the metabolic state and exercises adapted to decreased balance and steadiness can help reduce the risks of an exercise programme [Willey KA et al., 2003].

#### **Recommendation:**

**An exercise programme is recommended for older people with diabetes mellitus and should be adapted to the abilities of the patients. Concomitant diseases can present contraindications and should be clarified before if necessary; they should also be born in mind when selecting the exercises. Physical exercise leads primarily to an improvement in the emotional well-being and mobility of elderly people. (strength of recommendation C / grade of evidence D)**

### 11.2.2 Appropriate Nutrition for Diabetics

Fundamentally, there is no difference in the recommended diet for older people with diabetes mellitus and metabolically healthy or younger diabetics. However, glucose tolerance can be significantly improved through weight reduction, even in older overweight patients [Colman E et al., 1995, level III; Reaven GM, 1985, level III].

The benefit of special diabetic food in nursing home residents has not been confirmed. A normal diet in nursing home residents with diabetes mellitus does indeed increase the fasting blood glucose level (0.6 mmol/L over eight weeks) but, in the short term, does not lead to blood glucose imbalance or weight gain [Coulston AM et al., 1990, level Ib].

The intake of fruit, vegetables, fish and vitamin C is associated with low blood glucose levels [Feskens EJ, 1995, level III]. An improvement in the metabolism

can possibly be achieved through the supplementation of zinc, magnesium and vitamin E [Mooradian AD et al., 1987, level IV; Niewoehner CB et al., 1986, level III; Paolisso G et al., 1989, level IIa; Paolisso G et al., 1993, level Ib; Song MK et al., 1998, level IIa; Paolisso G et al., 1994, level Ib].

#### **Recommendation:**

**A balanced, varied diet adapted to the needs of the patient and based on the principles of the German Association of Nutrition (DGE) is recommended. The caloric intake should be adjusted to individual need. Special "diabetes diets" are not recommended. This applies especially to nursing homes. (strength of recommendation B / grade of evidence C)**

### 11.3 Reduction of Blood Glucose Through Pharmacotherapy

#### 11.3.1 Sulfonylureas

Sulfonylureas stimulate insulin release from the pancreatic beta cells through the inhibition of ATP-sensitive potassium channels in the plasma membrane [Scheen AJ, 1997, level IV, Panten et al., 1996]. During short-term use in older diabetics, they reduce the HbA<sub>1c</sub> level by 0.4 to 1.5 per cent and the fasting plasma glucose concentration by 56 mg/dL (3.1 mmol) [Brodows RG, 1992, level Ib, Kyllastinen M et al., 1985, level III; Tessier D et al., 1994, level Ib].

Glibenclamide is the only sulfonylurea available in Germany whose long-term use has been proven to lead to a significant reduction of microvascular complications in middle-aged patients with type 2 diabetes. Sulfonylureas cause weight gain [UK Prospective Diabetes Study (UKPDS) Group, 1998, level Ib].

The most important side effect of sulfonylureas is hypoglycaemia (incidence of severe hypoglycaemia attributable to glibenclamide, 1.4 per cent per year; cumulative incidence of mild hypoglycaemia over six

years, 45 per cent) [UK Prospective Diabetes Study (UKPDS) Group, 1998, level Ib]. Old age is the most important risk factor for severe hypoglycaemia; other risk factors are reduced food intake, restricted renal function, interaction with other drugs (ACE inhibitors, betablocker, coumarin derivatives, sulphonamide), increased physical activity and alcohol consumption [Asplund K et al., 1983, level III; Asplund K et al., 1991, level III; Bachmann et al., 1995, level III; Berger W et al., 1986, level III; Prato, 2003, level III; Rump A et al., 1987, level III; Schen RJ et al., 1976, level III; Sonnenblick M et al., 1986, level III; Stepka M et al., 1993, level III]. Studies that analysed cases of severe hypoglycaemia have found that the use of long-acting sulfonylureas (glibenclamide) bore a substantially higher risk for hypoglycaemia [Holstein, et al., 2001, level III]. For existing renal insufficiency sulfonylureas may not be prescribed with the exception of gliquidone [Pearson JG et al., 1986, level III; Rosenkranz B et al., 1996, level IIB; German Rote Liste, 2002, level IV].

#### **Recommendation:**

**Elderly patients with type 2 diabetes can be treated with a monotherapy of sulfonylureas only if their metabolism cannot be satisfactorily stabilised despite diet modification and exercise therapy and if they are not overweight or, if overweight, they do not tolerate metformin or contraindications for it are present. The risk for hypoglycaemia and patient drug compliance are particularly important criteria for the selection of the medicinal product. The patient and/or the caretaker must be informed about the risk for hypoglycaemia and trained to recognise the symptoms and in the therapeutic possibilities. During the course of the therapy, the occurrence of contraindications, e.g. limited renal function (with the exception of gliquidone) must be monitored. (strength of recommendation A / grade of evidence B)**

### 11.3.2 Glinides

The mode of action of glinides is similar to that of sulfonylureas. The medication is taken with meals. The reduction of HbA<sub>1c</sub> and fasting plasma glucose concentrations lies, independent of age, on the same order of magnitude as for sulfonylureas [Berger S et al., 1998, level III; Chehade J et al., 2001, level IV; Marbury T et al., 1998, level Ib; Moses R et al., 1997, level III; Wolffenbuttel BH et al., 1999, level Ib; Hatorp V et al., 1999, level IIB].

There are no long-term studies on glinides in older people with diabetes mellitus.

Hypoglycaemia is named as the most relevant side effect. In fact, no cases of hypoglycaemia were observed in a small collective [Hatorp V et al., 1999, level IIB]; however, previously published investigations do not allow any conclusion as to how much lower the risk for hypoglycaemia is during longterm treatment with repaglinide or nateglinide compared with sulfonylureas [Landgraf et al., 1998, level Ib; Marbury et al., 1999, level Ib; Hanefeld et al., 2000, level Ib].

#### **Recommendation:**

**Due to the lack of long-term studies in older diabetics, glinides can be only recommended with reservations. When regular food intake cannot be ensured, the use of the short-acting preparations repaglinide and nateglinide (only in combination with metformin) can be considered, in particular for attended patients. The drugs can also be taken immediately after the meal if food intake is uncertain. (strength of recommendation B / grade of evidence D)**

### 11.3.3 Metformin

Metformin decreases hepatic gluconeogenesis and increases glucose absorption in fatty tissues and in the skeletal musculature [Matthaei, 2000, level IV; Scheen AJ, 1997, level IV]. Metformin reduces the HbA<sub>1c</sub> level by 0.6 - 2.0 per cent and the fasting plasma glucose concentration by up

to 19 - 84 mg/dL in a dose-dependent manner [Garber AJ et al., 1997, level Ib].

In the United Kingdom Prospective Diabetes Study (UKPDS), metformin-treated overweight middle-aged patients with diabetes mellitus showed significant reduction in both microvascular and the macrovascular (stroke, coronary events, diabetes-related death) complications [Gadsby R, 1998, level Ib; UK Prospective Diabetes Study (UKPDS) Group, 1998, level Ib].

While using metformin, the weight remains constant; in isolated studies a loss of weight, a significant decline in the VLDL triglyceride levels and a rise in the HDL cholesterol levels were observed [Wu MS et al., 1990, level IIB]. A few smaller studies also demonstrated a positive influence on the glucose metabolism of elderly patients. The most frequent side effects are gastrointestinal complaints (incidence up to 30 per cent); metformin leads to a potentially fatal lactic acidosis in less than 1 in 10,000 patient-years [Josephkutty S et al., 1990, level Ib; Knight PV, 1986, level IV; Sirtori CR et al., 1994, level IV].

Metformin is contraindicated for use in renal impairment (creatinine clearance must be determined), hepatic insufficiency, cardiac insufficiency and all diseases with a risk for elevated lactate levels [Chehade J et al., 2001, level IV; Meneilly GS et al., 1995, level IV].

#### **Recommendation:**

**Metformin is an effective drug for elderly patients with characteristics of metabolic syndrome (abdominal obesity, fasting hyperglycaemia, dyslipidaemia, hypertension). There is no reason for an age-limited use. The use in older people is frequently restricted by the presence of contraindications that can also arise slowly (e.g. cardiac insufficiency) and sporadically (e.g. renal insufficiency due to exsiccosis). For long-term therapy it must be ensured that the patient is regularly checked for new occurrences of contraindications. Metformin should be discontinued before beginning a diet to lose weight (less than 1000 kcal or 4200 kJ/day), before planned operations with**

**general anaesthesia and before radiological examinations with intra-venous contrast medium. (strength of recommendation A / grade of evidence B)**

#### 11.3.4 PPAR- $\gamma$ Ligands (glitazones, thiazolidinediones)

Thiazolidinediones are selective agonists of the PPAR- $\gamma$  receptor and promote insulin sensitivity in fatty tissue, skeletal muscle and liver [Schatz et al., 2000, level IV; Matthaei et al., 2001, level IV; Lebovitz, 2002, level IV].

Pioglitazone and rosiglitazone couple their antihyperglycaemic efficacy with favourable effects on numerous components of the metabolic syndrome that are frequently present even at advanced ages [Ford et al., 2002].

In placebo-controlled studies in middle-aged patients, it was shown that thiazolidinedione lowered the HbA<sub>1c</sub> level by 0.7 to 1.3 per cent and the fasting plasma glucose by 42 to 56 mg/dL. Thus they develop their effect on the HbA<sub>1c</sub> level to same extent as sulfonylureas and metformin and more strongly than alpha-glucosidase inhibitors. There are no long-term studies specifically on the effect of thiazolidinediones in elderly patients with diabetes mellitus [Beebe KL et al., 1999, level III; Charbonnel B et al., 1999, level III; Chehade J et al., 2001, level IV; Grunberger G et al., 1999, level III; Maggs DG et al., 1998, level Ib; Pioglitazone 001 Study Group, 1999, level III; Rubin C et al., 1999, level III].

The clinically most important side effect is fluid retention, which can worsen cardiac insufficiency. Additional side effects are anaemia, headaches, flatulence, weight gain and hepatotoxicity [Kumar S et al., 1998, level Ib]. Contraindications are, thus, hepatic dysfunction, cardiac insufficiency (NYHA I and higher) and insulin therapy [summary of product characteristics Actos®, 2003, level IV].

#### **Recommendation:**

**The frequency of diabetes and metabolic syndrome both clearly increase with ad-**

**vancing age. In this context, PPAR- $\gamma$  ligands are also important in the treatment of older diabetic patients. Due to the lack of long-term studies generally and specifically on older diabetics, these drugs can be only recommended with reservations at this time. Cardiac insufficiency, as one of the common concomitant disease of older diabetics, is an exclusion criterion for this therapy. Patients and/or their caretakers must be informed about the possibility of the development of oedemas and respiratory distress (pulmonary oedema). Strict monitoring is essential. The initial monitoring of liver enzyme levels is mandatory. (strength of recommendation B /grade of evidence D)**

### 11.3.5 Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors reversibly block alpha-glucosidase in the small intestine and thus the hydrolysis of poly-, oligo- and disaccharides [Scheen AJ, 1997, level IV].

Alpha-glucosidase inhibitors lower the HbA<sub>1c</sub> level depending on the starting HbA<sub>1c</sub> level by 0.5 to 0.8 per cent [Reaveb GM, 1985, level III] and the postprandial blood glucose levels by 50 to 60 mg/dl; after weeks, the fasting blood sugar levels are also lowered secondarily by 20 to 40 mg/dl [Chehade J et al., 2001, level IV; Chiasson JL et al., 1994, level Ib; Coniff RF et al., 1995, level Ib; Hoffmann et al., 1994, level Ib; Holman RR et al., 1999, level Ib; Meneilly et al., Diabet Med 2000, level III; Johnston PS et al., 1998, level Ib; Meneilly et al., Diabet Care 2000, level Ib].

In elderly patients with type 2 diabetes, the almost maximal postprandial blood glucose reduction is already achieved with a single dose of 25 mg acarbose [Mooradian AD et al., 2000, level III]. The most frequent side effects (36 per cent) are flatulence, abdominal pain and diarrhoea, which often lead to a discontinuation of the therapy in elderly diabetics [Baron A et al., 1997, level Iib].

### **Recommendation:**

**Acarbose, in combination with a diet or in combination with a diet and other blood sugar lowering therapeutic drugs, is permitted. However, due to a lack of long-term studies on older people with diabetes mellitus, the drug can be recommended only with reservations at this time. When acarbose is to be used, it is very important that the dosage is increased gradually; that is, initially it is to be taken with only one, then later with two and, finally, with three or more meals. Through this, the subjectively very bothersome gastrointestinal side effects can be minimised. (strength of recommendation B / grade of evidence B)**

### 11.3.6 Combination Therapy with Oral Anti-diabetic Agents

Insulin secretion-stimulating oral anti-diabetic agents can be combined with metformin, PPAR- $\gamma$  ligands and alpha-glucosidase inhibitors. Other permitted combination therapies are the combination of metformin with acarbose and metformin with rosiglitazone or pioglitazone. Study results on these types of combination therapies specifically in older people are not available. In middle-aged patients, all combination therapies produce an additional reduction in the HbA<sub>1c</sub> level when compared to a monotherapy. The possibility of an elevated risk for diabetes-related death with the frequently used therapeutic combination of glibenclamide with metformin could not be excluded up until now. More details are published in the DDG evidence-based diabetes guideline "Anti-hyperglycaemic Therapy of Diabetes mellitus Type 2" [Häring HU et al., 2003].

### 11.3.7 Insulin

There are presently only a few studies available on insulin therapy in geriatric patients [Fritsche A et al., 2003]. Ideally an insulin therapy should begin in conjunction with a structured treatment and educational programme including patients of advanced

age [Zeyfang et al., 2001; Braun et al., 2004]. The use of insulin in poorly stabilised diabetics increases the quality of life and therapy satisfaction [Kloos et al., 2003; Braun et al., 2003].

In middle-aged people with diabetes mellitus, a stricter blood glucose control with insulin led to a 25 per cent reduction of microvascular events, but not to a reduction of macrovascular events [UK Prospective Study (UKPDS) Group, 1998, level Ib].

Hypoglycaemia is the most important limiting factor in blood glucose control with insulin; the rate of occurrence of hypoglycaemia when using insulin was 1.8 per cent per year in the UKPDS Study but could be higher in elderly patients [UK Prospective Study (UKPDS) Group, 1998, level Ib].

A direct comparison of a twice daily injection of mixed insulin containing 25 per cent regular insulin to mixed insulin containing 50 per cent regular insulin showed no difference in the achieved postprandial blood sugar values [Brodows et al., 1995].

A randomised crossover study in middle-aged patients showed comparably good metabolic stabilisation and satisfaction with the therapy under both conventional and supplementary insulin therapy [Kloos et al., 2003]. One limitation in the quality of life is related to the number of insulin injections that have to be made each day. The use of insulin in poorly stabilised diabetics does not worsen the quality of life [Rillig et al., 2003].

#### **Recommendation:**

**An insulin therapy is indicated when the individual therapeutic goal cannot be achieved through diet modification and/or oral antidiabetic agents (usually always for an HbA<sub>1c</sub> over 8 per cent) (see National Disease Management Guideline of the German Federal Medical Association). Two injections daily of a premixed insulin are advisable for most older diabetics. An alternative when a more flexible lifestyle is desired is the supplementary insulin therapy (three times daily preprandial insulin application). In individual cases, the**

**more intensive insulin therapy (application of short-acting insulin with meals and a long-acting insulin at night) or the single application of a NPH insulin at night can be considered. (strength of recommendation B / grade of evidence A)**

#### 11.3.8 Insulin Analogues

Studies on the clinical benefit of insulin analogues in the treatment of older people with diabetes mellitus are not yet available.

#### 11.3.9 Insulin Combination Therapies:

Differences in the efficacy and safety of insulin monotherapy and a combination of sulfonylureas and insulin have not been demonstrated in elderly diabetics. One third of the patients, who were stabilised with one insulin injection and oral antidiabetic agents, had to be changed over to two injections for a short time [Wolffenbuttel BH et al., 1996, level IIb].

Conversely, with the combination with a single dose of NPH-insulin at night, middle-aged diabetics in Finland achieved a good, long-term metabolic stabilisation [Yki-Jarvinen et al., 1999].

#### **Recommendation:**

**The combination of insulin and oral antidiabetic agents is also permitted for older diabetics. The advantages of such a regimen in contrast to a twice daily insulin injection have not been demonstrated.**

#### 11.4 Blood Pressure Reduction

Through strict blood pressure reduction to 140/90 mm Hg or lower, the risk for grave diabetes-associated outcomes is decreased (among others, cardiovascular outcomes) even in older diabetics by 32 to 51 per cent [Curb JD et al., 1996, level Ib; UKPDS 38, 1998, level Ib; UKPDS 39, 1998, level Ib]. Data on the reduction in mortality through the reduction of blood pressure in diabetics over 80 years of age are not available.

Per 10 mm Hg blood pressure reduction, the risk for diabetes-associated outcome is decreased on the average of 12 per cent [Sinclair AJ et al., 2000, level IV; UKPDS 39, 1998, level Ib].

The risk reduction through strict blood pressure control for the individual diseases is: cardiac insufficiency 56 per cent, vision deterioration 47 per cent, stroke 44 per cent, microvascular diseases 37 per cent, progression of retinopathy 34 per cent [Sinclair AJ et al., 2000, level IV; UKPDS 39, 1998, level Ib].

From the results of the Hypertension Optimal Treatment Study (HOT), there are indications that the more the blood pressure can be reduced, the lower the cardiovascular risk. The greatest benefit is attained by lowering the blood pressure to below 140/90 mm Hg. A further reduction presumably does not hurt, but does not produce any additional benefit [Hansson L et al., 1998, level Ib]. Which drug is used for the blood pressure reduction appears to be of secondary importance. Diuretics, beta-blockers, long-acting calcium antagonists and ACE inhibitors also provided good results [The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 2002; Curb JD et al., 1996, level Ib; UKPDS 38, 1998, level Ib]

The ALLHAT-Study showed that thiazide diuretics in comparison to calcium antagonists and ACE inhibitors prevented more cardiovascular events. An endorsement of these medicinal products for older diabetics is permissible only under certain conditions [The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 2002].

In older people the occurrence of isolated systolic hypertension is particularly common [Burt et al., 1995, level III; Sagie et al., 1993, level III]. In elderly patients the systolic blood pressure is a better predictor of cardio- and cerebrovascular events, as well as total mortality than the diastolic value. Long-acting calcium antagonists or diuretics are particularly well-suited for

elderly patients with isolated systolic hypertension [Curb JD et al., 1996, level Ib].

#### **Recommendation:**

**The blood pressure should be reduced to below 140/90 mm Hg in diabetics. Frequently a combination therapy is required to achieve this. The selection of the antihypertensives depends on the presence of concomitant diseases. A detailed presentation of the diagnosis and treatment of arterial hypertension is found in the guideline "Management of Hypertension in Patients with Diabetes mellitus" [Standl E et al., 2000]. (strength of recommendation A / grade of evidence A)**

### 11.5 Lowering Lipid Levels

The PROSPER study showed that through the treatment with pravastatin (40 mg/d) over an average period of 3.2 years, the LDL cholesterol and also the primary outcomes could be significantly lowered in older people (70 to 82 years; 2,804 men, 3,000 women) [Shepherd J et al., 2002, level Ib]. Death through CHD, nonfatal myocardial infarction and TIAs were significantly reduced. The incidence of strokes was unchanged.

In the ALLHAT study it was shown in 5,170 persons over 55 years with mild hypertension and hypercholesterolaemia that there was no reduction in the total mortality or cardiovascular mortality through the use of pravastatin over eight years [The Anti hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), 2002, level IIb].

Other studies show that the primary and secondary therapy with lipid-lowering agents reduces the risk for myocardial infarction in diabetics and in elderly people largely independent of the cholesterol level [La Rosa JC et al., 1999, level Ia; MRC/BHF Heart Protection Study, 2002, level Ib; Shepherd J et al., 2002, level Ib].

#### **Recommendation:**

**Elderly diabetics with a cardiovascular risk profile should probably also be**

**treated with lipid-lowering agents. The benefit of regularly monitoring the cholesterol level has not been demonstrated. (strength of recommendation A / grade of evidence A)**

### 11.6 Nicotine Consumption

Although there are no studies that explicitly investigate the influence of giving up smoking on the occurrence of diabetic complications in older diabetic smokers, there is no reason, on the other hand, to forego this measure to reduce cardiovascular risk [Haire-Joshu et al., 1999].

### 11.7 Hypoglycaemia

The risk for serious hypoglycaemia (if applicable, also with fatal consequences) increases exponentially with age. The incidence per 100 person-years is for therapy with sulfonylureas 1.23 and for insulin 2.78 [Shorr RI, 1997, level III]. Other risk factors are: use of more than five drugs, incorrect dosage of medications, recent hospital release, dietary errors, physical effort, alcohol consumption [Shorr RI, 1997, level III]. An additional specific problem is that older diabetics often do not know the symptoms of hypoglycaemia [Thomson FJ et al., 1991, level III].

Moreover, the symptoms of hypoglycaemia are less intensive and less specific in older diabetics than in younger persons. The following symptoms, among others, could appear: sweating, trembling, weakness, confusion, lack of coordination, dizziness, slurred speech, as well as falls [Brierley EJ, 1995, level III; Jaap AJ, 1998, level III].

#### **Recommendation:**

**Diabetics should be educated on the symptoms and the necessary measures for hypoglycaemia. The blood glucose target levels should make hypoglycaemia unlikely; drug interactions should be taken into consideration. (strength of recommendation C / grade of evidence D)**

## 11.8 Types of Hyperglycaemic Comas

### 11.8.1 Diabetic Ketoacidosis (DKA)

Hyperglycaemia with ketoacidosis can lead to diabetic ketoacidosis or diabetic coma [Croxson S, 2001, level IV]. Diabetic ketoacidosis or coma is not an age-specific complication. Twelve to twenty-two per cent of the patients are over 60 years old [Basu A et al., 1993, level III].

The total mortality from DKA clearly increases with age. In the 60 to 69-year olds, it is 8 per cent, in the 70 to 79-year olds, 27 per cent and in the over 80-year olds it is 33 per cent [Basu A et al., 1993, level III; Malone ML, 1992, level III].

Known risk factors for diabetic ketoacidosis or coma are infections, recently diagnosed diabetes and social isolation [Gale EA et al., 1981, level III; Wachtel TJ et al., 1991, level III].

Possible warning symptoms are deterioration of the overall condition, confusion, nausea and vomiting [Alberti KG, 1989, level IV].

#### **Recommendation:**

**In older diabetics with a sudden deterioration of the general condition could be caused by diabetic ketoacidosis. For each protracted incidence of hyperglycaemia, the level of ketones bodies in the urine or bicarbonate (BGA) / plasma acetone should be determined. (strength of recommendation C / grade of evidence D)**

### 11.8.2 Hyperosmolar Hyperglycaemic Nonketotic Coma (HHNC)

Hyperglycaemia with concomitant elevated osmolarity can lead to hyperosmolar hyperglycaemic nonketotic coma [Croxson S, 2001, level IV].

Important risk factors are undiagnosed diabetes mellitus and infections.

The mortality lies between 41 to 47 per cent [Gale EA et al., 1981, level III].

A hyperosmolar hyperglycaemic nonketotic coma can be triggered in older diabetics by their limited feeling of thirst, diffi-

culties in drinking [Alberti KG, 1989, level IV] or by the use of diuretics [Fonseca V et al., 1982, level III].

**Recommendation:**

**For the treatment of comas induced by hyperosmolarity, sufficient rehydration and strict monitoring of the electrolyte and blood glucose levels have priority. Insulin should be used cautiously; blood glucose levels should be lowered gradually. (strength of recommendation C / grade of evidence D)**

## 12 Diabetes and Quality of life

The quality of life in older diabetics is limited [Bourdell-Marchasson I et al., 1997; Paolisso G et al., 1994, level III; Wandell PE et al., 2000, level III]. The HbA<sub>1c</sub> level is not correlated with the quality of life [Pettersson T et al., 1998, level III]. The quality of life is more dependent upon sequelae and geriatric syndromes than the type of therapy [UKPDS 33, 1998, level Ib]. The frequency of insulin injections is linked with the quality of life. Single blood glucose measurements or blood glucose self-monitoring do not lower the quality of life [Gilden et al., 1990; Reza M et al., 1999, level III].

The quality of life is especially tightly coupled with the presence of geriatric syndromes. In particular, limitations in mobility and continence problems occur more often in diabetics [Zeyfang et al., 2002] and lower the quality of life [Gregg et al., 2003].

**Recommendation:**

**A generally applicable recommendation for increasing the quality of life in older diabetics cannot be made because the limitations and needs differ from individual to individual. The presence of pain and geriatric syndromes should be checked through specific questioning and/or assessment because the quality of life is particularly negatively affected by these two factors. Goals adapted to the individual should be defined; the initiation of a needed insulin therapy should not be delayed due to an alleged**

**encroachment on the quality of life. (strength of recommendation C / grade of evidence D)**

## 13 Diabetes in Homes for the Elderly and Nursing Homes

The prevalence of diabetics in homes for the elderly is between 7.2 and 33 per cent [Benbow SJ et al., 1997, level IV; National Center for Health Statistics, 1979, level IV; Sinclair AJ, 1997, level III; Sinclair AJ et al., 2001, level III; Tariot PN et al., 1999, level III].

Morbidity and the use of drugs by diabetics in homes for the elderly is higher than that of nondiabetics [Benbow SJ et al., 1997, level IV; Wolffenbuttel BH et al., 1991, level III]. Diabetics are admitted to hospitals more frequently and are hospitalised for a longer time than nondiabetics [Sinclair AJ et al., 1997, level III]. Both the diabetics and the nursing staff have little knowledge of diabetes mellitus [Sinclair AJ et al., 1997, level III].

**Recommendation:**

**Monitoring of blood glucose level and blood pressure, as well as checking for diabetes specific complications should be performed regularly. (strength of recommendation C / grade of evidence D)**

## 14 Educational Programmes

Older people with diabetes mellitus lack fundamental, diabetes relevant proficiency and knowledge, especially in regards to the symptoms of hypoglycaemia [Thomson FJ et al., 1991, level III; Pegg A et al., 1991, level III; Mutch WJ et al., 1985, level III]. Even geriatric patients can be educated on diabetes [Stelzl et al., 1999]. Nevertheless, half of the geriatric patients with diabetes are overtaxed by particular subjects of the usual educational programmes [Schiel et al., 2000].

Also cognitively impaired patients benefit from especially adapted educational programmes [Braun et al., 2003; Zeyfang et al., 2001], whereas strongly depressive patients benefit little. Through specifically designed geriatric programmes, the self-



management ability of elderly people can be improved [Kronsbein et al., 1988; Wilson W et al., 1987, level III].

This, however, was not confirmed by the field test data of the Association of Statutory Health Insurance Physicians in North Rhine (KV Nordrhein). Nevertheless, the specific group educational courses are just as successful as or more successful than individual consultations in regards to transfer of knowledge and self-management.

The participation in a structured treatment programme is associated with an improvement in the quality of life of elderly patients (age  $68.4 \pm 8.9$  years) with diabetes mellitus type 2; in particular, fears of hypoglycaemia can be reduced [Braun et al., 2003].

#### **Recommendation:**

**Specifically organised group educational courses have been developed for geriatric diabetics to help these people to technically and psychologically deal with the disease with more confidence. Such educational programmes should be also made available to mildly cognitively impaired diabetics. If possible, family members should be included in the educational programme. (strength of recommendation B / grade of evidence C)**

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## 15 Self-Help Groups

Self-help groups and the inclusion of family members increase the long-term success of patient education, even for older people with diabetes mellitus [Gilden JL et al., 1989, level III].

## 16 Final Thoughts and Future Goals

The preparation of the guideline showed that the amount of data available and thus, the basis for the evidence-based judgements for elderly patients with diabetes mellitus is still unsatisfactory. Hence, it is the declared opinion of the panel of experts that, in the future, studies on diabetes mellitus and its treatment should always include an adequate number of older diabetics. For this, the following age groups should be represented in numbers large enough to permit conclusions with sufficient reliability: the "young old" (65 to 75 years), the old (75 to 85 years) and also, if possible, the oldest old (over 85 years).

Furthermore, it is crucial that these types of studies are supplemented with an assessment of the status of the cognitive and affective functions and mobility, which facilitate a description of the

Patient's situation.

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## 18 Notes on Literature Search Strategy

Because at the time of the preparation of this guideline no model guidelines were available, a rough draft was drawn up after an extensive literature search was performed in the databases Medline / Pub Med, Cochrane Library and Embase employing the search list given below. The first draft encompassing approximately 150 pages was drawn up on the basis of the literature search results. This text was condensed into a guideline format. The database literature search was supplemented by searching by hand through the German and English literature. After this, experts from related special areas were contacted to search for missing literature in subject areas such as dementia, incontinence or depression. In particular literature on the complex topic “geriatric functional disorders” was found almost exclusively through hand search.

Afterwards relevant literature was selected by two evaluators on the basis of previously established criteria for detailed content-related and methodological appraisal of the studies. In this connection, it was ascertained that studies in the subject areas diabetology and geriatrics are primarily allocated to evidence classes III or IV.

The evidence-grading system used for evaluation was adapted from existing guidelines of the German Diabetes Association (DDG). Both the grade of evidence and the strength of recommendation are provided.

Three meetings of experts followed, in which representatives named by the scientific associations for diabetes (DDG) and geriatrics (DGG) corrected and revised the existing drafts. The drafts were discussed partly on the basis of the core conclusions of the literature that was read and evaluated; some of the original literature was discussed at the meetings of the experts. Separate chapters were additionally sent to external experts for review. The guideline draft at hand was compared with the currently available guidelines of the DDG.

There are numerous references to the existing guidelines; deviations are identified.

The search terms that formed the basis of the rough draft of the guideline are listed below. The terms “diabetes” and “age” were combined with all other search terms.

### **Diabetes:**

Diabetes mellitus  
Hyperglycemia  
Insulin Resistance  
Insulin-dependent Diabetes mellitus  
Prediabetic State

### **Age:**

Aged  
Aged, 80 and over  
Aging  
Elderly  
Frail Elderly

### **Risk Factors:**

Adipose Tissue/\*metabolism  
Age Factors  
Obesity in Diabetes/physiopathology  
Sex Characteristics  
Sex Factors

### **Diagnosis:**

Blood Glucose analysis  
Blood Pressure  
Body Composition  
Body Mass Index  
Body Weight  
Cholesterol  
Fasting blood  
Glucose Tolerance Test  
Glycosylated Analysis  
Hemoglobin A  
Insulin secretion  
Insulin/diagnostic use  
Ketone Bodies/blood/urine  
Mass Screening  
Triglycerides/blood

### **Therapy:**

Blood Glucose Self-Monitoring/\*standards  
Blood Glucose/drug effects/\*metabolism  
Diabetes Mellitus, Non-Insulin-Dependent/\*drug therapy  
Diabetes Mellitus/\*epidemiology/therapy  
Diabetic Diet  
Diet Therapy  
Drug Therapy  
Exercise Therapy

Hypoglycemic Agents/adverse effects/\*therapeutic use  
 Insulin/\*administration & dosage/adverse effects/therapeutic use  
 Nutrition  
 Patient Compliance  
 Patient Education  
 Patient Participation  
 Patient Satisfaction  
 Self Administration  
 Self Care  
 Self Examination  
 Self Monitoring  
 Treatment Goal  
 Weight Loss  
**Complications/Problems:**  
 Accidental Falls  
 Anxiety  
 Arteriosclerosis/epidemiology/\*prevention & control  
 Automobile Accidents  
 Cardiovascular Diseases/epidemiology/\*prevention & control  
 Cognition Disorders  
 Cognition  
 Complications  
 Coronary Disease/epidemiology/\*prevention & control  
 Delirium  
 Dementia/epidemiology/\*prevention & control  
 Depression/complications/psychology  
 Depression/epidemiology/\*prevention & control  
 Diabetic Angiopathies/epidemiology/\*prevention & control  
 Diabetic Coma/metabolism/mortality  
 Diabetic food/diagnosis/therapy  
 Diabetic Ketoacidosis/metabolism/mortality  
 Diabetic Nephropathies/epidemiology/\*prevention & control  
 Diabetic Neuropathies/epidemiology/\*prevention & control  
 Diabetic Retinopathy/epidemiology/\*prevention & control  
 Disease Progression

Falls  
 Foot Ulcers  
 Foot Amputation  
 Gait  
 Geriatric Assessment  
 Hypoglycemia/chemically induced/\*physiopathology Hypoglycemia/etiology/\*prevention & control  
 Impotence/epidemiology/\*prevention & control  
 Intelligence Tests/\*methods Lipids/blood  
 Lipoproteins, HDL Cholesterol/blood  
 Memory Memory  
 Short-Term Mental Health needs assessment  
 Urinary Disorders  
 Urinary Incontinence  
 Vibration  
 Vision Disorders/prevalence & complications  
 Wounds and Injuries/etiology/\*prevention & control  
**Health System:**  
 Ambulatory Care/economics  
 Attitude to Health  
 Bed Occupancy/statistics & numerical data  
 Best Practice  
 Community Health Services/\*utilization  
 Costs and Cost Analysis  
 Diabetes Mellitus/diagnosis/economics/\*epidemiology  
 Europe/Ethnology  
 German  
 Health Services for the Aged  
 Health Services for the Aged/\*supply & distribution/utilization  
 Health Services/utilization  
 Homes for the Aged  
 Hospitalization  
 Nursing Homes  
 Outpatient Clinics, Hospital  
 Patient Care  
 Primary Health Care/economics  
**Studies:**  
 Cohort Studies  
 Meta-Analysis  
 Quality of Life  
 Randomized Controlled Trial

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