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INTRODUCTION

1.1. Problem description and substantiation of the guidelines

Diabetes is a significant health problem of increasing incidence. Diabetes leads to significant complications: acute complications like hypoglycaemia, hyperglycaemia and ketoacidosis, but also chronic complications such as eye problems, nephropathy, neuropathy and foot problems. Type 2 diabetes patients are also at increased risk of cardiovascular disease. The above is accompanied by significant mortality and physical and psychosocial morbidity.

Prevention and treatment of diabetes complications involve extremely high direct and indirect costs both for the patients and for society at large¹. Large scale research² and trials in specific target groups³ provide incontrovertible evidence that strict monitoring and treatment of Type 2 diabetes can significantly reduce the scope and impact of complications.

Providing care to diabetes patients is a highly complex matter:

- Diabetes care is a multifaceted issue, involving education and advice on diet and exercise, development of therapeutic objectives, treatment of hyperglycaemia, monitoring cardiovascular risk factors, detection and treatment of chronic complications.
- A number of multidisciplinary care providers, each making specific contributions, are involved. In the monitoring and treatment of Type 2 diabetes, first-line care plays an important role⁴. This multidisciplinary approach requires a clear definition of responsibilities and good cooperation between providers ("shared care").
- Diabetes patient care requires a sustained effort. Once the diagnosis has been made, the patient must first and foremost make changes in his or her lifestyle. If applicable, the primary recommendations include smoking cessation, weight reduction, appropriate diet and more exercise. Complex treatment with various hypoglycaemics or insulin in combination with a number of other medications is often unavoidable. In addition, patients also often find it difficult closely to follow the proposed therapy⁵.

Hereditary predisposition is important in this condition, but lifestyle also plays a crucial role. In particular abdominal obesity and lack of physical exercise are triggering factors. The risk of developing the disease

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- ¹ In Europe, treatment costs of diabetes and its complications are estimated at around 5.8% of the total health care budget. This includes only specific treatments. These figures therefore most likely underestimate the real costs. In addition, intensive treatments for the prevention of complications result in a further increase in drug, medical and paramedical expenses.
- Williams R, Van Gaal L, Lucioni C. Assessing the impact of complications on the costs of Type II diabetes. *Diabetologia* 2002;45:13-7.
 - Massi-Benedetti M. CODE-2 Advisory Board. The cost of diabetes Type II in Europe: the CODE-2 Study. *Diabetologia* 2002;45:1-4.
 - Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. *Health economics* 2004;13.
 - Early view on line: <http://www3.interscience.wiley.com/cgi-bin/abstract/109608185/ABSTRACT>.
- ² By means of a ten-year follow-up study of diabetes patients, the "United Kingdom Prospective Diabetes Study" (UKPDS) demonstrated the benefits of good management.
- Wens J. Intensieve behandeling van diabetes type 2. *Huisarts Nu (Minerva)* 1999;28:125-6. Interpretation of: UKPDS Group. Turner RC, Stratton IM, Matthews DR, et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998; 352: 837-53.
- ³ Sunaert P, Feyen L. Steno-2 studie; Multifactoriële aanpak bij diabetes type 2. *Minerva* 2004;3:11-4. Interpretation of: Gaede P, Vedel P, Larsen N, et al. Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. *N Engl J Med* 2003;348:383-93.
- ⁴ The primary care physician is the best choice for follow-up of Type 2 diabetes patients, in collaboration with a multidisciplinary team that can consist of a diabetes educator, nurse, dietician, podiatrist, pharmacist etc.
- Griffin S. Diabetes care in general practice – meta-analysis of randomised controlled trials *BMJ* 1998; 317: 390-5.
- ⁵ Nagasawa N, Smith MC, Barnes JH, et al. Meta-analysis of correlates of diabetes patients' compliance with prescribed medications. *Diabetes educator* 1990;16:192-200.

increases with age. The condition generally manifests itself in middle age or older (whence the name formerly used to describe the disease, "old age diabetes"). Sometimes the disease is diagnosed following the appearance of symptoms of hyperglycaemia, but such symptoms only appear in acute cases. Mostly, this type of diabetes is discovered as a result of preventive examinations in at-risk patients, or following complaints as a result of developing micro or macrovascular complications.

In the years following diagnosis of Type 2 diabetes, there is a progressive decline in the number of β -cells while insulin resistance continues to rise slightly. This gradual decline means that, over time, more and more medication is required for glycaemic control. In addition, over the long term most Type 2 diabetes patients need to be started on insulin.

The insulin resistance of Type 2 diabetes has many consequences that go far beyond the metabolism of carbohydrates. It is associated with abdominal obesity, hypertension, dyslipidaemia, hyperuricaemia and hypercoagulability. A number of epidemiological studies have shown that this "*insulin resistance syndrome*" or "*metabolic syndrome*" goes hand in hand with strongly increased cardiovascular morbidity and mortality⁶. The treatment of Type 2 diabetes therefore involves more than mere control of blood glucose values. A broad cardiovascular approach becomes essential with diabetes patients.

For all the above reasons it makes sense to issue guidelines on diabetes mellitus, and more particularly on early detection, diagnosis, treatment and management. Since the first interdisciplinary consensus on the management of "non-insulin dependent diabetes mellitus" in Flanders⁷, new scientific evidence has become available on the prevention, diagnosis and treatment of diabetes. This brings about the need for a review that will take into account these new scientific research results.

Since at this time there is a structural lack of quality indicator data as concerns diabetes care in Belgium, it is not possible to stipulate clear objectives in the field of processes and outcomes in diabetes care among other areas. However, this set of good practice guidelines is a useful point of reference and departure for the improvement of the quality of care of people with diabetes.

1.2. Definitions

Diabetes mellitus is a metabolic disease characterised by an increased blood sugar level (hyperglycaemia), resulting in disorders of the carbohydrate, fat and protein metabolic functions. The condition is due to a defect in the secretion of insulin, the effect of the insulin, or both.

*Type 1 diabetes*⁸ is an autoimmune disease characterised by the destruction of pancreatic β -cells. Through the resulting lack of insulin, administration of this hormone becomes essential. This form of the disease usually manifests at a younger age. It is usually diagnosed upon onset of acute symptoms.

Type 2 diabetes is usually the result of a dual problem: on the one hand there is resistance of the peripheral tissues against insulin (insulin resistance), and on the other hand the cells can still produce insulin, but are unable to compensate for the insulin resistance.

Pregnancy, or gestational, diabetes is diabetes that develops during pregnancy. In many cases, this type of diabetes disappears after the end of the pregnancy. This type of diabetes not only has adverse effects on the foetus, but is also a precursor of Type 2 diabetes in the mother.

Impaired glucose tolerance (IGT) and *impaired fasting glucose (IFG)*⁹ are elevated blood glucose conditions that do not yet correspond to the diagnostic criteria for diabetes. They increase cardiovascular risk and the risk of developing diabetes (cf. also 3.1).

⁶ Ford ES. The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. *Atherosclerosis*. 2004;173:309-14.

⁷ Published under the title: "Interdisciplinaire consensus over het beleid van niet-insuline-dependente diabetes mellitus". WVVH / VDV, 1997.

⁸ Type 1 diabetes was formerly also called "insulin dependent diabetes mellitus", acronym IDDM, and Type 2 was called "non-insulin dependent diabetes mellitus", with the acronym NIDDM. International guidelines recommend that diabetes be no longer classified by type of pharmacotherapy, but rather on the basis of the corresponding aetiology.

- American Diabetes Association (ADA): Clinical Practice Recommendations 2005. *Diabetes Care* 2005;28:S4.

⁹ The terms used internationally are Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG).

Metabolic syndrome (or insulin resistance syndrome) is a metabolic disorder consisting of a combination of abnormal blood glucose levels, high blood pressure, obesity, and atherogenesis and dyslipidaemia (low HDL cholesterol and high triglyceride levels). Currently, metabolic syndrome is diagnosed according to International Diabetes Federation (IDF) criteria in the presence of abdominal obesity and two concurrent factors out of a list of four¹⁰. In Caucasians, abdominal obesity is defined as a waist girth ≥ 94 cm for men and ≥ 80 cm for women.

Additional factors:

- Triglycerides: ≥ 150 mg/dl (1.7 mmol/l) or appropriate treatment;
- HDL cholesterol < 40 mg/dl (1.0 mmol/l) or appropriate treatment;
- Blood pressure: systolic > 130 mmHg or diastolic > 85 mmHg or appropriate treatment;
- Fasting plasma glucose > 100 mg/dl (5.6 mmol/l) or Type 2 diabetes diagnosed at an earlier stage.

*Secondary diabetes*¹¹ is a form of diabetes in which another disease is at the root of the development of the diabetes. The most frequent causes of secondary diabetes are:

- Diseases of the pancreas: pancreatitis (alcohol abuse), neoplasia
- Metabolic conditions: hemochromatosis
- Endocrine disorders: hyperthyroidism, Cushing's syndrome, acromegaly, etc.
- Use of diabetogenics: diuretics, corticosteroids, nicotinic acid, etc.

MODY or "*Maturity Onset Diabetes of the Young*" is a relatively frequent special form of Type 2 diabetes that occurs at an early age (before age 25) and which is hereditary as an autosomal dominant characteristic. A recent British study demonstrated that approximately one out of every two children presenting with a clinical picture of Type 2 diabetes are afflicted by a form of MODY¹². A number of genetic defects have been found to be at the origin of this condition¹³.

LADA or "*Latent Autoimmune Diabetes of Adults*" is a special, slowly developing form of Type 1 diabetes¹⁴. Diagnosis sometimes only becomes obvious because treatment started with oral antidiabetics has little effect and the patient continues to complain of hyperglycaemia. In such cases, referral to a multidisciplinary diabetes team will become necessary.

MIDD or "*Maternal Inherited Diabetes and Deafness*" is a syndrome that should be taken into consideration when faced with a combination of diabetes and deafness¹⁵. It is a mitochondrial genetic defect that can only be transmitted through the maternal line.

¹⁰ International Diabetes Federation (IDF). http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf

¹¹ The term primary diabetes is no longer used in the literature.

¹² Ehtisham S, Hattersley A, Dunger D, Barrett T. First UK survey of paediatric type 2 diabetes and MODY. *Archives of Disease in Childhood* 2004;89:526-529.

¹³

- American Diabetes Association (ADA). Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003;26:S5-S20.
- American Diabetes Association (ADA). Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2005;28:S37-42.

¹⁴ Epidemiological research has demonstrated that the LADA syndrome accounts for approximately 10% of all diabetes patients. Thus its occurrence is virtually as frequent as that of rapidly progressing Type 1 diabetes.

- Isomaa B, Almgren P, Henricsson M, et al. Chronic complications in patients with slowly progressing autoimmune type 1 diabetes (LADA) *Diabetes Care* 22:1347-53.
- Biesenbach G, Auinger M, Clodi M, et al. Prevalence of LADA and frequency of GAD antibodies in diabetic patients with end-stage renal disease and dialysis treatment in Austria. *Nephrol Dial Transplant*. 2005;20:559-65.

¹⁵ MIDD is a maternally transmitted disease giving rise to diabetes and loss of hearing as a result of impaired perception of high tones. The disease results from a mutation from A to G on position 3243 in the mitochondrial DNA. Approximately 1.43% of Type 2 diabetes patients in the Netherlands carry this mutation. The most important defect in these people is reduced insulin secretion by the pancreas following glucose stimulation.

- Maassen JA, van den Ouweland JM, Losekoot M, et al. Van gen tot ziekte; mutatie in mitochondriaal DNA en MIDD. *Ned Tijdschr Geneesk*. 2001;145:1153-4.
- Maassen JA, van Essen E, van den Ouweland JM, et al. Molecular and clinical aspects of mitochondrial diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2001;109:127-34.

These recommendations refer exclusively to Type 2 diabetes mellitus in adult patients.

1.3.Epidemiology

Diabetes mellitus is an important health problem of worldwide incidence. The number of diabetes patients is on the rise everywhere in the world. In 2001, the "International Diabetes Federation" (IDF) estimated the number of diabetes patients worldwide at 177 million¹⁶. It is believed that in 2010 six per cent of the world's population will have diabetes¹⁷. The World Health Organisation (WHO) forecasts 366 million diabetics by 2030¹⁸.

The prevalence of diabetes in Europe is estimated at 4% of the total population, but only half of all those affected are actually diagnosed. Type 2 diabetes patients account for more than 90% of this population. The incidence of Type 2 diabetes increases with age; more than 10% of all people over 65 are diabetics. Because in our society there are ever more obese children with inappropriate eating habits and who have very little physical activity, there is also a greater frequency of development of Type 2 diabetes in younger years¹⁹.

The figures for Belgium are limited and partially incomplete. Every year, some 2,070 new Type 1 diabetes patients are diagnosed, 1,180 of whom are under the age of 14 and 890 are aged between 15 and 39 at the time of diagnosis. As concerns Type 2, some 23,500 new cases are diagnosed in Belgium every year²⁰. The prevalence of diabetes in Belgium (Types 1 + 2) is estimated at 5.2% of the total population, and that of IGT at 7.4%²¹.

The prevalence of Type 2 diabetes can differ significantly depending on the ethnic composition of the population, with rates two to six times higher in allochthonous than in autochthonous populations²². There are no figures available on the prevalence of Type 2 diabetes in allochthonous populations in Belgium²³.

¹⁶ IDF Clinical Guidelines Task Force. Global Guideline for type 2 diabetes. Brussels: International Diabetes Federation, 2005.
<http://www.eatlas.idf.org/>

¹⁷ Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabetic Medicine* 1997;14:1-85.

¹⁸

- Wild S, Roglic G, Green A. et al Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047-53.
- http://www.who.int/diabetes/facts/world_figures/en/

¹⁹

- Molnar D. The prevalence of the metabolic syndrome and type 2 diabetes mellitus in children and adolescents. [Review]. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity*. 2004;28 Suppl3:S70-74.
- Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. [Review]. *Journal of Pediatrics*. 2005;146(5):693-700.
- Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ & Heine RJ. Prevalence and determinants of glucose intolerance in a Dutch Caucasian population. The Hoorn Study. *Diabetes Care* 2005;18:1270-1273.

²⁰ Wens J, Van Casteren V, Vermeire E, et al. Diagnosis and treatment of type 2 diabetes in three Belgian regions. Registration via a network of sentinel general practices. *Eur J Epidemiol* 2001;17:743-50.

²¹ IDF Clinical Guidelines Task Force. Global Guideline for type 2 diabetes. Brussels: International Diabetes Federation, 2005: 45-7.
<http://www.eatlas.idf.org/>

²² Carter JS, Pugh JA, Monterrosa A. Non-insulin-dependent diabetes mellitus in minorities in the United States. *Ann Intern Med* 1996;125:221-32.

²³ A number of studies in the Netherlands showed that the prevalence of Type 2 diabetes is two to three times higher in allochthonous than in autochthonous populations (4.8% in Dutch people as compared to 9.9% in Turks and 12.1% in Moroccans). In addition, allochthonous diabetes patients are, on average, younger than Dutch patients (55.2 years vs. 68.6 years). When calculated by age cohorts, the difference was even more striking: in the 35-54 years cohort, prevalence was 6.7 times higher in allochthonous than in autochthonous populations; in the cohort older than 54 years the difference was 2.8 times.

The prevalence of diabetes complications varies depending of the duration of the disease and glycaemic control. Macrovascular and microvascular diseases are the most important causes of diabetes related morbidity and mortality. Diabetes is the most significant cause of blindness in adults, of non-trauma related lower limb amputation, and of kidney failure resulting in transplantation and dialysis. In addition, the risk of coronary heart disease is two to four times higher in diabetes patients and the risk of stroke or peripheral vascular disease is also strongly increased²⁴.

1.4. Issues at stake

These recommendations aim to provide an answer to the following issues:

- Which factors make diabetes screening desirable, and how should it be carried out?
- What are the criteria for formulating a diagnosis of diabetes mellitus?
- What treatment objectives are assumed in diabetes mellitus patient care?
- What constitutes useful advice in connection with diet and exercise?
- How is the treatment of hyperglycaemia in Type 2 diabetes patients managed?
- What risk factors are monitored to prevent cardiovascular complications?
- How can chronic complications (nephropathy, neuropathy, retinopathy, foot problems, cardiovascular complications) be detected and treated in their early stages?
- What is involved in a good diabetes education aimed at increasing “patient empowerment”²⁵?
- How can diabetes patient care be organised along the principles of “shared care”?

The differences in prevalence by ethnicity were comparable between men and women. Ethnicity appears to be the strongest indicator of Type 2 diabetes mellitus: OR 2.81 ± 1.80 – 4.39 for Turks; OR 3.21 ± 2.28 – 4.52 for Moroccans in comparison with Dutch people, even when corrected for sex, age and type of health insurance. The studies also showed differences in the age of patients at the time of diagnosis: Dutch patients were oldest (61.8 ± 8.1 years), preceded by Moroccan (57.7 ± 7.9 years) and Turkish patients (54.6 ± 7.6 years). There were no differences in the type of treatment. Most patients were treated directly by their GPs, regardless of their ethnic background.

- Querido JD. De prevalentie van diabetes mellitus type 2 in een achterstandsbuurt. Een onderzoek in drie huisartspraktijken. Huisarts Wet 1995;38:250-4.
- Kriegsman DMW, Van Langen J, Valk GD, et al. Hoge prevalentie van diabetes mellitus type 2 bij Turken en Marokkanen. Huisarts Wet 2003;46:363-8.

²⁴ American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care;28:S4-S36.

²⁵ There is no good Dutch equivalent for the concept of “empowerment”. The St. Vincent Declaration Primary Care group describes “empowerment” as: “A process that enables people to gain greater control over their health and its improvement”.

2. EARLY DETECTION

2.1. Early detection of Type 2 diabetes

2.1.1. Justification

A number of arguments speak in favour of earliest possible diagnosis of Type 2 diabetes:

- Diabetes is a serious disease of very frequent occurrence.
- It involves a long asymptomatic period. Population research shows that between 1/3 and 1/2 of all people with diabetes have not been diagnosed²⁶.
- On the basis of the presence of diabetic retinopathy (a disorder that is specific to diabetes), scientists are able to calculate that at the time of diagnosis the patient has often been affected by the disease for more than ten years²⁷. Insulin resistance syndrome, which is frequently at the root of Type 2 diabetes, and which significantly increases cardiovascular risk, is often found to have been present for an even longer period of time.
- The prevalence of Type 2 diabetes is shifting to a younger age. There have even been cases reported of Type 2 diabetes in children with morbid obesity.
- Unidentified diabetes is not a benign condition: at the time of diagnosis, chronic complications are often found to be present in a more or less developed form.
- The disease can be diagnosed by means of a simple and inexpensive blood test.
- Treatments of proven efficacy in the prevention of further complications are available.

It can therefore be expected that prognoses will improve as a result of earlier detection. However, to date there is no formal evidence to substantiate this presumption²⁸.

2.1.2. Strategy

A screening of the entire population²⁹ is not recommended due to an unfavourable cost-benefit ratio³⁰. On the other hand, targeted, opportunistic screening of persons at distinctly increased risk of Type 2 diabetes is recommended³¹. Obviously, such screening would be best envisaged as part of a global cardiovascular prevention strategy. The GP is in a good "case finding" position in connection with patient consultations.

²⁶

- Hortolanus-Beck D, Lefebvre PJ, Jeanjean MF. Le diabète dans la province belge du Luxembourg : fréquence, importance de l' épreuve de surcharge glucosée orale et d'une glycémie à jeûn discrètement accrue. *Diab Metabol* 1990;16:311-7.
- Mooy JM, Grootenhuys PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ, Heine RJ. Prevalence and determinants of glucose intolerance in a Dutch Caucasian population. The Hoorn Study. *Diabetes Care* 1995;18:1270-3

²⁷ Harris MI, Klein R, Welborn TA, Knudman MW. Onset of NIDDM occurs at least 4-7 yrs before clinical diagnosis. *Diabetes Care* 1992; 15: 815-19.

²⁸ Proving this requires randomised studies with an intervention group in which screening and early treatment are administered, as compared to a control group in which no intervention takes place. It is not very probable that such studies will be carried out in view of the methodological and ethical issues involved, as well as the related feasibility and costs.

²⁹ In 1968, Wilson and Jungner set up 10 criteria to be met by screening programmes.

- Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organisation, 1968.
- Buntinx F. Screening versus diagnostiek: complexe problemen. *Huisarts Wet* 2004;47:230-5.

³⁰ Screening the entire population is not useful: the cost-benefit ratio is negative, and there is a significant risk of missing high risk populations, while many people at low risk would be examined and unnecessarily worried.

- Engलगau MM, Narayan KM, Herman WH. Screening for type 2 diabetes. *Diabetes Care* 2000;23:1563-80.

³¹ In 2002 the Scientific Institute for Public Health (Wetenschappelijk Instituut Volksgezondheid (WIV)) developed a Belgian consensus on screening for Type 2 diabetes. This consensus came about following a literature study and

2.1.3. Which risk groups?

The following risk groups should be taken into consideration:

- People with a prior history of blood glucose disorders (e.g. gestational diabetes, stress hyperglycaemia due to surgical interventions);
- People treated with certain medications³² (e.g. corticoids, atypical neuroleptics³³, protease inhibitors, etc.) or suffering from certain conditions that may cause diabetes (e.g. pancreatitis, alcoholism);
- People aged 45 and over with a family history of first-degree relatives diagnosed with Type 2 diabetes;
- People aged 45 and over with signs of metabolic syndrome;
- People aged 65 and over, regardless of whether or not any additional risk factors are present.

Naturally, people with symptoms or complaints suggesting Type 2 diabetes (thirst, recurring urogenital infections, signs of diabetes complications etc.) should also be tested. Such cases, however, can be considered to fall within the “diagnostic” rather than “screening” category.

2.1.4. Which test and how often?

A measurement of fasting blood glucose is recommended. Ideally, laboratory assays of venous blood should be used³⁴.

Obviously, treatment should be started immediately if diabetes is found.

discussion with experts from Flanders (VDV, WVVH) and Wallonia (ABD, SSMG). This consensus was not tested for validity, but is considered to be highly valuable by the writers of the present recommendation. For this reason, its decisions were incorporated into the recommendations.

- In persons aged 18 to 45 years:
If ONE of the following conditions is met:
 - Previous history of gestational diabetes
 - Previous history of hyperglycaemia found on the occasion of surgery or hospitalisationOr if TWO of the following conditions are met:
 - Previous history of delivery of a baby weighing more than 4.5 kg
 - Diabetes in first-degree relatives
 - BMI ≥ 25 kg/m²
 - Waist girth >88 cm (women) or >102 cm (men)
 - Treatment for high blood pressure or chronic corticoid therapy.
- In persons aged 45 to 64 years inclusive:
 - If JUST ONE of the above conditions is met.
- In persons aged 65 years and over:
 - Regardless of whether or not there are additional risk factors.

<http://www.iph.fgov.be/epidemiologie/epinl/crospnl/consensusdiabete.pdf>

³² Hyperglycemie en diabetes mellitus door geneesmiddelen. Folia Farmacotherapeutica. February 2002.

³³ Lean MEJ, Pajonk FG. Patients on Atypical Antipsychotic Drugs: Another high-risk group for type 2 diabetes. Diabetes Care 2003;26:1597-1605.

³⁴ For interpretation of the figures, please refer to Section 3, Diagnosis of Type 2 diabetes mellitus. It should be taken into consideration that *glucose meters* have an error margin of 15-20% and that thus screening results are reliable only with distinctly high or low values. In addition, not all meters are calibrated in the same way (some on plasma, some on whole blood). For these reasons, the use of glucose meters is not advisable for screening purposes. In measuring *non-fasting glucose* there is a broad grey area, since results depend on how long after the meal the measurement is taken, the quantity and composition of the food taken and the gastric evacuation rate. An *oral glucose tolerance test* (OGTT) is not useful in clinical practice because it is cumbersome, must be performed under strictly standardised conditions, and its reproducibility is not good. The OGTT is primarily used in epidemiological studies. The determination of *glucosuria* is not recommended as a screening due to its low 21 to 64% sensitivity (many diagnoses are missed). The use of *HbA1c* for screening is not recommended because values are often still normal in the early stages of Type 2 diabetes. In addition, the measurement is not sufficiently standardised and is not reimbursed for this indication.

- Engelgau MM, Narayan KMV, Herman WH. Screening for Type 2 diabetes. Diabetes Care 2000; 23: 1563-80.

With impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (cf. diagnostic criteria, Section 3.1) annual screenings are recommended. If glycaemia levels are within the normal range, it is advisable to repeat the test every three years. Where there is a history of gestational diabetes or stress hyperglycaemia, the test should be repeated on an annual basis. Regardless of the results of the screening test, the controllable risk factors must be treated, both in order to reduce cardiovascular risk and in order to prevent or delay the development of such factors into fully-fledged diabetes³⁵.

2.2. Early detection of gestational diabetes

Gestational diabetes is defined as a glucose tolerance disorder developed during pregnancy. The prevalence of gestational diabetes varies between 1 and 14% of all pregnancies, depending on the population studied and type of diagnostic test used.

Gestational diabetes increases the risk of macrosomia, with its associated perinatal complications such as hypoglycaemia and birth trauma (shoulder dystocia, fractures, peripheral nerve damage etc.)³⁶. There are also potentially longer-term adverse effects for both the mother and the child³⁷.

In view of the importance of these issues for both mother and child, screening for gestational diabetes is also recommended, unless the risk is so small as to be negligible.

The risk of gestational diabetes should be evaluated during the very first consultation.

The risk factors are³⁸:

- BMI >25 kg/m² (in particular waist girth at the level of the navel of >88 cm) prior to pregnancy
- Positive family history of Type 2 diabetes in first-degree relatives
- Age >25 years
- Multiple pregnancy
- Earlier gestational diabetes
- Children with high weight at birth (≥4.5 kg)
- Earlier IFG with FPG = 100-125 mg/dl (5.5 – 7.0 mmol/l)
- Earlier IGT with OGTT 2-hour value 140-199 mg/dl (7.8 – 11.0 mmol/l)

If none of these risk factors are present, the screening procedure can be omitted. In the presence of at least one risk factor, the best time for screening is between pregnancy weeks 24 and 28.

If at the first contact there already appears to be a strongly increased risk (marked obesity, history of gestational diabetes, glucosuria or strong family history of diabetes), the screening should take place directly

³⁵ Prevention studies in the USA and in Finland have demonstrated that in patients with IGT weight loss of 4 kg reduces progression of Type 2 diabetes by 50 to 60% over 4 years.

- Tuomilehto, J, Lindstrom, J, Eriksson, JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344:1343.
- Knowler, WC, Barrett-Connor, E, Fowler, SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393.

³⁶ Blank A, Grave G, Metzger BE. Effects of gestational diabetes on perinatal morbidity reassessed: report of the International Workshop on Adverse Perinatal Outcomes of Gestational Diabetes Mellitus, December 3-4, 1992. *Diabetes Care* 1995;18:127-9.

³⁷ Potential adverse effects of gestational diabetes on the development of the child include lower intellectual development and increased risk of obesity and IGT.

- Rizzo TA, Metzger BE, Dooley SL, Cho NH. Early malnutrition and child neurobehavioural development: insights from the study of children of diabetic mothers. *Child Dev* 1997;68:26-38.
- Pettit D, Bennett PH, Knowler WC, Baird HR, Aleck KA. Gestational diabetes mellitus and impaired glucose tolerance during pregnancy: long-term effects on obesity and glucose intolerance in the offspring. *Diabetes Care* 1985;34:119-22.
- Silverman B, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism. *Diabetes Care* 1995;18:611-7.

For the mother, gestational diabetes creates a significant risk factor for developing diabetes.

- O'Sullivan JB, Mahan CM. Diabetes subsequent to the birth of a large baby: a 16-year prospective study. *J Chronic Dis* 1980;33:37-45.
- Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477-86.

³⁸ American Diabetes association (ADA). Gestational diabetes mellitus. *Diabetes Care* 2003;26:S103-5.

upon first contact. If this screening test is negative, a new screening test is then performed between weeks 24 and 28. The test is always performed on venous plasma. The use of glucose meters is not advisable for screening purposes (cf. above).

2.2.1. How to screen?

There are various different screening methods³⁹. We suggest screening for gestational diabetes on a venous blood sample drawn one hour after stressing with 50 g glucose (= challenge test). This test can be performed at any time of the day and the woman is not required to be fasting at the start of the test. In addition, this test method appears to be the most cost effective⁴⁰.

The screening test is positive if one hour after intake of the 50 g glucose, glycaemia is measured at ≥ 140 mg/dl (7.8 mmol/l). The diagnosis of gestational diabetes should then be confirmed by means of an OGTT.

2.2.2. Diagnosing gestational diabetes

Final diagnosis of gestational diabetes is made by means of an OGTT⁴¹. This involves glucose stress of 100 g following 8 to 10 hours overnight fasting.

The cut-off values are: fasting ≥ 95 mg/dl (5.3 mmol/l)
1 hour ≥ 180 mg/dl (10.0 mmol/l)
2 hours ≥ 155 mg/dl (8.6 mmol/l)
3 hours ≥ 140 mg/dl (7.8 mmol/l)

The test is positive if two or more cut-off values are exceeded.

If gestational diabetes is diagnosed, the patient should be referred to a multidisciplinary diabetes centre. With adequate treatment there is significant reduction of perinatal morbidity⁴².

³⁹ As concerns screening methods, the following possibilities exist:

- 50 g glucose stress test measuring glycaemia after one hour (50 g challenge test)
- Fasting or post-prandial glucose determination. With fasting glucose, the cut-off used is 86 mg/dl (4.8 mmol/l). Approximately 30% of all women must then undergo a diagnostic OGTT.
- Two-hour 75 g and/or three-hour 100 g glucose stress tests with determination of fasting glucose and glucose values one, two and/or three hours following the intake of glucose (OGTT). The 100 g OGTT is considered to be the golden standard. With 75 g glucose stress, the limits are 140 mg/dl (7.8 mmol/l) after one hour and 120 mg/dl (6.7 mmol/l) after two hours.

There is not sufficient evidence that would enable any one of these screening methods to be considered as being superior to another.

- Canadian Task Force on Preventive Health Care. Screening for Gestational Diabetes Mellitus. *Can Med Assoc J* 1992;147:435-43.
- Berger H, Crane J, Armson A, et al. Screening for gestational diabetes mellitus. *J Obstet Gynaecol Can* 2002;24:894-912.
- Vogel N, Burnand B, Vial Y, et al. Screening for gestational diabetes: variation in guidelines. *Eur J Obstet Gynaecol Reprod Biol* 2000;91:29-36.

⁴⁰ Nicholson WK, Fleisher LA, Fox HE, Powe NR. Screening for Gestational Diabetes Mellitus. A decision and cost-effectiveness analysis of four screening strategies. *Diabetes Care* 2005;28:1482-4.

⁴¹ Ultimately, to develop a diagnosis of gestational diabetes it is possible to choose between a one-step evaluation with an immediate OGTT test or a two-step evaluation by means of prior screening with the challenge test. The OGTT is much more cost-effective with patients at high risk. However, proper performance of the OGTT 100 gram stress test requires an accurate procedure. The test should be carried out in the morning after 8 to 14 hours' fasting, following several days of unrestricted diet (>150 grams carbohydrates per day) and unrestricted physical effort. The patient must remain seated during the test and may not smoke. (Report of the Expert Committee on the Diagnosis and Classification of Diabetes mellitus. American Diabetes Association - Professional Association. 1997 (revised 1999; republished 2003 Jan).

⁴² Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477-86.

2.3. After the pregnancy

The risk that a patient with gestational diabetes will develop Type 2 diabetes after her pregnancy is of between 30 and 60%⁴³. For this reason, following a diagnosis of gestational diabetes it is best to screen on an annual basis for Type 2 diabetes (cf. above), and certainly in the event of overweight or other risk factors. It is very important to identify this risk group in a timely manner in order to treat such risk factors as obesity and lack of physical exercise.

⁴³ O'Sullivan JB, Mahan CM. Diabetes subsequent to the birth of a large baby: a 16-year prospective study. *J Chronic Dis* 1980;33:37-45.

3. DIAGNOSIS OF DIABETES MELLITUS

3.1. Diagnostic criteria

For basic information please refer to the criteria of the American Diabetes Association⁴⁴. They suggest using fasting glucose determined in venous plasma in clinical practice. The test is easy to perform, patient friendly, inexpensive and easily reproducible. Fasting means that the patient will not have consumed food (calories) for at least eight hours prior to the test. The oral glucose tolerance test (OGTT) is only recommended for research purposes, or to diagnose gestational diabetes (cf. section on early detection).

Fasting

A value of <100 mg/dl (5.5 mmol/l) is normal. Values between 100 and 125 mg/dl (5.5 and 6.9 mmol/l) are referred to as “impaired fasting glucose” (IFG). This creates an increased risk of developing diabetes. A fasting glucose value of ≥126 mg/dl (7.0 mmol/l) can already indicate the existence of diabetes. In view of the impact of the diagnosis, confirmation is required if abnormal fasting glucose values are returned. Two measurements on different days are necessary before a final diagnosis can be made. The diabetes diagnosis is automatically confirmed with a repeat value of ≥126 mg/dl.

Non-fasting

When measuring non-fasting glucose, values ≥126 mg/dl (7.0 mmol/l) must be checked by means of a fasting blood sample. Non-fasting glucose values of (≥200 mg/dl (11.1 mmol/l) automatically indicate diabetes.

Medical stress (infection, trauma, surgery, medication, etc.) can temporarily increase blood glucose levels. These values must then be measured again outside of the acute period. Patients with temporary “stress hyperglycaemia” must be monitored, as they are at high risk of developing diabetes (cf. section on early detection).

Table 1. Diagnostic criteria for Type 2 diabetes

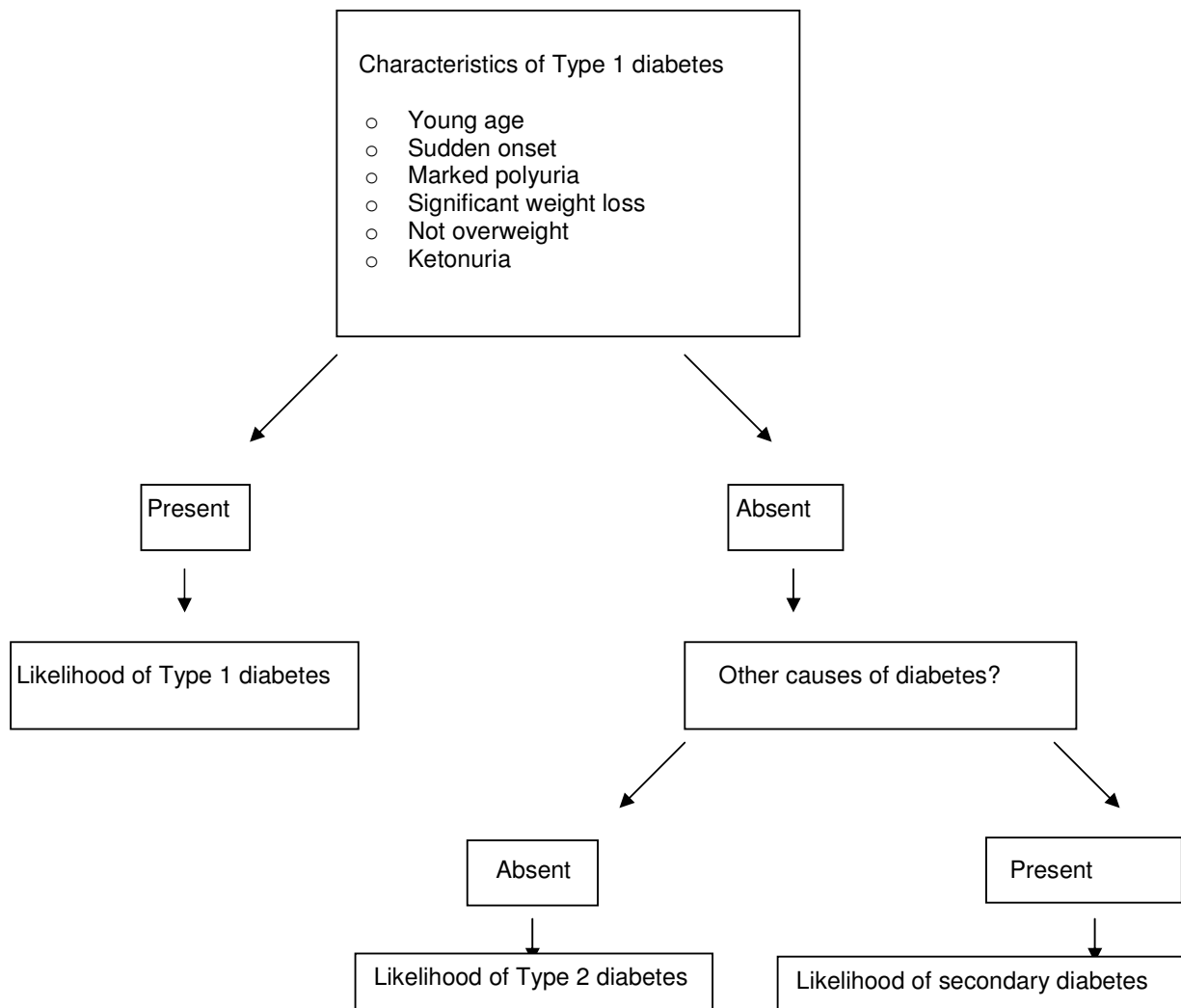
Fasting	
<100 mg/dl (5.5 mmol/l)	normal
≥100 mg/dl and <126 mg/dl (5.5 mmol/l and 7.0 mmol/l)	impaired fasting glucose (IFG)
≥126 mg/dl (7.0 mmol/l)	diabetes mellitus
Not fasting	
≥126 mg/dl and <200 mg/dl (7.0 mmol/l and 11.1 mmol/l)	repeat under fasting conditions
≥200 mg/dl (11.1 mmol/l)	diabetes mellitus
2 hours after stress with 75 g glucose (OGTT)	
≥140 mg/dl and <200 mg/dl (7.8 mmol/l and 11.1 mmol/l)	impaired glucose tolerance (IGT)
≥200 mg/dl	diabetes mellitus

⁴⁴ American Diabetes Association (ADA). Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2005;28:S37-42.

3.2. Difference between Type 1 and Type 2 diabetes

A number of clinical parameters are used in order to differentiate between Type 1 and Type 2 diabetes. They are summarised in the following flowchart.

Difference between Type 1 and Type 2 diabetes



It is not always simple to distinguish between Type 1 diabetes mellitus, Type 2 diabetes mellitus and secondary diabetes mellitus based on age, symptoms and glucose values. To the extent that the patient is younger and thinner and has higher blood sugar levels, there is a greater chance that Type 1 diabetes mellitus is involved.

In Type 1 diabetes mellitus, the following specific symptoms are often in evidence: marked polyuria; polydipsia; weight loss and ketonuria. Type 2 diabetes mellitus can develop asymptotically for a long time. Symptoms are often non-specific: fatigue, recurring infections; poorly healing wounds. Frequently the disease is diagnosed upon discovery of a diabetes mellitus complication (e.g. retinopathy, neuropathy).

4. TREATMENT OBJECTIVES

The goal of diabetes treatment is to promote the well-being of persons with diabetes to enable them to lead lives that are qualitatively and quantitatively equivalent to those of people who do not have diabetes. Specifically, this means⁴⁵:

- Preventing symptoms of hyperglycaemia,
- Preventing acute complications (hypoglycaemia, hyperglycaemia),
- Preventing chronic complications,
- Reducing associated mortality,
- Maintaining patient autonomy and self-reliance,
- Fighting social discrimination.

In order to accomplish all the above, one should not concentrate exclusively on the treatment of specific diabetes related problems such as

- Ensuring good blood glucose control
- Early detection (at a reversible stage) of diabetes complications

but simultaneously fight the overall cardiovascular risk.

To do so, the following action must be taken:

- Reducing excess weight if applicable (cf. Section 5)
- Stimulating physical activity (cf. Section 5)
- Discouraging smoking (cf. Section 7)
- Treating hypertension (cf. Section 7)
- Starting a statin if there are no concomitant cardiovascular risk factors (cf. Section 7)
- Evaluating whether to start the patient on a low aspirin dose (cf. Section 7)

All these actions are discussed in greater detail in the following sections.

Strict goals have been assumed in connection with each of these risk factors⁴⁶. It is however impossible to formulate absolute and universally valid treatment objectives. In addition, these goals are considered to be "moving targets" which will undoubtedly change in the future. Evolving treatment goals will always be clearly identified in follow-up reports to this recommendation.

The most important issue is the achievability of these strict objectives. Keeping the overall quality of life and welfare and well-being of each patient on an optimal level remains of the utmost importance.

The table below shows clinical target values that can be attained by many people with diabetes⁴⁷. These goals will be discussed in greater detail elsewhere in this document.

⁴⁵ For the scientific foundation of treatment goals the reader is referred to later sections in the present recommendation, in which these various topics are analysed in detail.

⁴⁶ The lowest possible value is aimed for at every stage of the disease. Thus at an early stage of diabetes, HbA1c = 6 is sometimes still possible, while it would no longer be achievable at a later stage.

⁴⁷ The goals as formulated are based on various national and international guidelines. Only the most important will be identified here. The following sections of the present recommendation contain further references to the available literature.

- American Diabetes Association (ADA): Clinical Practice Recommendations 2005. Diabetes Care 2005;28. Suppl1. http://care.diabetesjournals.org/content/vol28/suppl_1
- Clinical Guidelines for type 2 diabetes. Management of blood glucose. Full Report. A collaborative program between the Royal college of General Practitioners, Diabetes UK, the Royal college of Physicians, the Royal college of Nursing. Publication date September 2002. Review date September 2005. <http://www.nelh.nhs.uk/guidelinesdb/html/front/Bloodglucose2.html>
- National Institute of Clinical Excellence (NICE): Management of Type 2 Diabetes - management of blood pressure and blood lipids (Guideline H). http://www.nice.org.uk/pdf/NICE_INHERITED_Hv8.pdf
- European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by

Table 2. Goals

	Goal	Unit
Smoking	Cessation	
Weight reduction with obesity	5 to 10% / 1 year	
HbA1c	<7,0	%
Fasting glucose	≤125	mg/dl
Blood pressure	<130 / 80	mmHg
LDL cholesterol ⁴⁸	<100	mg/dl

Targeted blood pressure values are a little lower with nephropathy (<125 / 75 mmHg).

representatives of eight societies and by invited experts). De Backer G (chairperson), Ambrosioni E, Borch-Johnsen K, et al. *Atherosclerosis* 2004;173:381-91.
Executive summary available at: <http://eurheartj.oxfordjournals.org/cgi/content/full/24/17/1601>

⁴⁸ LDL cholesterol determination is not reimbursed in Belgium. The laboratories therefore often give a calculated value. The analysis is calculated by means of total cholesterol, HDL cholesterol and triglycerides in the form $LDL = CHOL - (TG/5) - HDL$. With a triglyceride content >400 mg/dl the formula is less accurate.

5. Diet and exercise advice

We will discuss diet measures and advice regarding physical activity for Type 2 diabetes patients in one and the same section as these two issues are closely related and the necessary patient education methods are quite comparable.

The objective of both measures consists, on the one hand, in preventing or delaying the onset of Type 2 diabetes and, on the other hand, in creating a foundation for the control of the most important treatment parameters in existing cases of diabetes: weight, blood pressure, glucose and lipid levels⁴⁹.

5.1. Prevention of Type 2 diabetes

The presence of IFG, IGT or both is today considered to indicate a pre-diabetic condition. The detection of pre-diabetes is not a goal in itself, but it helps identify a population at (strongly) increased risk of developing Type 2 diabetes.

In this high-risk group, diabetes can be prevented by means of lifestyle changes⁵⁰. This requires substantial effort. The use of metformin is also effective in diabetes prevention, but lifestyle changes appear to be more effective still⁵¹.

A recent literature review evaluated the possibilities to prevent diabetes by means of lifestyle changes in the general population⁵². The findings are less clear, primarily due to methodological limitations.

Properly controlled studies involving one arm in which lifestyle changes were evaluated always demonstrated that significant effort was required in order to achieve even moderate change in eating and exercise habits⁵³.

49

- Franz MJ, Bantle JP, Beebe CA, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 2002;25:1869-75.
- Pritchard DA, Hyndman J, Taba F. Nutritional counselling in general practice: a cost effective analysis. *J Epidemiol Community Health* 1999;53:311-16.

50 The "Diabetes Prevention Study" randomised 522 obese (average BMI = 31 kg/m²) middle-aged patients (average age 55 years) with IGT. The intervention group received personalised counselling aimed at weight reduction, reduced overall intake of fats and reduced intake of saturated fats, increased fibre intake and greater physical activity. The cumulative incidence of diabetes after 4 years was 11% (95% CI 6-15) in the intervention group and 23% (95% CI 17-29) in the control group. During the trial the risk of onset of diabetes was reduced by 58% (p<0.001). The reduction in the incidence of diabetes could be entirely ascribed to lifestyle changes.

- Wens J. Kan een gezonde leefstijl diabetes voorkomen? *Huisarts Nu (Minerva)* 2002;31(1):45-7. Interpretation of: Tuomilehto J, Lindstrom J, Eriksson J, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*. 2001;344(18):1343-1350.

51 The "Diabetes Prevention Programme" randomised 3,234 patients with IFG and IGT (average BMI = 34 kg/m², average age 51 years) into three groups: placebo, metformin and lifestyle changes. The goals of the lifestyle programme were a weight reduction of at least 7% and moderate effort of at least 150 minutes physical activity per week. The average follow-up period was 2.8 years. The incidence of diabetes was 11.0 per 100 person years in the placebo group, 7.8 in the metformin group and 4.8 in the lifestyle group. In this study, too, lifestyle interventions limited the incidence by 58% (95% CI 48-66) and metformin by 31% (95% CI 17-43) as compared to placebo. In order to prevent one case of diabetes in 3 years, 6.9 people had to participate in the lifestyle group, and 13.9 in the metformin group.

- Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Eng J Med* 2002;346:393-403.

52 Satterfield DW, Volansky M, Caspersen CJ, et al. Community-based lifestyle interventions to prevent type 2 diabetes. Review. *Diabetes Care*. 2003;26:2643-2652.

53 The "Diabetes Prevention Study" (Tuomilehto) showed an average weight reduction of 4.2 kg after one year, 3.5 kg after two years, and 2.1 kg after five years. In the "Diabetes Prevention Project" (Knowler) the lifestyle changes group lost ±5.4 kg after two years, and ±4 kg after three years. The average weight loss in this study was ±5.4 kg or 6% of the initial weight. In both studies, most of the subjects were obese (BMI >30 kg/m²).

- Wens J. Kan een gezonde leefstijl diabetes voorkomen? *Huisarts Nu (Minerva)* 2002;31:45-7. Interpretation of:

5.2. Treatment approaches to Type 2 diabetes

5.2.1. Diet counselling

The principles involved in diet recommendations are:

- Calorie limitation for overweight patients;
- A balanced and varied diet based on the rules of the diet triangle⁵⁴ (healthy eating) with specific ratios between carbohydrates, fats and proteins;
- Diet products for diabetics seldom qualify for selection because they can contain too much fat as compared to standard products and they are also often rather more expensive. Low-calorie sweeteners are allowed,
- Alcohol can be consumed in moderation (maximum of 2 drinks per day), with extra care in cases of obesity⁵⁵,
- Limiting salt and healthy eating are recommended.

In cases of obesity, a weight loss of 5 to 10% suffices in order significantly to lower insulin resistance and improve glycaemic control⁵⁶. The same amount of weight loss also reduces blood pressure, cholesterol levels and overall cardiovascular risk⁵⁷.

Please refer to the subject specific recommendations as concerns obesity management⁵⁸.

When changing eating habits, it is important to take the patient's current habits as a point of departure. The diet pattern is recorded in an eating diary. Individual goals can then be discussed with the patient on the basis of the existing eating pattern. This process requires a lot of time and specific skills⁵⁹. For this reason it is recommended to work with a dietician in the management of the dietary habits of diabetes patients⁶⁰.

Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Eng J Med* 2001;344:1343-50.

- Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Eng J Med* 2002;346:393-403.

⁵⁴ The diet triangle provides guidelines (starting from age six) of what should be eaten in order to achieve appropriate nutrition. The recommendations are aimed at the general population with moderate physical activity. People who exercise strenuously, perform heavy physical work or who are on a special diet should seek the advice of a dietician regarding the appropriate quantities, choice and variation of foods. Athletic effort, for example, causes a greater fluid intake requirement than the recommended 1.5 litres we should drink under normal circumstances. Each food in itself provides a certain amount of fluid. No single individual food provides all required nutrients. The diet triangle has seven groups of nutrients, each of which is a component contributing to a healthy, varied and balanced diet. The apex of the diet triangle contains the "extras".
For detailed diet information, please consult "De praktische voedingsgids" ["The Practical Diet Guide"]. It is available free of charge on the Internet http://www.vig.be/content/pdf/VD_praktischegids.pdf

⁵⁵ Epidemiology studies demonstrate reduced risk of cardiovascular disease with light to moderate alcohol consumption. This also applies to Type 2 diabetes patients. However, alcohol consumption often is a significant source of additional calories. This can lead to weight gain. Therefore, Type 2 diabetes patients who consume alcohol are advised to do so in moderation: no more than two drinks per day for men, and one drink per day for women.

- Sunaert P. Is alcohol goed voor diabetes? *Huisarts Nu (Minerva)* 2000;29:464-5. Interpretation of: Valmadrid, Klein R, Moss ES, et al. Alcohol intake and the risk of coronary heart disease mortality in persons with older-onset diabetes mellitus. *JAMA* 1999;282:239-46.

⁵⁶ Goldstein D. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord* 1992; 16: 397-415.

⁵⁷ Van Gaal L, Wauters M, De Leeuw I. The beneficial effects of modest weight loss on cardiovascular risk factors. *Int J Obes Relat Metab Disord* 1997; 21:S5-9.

⁵⁸ WVVH Obesity Recommendations, 2005. (in press)

⁵⁹ Franz MJ, Monk A, Barry B, McClain K, Weaver T, Cooper N, et al. Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. *J Am Diet Assoc* 95;95:1009-17

⁶⁰

- American Diabetes Association (ADA): Clinical Practice Recommendations 2005. *Diabetes Care* 2005;28(S1):S11

The GP continues to play an important role from the point of view of patient motivation⁶¹.

Standardised referral and back-referral letters ensure that the necessary and appropriate information is exchanged. The Diabetes Passport and the related right to reimbursement for diet consultations with a dietician can have a threshold lowering effect (cf. Section 11.4, The Diabetes Passport).

5.2.2. Physical activity

Generally it is recommended to do physical activity that increases the pulse rate and/or leaves the person slightly short of breath (fast walking, bicycling, using home exercise equipment, etc.) on most days of the week for 30 to 45 minutes each time. Encouraging exercise has a better chance of success if only moderate effort is recommended that can easily be integrated into each individual patient's daily life. Existing co-morbidities must be taken into account when beginning a programme to increase physical activity⁶².

Certainly in the case of obese patients it is best to increase physical activity only gradually⁶³. Going for a half-hour walk three times per week is a realistic starting point. Then the intensity (brisk walking) and frequency (almost every day of the week) can be increased⁶⁴. The long-term goal is to perform a moderate physical effort for 30 to 45 minutes almost every day of the week (walking, swimming, cycling etc.)⁶⁵. Some potential side effects of increased physical activity are muscle and/or joint lesions and cardiovascular events⁶⁶.

If a patient selects to do strenuous physical activity, it should be considered first to perform a cardiac stress test. Sustained effort is permissible, as it hardly increases the absolute risk of sudden death at all⁶⁷. Any

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- Pastors, JG, Warshaw H, Daly A, Franz M, Kulkarni K. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care* 2002;25:608-13.

⁶¹ An RCT showed that overweight patients who had been motivated and referred to a dietician by their GP lost more weight than people who had been addressed directly by the dietician for therapy. In an "intention to treat" analysis, patients in the GP/dietician group (n= 92) lost 6.7 kg or 7.3% of their initial weight as compared to the control group (n=90) (95% CI 6.5-8.3%). Patients in the dietician group (n=88) lost 5.6 kg or 6.6% of their initial weight as compared to the control group (n=90) (95% CI 5.8 -7.6%).

The group referred by the GP also included fewer people who withdrew from the therapy. This would seem to indicate that the GP plays a crucial role in patient motivation. This did refer to a group of overweight patients, with just 6 patients with diabetes in each subgroup.

- Pritchard D, Heyndman J, Taba F. Nutritional counselling in general practice: a cost effective analysis. *J Epidemiol Community Health* 1999;53:311-6.

⁶² This means active detection of microvascular and macrovascular complications. Cardiovascular risk factors are monitored on an annual basis. In persons with a sedentary lifestyle, aged over 35 and wishing to start strenuous physical activity it is necessary to perform a cardiac stress test (stress ECG).

- American Diabetes Association (ADA): Clinical Practice Recommendations 2005. *Diabetes Care* 2005;28:S13.

⁶³ Exercise is not limited to sports. It is important that the patient should incorporate as much physical activity as possible into his or her life. Thus the patient should take the stairs rather than the lift, walk or cycle to the shops rather than drive, and limit "sedentary activities" such as watching TV as much as possible.

- American College of Sports Medicine. Position Stand on the Appropriate Intervention Strategies for Weight loss and Prevention of Weight Regain for adults. *Med. Sci Sports Exerc* 2001; 33:2145-56.

⁶⁴ Whenever a patient performs a moderate physical effort for 45 minutes on at least five days per week, he or she "wins" approximately 100-200 kcal per day.

- National Institute of Health, National Heart, Lung and Blood Institute. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults-the evidence report. *Obes Res* 1998;6: 51S-209S. http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm

⁶⁵ Moderate physical effort = effort with maximum pulse rate between 55 and 70% of the age defined maximum heart rate (220 - age).

⁶⁶ The writing group for the Activity Counseling Trial Research Group. Effects of Physical activity counseling in Primary care. The Activity Counseling Trial: A randomised controlled Trial. *JAMA* 2001;286:677-87.

⁶⁷ The absolute risk of sustained physical effort remains low, and is estimated at 6 deaths per 100,000 middle-aged men per year or 0.3 to 2.7 incidents per 10,000 man hours of effort.

- Thompson PD. The cardiovascular complications of vigorous physical activity. *Arch Intern Med* 1996;156:2297-302.
- Sigal RJ, Malcolm JC, Meggison HE. Prevention of cardiovascular events in diabetes. BMJ Publishing group Ltd. Clinical evidence, edition 2005. www.clinicalevidence.com

potential complications arising from such physical activity must be taken into account in selecting the type of exercise.

Both diet and exercise advice have a better chance to succeed if they are customised for the patient and are regularly repeated, reviewed and adapted. This structured approach requires a lot of time and specific expertise⁶⁸.

A combination of diet, behavioural and exercise advice is more effective in achieving weight loss and maintenance than any of these therapies by itself. Weight loss is primarily caused by dietary measures. A sustained increase in physical activity is important in order to maintain the weight loss⁶⁹.

⁶⁸ Thijs G, Van Nuland M, Govaerts F. Op de grens tussen 'CURE' en 'CARE'. Begeleiding van gedragsverandering door de huisarts. *Huisarts Nu* 2005;34:186-91.

⁶⁹ Increased physical activity (3 to 7 times per week moderate aerobic effort during 30-60 minutes) ensures additional weight loss of a few kilograms in combination with diet therapy. Longitudinal studies over long follow-up periods (2-10 years) have demonstrated that sustained physical activity leads to lower weight gain following weight loss. A number of intervention studies have also demonstrated that physical activity as a treatment component is also an indicator of weight loss.

- National Institute of Health, National Heart, Lung and Blood Institute. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults - The evidence report. *Obes Res* 1998; 6: 51S-209S. [Http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm](http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm)
- Finnish Medical Society Duodecim. Physical activity in the prevention, treatment and rehabilitation of diseases. Helsinki, Finland: Duodecim Medical Publications Ltd; 2002 May 7.
- Thorogood M, Hillsdon M, Summerbell C. Changing behaviour, option: lifestyle interventions for sustained weight loss. BMJ Publishing Group Ltd. *Clinical Evidence*. Edition 2005. Update 20040901.

6. Pharmacotherapy for Type 2 diabetes

Treating hyperglycaemia

Patients receiving intensive treatment for optimal glucose control experience fewer chronic diabetes complications⁷⁰. However, good glycaemic control is not enough for maximum prevention of complications (especially in the macrovascular area). For optimal effects, hyperglycaemia treatments must be integrated into multifactorial approaches including the correction of cardiovascular risk factors and early detection and treatment of complications. (cf. also Section 7, Monitoring Risk Factors to Prevent Cardiovascular Complications).

Type 2 diabetes is characterised by a progressive decline in the pancreas' ability to release insulin. The rate at which this decline takes place differs from patient to patient. To maintain good glycaemic control, the treatment doses must be increased gradually. It is important to explain this to the patient directly at the time of diagnosis. This prevents the patient from becoming discouraged when the therapeutic dose is increased⁷¹.

Hyperglycaemia reductions are best monitored by means of the HbA1c value. The fasting glucose value and the self-test results can be used for day-to-day diabetes management. The treatment should be adapted whenever the therapeutic goal is not reached. The more the results deviate, the faster the adjustment should be made. There is no minimum HbA1c threshold value, so that the lower the value, the lower the risk of complications. Because Type 2 diabetics are less sensitive to insulin (insulin resistance) the risk of severe hypoglycaemia is lower than in patients with Type 1 diabetes⁷². For this reason, with most patients it should be attempted to attain a low HbA1c value of less than 7%.

⁷⁰ Two important prospective studies have determined that there is a direct correlation between diabetes complications and glucose values. The first Diabetes Control and Complications Trial (DCCT) refers exclusively to Type 1 patients.

- The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *The New England Journal of Medicine* 1993;329: 977-86.
- The DCCT Research Group. The absence of a glycemic threshold for the development of long-term complication: the perspective of the Diabetes Control and Complications Trial. *Diabetes* 1996;45: 1289-98.
- The DCCT Research Group. Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care* 1995;18: 1415-27.

The second United Kingdom prospective Diabetes Study (UKPDS) concerns Type 2 patients. The UKPDS randomised 5102 patients just diagnosed with Type 2 diabetes in intensively treated groups versus a conservatively treated control group. In the intensive approaches, glucose lowering medication was used as soon as fasting glucose was >110 mg/dl. In conservative approaches, it was attempted to control glucose for as long as possible with dietary measures alone. Medication was used only with fasting glucose >270 mg/dl. A median HbA1c of 7.0% was achieved in the intensive group, with 7.9% in the conventional group over a follow-up period of 10 years. Improved glucose control primarily resulted in a significant 25% reduction of microvascular diabetes complications (retinopathy requiring laser treatment). No significant effect was found as regards macrovascular complications, although in the obese Type 2 diabetic subgroup a significant reduction of macrovascular complications was seen with metformin.

- Wens J. Intensieve behandeling van diabetes type 2. *Huisarts Nu (Minerva)* 1999;28:125-6. Interpretation of: UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
- Wens J. Intensieve behandeling van obese diabetes type 2 patiënten. *Huisarts Nu (Minerva)* 1999;28:127-8. Interpretation of: UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65.

⁷¹ The UKPDS study did not succeed in accomplishing good long-term glucose control. As the study progressed, even the intensive treatment group recorded progressive increases in HbA1c, although most patients were started on combination therapy with various glucose lowering drugs. The protocol followed current practice according to which ancillary glucose lowering drugs are only added in cases of significant glucose dysregulation. A more aggressive approach must be taken in order to avoid long periods of hyperglycaemia, switching more quickly to combination therapy. It is essential to strive for good figures and keep to a clear treatment goal. This is called "treating to target".

- Vermeire E. Diabetes type 2: behandelingen combineren. *Huisarts Nu (Minerva)* 2000;29:275-6. Interpretation of: Turner R, Cull C, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. Progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999;281:2005-12.

⁷² Shorr R, Ray W, Daugherty J, Griffin M. Incidence and risk factors for serious hypoglycaemia in older persons using insulin or sulphonylureas. *Arch Intern Med* 1997;157:1681-6.

The diagnosis should be reviewed whenever the treatment appears to have little effect and the patient continues to complain of hyperglycaemia⁷³.

6.1.Oral antidiabetics (OAD)

There are five classes of oral antidiabetics, each of which has its own specific advantages and disadvantages (cf. Table 4)⁷⁴:

- Biguanides, which promote insulin function by lowering glucose production in the liver⁷⁵
- Hypoglycaenogenic sulfamides (sulfonylureas), which stimulate insulin release
- Glinides (also known as meglitinides), which have the same effect as sulfonylureas
- Glitazones (also known as thiazolidinediones), which reduce insulin resistance
- Alpha-glucosidase inhibitors, which inhibit the intestinal absorption of glucose.

Biguanides and hypoglycaenogenic sulfamides are the drugs that have been used for the longest time in the treatment of Type 2 diabetes. Their action is well-known and they have proved effective in connection with hard endpoints. To date there have been no studies to research the effect of glinides and glitazones on the development of diabetes complications⁷⁶.

Metformin

In the absence of contraindications, metformin is a first choice in starting pharmacotherapy⁷⁷. It reduces insulin resistance by slowing down glucose production by the liver and by means of improving muscle uptake of glucose. Metformin inhibits weight gain, does not cause significant hypoglycaemia, is inexpensive and inhibits cardiovascular complications in obese patients⁷⁸.

An extremely rare but sometimes lethal adverse effect of metformin is lactic acidosis. For this reason, metformin is contraindicated in situations in which the production of lactic acid can strongly increase or its clearance is impaired⁷⁹. Impaired kidney function (starting at creatinine ≥ 1.5 mg/dl in men and ≥ 1.4 mg/dl in women)⁸⁰ is therefore a contraindication for metformin.

⁷³ This could be a slowly developing form of Type 1 diabetes (also named LADA or "Latent Auto-immune Diabetes of Adults", see above). In such cases, referral to a multidisciplinary diabetes team (internist, diabetes educator, dietician) is recommended. It is advisable that every patient under 40 years of age should, regardless of type of diabetes, be referred to a diabetes team as soon as diagnosed.

⁷⁴ Inzucchi S. Oral antihyperglycemic therapy for type 2 diabetes. Scientific review. JAMA 2002;287:360-72.

⁷⁵ In the biguanides class there is only one product, i.e. metformin. Further on in the recommendation, this compound, rather than the class, will be discussed.

⁷⁶ Royal Institute for Health and Disability Insurance. Consensus meeting: Targeted use of oral antidiabetics. Jury Report, 2003 Complete text, p. 29.
<http://inami.fgov.be/drug/nl/pharmanet/consensus/2003-11-13/pdf/lv-nl.pdf>

⁷⁷ Because metformin does not cause significant hypoglycaemia, it can be started directly upon diagnosis. Gastrointestinal disorders are a frequent side effect. The risk of developing such disorders is lower when the product is started at low doses that are then slowly increased. In the event of persistent gastrointestinal stress the dose must be reduced or the product stopped altogether.

⁷⁸ Metformin has several advantages when treating obese patients. It does not interfere with a weight loss diet because (as opposed to most other oral antidiabetics) it does not cause weight gain or cause significant hypoglycaemia. Furthermore, the UKPDS demonstrated a favourable effect on macrovascular complications in obese Type 2 diabetics.

- UKPDS Group. Relative efficacy of randomly allocated diet, sulphonylurea, insulin or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years (UKPDS 13). BMJ 1995;310:83-88.
- Wens J. Intensieve behandeling van obese diabetes type 2 patiënten. Huisarts Nu (Minerva) 1999;28:127-8. Interpretation of: UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65.

⁷⁹ Metformin can cause lactic acidosis, a complication associated with a very high degree of mortality. However, the risk is much smaller than with the phenformin previously used in the USA. In fact, a Cochrane review of 176 studies with a total of 17,156 patients on metformin did not report any cases of lactic acidosis at all. Severe lactic acidosis is

Sulfonylureas

Sulfonylureas are a good second choice. In the UKPDS study they were also proven to reduce the onset of microvascular diabetes complications, and they are relatively inexpensive. Sulfonylureas stimulate insulin release by the pancreatic beta-cells. A potential danger when using sulfonylureas is the possibility of hypoglycaemia⁸¹.

Glinides

Glinides (repaglinides) are related to sulfonylureas⁸². Over the long term, the effects of glinides are perhaps highly comparable to those of sulfonylureas⁸³. Repaglinide is a fast-acting agent. Therefore there is little risk of developing hypoglycaemia. As are fast-acting sulfonylureas, glinides are a good choice for patients whose

reported in the literature only in the presence of predisposing factors. The following contraindications are therefore applied in the use of metformin:

- Impaired kidney function, starting with a serum creatinine level ≥ 1.5 mg/dl
 - Severe hepatic dysfunction (acute hepatitis, liver cirrhosis Child B/C)
 - Excessive alcohol consumption
 - Severe hypoxemic lung disease
 - Severe cardiac insufficiency with risk of lung oedema
 - Acute situations capable of causing cardiovascular collapse: acute myocardial infarction, CVA, sepsis, surgery
 - Use of iodinated contrast media: because these products can induce acute kidney failure, metformin should be discontinued the evening prior to the examination and not started again until it is certain that the kidney function will remain adequate.
- Salpeter S, Greyber E, Pasternak G, Salpeter E. Cochrane Database Syst Rev 2002;2:CD002967.
 - Stades A, Heikens J, Erkelens D, Holleman F, Hoekstra J. Metformin and lactic acidosis: cause or coincidence ? A review of case reports. J Int Med 2004;255:179-87.

⁸⁰ There is a rather large interval in kidney function (clearance) in relation to creatinaemia. A 50 kg, 70 year old woman with a creatinine level of 1.5 mg/dl has a clearance rate of 27.5 ml/min while a 90 kg, 70 year old man with a creatinine level of 1.5 mg/dl has a clearance rate of 58.3 ml/min. The FDA has chosen to use creatinaemia as a cut-off due to its ease of use.

⁸¹ To limit the risk of hypoglycaemia it is therefore best first to evaluate the effect of diet and exercise adjustments before starting the patient on sulfonylureas. Hypoglycaemia makes slimming difficult (patients need to eat something all the time), and gives the patient the impression that strict diet compliance makes them feel faint. Always start with a low dose and increase it carefully. When using low doses (at the start of the therapy) and in patients with lifestyles involving an irregular schedule it is best to favour use of fast-acting products. In higher doses, compliance can be improved by using a slow-acting product to be taken only once a day. Caution should be used in patients with impaired kidney or liver function.

⁸² Glinides close the same K^+_{ATP} channel in the pancreatic β -cells as do sulfonylureas. They also stimulate pancreatic beta-cell insulin release.

⁸³ Due to their effect on the K_{ATP} channels of heart muscle cells, sulfonylureas and glinides can have a negative effect in cases of myocardial ischaemia. These channels are opened in the event of ischaemia and play a role in ischaemic pre-conditioning, namely the defence of heart muscle cells against ischaemia. Thus closure of these channels by some sulfonylureas and glinides is theoretically undesirable in cases of myocardial ischaemia.. The UKPDS however revealed no negative cardiovascular effect of sulfonylureas. On the contrary, a 16% reduction in the combination of fatal and non-fatal myocardial infarction or sudden death was found. This was not statistically significant ($p=0.052$), perhaps because the difference in HbA1c between the intensive and conventional groups was only small (0.9%).

- Wens J. Intensieve behandeling van diabetes type 2. Huisarts Nu (Minerva) 1999;28:125-6. Interpretation of: UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

Epidemiological analysis of the UKPDS data revealed a 14% reduction in myocardial infarctions for every 1% reduction in HbA1c. A stronger effect can therefore be expected with a more significant decrease in HbA1c. As a consequence, on the basis of these data there is no reason to advise against the use of sulfonylureas. For safety reasons it is however advisable to discontinue sulfonylureas in the event of unstable angina and myocardial infarction.

- Wens J. Glycemie en vasculaire complicaties bij diabetes type 2. Huisarts Nu (Minerva) 2001;30(3):132-4. Interpretation of: Stratton I, Adler A, Neil A, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-11.

lifestyle involves an irregular schedule, and for patients in whom hypoglycaemia must absolutely be prevented (e.g. professional drivers). Owing to their rapid action, glinides must be taken with every meal. However, the drug need not be taken if a meal is skipped.

Glitazones

Glitazones improve insulin sensitivity in fatty tissues and in the liver⁸⁴. Their blood glucose lowering action is gradual and reaches its maximum after approximately 6-12 weeks. Glitazones have potentially positive cardiovascular effects as they influence various components of the insulin resistance syndrome⁸⁵. However, they induce fluid retention, which can aggravate existing cardiac decompensation⁸⁶. To gain an appropriate impression of the place of glitazones in treatment, it is necessary to compare the association glitazones + metformin or glitazones + sulfonyleureas with another association or with insulin, which has not been done yet.

Acarbose

Acarbose, an alpha-glucosidase inhibitor, impedes the split of oligosaccharides and polysaccharides in the small intestine, thus inhibiting glucose uptake. This compound is not often used as it is not very strong and often causes intestinal stress due to the gases that develop in the bacterial breakdown of the not entirely digested saccharides in the colon. Acarbose is not reimbursed.

Since all the abovementioned products have approximately the same maximum glycaemia lowering effect (except for the weaker acarbose), there is no advantage in changing over to another product of the same class in the event of unsatisfactory performance⁸⁷. In such cases it is better to add a second oral

⁸⁴ Glitazones work via the peroxisome proliferator activated receptor (PPAR)-gamma in the cell nucleus. Stimulation of this receptor leads to either expression or suppression of a number of genes that play a role in the metabolism of glucose, albumin and lipids. They cause weight gain, partially as a result of fluid retention. The first glitazone, troglitazone, caused hepatotoxicity. The newer drugs, rosiglitazone and pioglitazone, do not have this side effect. It is nonetheless recommended to check liver enzymes a few times during the first year of treatment. No studies proving long-term safety of glitazones are available to date, and the product is particularly expensive. In Belgium, glitazones are reimbursed only as part of a combination therapy.

⁸⁵

- Wens J. Glitazones, een nieuwe behandeling voor diabetes type 2? Huisarts Nu (Minerva) 2000;29(10):462-4. Interpretation of: Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. A randomised controlled trial. JAMA 2000;283:1695-701.
- Yki-Jarvinen H. Thiazolidinediones. N Engl J Med 2004;351:1106-18.

⁸⁶ The risk of fluid retention is greatest in combination with insulin. For this reason glitazones should not be used in patients with moderate to severe cardiac decompensation (NYHA Classes 3 and 4), or in patients on insulin therapy. Even in asymptomatic patients, and certainly in those with risk factors for heart failure, recent international guidelines call for caution and starting and adjusting doses slowly. Caution is required in concomitant treatments with medicinal products that can cause fluid retention (e.g. NSAIDs), monitoring for signs and symptoms of cardiac decompensation (shortness of breath, fatigue, ankle oedema, weight gain >3 kg).

- Gecommentarieerd geneesmiddelenrepertorium 2005 [Annotated Therapeutic Drug Index 2005].
- Royal Institute for Health and Disability Insurance. Consensus meeting: Targeted use of oral antidiabetics. Jury Report. Complete text, p. 29. <http://inami.fgov.be/drug/nl/pharmanet/consensus/2003-11-13/pdf/lv-nl.pdf>
- Nesto R, Bell D, Bonow R, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care 2004;27:256-63.

⁸⁷ From a pharmacological point of view, it is to be expected that drugs with different points of attack have a cumulative action when used in combination. Thus in principle all combinations of two blood glucose lowering medications is rationally justified provided that they have different mechanisms of action. In combining more than two groups both the number of medications to be taken and the number of adverse side effects can become unacceptably high.

- Transparency Sheet of the Belgian Centre for Pharmacotherapeutic Information [Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI)]: Treatment approaches to Type 2 diabetes (update January 2005) p. 13. http://www.bcfi.be/PDF/TFT/TN_DIAB.pdf

antidiabetic⁸⁸, selecting a product with a different mechanism of action. The most frequently used combination in those cases is metformin and a sulfonylurea⁸⁹.

In a stable treatment situation, a combination drug can be used⁹⁰ to reduce the ultimate number of “pills” the patient needs to take. Fewer pills can lead to better treatment compliance.

If insufficient results are obtained with the combination of two oral antidiabetics, no time should be wasted by adding a third oral agent – in such cases it is better to switch directly to insulin.

Table 3

Class	Generic name	Products
Biguanides	metformin	Glucophage [®] , Metformax [®] , and generics
Sulfonylureas		
Rather fast-acting	gliclazide glipizide gliquidone	Diamicon [®] and generic product Glibenese [®] , Minidiab [®] Glurenorm [®]
Slow-acting	glibenclamide glimepiride gliclazide	Bevoren [®] , Daonil [®] , Euglucon [®] Amarylle [®] Uni-Diamicon [®]
Glinides	repaglinide	NovoNorm [®]
Glitazones	pioglitazone rosiglitazone	Actos [®] Avandia [®]
Glucosidase inhibitors	acarbose	Glucobay [®]
Combination products		
	glibenclamide + metformin	Glucovance [®]
	metformin + rosiglitazone	Avandamet [®]

⁸⁸ In the UKPDS, a significant increase in mortality was determined after adding metformin in a subgroup of 537 obese and non-obese patients in whom sulfonylurea monotherapy had provided only inadequate control. This is in sharp contrast with the significantly reduced mortality in the 324 obese patients who had initially been started on metformin (and to most of whose treatment sulfonylureas had also been added at a later stage).

- Wens J. Intensieve behandeling van obese diabetes type 2 patiënten. Huisarts Nu (Minerva) 1999;28:127-8. Interpretation of: UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65. In the UKPDS Post Study Monitoring Programme, the abovementioned adverse effect disappeared in more extended follow-up. There is thus insufficient evidence to dismiss the option of combination therapy of sulfonylureas and metformin.
- American Diabetes Association (ADA). Clinical practice recommendations 2002. Implications of the United Kingdom Prospective Diabetes Study. Diabetes Care 2002;25:S28-S32.

⁸⁹ Combining a sulfonylurea with a glinide is not useful, as they close the same K⁺_{ATP} channel in the β-cells. On the other hand, metformin can perfectly well be combined with a glitazone. Metformin primarily inhibits glucose production in the liver, while glitazones primarily improve the use of glucose in the muscles. Thus, each has an effect on a different component of insulin resistance for which combination can be useful. If metformin is either not well tolerated or actually contraindicated, a sulfonylurea can be combined with a glitazone.

⁹⁰

- Jones TA, Sautter M, Van Gaal LF, et al. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. Diabetes Obes Metab. 2003;5:163-70.
- Garber A, Marre M, Blonde L, Allavoine T, et al. Influence of initial hyperglycaemia, weight and age on the blood glucose lowering efficacy and incidence of hypoglycaemic symptoms with a single-tablet metformin-glibenclamide therapy (Glucovance) in type 2 diabetes. Diabetes Obes Metab. 2003;5:171-9.

Table 4

	Biguanides: metformin	Sulfonylureas	Glinides	Glitazones	Acarbose
Mechanism of action	insulin resistance ↓ hepatic glucose production ↓	insulin secretion ↑	insulin secretion ↑	insulin resistance ↓	delaying intestinal carbohydrate resorption
HbA1c ↓ with monotherapy	1.5 - 2.0 %	1.5 - 2.0 %	1.5 - 2.0 %	0.7 - 2.0 %	0.5 - 1.0 %
Additional effects	Favourable effect on cardiovascular risk factors	–	=	Favourable effect on cardiovascular risk factors	Lowers triglycerides
Risk of hypoglycaemia	–	+	±	–	–
Weight	↓ or =	↑	↑	↑	=
Favourable effect on complications	proven (UKPDS)	proven (UKPDS)	no studies to date	no studies to date	no studies to date
Primary adverse effects	- intestinal stress - lactic acidosis (rare) situations where risk of lactic acidosis ↑: - renal insufficiency (creat ≥1.5 mg/dl) - liver failure - severe cardiac decompensation - severe COPD	- hypo-glycaemia - weight gain renal insufficiency (except for gliquidone)	Can be used in cases of renal insufficiency	- weight gain - oedema - heart failure - liver failure - cardiac decompensation - insulin combination	- intestinal stress renal insufficiency
Primary contraindications					
Cost	€	€	€	€ € €	€ €
Reimbursement in Belgium	OK	OK	OK	only in combination with SU or metformin (special form to be obtained)	not reimbursed

Table 5

Posology	Time of administration ⁹¹	Number of doses / day	Initial dose	Rate of increase	Maximum dose
Metformin	during or after meals	2	1x 500 mg or ½x 850 mg	slow (1x / week)	2 to 3 x 850 mg/d
Sulfonylureas	Fast acting products 15-30 min. before a meal (less important with slow-acting products)	2 (Amarylle [®] and Uni-Diamicon [®] 1)	½ tablet	slow (1x / week)	3-4 tablets / d (glimepiride 6 mg)
Repaglinide	15-30 min. before a meal	before each meal	½ mg / meal	slow (1x / week)	3 to 4x 4 mg / d
Glitazones	not related to mealtimes	pioglitazone 1 rosiglitazone 1 to 2	1 tablet	slow (1x / week)	2 tablets / d
Acarbose	at the start of the meal	before each meal	1x 25 mg	slow (1x / week)	3 x 100 mg / d

6.2. Insulin

Insulin should be the drug of choice in the following situations:

- Suspected Type 1 diabetes: important symptomatology (e.g. significant weight loss) and/or ketosis (ketones in blood or urine positive).
- Very high fasting blood glucose of >300 mg/dl that does not immediately reduce with dietary measures. It can then be difficult, even in patients with Type 2 diabetes, to break the glucotoxicity cycle. After getting the glucose dysregulation under control with insulin, an attempt can be made to start oral antidiabetics.
- Pregnancy (start directly at the time of planning the pregnancy). Oral antidiabetics are contraindicated with pregnancy.
- Contraindications for oral antidiabetics.

Insulin is often temporarily required with acute glucose dysregulation as can be the case with infection, myocardial infarction, surgery, use of corticoids etc.

Switching to or adding insulin is necessary if it is not (any longer) possible to maintain glycaemic control with oral antidiabetics. In such cases it is possible either completely to switch over to insulin or to use insulin in combination with oral antidiabetics⁹². It is generally easier to add insulin to an existing oral antidiabetic therapy than to start insulin monotherapy⁹³.

⁹¹ Although it is recommended to take fast-acting sulfonylureas 15-30 minutes before a meal, the pharmacodynamic advantage of doing so is limited in accomplishing a steady state. With repaglinide, peak plasma concentrations are achieved within one hour after administration. Because taking repaglinide with a meal lowers the peak concentration by ± 20%, it is best taken 15-30 minutes before the meal. Metformin is taken during or after the meal to improve gastrointestinal tolerance.

Glitazones can be taken independently from meals, as they are slow-acting and cause no gastrointestinal problems or hypoglycaemia. Acarbose should be taken at the beginning of the meal in order to block the α -glucosidase enzymes in connection with carbohydrate consumption.

- De Smet P, Fischer H. het juiste innametijdstip van sulfonylureumderivaten. Ned Tijdschr Geneeskd 2000;144:1206-1209.
- Melander A. Kinetics-effect relations of insulin-releasing drugs in patients with type 2 diabetes. Brief Overview. Diabetes 2004;53:S151-5.

⁹² Yki-Jarvinen *et al* compared different insulin regimens in patients with Type 2 diabetes and inadequate glycaemic control under oral antidiabetics: NPH at bedtime in combination with metformin, in combination with glyburide, in combination with metformin + glyburide, or in combination with a second injection of NPH before breakfast. The combination of metformin and insulin scored best, with better glycaemic control, less weight gain and less hypoglycaemia.

With most Type 2 diabetics it is primarily the fasting glucose that is difficult to control. When one insulin injection before bedtime is added in order to bring fasting glucose back to normal, daytime glycaemia can mostly still be kept under control for a significant period of time by means of oral antidiabetics⁹⁴.

Insulin can safely be started as a first-line therapy if a number of ancillary conditions are satisfied (cf. section on Ancillary Conditions)⁹⁵. These ancillary conditions are currently not fully met in Belgium. Thus self-care supplies are not reimbursed for patients in the transition to insulin therapy, or if only one insulin injection per day is required⁹⁶. As soon as the patient needs two injections, reimbursement takes place via the Diabetes Convention⁹⁷.

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- Yki-Järvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomised controlled trial. *Ann Intern Med* 1999;130:389-96.

⁹³ In those cases, with a few full-day glucose curves it is possible to determine at what time(s) of the day the effect of the oral antidiabetics is inadequate. This makes it possible to select the type of insulin and the time of administration. In glitazone therapies, these agents should be stopped beforehand.

⁹⁴ Patients can be started on 8 - 12 U of a moderately fast-acting NPH-insulin (Insulatard® or Humuline NPH®) at bedtime. An alternative is the ultraslow acting insulin analog glargine (Lantus®). It has a flatter action profile, which reduces the risk of hypoglycaemia. It works around the clock, which means that it can be injected at any time. This is particularly useful with older patients receiving injections at home from a home nurse or a family member. Riddle *et al* compared starting NPH versus glargine at bedtime in patients with Type 2 diabetes and inadequate glycaemic control under oral antidiabetics. Both insulins give the same improvement in the HbA1c level, but with significantly less hypoglycaemia when using glargine.

- Riddle M, Rosenstock J, Gerich J. The treat-to-target trial. Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080-6.

However, glargine is more expensive than NPH and is therefore subject to strict reimbursement criteria in Belgium. With one injection per day in combination with oral antidiabetics, in Belgium Lantus is reimbursed only in the following indications:

- for patients with HbA1c >7.5% under the combination of oral antidiabetics with one daily administration of NPH, Ultratard HM, Humuline Long or an insulin mix,
- for patients who have experienced severe hypoglycaemia (requiring third party help) under this combination, and
- to obtain reimbursement extension after 12 months, the HbA1c level must be <7%.

When starting insulin treatment, the NPH or glargine dose should be increased every 2-3 days by 2-4 U based on fasting glucose values. Patients with marked insulin resistance sometimes require very high doses of insulin. Whenever it is necessary to increase the dose very significantly (e.g. >40 U) it is advisable to refer the patient to an internist/diabetologist in order to determine whether a switch to a more complex insulin regimen is necessary.

⁹⁵ The general practitioner must have sufficient knowledge of the profiles of action of the different kinds of insulin. He or she must be able to work together with a nurse or reference nurse specialised in the treatment of diabetics and a dietician in order to provide thorough education for the patient (and/or their entourage). This is especially necessary for patients who wish to administer their own insulin treatment (something which of course should be encouraged as much as possible). These patients must be taught how to inject the insulin, how to check their blood glucose levels and how to adjust their insulin dose on the basis of their blood glucose levels, and be educated about the effects of food, exercise and illness on glycaemia and the prevention and treatment of hypoglycaemia.

- Muller U, Muller R, Starrach A, et al. Should insulin therapy in type 2 diabetic patients be started on an out- or inpatient basis ? Results of a prospective controlled trial using the same treatment and teaching programme in ambulatory care and a university hospital. *Diabetes Metab* 1998;24:251-5.

⁹⁶ Some mutual insurance schemes do reimburse glycaemia test strips within the scope of the free complementary insurance. This varies from region to region.

⁹⁷ Since 1987 Belgium has had what is referred to as a "Diabetes Convention". This is an agreement between the State Institute for Health and Disability Insurance [Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (R.I.Z.I.V.)] and various diabetology centres. These centres can then, under certain conditions, provide people with diabetes with supplies for glucose self-monitoring.

For additional information, please see:

- Wens J. Revalidatieovereenkomst inzake zelfregulatie van diabetes mellitus patiënten (de diabetesconventie). Een vertaling uit het juridische jargon. *Huisarts Nu* 2005(34). In Press.
- Nobels F, Scheen A. Le role des centres de convention du diabète en Belgique. *Rev Med Liège* 2005;60:619-23.

Recently, a possibility to involve a reference nurse when starting insulin as a first-line therapy was provided for⁹⁸. Referral to a specialised service is recommended if in spite of this help insulin cannot be started as first-line therapy in a timely and accurate manner.

Once an insulin regimen is started, it is the responsibility of the GP to monitor the results of the therapy and to adjust the insulin doses if applicable, taking into account patient glycaemia and HbA1c objectives.

Table 6: Types of insulin available

Class	Insulin	Brand name	Action starts in	Peaking after	Active period
Ultrafast	lispro insulin	Humalog	5-15 min.	1 hr	3-5 hrs
	aspart insulin	Novorapid	5-15 min.	1 hr	3-5 hrs
Fast	regular insulin	Actrapid	20-30 min.	2 hrs	6-8 hrs
		Humuline Regular	20-30 min.	2 hrs	6-8 hrs
Intermediate	NPH suspension	Insulatard	1-2 hrs	4-6 hrs	10-18 hrs
		Humuline NPH	1-2 hrs	4-6 hrs	10-18 hrs
Slow	zinc suspension	Monotard	1-2 hrs	4-6 hrs	10-18 hrs
		Ultratard	4 hrs	6-8 hrs	20-24 hrs
Ultraslow	glargine insulin	Lantus	2 hrs	none	24 hrs
		Levemir	2 hrs	3 to 4 hrs	18-24 hrs
Combinations*	regular + NPH	Humuline ^{30/70}			
		Humuline ^{50/50}			
		Mixtard ¹⁰			
		Mixtard ²⁰			
		Mixtard ³⁰			
		Mixtard ⁴⁰			
		Mixtard ⁵⁰			
	aspart + aspart-protamine NPL	Novomix ³⁰			

* In the combinations, the first figure in the brand name indicates the percentage of fast action insulin.

In Belgium, insulin preparations contain 100 IUs insulin per ml. The presentation is in vials for administration with insulin syringes or pumps, cartridges (or pen refills) for insulin pens or insulin pumps, and pre-filled disposable pens.

6.3. Instructions for the correct use of insulin⁹⁹

6.3.1. Storage of insulin

Unopened packages of insulin can be stored in a cool place (i.e. between 2 and 8°C) for a minimum of three years. Insulin, regardless of type, must not be frozen; when flying, it is recommended to take insulin in the hand luggage since the temperature tends to fall below freezing in airplane holds. Once a cartridge is introduced into a pen, it can be used for up to four weeks after installation. An insulin preparation that is in use is best not repeatedly placed in the refrigerator in order to prevent temperature fluctuations.

6.3.2. Administration of insulin

Insulin is injected subcutaneously into the arm, leg, buttocks or abdomen. Resorption speed is determined among other things by the vascularisation of the part of the body into which the injection is made, and is highest in the abdomen, lower in the buttocks, and lower still in the arm or leg. Insulin is best not injected into moles, birthmarks or scars. The suspension must be homogeneous at the time of withdrawing the suspension. The consistency of the suspension must be homogeneous at the time of withdrawing the

⁹⁸

desired amount of insulin. When an insulin mixture, e.g. 30/70, is not sufficiently homogenised prior to administration, there will be a significant difference in the effect of the first and the last few millilitres of the contents of the vial. Insulin can be homogenised by agitating by inversion of the vial or pen at least ten times; standard shaking is not enough. In performing the injection, after having fully depressed the plunger of the syringe, it is necessary to wait for 5 to 10 seconds before withdrawing the needle to ascertain that all units have been injected.

6.3.3. Changing the injection site

In the administration of insulin it is important to change the injection site each time. In particular with the slower-acting drugs, lipodystrophy can develop if the same injection site is used too often. Injection into skin areas in which this symptom appears should be avoided for a few months.

6.3.4. Needle length

Given that the thickness of the skin of the abdomen, arms and legs varies, it can be useful to adapt the length of the needle employed accordingly. The desired needle length can be determined by taking a loose skin fold between thumb and forefinger to determine its thickness; the appropriate needle length is approximately half of this thickness.

6.3.5. Disinfecting the skin

Disinfecting the skin is not necessary. It should, however, be clean.

6.3.6. Changing the needle

There are different schools of opinion in regard to changing the needle when using insulin pens. Officially, it is recommended to use a new needle for each injection. On the other hand it is also posited that with multiple injections per day, using just one needle is acceptable.

6.4. Administration using an insulin pen

The injection pen represents a simplification of the administration of insulin as it eliminates the need to perforate the vial. Pens are available under various different brand names. There are also pre-filled, disposable pens; the user merely needs to mount the needle on them. Not all insulins are appropriate for use in a pen; thus, for instance, insulin preparations that contain zinc are not suitable for use with this injection method.

Table 7. Insulin pen brand names

Humapen:	Suitable for all 3 ml pen charges produced by Lilly: Humuline (regular, NPH and mixtures) and Humalog
Novopen 3:	Suitable for all 3 ml pen charges produced by Novo: Actrapid, Insulatard, Novorapid, Levemir, and Mixtard mixtures.
Optipen Pro 1:	Suitable for use with Lantus products
Autopen 24:	Suitable for all 3 ml pen charges produced by Lilly (see above) and for Lantus products. The pen exists in 2 versions, one releasing 1 U, and another releasing 2 U per click.

This range of pens is regularly updated

7. MONITORING RISK FACTORS TO PREVENT CARDIOVASCULAR COMPLICATIONS

Cardiovascular conditions¹⁰⁰ are the most significant cause of morbidity and mortality in Type 2 diabetes patients¹⁰¹. As compared to non-diabetes patients, Type 2 diabetes patients are at two to four times higher risk of death from cardiovascular causes¹⁰². In a Finnish cohort study (7-year follow-up) the risk of experiencing myocardial infarction in Type 2 diabetes patients without a prior history of coronary conditions was the same as in non-diabetes patients with a prior history of coronary conditions¹⁰³. In acute vascular conditions there is often a significant diabetic dysfunction that is, in turn, associated with a poorer prognosis¹⁰⁴.

Most Type 2 diabetes patients are at high risk of cardiovascular conditions¹⁰⁵ and this means that with most patients an aggressive approach to the cardiovascular risk factors is indicated in addition to treating the hyperglycaemia.

¹⁰⁰ Cardiovascular disease usually includes: coronary heart disease (angina, myocardial infarction), cerebrovascular events (TIA, CVA) and peripheral vascular disease (claudication, gangrene, vascular impotence).

¹⁰¹ Diabetes is in itself an independent risk factor for macrovascular disease. In addition, other risk factors for cardiovascular disease are more often seen in Type 2 diabetes patients within the scope of metabolic syndrome. Other factors such as smoking, sedentary lifestyle and cardiovascular disease in first-degree relatives additionally increase the risk. Furthermore, the risk increases with age and the duration of the diabetes. Microalbuminuria is an important risk marker for cardiovascular disease and is associated with a two to three times higher risk of cardiovascular morbidity and mortality.

- Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin-dependent diabetes mellitus (UKPDS 23). *BMJ* 1998;316:823-28.
- Dinneen SF, Gerstein HC The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus : a systematic review of the literature. *Arch Intern Med* 1997;157:1413-8.
- Valmadrid CT, Klein R, Moss SE, et al. The risk of cardiovascular disease associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Int Med* 2000;160:1093-100.

¹⁰²

- Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971-1993. *Diabetes Care* 1998; 21: 1138-45.
- Koskinen SV, Reunanen AR, Martelin TP, et al. Mortality in a large population-based cohort of patients with drug-treated diabetes mellitus. *Am J Public Health* 1998; 88: 765-70.
- Gatling W, Tufail S, Mullee MA, et al. Mortality rates in diabetic patients from a community-based population compared to local age/sex matched controls. *Diabet Med* 1997; 14: 316-20.
- Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-44.

¹⁰³ Haffner SM, Lehto S, Ronnema T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-34.

¹⁰⁴ Clement S, Braithwaite S, Magee M, Ahmann A, Smith E, Schafer R, Hirsch I. Management of diabetes and hyperglycemia in hospitals. *American Diabetes Association Technical Review. Diabetes Care* 2004;27:553-91.

¹⁰⁵ Different risk tables calculate an estimation of either the overall cardiovascular risk (coronary and vascular, morbidity and mortality), or of the risk of coronary pathology (morbidity and mortality), or else cardiovascular mortality. The incidence of coronary pathology is much greater than that of the other cardiovascular conditions. It is assumed that the coronary risk is three to four times higher than the overall cardiovascular risk.

- Chevalier P. Evaluatie van het cardiovasculaire risico: de verschillende risicotabellen doorgelicht. *Minerva* 2004;3:36-40.

The consensus gives the following definition for "high risk": A risk of >20% of a cardiovascular incident in the next 10 years. Type 2 diabetes patients with a prior history of cardiovascular disease are always at significantly higher risk. There are no good tables available for the calculation of risk in patients without a prior history of cardiovascular disease. The recent SCORE tables do not apply to diabetes patients.

- Conroy R, Pyorola K, Fitzgerald A et al. SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24:987-1003.

In the European Task Force all Type 2 diabetes patients are considered to be a high risk group.

- De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European Guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on cardiovascular disease prevention in clinical practice.(constituted by representatives of eight societies and by invited experts. *Atherosclerosis* 2004;173:381-91.

There is also convincing evidence that a strict approach to cardiovascular risk factors can prevent or delay the onset of cardiovascular conditions in Type 2 diabetes patients¹⁰⁶.

7.1. Managing cardiovascular risk

Approaches to cardiovascular risk are always multifactorial, addressing both the prevention of cardiovascular disease and the early detection of existing complications¹⁰⁷.

This approach always involves the following elements:

- Smoking cessation
- Seeking an achievable weight reduction for patients who are overweight or obese
- Stimulating physical activity
- Starting a statin (unless there are no additional cardiovascular risk factors)¹⁰⁸
- Trying to achieve optimal blood pressure
- Trying to achieve optimal blood glucose levels
- Considering starting acetylsalicylic acid

The approach is designed to manage all these risk factors in each diabetes patient, but always on an individual basis. Seeking to accomplish individually achievable and flexible goals helps prevent demotivation in both doctor and patient, which would result in the patient no longer undergoing optimal treatment.

The Diabetes Passport is a useful instrument to analyse the “controllable” cardiovascular risk factors with the patient and to agree on achievable targets. We are recommending repeating this analysis on an annual basis. In determining patient goals it is important to emphasise that every accomplishment, no matter how small, will result in significant advantages¹⁰⁹.

To calculate cardiovascular risk in diabetes it is possible to use the “UKPDS risk meter” available for downloading from (www.dtu.ox.ac.uk/riskengine). This useful tool calculates an individual’s risk of experiencing (fatal) coronary disease and (fatal) CVAs on the basis of gender, age, ethnicity, smoking status, whether or not atrial fibrillation is present, HbA1c values, systolic blood pressure, total cholesterol and HDL cholesterol.

- Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus. (UKPDS 23) *BMJ* 1998;316:823-28.
- Stevens RJ, Kothari V, Adler AL, et al. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes. (UKPDS 56) *Clinical Science* 2001;101:671-9.

¹⁰⁶ Sigal RJ, Malcolm JC, Meggison HE. Prevention of cardiovascular events in diabetes. *BMJ Publishing Group. Clinical Evidence*. 2005 edition. www.clinicalevidence.com

¹⁰⁷ The importance of a multifactorial approach is confirmed by the Steno-2 study in Type 2 diabetes with microalbuminuria. In this study, an intensive multifactorial approach (n = 80) was compared with a more conventional approach in general practice (n=80). The intervention consisted of behavioural changes (diet, exercise, smoking cessation) and step-by step pharmacotherapy for the various risk factors, targeting strict treatment goals. The intensive approach was associated with a 50% relative reduction in the risk of cardiovascular complications.

- Sunaert P, Feyen L. Steno-2 studie: multifactoriële aanpak bij diabetes type 2. *Minerva* 2004;3:11-4. Interpretation of: Gaede P, Vedel P, Larsen N et al. Multifactorial Intervention and Cardiovascular Disease in Patiënts with Type 2 Diabetes. *N Engl J Med* 2003;348:383-93.

¹⁰⁸ In Type 2 diabetes statins are always started, even in lipid profiles that would until recently have been considered to be favourable. This rule may be diverged from only if the patient has no additional risk factors. These additional risk factors are: hypertension, smoking, microalbuminuria and retinopathy.

- Sunaert P, Christiaens T, Feyen L. Statinen voor alle diabetespatiënten? *Minerva* 2005;4:87-9 Interpretation of: Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685-96.
- Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004;363:757-67.
- M. Lemiengre. Statines en cardiovasculaire preventie : de ‘Heart Protection Study’. Interpretation of: Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.

¹⁰⁹ All the risk factors exponentially increase the risk. In the steep portion of the curve, a small improvement results in a significant risk reduction.

7.1.1. Smoking cessation

Smoking increases the risk of cardiovascular morbidity and mortality in diabetes patients¹¹⁰. Even second-hand smoke is a significant and avoidable cause of ischaemic heart disease¹¹¹.

Stopping smoking is therefore an important measure for diabetes patients in order to reduce their cardiovascular risk¹¹².

Smoking cessation counselling begins with a clear and personal recommendation from the treating physician. At this time, only very few patients have the feeling that they are clearly being asked to stop smoking. There are different methods to help smokers succeed in the cessation process¹¹³.

Smoking cessation counselling must be followed by ongoing support, ideally including the patient's immediate entourage.

7.1.2. Pursuit of an achievable weight reduction for patients who are overweight or obese

Weight reduction is an important treatment goal in cases where the patient is overweight or obese¹¹⁴. A body weight reduction of 5 to 10% is considered to be an achievable goal. Moderate weight loss improves glycaemia, HbA1c and the cardiovascular risk profile¹¹⁵. Long-term maintenance of the weight loss is more

¹¹⁰ Data concerning the relationship between smoking and cardiovascular disease in diabetes patients were obtained from observational studies. Smoking also increases the risk of microvascular complications. Furthermore, smokers are at greater risk of developing Type 2 diabetes mellitus, probably because of an increase in insulin resistance.

- Sigal RJ, Malcolm JC, Meggison HE. Prevention of Cardiovascular events in diabetes. BMJ Publishing Group Ltd. Clinical Evidence, 2005 edition. (update 20040501).
- Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes (Technical Review). Diabetes Care 1999;22:1887-98.

¹¹¹ Passive smoking increases the risk of coronary disease at age 65 by approximately 25%.

- Law MR, Morris JK, Wald NJ Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. BMJ 1997;315:973-80.

¹¹² According to evidence from observational studies, smoking cessation in non-diabetes patients is effective. No specific RCTs have been carried out about smoking cessation in diabetes patients. However, the effect of smoking cessation is at least as effective as in non-diabetes patients.

- US Department of Health and Human Services. The health benefits of smoking cessation: a report of the surgeon general. Bethesda, Maryland: US DHSS; 1990.
- Al-Delaimy WK, Manson JE, Solomon CG, et al. Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. Arch Intern Med 2002;162:273-9.
- Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med 2000;160:939-944.
- Pignone M, Rihal CS, Bazian Ltd. Secondary prevention of ischaemic cardiac events. BMJ Publishing Group Ltd. Clinical Evidence, 2005 edition. (update 20040501).

¹¹³ Hoengenaert JP. Aanbeveling voor goede medische praktijkvoering: Stoppen met roken. Huisarts Nu 2001; 30:242-54.

¹¹⁴ Obesity is an independent risk factor for hypertension, hyperlipidaemia and cardiovascular disease.

- Klein S, Sheard NF, Pi-Sunyer X, et al. Weight Management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. Diabetes Care 2004;27:2067-73.

In a prospective cohort study in 4970 obese diabetes patients with a 12-year follow-up period, a moderate weight loss (10 to 15% of baseline weight) was paired with a 25% reduction in total mortality (RR = 0.75, 95% CI = 0.67-0.84), and a 28% reduction in the cardiovascular risk and diabetes related mortality (RR = 0.72, 95% CI = 0.63-0.82).

- Williamson DF, Thompson TJ, Thun M, et al. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care 2000;23:1499-504.
- Van Gaal L, Wauters M, De Leeuw I. The beneficial effects of modest weight loss on cardiovascular risk factors. Int J Obes Relat Metab Disord 1997;21: 5-9.

important than initial slimming¹¹⁶. As regards the treatment of obesity, please refer to the relevant recommendation¹¹⁷.

7.1.3. Stimulating physical activity

An increase in physical activity goes hand in hand with a reduction of cardiovascular risk. The goal is to do 30 to 45 minutes' moderate physical activity on most days of the week¹¹⁸. Such physical activity is best built into the daily routine (e.g. walking)¹¹⁹.

Physical exercise is also an important component of the weight reduction programme. While a limitation in calorie consumption primarily contributes to an initial weight loss, regular physical effort helps maintain the weight loss and prevent new gain.

7.1.4. Starting a statin unless there are no attendant cardiovascular risk factors

Lipids control is an implicit component of the follow-up of diabetes patients. It is recommended that the values of cholesterol (both HDL and LDL cholesterol) and triglycerides in blood be measured on an annual basis. Fasting blood samples are required. Diabetes patients have a strong post-prandial rise in the level of triglycerides, which also increases their cholesterol levels¹²⁰. LDL and HDL cholesterol are independent risk factors for coronary disease in diabetes patients too¹²¹.

Treatment with a statin, aimed at reducing LDL cholesterol, significantly lowers cardiovascular risk both in patients with and without a history of cardiovascular disease¹²². The reduction takes place regardless of the

¹¹⁶ The chances of permanent success are increased with a diet low in calories (\pm 1400 Kcal/day) and fats (24% of total energy intake), if body weight is regularly checked, and if regular physical effort can be performed. People who were able successfully to reduce their weight reduced the size of their portions and the number of snacks, ate breakfast on a daily basis, ate out less than three times per week and watched TV for less than three hours per week on average.

- Jakicic JM, Winters C, Lang W, Wing RR: Effects of intermittent exercise and use of home exercise equipment on adherence, weight loss, and fitness in overweight women: a randomized trial. *JAMA* 1999;282:1554–60.
- Wing RR, Hill JO: Successful weight loss maintenance. *Annu Rev Nutr* 2001;21:323–341.

¹¹⁷ WVVH [Flemish association of GPs] Guidelines for Good Medical Practice. Treating obesity. 2005. In Press.

¹¹⁸ The lack of physical activity is an independent risk factor for cardiovascular disease. Observational studies demonstrate that regular physical activity reduces cardiovascular risk in Type 2 diabetes patients. Physical activity protects both directly and indirectly (by reducing lipids, blood pressure and overweight) against cardiovascular disease. The effect is “dose related”. The favourable effects of physical activity on cardiovascular risk can probably be explained by means of an effect on insulin sensitivity.

- American Diabetes Association Physical Activity/Exercise and Diabetes. *Diabetes Care* 2004;27:S58-62.
- Tanasescu M, Leitzmann MF, Rimm EB, et al. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation* 2003;107:2435-9.

¹¹⁹ Gregg EW, Gerzoff RB, Caspersen CJ, et al. Relationship of walking to mortality among US adults with diabetes. *Arch Intern Med* 2003;163:1440-7.

¹²⁰ The most frequently occurring lipid pattern in Type 2 diabetes patients consists in elevated triglycerides and low HDL cholesterol. The LDL cholesterol values do not usually differ much from those of non-diabetes patients, so that the dyslipidaemia does not seem so “serious” at first sight. Insulin resistant Type 2 diabetes patients however often have smaller, dense LDL particles (‘small dense LDL’) that are highly atherogenic. These particles are not identified in clinical laboratory tests. It can be assumed that they are present in elevated levels in hypertriglyceridaemia. This abnormality in the lipid profile can be the result of inadequate glycaemic control. Better glycaemic control usually significantly lowers triglyceride values but generally has little effect on LDL and HDL cholesterol values.

¹²¹ Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus (UKPDS 23). *BMJ* 1998;316:823-8.

¹²² A meta-analysis of 6 primary prevention studies demonstrates that the use of lipid lowering medication reduces the risk of cardiovascular endpoints in Type 2 diabetes patients. The absolute risk reduction was 0.03 (95% CI 0.01-0.04) after 4.3 years of treatment; 34 to 35 patients must be treated for 4.3 years in order to prevent one cardiovascular endpoint in primary prevention. A meta-analysis of eight studies in secondary prevention

initial lipid values, i.e. also in lipid profiles that would normally be considered to be favourable. In considering whether to start a statin the patient's overall risk profile therefore carries more weight than the lipid values themselves¹²³. This means that most Type 2 diabetes patients will be started on a statin¹²⁴.

At the moment there is insufficient evidence as to the target values to be favoured. Goals are set by consensus. When a statin treatment is started within the scope of a lipids disorder, the currently proposed LDL cholesterol value is <100 mg/dl. In secondary prevention, it is argued that the target value should be <70 mg/dl¹²⁵.

There are no treatment goals for HDL cholesterol and triglycerides, but these values are nonetheless used to help evaluate cardiovascular risk¹²⁶.

Increased triglycerides and low HDL cholesterol are initially approached via diet recommendations, physical exercise and optimisation of glucose control. On the pharmacological level, fibrates are more effective than statins as concerns triglycerides and HDL cholesterol. However, there are no large randomised studies of diabetes patient populations examining the effect of these products on hard endpoints. For this reason the use of statins should be a preferred choice in the treatment of Type 2 diabetes at increased cardiovascular risk¹²⁷.

In the event of complaints and symptoms that could be indicative of muscle involvement, after starting a statin or fibrate it is advisable to determine the creatinine kinase (CK) level within the scope of a myopathy or rhabdomyolysis. The treatment should be suspended if CK levels reach a point greater than five times the

demonstrates an absolute risk reduction of 0.07 (95% CI 0.03 - 0.12) after 4.9 years of treatment; 13 to 14 diabetes patients must be treated for 4.9 years in order to prevent one cardiovascular endpoint in secondary prevention.

- Vijan S, Hayward RA. Pharmacologic Lipid-Lowering Therapy in Type 2 Diabetes Mellitus: Background Paper for the American College of Physicians. *Ann Intern Med* 2004;140:650-8.

¹²³ The Heart Protection Study and the CARDS study deliver evidence for the fact that this risk reduction is also found in primary prevention, independently of the initial LDL cholesterol values, and that it is also present in cholesterol values that had until now been considered as being "normal".

- Heart Protection Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5693 people with diabetes: a randomised controlled trial. *Lancet* 2003;361:2005-16.
- Lemiengre M. Statines en cardiovasculaire protectie. *Minerva* 2003; 2:8-13. Interpretation of: Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
- Sunaert P, Christiaens T, Feyen L Statinen voor alle diabetespatiënten? *Minerva* 2005;4:87-9 Interpretation of: Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685-96.

¹²⁴ This certainly applies to all patients with a prior history of cardiovascular disease (secondary prevention). It also applies to patients without a prior history of cardiovascular disease (primary prevention) in the presence of one or more of the following risk factors: hyperlipidaemia, hypertension, smoking, microalbuminuria, retinopathy.

¹²⁵ The American Diabetes Association (ADA) reports targeting LDL cholesterol values <70 mg/dl in patients at high risk of cardiovascular disease with high doses of statins as an option.

- American Diabetes Association Standard of Medical Care in Diabetes. *Diabetes Care* 2005;28:S4-36. Some studies have tested out working with these targets in a population with prior history of coronary disease, including a minority of patients with Type 2 diabetes.
- Cannon CP, Braunwald E, McCabe CH, et al. The PROVE IT study. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. *N Engl J Med* 2004;350:1495-1504.
- LaRosa JC, Grundy SM, Waters DD, et al. The Treating to New Targets (TNT) Study. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. *N Engl J Med* 2005;352:425-35.

¹²⁶ HDL cholesterol values of <40 mg/dl in men and <46 mg/dl in women indicate increased risk. With triglycerides, increased risk starts at fasting values ≥150 mg/dl.

- De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European Guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on cardiovascular disease prevention in clinical practice.(constituted by representatives of eight societies and by invited experts. *Atherosclerosis* 2004;173:381-91.

¹²⁷ Statins giving the most significant LDL reduction also have the greatest effect on cardiovascular risk reduction.

normal value¹²⁸. Determining the CK level in patients without muscle complaints is not productive, except in patients at increased risk already prior to starting the statin.

In starting a statin and/or a fibrate it is also recommended to check liver function. The treatment should be suspended if transaminases increase to reach three times the normal level.

7.1.5. Trying to achieve optimal blood pressure

Blood pressure control is another essential component of the follow-up of Type 2 diabetes patients¹²⁹. It is recommended to check blood pressure every three months. At present, there is convincing evidence that keeping a tight control on blood pressure significantly reduces the risk of cardiovascular morbidity and mortality in Type 2 diabetes patients. This also applies to patients with isolated hypertension and to older diabetes patients¹³⁰.

International recommendations currently advocate consensus target blood pressure values of <130 mmHg systolic and <80 mmHg diastolic¹³¹. The lowest attainable systolic value can be aimed for, as there is no threshold value under which there are no further complications. Diabetes complications systematically increase along with an increase in systolic blood pressure¹³². Evidence that a diastolic blood pressure of ≤ 80 mmHg is desirable is provided by the results of the HOT study¹³³.

¹²⁸ Gecommentarieerd geneesmiddelenrepertorium 2004 [Annotated Therapeutic Drug Index 2004], p. 63-64. Folia farmacotherapeutica, September 2001 and July 2002. (www.bcfi.be).

¹²⁹ Hypertension is found 1.5 to 3 times more frequently in Type 2 diabetes patients than in non-diabetes patients and is often already present at the time of diagnosis. In Type 2 diabetes patients, the presence of hypertension significantly increases the risk of macrovascular and microvascular complications. Strict treatment of blood pressure is therefore an important aspect of the treatment of Type 2 diabetes.

¹³⁰ In the UKPDS study, strict blood pressure treatment (target values <150/85 mmHg versus <180/105 mmHg) lowered the risk of diabetes related mortality by 32% and that of a CVA by 44%. The risk of myocardial infarction was reduced by 21% but this reduction was not significant.

- Vermeire E. Strikte bloeddrukcontrole bij diabetes type 2 patiënten. Huisarts Nu (Minerva) 1999;28:129-30. Interpretation of: The UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes : UKPDS 38. BMJ 1998; 317:703-13.
- De Cort P. Behandeling van Hypertensie. Huisarts Nu (Minerva) 1999;27:322-5. Interpretation of: Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-62.
- Curb JD, Pressel SL, Cutler JA, et al. Effect of a diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension: Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA 1996;276:1886-92.
- De Cort P. Calciumantagonisten bij hypertensieve diabetes. Huisarts Nu (Minerva) 2000;29(7):330-1. Interpretation of: Tuomilehto J, Rastenyte D, Birkenhäger W H, et al. The Systolic Hypertension in Europe Trial Investigators Effects of calcium channel blockade in older patients with diabetes and systolic hypertension. N Eng J Med 1999;340:677-84.

¹³¹

- American Diabetes Association. The Treatment of Hypertension in Adult Patients With Diabetes. Diabetes Care 2003; 26: S80-82.
- De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European Guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts. Atherosclerosis. 2004;173:381-91.

¹³² Epidemiological analysis of the UKPDS data demonstrates that for every 10 mmHg reduction in systolic blood pressure the risk of diabetes related mortality fell by 15%, the risk of suffering a CVA by 19% and the risk of myocardial infarction with 11%.

- Wens J. Bloeddruk en het risico op complicaties bij diabetes type 2. Interpretation of: Adler AI, Stratton IM, Haw, N, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321: 412-19. Huisarts Nu (Minerva) 2001;30:134-7.

¹³³ In this study, a group of diabetes patients with target blood pressure values ≤ 80 mmHg was compared with groups with target values of ≤ 85 mmHg and ≤ 90 mmHg. At the lowest blood pressure levels there was a 50% reduction in the risk of cardiovascular complications.

At first, non-medication measures are implemented for high blood pressure: weight reduction, exercise, smoking cessation, moderate salt limitation and moderate alcohol consumption. There is no evidence in regard to these measures as applied to diabetes patients. In patients with essential hypertension, however, it has been sufficiently proven that these measures are effective in lowering blood pressure¹³⁴.

If non-drug measures fail, it is necessary to start pharmacotherapy. ACE inhibitors, diuretics, β -blockers and calcium antagonists significantly lower cardiovascular mortality and morbidity in hypertensive diabetics¹³⁵. The different classes described above all have approximately the same blood pressure lowering effect, i.e. an expected average blood pressure reduction of 10 to 20%. There are no good long-term studies available on the effect of alpha blockers and antihypertensive drugs with central action.

Patients with micro-albuminuria should be started on an ACE inhibitor. If the therapy is not well tolerated, the patient should be started on an angiotensin-II-receptor antagonist because these types of drug inhibit the progression of nephropathy¹³⁶.

Standard indications and contra-indications apply in selecting whether or not to start the patient on a specific class. Please refer to the subject specific recommendations on hypertension¹³⁷.

Monotherapy is often not enough to attain optimal blood pressure target values. In such cases, a combination of different classes will be necessary¹³⁸. Whether the target value is attained will depend on a number of different factors, e.g. the starting blood pressure and the appearance of side effects (e.g. orthostatic hypotension).

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- De Cort P. Behandeling van hypertensie. Huisarts Nu (Minerva) 1999;27(3):322-5. Interpretation of: Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-62.

¹³⁴ De Cort P, Philips H, Govaerts F, et al. Aanbeveling voor goede medische praktijkvoering: Hypertensie. Huisarts Nu 2003;32:387-411.

¹³⁵

- Sigal RJ, Macolm JC, Meggison HE. Prevention of Cardiovascular events in diabetes. BMJ Publishing Group Ltd. Clinical Evidence, edition 2005. (Update 20040501)
- Vijan S, Hayward RA. Treatment of Hypertension in Type 2 Diabetes Mellitus: Blood Pressure Goals, Choice of Agents, and Setting Priorities in Diabetes Care. Ann Intern Medicine 2003;138:593-602.
- Arauz-Pacheco C, Parrott MA, Raskin P. The Treatment of Hypertension in Adult Patients With Diabetes. Technical Review Diabetes Care 2002;25, 134-47.
- Staessen JA, Wang J, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001;358:1305-15.

¹³⁶ As compared to placebo and certain other antihypertensives, both ACE inhibitors and angiotensin receptor (AR) antagonists scored as having greater efficacy as regards the progression of nephropathy: doubling creatinaemia, proteinuria and/or of the time to the development of terminal kidney failure.

- Breyer JA, Hunsicker LG, Bian R, et al. Angiotensin converting enzyme inhibition in diabetic nephropathy. The Collaborative Study Group. Kidney International Supplement 1994;45:156-60.
- Verpooten GA, Tomas MCF. De rol van sartanen bij diabetische retinopathie. Huisarts Nu (Minerva) 2002;31:363-69. Interpretation of: Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.
- Verpooten GA, Tomas MCF. De rol van sartanen bij diabetische retinopathie. Huisarts Nu (Minerva) 2002;31:363-69. Interpretation of: Parving HK, Lehnert H, Brochner-Mortensen J, et al The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.
- Barnett AH; Bain SC; Bouter P; Karlberg B; Madsbad S; Jervell J; Mustonen J. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004; 351: 1952-57.

¹³⁷ De Cort P, Philips H, Govaerts F. Aanbeveling voor goede medische praktijkvoering: Hypertensie Huisarts Nu 2003;32:387-411.

¹³⁸

- In the UKPDS study, 29% of the patients in the group with blood pressure values <150/85 mmHg required three or more drugs; only 56% of the strictly monitored group actually achieved a value <150/85 mmHg.
- Vermeire E. Strikte bloeddrukcontrole bij diabetes type 2 patiënten. Huisarts Nu (Minerva) 1999;28:129-30. Interpretation of: UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.

7.1.6. Trying to achieve optimal blood glucose levels

Evidence for the relationship between glycaemic control and cardiovascular diseases is primarily found in observational studies. The relationship between hyperglycaemia and macrovascular complications is not as strong as the relationship with microvascular complications¹³⁹.

In obese patients, strict glycaemic control with metformin leads to more significant risk reduction for diabetes related endpoints than a treatment with sulfonylureas or insulin, perhaps because this product provides additional cardiovascular protection by lowering insulin resistance¹⁴⁰.

7.1.7. Acetylsalicylic acid

Platelet aggregation disorders are often found in Type 2 diabetes patients. The platelets of diabetes patients are hypersensitive to platelet aggregation substances. The most important factor is probably an increased production of thromboxanes. Aspirin blocks the formation of thromboxanes.

There is evidence that the intake of low doses of aspirin in secondary prevention and in high-risk patients reduces the risk of cardiovascular disease. The positive effect of aspirin is however less pronounced in diabetes patients than in non-diabetics¹⁴¹.

Based on current evidence we would advise an aspirin derivative in low doses (75-100 mg) in Type 2 diabetes patients in secondary prevention. More data is required before aspirin use can generally be recommended to diabetes patients in primary prevention¹⁴².

¹³⁹ No significant reduction in cardiovascular risk could be demonstrated in the tightly controlled group of the UKPDS 33 study. Epidemiological analysis of the UKPDS data demonstrates that for every 1% HbA1c reduction, diabetes related mortality fell by 21%, and the risk of myocardial infarction by 14%.

- Wens J. Intensieve behandeling van diabetes type 2 patiënten. Huisarts Nu (Minerva) 1999;28:125-6. Interpretation of: UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) Lancet 1998;352:837-53.
- Wens J. Glycemie en vasculaire complicaties bij diabetes type 2 (UKPDS 35). Interpretation of: Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:412-9. Huisarts Nu (Minerva) 2001;30:132-4.

¹⁴⁰ The addition of metformin to a sulfonylureas therapy (in obese and non-obese patients) on the other hand was paired with an increase in both overall mortality and in diabetes related mortality. A long-term evaluation will be required to provide greater clarity in this regard.

- Wens J. Intensieve behandeling van obese diabetes type 2-patiënten. Huisarts Nu (Minerva) 1999;28:127-8. Interpretation of: UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-65. Erratum in: Lancet 1998;352:1557.

¹⁴¹ In a meta-analysis of studies of the effect of aspirin on cardiovascular disease in secondary prevention and in high risk patients, the use of aspirin reduced the risk of cardiovascular disease in the total group by 22%; in the diabetes patient group the reduction was only 7% (not significant). To date there exists no clear evidence to indicate that aspirin would be any less effective in diabetes patients.

- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
- Sigal RJ, Malcolm JC, Meggison HE. Prevention of cardiovascular events in diabetes. BMJ Publishing Group Ltd. Clinical Evidence, 2005 edition. (update 20040501).

The PPP trial could not demonstrate any efficacy for a low dose of aspirin in diabetes patients without a prior history of cardiovascular disease.

- Sacco M, Pellegrini F, Roncaglioni MC, et al. Primary Prevention of Cardiovascular Events With Low-Dose Aspirin and Vitamin E in Type 2 Diabetic Patients: Results of the Primary Prevention Project (PPP) trial Diabetes Care 2003;26:3264-72.

¹⁴² At present there is no evidence to recommend any specific aspirin dose. Most studies used an aspirin dose between 75 and 325 mg per day. The use of the lowest possible dose can help prevent side effects.

- American Diabetes Association. Aspirin Therapy in Diabetes (position statement). Diabetes Care 2004;27:72-3.
- Standards of medical care in diabetes. Diabetes Care 2005;28:17.

Treatment with acetylsalicylic acid does not increase the risk of vitreous body or retinal bleeding¹⁴³. The contraindications for aspirin treatment include allergy, bleeding diathesis, anticoagulation therapy, recent gastro-intestinal bleeding and clinically active liver disease. There is insufficient evidence to indicate that other anti-aggregants such as clopidogrel are safer, although clopidogrel is perhaps just as safe and effective as acetylsalicylic acid¹⁴⁴. A combination of acetylsalicylic acid and clopidogrel increases the risk of major bleeding in patients recently having experienced an ischaemic CVA or TIA and who have at least one other cardiovascular risk factor¹⁴⁵.

7.2. Early detection of cardiovascular disease

Looking for symptoms¹⁴⁶ of vascular disease and clinical signs of vascular problems (pulsations, vascular murmurs) is part of the routine check-up to be practiced on diabetes patients. However, many diabetes patients develop signs of “silent ischaemia” without any classical angina symptoms. Therefore, asking the patient about “angina equivalents” such as marked shortness of breath or nausea with effort should be systematically undertaken.

We recommend an “at rest” ECG upon diagnosis of Type 2 diabetes mellitus. This test can be useful as a reference point in the event of later heart complications. The evidence available at the moment is insufficient in order to repeat an at-rest ECG on an annual basis in all diabetes patients.

There are no validated data available on the usefulness of systematic screening with technological resources (duplex, stress ECG, etc.) for asymptomatic vascular disease in diabetes patients. Such tests are recommended only when there is a clinical presumption of the existence of this type of disease.

¹⁴³ Chew EY, Klein ML, Murphy RP, et al. Effects of aspirin on vitreous/preretinal hemorrhage in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report no. 20. Arch Ophthalmol 95;113:52-5.

¹⁴⁴ Pignone M, Rihal CS, Bazian Ltd. Secondary prevention of ischaemic cardiac events. BMJ Publishing Group Ltd. Clinical Evidence, 2005 edition. Update 20040501.

¹⁴⁵ Boagert M. Aspirine toevoegen aan clopidogrel in secundaire preventie? Minerva 2005;4:73-5. Interpretation of: Diener H, Bogousslavsky J, Brass LM, et al. on behalf of the MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2005;364:331-7.

¹⁴⁶ Ischaemic heart disease can often present atypically in people with diabetes (fatigue, dyspnoea and/or nausea with effort), or develop asymptotically due to neuropathy. With peripheral vascular disease there is often damage to the peripheral fine arteries, which frequently makes vascular surgery difficult or impossible. A Doppler examination of the lower limbs can sometimes return false-positive pressures in diabetes patients due to medial calcifications.

8. ACUTE AND CHRONIC COMPLICATIONS (detection and treatment)

8.1. Acute complications

8.1.1. Hypoglycaemia

Diagnosis

Hypoglycaemia is due to an excessive level of insulin in blood and results in exceptionally low glucose values. Hypoglycaemia is defined as an event in which the typical symptoms of hypoglycaemia are combined with a plasma glucose concentration of ≤ 70 mg/dl (3.9 mmol/l)¹⁴⁷.

The symptoms are of both adrenergic and neuroglycopenic nature. Adrenergic symptoms include, among others, perspiration, shivering and palpitations. Neuroglycopenic phenomena include concentration problems, behavioural disorders, changes in consciousness and, ultimately, coma. The adrenergic disorders can be masked by the use of some drugs such as β -blockers.

In older patients, hypoglycaemia occasionally manifests in an unusual manner such as temporary paresis, CVA-like clinical symptoms, behavioural disorders or confusion. These neuroglycopenic pictures can sometimes be very misleading.

Hypoglycaemia significantly occurs exclusively in patients taking sulfonylureas, glinides or insulin. When the treatment consists exclusively of diet, metformin, glitazones or alpha-glucosidase inhibitors, the risk of hypoglycaemia is more negligible.

Because most Type 2 diabetics have insulin resistance, they are less at risk of hypoglycaemia than Type 1 diabetics (who are generally highly sensitive to the action of exogenously administered insulin). For this reason, with Type 2 diabetes it is generally possible to aim for stricter glycaemic control than with Type 1 diabetes. Physicians must avoid being excessively careful with blood sugar lowering medication out of fear of hypoglycaemia.

Factors that increase the risk of hypoglycaemia

- Skipping a meal
- Unusual physical effort
- Alcohol use, in particular without food
- sulfonylureas with long-term action (especially glibenclamide)
- Sulfonylurea use with impaired kidney function
- Sulfonylurea interference with other drugs (sulphonamides, certain NSAIDs, fibrates, coumarin derivatives)
- Insulin treatment

Approach

Hypoglycaemia requires immediate treatment. If analytical material is available, a blood glucose determination should first be performed in order to confirm the diagnosis.

The following steps should be taken with a patient who is still conscious:

- Administer fast carbohydrates (10 to 15 g): give two to three sugar lumps, three to five tablets grape sugar, one half glass of a soft drink or fruit juice (no "light" products)¹⁴⁸.
- It usually takes 10-15 minutes for the symptoms to disappear. The previous step can be repeated if necessary.
- Then, slow carbohydrates should be consumed (e.g. a slice of bread, a piece of fruit or a glass of milk).

¹⁴⁷ American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes. *Diabetes Care* 2005;28:1245-9.

¹⁴⁸ Administration of sucrose (saccharose) is not useful when the patient is being treated with Acarbose®. Acarbose is an α -glucosidase inhibitor that inhibits the breakdown of disaccharides (sucrose), but has no influence on the resorption of monosaccharides.

Patients with distinctly reduced consciousness should be managed as follows:

- No oral carbohydrates due to the danger of aspiration pneumonia,
- One ampoule intravenous hypertonic glucose (preferably 20 ml glucose 30% = 6 g), repeating if necessary; or 1 mg glucagon (Glucagen®) by subcutaneous, intramuscular or intravenous administration¹⁴⁹.
- Oral carbohydrates as soon as the patient regains consciousness.

Hypoglycaemias induced by the slower-acting sulfonylureas and/or insulins can be highly refractory and recurrent. In these circumstances, the action of glucagon is also less effective. It is therefore important in such cases to monitor the glucose levels for 24 hours. Often, a longer period of glucose infusion may become necessary, even requiring the patient to be admitted to hospital.

E d u c a t i o n

Patients treated with sulfonylureas and/or glinides must be educated about the prevention and treatment of hypoglycaemia. In doing so, it is useful also to involve family members.

Such education should cover the following subjects:

- How can you prevent hypoglycaemia? (e.g. not skipping meals, extra snack in case of physical effort),
- How can you recognise the symptoms of hypoglycaemia?
- How can you correct a hypoglycaemia all by yourself?

Education on the use of glucagon is generally not necessary in cases of Type 2 diabetes (as opposed to Type 1 diabetes in which the risk of hypoglycaemic coma is much higher).

8.1.2. Hyperglycaemia, risk of ketoacidosis

D i a g n o s i s

Glucose dysregulation can happen quickly when the patient is acutely ill. These situations most frequently come about as a result of infectious diseases such as the flu or urinary infections. Corticoid therapy too can cause a dysregulation.

The symptoms of the intercurrent disease often displace the clinical signs of the diabetes dysfunction. Therefore, glucose levels must also be monitored in the event of intercurrent disease.

A p p r o a c h

- Treat the intercurrent condition
- Control the glucose levels. In view of the fact that the risk of developing ketosis-ketoacidosis is not significant with Type 2 diabetes it is not necessary to measure ketones, unless the patient experiences strong vomiting and/or seems very ill
- In the event of persisting significant hyperglycaemia, oral antidiabetics should temporarily be increased, or insulin treatment should be started, or the existing insulin dose should be increased on a temporary basis
- Ensure sufficient liquid intake
- The need for hospitalisation is determined, among other things, by:
 - The opportunity to ensure that the necessary fundamental conditions for blood glucose monitoring and insulin administration (availability of family members or home care) are met,
 - The seriousness of the patient's condition,
 - The need for parenteral fluid administration: vomiting and polyuria can quickly result in dehydration and require parenteral therapy.

E d u c a t i o n

The education programme aimed at Type 2 diabetes patients should include guidelines regarding the action to be taken in connection with hyperglycaemia and illness:

- If already instituted, ensure stricter glucose self-monitoring,
- Ensure adequate fluid intake (water, tea, broth),

¹⁴⁹ Intravenous glucose has immediate effect, glucagon only after ten to fifteen minutes. Glucagon does not work as well with long-standing hypoglycaemia. Glucagen Hypokits® can be stored for 18 months at room temperature under 25 °C, and three years if refrigerated.

- Consume milk or lightly sugared drinks if it is difficult to ingest solid food,
- Do not interrupt the treatment with oral medication or insulin, but, rather, consult a doctor,
- Make sure to involve a doctor in a timely manner, certainly if food intake is affected, or if you experience vomiting, fever or changes in consciousness.

8.2.Chronic complications

Some of the problems described below can also occur entirely independently from diabetes mellitus, but they are much more frequent with diabetes (e.g. cataracts); others are specific to diabetes (e.g. retinopathy, nephropathy).

8.2.1. Retinopathy

Diabetic retinopathy continues to be the most frequent cause of acquired blindness in Western countries in the 25 to 75 age group¹⁵⁰. Strict blood glucose¹⁵¹ and blood pressure¹⁵² regulation can prevent retinopathy or slow its progression.

At the time of being diagnosed with Type 2 diabetes, 20% of all patients already have retinopathy lesions. The reason for this phenomenon is that often, at the time of diagnosis, the patient has already suffered from diabetes for several years.

In view of the fact that retinopathy can cause irreversible lesions long before there are subjective vision changes, systematic monitoring is essential. For this reason, the following examinations must be performed at diagnosis and annually thereafter:

- Vision check-up for both eyes,
- Retinal examination with dilated pupils in a darkened room,
- Intraocular pressure measurement.

These examinations require special expertise and must therefore be performed by an ophthalmologist. Do not forget to inform the patient to arrange for transport, as vision may remain clouded for a few hours after the examination (as a result of the eye dilation drops).

Diabetic retinopathy is characterised by different degrees of microaneurisms, bleeding, exudates, venous changes, formation of new blood vessels and retinal thickening. The condition can affect both the peripheral retina and the macula. Depending on the seriousness of the patient's condition, the disease can be classified as either:

- non-proliferative retinopathy (slight, moderate to severe)
- proliferative retinopathy

If the macula (the central vision area) is affected, the condition is termed maculopathy. Except for slight to moderate non-proliferative retinopathy, the other stages require urgent attention and treatment.

Diabetic retinopathy is aided by poor diabetes regulation, hypertension and renal insufficiency. Early treatment of a diabetic retinopathy (using laser technology) can inhibit or stabilise the development of the disease in more than 50% of all cases¹⁵³.

¹⁵⁰ In the U.K., diabetes is responsible for 12% of all cases of registered blindness.

- Evans J, Rooney C, Ashwood F, et al. Blindness and partial sight in England and Wales: April 1990–March 1991. *Health Trends* 1996;28:5–12.

¹⁵¹

- Diabetes Control and Complications Trial Research group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 1995;44:968-83.
- The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Eng J Med* 2000;342:381-9.
- Wens J. Intensieve behandeling van diabetes type 2. *Huisarts Nu (Minerva)* 1999;28(3):125-6. Interpretation of: UKPDS Group. Intensive blood glucose control with sulphonylureas or insuline compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.

¹⁵² UKPDS group. Risk of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus (UKPDS 69). *Arch Ophthalmol* 2004;122:1631-40.

¹⁵³ Peripheral retinal photocoagulation reduces the risk of severe vision impairment with pre-proliferative retinopathy,

8.2.2. Nephropathy

Approximately 20 to 30% of Type 2 diabetes patients develop microalbuminuria. Of this population, 20 to 40% develop distinct kidney disease with macroalbuminuria¹⁵⁴. Of this group, 20% will further deteriorate into renal insufficiency¹⁵⁵. This last figure is somewhat limited by the fact that many patients die from cardiovascular problems before kidney failure can occur.

Microalbuminuria is often already present at the time when Type 2 diabetes mellitus is first diagnosed, because the disease frequently has been present for years and because in Type 2 diabetes microalbuminuria is a less specific indicator of kidney disease.

Detection of microalbuminuria

The first sign of nephropathy is the presence of low but abnormal quantities of albumin in urine (microalbuminuria). Microalbuminuria should be monitored annually. The measurement can be performed in different ways, but in practice it is recommended to have a morning sample (first urine after waking up) analysed in the laboratory to determine microalbumin and creatinine levels¹⁵⁶. Microalbuminuria is the term used when albumin excretion is >30 mg/g creatinine. This test is reimbursable for diabetes patients.

The changing concentrations of albumin in urine require repeating a positive test before a diagnosis of persistent microalbuminuria can be made (cf. microalbuminuria monitoring schedule).

A number of factors (urinary tract infections, physical effort, fever, cardiac decompensation etc.) can produce a false positive result.

Plasma creatinine levels should be checked annually in Type 2 diabetes patients under pharmacotherapy in order to be able to adjust the medication in a timely manner in the event of an impairment of the renal function.

Microalbuminuria monitoring flow-chart

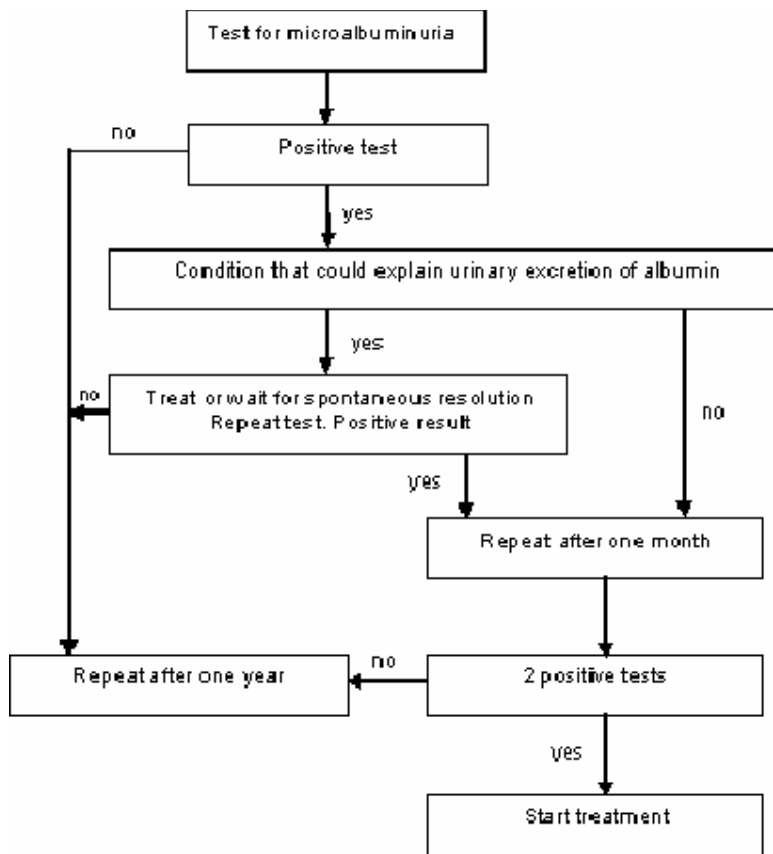
proliferative retinopathy and maculopathy. Macular laser photocoagulation reduces vision impairment by two to three years in eyes affected by macular oedema and moderate pre-proliferative diabetic retinopathy.

- Harding S. Diabetic retinopathy. BMJ Publishing Group Ltd. Clinical Evidence, 2005 edition. Updated 20041001.

¹⁵⁴ Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int.* 2003;63:225-32.

¹⁵⁵ American Diabetes Association (ADA). Nephropathy in Diabetes. *Diabetes Care* 2004;27:S79-83. Progression towards renal insufficiency is much less frequent in Type 2 diabetes than in Type 1, but because of the greater prevalence of Type 2 diabetes more than half of all diabetic dialysis patients fall within Type 2.

¹⁵⁶ The determination of creatinine in urine allows for a correction of the concentration of the urine sample and renders the determination more accurate. Determination based on 24-hour collection is most reliable although cumbersome. There is a strip test for microalbuminuria (Micral test), but this test is less accurate, fairly expensive and not reimbursable.



Treatment of microalbuminuria

Whenever microalbuminuria is diagnosed, strict management is necessary in order to prevent further progression towards renal insufficiency. This includes:

- Detection and treatment of cardiovascular risk factors:
Microalbuminuria is an important risk marker for cardiovascular disease and is associated with a two to three times higher risk of cardiovascular morbidity and mortality¹⁵⁷,
- Strict blood pressure control
Hypertension accelerates the evolution towards renal insufficiency. Strict blood pressure control (blood pressure $\leq 130/80$ mm Hg) inhibits development of the disease. In the event of microalbuminuria the patient should be started on an ACE inhibitor or an angiotensin-II-receptor antagonist¹⁵⁸. Only ACE inhibitors have been demonstrated to reduce mortality and are therefore the treatment of choice¹⁵⁹.

¹⁵⁷

- Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus: a systematic review of the literature. *Arch Intern Med* 1997;157:1413-8.
- Valmadrid CT, Klein R, Moss SE, et al. The risk of cardiovascular disease associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Int Med* 2000;160:1093-100.
- Sunaert P, Feyen L. Steno-2 Studie: multifactoriële aanpak bij diabetes type 2. *Minerva* 2004;3:11-4. Interpretation of: Gaede P, Vedel P, Larsen N, et al. Multifactorial Intervention and Cardiovascular Disease in Patiënts with Type 2 Diabetes. *N Engl J Med* 2003;348:383-93.

¹⁵⁸ As compared to placebo and certain other antihypertensives, both ACE inhibitors and angiotensin receptor (AR) antagonists scored as having greater efficacy as regards the progression of nephropathy: doubling creatinaemia, proteinuria and/or of the time to the development of terminal kidney failure.

- Breyer JA, Hunsicker LG, Bian R, et al. Angiotensin converting enzyme inhibition in diabetic nephropathy. The Collaborative Study Group. *Kidney International Supplement* 1994;45:156-60.

- Strict glycaemic control
The protective effect of good glycaemic control on kidney health has been unambiguously demonstrated in Type 1 diabetes. Although two recent studies suggest a similar protective effect for Type 2 patients,¹⁶⁰ there is however no hard evidence available for this theory to date.
- Annual kidney function check-up by means of plasma creatinine determination
- Referral to a specialist is desirable in the event of an evolution towards macroalbuminuria.

8.2.3. Neuropathy

After 25 years of suffering the disease, approximately half of all diabetes patients show neuropathies that are directly linked to the degree of metabolic control. Neuropathy can cause severe morbidity.

The most frequent form attacks the distal sensory nerves, manifesting with paraesthesias, pain and finally reduced sensation, usually symmetrically in the lower legs. The motor nerves (paresis) and the autonomic nervous system (impotence, gastroparesis, orthostatic hypotension, bladder retention etc.) can also be affected.

Sensory neuropathy in the lower limbs significantly increases the risk of diabetic foot lesions (cf. Section 9.2.4 Foot Problems). Patients often do not realise that they have less sensitivity in their feet, so that screening becomes necessary. In addition, advanced neuropathy is irreversible.

Screening and detection

Accurate screening and detection require the following elements:

- Targeted anamnesis:
 - *Sensory nerves*: paraesthesias, pain, numbness, foot lesions
 - *Motor nerves*: paresis
 - *Autonomic nerves*: impotence, gastroparesis, orthostatic hypotension, bladder retention
- Clinical examination:
 - Careful examination of feet and monofilament sensitivity testing (cf. Section 9.2.4., Foot Problems).

Electromyograms (EMG) are not useful in screening for peripheral neuropathy. The test can produce entirely normal results with painful sensory neuropathies and delivers inadequate information about the risk of diabetic foot lesions.

Treatment

With good glucose control, painful distal neuropathy can be reversible at an early stage¹⁶¹. At more advanced stages the damage is irreversible. In those cases, good glucose control is still important in order to inhibit the progression of the neuropathy.

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- Verpoeten GA, Tomas MCF. De rol van sartanen bij diabetische nefropathie. Huisarts Nu (Minerva) 2002;31:363-9. Interpretation of:
 - Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
 - Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.
 - Parving HK, Lehnert H, Brochner-Mortensen J, et al The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.
 - Barnett AH, Bain SC, Bouter P, et al. Angiotensin-Receptor Blockade versus Converting-Enzyme Inhibition in Type 2 Diabetes and Nephropathy. N Engl J Med 2004;351:1952-61.

¹⁵⁹ Stripolli GFM, Craig M, Deeks JJ, et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: a systematic review. BMJ 2004;329:828-39.

¹⁶⁰ The risk of an accelerated decline of the glomerular function increases if HbA1c is consistently higher than 7.5% and post-prandial glycaemia values are higher than 200 mg %.

- Nosadini R, Tonolo G. Relationship between blood glucose control, pathogenesis and progression of diabetic nephropathy. J Am Soc Nephrol 2004 Jan; 15 Suppl 1: S1-5.
- Wens J. Intensieve behandeling van diabetes type 2. Huisarts Nu (Minerva) 1999;28(3):125-6. Interpretation of: UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) Lancet 1998;352:837-53

Analgesics (e.g. paracetamol 1g 4x/d) can ease the symptoms, but are often inadequate. In those cases, combination treatment with amitriptyline (Redomex®, Tryptizol®) can be helpful¹⁶².

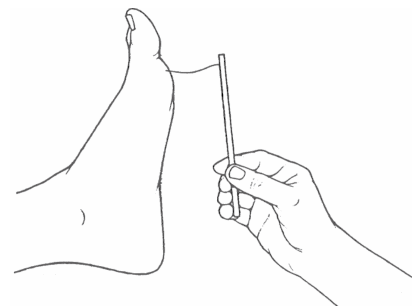
Treatment with vitamin B is helpful only in rare cases of vitamin B deficiency (pernicious anaemia, alcoholism). Long-term administration of high doses of vitamin B can itself induce neuropathy.

Referral to a specialist is desirable in the following cases:

- Severe pain in the lower limbs, not responding to treatment with amitriptyline. In such cases, gabapentin (Neurontin®) can be used as an alternative¹⁶³.
- Distal neuropathy with atypical presentation (asymmetrical, significant motor component). Further examination (including EMG) is then necessary in order to rule out non-diabetic neuropathy,
- Severe impairment of sensitivity in the feet (cf. "Foot Problems"). Further management in a diabetes foot clinic is then advisable,
- Isolated mononeuropathy: e.g. paralysis of the eye muscles or severe muscular atrophy,
- Signs of autonomic neuropathy, such as vomiting, diarrhoea, recurring urinary infections, postural hypotension, post-prandial fullness and signs of a "hypo" shortly after a meal (suggesting gastroparesis).

8.2.4. Foot Problems

Foot problems are a very frequent occurrence in diabetes¹⁶⁴. Diabetics with neuropathy and/or peripheral vascular disease are at increased risk of developing ulcerations, infections and/or gangrene in the feet. The risk of amputation is 15 to 45 times higher in these patients than in non-diabetics. Early screening of patients at risk, timely prevention and appropriate treatment of the foot problems can lead to a significantly improved prognosis.



¹⁶¹ Young R, Ewing D, Clarke B. Chronic and remitting painful diabetic polyneuropathy. Correlations with clinical features and subsequent changes in neurophysiology. *Diabetes Care* 1988;11:34-40.

¹⁶² To reduce the risk of experiencing central nervous system side effects (daytime somnolence, nausea) it is best to start with a low dose of 10 to 25 mg at bedtime. Amitriptyline sometimes has a soporific effect, helping rest at night, which is often disturbed by neuropathic pain.

- Max M, Lynch S, Muir J, Shoaf S, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992;326:1250-6.

The dose can be slowly increased to a maximum of 150 mg/d. Closed angle glaucoma and the risk of urine retention are the most important contraindications.

- Gecommentarieerd geneesmiddelenrepertorium 2005 [Annotated Therapeutic Drug Index 2005]. Antidepressants: Posology p. 177.

¹⁶³ Adults aged 18 and over can be started on gabapentin (Neurontin®), which in Belgium is reimbursed for the diabetic neuropathy indication. The drug's tolerability and efficacy in patients younger than 18 years have not been determined.

- Gecommentarieerd geneesmiddelenrepertorium 2005 [Annotated Therapeutic Drug Index 2005]. More recent anti-epileptics: p. 195.
- Backonja M, Beydoun A, Edwards K, Schwartz S, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 1998;280:1831-6.
- Morello C, Leckband S, Stoner C, Moorhouse D, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999;159:1931-7.

¹⁶⁴

- Van Acker K. The Diabetic Foot, dissertation. Antwerp 2001.
- Feyen L, Sunaert P, Goeman A, et al. Opsporen van risicovoeten bij diabetes-type-2-patiënten in de huisartspraktijk. *Tijdschr Geneesk* 2000;56:802-6.

Detecting increased risk

The risk of foot lesions is evaluated on an annual basis by means of a simple screening examination. This includes:

- Careful inspection of the feet, paying particular attention to skin and nail changes, and including an evaluation of potential orthopaedic deformities.
- Evaluation of static abnormalities in feet and toes: prominent metatarsal heads (often covered in callosities), hammer toes, hallux valgus (bunions), crossed toes, earlier amputations, Charcot foot (a fragmentation of the small bones of the foot with loss of the arch structure),
- Detection of impaired sensitivity in the feet with a Semmes-Weinstein monofilament¹⁶⁵,
- Detection of peripheral vascular disorders by asking about complaints of claudication and/or pain at rest (diabetics with neuropathies often lose these pain alarms) and by means of palpation of the arterial pulses in the feet. A foot that is erythematous while dependent but pale when raised is a sign of critical vascular disease.

The results of these findings and the prior history of foot lesions can be summarised as a risk score (cf. also Diabetes Passport).

Risk Group	0	1	2a	2b	3 (one of these)
Neuropathy *	No	Yes	Yes	Yes	
Orthopaedic deformities **	No	No	Slight*	Severe	Charcot***
Vascular disease	No	No	No	No	Yes
Earlier foot lesions or amputations	No	No	No	No	Yes
Risk	Low	Moderate	High	Very high	Extremely high

* With a monofilament test: positive if 2 of the 3 pressure points are not felt.

** Orthopaedic deformities **:

Slight = Prominent metatarsal heads with minimal callosities and/or supple hammer or claw toes and/or limited hallux valgus <30°,

Severe = Serious orthopaedic abnormalities,

*** Charcot foot, a fragmentation of the small bones of the foot with loss of the arch structure, indicates a very high risk of developing diabetic foot lesions.

¹⁶⁵ Feeling in the feet is best checked with a 2 g or 10 g Semmes-Weinstein monofilament.

The monofilament is a flexible plastic wire mounted on a holder. The filament is briefly pressed perpendicularly against the skin of the foot until its shape resembles that of the letter C. This creates a standardised pressure of 10 g. The monofilament must briefly be placed against the skin (for approximately 1 second) and must not glide over the skin in so doing. Areas with callous should be avoided. It is recommended to test the following three areas: plantar at the level of the hallux, over the metatarsal heads 1 and 5. The patient is asked to close his/her eyes and to state when the filament touches the foot and where. Not feeling the filament in ≥ 2 places indicates significant sensory neuropathy with an increased risk of foot lesions. A number of studies have demonstrated that not feeling a 10 g pressure is a discriminatory element. This situation is referred to as a loss of protective sensitivity. There are also monofilaments that provide more or less pressure, but this provides no extra advantage in screening. It is also possible to use a 128 Hz tuning fork, but as the tuning fork is not always struck with the same intensity, this is less reproducible (and thus less reliable).

- Kamei N, Yamane K, Nakanishi S, et al. Effectiveness of Semmes-Weinstein monofilament examination for diabetic peripheral neuropathy screening. *J Diabetes Complications* 2005;19:47-53.
- Valk GD, de Sonnaville JJ, van Houtum WH, et al. The assessment of diabetic polyneuropathy in daily clinical practice: reproducibility and validity of Semmes Weinstein monofilaments examination and clinical neurological examination. *Muscle Nerve* 1997;20:116-8.
- Kumar S, Fernando DJ, Veves A, et al. Semmes-Weinstein monofilaments: a simple, effective and inexpensive screening device for identifying diabetic patients at risk of foot ulceration. *Diabetes Res Clin Pract* 1991;13:63-7.

Approach

Risk Group	0	1	2a	2b	3
Education	1x / 12 months	≥1x / 6 months	≥1x / 6 months	≥1x / 6 months	≥1x / 3 months
Foot care	None	1x / month	1x / month	1x / month	1x / month
Insoles	None	Comfort	Custom	Custom	Custom
Shoes	Off-the shelf	Off-the shelf	Semi-orthopaedic	(Semi-) orthopaedic	(Semi-) orthopaedic
Medical check-up	1x / 12 months	1x / 6 months	1x / 3 months	1x / 3 months	1x / 3 months

Table: Preventive management based on degree of risk

The following preventive measures must be taken will all patients at increased risk:

- Thorough education (see below),
- Regular foot care by a pedicurist or podiatrist¹⁶⁶ (nail care, callous removal). In patients with orthopaedic abnormalities (starting with Risk Class 2a) it is best to involve a podiatrist¹⁶⁷,
- Wearing good socks, stockings and shoes, both indoors and outdoors¹⁶⁸,
- Regular foot examination and shoe inspection by a doctor: monitoring of the results of preventive measures, detection of callous, blisters, lesions and fungus infections (interdigital, nails).

Education

The following points are important in proper patient education¹⁶⁹:

- Ensure good foot hygiene:
 - Wash feet thoroughly on a daily basis and dry properly (to prevent softening between the toes),
 - Prevent chapping (especially of the heels), use a hydrating cream,
 - Take care of the nails: they should be clipped straight to prevent in-growing, sharp edges should be filed away, preferably with a non-traumatic (cardboard) nail file¹⁷⁰.
- Wear good socks, stockings and shoes, both indoors and outdoors (see above).
- Avoid traumas:
 - Do not walk barefoot,
 - Avoid contact with heat sources,
 - Do not try to manage calluses and corns yourself but use a pedicurist or podiatrist instead,

¹⁶⁶ A podiatrist (or podology graduate) has an A1 diploma obtained after three years' full-time day training. In Belgium, pedicurist is not a recognised title; training courses are short and of widely differing quality. It is therefore useful to evaluate the quality of the pedicurist with whom the patient will be working. Some pedicurists call themselves podiatrists, which further increases the confusion.

¹⁶⁷ Two foot care consultations with a recognised podiatrist are reimbursed per year for patients in Risk Groups 2b and 3 who hold a Diabetes Passport. The risk group should be indicated on the prescription.

¹⁶⁸ Socks or stockings must be sufficiently thick and must not have been darned or have seams. Shoes must have good closures at the instep to prevent the foot from shifting, should have relatively low heels, provide adequate room for the toes, and have a smooth, even lining. Off-the-shelf inlays (also referred to as comfort soles) can help patients without orthopaedic problems better to distribute the pressure over the sole of the foot. Custom orthopaedic soles should be chosen in the event of orthopaedic problems. With slight abnormalities (Risk Class 2a) these soles can be built into semi-orthopaedic footwear (off-the shelf orthopaedic footwear); with more significant abnormalities (starting with Risk Class 2b) they should be made to measure by an orthopaedic shoemaker.

¹⁶⁹

- Singh N, Armstrong DG, Lipsky BA. Preventing Foot Ulcers in Patients With Diabetes. JAMA 2005;293:217-28.
- Valk, GD; Kriegsman, DMW; Assendelft, WJJ. Patient education for preventing diabetic foot ulceration. Systematic review. Cochrane Database of Systematic Reviews. 2, 2005.

¹⁷⁰ Many older people and patients with poor eyesight can no longer perform this care by themselves. It then becomes necessary to work with a pedicurist or podiatrist.

- Check shoes for roughness and foreign objects every time before putting them on,
- ‘Compensate’ for the reduced pain alarm with daily visual and tactile examination of the feet. If necessary, the help of a person living with the patient or of a home care professional should be sought,
- Consult a doctor immediately if any blisters or lesions should appear.

Referral

Patients at strongly increased risk of developing foot problems (Risk Class 2b onwards) should be referred to a diabetes foot clinic at an early stage for a thorough evaluation of the problem¹⁷¹.

Active foot problems such as ulcerations, infections or gangrene in diabetes patients should be considered to be serious problems and require urgent referral.

Incorrect treatment of a foot ulcer in a diabetes patient can lead to amputation. In a large percentage of cases amputations can be prevented by swift and appropriate treatment. The decision to perform an amputation should only be made following consultation with a multidisciplinary diabetes foot team.

8.2.5. Sexual Problems

In treating diabetes mellitus patients it can be useful to enquire about sexual dysfunctions in a tactful but thorough manner: erectile dysfunction in men¹⁷² and inadequate lubrication, dyspareunia and reduced libido in women¹⁷³.

Because of the multiple factors involved in its etiopathogenesis, the treatment of erectile dysfunction often requires a multidisciplinary approach, which will necessarily include psychosexual counselling and a urologist’s opinion. Hormonal dysfunction (prolactin, testosterone) should be ruled out. Often a treatment is

¹⁷¹ In a diabetes foot clinic, the internist/diabetologist works together with a multidisciplinary team of care providers: at least one surgeon, one nurse, one podiatrist and one shoemaker to guarantee an expert approach to foot problems. In these foot clinics, treatment consists of:

- Thorough debridement of the lesion with removal of necrotic material, abscesses and areas of osteomyelitis. This often requires surgery.
- Ensuring that there is adequate arterial perfusion. This can often require balloon dilatation or bypass surgery.
- Infection fighting with antibiotics if necessary.
- Pressure relief: a wound walked on will never heal! Depending on the type and location of the wound, different techniques can be applied: felt therapy, wound shoes, total contact casts, etc. This requires involving the expertise of a podiatrist and an orthopaedic shoe technician.
- Spencer S. Pressure relieving interventions for preventing and treating diabetic foot ulcers. Systematic review. Cochrane Database of Systematic Reviews. 2, 2005.
- Appropriate wound care. The type of cream or bandage applied can be determining for the success of the treatment.
- Optimisation of glycaemic control.

¹⁷² An erection is a complex neurovascular event involving both spinal and supraspinal pathways. Ultimately, NOs (nitrogen oxides) are released, both from endothelial cells and from neurons. NO is broken down by means of phosphodiesterase (PDE) type 5, present in the penis. NO causes vasodilation which causes penile erection. Erectile dysfunction occurs when the neurovascular pathway is blocked by a disease or medication. In diabetes mellitus patients erectile dysfunction (ED) occurs three times as often as in the healthy population. Incidence increases with age, the duration of the diabetes and lesser metabolic control. ED exercises a distinct influence on the quality of life.

- Parkerson GR jr, Willke RJ, Hays RD. An international comparison of the reliability and responsiveness of the Duke Health Profile for measuring health-related quality of life of patients treated with alprostadil for erectile dysfunction. Medical Care 1999;37:56-67.

¹⁷³ The risk of lubrication disorders in women with Type 2 diabetes is twice that of an equal age control group without diabetes. Dyspareunia and decreased libido are also frequent occurrences. In addition, women with diabetes are significantly more concerned with the problem of sexual rejection and suffer more from anxiety and its consequences. Despite this higher prevalence, there are very few studies evaluating the impact of sexual dysfunction on these women’s lives or suggesting a treatment.

- Enzlin P, Mathieu C, Vanderschueren K, et al. Diabetes mellitus and female sexuality: a review of 25 years’ research. Diabetic Med 1998; 15: 809–15.
- Young E, Barthalow P, Bailey D. Research comparing the dyadic adjustment and sexual functioning concerns of diabetic and nondiabetic women. Health Care Women Int 1989;104: 337–94.

started with oral phosphodiesterase inhibitors¹⁷⁴ such as: sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis). Patients should be warned about side effects such as headache, nasal congestion and dyspepsia. An absolute contraindication is the concomitant use of oral nitrates for coronary pathologies. If the oral therapy should fail, there are various options that can be added to the PDE5 inhibitor therapy¹⁷⁵.

There are no treatments of proven efficacy for sexual problems in female diabetes patients other than the use of lubricants during intercourse. It is most important to be able to talk about the problem in an open atmosphere. This can also be accomplished with the help of friends or women's organisations¹⁷⁶.

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- Rendell M, Rajfer J, Wicker PA, et al. Sildenafil for Treatment of Erectile Dysfunction in Men With Diabetes: A Randomized Controlled Trial. *JAMA* 1999;281:421-6.
- Behrend L, Vibe-Petersen J, Perrild H. Sildenafil in the treatment of erectile dysfunction in men with diabetes: demand, efficacy and patient satisfaction. *Int J Impot Res* 2005;17:264-9.
- Goldstein I, Young JM, Fischer J, et al. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. *Diabetes Care* 2003;26:777-83.
- Tadalafil has a longer half-life, resulting in greater flexibility in sexual activities for the user.
- Saenz de Tejada I, Anglin G, Knight JR, et al. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care* 2002;25:2159-64.

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- The value of the different additive therapies is still to be demonstrated. At stake are: intraurethral or intracavernosal alprostadil (caverject®, Prostin VR®), Propionil-L-carnitin, antioxidants, oral testosterone undecanoate, which can also result in improved glucose homeostasis, and sublingual apomorphine.
- Gentile V, Vicini P, Prigiotti G, et al. Preliminary observations on the use of propionyl-L-carnitine in combination with sildenafil in patients with erectile dysfunction and diabetes. *Curr Med Res Opin* 2004;20:1377-84.
 - De Young L, Yu D, Bateman RM, et al. Oxidative stress and antioxidant therapy: their impact in diabetes-associated erectile dysfunction. *J Androl* 2004;25:830-6.
 - Kalinchenko SY, Kozlov GI, Gontcharov NP, et al. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male* 2003;6:94-9.
 - Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 2003;6:1-7.

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- Sarkadi A, Rosenqvist U. Contradictions in the medical encounter: female sexual dysfunction in primary care contacts. *Family Practice* 2001;18: 161–6.
- Loehr J, Verma S, Seguin R. Issues of sexuality in older women. *J Women's Health* 1997;6:451–7.

9. DIABETES EDUCATION

Optimal diabetes treatment begins with lifestyle adjustments. The patient plays an important role in this aspect of the treatment. Every day he or she is obliged to make large and small decisions that will have an influence on his or her condition. Striving for a healthy lifestyle will become a life-long concern for the patient. Education to achieve optimal self-care is therefore an important component of diabetic care¹⁷⁷.

The objective of self-care education is to teach patients how to manage their disease in an independent and self-reliant way (empowerment). Provided with correct information, diabetes patients can make their own decisions about their day-to-day treatment, thus becoming equal partners in their care¹⁷⁸.

Over the short term (<6m) self-care education has a positive effect on HbA1c values and parameters related to the quality of life¹⁷⁹. In order to be effective over the longer term, it is important that patient education be a continuous process and not a one-time intervention¹⁸⁰.

Educating the patient and providing support for lifestyle changes is a gradual process that takes place in small increments over time.

The following topics should be discussed with the patient:

- Psychosocial consequences of the diabetes diagnosis for the patient,
- Individually customised treatment objectives,
- Personal diet requirements (with a meal plan),
- The role of physical activity in the treatment,
- Interaction between food intake, physical activity and oral antidiabetics/insulin,
- Possible lifestyle improvements: for example, the unfavourable effects of smoking and excessive alcohol consumption, safe and correct taking/administration of medication,
- Administration and adjustment of insulin as necessary,
- Glucose self-monitoring and the meaning of the results within the scope of potentially required action,
- Recommended reaction in the event of dysregulation (both hypoglycaemia and hyperglycaemia) or illness,
- Prevention and early detection of chronic complications, paying special attention to foot care,
- The use of the Diabetes Passport,
- Optimal use of existing health facilities,
- Necessary administrative modifications to the driver's licence.

Discussing all these topics personally with the patient is impossible for the GP.

¹⁷⁷

- American Diabetes Association. National standards for diabetes self-management education. *Diabetes Care* 2005;28:72-9.
- IDF Clinical Guidelines Task Force. Global Guideline for type 2 diabetes. Brussels: International Diabetes Federation, 2005.
- <http://www.eatlas.idf.org/>
- New Zealand Guidelines Group (NZGG). Management of type 2 diabetes. Wellington (NZ): New Zealand Guidelines Group (NZGG) 2003.

¹⁷⁸ Anderson R, Funnell M, Carlson A, et al. Facilitating self-care through empowerment. In: *Psychology in diabetes care*. Snoek F., Skinner T. [Eds.] 279p. ISBN. 0471977039. John Wiley And Sons, Incorporated. 2000.

¹⁷⁹ A review and meta-analysis by Norris demonstrated a positive effect of self-care education programmes on HbA1c values. The studies included in this review and meta-analysis were of varying quality, and the types of interventions, theoretical foundations, topic(s) covered in the training and the care providers responsible for training varied widely.

- Norris L, Engalgau M, Venkat Nraya K. Effectiveness of self-management training in type 2 diabetes. A systematic review. *Diabetes Care* 2001;23:561-87.
- Norris S, Smith L, Schmid C, et al. Self management education for adults with type 2 diabetes. A meta-analysis of the effect on glycemic control. *Diabetes Care* 2002;25:1159-71.

A review by Steed demonstrated a positive effect of self-care education on parameters related to the quality of life.

- Steed L, Cooke D, Newman S. A systematic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. *Pat ed Counseling* 2003;51:17-28.

¹⁸⁰ Goudswaard A, Stolk R, Zuihthoff N, et al. Long-term effects of self-management education for patients with type 2 diabetes taking maximal oral hypoglycemic therapy: a randomized controlled trial in primary care. *Diabetic Medicine* 2004;21:491-6.

Therefore, diabetes education will involve different care providers: doctors, dieticians, nurses, podiatrists, diabetes educators, etc.

Patient organisations like the Vlaamse Diabetes Vereniging (VDV – Flemish Diabetes Association) can also play an important role in patient education (see below). Patient education appears to be most successful when it is imparted in a coordinated manner by the different care providers (shared care). This issue is discussed in greater detail in the section on care organisation.

Furthering and hindering factors

There is often prejudice or misconception regarding both the disease and its treatment, which can only be removed by means of proper understanding of the condition.

The individual belief in the possibility of self-care and the influence each person can have on his or her own health vary from patient to patient. Emotional factors (denial, anger, guilt, depression, acceptance) can significantly influence the education process. The more drastic the changes in lifestyle and the more complex the therapy conditions, the more difficult it is to attain the treatment goal. The greater the openness and respect in the relationship between the patient and the care provider, the greater the chances of success. Communication is essential to attain success. In that situation, listening is as important as talking.

Successful diabetes education requires the following elements:

- It is often important to take the patient's current situation as a point of departure,
- Things that are already being done right must first be consolidated and encouraged,
- The changes require the patient's consent,
- Whenever it is advised not to do something, alternatives should be provided whenever possible,
- It is important to use simple language and provide visual aids,
- Guidelines should always be very simple and concrete,
- It is necessary to verify whether the patient has understood the recommendations,
- A written summary is often recommended as an *aide mémoire* for the patient,
- It is useful to involve the patient's entourage (partner, family, colleagues).
- Repetition is important.

10. SELF-MONITORING

Just as with any other chronic disease, it is also recommended to involve the diabetes patient as much as possible in monitoring his disease. The patient can manage a number of issues independently: recording weight and physical activity, self-measurement of blood pressure and glucose values are some examples. The patient must be given the appropriate self-management information and its practical feasibility must be individually evaluated.

10.1. Glucose Self-Monitoring

Glucose self-monitoring is recommended for all Type 1 diabetes patients as it is essential for their treatment¹⁸¹. Type 1 patients are much more exposed to large fluctuations in the blood glucose level and are also at greater risk of hypoglycaemia.

There is some controversy surrounding the use of glucose self-monitoring in Type 2 diabetes¹⁸². Selective use of self-monitoring, integrated into a treatment plan with clear glycaemic objectives that meet with the patient's agreement, is certainly a sensible measure¹⁸³. Glucose self-monitoring can provide people with Type 2 diabetes with greater insight into their condition, thus contributing to the correct decisions for living with diabetes (empowerment)¹⁸⁴.

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- American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2003;26:33-50.
- American Diabetes Association. Tests of glycemia in diabetes. *Diabetes Care* 2003;26(Suppl 1):S106-108.
- American Association of Clinical endocrinologists. Medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management – 2002 update. *Endocr Pract* 2002;8:5-11.

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- Owens D, Barnett AH, Pickup J, Kerr D, Bushby P, Hicks D, et al. Blood glucose self-monitoring in type 1 and type 2 diabetes: reaching a multidisciplinary consensus. *Diabet Primary Care* 2004;6: 8-16.
- Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R. Self-monitoring in type 2 diabetes mellitus: a meta-analysis. *Diabet Med* 2000;17:755-61.

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National Institute for Clinical Excellence (NICE). *Management of type 2 diabetes: management of blood glucose*. London: NICE, 2002. www.nice.org.uk/pdf/NICE_INHERITEG_guidelines.pdf

A recently published systematic review with meta-analysis demonstrated a positive effect of blood glucose self-monitoring as part of a multifactorial diabetes management programme. The meta-analysis with Type 2 diabetes patients demonstrated an average reduction in HbA1c of 0.39% (95% CI 0.21-0.54) over a study period of 12 to 44 weeks.

- Sarol JN, Nicodemus NA, Tan KM, Grava MB. Self-monitoring of blood glucose as part of a multi-component therapy among non-insulin requiring type 2 diabetes patients: a meta analysis (1966-2004). *Curr Med Res Opin* 2005;21:173-83.
- Welschen LM, Bloemendal E, Nijpels G, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care* 2005;28:1510-7.

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In blood glucose monitoring people can directly see the effect of their eating and exercise behaviour on the glucose concentration in their blood. This information may contribute to behavioural changes in this area.

- NHS Modernisation Agency, Clinical Governance Support Team. *National diabetes support team*. Leicester: CGST, 2003. www.cgsupport.nhs.uk/diabetes/The_NDST (accessed 30 Jul 2004).

On the other hand, blood glucose monitoring can also have disadvantages as regards quality of life, contributing more worry, anxiety and depression, certainly if several measurements per day are required.

- Franciosi M, Pellegrini F, De Beradis G, Belfiglio M, Cavaliere D, Di Nardo B, et al. Impact of blood glucose monitoring on metabolic control and quality of life in type 2 diabetic patients. *Diabetes Care* 2001;24: 1870-7.
- If patients still have some limited endogenous insulin secretion, the scope of post-prandial glycaemic fluctuations can still be limited. Positive values obtained with self-monitoring can then give patients a false sense of security.

The stability of the patient's glycaemic control and the risk of hypoglycaemia must be taken into account in deciding whether to employ glucose self-monitoring.

- **Stable patients**

- In stable patients not being treated with medication, or else with medication involving little risk of hypoglycaemia (metformin or glitazones) glucose self-monitoring is of only limited usefulness.
- In stable patients taking oral antidiabetics capable of causing hypoglycaemia (sulfonylureas, glinides) self-monitoring can be useful in people with active, irregular schedule lifestyles, or for safety reasons (professional drivers, overhead workers).
- Patients taking insulin require ongoing self-monitoring, but in contrast to Type 1 diabetes, it is not generally necessary to measure glucose four times a day. In any event, Type 2 diabetes involves a lesser risk of acute hypoglycaemia or hyperglycaemia. As soon as patients require two or more insulin injections, they can be included in the Diabetes Convention, which means that test supplies are made available to them (cf. Section 6).

- **Unstable patients**

In unstable patients on medication capable of causing hypoglycaemia or in whom the HbA1c goals cannot be reached, self-monitoring can be useful in order to adjust the therapy. We advise that in such cases a few all-day curves should be recorded in order to be used in adjusting the treatment¹⁸⁵.

- In starting one evening injection of insulin in patients who continue to take oral antidiabetics during the day, as a rule usually three fasting glucose tests per week are sufficient in order to titrate the insulin dose. After 2 to 3 weeks it is best to develop a complete all-day glucose curve in order to adjust the oral antidiabetic dose. In increasing the evening insulin dose, it is often necessary to reduce the morning and noon dose of sulfonylureas or glinides.
- In acute dysregulation due to an intercurrent disease or the use of corticoids, temporary glucose self-monitoring (a few all-day curves) can help adjust the treatment.

10.2. Self-monitoring techniques

Self-monitoring requires good education and support, not only as concerns its technical aspects, but also in regard to the interpretation of the data obtained. At first, it is possible to use a home nurse until the patient is able to perform the measurements on his/her own. Some patients will require permanent help from a home nurse or a family member.

The results of the blood tests are best recorded in a diary brought to each contact with (diabetes) care providers by the patient. In this diary the patient can record ancillary information on diet, exercise, etc.

¹⁸⁵ Non-reimbursement of test supplies to diabetes patients not included in the Convention is an important issue in the more extensive use of self-monitoring supplies. The Flemish Diabetes Association (VDV) makes supplies available to its members at reduced rates. Mutual insurance schemes sometimes provide for limited reimbursement of self-monitoring materials within the scope of supplementary insurance. This reimbursement is often organised on regional bases, so that even within one and the same mutual insurance scheme there can be differences in reimbursement from one region to the next.

10.2.1. Quality control for measuring techniques

Inaccurate measurements can occur either due to defects in the measuring device or in the test strips, or due to faulty measuring techniques. The more recent measuring devices are considerably more reliable than the older glucose meters¹⁸⁶.

The treating physician or diabetes nurse should carry out a quality control of the glucose self-monitoring procedure at least every six to twelve months¹⁸⁷.

10.2.2. Acceptance

Some patients still experience some inhibitions in carrying out self-monitoring. These inhibitions express themselves as shame about having to prick themselves in the presence of others, or having to prick themselves at different times and in different situations, being anxious about pricking themselves or not being able to operate the meter, and therefore being dependent on others. GPs can help their patients to put these feelings into words and thus help prevent the diabetes self-monitoring taboo.

Pricking their fingertips can also put some patients off. For this reason it is recommended always to use a pricking device and to prick the side of the finger to cause less pain. There are also meters that make it possible to prick in different alternative areas¹⁸⁸.

10.3. Availability of self-monitoring supplies

Self-monitoring supplies are easy to get at the first-line treatment level, but reimbursement is not consistent. Pharmacists can propose a wide range of glucose meters and the corresponding strips. Supplies can also be obtained directly from the manufacturers and (local chapters of) patient associations. In view of the smaller profit margin applied, the latter option usually represents a less expensive solution.

Some private (mutual) health insurance schemes provide for limited reimbursement of self-monitoring supplies, whether or not within the scope of supplementary insurance. These regulations, which are different in the different insurance schemes, can also widely differ on a regional basis, so that no global information can be reported on this subject.

¹⁸⁶ When starting a new pack of strips, the proper calibration code has to be entered into the meter. Care must be taken not to exceed the expiry date of the strips, and that they are properly stored (dry, refrigerator or room temperature). Some meters (those based on photometric principles) should be cleaned regularly.

¹⁸⁷ The possibility of unreliable measurements should be borne in mind whenever results are not in line with HbA1c values. Patients can demonstrate their experience with self-monitoring on the occasion of a consultation. This provides an opportunity to remove uncertainties and errors and simultaneously makes it possible to carry out a comparison with a laboratory venous blood glucose measurement on a sample taken at the same time. This should ideally happen in a fasting state because post-prandial venous blood glycaemia is lower than in capillary blood. Whole blood glycaemia (glucose meter) is also a little lower than that measured in plasma (laboratory), but this is taken into account in the calibration of the glucose meters. In practice it could be said that a value obtained with a glucose meter should not differ by more than 20% from a laboratory measurement carried out on a venous blood sample taken at the same time.

- Nobels F, Beckers F, Bailleul E, De Schrijver P, Sierens L, Van Crombrugge P. Feasibility of a quality assurance programme of bedside blood glucose testing in a hospital setting: 7 years experience. *Diabetic Medicine* 2004;21:1288-91.

¹⁸⁸ This "alternate site testing" (AST) uses less well-irrigated areas such as the balls of the thumb and little finger and the forearm. With rapid changes in the blood glucose level after a meal, exercise effort or insulin administration it should be taken into account that glycaemia in alternative pricking areas changes more slowly than in the fingers. Thus hypoglycaemia will be detected later in such alternative sites.

- Fedele D, Corsi A, Noacco C, et al. Alternative site blood glucose testing: a multicenter study. *Diabetes Technol Ther* 2003;5:983-9.
- Glucose meters and diabetes management. New technologies: minimally-invasive and non-invasive glucose meters. U.S. Food and Drug Administration (FDA) Website. <http://www.fda.gov/diabetes/glucose#12>.

11. ORGANISING THE CLINICAL FOLLOW-UP

We recommend using a clearly organised paper or electronic file for proper patient follow-up. This will make it possible quickly to see what tests and examinations were recently carried out and which need to be planned.

Patients with a global medical file (Dutch acronym: GMD) can be recalled by the GP to perform certain examinations and tests in a timely manner. Such recalls can contribute to a better quality of diabetes care¹⁸⁹.

11.1. The Diabetes Passport

Since 1 March 2003 Belgium has had a Diabetes Passport¹⁹⁰. By means of the diabetes passport, patients are encouraged to seek the advice of their GP¹⁹¹. The patient's basic treatment does not require sophisticated interventions, as it could rather be qualified as "low-tech", and includes

- Careful anamnesis with targeted advice,
- Regular monitoring of
 - Weight
 - Blood pressure
 - Pulse
 - Foot examination using a monofilament
- and some biochemical parameters
 - Glycaemia
 - HbA1c
 - Lipids (total cholesterol, HDL, LDL, triglycerides)
 - Serum creatinine
 - Microalbuminuria.
 - ...
 - and an annual eye examination (to be performed by an ophthalmologist)

This enables virtually complete follow-up of diabetes. The data will make it possible to manage glucose regulation, develop an approach to cardiovascular risk factors and detect and treat chronic diabetes complications at an early stage.

¹⁸⁹ Renders, CM; Valk, GD; Griffin, S; Wagner, EH; Eijk van, JThM; Assendelft, WJJ. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings (Review). The Cochrane Database of Systematic Reviews. 2005;3.

¹⁹⁰

- Wens J, Nobels F, Baeten H, et al. De invoering van een diabetespas in België. Een opportuniteit voor een betere diabeteszorg. Huisarts Nu 2003;32:138-46.
- Wens J, Nobels F. De diabetespas in België: een evaluatie na 18 maanden beschikbaarheid. Huisarts Nu. In press.

¹⁹¹

- The use of the Diabetes Passport is advantageous for both the patient and the GP.
- For the patient there are certainly important advantages related to the appropriate use of the Diabetes Passport as a means of "patient empowerment". The patient will be more aware of necessary measures and examinations proposed to help manage his or her health. Writing down personal and achievable goals also helps patients better understand the goals towards which they are being guided by the various care providers. By means of better communication among themselves and with the patient, care providers can also develop a better image as a team focused on the patient. By making use of a structured approach, there is less risk of overlooking something, ultimately resulting in a greater chance that the entire care process will actually be carried out. By reimbursing dietary advice and foot care consultations in cases of increased risk of "diabetic foot" these essential aspects of diabetic care become more accessible.
 - For the GP, too there are incontestably important advantages related to the introduction of the Diabetes Passport. In addition to the recognition thus earned by the GP as coordinator of the patient's diabetic care, the Passport provides a more systematic approach to the implementation of this task. This structured care system guarantees completeness of care. In implementing all these items, the GP provides adequate diabetes care: no more, but certainly no less. The GP's task of encouraging the patient to apply the diet and foot care advice will perhaps become a little easier through better first-line management by reimbursement of these services.

Year 200..	Date	.. / .. / / .. / / .. / / .. / / .. / / .. / ..
Objectives	In each quarter	More or less frequently as required					
	Weight						
	Smoking						
	Exercise						
	Blood pressure						
	Fasting blood glucose						
	HbA1c (i.e. to)						
	Check medication						
	Annually	More or less frequently as required					
	Consultation with dietician*						
	Evaluation of foot risk						
	Consultation with podiatrist*						
	Cholesterol						
	HDL cholesterol						
	Triglycerides						
	Serum creatinine						
	Microalbumin						
	Electrocardiogram						
	Eye examination						
	Glucose meter inspection						

* **Reimbursed:** Dietary counselling 2 x 30 minutes / year, unless the patient enjoys this benefit within a different regulatory or contractual framework; foot care by a podiatrist 2 x / year in high-risk cases.

Although the use of the Diabetes Passport has been recommended on an ongoing basis, its introduction in Belgium faced a number of difficulties. A poor promotion campaign, a shaky start-up phase and the absence of a support infrastructure created significant resistance among care providers.

In other countries, too, the efforts to optimise diabetes care and to help patients be more self-reliant by means of the use of a Diabetes Passport have met with varying levels of success¹⁹².

¹⁹² In New Zealand the goal was to provide poorly controlled diabetes patients with a tool to help them in communication and education. A controlled intervention with 398 patients found a significant decline in HbA1c of 0.4% (p=0.017) after 12 months, but no changes in the knowledge or attitudes about diabetes, or about the presence of risk factors for tissue damage.

- Simmons D, Gamble GD, Foote S, Cole DR, Coster G. The New Zealand Diabetes Passport Study: a randomized controlled trial of the impact of a diabetes passport on risk factors for diabetes-related complications. *Diabetic Medicine* 2004;21:214-217.

In the Netherlands, a qualitative study was carried out to determine the types of resistance to the introduction of a Diabetes Passport in second-line care in preparation to generalised implementation. Although patients did indeed feel the Diabetes Passport would be a helpful tool, they expected little in the way of cooperation on the part of doctors. Doctors do indeed have mixed feelings about the introduction of Diabetes Passports. The most cited complaints on the part of doctors were primarily lack of motivation and lack of time. Diabetes nurses had the highest expectations in regard to the introduction of the Diabetes Passport and considered themselves to be the group that would perhaps best work with this new tool. The most significant barrier that was indicated was that the Diabetes Passport was difficult to fit into the already existing system of care.

- Dijkstra R, Braspenning J, Grol R. Empowering patients: how to implement a diabetes passport in hospital care. *Patient Educ Couns.* 2002;47:173-177.

The United States also started various projects involving a Diabetes Passport. In Arizona, a booklet greatly resembling the Belgian Diabetes Passport was made available, and in Cleveland (Ohio) diabetes patients are also offered a passport so that they can participate in determining their care regimen and receive the appropriate education.

- http://www.rho.arizona.edu/diabetes/RT2/downloads/HSAG_passport.pdf
- <http://www.cchs.net/quality/newsWinter2003.pdf>

In Finland, the introduction of a Diabetes Passport is seen as a key action for the future.

- <http://www.diabetes.fi/english/brochure.pdf>

Switzerland, too, introduced a Diabetes Passport to encourage patient self-care. There, too, the Passport is a booklet in which individual treatment goals are clearly set out and the most recent results of clinical examinations are recorded. However, there are hardly any results available in relation to all these efforts.

- Puder JJ, Keller U. Quality of diabetes Care: problem of patient or doctor adherence? *Swiss Med Wkly* 2003;133:530-534.

11.2. Agreeing on treatment objectives

The patient needs to overcome a certain level of resistance in order to be able to follow the proposed care regimen. There is a risk that the patient may ultimately “drop out” and limit his or her care to the resolution of acute problems without thinking of the longer-term risks.

Setting objectives is a useful aid in accomplishing them. Although the literature is convincing as concerns the fact that strict blood glucose, blood pressure, lipid control etc. guarantee the best results, not every patient is best served by such a strict regimen¹⁹³. An ideal therapy is often not achievable. In such cases it is better to work with realistic objectives that can be adapted to each patient’s needs¹⁹⁴. Joint discussion of what may be achievable takes time, but results in greater satisfaction and better results. This approach also helps limit frustration as regards what cannot be accomplished, both for the patient and the doctor.

The following principles should be applied in determining treatment goals:

- Treatment goals must be individually adapted to each patient. In doing so, scientific data, life prognosis, feasibility (the possibility for each patient to engage in and follow a specific therapy) and treatment risks (especially hypoglycaemia) should be taken into account¹⁹⁵;
- Treatment goals should be determined jointly with the patients and must be fully understood by him/her;
- The treatment goals should also be communicated to the other team members.

11.3. Treatment compliance

In order to limit the risk of developing complications, diabetes patients are advised to take a number of different medicines and to comply with a tight monitoring and follow-up schedule. These issues of treatment compliance in regard to medication and recommendations are often not taken into consideration while no problems are experienced.

The research into factors influencing therapy compliance is rather sparse. As opposed to dozens and dozens of RCTs on individual drugs and treatments, there are only a few comparable trials investigating the problem of treatment compliance. Although difficult to evaluate, treatment compliance failure is estimated at 30 to 50 % of all patients, independently of the type of disease, the prognosis or the setting¹⁹⁶.

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- <http://www.smw.ch/pdf200x/2003/39/smw-10290.pdf>

¹⁹³ When the Diabetes Passport was launched (01 March 2003) the goals were different than at the time of publication of the present recommendation (15 October 2005). The cut-off values for the treatment goals, used in the Diabetes Passport, were arrived at by consensus of the experts in the working group. Most scientific organisations like the American Diabetes Association (ADA), the International Diabetes Federation (IDF) and the European Association for the Study of Diabetes (EASD) mostly indicate only one cut-off value and no “scale”. The experts in the working group preferred to work with different cut-off values. The goal is primarily to reiterate that significant benefits can already be recorded, even if the “ideal” has not yet been attained.

¹⁹⁴ The risk factors are continuous variables. The goals are “moving targets”. Scientific research continues regularly to fine-tune these goals. They are likely to continue to be adapted to the information available in the future.

¹⁹⁵ The risk of hypoglycaemia is up to three times higher with more aggressive treatment of Type 1 diabetes patients.

- DCCT, the Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329: 977-86.

¹⁹⁶

- Morris LS, Schultz RM. Patient compliance: an overview. *Journal of clinical pharmacy and therapeutics* 1992;17:183-95.
- Sackett DL, Snow JC. The magnitude of compliance and non-compliance. In Haynes RB, Taylor DW, Sackett DL. Eds. *Compliance in health care*. 1979. Baltimore. The John Hopkins University Press.
- Lassen LC. Patient compliance in general practice. *Scandinavian Journal of Primary Health Care*, 1998;7:179-80.
- Donovan JL. Patient decision making. The missing ingredient in compliance research. *International Journal of Technology Assessment in Health Care*. 1995;11:443-55.
- Griffin S. A review of the factors associated with compliance and the taking of prescribed medicines. *British Journal of General Practice*. 1990;40:114-6.

Poor treatment compliance is also considered to be the culprit in significant financial losses, which in the US are estimated at an annual cost of 100 billion US dollars, which include 10% of hospital admissions and 23% of referrals to rest and nursing homes¹⁹⁷.

A recent comprehensive literature study¹⁹⁸ reviews thirty years of research on treatment compliance. The most important issues concern the definition and measurement of treatment compliance. Furthermore, this study also examines in depth the causes of poor treatment compliance and options for improvement¹⁹⁹.

To date there seems to be no evidence to prove that any one method has a more positive effect on treatment compliance than another. A supportive and non-judgmental approach, as well as an exploration of what is achievable with each individual patient seems to promote treatment compliance²⁰⁰. This suggests that a selective range of treatment compliance promoting strategies is necessary in order to be able to make appropriate choices for each patient and therapy. Training patients and doctors in communication skills can be a cost-effective way to increase treatment compliance and improve overall patient health.

The doctor-patient relationship

Exploring the patient's own ideas and expectations in connection with illness and health is fairly new in treatment compliance research²⁰¹. The doctor's attitude towards the patient and his or her ability to discover and respect the patient's concerns, to make easily comprehensible information available to the patient and to react empathetically are extremely important.

Studies on the relationship between communication and outcomes have demonstrated that there is a correlation between the quality of clinical communication and health outcomes²⁰². Agreement between doctor and patient in the analysis of the nature and significance of a clinical problem leads to an improvement and the solution of the problem. Increased patient participation in the contact improves satisfaction, treatment compliance and therapy outcomes.

¹⁹⁷ Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision making? *Society Science Medicine* 1992;34:507-513.

¹⁹⁸ Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. *Journal of Clinical Pharmacy and Therapeutics* 2001;26:1-12.

¹⁹⁹ Methods that have already been tried in order to increase treatment compliance include shorter-term courses of treatment, reducing the number of administrations per day, reducing the cost of medication, developing user-friendly packaging, numerous methods to remind patients of their medication, customising treatment, education, and patient satisfaction surveys. No single method stands out as being more suitable than any other, and this applies in particular to chronic treatments and asymptomatic diseases.

- Di Mateo MR. Enhancing patient adherence to medical recommendations. *JAMA* 1994;271:79-83.

A combination of education and strategies for behavioural modification appears to be necessary to achieve better treatment compliance. Some examples of these strategies are: involving the patient in the negotiation of his/her treatment goals, reducing the complexity of the treatment plan, fitting in and adapting the treatment to the individual patient's lifestyle, using reminder methods, encouraging support from family and friends, informing the patient about side effects and providing patients with feedback.

- Sanson-Fisher RW, Campbell EM, Redman S, Hennikus DJ. Patient-provider interactions and patient outcomes. *Diabetes education* 1989;15:134-138.
- Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Medical Care* 1998;36:1138-1161.

²⁰⁰ Mullen PD. Compliance becomes concordance. Making a change in terminology produces a change in behaviour. *British Medical Journal*, 1997;314:691-692.

²⁰¹ It seems important to know what significance patients assign to advice given them. When patients come for a consultation, they have certain ideas regarding illness and health. Once confronted with a specific diagnosis they will first try to deal with it, preferring not to give up control over their body by taking medication.

- Donovan JL, Blake DR, Fleming WG. The patient is not a blank sheet: lay beliefs and their relevance to patient education. *British Journal of Rheumatism* 1989;28:58-61.

²⁰² Ley P. Towards better doctor-patient communication. In Bennett AE ed. *Communication between doctors and patients*. 1976 Oxford: Oxford University Press, 77-96.

For this reason it can be very useful to fathom out the patient's own perception of his or her disease and the associated feelings and expectations, to learn active and sympathetic listening methods, provide clearer explanations, evaluate the patient's conceptions or apprehensions, negotiate a treatment plan and test the patient's intentions actually to comply with it. All these (new) skills can be acquired or improved with training.

12. Approach to Type 2 diabetes patient care

As is the case in most neighbouring countries, Type 2 diabetes patients are primarily managed with first-line care, while second-line care is normally used for Type 1 patients. The differentiation between first and second-line care should not be seen as a strict dividing line, to the extent that management of both Type 1 and Type 2 patients will require joint consideration and cooperation between the different disciplines. Over the last few years there has been ever more frequent demand for a properly functioning “shared care” model with coordination of care for Type 1 patients in the second line, and in the first line for Type 2 patients.

12.1. The diabetes team in second-line care

Rehabilitation agreement concerning self-monitoring for diabetes mellitus patients: the “Convention”.

In 1988 a system was set up in Belgium to help diabetes patients be followed in a structured manner to achieve maximum self-care. This involved agreements between the authority (RIZIV) that finances the system, and the hospitals that need to comply with certain requirements.

The purpose of the agreement is to offer a self-monitoring programme to selected diabetes patients, with conditional reimbursement from the RIZIV.

All diabetes patients treated on an outpatient basis and requiring at least two insulin administrations per day are eligible for the programme. An additional condition is that these patients should be able to and willing to learn how to adjust their treatment themselves on the basis of, among other information, self-monitored glucose values, and actually do so²⁰³.

A rehabilitation programme must fulfil at least the following aspects:

- It is individually defined
- It mandatorily involves the four essential aspects of diabetes treatment: insulin therapy, education, diet and exercise
- It mandatorily integrates the following medical prevention measures:
 - o Annual fundus examination by an ophthalmologist
 - o Annual kidney function check-up with detection of microalbuminuria
 - o Annual clinical examination for peripheral neuropathy
 - o Annual clinical foot examination
- It fits into an overall cardiovascular prevention programme managed by the treating physicians, including the GP. Special attention is paid to weight, blood pressure, lipids and smoking habits.

The rehabilitation plan²⁰⁴ must at least describe in greater detail the special strengths of the rehabilitation programme, the members of the rehabilitation team (by name) and the special conditions under which a

²⁰³ Depending on the complexity of the insulin treatment (two, three, several injections or insulin pump) there are different interest groups:

Group 1: Very intensive patients. These patients require three or more insulin administrations per day and carry out four glucose measurements per day.

Group 2: These patients also require three or more insulin administrations per day, but have less self-monitoring: Four all-day curves per week with a minimum of 60 measurements per month.

Group 3: These patients require two or more insulin administrations per day. Self-monitoring is even less necessary in this group. These patients will develop two all-day curves per week or a minimum of 30 glucose measurements per month.

²⁰⁴ A programme consists of two different interdependent aspects:

The education aspect: the mission of the diabetes team is to develop a strategy jointly with the patient that will lead to individual self-monitoring and self-control of diabetes. This includes:

- instruction in glucose measurement techniques and the related therapy adjustments,
- checking knowledge and skills
- skills and knowledge maintenance.

The device aspect: the necessary materials and supplies for self-monitoring are provided. This includes:

- a lancet holder
- one lancet for each instance of self-monitoring
- strips for glucose determination

diabetes patient can be accepted into rehabilitation, including his or her input or contribution and what he or she can expect from the rehabilitation agreement. The role of the GP in the rehabilitation to self-monitoring and the other aspects of diabetes treatment must be described in greater detail, as well as what the GP can expect from the hospitals in charge of rehabilitation.

To follow a prescribed rehabilitation programme, the diabetes patient must confirm his commitment in writing to do so, including compliance with a minimum number of glucose measurements. The diabetes team makes the patient aware of the importance of his/her own contribution/input in achieving the targeted goal and of the cooperation between the various care providers, primarily the GP but also the pharmacist. The medical prescription attached to the application must be signed by a diabetologist. This prescription comprises the specific education programme and the indications. Reimbursement is possible only following approval of the Advising Physician. The application is valid for a maximum of 12 months.

Specific rehabilitation programmes are reimbursed on a monthly basis for each diabetes patient. Prices and fees depend on the patient's reimbursement bracket²⁰⁵.

The programmes also require the collection of data to enable epidemiological evaluation and to further the quality of care²⁰⁶.

12.2. The diabetes team in first-line care

With properly structured cooperation, Type 2 diabetes can be entirely managed within first-line care²⁰⁷. At present, the existing cooperation between care providers is not optimally structured or organised²⁰⁸. However, significant efforts have been made over the last few years to improve the care provided to diabetes patients. The importance of certain disciplines in diabetes care, such as dieticians, podiatrists and reference nurses²⁰⁹ has only recently been recognised. Currently, diabetes educators are only used in second-line

-
- an operational glucose reading device answering to the patient's needs, and checked for reliability by the diabetes team.

- ²⁰⁵ Group 1: € 111.40; that is € 99.58 for self-monitoring materials and € 11.82 for education, administration and quality assurance.
Group 2: € 62.82; that is € 51.00 for self-monitoring materials and € 11.82 for education, administration and quality assurance
Group 3: € 25.41; that is € 21.86 for self-monitoring materials and € 3.54 for education, administration and quality assurance

The non-device aspect is adjusted to the Consumer Price Index on an annual basis. The rehabilitation institution may not demand any surcharges from diabetes patients. The medical services provided for in the nomenclature are not included herein, nor are individual treatments by psychologists or podiatrists. The abovementioned mandatory minimum medical prevention measures are also not included in the rehabilitation programme.

- ²⁰⁶ This is partially financed from the abovementioned fees at a flat monthly rate of € 0.25. The overall results are submitted on an annual basis to the Board of Approval and to the insurance committee of the medical care service.

²⁰⁷

- Greenhalgh PM. Shared care for diabetes. A systematic review. Occasional paper 67, London. The Royal College of General Practitioners, 1994.
- Griffin S. Diabetes care in general practice – meta-analysis of randomised controlled trials BMJ 1998; 317: 390-5.

²⁰⁸

- Currently, cooperation takes place via informal cooperation groups, and all too often it still stops with referral. For a number of aspects of care the GP may call on other first-line disciplines (dieticians, nurses, pedicurists, podiatrists, pharmacists etc.) and, if necessary, work with second-line professionals (ophthalmologists, internists/diabetologists). At best, these care providers will form a team coordinated by the GP. At present, the most important points in the interdisciplinary cooperation are the lack of clear task delimitation, task coordination and good communication.
- Sunaert P, Feyen L, Vyt A, De Maeseneer J. Interdisciplinaire samenwerking bij diabetesproblematiek. In: Multidisciplinaire aanpak van diabetes mellitus. De Pover M, Roosen Ph, Vyt A. [Eds.] p.195-216. Antwerpen – Apeldoorn. Garant. 2004.

²⁰⁹

- Reference nurses are nurses who, with the support of the organisation, specialise intensively in a specific field and transfer their knowledge and skills to their colleagues. If necessary, they also provide hands-on support to colleagues. The GP and other care providers can also, if they so wish, always contact our reference nurses for a discussion, together with the nurse concerned, concerning a specific patient. Currently, the following areas are included: wound care, colostomy care, diabetes, geriatrics and dementia, palliative care and social services.

care. How best to integrate these specially trained paramedics into first-line diabetic care is currently still under review.

12.2.1. Diabetology reference nurses

Nurses who teach self-care to diabetics have been reimbursed since 1 July 2003, while this had not been the case before. The new rule is part of a larger review of the home nursing nomenclature²¹⁰.

Education involves on the one hand a self-care course for new patients choosing at-home care once insulin injections have been prescribed²¹¹ and on the other, an appropriate two-hours education programme for patients unable to self-administer the injections. They receive instruction in lifestyle rules they will need to follow²¹².

The education programme is implemented by reference nurses specialised in diabetes care who, together with the home care nurse, ensure optimal diabetes care by means of a specific nursing care plan. This involves close cooperation with the patient's GP and/or diabetologist. This follow-up is not sil

entirely in the

Recently, the Government provided for reimbursement of podiatry services as first-line care for diabetes patients with a Diabetes Passport who are at increased risk of foot complications (Stage 2b onwards). A list of podiatrists accredited within the scope of the Diabetes Care Review Project is available on the Diabetes Passport website²¹⁴.

12.2.3. The Dietician

The dietician is the primary expert in the area of diet and nutrition. Dieticians/nutritionists follow a three-year higher education course (Bachelor's in Nutrition and Dietetics). Dieticians are therefore trained in professional diet consultations.

The profession of dietician was statutorily recognised in 1997 (R.O. 78 concerning the exercise of the healing arts, nursing and the paramedical professions). This Royal Order also stipulated the qualification requirements for exercising the profession and listed the technical services a doctor may delegate to a dietician.

Recently, the Government also provided for limited reimbursement of dietary counselling as part of first-line care. A list of dieticians accredited within the scope of the Diabetes Care Review Project is available on the Diabetes Passport website.²¹⁵

12.3. Communication between care providers

We advise patients to use their Diabetes Passport to improve the communication between the individual care providers. By means of the Diabetes Passport, each individual patient's goals are shared with the other care providers. This prevents patients from getting contradictory messages from the different care providers.

The focus of care should always be on the patient. More and more frequently, it is assumed that the patient has a central place in the decision-making process. Doctors and other care providers must therefore adequately inform, care for and support the patient in making the "right" decisions.

The Diabetes Passport also represents a tool for communication with the patient. It makes it possible to agree the most realistic and achievable goals with the patient. In addition, it also enables treatment priorities to be defined by mutual agreement. Clearly, the patient's role in doing so is essential.

This approach, in which the patient is an equal partner in the care process, requires a new approach to communication on the part of the doctor²¹⁶.

²¹⁴ <http://www.diabetespas.be/page?page=articles&orl=539&ssn=<r=&are=783&mi=515&mi=814>

²¹⁵ <http://www.diabetespas.be/page?page=articles&orl=539&ssn=<r=&are=285&mi=515&mi=529>

²¹⁶ Steward M. Brown JB, Weston WW, McWhinney IR, McWilliam CL, Freeman TR. Patient-Centered Medicine. Transforming the Clinical Method. Oxon: Radcliffe Medical press Ltd, 2003.

Patients with chronic conditions, such as diabetes patients, make treatment choices that best fit in with their own expectations and personal circumstances. They can therefore have distinctly personal reasons for not always following a strict treatment regimen.

- Vermeire E, Van Royen P, Coenen S, et al. The adherence of type 2 diabetes patients to their therapeutic regimens: patients' perspective. A qualitative study. *Pract Diabetes Int* 2003;20:209-14.
- Vermeire E, Van Royen P, Coenen S, et al. Therapietrouw bij diabetes type 2-patiënten vanuit het standpunt van de patiënt. *Huisarts Nu*. 2005;34:118-25.

Rather than blaming the patient if the goals are not achieved, the doctor should investigate why this is so.

- Donovan JL. Patient decision making. The missing ingredient in complex research. *Int J Technological assessment in Health Care* 1995;11:443-55.

If the desired goal is that patients should optimally comply with their treatment plan, then this rests on a responsibility shared between doctor and patient, with personally achievable goals being explicitly addressed. Exploring the patient's expectations in regard to his/her disease and treatment, and translating these individual expectations into achievable and realistic goals for the patient and together with the patient is an important communication job for the GP.

- Wens J, Vermeire E, Van Royen P, et al. GPs perspectives of type 2 diabetes patients' adherence to treatment. A qualitative analysis of barriers and solutions. Wens J, Vermeire E, Van Royen P, et al. GPs' perspectives of type 2 diabetes patients' adherence to treatment. A qualitative analysis of barriers and solutions. *BMC Family Practice* 2005;6:20.

There is now sufficiently strong evidence that, for care providers, certain instruction interventions result in more patient-oriented consultation management.

12.4. Patient associations

Vlaamse Diabetes Vereniging vzw [Flemish Diabetes Association, a non-profit organisation]

Ottergemsesteenweg 456
9000 Ghent
Tel: 09/220.05.20
Fax: 09/221.00.82
e-mail: vdv@diabetes-vdv.be
Website: www.diabetes-vdv.be

The Vlaamse Diabetes Vereniging (VDV) is an association serving the different aspects of diabetes. Its goals are:

- The prevention and care of diabetes and the improvement of the quality of life of all those touched by diabetes;
- Promoting the prevention of diabetes;
- Furthering early diagnosis of diabetes;
- Furthering prevention of complications by optimising treatment and care of diabetes patients, and by promoting self-care;
- Fighting social obstacles;
- The promotion of diabetes research.

The VDV had 22,500 members in 2005. The membership consists not only of diabetes patients and their entourage, but also of care providers. Its broad based membership enables the VDV to provide balanced information and to be an advocate for the needs of diabetes patients.

The VDV has a number of publications, including the bimonthly magazine Diabetes Info, which is distributed to all members. Care providers can subscribe to a monthly e-mail newsletter. The free Infoline (0800 / 96 333) answers questions asked by telephone and e-mail by people with diabetes and their entourage and by care providers. The VDV has 26 local chapters throughout Flanders, which bring the association as close as possible to people with diabetes. They organise information evenings, discussion forums and leisure activities, and make available self-care supplies at advantageous prices.

The VDV cooperates closely with the WVVH in Type 2 diabetes projects, e.g. the Flanders Diabetes Project, the Diabetes Care Review Project and the Diabetes Passport, and the present WVVH-VDV recommendation.

Social discrimination

In order to remove social discrimination against people with diabetes it is important to change the image society has of this disease²¹⁷. Most social obstacles in connection with diabetes are the consequence of preconceived opinions and an overestimation of the incidence of acute and chronic complications. Education, self-monitoring, treatment options for associated risk factors and intensive insulin therapy have helped significantly improve the outlook and prognosis of the great majority of people with diabetes.

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- Lewin SA; Skea ZC; Entwistle V, et al. Interventions for providers to promote a patient-centred approach in clinical consultations. [Review] The Cochrane Database of Systematic Reviews. The Cochrane Library, Copyright 2004, The Cochrane Collaboration. 2004, Volume (4).

In doing so, professionals concentrate among other things on the patient's complaints and expectations, on reaching agreement in regard to various treatment options, and on a sympathetic doctor/patient relationship. Training care providers in patient-oriented consultation management can increase patient satisfaction with the care they receive.

- Stott NC, Rollnick S, Rees MR, et al. Innovation in clinical method: diabetes care and negotiating skills. Family Practice 1995;12:413-8.

It is however possible, from a methodology point of view, to measure the effect of such training by means of physiological patient outcome data. To date there is no convincing evidence that patient-centred consultations result in better patient outcomes.

- Mead N, Bower P. Patient-centred consultations and outcomes in primary care: a review of the literature. Patient Education and Counseling 2002;48:51-61.

²¹⁷ Vuyt A, De Pover M, Roosen P. Multidisciplinaire aanpak van diabetes mellitus. Apeldoorn: Garant, 2004: 238.

In evaluating the risk profile, each diabetes patient must be regarded as an individual and not as a member of a group. This applies to job applications as well as to insurance contracts and requesting a driver's licence. The VDV publishes separate brochures on all the above issues.

Access to and reimbursement of diabetes care

In addition to medication, modern treatment of diabetes also requires the use of appropriate materials (such as injection material and supplies for blood glucose self-monitoring) as well as sound diabetes education (imparted by doctors, nurses, dieticians) to achieve optimal self-care.

Several services are currently not reimbursed, as they are not included in the nomenclature (diet consultation, education, etc.). This restricts access to these treatment options for some people (e.g. the disadvantaged).

Diabetes and employment

The right to work is a fundamental human right and thus also applies to diabetes patients. Nevertheless, people with diabetes can experience difficulties in looking for, or keeping, a job. In principle, all jobs are available to people with diabetes, provided that they have the proper training and are medically eligible for it.

Diabetes cannot be a cause for discrimination on application²¹⁸. People with diabetes must be evaluated on an individual basis: the specific requirements and risks of a specific job must be weighed against the diabetic's health condition and treatment methods (diet, tablets, insulin, self-monitoring).

Diabetes and the driver's licence

It is also desirable that the evaluation of a diabetes patient's driving safety be based on individual evaluation (as opposed to being classified as a member of the "diabetes group"). For this purpose, it is best to use a standardised relevant medical condition and driving performance questionnaire. This questionnaire should be answered in part by the treating physician²¹⁹, and partially by the patient²²⁰.

Diabetes and insurance

In subscribing to insurance policies, too, diabetes patients must be evaluated as individuals, taking into account all their risk factors. All too often, diabetics are evaluated as a group and therefore assigned a high risk score. This excludes them from certain types of insurance (e.g. hospital insurance), or forces them to pay an unjustifiably high premium surcharge (e.g. for life insurance).

It is therefore not appropriate systematically to refuse certain types of insurance to people with diabetes. This applies primarily to hospital insurance, but can also occur with insurance for a guaranteed minimum income²²¹.

²¹⁸ At present, there is a number of professions (safety functions, occupations requiring a C or D driver's licence etc.) that are, without exception, legally inaccessible to all diabetics treated with insulin. This ban is mainly based on the risk of hypoglycaemia, which is frequently overestimated. With today's modern therapies, however, some diabetics can meet the requirements associated with such jobs.

²¹⁹ The evaluating physician (who decides whether or not the patient is fit to drive) must not be the treating physician.

²²⁰ All necessary standards and certifications in connection with the physical and mental aptitude for driving a motor vehicle are available on <http://www.wegcode.be/wet.php?wet=9&node=bijl6>

²²¹ The insurance company needs to use a relevant medical questionnaire precisely in order to be able to evaluate the individual risk of an insurance applicant with diabetes objectively. This questionnaire should be adapted to the relevant type of insurance. It is thus evident that the question as to the presence or absence of hypercholesterolaemia is indeed relevant for underwriting life insurance, but not for car insurance.

13. CONCLUSION AND RECOMMENDATIONS

Core message	Degree of evidence
Systematic screening of the entire population for Type 2 diabetes is not advised. If risk factors are present, targeted opportunistic screening (case-finding) is recommended. (cf. 2.1)	3
In pregnancy, systematic screening for gestational diabetes is recommended, unless there are no risk factors at all. (cf. 2.2)	2
The diagnosis of Type 2 diabetes (mellitus) is made by means of two tests performed on venous blood. We recommend using the fasting glucose value for the diagnosis. Two values ≥ 126 mg/dl indicate diabetes. The use of an OGTT is not advisable for first-line diagnoses. (cf. 3.1)	3
The treatment of Type 2 diabetes is based on objectives that are individually customisable and should thus be achievable for each individual patient. We advise working with a tool (the Diabetes Passport) that increases patient participation and renders the specified objectives more concrete. (cf. 4 and 12)	3
Targeted and structured education by properly trained educators increases patient self-reliance for achieving his/her own personal goals (cf. 9).	1
Obese Type 2 diabetes patients should aim for a permanent weight reduction of 5 to 10% of their body weight. (cf. 5.2.1)	2
In obese Type 2 diabetes patients, pharmacotherapy is started with metformin. (cf. 6.1)	1
If treatment goals cannot be achieved with maximum oral therapy, insulin should be started without delay. (cf. 6.2)	1
Insulin treatment requires blood glucose self-monitoring. These measurements must be carried out on an intensive basis in the run-up to and the starting phase of the insulin treatment. (cf. 6.2)	3
Hyperglycaemia should not be undertreated due to unfounded fear of hypoglycaemia. Chronic hyperglycaemia always causes much greater morbidity and mortality in Type 2 diabetes than acute hypoglycaemia. (cf. 6)	2
Early detection and treatment of eye problems by an ophthalmologist can prevent blindness. (cf. 8.2.1)	2
All patients with Type 2 diabetes must receive maximum protection against cardiovascular problems. This includes: Smoking cessation counselling, blood pressure control and statin therapy. This applies all the more if microalbuminuria is found. If in doubt, a cardiovascular risk meter can clarify the usefulness of this	1

combination therapy. (cf. 7.1)	
At-risk feet must be proactively and systematically detected by means of inspection, palpation and monofilament examination. Severe orthopaedic ailments and/or ulcers should be referred to a multidisciplinary foot centre without delay. (cf. 8.2.4)	1
The treatment of Type 2 diabetes patients requires cooperation between all care providers concerned and also with the patient. (cf. 11)	3

14. Fundamentals

- Caring for people with diabetes requires systematic involvement of other, recognised (!) first-line providers: educators, (reference) nurses, dieticians, pharmacists, physiotherapists, psychologists, practice assistants.
- Structural cooperation with the second (and third) line of treatment is necessary, based on equality and complementarity and supported by validated care paths in which competitive concerns have no place.
- The exchange of information via the patient as conceived with the Diabetes Passport is essential in achieving this end, but is optimally accomplished in an automated manner enabling all care providers to review the patient's file.
- To increase the quality of care, a local diabetes bank should be developed to provide the GPs of the region with quality feedback.
- GPs and other physicians should develop the necessary communication skills to manage chronic patient care. In chronic care situations, special attention should be devoted to developing personal goals and voicing and discussing treatment compliance problems.
- The GP must be structurally supported in order to be able to assume his role as care coordinator. This requires mandatory registration of all diabetes patients in a GMD [Dutch acronym for Globaal Medisch Dossier, Global Medical File] at a GP's office of their choice.
- Caring for people with diabetes in general practice requires compensation that is in proportion to the duration and complexity of the care process. Such compensation should not invite short and frequent doctor/patient contacts.
- Every GP should be able to access quickly and easily available (free) evidence-based information (such as recommendations, Minerva etc.) in order to be able to perform objective management of diabetes patients.
- Patients should be able to gain temporary access to a glucose meter, a prick pen and test strips whenever necessary, as well as in the event of illness or insufficient therapeutic response. Patients on insulin (even if only one injection) should be able to have permanent access to supplies.
- In addition, patients should be able to get access to a limited number of test strips to perform self-monitoring over a short period of time.

15. RESEARCH AGENDA

- What is the validity of current early detection criteria (case-finding) in Type 2 diabetes? How often should this type of detection be repeated?
- How is ideal collaboration between GPs and other first-line workers developed in regard to diet advice? What is the ideal frequency for referral to the dietician in order to achieve the best possible outcome in Type 2 diabetes patients?
- What type and frequency of physical activity counselling delivers the best outcomes in Type 2 diabetes patients?
- When is it best to start oral antidiabetics, and when is it best to start insulin? What is the ideal step-by-step plan for combining therapies?
- What are the ideal prerequisites for starting insulin in first-line care?
- On the basis of what decision-making model can the approach to cardiovascular risk be improved in Type 2 diabetes?
- How can early detection of eye problems be improved? What are the ideal referral strategies in this case? What contribution can be derived from new technical options?
- What is the value of self-monitoring in the follow-up of Type 2 diabetes? How frequently should measurements take place and which parameters should ideally be used to obtain better outcomes?
- How can the Diabetes Passport and the use of a clear and easily accessible medical file improve the collaboration between care providers and patients to obtain optimal outcomes?
- What is the effect of shared care (clinical care paths) on the outcomes of diabetic care in Type 2 diabetes?

16. IMPLEMENTATION

This recommendation is the result of broad research that looked into the desirability of diabetes screening, the proper diagnostic procedures for Type 2 diabetes, the related goals, the wisdom of lifestyle counselling and self-care education as well as the correct type of treatment as concerns oral antidiabetics and insulin. The treatment of diabetes complications and the follow-up of cardiovascular risk factors were also discussed within the broader scope of shared care.

The point of departure was the “Consensus for the Detection and Treatment of Type 2 Diabetes Mellitus” published in 1997 as a result of a collaboration between the WVVH and the VDV.

A multidisciplinary group of authors was assembled to perform this task (Dr J. Wens, Prof. Dr P. Van Royen, Dr H. Bastiaens, Dr P. Sunaert and Dr L. Feyen (GPs) as well as Dr F. Nobels and Dr P. Van Crombrugge (endocrinologists)). They further developed and updated the scope of the study. To aid in obtaining answers to the various questions raised in the study, the relevant literature was systematically reviewed by means of the virtual library of the Cebam [Belgian Centre for Evidence-Based Medicine]. Searches targeted systematic reviews, whether or not with meta-analyses (DARE and Cochrane databases), quality recommendations (National Guideline Clearinghouse and Guidelines Finder UK) and primary literature (MedLine). The most significant keywords used throughout were the following MESH terms: diabetes mellitus, non-insulin-dependent, diabetes mellitus, Type 2. Searches concentrated on literature published after 2000. Depending on the different section headings, these search terms were combined with relevant key words. Clinical Evidence and Minerva were also used whenever relevant topics were found to be available in these sources. This resulted in a first draft entitled “Type 2 Diabetes Mellitus”.

A first working text was rewritten taking into account the remarks made by the experts: GPs Dres Thierry Christiaens, Koen Cornelli, Geert De Loof, Geert Goderis, Annie Goeman, Stefan Teughels and Bouma (Nederlands Huisarts Genootschap NHG – Dutch GP Association); endocrinologists Prof. Dr Chantal Mathieu, Prof. Dr Raoul Rottiers, Dr An Verhaegen; cardiologist Prof. Dr Benoit Boland, ophthalmologist Dr E. Smets, Ms Ria Patteet (nurse / diabetes educator), Ms M. Marcipont (dietician), Mr Guy Noldus and Ms Hilde Layaye (Flemish Diabetes Association VDV), Prof. Dr Guy De Backer (public health specialist) and Prof. Dr Erik Muls (preventive health care). A mention of a contributor as being an expert does not necessarily imply that each expert subscribes to the recommendation in every detail. Then the revised text was tested in four Flemish local quality groups [LQGs] (Heppen, Mortsel, Kortrijk and Herk-de-Stad).

The final text was amended taking into account the remarks from the LQGs and was then submitted to the editors of Huisarts Nu. Following a final edit, the recommendation was ultimately submitted to the CEBAM Validation Commission. The text will be updated on an annual basis, and the recommendation will be entirely reviewed after five years. In the follow-up, the primary focus will be on whether the key messages do not require changes; this will be decided on the basis of a systematic literature search in the literature for the previous year. The same search terms will be used in this literature search as in that underlying the development of this recommendation. Only meta-analyses, systematic reviews and controlled trials will be taken into account.

The authors and the members of the Recommendations Steering Group have no connection with the pharmaceutical industry. No conflicts of interest are known to exist.

17. LEVELS OF EVIDENCE

Pronouncements and opinions in the WVVH recommendations for good medical practice are based on a level of evidence that reflects the reliability of the pronouncements:

Level 1

The requirement for Level 1 is that there should be at least two studies with equivalent results, carried out independently from each other, and falling within one of the following categories:

- a good quality RCT;
- a good quality independent blind comparison of a diagnostic test with the reference test (i.e. with a target group of consecutive patients and where both the diagnostic and the reference test were performed);
- a good quality prospective cohort study with 80% or greater follow-up.

A highly consistent systematic review or meta-analysis of this type of article is also sufficient for this level of evidence.

As a conclusion for such studies we state that "*it has been demonstrated that ...*".

Level 2

The requirement for Level 2 is that there should be at least two studies with equivalent results, carried out independently from each other, and falling within one of the following categories:

- a moderate quality RCT;
- a moderate quality independent blind comparison of a diagnostic test with the reference test (i.e. with a limited portion of the target group or where the reference test is not performed on each subject);
- a moderate quality (retrospective) cohort study or patient monitoring study.

A highly consistent systematic review or meta-analysis of this type of article is sufficient for this level of evidence.

If there is only one study available out of those listed under Level 1, the result is a Level 2.

As a conclusion for such studies we state that "*it can be assumed that ...*".

Level 3

An absence of good quality comparative studies results in a third level of evidence, meaning that:

- there are no good quality RCTs;
- there is only one moderate quality study and there are no meta-analyses of moderate quality studies;
- the conclusions of the RCTs or meta-analyses are contradictory.

This level also includes the consistent opinion of at least two experts, a recommendation or conclusion arrived at after consideration of all available material and consensus within the group of authors. In all these cases we only refer to "*an indication that ...*" – or to that "*the working group is of the opinion that ...*".

18. Definitions

Abdominal obesity	In Caucasians, abdominal obesity is reported with a waist girth ≥ 94 cm for men and ≥ 80 cm for women. The term “central obesity” is used as a synonym.
IGT = Impaired glucose tolerance	Plasma glucose 2 hours after stressing = ≥ 140 mg/dl and < 200 mg/dl (7.8 mmol/l and 11.1 mmol/l)
Glucotoxicity	The adverse effect of high glucose levels on insulin secretion and insulin sensitivity
IFG = Impaired fasting glucose	Fasting plasma glucose with a value of ≥ 100 mg/dl and < 126 mg/dl (5.5 mmol/l and 7.0 mmol/l)
Hypoglycaemia	An event in which the typical signs of hypoglycaemia (sweating, shivering, palpitations and also concentration and behavioural problems and changes in consciousness) are combined with a plasma glucose concentration of ≤ 70 mg/dl (3.9 mmol/l).
LADA = Latent Autoimmune Diabetes of Adults	This is a special, slowly developing form of Type 1 diabetes. Diagnosis sometimes only becomes obvious because treatment started has little effect and the patient continues to complain of hyperglycaemia. In such cases, referral to a multidisciplinary diabetes team will become necessary.
Metabolic syndrome ²²²	Metabolic syndrome is diagnosed in the simultaneous presence of abdominal obesity and two concurrent factors out of a list of four. Abdominal obesity is defined as a waist girth ≥ 94 cm for European men and ≥ 80 cm for European women. Additional factors: <ul style="list-style-type: none"> - Triglycerides: ≥ 150 mg/dl (1.7 mmol/l) or treatment therefor - HDL cholesterol < 40 mg/dl (1.0 mmol/l) or treatment therefor - Blood pressure: systolic > 130 mmHg or diastolic > 85 mmHg or treatment therefor - Fasting plasma glucose > 100 mg/dl (5.6 mmol/l) or Type 2 diabetes diagnosed at an earlier stage.
MIDD = Maternally Inherited Diabetes and Deafness	In combinations of diabetes and deafness, genetic mitochondrial defects transmitted only through the maternal line should be taken into consideration: “Maternally Inherited Diabetes and Deafness”
MODY = Maturity-Onset Diabetes of the Young	This is a relatively frequent special form of Type 2 diabetes that occurs at an early age (before age 25) and which is hereditary as an autosomal dominant characteristic. A number of genetic defects have been found to be at the origin of this condition.
FPG = Fasting Plasma Glucose	
OGTT = Oral Glucose Tolerance Test	Proper performance of the OGTT 100 g stress test requires an accurate procedure. The test should be carried out in

²²² Definition according to the new IDF criteria. Available on http://www.idf.org/webdata/docs/Metac_syndrome_def.pdf.

	the morning after 8 to 14 hours' fasting, following several days of unrestricted diet (>150 g carbohydrates per day) and unrestricted physical effort. The patient must remain seated during the test and may not smoke.
Secondary diabetes	<p>Secondary diabetes is a form of diabetes in which another disease is at the root of the development of the diabetes. The most frequent causes of secondary diabetes are:</p> <ul style="list-style-type: none"> - Diseases of the pancreas: pancreatitis (alcohol abuse), neoplasia - Metabolic conditions: hemochromatosis - Endocrine disorders: hyperthyroidism, Cushing's syndrome, acromegaly, etc. - Use of diabetogenics: diuretics, corticosteroids, nicotine acid, etc.
Stress hyperglycaemia	Medical stress such as infection, trauma, surgery or use of certain drugs can result in temporarily increased glycaemia. This is called stress hyperglycaemia.
Gestational diabetes	Diabetes that develops during pregnancy.