

IQWiG Reports - Commission No. V09-03

**Systematic guideline
search and appraisal, as
well as extraction of new
and relevant
recommendations, for the
DMP “diabetes mellitus
type 1”¹**

Executive Summary

¹ Translation of the executive summary of the final report “Systematische Leitlinienrecherche und -bewertung sowie Extraktion neuer und relevanter Empfehlungen für das DMP Diabetes mellitus Typ 1” (Version 1.0; Status: 24.06.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Background

The Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a literature search for clinical practice guidelines on diabetes mellitus type 1 (resolution of 17.12.2009). The recommendations extracted from evidence-based guidelines were consequently to serve the legally specified regular update of the disease management programme (DMP).

Research questions

The aim of this study was to specify a potential need for updating and supplementation of the existing DMP “diabetes mellitus type 1” by systematically searching for new, topic-relevant, evidence-based guidelines and by synthesizing the guideline recommendations.

The study was organized according to the following working steps:

- Literature search for and selection of current guidelines on diabetes mellitus type 1
- Appraisal of the methodological quality of selected guidelines
- Extraction and synthesis of guideline recommendations relevant to the existing DMP “diabetes mellitus type 1”²
- Labelling of recommendations justifying a potential need for revision of the DMP

Methods

An Internet search for topic-specific guidelines was conducted via the guideline databases of the German Association of the Scientific Medical Societies,³ the Guidelines International Network (G-I-N), and the National Guideline Clearinghouse (NGC), as well as by searching the websites of multidisciplinary and specialist guideline providers. In addition, a search was conducted in the bibliographic databases MEDLINE and EMBASE. The publication period started in 2005. Besides the languages German, English and French, a further inclusion criterion was the country in which the guidelines had been developed. According to the commission, only guidelines transferable to the German health care system were to be searched for and selected. The classification of nations from the World Health Report 2003, published by the World Health Organization (WHO), was used to operationalize the transferability of guidelines to the German health care system. The documentation of the evidence base of a guideline was a further important inclusion criterion. In the following report, “evidence-based” guidelines are understood to be guidelines whose recommendations are a) based on a systematic literature search, b) allocated as a matter of principle to a level of

² The recommendations extracted from the guidelines are to be understood as citations whose underlying evidence was not as such reassessed.

³ Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF

evidence (LoE) and/or grade of recommendation (GoR), and c) linked to citations of the underlying primary and secondary literature.

The guidelines included were appraised methodologically by 2 reviewers by means of the Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument.

The recommendations relevant to the research questions were extracted and allocated to the health care aspects noted in Appendix 7 of the 20th Risk Adjustment Scheme Amendment Act⁴ (RAS-AA) of 23.06.2009. Finally the extracted recommendations were synthesized according to the items of Appendix 7 of the RAS-AA and compared with the requirements of the DMP “diabetes mellitus type 1”.

A potential need for updating and supplementation was determined for recommendations that were consistent in content and largely showed a high grade of recommendation (GoR) or level of evidence (LoE). A potential need for updating and supplementation was to be discussed for recommendations that were consistent in content in various guidelines and showed, at least in part, a high grade of recommendation or level of evidence. A potential need for updating and supplementation was also to be discussed in the event that new aspects for the DMP were presented in only one single guideline but were labelled with a high grade of recommendation or level of evidence. In this context, the two highest grades of recommendation were considered for all guidelines with their different grading systems.

In the event of a potential need for updating and supplementation with regard to an item of Appendix 7 of the RAS-AA, it was assessed whether further IQWiG reports on this topic were available. When a potential need for updating and supplementation was determined, the corresponding IQWiG reports were taken into account.

In the assessment of a potential need for updating and supplementation of Appendix 7 of the RAS-AA, for the drugs mentioned in the guidelines, the indication-specific reimbursability in Germany was additionally drawn upon as a further criterion.

Results

After exclusion of 47 duplicates, a total of 609 potentially relevant full-text guidelines were screened. After examination of the inclusion criteria, 23 guidelines were included in the report.

⁴ Risikostrukturausgleichs-Änderungsverordnung, RSA-ÄndV

Methodological appraisal of the included guidelines following AGREE

The highest standardized domain score of 0.92 was achieved by one guideline in domain 6 (editorial independence). Other guidelines were awarded the lowest standardized domain score, i.e. the minimum score possible, in the domains 1 (scope and purpose), 2 (stakeholder involvement), 4 (clarity and presentation), 5 (applicability), and 6 (editorial independence).

If one compares the guidelines with regard to the achieved standardized domain scores, it is notable that the guidelines “DDG 2011” and “NVL 2010” achieved the highest standardized domain score in 3 and 2 of the total of 6 domains respectively. The guideline “DDG 2006”, which achieved the minimum possible score of 0.00 in 4 of 6 domains, is also notable. Regarding the European guidelines, the guideline “SIGN 2010” is also notable. It did not achieve the highest standardized domain score in any domain, but achieved either the second or third highest standardized domain score in 4 of 6 domains.

Handling of unpublished data by authors of guidelines

Out of 23 guidelines included in the analysis, 5 provided information on the handling of unpublished data by authors of guidelines. Few indications were found in the guidelines regarding the utilization of unpublished data in the formulation of recommendations.

Need for updating and supplementation of the DMP “diabetes mellitus type 1”

The recommendations of the guidelines included in the present report are by and large consistent with the requirements of Appendix 7 of the 20th RAS-AA of 23.06.2009, but are largely more detailed. The guidelines do not address all relevant aspects of health care for diabetes mellitus type 1.

For some areas of Appendix 7, deviations from the guideline recommendations can be found. Items or sub-items for which a potential need for updating or supplementation was identified are described first. Then items or sub-items are reported for which a potential need for updating or supplementation can be discussed. Areas for which no deviations between Appendix 7 and guidelines were found are subsequently presented. Items for which no guideline recommendations could be identified are named last.

A potential need for updating and supplementation was identified for the following items or sub-items:

Items 1.3.3: Structured training and treatment programmes and 4.2: Training programmes for insured members

Several guidelines provide recommendations (largely with a high GoR or LoE) on training programmes concerning dietary advice / medical nutritional therapy. Compared to the RAS-AA, the guidelines include additional recommendations. The item “Structured training and treatment programmes” of Appendix 7 does not contain the sub-item “Dietary advice /

medical nutritional therapy”. A potential need for updating and supplementation arises regarding “Dietary advice / medical nutritional therapy”.

Item 1.4: Hypoglycaemic and ketoacidotic metabolic imbalances

Several guidelines provide recommendations (with inconsistent GoR or LoE) regarding hypoglycaemic metabolic imbalances. Compared to Appendix 7 of the RAS-AA, the guidelines include additional recommendations. After several hypoglycaemic episodes, 3 guidelines recommend (largely with a high GoR) increasing the HbA1c level. A potential need for updating and supplementation arises regarding the increase in the HbA1c level after several hypoglycaemic episodes.

Item 1.5: Accompanying diseases and late complications of diabetes mellitus type 1

Item 1.5.1: Late microvascular complications

Item 1.5.1.1: General measures

Several guidelines provide recommendations (with an inconsistent GoR or LoE) regarding the item “General measures” in patients with late microvascular complications. Compared to the RAS-AA, the guidelines include additional recommendations. Two guidelines recommend (with a high GoR) evaluation of the option of a kidney/pancreas transplant in patients with diabetes type 1 and advanced kidney failure, as well as in patients with potentially reversible diabetes-related complications. There is a potential need for updating and supplementation regarding the evaluation of a combined transplantation in specific patients.

Item 1.5.1.3: Diabetic retinopathy

Several guidelines provide recommendations (largely with a high GoR or LoE) with regard to diabetic retinopathy. Compared to the RAS-AA, the guidelines include additional recommendations. Several guidelines provide recommendations (with a high GoR) on the treatment of clinically relevant macula oedema. A potential need for updating and supplementation arises regarding the treatment of clinically relevant macula oedema.

Item 1.5.2: Diabetic neuropathy

Several guidelines provide recommendations (largely with a high GoR or LoE) on the examination of diabetic neuropathy. Compared to the RAS-AA, the guidelines include additional recommendations. Three guidelines provide different recommendations (largely with a high GoR) regarding the approach to testing for neuropathy in patients with diabetes. A potential need for updating and supplementation arises with regard to testing for neuropathy.

Several guidelines provide recommendations (with an inconsistent GoR or LoE) regarding neuropathic pain. Compared to the RAS-AA, the guidelines contain additional

recommendations: 3 guidelines provide recommendations (largely with a high GoR) on treatment with opioid analgesics. A potential need for updating and supplementation arises regarding the use of opioid analgesics for treatment of neuropathic pain.

Item 1.5.4: Macroangiopathic diseases

Item 1.5.4.1: Arterial hypertension in diabetes mellitus type 1

Item 1.5.4.1.2: Therapeutic measures for hypertension

Two guidelines provide recommendations (with a largely high GoR) on the use of calcium channel blockers, which are not mentioned by the RAS-AA. Consequently, a potential need for updating and supplementation arises regarding the use of calcium channel blockers.

Item 1.5.4.2: Statin therapy

Several guidelines provide recommendations (largely with a high GoR or LoE) regarding statin therapy. Compared to the RAS-AA, the guidelines contain additional recommendations.

Two guidelines recommend (with a high GoR or LoE) statin therapy also in primary prevention for patients with diabetes type 1 aged 40 years and older. Consequently, a potential need for updating and supplementation arises regarding primary prevention with statins in certain patients.

Several guidelines recommend (largely with a high GoR or LoE) statin therapy for patients with a moderate risk of late complications. Consequently, a potential need for updating and supplementation arises regarding statin therapy in patients with such a moderate risk.

Several guidelines provide recommendations (largely with a high GoR or LoE) on alternative medication in the event of statin intolerance. Consequently, a potential need for updating and supplementation arises regarding statin therapy.

Item 1.6: Pregnancy in diabetes mellitus type 1

Several guidelines provide recommendations (with an inconsistent GoR or LoE) on the prevention of late complications of diabetes. In contrast to the RAS-AA, the guidelines contain additional recommendations. Four guidelines recommend (largely with a high GoR) substitution of folic acid before and during pregnancy. Consequently, a potential need for updating and supplementation arises. Several guidelines provide recommendations (largely with an inconsistent GoR) on foetal examinations. Compared to the RAS-AA, the guidelines contain additional recommendations. Two guidelines recommend (with a high GoR) offering sonography of the foetal heart to pregnant women. Consequently, a potential need for updating and supplementation arises regarding sonography of the foetal heart.

A potential need for updating and supplementation can be discussed for the following items:

Item 1.4: Hypoglycaemic and ketoacidotic metabolic imbalances

Several guidelines provide recommendations (with an inconsistent GoR or LoE) on ketoacidotic metabolic imbalances. One guideline recommends (with a high GoR) inpatient treatment for non-minor ketoacidosis. Regarding treatment of ketoacidosis, a need for updating and supplementation can be discussed.

Item 1.5: Accompanying diseases and late complications of diabetes mellitus type 1

Item 1.5.1: Microvascular late complications

Item 1.5.1.2: Diabetic nephropathy

Several guidelines provide recommendations (largely with a high GoR or LoE) regarding diabetic nephropathy. Compared to RAS-AA, the guidelines contain additional recommendations. One guideline provides several recommendations (largely with a high GoR) regarding renal replacement therapy; however, Appendix 7 only includes requirements regarding prevention of the progression of nephropathy and renal replacement therapy. A potential need for updating and supplementation can be discussed for renal replacement therapy.

Item 1.5.2: Diabetic neuropathy

One guideline recommends (with a high GoR) the use of dopamine or dopamine agonists in patients with restless leg syndrome. A potential need for updating and supplementation can be discussed in this regard.

Item 1.5.4: Macroangiopathic diseases

Item 1.5.4.1: Arterial hypertension in diabetes mellitus type 1

Item 1.5.4.1.2: Therapeutic measures for hypertension

Several guidelines provide recommendations (with an inconsistent GoR or LoE) regarding general measures for therapy of arterial hypertension. Compared to the RAS-AA, the guidelines contain additional recommendations. Appendix 7 of the RSA-AA does not contain this sub-item.

Several guidelines provide recommendations (with an inconsistent GoR or LoE) on blood pressure target values (130/80 mmHg) under treatment, whereas Appendix 7 of the RAS-AA calls for a blood pressure target value of < 140/90 mmHg. A potential need for updating and supplementation regarding potential blood pressure target values can be discussed.

Only one guideline provides a recommendation (with a high GoR) regarding antihypertensive treatment with alpha-receptor blockers, stating that they should not be used as first-line medication in patients with diabetes. Compared to the RAS-AA, the guideline contains an additional recommendation. Alpha-receptor blockers are not mentioned in Appendix 7 of the RAS-AA. A potential need for updating and supplementation can be discussed regarding the negative recommendation on alpha-receptor blockers.

Item 1.7: Treatment of children and adolescents

Item 1.7.3: Training programmes

One guideline provides several recommendations (largely with a high GoR) on the handling of needles and syringes, as well as on injection techniques. In contrast to the RAS-AA, the guidelines contain additional recommendations. Appendix 7 of the RAS-AA does not mention the handling of this assistive equipment. A potential need for updating and supplementation regarding training in the handling of assistive equipment can be discussed.

Item 1.7.5: Prevention of late complications and associated diseases

Three guidelines provide recommendations (largely with a low GoR) on general measures concerning the prevention of late complications and associated diseases. Compared to the RAS-AA, the guidelines contain additional recommendations.

Only one guideline provides recommendations (with a high GoR) regarding monitoring of the HbA1c level every 3 months in order to reduce late complications. A need for updating and supplementation can be discussed in this regard.

One guideline recommends (with a high GoR) screening for neuropathy in poorly controlled diabetes or after a disease duration of more than 5 years. A potential need for updating and supplementation can be discussed regarding testing for neuropathy in children with poorly controlled diabetes or with longer disease duration.

One guideline recommends (with a high GoR) testing for dyslipidaemia in children and, if appropriate, offering dietary advice. A potential need for updating and supplementation can be discussed with regard to testing for dyslipidaemia and provision of corresponding dietary advice.

One guideline recommends (with a high GoR) regular screening for thyroid disease. A potential need for updating and supplementation can be discussed with regard to testing for thyroid disease in children.

Six guidelines contain consistent information on coeliac disease. Of these, one guideline provides recommendations (with a high GoR) regarding testing for coeliac disease in symptomatic children and treatment in the event of a pathological test result. A potential need

for updating and supplementation can be discussed regarding testing for coeliac disease in symptomatic children and, if appropriate, subsequent treatment.

No need for updating and supplementation was identified for the following items:

Item 1.2: Diagnosis (initial diagnosis)

Item 1.3.1: Therapy goals

Item 1.3.2: Differentiated therapy planning

Item 1.3.3: Structured training and treatment programmes and 4.2 Training of insured members, regarding

- general training measures
- training on self-management
- training on metabolic imbalances, late complications and accompanying diseases
- training on adaptation of lifestyle
- training on protein restriction in patients with nephropathy (stages 1-3)

Item 1.3.4: Insulin substitution, regarding

- the use of human insulin
- the use of insulin analogues (see also IQWiG reports A05-01, A05-02 and A08-01)

Item 1.5.2: Diabetic neuropathy, regarding

- autonomic neuropathy
- phosphodiesterase-5-inhibitors for erectile dysfunction
- herbal remedies, dietary supplements, and surgery to relieve symptoms

Item 1.5.3: Diabetic foot syndrome

Item 1.5.4: Macroangiopathic diseases

Item 1.5.4.1: Arterial hypertension in diabetes mellitus type 1

Item 1.5.4.1.1: Definition and diagnosis of hypertension

Item 1.5.4.1.2: Therapeutic measures for hypertension, regarding antihypertensive therapy

- with diuretics
- with beta blockers
- with angiotensin-converting enzyme (ACE) inhibitors / angiotensin (AT)-1-receptor antagonists

Item 1.5.4.2: Statin therapy, regarding

- combination therapy of statins and further lipid-lowering drugs (statin plus ezetimibe, statin plus a fibrate, or statin plus niacin) in the event of unsuccessful monotherapy with statins
- treatment of lipometabolic disorders beyond the use of statin therapy (see also IQWiG report A10-02)
- information on blood lipid target values

Item 1.5.4.3: Thrombocyte aggregation inhibitors (see also IQWiG reports A04-01A, A04-01B, A09-01)

Item 1.5.4: Macroangiopathic diseases – further medications

Item 1.5.5: Provision of psychological, psychosomatic and psychosocial care

Item 1.6: Pregnancy in women with diabetes mellitus type 1, regarding

- provision of advice and care for pregnant women
- glycaemic control in pregnant women
- insulin substitution during pregnancy
- medical monitoring and blood-glucose monitoring during birth
- contra-indications for various medications and warning about ketoacidotic metabolic crises during pregnancy

Item 1.7: Treatment of children and adolescents

Item 1.7.1: Therapy goals (for children and adolescents)

Item 1.7.2: Therapy, regarding

- general measures
- target values for blood glucose and HbA1c
- glycaemic control
- use of insulin analogues

- hypoglycaemic metabolic imbalances
- hyperglycaemic metabolic imbalances or ketoacidosis
- vaccinations against influenza and streptococcus pneumoniae
- measures against smoking

Item 1.7.3: Training, regarding

- dietary advice and medical nutritional therapy
- hypoglycaemic metabolic imbalances
- ketoacidotic metabolic imbalances
- physical exercise for children and adolescents
- further preventive measures
- course of the disease and continuous care
- self-help groups and social benefits
- procedures of alternative medicine

Item 1.7.4: Psychosocial care, regarding

- the psychological care of children and adolescents, as well as their families in general
- the non-compliant behaviour of adolescents
- eating disorders
- the care of children and adolescents in facilities
- cognitive functional impairment in children and adolescents
- the change from paediatric to adult care

Item 1.7.5: Prevention of late complication and associated diseases, regarding

- diabetic retinopathy
- diabetic nephropathy
- diabetic foot syndrome
- hypertension
- regular monitoring of dental health

Item 1.8: Cooperation of healthcare sectors

Item 1.8.1: Coordinating physician

Item 1.8.2: Referral by the coordinating physician or the coordinating facility to the qualified specialist or qualified facility

Item 1.8.3: Referral to a hospital for inpatient treatment

Item 1.8.4: Inducement of a rehabilitation service

No recommendations in the guidelines could be identified for the following items:

Item 1.1: Definition of diabetes mellitus type 1

Conclusions

By comparing recommendations extracted from current evidence-based guidelines with the requirements of Appendix 7 of the RAS-AA, which forms the basis of the DMP diabetes mellitus type 1, health care aspects could be identified for which a potential need for updating and supplementation exists or can be discussed.

A potential need for updating and supplementation exists for the following items of Appendix 7 of the RAS-AA:

Items 1.3.3: Structured training and treatment programmes and 4.2: Training programmes for insured members

- regarding dietary advice / medical nutritional therapy

Item 1.4: Hypoglycaemic and ketoacidotic metabolic imbalances

- regarding the increase in the HbA1c level after several hypoglycaemic episodes

Item 1.5: Accompanying diseases and late complications of diabetes mellitus type 1

Item 1.5.1.: Late microvascular complications

Item 1.5.1.1: General measures

- regarding the evaluation of the option of a combined kidney/pancreas transplantation in specific patients

Item 1.5.1.3: Diabetic retinopathy

- regarding the treatment of clinically relevant macula oedema

Item 1.5.2: Diabetic neuropathy, regarding

- testing for neuropathy
- the use of opioid analgesics for treatment of neuropathic pain

Item 1.5.4: Macroangiopathic diseases

Item 1.5.4.1: Arterial hypertension in diabetes mellitus type 1

Item 1.5.4.1.2: Therapeutic measures for hypertension

- regarding the use of calcium channel blockers

Item 1.5.4.2: Statin therapy, regarding

- primary prevention with statins in certain patients
- statin therapy in patients with a moderate risk of late complications
- alternative therapy to statins

Item 1.6: Pregnancy in diabetes mellitus type 1, regarding

- substitution of folic acid before and during pregnancy
- sonography of the foetal heart

A potential need for updating and supplementation can be discussed for the following items of Appendix 7 of the RSA-AA:

Item 1.4: Hypoglycaemic and ketoacidotic metabolic imbalances

- regarding inpatient treatment of non-minor ketoacidosis

Item 1.5.1.2: Diabetic nephropathy

- regarding renal replacement therapy

Item 1.5.2: Diabetic neuropathy

- regarding the use of dopamine or dopamine agonists in patients with restless leg syndrome

Item 1.5.4: Macroangiopathic diseases

Item 1.5.4.1: Arterial hypertension in diabetes mellitus type 1

Item 1.5.4.1.2: Therapeutic measures for hypertension, regarding

- blood pressure target values
- the negative recommendation on alpha-receptor blockers

Item 1.7: Treatment of children and adolescents

Item 1.7.3: Training programmes

- regarding training in the handling of assistive equipment

Item 1.7.5: Prevention of late complications and associated diseases, regarding

- monitoring of the HbA1c level every 3 months in order to reduce late complications
- testing for neuropathy in children with poorly controlled diabetes or those with a disease duration of more than 5 years
- testing for dyslipidaemia and provision of dietary advice
- testing for thyroid disease
- testing for coeliac disease in symptomatic children and treatment in the event of a pathological test result

It is unclear whether the lack of consideration of unpublished data in the included guidelines leads to bias in the external evidence underlying the recommendations. If this does result in bias, the direction and extent of bias cannot be judged on the basis of the information available.

Keywords: disease management programme (DMP), diabetes mellitus type 1, methodological guideline appraisal, evidence-based guideline

The full report (German version) is published under www.iqwig.de