DIET AND ALPHA-GLUCOSIDASE INHIBITION IN THE EARLY TREATMENT OF TYPE 2 DIABETES MELLITUS

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Voor mijn ouders

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Chapter 1

Introduction and outline

Introduction and outline

Type 2 diabetes mellitus (DM2) is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production resulting in a raised blood glucose (1). DM2 goes hand in hand with adiposity, hypertension and dyslipidemia, all components of the 'metabolic syndrome'. The majority of patients with DM2 die of atherosclerosis and its complications (2).

DM2 and other diseases such as heart diseases and cancer are an increasing problem around the globe, especially in the developed world (3). Currently, in the Netherlands the prevalence of DM2 is approximately 3.5% and this number is expected to increase by at least 32% in the next decades. This is due to the changing demographic characteristics (more elderly people), increasing problem of overweight and the improved and early detection of patients with DM (4).

In the Netherlands, patients with DM2 are predominantly managed by their general practitioner (GP). The management of DM2 confronts the GP with many challenges with respect to prevention, diagnosis and treatment. The GP has a role in promoting a healthy life style in all individuals, and especially those at risk for DM2 (Table 1.1). Next, the GP should diagnose DM2 as early as possible because a large proportion of patients have already developed complications at diagnosis, and the existence of such complications showed to be an unfavourable prognostic factor (5). For an early diagnosis the recognition of signs and symptoms of diabetes (e.g., thirst, unexplained weight loss, unexplained pruritus), and blood glucose screening in patients with an increased risk for DM2 is warranted (6). Once the diagnosis has been established, the GP has to closely monitor the patients' metabolic, cardiovascular, renal and ophthalmic status. The GP also has to screen for other complications, such as neuropathy, foot problems and sexual problems. At the same time, the GP has to work together with and co-ordinate the other primary care professional involved in the treatment of the patient (e.g., dieticians, practice nurses, podotherapist). Together with the other members of the multidisciplinary team the GP has to inform, educate and 'empower' the patient to cope with the consequences of the disorder. In addition, therapy should be initiated to correct possible (threatening) metabolic disturbances and to prevent complications.

It is important to note that the majority of patients with DM2 in general practice are asymptomatic and feel perfectly healthy. This particularly pertains to patients who are diagnosed coincidentally or by case-finding. In these patients, the treatment could therefore be merely regarded as a form of prevention, rather than as a treatment for illness. Especially in preventive treatments, the 'doubt' from the old adage 'in dubio abstine', should be taken seriously as medicalisation is at stake. Therefore, especially in patients with DM2, there is a need to achieve a maximum effect through the application of minimal interventions.

In this thesis we assessed the evidence base of two interventions in the treatment and prevention of DM2: diet and alpha-glucosidase inhibitors. In the first part of this thesis, the evidence for the usefulness of dietary treatment was assessed. We focused on dietary patterns of patients with DM2, and on factors that determine patients' motivation to change their diet. In the second part of this thesis, we assessed the effectiveness of oral treatment with alpha-glucosidase inhibitors, in the treatment and prevention of DM2.

Table 1.1. Risk factors for developing type 2 diabetes mellitus (8)

- A positive family history of type 2 diabetes
- Hypertension
- Existing cardiovascular disease
- Disorders of lipid metabolism
- Hindu, Turkish, Moroccan or Surinam descent
- Overweight
- History of gestational diabetes

Diet in type 2 diabetes mellitus

The evidence base for diet therapy in DM2

Diet and other life-style measures are traditionally seen as the cornerstone in the treatment of DM2 (7). The guidelines of the Dutch College of General Practitioners therefore recommend to refer all newly diagnosed patients to a dietician for individually tailored dietary advice (8). The major goals of dietary treatment are: (1) to reach and maintain a desirable body weight; (2) to reach and maintain optimal blood glucose levels, if necessary by balancing food intake with the use of oral medication or insulin; (3) to reduce (LDL) cholesterol levels; (4) to lower blood pressure; (5) to prevent or treat possible complications such as diabetic nephropathy. In order to achieve these goals, patients receive nutritional recommendations that are roughly in line with those for the general population (Table 1.2). These recommendations are based on a review of the literature and subsequent consensus meetings of experts (9, 10). The strength of the evidence is different per recommendation and many questions remain unresolved. In *chapter 2* we have assessed the evidence for all different aspects of diet therapy by means of searching and reviewing high quality systematic reviews.

Table 1.2. Nutritional recommendations for patients with type 2 diabetes mellitus (9)

- **Total energy intake**
  - Caloric intake aimed at reducing body weight in case of overweight, otherwise balanced with expenditure
- **Fat**
  - Total fat intake ≈30% of energy intake (less in case of overweight)
  - Saturated fat ≤10% of energy intake
  - Minimization of *trans* fat (<1 energy%)
  - Total cholesterol <300 mg/day
- **Carbohydrates**
  - ≥40 energy% of digestible carbohydrates per day
- **Protein**
  - 10-20 energy%, in patients with micro- or macroalbuminuria: 0.8 g protein/kg ideal body weight
- **Fibres**
  - 30-40 grams of soluble fibres per day

Dietary habits of patients newly diagnosed with DM2 and eating behaviour as a predictor of short- and long-term dietary changes

Although patients with DM2 are widely advised to adapt a healthier diet, little is known on their actual diet. This is especially true for newly diagnosed patients. Only a few studies on fat and total energy intake in these patients have been reported. One study in newly diagnosed patients with DM2 showed a relatively high intake of fat, as compared to the recommended intake (11). A study in patients with newly diagnosed diabetes reported no differences in intake of fat and total energy compared to non-diabetic subjects (12). Moreover, little is known about the adherence to dietary recommendations in patients with DM2 from the moment of diagnosis. Although some limited success has been reported in small samples of patients with diabetes (13), GPs are generally pessimistic about the long term effects of dietary advise, especially in regards to weight loss (14-16).

In order to improve the effectiveness of dietary treatment, studies are needed to assess the actual dietary habits of patients with DM2 and to determine factors that are relevant to their motivation to adapt and adhere to dietary changes.

In our studies of newly diagnosed patients with DM2, we investigated dietary intake (e.g., intake of total energy, fat) and eating behaviour (*chapter 3*). Eating behaviour results from a complex mix of biological, socio-cultural and psychological

mechanisms. To assess eating behaviour, we used the psychological concept of restrained eating and disinhibition of eating (i.e., emotional and external eating). Restrained eating refers to deliberately eating less in order to loose weight. Emotional eating is characterized by overeating triggered by mostly negative emotions such as grief and anxiety. External eating pertains to situations, when people eat more than planned or continue to eat when one's eaten fill of, as a result of the influence of external factors such as the good look or smell of food. Restrained, emotional, and external eating can be measured using a questionnaire which has been advocated for use in general practice (17).

In *chapter 3.1* we assessed fat and total energy consumption in a cohort of newly diagnosed patients with DM2 and compared it with the general population. In addition, we measured changes in fat and total energy consumption shortly after standardized dietary consultations and after four years of usual care. In the same cohort we measured restrained, emotional and external eating behaviours, and we compared these behavioural patterns with those in the general population (*chapter 3.2*). In addition, we assessed the relation between eating behaviour and fat and total energy consumption at diagnosis, and the relation between eating behaviour and changes in fat and total energy consumption following dietary advise (*chapter 3.2*).

Although restrained eating behaviour might seem a key target of dietary intervention in diabetes type 2, it is not unequivocal. Restrained eating is sometimes even described as being counterproductive. The 'restrained eating theory' states that patients who strive for weight reduction by eating less (restrained eating), will gain weight in the end, and therefore dieting might even be harmful (18). This is specifically important in DM2, as the importance of losing weight is one of the cornerstones of its treatment. Therefore, it is important that this 'dieting dilemma' is known to GPs, practice nurses and dieticians and is dealt with before encouraging people to eat less. In *chapter 3.3* we addressed this 'dieting dilemma', i.e. the paradoxical question whether or not restrained eating is associated with weight gain.

Alpha-glucosidase inhibitors for treatment of type 2 diabetes mellitus

If diet and exercise alone fail to sufficiently control blood glucose levels, starting oral drug therapy is recommended (8). To date, six classes of oral antihyperglycemic drugs are available: biguanides (metformin), sulphonylurea (e.g., tolbutamide), glinidines (e.g., repaglinide), thiazolidinediones (e.g., pioglitazone), dipeptidyl peptidase IV inhibitors (e.g., sitagliptin) and alpha-glucosidase inhibitors (e.g., acarbose) (19).

The choice for a first-line glucose-lowering drug depends on its effectiveness, safety, tolerability, user-friendliness and costs. Ideally, the drug should be able to prevent or delay diabetes-related mortality and morbidity, without causing dangerous or disturbing side-effects, is easy to use and has low costs. Thus far, no drug seems to meet all those demands. Metformin seems to have the best track record, since it has been shown to reduce mortality and diabetes-related complications more effectively

than sulphonylurea or insulin. However, these data are derived from one single study (20) and not confirmed in other trials (21). Metformin is contra-indicated in patients with impaired renal function, and a considerable proportion of patients experience gastro-intestinal side-effects. Sulphonylurea are the oldest available oral drugs for DM2 and widely used as first-line treatment. They have a clear effect on glycemic control, but, remarkably, beneficial effects on mortality or diabetes related morbidity that can directly be attributed to sulphonylurea have never been shown. Sulphonylurea may cause weight gain and carry the risk of (dangerous) hypoglycaemic events. Glinidines are short-acting insulin-secretagogues, and mainly effect post-prandial blood glucose levels. Data on the effects of glinidines on clinically relevant endpoints are still lacking. Preliminary studies on thiazolidinediones suggest beneficial effects on cardiovascular endpoints (22), however, this remains to be confirmed (23). Side effects of thiazolidinediones include weight gain and oedema. Therefore, these drugs are contra-indicated in patients with an increased risk for heart failure. Alpha-glucosidase inhibitors such as acarbose act by inhibiting the breakdown of complex carbohydrates in the small intestine, thereby reducing carbohydrate uptake and post-prandial blood glucose peaks. Because alpha-glucosidase inhibitors work solely in the gut, side effects are of gastro-intestinal nature and include diarrhoea, flatulence and stomachache. Weight gain, hypoglycaemic events or other life-threatening side-effects have not been observed, even at overdoses. However, rare cases of hepatic injury due to acarbose were described (24). In view of its safety record and the absence of weight gain, alpha-glucosidase inhibitors might offer a safe alternative for currently favoured oral treatment strategies in newly diagnosed patients with DM2, provided that alpha-glucosidase inhibitors are at least equivalent to other drugs with respect to their effects on mortality, morbidity and glycemic control.

In *chapter 4.1* we report a double-blind randomized trial on the effects of acarbose versus tolbutamide on plasma glycated haemoglobin, fasting and post-load blood glucose, plasma insulin, plasma lipids, as well as their side effects. We systematically reviewed the literature to assess the effects of alpha-glucosidase monotherapy (acarbose, miglitol, voglibose) as compared to all possible other interventions (*chapter 4.2*). In addition, we critically review a published meta-analysis that claims that acarbose reduces the incidence of myocardial infarctions (*chapter 4.3.1*). In response, the authors of this meta-analysis made comments on our systematic review. *Chapter 4.3.2* contains our reply to those comments.

The effectiveness of alpha-glucosidase inhibitors in patients with impaired glucose tolerance or impaired fasting blood glucose

DM2 is not a clear-cut disease, but merely the result of an arbitrarily chosen point somewhere between the absence of insulin resistance and normal insulin secretion, and advanced peripheral insulin resistance and absence of insulin production.

Therefore, the optimal moment to start treatment is not unequivocal. Specific criteria have been defined for those people who have a raised post-prandial and/or fasting blood glucose, but who do not meet the criteria for DM2. This condition is referred to as 'impaired glucose tolerance' (IGT) when post-prandial blood glucose levels are elevated, and 'impaired fasting blood glucose' (IFBG) in case of elevated fasting blood glucose (criteria: Table 1.3).

Table 1.3. Current definitions for diabetes mellitus, impaired glucose tolerance and impaired fasting blood glucose

	WHO 2006 (31)	ADA 2007 (32)	DCGP 2006 (8)
Diabetes Mellitus	FPG ≥7.0 **OR** 2HPG ≥11.1	Symptoms of diabetes* plus CPG ≥11.1 **OR** FPG ≥7.0 **OR** 2HPG ≥11.1†	Symptoms of diabetes* plus CPG ≥11.1 **OR** FPG ≥7.0 on two occasions
Impaired Glucose Tolerance	FPG <7.0 **AND** 2HPG 7.8-11.0	2HPG 7.8-11.0‡	No definition
Impaired Fasting Blood Glucose	FPG 6.1-6.9 **AND (if measured)** 2HPG <7.8	FPG 5.6-6.9‡	FPG >6.1 AND <6.9‡

All values are venous plasma glucose concentrations (mmol/l)
2HPG = 2-hours Plasma Glucose, glucose concentration 2-hours after ingestion of 75 grams glucose, CPG = Casual Plasma Glucose, casual is defined as any time of day without regard to time since last meal, FPG = Fasting Plasma Glucose, fasting is defined as no caloric intake for ≥8 hours
* The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss
† These criteria should be confirmed by repeat testing 'in the absence of unequivocal hyperglycemia'
‡ Excluding patients fulfilling the criteria for type 2 diabetes

If one decides to treat this condition, diet and exercises are an effective method to improve glucose tolerance and are recommended as first choice treatment (25). With life-style modifications, a relative-risk reduction (RRR) in the progression to DM2 of 58% may be achieved (26). Pharmacological treatment of IGT and IFBG may seem controversial, since it may implicate medicalisation of the non-ill. According to a limited number of studies, especially drugs that improve insulin sensitivity may be useful in IGT and IFBG. Studies have been carried out with metformin (RRR of 31%, endpoint DM2) (27), and rosiglitazone (RRR of 60%, combined endpoint diabetes and death) (28). In a large-scale multi-centre study with acarbose for patients with

IGT, it was found that acarbose might prevent or delay DM2 (RRR of 25%) and, interestingly, the data also pointed at a reduction of cardiovascular events. However, it should be noted that this study was heavily debated because of suspected bias (29, 30).

In this thesis we performed a systematic literature review assessing the effects of monotherapy with acarbose, miglitol or voglibose in subjects with IGT or IFBG with respect to the development of DM2, cardiovascular disease, glycemic control, serum lipid profile, blood pressure, body weight and side effects (*chapter 5*).

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Chapter 2

Limited evidence for effects of diet for type 2 diabetes from systematic reviews

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Abstract

Objective. Systematic reviews are an appraised method to summarize research in a concise and transparent way, and may enable to draw conclusions beyond the sum of results of individual studies. We assessed the results, quality and external validity of systematic reviews on diet in patients with type 2 diabetes.

Design, Setting, Subjects. We systematically searched for systematic reviews on nutritional interventions in patients with type 2 diabetes that used a reproducible search strategy in at least one major database that applied some form of quality assessment. We assessed quality and the external validity of the retrieved systematic reviews. Outcomes were defined as statistical meta-analyses or narrative results using a predefined and reproducible method.

Results. Six systematic reviews met the inclusion criteria, investigating dietary interventions in general (n=3), chromium supplementation (n=1), fish oil (n=1) or herbs and nutrition supplements (n=1). Quality assessment showed minimal/minor flaws in four cases and major/extensive flaws in two cases. All reviews had insufficient data needed to judge external validity. In reviews with minimal/minor flaws we found beneficial effects of very-low-calorie diets and fish oil supplements. However, the external validity of these results could not be assessed sufficiently.

Conclusions. Systematic reviews largely failed to produce knowledge beyond the sum of the original studies. Furthermore, judgment of external validity was hampered in most cases owing to missing data. To improve the quality and usefulness of systematic reviews of dietary interventions, we recommend the application of more focused research questions, but with broader inclusion criteria, for example, the use of observational studies.

Introduction

Diet is an important aspect in the management of type 2 diabetes. It is directly related to main treatment goals such as the establishment of a (near) normal body weight, control of plasma lipids and hyperglycaemia, renal protection and the avoidance of hypoglycaemic episodes (1). In order to establish beneficial dietary changes in patients with type 2 diabetes, a clinician has to be informed about many aspects of diet in type 2 diabetes, including the effects of macro- and micronutrients and food supplements. In addition, it is important to know how to bring about persistent beneficial changes in patients' dietary habits.

It is virtually impossible for both researcher and clinician to keep track of all published research in the field. Systematic reviews offer an appraised method to summarize all relevant studies in a concise and transparent way, and they may enable to draw conclusions beyond the sum of results of individual studies. In addition, systematic reviews may help researches to refine hypotheses, estimate sample sizes, and help to define future research agendas (2).

In the last decade, systematic reviews became increasingly popular. For example, the Cochrane Library, a collection of regularly updated high-quality systematic reviews, has grown from 36 systematic reviews in 1995 to 2356 systematic reviews in 2005 (4% of which dealt with nutrition (3)). A quick look in Pubmed (Medical Subject Heading 'diabetic diet') revealed more reviews (n=485) than clinical trials (n=360). Also, there is an increased awareness of the impact of systematic reviews for practice and research as can be read from different editorials in leading journals (4, 5). And, in an attempt to improve the uniformity and completeness of the reporting of systematic reviews, an evidence based guideline was developed (6).

It is important to distinguish systematic reviews from narrative reviews: in contrast to narrative reviews, systematic reviews should have a clear and narrow research question and should be conducted by a reproducible method. Therefore, systematic reviews are considered a scientific exercise in itself. However, still a considerable amount of so-called systematic reviews, especially those sponsored by the industry or non-Cochrane reviews, appear to have methodological flaws (7). Moreover, studies on the same topic that were found to be of good quality may produce contradictory evidence (8, 9).

In this study, we systematically searched, and critically appraised all systematic reviews on the topic of type 2 diabetes and diet. Our aims were to establish the highest levels of evidence by means of systematic reviews for different topics on diet and type 2 diabetes, to identify research gaps, and to analyze methodological problems in systematic reviews of studies in the nutrition field.

Methods

Search strategy

We searched PUBMED (which contains MEDLINE and a number of additional journals), EMBASE and the Cochrane Database of Abstracts of Review of Effects (DARE). In addition, we checked bibliographies from guidelines and known reviews, we contacted experts in the fields and we searched our own personal files. We used a combined sensitive search strategy for 'systematic reviews', 'type 2 diabetes' and 'dietary interventions' (Appendix A). The last search was in December 2005 for PUBMED and DARE, and in October 2005 for EMBASE. Two independent reviewers (FVDL, JVB) assessed all titles and abstracts and extracted all data. Interrater agreement was calculated by kappa-statistics. If a study could not be excluded on basis of title and/or abstract alone, we retrieved the full article for further assessment.

The inclusion criteria were: (1) studies primarily aiming to review the literature, (2) using a reproducible search strategy, in (3) at least one major electronic database (MEDLINE, EMBASE or CENTRAL), (4) the main focus should be on a nutritional intervention in patients with type 2 diabetes (reviews that studied interventions to change eating habits and/or reduce body weight, and studies assessing the effects of a specific food composition or foodstuff (e.g., fish oil) were included) and (5) there should be some form of assessment of the quality of included studies. This way, systematic reviews were distinguished from narrative ones.

We excluded studies in another language than English, Dutch, German, French or Italian.

Data extraction and quality assessment

Two reviewers (FVDL, JVB) extracted independently all data and assessed quality on a pre-tested data extraction form. Cases of disagreement were resolved by consensus or by consultation of the third reviewer (RA). We extracted the following items:

1) General aspects: language, sponsor, and background of authors
2) Methods / quality items: sources used, inclusion criteria, exclusion criteria and restrictions (language, unpublished studies), number of reviewers that assessed abstracts and extracted data, handling of missing data, method of quality assessment, method of investigating and handling heterogeneity (including heterogeneity caused by differences in setting), statistical method of meta-analyses, method of incorporating quality items in results. External validity: setting (e.g., general practice, hospital), patients (e.g., duration of type 2 diabetes), type of intervention, length of follow-up.
3) Outcome assessment: outcomes were first subdivided in type of intervention (e.g., very-low-calorie diet, low-glycemic index diet, etc.); next we clustered the result per type of intervention (e.g., effect on body weight, effect on blood glucose). We considered the following as being an outcome from a systematic

review: (A) numeric data from meta-analyses with appropriate handling of possible heterogeneity or (B) an overall judgment of the effect of a certain intervention, using a predefined method, ideally taking into account quality and heterogeneity. A straightforward list of the results and/or conclusions of the included studies was not considered to be a result of a systematic review. The following outcomes were extracted: mortality, diabetes-related morbidity (cardiovascular disease, nephropathy, retinopathy, neuropathy) and quality of life, body weight (or body mass index), indicators for blood glucose (glycated hemoglobin, blood glucose, plasma insulin), risk factors for cardiovascular disease (plasma lipids, blood pressure), indicators for renal disease (creatinin) and compliance.

Overall quality was assessed with the Overview Quality Assessment Questionnaire (OQAQ), a validated tool for the critical appraisal of systematic reviews (10). The instrument consisted of nine questions (yes, no, cannot tell) about different aspects of the methodological quality and one overall score rated from 1 (extensive flaws) to 7 (minimal flaws). Both reviewers discussed and rated all included studies. In case of disagreement, a third reviewer (RA) was consulted. In addition, we assessed whether and how heterogeneity was assessed, and we evaluated whether and how the results of the quality assessment were incorporated in the results.

External validity is the extent to which results are applicable to other circumstances. It cannot be formally tested and judgment depends on study aspects with respect to patients, treatment regimens, settings and length of follow-up (11). Although, no guideline for formal assessment of external validity exists, we attempted to gain insight in external validity by recording whether the systematic reviews assessed the following characteristics of included studies: patient characteristics (age, sex, duration of diabetes, body weight), details of treatment regimens, setting (country, level of care) and length of follow-up.

Results

The search in PUBMED, EMBASE and DARE, resulted in 153, 1533 and 166 records, respectively. In EMBASE, the number of records was significantly higher compared with other sources because the search string for 'systematic reviews' was made less specific owing to browser differences. The kappa for interrater agreement was 0.87 (95% confidence interval (CI) 0.73-1.00). We included six systematic reviews (Table 2.1) (12-18).Two articles referred to the same systematic review (16, 18). Ten other systematic reviews were initially included, but excluded after reading the full article: seven systematic reviews because it was unclear whether and how quality assessment was done (19-25) one because its focus was on both diabetic and non-diabetic renal disease (26), one systematic review did not study the effects of diet, but

the impact of weight gain in patients with diabetes (27), and one systematic review focused on enteral nutritional support for specific subgroups of patients with diabetes (e.g., post-operative, slow-healing ulcers) (28).

All other records were excluded on basis of the title and/or abstract. We kept track of the reasons for exclusion for a random sample of 50 records for each database. The possible reasons were: (1) the study was not a systematic literature review, (2) the study did not focus on patients with type 2 diabetes, (3) the study did not focus on a dietary intervention or (4) a combination of two or three of the previously mentioned reasons. This yielded the following results for PUBMED: (1) 14%, (2) 14%, (3) 10%, (4) 62%; EMBASE: (1) 6%, (2) 0%, (3) 10%, (4) 84%; DARE: (1) 0% (DARE only includes systematic reviews), (2) 72%, (3) 2%, (4) 26%.

Characteristics and quality of systematic reviews (Tables 2.1 & 2.2)

Of the six included systematic reviews two focused on strategies, including diet, that promote weight loss in patients with type 2 diabetes (13, 14). One investigated dietary advice in general (12), and three other studies focused on the effects of specific dietary interventions: the use of chromium supplements (15), fish oil supplements (16) both herbal remedies and dietary supplements (17).

In all systematic reviews more than one source had been used: varying from two major electronic databases and reference checking (15), to searching in nine databases (14). The inclusion of studies in the systematic review differed widely: four of six reviews included only randomized studies, the other two also included non-randomized studies (13, 17). All systematic reviews selected studies in type 2 diabetic patients, but in addition also studies with healthy volunteers (15, 17), and patients with impaired glucose tolerance or type 1 diabetes were included (17). One review restricted inclusion to studies with obese patients with type 2 diabetes (13). Three reviews applied a minimum study duration for inclusion of 1 (16), 6 (12), or 12 (14) months.

In all systematic reviews two investigators performed data extraction. Three systematic reviews reported that in case of missing data the original authors were contacted (12, 14, 15), but it remains unclear whether these attempts were successful. One systematic review reported additional data from one author (16), but it remains unclear whether the same effort was made for other missing data.

Internal validity, that is, the quality of included studies, was assessed by the Jadad scale (12, 16, 17), by the method of Chalmers et al. (15, 29), the method recommended by the Cochrane Collaboration (14), or by an own, separately published method (13). But, even though all six systematic reviews reported some form of quality assessment, it was unclear in three systematic reviews how quality data were incorporated in the (weighing of) results (13, 15, 17). In the other three systematic reviews the quality data were integrated narratively (12) or by sensitivity and metaregression analyses (14, 16). Four systematic reviews reported methods to handle heterogeneity (12, 14-16), the other two did not report or perform an assessment of

Table 2.1. Characteristics and quality of systematic reviews on dietary interventions for type 2 diabetes

Study	Sources (n)	Inclusion criteria	Assessment of study quality	Assessment of heterogeneity	Incorporation of quality in results	Data synthesis method
(12)	7	Studies: randomized controlled trials, subjects: ≥18 years, >90% with type 2 DM; interventions. dietary advice aimed at reducing weight or severity of type 2 diabetes, duration: ≥6 months	A (high) to C (low) scale adapted from Jadad	Visual inspection forest-plots, Chi^2- and I^2-test, subgroup analyses	Narrative	Statistical meta-analyses & narrative
(13)	5	Studies controlled and uncontrolled studies with data that permitted calculation of effect sizes, interventions: different kinds of strategies to promote weight loss*; subjects: obese adults, type 2 DM; outcomes: measure of weight loss; other same setting should be applied for treatment and controls	Assessment of (0 low - 21 high)· overall design, selection of study sample, specification of illness, description of intervention, clarity of outcome definitions, directness and objectiveness of outcome measures	Unclear	Unclear	Statistical meta-analysis
(14)	9	Studies: randomized controlled trials, interventions· weight loss/control strategies with diet, physical activity, or behavioural interventions*, subjects: ≥18 yrs, type 2 DM, duration· ≥12 months (follow-up); outcomes. weight or BMI	Selection, attrition and detection bias assessed separately	Sensitivity analyses, meta-regression analyses	Sensitivity- and meta-regression analyses	Statistical meta-analysis
(15)	3	Studies: randomized controlled trials, interventions: chromium supplementation, control placebo or active (e.g., picolinate or yeast); subjects: healthy people, type 2 DM, glucose intolerance†	Selection, attrition, detection bias assessed in published data-extraction form	Chi^2-tests	Unclear	No meta-analysis for type 2 DM subgroup; narrative

Table 2.1 continued

Study	Sources (n)	Inclusion criteria	Assessment of study quality	Assessment of heterogeneity	Incorporation of quality in results	Data synthesis method
(16)	7	Studies: randomized controlled trials, interventions: fish oil compared with placebo or vegetable oil, subjects: adults, type 2 DM; duration: ≥1 month, outcomes: 'clinically relevant outcome measures'	Jadad criteria (0 low - 5 high)	Chi^2 - tests, funnel plots, sub-group analyses, sensitivity analyses	Sensitivity analyses	Statistical meta-analysis
(17)	5	Studies: controlled trials; interventions: herbs and supplements, subjects: type 1 or 2 DM, IGT or those specifically at risk for diabetes, healthy volunteers†; other: english language	Jadad criteria	Unclear	Unclear	Evidence rated by predefined criteria, data from observational studies used as additional evidence

Abbreviations: BMI, body mass index; DM, diabetes mellitus; IGT, impaired glucose tolerance
* We only considered results for the dietary interventions
† We only considered results for patients with type 2 diabetes

heterogeneity (13, 17). Examples of methods used to assess heterogeneity were: Chi-square tests (12, 15, 16), and sub-group analyses (12, 14, 16). Four systematic reviews accounted for assumed heterogeneity with the use of a random effects model (12, 14-16).

Statistical meta-analyses were presented in three systematic reviews (13, 14, 16) and planned in two other systematic reviews but owing to low numbers of included studies results were presented narratively (12, 15). One review rated the evidence by using the US Preventive Task Force Criteria and American Diabetes Association Evidence Grading System for clinical recommendations (17).

Details about external validity are summarized in Table 2.3. All but one systematic review reported details of treatment regimens. The setting and the duration of diabetes were the least frequently reported.

Table 2.2. Methodological quality of included systematic reviews according to Overview Quality Assessment Questionnaire (OQAQ) (10)

Study	(12)	(13)	(14)	(15)	(16)	(17)
1 Were the search methods stated?	Y	Y	Y	Y	Y	Y
2 Was the search reasonably comprehensive?	Y	Y	Y	Y	Y	Y
3 Were the inclusion criteria reported?	Y	Y	Y	Y	Y	Y
4 Was bias in the selection of the studies avoided?	Y	Y	Y*	Y	Y	Y*
5 Were the criteria used to assess validity reported?	Y	Y	Y	Y	Y	Y
6 Was validity assessed using appropriate criteria?	Y	N†	Y	Y	Y	Y
7 Were methods used to combine findings of studies reported?	Y	Y	Y	Y	Y	Y
8 Were findings of relevant studies combined appropriately?	Y	N	Y	Y	Y	N
9 Were the conclusions supported by reported data?	Y	Y	Y	Y	Y	Y
10 Overall quality (1-7)¶	7	2	6	7	7	3

Y = yes, N = no

* Number of authors that searched trials not reported.

† Allocation concealment, method of blinding and attrition not assessed, own developed scoring form. Instrument not validated

¶ Overall score should be based on the answers to the first nine questions. We used the following guidelines: if the 'no' option was used on question 2, 4, 6 or 8, the review is likely to have major flaws (awarded with a score of 3 or less)

Outcomes of the systematic reviews

Dietary advice in general. One systematic review focused on dietary advice in general for patients with type 2 diabetes (12). Eighteen studies were included, but nine of these compared dietary advice with dietary advice and exercise or behavioural interventions. The nine studies on dietary interventions were sub-divided in three comparison groups: an ADA exchange diet versus a reduced fat diet (two studies), a low-fat diet versus a moderate fat or low-carbohydrate diet (five studies) and very-low-calorie diet versus low-calorie diet (two studies). Statistical meta-analyses could not be performed owing to the low number of studies, heterogeneity and low quality of included studies, thus no conclusions were drawn.

Table 2.3. Report of items related to external validity

Study		(12)	(13)	(14)	(15)	(16)	(17)
Patients.	Age	+	-	-	+	+	-
	Sex	+	-	-	-	+	-
	Duration of diabetes	-	-	-	-	+	-
	Body weight or BMI	+	-	+	-	-	-
Details of treatment regimens		+	-	+	+	+	+
Setting	Country	+	-	-	+	-	
	Care level (e.g., primary care)	+	-	-	-	-	-
Length of follow-up		+	-	+	+	+	+

Information about characteristics of included studies are reported adequately (+) if the information is reducible to individual included studies; (-) = not reported

Diet for losing or controlling body weight. In two systematic reviews, diet for the purpose of controlling or losing weight was being studied as a part of a broader research question that also included other interventions for controlling weight (e.g., exercise). A systematic review published in 1996 included 89 studies of which, 40% involved dietary interventions (13), 72% of includes studies were non-experimental (one-group pre-post-test design). In the main meta-analysis, all dietary approaches were considered together and the lengths of the interventions ranged from 'immediate' outcomes to more than 1 year. Dietary interventions (ADA reduced calorie, very-low-calorie diet, protein sparing modified fast diet) lowered body weight by approximately 9 kg (20 lb) and reduced glycated haemoglobin by 2.7%.

Another systematic review of more recent date investigated dietary and behavioural interventions to reduce body weight. Twenty-two studies were eligible for inclusion in the meta-analyses. However, pooled results for diet-only studies were sparse. A meta-analysis of two studies compared very-low-calorie diet with low-calorie diets (14), this resulted in a decrease in body weight of 3 kg (95% CI 0.5 to 6.4) in favour of the very-

low-calorie diet. In an additional meta-analyses, the effects of treatment in individual study arms (i.e. pre-test value considered control, post-test value intervention), the effect of 'usual care' was a decrease of 2 kg in body weight (95% CI 0.6 to 3.5) and low calorie diet resulted in a decrease of 3.7 kg (95% CI 2.3 to 5.1). Details for 5 out of 8 items necessary to assess external validity were missing (Table 2.3).

Effects of supplements. Althuis et al. reviewed the effect of chromium supplements on glucose and insulin concentration (15). Only four of the included studies were performed in patients with type 2 diabetes. Duration ranged from 8 to 24 weeks and the dosage of chromium ranged from 10.8 µg in yeast to 1000 µg chromium piccolinate. No meta-analyses in this subgroup were performed. No overall result of the systematic review in the type 2 diabetes subgroup was given, as the results of the individual studies were inconclusive.

Farmer et al. performed a systematic review on the efficacy of fish oil supplementation in patients with type 2 diabetes mellitus. Eighteen studies were included in the review. The dosage of fish oil ranged from 1.1 to 5.2 grams eicosapentaenoic acid and 0.3 to 4.8 grams docosahexaenoic acid, and the control interventions were placebo tablets or vegetable oil. The duration of studies ranged from 3 to 24 weeks. In meta-analyses, the use of fish oil resulted in a statistically significant decrease in triglycerides of 0.56 mmol/l (14 trials, 95% CI 0.40-0.71) and a statistically significant increase of LDL-cholesterol of 0.24 mmol/l (11 trials, 95% CI 0.05 to 0.43). No statistically significant effects were found for glycated haemoglobin, fasting glucose, total- and HDL-cholesterol and body weight.

Finally, Yeh et al. reported results of a systematic review on the effects of herbs and dietary supplements (17). They included 108 trials with 26 different substances that were subdivided in three main groups: single herbs, combination herbs and vitamin/mineral supplements. No statistical meta-analyses were performed. Instead, evidence was rated by using two different sets of criteria as mentioned before. Whether the summarized trials of one certain compound was awarded the highest level of evidence (level I, level A), did not depend on the quality of the trials. Nor was a 'level 1' label a guarantee for a clear outcome. For example, the conclusions for the substance *Coccinia indica* (ivy gourd) was that 'the potential role of Coccinia indica warrants further study', which was awarded with the highest level of evidence (I, A). This way, 'preliminary' or 'suggestive' evidence for, or 'potential effects' on glycemic control were found for ginseng, fenugreek, nopal (a cactus species), *gymnema sylvestre, momordica charantia, aloe vera,* traditional Chinese medicine and vanadium formulas were found. In addition, 'preliminary' evidence for no effect was found for *bauhinia forficate, myrcia uniflora* and combination formulas in Native American medicine. Inconclusive results were reported for ivy gourd, garlic species, holy basil, fig leaf, milk thistle, combination formulas in Tibetan medicine, chromium, magnesium, L-Carnitine and alpha-lipoic acid. Results for studies with type 1 and type 2 diabetic patients were considered together; however only four studies were done in type 1 diabetic patients.

Discussion

Our review of systematic reviews of diet in patients with type 2 diabetes showed that most systematic reviews resulted in inconclusive findings, and if a statistically significant finding was reported, interpretation was difficult because data necessary to assess external validity were mostly lacking. Therefore, to assess the value of nutritional interventions in type 2 diabetes, systematic reviews are currently not helpful. A 'technical review' such as published by the American Diabetes Association (1) may provide a comprehensive overview of the evidence for the different topics in dietary treatment of type 2 diabetes, but it should be noted that such a narrative approach is susceptible for many sources of bias.

Previous studies attempted to review systematic reviews and meta-analyses in the fields of asthma (7), back and neck pain (8, 30, 31), analgesia and anaesthesia (9, 32), emergency medicine (33) and surgery (34). With no exception, those studies discussed the (predominantly low) quality of systematic reviews. The applicability of the results for practice was not a topic and none of those studies assessed external validity. We are not aware of any comparable study in the field of nutrition.

The results of our exercise have been influenced by factors on three different levels. First, the approach of a systematic overview of systematic reviews has its own strengths and limitations. Second, outcomes are directly influenced by the methodological quality of the included systematic reviews. And finally, the results are influenced in an indirect way by the studies included in the systematic reviews.

Strengths and limitations of a review of systematic reviews

Because no clear-cut guidelines for the systematic evaluation of systematic reviews exist, we roughly followed similar methodology as in normal systematic reviews. This means that we tried to reduce selection and detection bias by rigorous methods in defining in- and exclusion criteria, searching of studies, extracting data, quality assessment and combining results. We experienced problems in the assessment of quality, external validity and method of reporting and combining outcomes. With respect to quality assessment, we used the OQAQ, to date the only validated instrument to rate quality of systematic reviews. In addition we assessed two other important aspects of quality, namely the method of heterogeneity assessment and the method of incorporating quality aspects in the results. The fact that the OQAQ fails to rate those aspects is a drawback of the instrument. Our results showed that the method of incorporation of quality in the results is unclear in three out of seven cases, confirming previous findings that there is substantial room for improvement regarding the incorporation of quality data in the results (35, 36). The assessment of external validity was the second problem we encountered. This is an underexposed topic in the appraisal of systematic reviews (37). As there are no accepted guidelines on how external validity of systematic reviews should be assessed, we used a self-developed approach. We found that data necessary to assess external validity is mostly

missing, and this hampers the judgment of generalizability of the results. Finally, we had difficulties in establishing the outcomes. Systematic reviews are original research in itself, and should therefore add new information to what is already known. We decided *a priori* that results from statistical meta-analyses or overall judgment of effectiveness reached by predefined methods should be considered outcomes of a systematic review. Doing so, we only found clear outcomes in the systematic review on fish oil supplements (16). The other systematic reviews yielded no outcomes (12, 15) or very limited outcomes of which the external validity remained largely unclear (13, 14, 17).

Quality of included reviews

Overall quality according to the OQAQ was good: five out of seven systematic reviews had minor to minimal flaws. The two studies with low scores on the OQAQ (13, 17) both failed on the issues of heterogeneity assessment and incorporation of quality in the results, whereas among the other systematic reviews only one study failed on the issue of incorporating quality (15). The relatively high scores for quality can for a large extent be explained by the inclusion criteria we applied. We decided *a priori*, that only systematic reviews that reported to have searched in at least one major database, and that had done a quality assessment were included. Therefore, all systematic reviews automatically scored 'yes' in three out of nine questions in the OQAQ.

Despite those overall good quality scores, it is quite remarkable that the results are mostly inconclusive. One reason might be in the so-called 'stainless steel' law of systematic reviews, that is, the more rigorous the review, the less evidence that an intervention will be effective (38).

Another reason for the inconclusive results might be that, except for the reviews on fish oil and chromium supplementation, reviews had broad instead of focused research questions resulting in a *post hoc* division in treatment groups (12-14, 17). A more optimal approach in, for example the systematic review on herbs (17), would be that each herb would be investigated in a single systematic review. Only that way, sufficient detail and transparence can be achieved.

Quantity and quality of studies included in the systematic reviews

It is very difficult to conclude about the quantity and quality of primary studies from an overview of systematic reviews. The number of studies that actually exists, and the method and rigorousness of the selection method determine the quantity of primary studies in systematic reviews. All studies scored 'yes' on the question whether search strategies were reasonably comprehensive. So differences in numbers of included studies will be largely determined by differences in inclusion criteria. The two reviews about dietary advices in general (12) and interventions aimed at reducing weight (14) included 18 and 22 studies respectively. This is a relatively low number of studies, especially when one considers the broadness of the topic. The other review on weight

loss interventions retrieved 89 studies (13). This difference might be explained by the fact that the latter review included studies of short duration and did not exclude uncontrolled designs. Unfortunately, this review was at high risk for bias (OQAQ score 2) and failed to produce data for the assessment of external validity.

Recommendations for future research

We conclude that currently there is only scarce evidence from systematic reviews for diet in patients with type 2 diabetes. However, this finding should not lead to the conclusion that dietary treatment is useless. After all, absence of evidence does not imply evidence of absence (39). To effectively assess the state of the evidence and to identify the needs for new primary studies, we recommend performing systematic reviews with more focused research questions but broader inclusion criteria, such as inclusion of short-term studies and the cautious use of non-randomized studies (3, 40).

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Appendix A

1 (http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html accessed 17-01-2005)

(("systematic review*" OR "systematic literature review*" OR meta-analysis [pt] OR meta-analysis [ti] OR metaanalysis [ti] OR meta-analyses [ti] OR evidence-based medicine OR (evidence-based AND (guideline [tw] OR guidelines [tw] OR recommendations)) OR (evidenced-based AND (guideline [tw] OR guidelines [tw] OR recommendation*)) OR consensus development conference [pt] OR health planning guidelines OR guideline[pt] OR cochrane database syst rev OR acp journal club OR health technol assess OR evid rep technol assess summ OR evid based nurs OR evid based ment health OR clin evid) OR ((systematic [tw] OR systematically OR critical [tw] OR (study [tiab] AND selection [tiab]) OR (predetermined OR inclusion AND criter* [tw]) OR exclusion criter* OR "main outcome measures" OR "standard of care") AND (survey [tw] OR surveys [tw] OR overview* OR review [tw] OR reviews OR search* OR handsearch OR analysis [tw] OR critique [tw] OR appraisal OR (reduction AND risk AND (death OR recurrence))) AND (literature [tw] OR articles OR publications [tw] OR publication [tw] OR bibliography [tw] OR bibliographies OR published OR unpublished OR citation OR citations OR database OR internet [tw] OR textbooks [tw] OR references OR trials OR meta-analysis [mh] OR (clinical [tw] AND studies) OR treatment outcome)) NOT (case report [ti] OR editorial [ti] OR editorial [pt] OR letter [pt] OR newspaper article [pt]))

#2
(("Diabetes Mellitus, Type II"[MeSH] OR "Insulin Resistance"[MeSH] OR "Metabolic Syndrome X"[MeSH] OR "Obesity in Diabetes"[MeSH] OR impaired glucose tolerance [TW] OR "glucose intolerance" [TW] OR "insulin resistance" [TW] OR "obese diabetes" [TW] OR "obesity diabetes" [TW] OR "obese diabetic" [TW] OR MODY [TW] OR NIDDM [TW] OR "non insulin dependent" [TW] OR "noninsulin dependent" [TW] OR "non insulindependent" [TW] OR "noninsulindependent" [TW] OR "non-insulin dependent" [TW] OR noninsulinodependent [TW] OR "non insulin treated" [TW] OR "noninsulin treated" [TW] OR "non insulintreated" [TW] OR "noninsulintreated" [TW] OR "non-insulin treated" [TW] OR noninsulinotreated [TW] OR ((non insulin [tw] OR noninsulin [tw] OR type 2 [TW] OR type II [tw]) AND diabetes [tw]) OR type 2 DM [TW] OR type II DM [TW] OR DMNID [TW] OR "type II diabetes" [TW] OR "type 2 diabetes" [TW] OR "type II diabetic" [TW] OR "type 2 diabetic" [TW] OR diabetes type 2 [TW] OR diabetes type II [TW] OR diabetes mellitus type 2 [TW] OR diabetes mellitus type II [TW] OR "adult diabetes" [TW] OR "maturity onset diabetes" [TW] OR "late onset diabetes" [TW] OR "stable diabetes" [TW] OR "adult diabetic" [TW] OR "maturity onset diabetics" [TW] OR "late onset diabetics" [TW] OR "stable diabetics" [TW] OR metabolic syndrome [TW] OR syndrome X [TW]) NOT ("Diabetes Insipidus"[MeSH] OR "diabetes insipidus" [TW]))

#3
(("Diet"[MeSH] OR "Diet, Sodium-Restricted"[MeSH] OR "Diet, Protein-Restricted"[MeSH] OR "Diet, Fat-Restricted"[MeSH] OR "Diet, Vegetarian"[MeSH] OR "Diet Therapy"[MeSH] OR "Diet, Mediterranean"[MeSH] OR "Diet, Macrobiotic"[MeSH] OR "Diet, Atherogenic"[MeSH] OR "Diabetic Diet"[MeSH] OR "diet therapy"[Subheading] OR "Dietetics"[MeSH] OR "Nutrition Therapy"[MeSH] OR "Dietary Supplements"[MeSH]) OR ("diabetic diet" [TW] OR "diet therapy" [TW] OR "diet treatment" [TW] OR "dietary treatment" [TW] OR "dietary counseling" [TW] OR "dietary fat" [TW] OR "dietary fats" [TW] OR "dietary sugar" [TW] OR "dietary sugars" [TW] OR "reducing diet" [TW] OR "weight management" [TW] OR fat restricted diet [TW] OR carbohydrate diet [TW] OR "carb diet" [TW] OR restricted diet [TW] OR glycemic diet [TW] OR dietary advice [TW] OR Mediterranean diet [TW] OR atherogenic diet [TW] OR vegetarian diet [TW] OR diabetic meal [TW] OR sugar diet [TW] OR vegetable diet [TW] OR fat diet [TW]))

#4 #1 AND #2 AND #3

Chapter 3.1

Fat intake in patients newly diagnosed with type 2 diabetes: a 4-year follow-up study in general practice

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Abstract

Background. Although treatment targets for the consumption of dietary fat in type 2 diabetes are well accepted, little is known about the actual fat consumption by newly diagnosed patients or the dietary adjustments that they make in the following years.
Aims. To measure fat intake in patients with type 2 diabetes in general practice at diagnosis, shortly after dietary consultation, and after four years.
Research Design and Methods. This is a prospective cohort study that included 144 Patients from 33 general practices (49% male, mean age (SD) 57.6 (8.2) years) with newly diagnosed type 2 diabetes mellitus. All patients were referred to a dietician and fat consumption (main outcome measure) was assessed at diagnosis, eight weeks and after four years with a 104-item food-frequency questionnaire. Reference values for fat consumption were obtained from an age-matched sample of a population-based survey.
Results. At diagnosis, total energy intake was 10.6 MJ/day and cholesterol intake 300 mg/day. Total fat consumption was 40.9%, saturated fatty acids 15.0%, monounsaturated fatty acids 14.3% and polyunsaturated fatty acids 9.2% of energy intake. All levels except for polyunsaturated fatty acids were significantly unfavourable compared with those from the general population. After eight weeks, all levels except saturated fatty acids, which was lower, had decreased to levels similar to those in the general population. After four years there was a slight increase in consumption of total fat and monounsaturated fatty acids but consumption of cholesterol and saturated fatty acids decreased further.
Conclusions. We conclude that patients with newly diagnosed type 2 diabetes have an unfavourable fat consumption at diagnosis. They adapt a more desirable consumption shortly after diagnosis, and sustain this improved dietary behaviour after four years. Recommendations regarding consumption of total- and saturated fat are, in contrast to those for cholesterol, by far not met by patients in general practice.

Introduction

The treatment of type 2 diabetes mellitus requires counselling on lifestyle modifications and dietary advice. Consultation with a registered dietician is advised in most guidelines for type 2 diabetes (1, 2). The recommended dietary advice should be tailored to patients' individual needs and aims. Diet therapy aims at reducing risk factors such as overweight and dyslipidemia. To achieve these aims, (modest) weight loss by reducing total energy intake and the proportion of total fat (<30% of energy intake) as well as a reduction of saturated fat intake (<10% of energy intake) and cholesterol intake (<300 mg/day) are strongly recommended. Moreover, minimising trans-unsaturated fatty acid intake and a modest intake of polyunsaturated fat (~10% of energy intake) is advised (1).

Although these guidelines are based on solid evidence from mostly experimental studies, they do not take into account the normal dietary habits from the general population. This might be partly because little is known about the fat consumption by recently diagnosed patients with type 2 diabetes in general practice, nor about alterations in dietary habits after diagnosis and treatment. In the United Kingdom Prospective Diabetes Study, the intake of total fat in a sample of 65 patients both at baseline (38.2% of energy intake) and after three years (36.9% of energy intake) was higher than the recommended 30 to 35% of energy intake (3). Data from a Dutch cross-sectional study showed no significant differences between diabetic and non-diabetic subjects regarding total energy intake or the consumption of total, saturated or polyunsaturated fats (4).

The necessity for sensible treatment targets, which are rooted in the population that is aimed at, has been discussed before in relation to type 2 diabetes mellitus. So far, targets for the treatment of type 2 diabetes mellitus do not account for what is feasible for patients in normal daily life (5). Therefore we investigated the fat consumption of patients with newly diagnosed patients with type 2 diabetes in general practice. The development of diabetes is associated with unfavourable eating habits such, as high consumption of total and saturated fat (6-8). We expected that the amount of energy and the amount and type of dietary fat consumed by patients newly diagnosed with type 2 diabetes is unfavourable when compared with the intake by the general population. Confirmation of this hypothesis would support the above-mentioned advice to refer all newly diagnosed patients with type 2 diabetes to a dietician.

We conducted a study with the following research questions: what is the fat consumption of patients with newly diagnosed type 2 diabetes in Dutch general practice compared with reference values for the general population? What are the alterations in fat consumption eight weeks after the initial diagnosis and referral to a dietician according to the Dutch guidelines for treatment of type 2 diabetes (2) and what is fat consumption after four years of follow-up compared with initial consumption in these patients?

Methods

This study was designed as a prospective cohort study. Reference values for the general population were obtained from the Dutch National Food Consumption Survey (DNFCS) 1998 (9).

Patients and practices

Forty-six general practitioners working in 33 general practices throughout the Netherlands included patients with newly diagnosed type 2 diabetes aged between 40 and 70 years. Diabetes mellitus was defined according to the criteria established by the World Health Organization (10): patients were eligible for the study when they had complaints suggestive for diabetes mellitus and a fasting blood glucose (FBG) ≥6.7 mmol/l and <20.0 mmol/l. In patients with asymptomatic newly diagnosed diabetes, the FBG had to be ≥6.7 mmol/l at two or more occasions.

Treatment

In accordance with the Dutch guidelines for the treatment of type 2 diabetes mellitus (2), all included patients were referred to a registered dietician. Dietary intervention consisted of two consultation sessions within a 4-weeks period, in which patients received dietary advice concerning all aspects of medical nutritional therapy for diabetes, tailored to their individual needs. The dieticians were informed about baseline fat consumption in all patients. Otherwise, the dieticians did not receive extra training nor used special protocols. Patients who still had a FBG ≥6.7 mmol/l after eight weeks were eligible for oral anti-diabetic therapy. These patients were asked to participate in a 30-weeks randomised controlled trial comparing acarbose with tolbutamide (11). After these thirty weeks, all patients received usual care by their GP.

Measurements

Measurements took place at diagnosis, after eight weeks, and after 4 years. The consumption of dietary fat was measured using a 104-item food-frequency questionnaire (FFQ), in which the past month is used as the reference period (12, 13). This questionnaire was filled out by the patient and checked for errors by the investigator. Values for total energy per day (MJ/day), total fat (% of energy intake), saturated fatty acids (% of energy intake), monounsaturated fatty acids (% of energy intake), polyunsaturated fatty acids (% of energy intake) and cholesterol (mg/day) were calculated using a computer program (VET Expres1.02, BaS Nutrition Software, The Netherlands) designed especially for the questionnaire. At the 4-years measurement, an updated version of the questionnaire was used (Wageningen University, The Netherlands, not published), including an updated calculation program (Komeet 3.0, BaS Nutrition Software, The Netherlands).

Body weight and height were measured without shoes and with light clothing. Data on medical history, co-morbidity and use of medication were obtained from the patient's record by the GP. Additional visits to a dietician or the use of other sources for dietary information were recorded with a short questionnaire. At four years follow-up the GP made the same assessment on medical history and co-morbidity. Furthermore, the GP provided information about the use of anti-diabetic and cholesterol-lowering medication during the interval. Central laboratories (Andreas Hospital Amsterdam for baseline and short term, Canisius Wilhelmina Hospital Nijmegen for 4-years measurements) using standard techniques and reference ranges measured HbA_{1c} and lipids. Glucose measurements were performed locally using a calibrated glucose analyser.

Reference values

Data from the Dutch National Food Consumption Survey 1998 (DNFCS) were used to serve as reference values for fat intake by the general population. The DNFCS is a cross-sectional study in a representative sample of the Dutch population, comprising 6250 subjects (aged 1-97 years) using a 2-days dietary record method. To match with the cohort of patients with newly diagnosed diabetes, we used the proportion of subjects aged 40-70 years (n=2296).

Statistical analysis

Results are given in mean ± standard deviation (SD). For comparison between groups (i.e. missing / non-missing, male / female), Student's two-sample t-tests were performed. For comparison of results between subsequent measurements, Student's one-sample test was used. Additionally, a repeated measure analysis was performed to assess an overall time-effect. In order to correct for multiple testing, alpha was divided by the number of tests used. Therefore, for the T-tests $P<0.0024$ and for the repeated measure analysis $P<0.0072$ was considered significant.

Ethics approval

This study was performed in accordance with the declaration of Helsinki. The protocol for the 8-weeks study was approved by the Central Medical Committee for Studies in General Practice. The Local Ethics Committee of the University Medical Centre Nijmegen approved the protocol for the 4-years study. All patients gave their informed consent.

Results

The general practitioners included 144 patients with newly diagnosed type 2 diabetes. Baseline measurements were performed in all 144 patients; the 8-weeks measurements were performed in 110 of the 144 patients. 106 Patients participated in the long-term

follow-up (4-years measurement) after a mean of 3.9 years (SD 1,0) (Figure 3.1.1). The baseline characteristics of these 144 patients are displayed in Table 3.1.1. With respect to blood glucose and lipid profile the study population was representative for patients newly diagnosed with type 2 diabetes (14). Baseline results of patients who did not participate in the 8-weeks or 4-years evaluation did not differ significantly from results of the patients whose measurements were not missing (data not shown).

Table 3.1.1. Baseline characteristics in 144 newly diagnosed patients with type 2 diabetes in general practice

	n	Mean	SD
Male / female	69/75		
Age (years)	144	57.8	8.3
Body mass index (kg/m^2)	134	29.5	5.2
Fasting blood glucose (mmol/l)	144	10.5*	6.7-19.6†
HbA_{1c} (%)	131	9.0	2.6
Diastolic blood pressure (mmHg)	134	86	10
Systolic blood pressure (mmHg)	134	145	20
Total Cholesterol (mmol/l)	130	6.2	1.1
LDL Cholesterol (mmol/l)	125	3.9	1.0
HDL Cholesterol (mmol/l)	126	1.1	0.3
Triglycerides (mmol/l)	131	2.7	1.5

* Median; † Range

Fat consumption

Table 3.1.2 shows the mean (SD) values for energy intake and fat consumption for newly diagnosed patients with type 2 diabetes at diagnosis, after 8-weeks and after four years. Compared to reference figures for the general population, patients had a higher intake of energy and fat consumption. The mean changes for the three possible intervals are shown in Table 3.1.3. At 8-weeks follow-up, we found a decrease of total energy intake, total fat, saturated fatty acids and monounsaturated fatty acids. Polyunsaturated fatty acids and the relative cholesterol intake (mg/MJ) did not change significantly. At 4-years consumption of total fat and monounsaturated fatty acids increased significantly compared to 8-weeks but remained significantly lower than at baseline. Consumption of cholesterol decreased significantly compared to baseline and 8-weeks. Other values did not differ significantly from 8-weeks. The repeated measure analysis showed similar results with exception of the fact that the difference in

consumption of total fat between 8-weeks and four years was not significant. Male and female patients showed similar fat consumption at baseline, except for energy and cholesterol intake, which was higher in men. Women showed a more profound decrease in the consumption of total fat, monounsaturated fatty acids and saturated fatty acids at both 8-weeks and 4-years measurement (data not shown). When stratified for body weight (BMI <25, ≥25 and ≤30, >30 kg/m^2), results were similar. In both our study at all three time-points, and in the reference figures for the general population, the people with BMI >30 kg/m^2 reported the lowest energy intake (data not shown).

Table 3.1.4 reports the percentage of patients that meet the guidelines for fat consumption. The percentage of patients that met the guideline regarding saturated fatty acids (≤10% of energy intake) increased from 7.6% at baseline to 27.4% at 4-years measurement. Similarly, the percentage of patients that consumed less than 7% of energy intake by way of saturated fatty acids increased from 0.7% to 9.4%.

Table 3.1.2. Consumption of total energy and fat by patients newly diagnosed with type 2 diabetes compared to reference values for the general population of similar age. All values are means (SD)

	Newly diagnosed patients with type 2 diabetes			Reference values
	Diagnosis (n=144)	8-weeks (n=110)	4-years (n=106)	population (n=2296)
Energy intake (MJ/day)	10.6 (3.4)	8.3 (2.2)	8.9 (2.7)	9.1 (2.8)
Total fat (En%)	40.9 (7.3)	35.5 (7.0)	37.7 (7.8)	36.3 (6.7)
Saturated fatty acids (En%)	15.0 (2.8)	12.5 (2.6)	11.9 (3.1)	14.4 (3.4)
Monounsaturated fatty acids (En%)	14.3 (3.0)	11.8 (3.1)	12.8 (3.5)	12.6 (2.9)
Polyunsaturated fatty acids (En%)	9.2 (3.2)	9.3 (3.0)	9.9 (3.9)	6.8 (2.5)
Cholesterol intake (mg/day)	300.8 (123.3)	226.3 (95.2)	201.1 (99.7)	225 (112)
Cholesterol intake (mg/MJ)	28.7 (8.2)	27.5 (8.5)	22.5 (6.0)	25.1 (11.3)

En% = % of energy intake

Table 3.1.3. Changes in consumption of total energy and fat by patients newly diagnosed with type 2 diabetes: mean changes from diagnosis to 8-weeks, from diagnosis to 4-years and from 8-weeks to 4 years. A negative value indicates a decrease in time.

	Change in mean difference Diagnosis – 8-weeks (n=110)	Change in mean difference Diagnosis – 4-years (n=106)	Change in mean difference 8-weeks – 4-years (n=86)
	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
Energy intake (MJ/day)	-2.2 (-2.6, -1.7)	-1.8 (-2.3, -1 2)	0.5* (0.09, 0.9)
Total fat (En%)	-5.1 (-6.6, -3.5)	-3.0 (-4.8, -1 2)	2.5 (1.1, 3.9)
Saturated fatty acids (En%)	-2.4 (-3 0, -1.8)	-3 1 (-3.8, -2.3)	-0.5* (-1.1, 0.1)
Monounsaturated fatty acids (En%)	-2.5 (-3.1, -1.8)	-1 5 (-2.3, -0.6)	1.0 (0.4, 1.6)
Polyunsaturated fatty acids (En%)	0.3* (-0.4, 0.9)	0.9* (0.0, 1.7)	0.9* (0.0, 1.8)
Cholesterol intake (mg/day)	-63 1 (-77 8, -48.3)	-99.7 (-120.0, -79.4)	-33.6 (-48 3, -18.8)
Cholesterol intake (mg/MJ)	-0.3* (-1.5, 1.0)	-6 2 (-7.8, -4.6)	-5.6 (-7.2, -4.0)

All values are significant (p<0 0024) except those indicated with an asterisk (*). Significance tests are done with an alpha of 0.0024 (0.05:21) in order to account for multiple testing; En% = % of energy intake

Plasma lipids, glycemic control and body weight

After eight weeks and two consultations with a dietician 25.7% of the patients had a fasting bloodglucose <6.7 mmol/l. HbA_{1c}% had decreased from 9.0 tot 7.8%, all plasma lipid values except for HDL-cholesterol and triglycerids had improved at 8-weeks measurement (data not shown). After 4 years, HbA_{1c}% and plasma lipids had significantly improved compared to baseline and, except for triglycerides, to 8-weeks measurement. BMI decreased at 8-weeks measurement (29.5 to 28.3 kg/m^2, p<0.01) but was back at its baseline value at 4-years measurement.

Diabetes treatment

At 4-years measurement 19 of the 106 patients (18%) were still treated with lifestyle modification alone and for two patients the use of medication was not known. The use of cholesterol lowering medications increased from 10/144 (7%) at baseline, to 34/106 (32%) at 4-years follow-up (unknown for 2 patients). On average, after the first two visits, patients visited a dietician 0.6 times per year (SD 0.9). 77% of the patients visited a dietician less than 1.0 times per year, 13% had between 1 and 2 consultations, and 10% had 2 or more consultations.

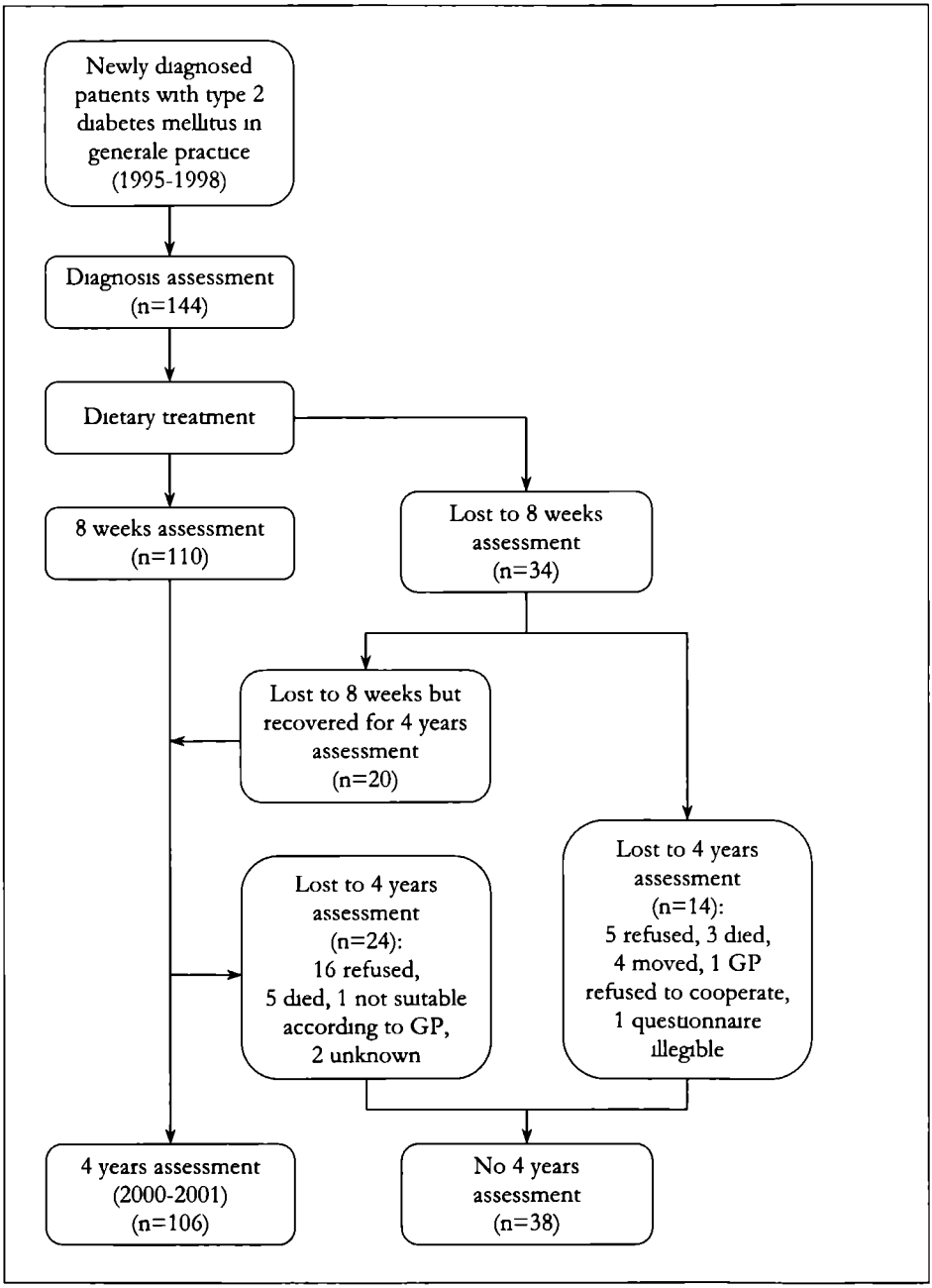

Figure 3.1.1. Study flow diagram

Table 3.1.4. Proportion of patients newly diagnosed with type 2 diabetes at diagnosis, after 8-weeks and after 4-years that meet recommendations for the consumption of fat. All numbers are percentages (%)

		Newly diagnosed patients with type 2 diabetes			
		Diagnosis (n=144)	8-weeks (n=110)	4-years (n=106)	Recommended*
Total fat	≤30 En%	8.3	21 8	17.0	<30 (35) En%
	≤35 En%	21.5	45.5	37.7	
Saturated fatty acids	≤7 En%†	0.7	2 7	9.4	
	≤10 En%	7.6	20 9	27.4	<10 En%
	≤12 En%	15.3	50.0	57.5	
Polyunsaturated fatty acids	<9 En%	41 7	39.1	40.6	
	9-11 En%	36.1	39.1	30.2	~10 En%
	>11 En%	22.2	21.8	29.2	
Monounsaturated fatty acids	<9 En%	2.8	11.8	13.2	
	9-11 En%	12.5	38.2	25 5	‡
	>11 En%	84.7	50.0	61 3	
Cholesterol	≤200 mg/day†	16.0	47.3	54.7	
	≤300 mg/day	60.4	84 5	93.4	<300 mg/day

* ADA 2002, † Patients with LDL ≥2.6 mmol/l may benefit from saturated fatty acids ≤7% of energy intake and a cholesterol ≤200 mg/day, ‡ No specific recommendation; En% = % of energy intake

Discussion

Summary and interpretation of main findings

This study showed that patients in general practice at the moment that type 2 diabetes was diagnosed have an unfavourable fat intake compared to reference values for the general population. Shortly after the first dietary consultation, fat consumption decreased to levels similar to the general population. After four years, consumption of total fat had increased again, but was still lower than baseline. This increase was due to a higher intake of both poly- and monounsaturated fatty acids. The intake of cholesterol was decreased at the 8-weeks assessment and decreased further after four years.

The observed changes in the reported fat consumption may be due to several factors. First, ongoing treatment for type 2 diabetes, including education by GP's and dieticians, may have a sustained effect on habits. The patients included in our study

received usual care by their GP's, including an initial dietary advice in two consultations, according to the Dutch guidelines on diabetes. Some patients got more consultations on their own initiative or advised by their GP. No further interventions or efforts were made to improve compliance with diet. Of course, from the data of this observational study we cannot measure the contribution of specific aspects of diabetes counselling on the outcomes. But because we observed patients who received usual care, we feel that the presented results should be regarded as the minimally achievable goals that can be reached regarding fat consumption.

Second, food habits in the general population are not constant. In the adult general population in The Netherlands, consumption of total fat decreased almost 1% of energy intake but saturated fatty acids increased about 1% of energy intake from 1992 to 1998 (9). In our study the decrease of total fat consumption was more profound and the consumption of saturated fatty acids decreased. Therefore, it is not likely that our main results are merely a reflection of the trend in the general population.

Thirdly, the content of foodstuffs is not constant. Since 'light' and low-fat products are fashionable nowadays, manufacturers may tend to change the amount and sorts of fat in their products. In theory it is possible that someone who does not alter his consumption in terms of foodstuffs, will have a different consumption in terms of nutrients because the content of the foodstuffs have been changed. We have not identified studies in the literature to assess the influence of this potential bias.

Finally, the method of measuring food habits is a possible source of bias (15). All available instruments to measure food intake are subject to recall-bias and therefore a real gold standard doesn't exist. We used a semiquantitative food-frequency questionnaire, whereas the reference figures for the general population are based on a dietary record method. Therefore, the comparison of the data from patients with type 2 diabetes with those from the general population should be interpreted with caution.

Strengths and limitations of this study

The main strengths of our study were that it provided follow-up data: a) of sufficient length. b) in a cohort of newly diagnosed patients with type 2 diabetes. Data that provides knowledge of what happens during a patients' 'career' is important because it is helpful for formulating feasible treatment goals; c) with a good long-term participant rate of 74%; d) rooted in general practice. In the Netherlands as in the UK, approximately 75% of patients with type 2 diabetes are treated by their GP.

One of the drawbacks of our study was that a relatively high number of patients did not complete the FFQ at 8-weeks measurement, partially due to loss of motivation in the patients and the GP's. For the 4-years follow-up, 20 of these 34 patients could be included again. The possibility of selective dropout was examined by comparing essential characteristics of patients with missing data at short- and 4-years follow-up. No significant differences were observed, thus attrition bias is less probable. Further, this study lacks a control-group. We emphasise that this study is not meant as an intervention study but as a long-term study to assess the changes under usual care.

The referral to a dietician is in concordance with the Dutch guidelines. After the first eight weeks patients were not given extra care regarding their lifestyle. Thus, diabetic patients as control would be unethical because in our view, we would deliberately have undertreated them. Aged-matched healthy volunteers as controls would have been helpful to estimate the secular trend for fat-consumption.

Comparison with existing literature

To our knowledge, only one previous study assessed fat consumption in newly diagnosed patients with type 2 diabetes at diagnosis and after several years (3). In a small sample of the UKPDS population (n=65) half of the patients complied with recommendations regarding total energy intake, at three years of follow-up. The results of this study cannot easily be compared to the findings in the present study, because the types of fat were not specified. The overall decrease in total fat consumption is larger in our study (≈3 versus 1% of energy intake in the UKPDS). The differences between men and women that were found in the UKPDS population could not be confirmed in our study

Implications for future research and policy

The results regarding the percentage of patients that meet with recommendations might be of particular interest in the development of future guidelines and treatment targets. The most important treatment targets are those for saturated fatty acids and cholesterol consumption, being <10% of energy intake and <300 mg/day respectively, and <7% and <200 mg/day for patients with LDL cholesterol ≥2.6 mmol/l (which is the case for most patients in our study at diagnosis). Only 27% of patients consumed less than 10% of saturated fatty acids measured as % of energy intake, and only 9% of the patients consumed less than 7% of their energy intake by way of saturated fatty acids. In contrast to this disappointing result 93% (<300 mg/day) and 55% (<200 mg/day) of patients met the target for cholesterol intake. So, the target for the consumption of cholesterol seems to be realistic and attainable for this GP-population whereas the target for the consumption of saturated fatty acids is not.

This study reports food-habits in terms of nutrients. We realise that in normal day life, patients and doctors don't talk about mono- or polyunsaturated fatty acids but about french fries, eggs and tomatoes instead. Future research should investigate what alterations in the choice of foodstuffs (beef, chicken, peanut-butter) are more likely to be sustained. Further, a better understanding of the characteristics of patients that have a very good or a very bad compliance with dietary advice might contribute to more effective dietary intervention strategies.

This study might take away some of the scepticism of doctors about the feasibility of initiating and maintaining more favourable dietary habits. However, the very strict treatment targets for consumption of saturated fatty acids and total fat are not very realistic. To optimise the dietary treatment of type 2 diabetes any further lastingly care

for diet and lifestyle but also a reconsideration of treatment targets for dietary fats among diabetic patients remain necessary.

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Chapter 3.2

Eating behaviour and adherence to diet in patients with type 2 diabetes mellitus

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Abstract

Aims. To assess restrained, emotional and external eating behaviour in patients newly diagnosed with type 2 diabetes compared with the general population, and to assess the relationship of eating behaviour to changes in fat and energy intake.
Methods. We assessed emotional, external, and restrained eating behaviour and measured fat and energy intake in a cohort of patients with newly diagnosed type 2 diabetes. Data from a comparable sample of the general population served as reference figures. We calculated correlation coefficients of the three different types of eating behaviour at diagnosis between: (i) energy and fat intake at diagnosis and (ii) changes in energy and fat intake between diagnosis and both 8 weeks and 4 years later. In addition, we used a stepwise multiple regression model with energy and fat intake or changes in energy and fat intake as dependent variables.
Results. The distribution of the three types of eating behaviour was similar in patients with type 2 diabetes and the general population. Emotional and external eating was associated with increased intake of energy and fat. Conversely, restrained eating showed an inverse correlation with energy and fat intake. External eating, but not emotional eating, showed a statistically significant relation with a decrease in energy intake in women. We found no statistically significant correlations between eating behaviour (measured at diagnosis) and changes in energy and fat intake between diagnosis and 4 years.
Conclusions. Patients newly diagnosed with type 2 diabetes have similar eating behaviour compared with the general population. At diagnosis, external eating behaviour and emotional eating behaviour are associated with high-energy intake and restrained eating behaviour with low-energy intake. Women with high scores for emotional eating behaviour seem to be less able to make initial dietary changes after being diagnosed and having received dietary advice.

Introduction

In the treatment of patients with type 2 diabetes, lifestyle adjustments consisting of dietary improvements and increased physical exercise are the first measures to be taken and remain important throughout the course of the disease. However, in contrast to taking medication or self-monitoring of blood glucose, lifestyle changes are not clear-cut and are more difficult to implement and maintain (1). Therefore, it is of great importance that potential obstacles or supportive factors are identified to improve strategies to optimize dietary habits and other lifestyle factors (1, 2).

It is evident that our food choices are more than just the product of a full conscious process (3). In this study, we examined eating behaviour in relation to energy and fat intake and subsequent changes in intake in patients newly diagnosed with type 2 diabetes. Van Strien *et al.* Distinguished three types of eating behaviours: (i) emotional eating behaviour (eating more when experiencing negative emotions); (ii) external eating behaviour (easily responding to food-related stimuli such as good smells or the look of attractive food); (iii) restrained eating behaviour (fixed on losing weight) (4). These types of eating behaviour can be assessed with a short questionnaire which is easy to use in daily clinical practice.

Thus far, research on eating behaviour and type 2 diabetes has focused predominantly on eating disorders such as bulimia or binge-eating disorder (5-7), while non-pathological variations of eating behaviours, which may also play a role in the (un)successful adoption of healthy dietary choices (8), have received less attention.

However, there is evidence that, in subjects recruited from the general population, a combination of external and/or emotional eating is associated with higher body mass index (BMI) and weight gain, and that restrained eating attenuates that relation (9). In individuals with impaired glucose tolerance, restrained eating was significantly related to lower BMI, and emotional eating (external eating was not assessed or reported) had the opposite relation (10). We are not aware of studies investigating non-pathological variations of eating behaviour in patients with type 2 diabetes.

Therefore, to better understand the role of eating behaviour in the (un)successful adoption of a healthy diet in patients with type 2 diabetes, we formulated the following research questions: (i) what is the distribution of restrained, emotional and external eating behaviour in patients newly diagnosed with type 2 diabetes in general practice, compared with reference values for the general population, (ii) what is the relation between eating behaviour and energy and fat intake in patients with newly diagnosed type 2 diabetes, and (iii) what is the relation between eating behaviour and changes in energy and fat intake, respectively, 8 weeks and 4 years after diagnosis?

Methods

This study was part of a prospective cohort study that assessed alterations in energy and fat intake of patients newly diagnosed with type 2 diabetes in general practice. Details about study design and patient flow are described elsewhere (11).

Patients and procedures

One hundred and forty-four patients with type 2 diabetes aged 40-70 years at the time of diagnosis, were recruited through 46 general practitioners (GPs) working in 33 general practices throughout the Netherlands from 1995 to 1998 (Table 3.2.1). Diabetes mellitus was defined according to the World Health Organization (WHO) criteria (12). In accordance with the Dutch guidelines for the treatment of type 2 diabetes mellitus (13), all patients were referred to a registered dietician. During two consultation sessions in the first weeks after diagnosis, all patients received dietary advice tailored to their individual needs and in accordance with current guidelines (that is, reduction of energy in case of overweight, reduction of total fat to a maximum of 30% energy, saturated fat to a maximum of 10% energy, and cholesterol intake to a maximum of 300 mg per day). Eight weeks after diagnosis, energy and fat intake were reassessed (n=110). On average, 4 years later, all baseline measurements were repeated and information about treatment and health status was obtained from the GPs records (n=106). During the follow-up interval, all patients received care as usual by their general practitioner. The baseline characteristics of patients who did not participate in the 8-week or 4-year evaluation did not differ significantly from those of the participants (data not shown).

Most patients lived with a partner (87.2%) and the educational level was low as 67.4% had primary or basic vocational education only. The blood glucose and lipid profile of the study population was representative for patients with newly diagnosed type 2 diabetes (14).

Measurements

Energy and fat intake were measured at diagnosis, after 8 weeks and after 4 years by a validated 104-item food-frequency questionnaire (FFQ) (15, 16) with a reference period of 1 month to measure fat intake. This list was completed by the patients and checked for errors by the investigator (FvdL). The mean intake for total energy (kJ/day), total fat (% energy), saturated fat (% energy), and cholesterol (mg/day) were calculated using a computer program (VET Expres 1.02, BaS Nutrition Software, Arnhem, The Netherlands). To account for possible changes in the composition and availability of foodstuffs, we used an updated version of the questionnaire for the 4-year measurement (Wageningen University, The Netherlands, unpublished data, 1997), including an updated calculation program (Komeet 3.0, BaS Nutrition Software).

Table 3.2.1. Baseline characteristics in 144 newly diagnosed patients with type 2 diabetes in general practice

	n	Mean	SD
Male / female	69/75		
Age (years)	144	57.8	8.3
Body mass index (kg/m^2)	134	29.5	5.2
Fasting blood glucose (mmol/l)	144	10.5*	6.7-19.6†
HbA_{1c} (%)	131	9.0	2.6
Diastolic blood pressure (mmHg)	134	86	10
Systolic blood pressure (mmHg)	134	145	20
Total Cholesterol (mmol/l)	130	6.2	1.1
LDL Cholesterol (mmol/l)	125	3.9	1.0
HDL Cholesterol (mmol/l)	126	1.1	0.3
Triglycerides (mmol/l)	131	2.7	1.5

* Median; † Range
HDL, high-density lipoprotein, LDL, low-density lipoprotein

Eating behaviour was assessed at diagnosis and after 4 years with the validated Dutch Eating Behaviour Questionnaire (DEBQ) (4). This is a 33-item questionnaire that contains three scales measuring emotional eating behaviour (13 questions, e.g., 'Do you have the desire to eat when you are worried?'), external eating behaviour (10 questions, e.g., 'If food smells and looks good, do you eat more than usual?') and restrained eating behaviour (10 questions, e.g., 'If you have put on weight, do you eat less than you usually do?'). All items were rated on a five-point scale ranging from 1 (seldom) to 5 (very often) and by dividing the total score by the number of valid answers, the overall score per type of eating behaviour was calculated (range 1-5). Internal reliability coefficients (Cronbach's α) were 0.95 for the emotional eating scale, 0.81 for the external eating scale and 0.95 for the restraint scale in a sample of non-obese women. Factor analysis of the current data reproduced the same factor structure as in the initial validation study (4).

Reference figures for the general population

Eating behaviour in the general population was assessed in a sample from the Dutch National Food Consumption Survey (DNFCS) 1998 (17). The DNFCS was conducted by a market research institute experienced in nation wide surveys, in close cooperation with a steering committee of experts in food consumption studies. Taken from an existing panel, 2564 households participated in the study. This panel

consisted of a stratified probability sample of non-institutionalised households living in the Netherlands. Institutionalised subjects, households whose head housekeeper was aged 75 or over, and households whose members could not speak Dutch were not included. A total of 6250 persons, aged 1-97 years, participated in the study. Response rate was 70.5% at the household level and 68.6% at the individual level. An additional questionnaire, which included the Dutch Eating Behaviour Questionnaire (4), was submitted to a subpopulation of the third DNFCS. In total, 2270 subjects (response rate 82%) completed the additional questionnaire: 1449 women principally responsible for domestic affairs (aged 19 years and over), 246 young people (13-22 years) and 575 men of 22 years and older. We used a random sample with a similar age range (40-70 years, n=1083, mean age 52.4 years ± 8.6, mean BMI 25.6 kg/m^2 ± 4.3, 71.2% female) from this subpopulation to compare their eating behaviour with the cohort of patients with newly diagnosed type 2 diabetes.

Statistical analysis

Results are given as means ± standard deviation. For comparison of results between diagnosis and 4-year measurements, the Student's one-sample t-test was used and, for comparisons between the general population and the group of patients with diabetes at diagnosis, Student's two-sample t-test was used. In order to account for multiple testing, we considered a lower than usual P-value ($P < 0.01$) as statistically significant.

We calculated correlation coefficients between the three different types of eating behaviour and energy and fat intake at diagnosis, and between eating behaviour and the changes in energy and fat intake (changes between diagnosis and both 8 weeks and 4 years later). In addition, we studied the three types of eating behaviour in a stepwise multivariate regression model. For the dependent variables, we used energy percentages of total fat, saturated fat and cholesterol intake (mg/day and mg/MJ) because those values reflect the most important dietary aims for optimizing fat intake in patients with type 2 diabetes. We also used energy intake (MJ/day) as a dependent variable, because most patients with type 2 diabetes are overweight and reduction of energy intake is recommended in most cases.

Ethics approval

This study was performed in accordance with the declaration of Helsinki. The protocol for the short-term study was approved by the Central Medical Committee for Studies in General Practice. The Local Ethics Committee (Radboud University Nijmegen Medical Centre) approved the protocol for the long-term study.

Results

At diagnosis, energy intake was 10.6 ± 3.4 MJ/day, mean intake of total fat was 40.9 ± 7.3, saturated fat 15.0 ± 2.8% energy and cholesterol intake 301 ± 123 mg/day. From

diagnosis to the 8-week measurement, energy intake (change=-2.2 MJ/day, T(109)=-9.59, P<0.0001), intake of total fat (change=-5.1% energy, T(109)=-6.52, P< 0.0001), saturated fat (change=-2.4% energy, T(109)=-7.94, P<0.0001) and total cholesterol intake (change=-63 mg/day, T(109)=-8.49, P<0.0001) significantly decreased. Significant decreases were also found from diagnosis to the 4-year measurement: energy intake (change=-1.8 MJ/day, T(106)=-6.37, P<0.0001), intake of total fat (change=-3.0% energy, T(106)=-3.26, P=0.0015), saturated fat (change=-3.1% energy, T(106)=-8.31, P<0.0001) and total cholesterol intake (change=-100 mg/day, T(106)=-9.74, P<0.0001) (11).

Eating behaviour of patients with type 2 diabetes and the general population

The scores for emotional, external and restrained eating behaviour at diagnosis, both from patients with diabetes and the general population, are presented in Table 3.2.2. Pearson correlation coefficients between restrained and emotional eating were: 0.28 (P<0.05, females) and 0.34 (P<0.05, males); between restrained and external eating: 0.23 (NS, females) and 0.18 (NS, males); and between emotional and external eating: 0.55 (P<0.01, females) and 0.60 (P<0.01, males).

Values for all three types of eating behaviour in the general population were similar to those in the group of newly diagnosed patients.

In the 4-year assessment, the mean values for external eating behaviour decreased significantly and for restrained eating behaviour increased significantly. Emotional eating behaviour did not change.

Eating behaviour and energy and fat intake at diagnosis (Table 3.2.3)

All statistically significant (P<0.05) correlation coefficients between eating behaviour and energy and fat intake at diagnosis had a positive value for external and emotional eating behaviour and a negative value for restrained eating behaviour in both sexes. This means that higher scores on external and emotional eating behaviour were associated with higher energy and fat intake and higher scores on restrained eating behaviour with lower energy and fat intake.

In women, both external and emotional eating behaviour were correlated with higher energy intake at diagnosis, and restrained eating correlated with lower energy intake. In the stepwise multivariate regression analysis, external eating (partial R^2=0.31, slope=2409 kJ/day more intake per 1 point higher score on external eating, P<0.0001) and restrained eating (partial R^2=0.06, slope=-808 KJ/day/score point, P=0.02) were entered in the final model (R^2 whole model 0.37). External eating was correlated with higher intake of saturated fat (partial R^2=0.08, slope 1.2% energy/score point, P=0.02) and restrained eating with lower saturated fat intake (partial R^2=0.07, slope=-0.9% energy/score point, P=0.02) (R^2 whole model 0.15). Restrained eating was correlated with decreased intake of total fat (R^2=0.13, slope=-3.3% energy/score point, P=0.002).

In men, a higher score on external eating was correlated with higher levels of energy intake, and restrained eating was significantly correlated with lower energy intake at diagnosis. In the stepwise multivariate analysis, external eating (partial R^2=0.11, slope=2065 KJ/day/score point, P=0.008) and restrained eating (partial R^2=0.12, slope=–1434 KJ/day/score point, P=0.003) were entered in the final model (R^2 whole model 0.23) for energy intake. Both emotional and external eating correlated significantly with cholesterol intake at diagnosis. However, when the relative (mg/MJ) instead of the total intake (mg/day) of cholesterol was used, no significant results were found.

Table 3.2.2. Eating behaviour of patients newly diagnosed with type 2 diabetes and after 4 years compared with the general population

	Patients with type 2 diabetes Diagnosis		4-years		General population (40-70 years)	
Eating behaviour	Male (n=64)	Female (n=72)	Male (n=51)	Female (n=56)	Male (n=312)*	Female (n=771)*
Emotional	1.6 (0.7)	1.9 (0 7)	1 6 (0 6)	2.0 (0.7)	1.8 (0 7)	2 1 (0 8)
External	2 4 (0.7)	2.3 (0.7)	2.2 (0.6)	2.1 (0.5)	2.5 (0 6)	2.4 (0.6)
Restrained	2.3 (0.9)	2.6 (0.8)	2.6† (0.9)	3 0‡ (0.9)	2.4 (0.8)	2.8 (0.9)

*Number of patients may be slightly lower in subscores as a result of missing items.
Student's one-sample t-test for comparison 4-year measurement with diagnosis: † P<0.01, ‡ P<0.001.
Student's two-sample t-test for comparison general population and patients with type 2 diabetes at diagnosis: no significant differences.

Eating behaviour and change in energy and fat intake (Table 3.2.4)

In women, external eating predicted a significant decrease in energy intake from diagnosis to 8 weeks (R^2=0.21, slope=1486 KJ/day/score point, P=0.0005) but not from diagnosis to 4 years (R^2=0.05, slope 954 KJ/day/score point, P=0.09). In contrast, emotional eating behaviour showed no significant correlation coefficients for changes in energy or fat. In men no significant results were found.

Discussion

Summary and interpretation of main findings

In this study, we found that patients with newly diagnosed type 2 diabetes have similar eating behaviours compared with the general population. Eating behaviour seemed to be related more to the quantity (energy) of food, than to the quality (% energy of fat). Both external and emotional eating behaviour showed a positive relationship with

energy intake at diagnosis. An inverse relation was found for restrained eating With respect to change in energy and fat intake, we found that external eating predicted a decrease in energy intake in women, whereas emotional eating was not related to change in energy intake Therefore, we conclude that women with a high score on external eating are, in contrast to those with high scores for emotional eating, to a larger extent susceptible to initial dietary changes.

Table 3.2.3. Results from a bivariate correlation analysis (P-value) of eating behaviour and energy and fat intake of male and female patients with type 2 diabetes at diagnosis

	Energy	Total fat	Saturated fat	Cholesterol
Men (n=64)				
Emotional eating	0 23 (0 06)	0 23 (0 07)	0 19 (0 13)	0 29 (0 02)*
External eating	0 33 (0 008)*	0 08 (0 51)	0 05 (0 67)	0 33 (0 007)*
Restrained eating	-0 27 (0 03)*	0 04 (0 70)	0 14 (0 29)	-0 19 (0 11)
Women (n=72)				
Emotional eating	0 36 (0 002)*	0 07 (0 55)	0 10 (0 42)	0 18 (0 13)
External eating	0 56 (<0 0001)*	0 15 (0 21)	0 29 (0 02)*	0 32 (0 006)*
Restrained eating	-0 28 (0 02)*	0 35 (0 002)*	0 28 (0 02)*	-0 12 (0 32)

*Significant values

The question arises how these differences in 'effects' of emotional and external eating should be explained, especially as both eating behaviours are correlated. The finding of a significant correlation between emotional and external eating is not new, having being reported in the original validation study (4). The question arises whether they are distinct or overlapping constructs. Although emotional and external eating often coexists, it is assumed that they should be conceived as independent constructs The main reason for this is that the pathogenesis of both excessive emotional and external eating is essentially different. The concept of emotional eating is derived from psychosomatic theory. It implies that, whereas the normal reaction to emotional distress is an increased feeling of satiety, subjects with high scores for emotional eating respond with hunger. The concept of 'external eating' is derived from externality theory. In a similar way to psychosomatic theory, externality theory posits that disturbed eating behaviour is comparatively unresponsive to internal physiological signs. However, in contrast to emphasis placed on poor interoceptive awareness of physiological signals accompanying emotions, externality theory focuses on the external food environment as a determinant of eating behaviour. However, previous experimental studies showed that emotionality and food cues operated conjointly to elicit food consumption (18).

Table 3.2.4. Results from a bivariate correlation analysis (P-value) of eating behaviour and changes in energy and fat intake of male and female patients with type 2 diabetes between three different time points (diagnosis, 8 weeks, 4 years)

	Diagnosis – 8 weeks				Diagnosis – 4 years			
	Energy (kJ/day)	Total fat (% energy)	Saturated fat (% energy)	Cholesterol (mg/day)	Energy (kJ/day)	Total fat (% energy)	Saturated fat (% energy)	Cholesterol (mg/day)
Men	*n=50*				*n=47*			
Emotional eating	0.14 (0.31)	0.17 (0.23)	0.09 (0.54)	0.28 (0.053)	0.07 (0.62)	0.15 (0.33)	0.09 (0.53)	0.16 (0.30)
External eating	0.23 (0.11)	0.06 (0.66)	0.00 (0.97)	0.11 (0.44)	0.10 (0.51)	-0.11 (0.44)	0.06 (0.71)	0.13 (0.37)
Restrained eating	-0.18 (0.21)	0.16 (0.26)	0.04 (0.78)	-0.10 (0.50)	-0.28 (0.054)	-0.01 (0.96)	-0.04 (0.78)	-0.01 (0.94)
Women	*n=55*				*n=55*			
Emotional eating	0.21 (0.13)	-0.09 (0.49)	0.04 (0.77)	0.21 (0.12)	0.08 (0.56)	0.04 (0.75)	0.10 (0.45)	0.03 (0.84)
External eating	0.45 (0.0005)*	0.08 (0.59)	0.18 (0.18)	0.33 (0.02)*	0.23 (0.09)	0.06 (0.67)	0.12 (0.37)	0.14 (0.29)
Restrained eating	-0.10 (0.47)	-0.09 (0.52)	-0.04 (0.80)	-0.01 (0.92)	0.10 (0.49)	-0.11 (0.41)	0.03 (0.85)	-0.02 (0.91)

A positive correlation coefficient indicates a decrease of fat or energy
*Significant values

As to the question why emotional eating predicted no decrease in energy intake, in contrast to external eating, evidence is accumulating that this type of eating behaviour is more resistant to therapy (19). Emotional eating is associated with disturbed psychological functioning that hampers a successful adoption of a healthy diet after dietary advice alone. Previous research showed that emotional eating is associated with alexithymia (difficulty in describing or recognizing one's own emotions) (20), impulsivity (21) and depression (22). For external eating such relationships have hardly been investigated. However, recent research from our university (unpublished data) showed no correlations between external eating and both alexithymia and depression, and only a very small correlation with impulsivity. Further, there is evidence that emotional eating, in contrast to external eating, is related to a deficit in brain-dopamine (23), and this deficit may make individuals more receptive to the reinforcing value of food (24). In the present study no specific intervention had been directed to alexithymia, impulsivity or depression. This might explain the unfavourable outcomes for patients with high scores on emotional eating.

Our findings, that restrained eating is correlated with lower energy intake and that emotional eating is correlated with higher energy intake, corresponds with findings in subjects with impaired glucose tolerance, in which a higher BMI was correlated with low scores for restrained eating and high scores for emotional eating (10). We have also partly confirmed the findings from another study in healthy women (9) as we found that 'disinhibition' (i.e. a combination of external and emotional eating) was associated with higher energy intake. However, the relation between disinhibition and long-term weight gain could not be confirmed as we found no significant relationships between eating behaviour and changes between diagnosis and 4-year dietary intake.

The associations between restrained eating and lower energy intake seem logical. The essence of restrained eating is losing weight by reducing caloric intake. However, literature is equivocal on this issue. It has been suggested that people with high scores on scales for restrained eating behaviour are at increased risk for weight gain and bulimia, and this has even led to the suggestion that dieting (i.e. restrained eating) should be discouraged (25). Alternatively, it has been argued that a tendency toward overeating, i.e. emotional and or external eating, may cause increased food intake and weight gain (26, 27). The conflicting results could be explained by the use of 'impure' questionnaires for restrained eating in which behaviours that explain loss of control over eating are included (e.g., 'do you eat sensibly in front of others and splurge alone?') (28). In the DEBQ, a 'pure' restrained scale is combined with two possible explanations for 'loss of control': external and emotional eating behaviour. Thus, our study underlines the theory that restrained eating behaviour itself does not lead to increased food intake and that 'loss of control' may be explained by other factors such as emotional or external eating.

Strengths and weaknesses of this study

One of the main strengths of this study is that it included patients at the time of diagnosis with type 2 diabetes, a severe and chronic disease. The period shortly after diagnosis is of special importance and might set trends for later. At diagnosis, the motivation of patients to change their lifestyle is probably high. This may be partly as a result of the 'shock' of the diagnosis, and partly the possibility that patients have not become disappointed as a result of previous failure to change behaviour. The results from this study may contribute to the development of effective strategies to stimulate and maintain beneficial lifestyles in a crucial phase of the disease.

We calculated changes in energy and fat intake by using a validated food frequency questionnaire at three different time points instead of asking patients whether or not they think they have changed their diet. Such a longitudinal design gave the opportunity to study changes in behaviour over time.

Weaknesses of this study that should be recognised are the method of assessment of food intake and eating behaviour. Patients with high scores for restrained eating behaviour might have underreported food intake. A clue for this assumption could be found in our previous observation that especially overweight people (patients with diabetes and in population) reported less energy intake (11).

Another problem is that it remains impossible to distinguish pathological eating behaviour from the normal range of eating behaviours. The finding that patients with diabetes do not differ with respect to eating behaviour from the general population underlines the fact that we do not deal with eating 'abnormalities' but with a trait instead. Further, the different types of eating behaviour cannot be defined within a single patient and scores for the different types of eating behaviour exist simultaneously. For these reasons, we did not aim to categorise patients into a single predominant eating behaviour. Therefore the results should be seen as explorative instead of 'hypothesis-testing' and should give direction to further research.

Our study did not have a control group. However, our main goals were not to assess changes in eating behaviour over time, or to assess the effect of an intervention directed to eating behaviour. Instead, our main objective was to assess the relation of eating behaviour with energy and fat intake at diagnosis and with subsequent changes in intake after short- and long-term follow-up.

Implications for policy and future research

In daily practice, the DEBQ could be of help for the GP or dietician to identify patients that are less likely to adhere to dietary recommendations. Women with high scores on emotional eating might need special attention, because emotional eating is associated with high-energy intake and (in contrast to external eating) emotional eating was not predictive for beneficial changes in dietary intake. For these patients, routinely dietary advice, aimed at informing and educating the patient, might be insufficient or even contraindicated. After all, 'failing' dietary adherence is not without risk as it might induce feelings of incompetence in the patient and as a consequence reduce

self-efficacy. Thus, patients with high scores on emotional eating behaviour might be better off with a psychological intervention (e.g., cognitive therapy) in addition to regular advice. As mentioned above, cut-off scores have yet to be determined for patients with severely problematic emotional eating behaviour. For the time being, dieticians could use the data presented in this study as a reference. Further research should aim at evaluating tailored approaches that take into account a patient's eating behaviour.

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Chapter 3.3

The dieting dilemma in patients newly diagnosed with type 2 diabetes: Does dietary restraint predict weight gain four years after diagnosis?

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Abstract

Objective. To examine whether dieting – restriction of food intake for the purpose of weight control – suppresses or promotes excessive food intake and weight gain.
Design. A 4-year follow-up study of a dietary intervention in a sample of 97 patients with newly diagnosed type 2 diabetes.
Main Outcome Measures. Weight gain, change in body mass index (measured weight in kilograms divided by measured height squared), and intake of energy, as measured with a food frequency questionnaire were assessed in relation to dietary restraint and tendency to overeat (emotionally or externally induced overeating), as assessed with the Dutch Eating Behaviour Questionnaire.
Results. Tendency to overeat at diagnoses and not dietary restraint was associated with weight gain and intake of energy 4 years after diagnosis.
Conclusion. These findings suggest that the success of a dietary intervention can be predicted by a subject's tendency toward overeating. The possibility of matched treatment of obesity is discussed on the basis of the distinction between patients with low versus a high tendency to overeat.

Introduction

Dieting, or the restriction of food intake for the purpose of weight control: Does it suppress or promote excessive food intake and weight gain? This question has been called the *dieting dilemma* (1). Studies on the effects of dieting show contradictory findings. Some experimental and prospective studies that have measured self-reported dieting tendencies suggest that dieting is associated with excessive food intake, bulimic pathology and weight gain (2-4). Because these findings suggest that dieting may be worse than the disease (overweight and obesity), it has been advocated that the best treatment for overweight is to stop dieting and simply accept one's "natural" heavy weight (5, 6). Other experimental studies, however, found no link between self-reported dietary restraint and overeating (7, 8). Also, prospective intervention studies that have assigned people to a weight loss diet show contradictory results (9). Further, dieters with successful maintenance of lost body weight have been reported (10-12), and actual caloric deprivation was even found to reduce bulimic pathology (13). Hence, it is also possible that dieting is not the widely accepted risk factor for weight gain and bulimic pathology, as it was also shown to result in successful reduction of body weight (14).

Much is at stake. Obesity is a prevalent disorder that might have severe medical consequences, such as diabetes, hypertension, cardiovascular disease and some cancers (15). For decades, dieting has been the treatment of choice for obesity, and without this treatment care providers seem to stand empty handed. So it is of utmost importance that the dieting dilemma is addressed.

In the present article, we address the dieting dilemma in a cohort of patients with newly diagnosed type 2 diabetes in whom we may assume high motivation for weight loss as this is one of the main treatment targets. Therefore, all patients in the study had been referred to a registered dietician for a dietary intervention aimed at an optimization of fat consumption (i.e., reduction of total and saturated fat and cholesterol intake) and a reduction of calorie intake in overweight patients. This study assessed intake of energy and long-term changes of body weight 4 years after the diagnosis, in relation to the patients' dietary restraint.

In addition to dietary restraint, the patients' tendency toward overeating was analyzed. It is still unresolved whether restrained eating is a cause or a consequence of overeating tendencies or whether they are reciprocally related (2, 16-18). In a 1-year follow-up study in female college students, Spoor et al. found that dietary restraint did not predict future bulimic pathology (uncontrollable overeating) (16). This finding is consistent with the outcome of Stice's highly similar study (17) but inconsistent with the outcome of a study involving a 2-year prospective investigation of adolescent girls (18). In contrast to Stice (17), however, Spoor et al. (16) did not find that bulimic pathology had an effect on future dietary restraint. Further, in the study by Stice et al. (18), apart from dieting, depressive symptoms and emotional eating were risk factors for the onset of binge eating. This finding suggests that there may be qualitatively

different pathways to binge eating and that dieting may promote overeating in only a subset of individuals (19).

The precise direction of the relationship between dietary restraint and overeating tendencies is as yet unclear and may even differ for various subgroups: The fact is that restrained eating (an inhibition factor) is often empirically linked to overeating tendencies (disinhibition factors), and overeating tendencies may therefore contaminate correlations between restraint, food intake, and change in body weight (20-22). Two different aspects of overeating are distinguished. The first aspect, *emotional eating,* is derived from the *psychosomatic theory* (23) and refers to the tendency to overeat in response to negative emotions such as anxiety or irritability. The second aspect, *external eating,* is derived from the *externality theory* (24) and refers to the tendency to overeat in response to external food related cues, such as attractive sight and smell of food.

Psychosomatic theory departs from the human individual difference effect model of food intake in response to negative affect (25). In this model, the normal response to distress is loss of appetite as a result of physiological mechanisms: the inhibition of gastric contractions and the elevation of blood sugar (26). The abnormal response is stress induced (emotional) eating, and it occurs in people with a lack of interoceptive awareness: As a result of faulty learning experiences in early life, these persons confuse physiological correlates of emotional distress with hunger (27, 28).

Externality theory, similar to psychosomatic theory, also posits that eating behaviour is unresponsive to internal physiological signals such as gastric motility. But in contrast to the emphasis placed on internal, emotional factors in psychosomatic theory, externality theory focuses on the external food environment as a determinant of eating behaviour. External eaters overeat as a result of their hyperresponsiveness to external food-related cues.

In the present study, in patients with newly diagnosed type 2 diabetes, we examined the relation between eating behaviour, body weight change, and energy intake 4 years after diagnosis. In addition, we assessed possible moderating effects of dietary restraint and overeating tendencies.

Methods

Subjects and procedure

We used data from a prospective cohort study, in which patients with newly diagnosed type 2 diabetes (aged 40-70 years) were included from 33 general practices throughout the Netherlands (n=144).[1] Our primary aim was to assess alterations in energy and fat

[1] Diabetes mellitus was defined according to the criteria established by the World Health Organization. Patients were eligible for the study when they had symptoms suggestive of diabetes mellitus and a fasting blood glucose greater than or equal to 6.7 mmol/l and less than 20 0 mmol/l. In patients with asymptomatic diabetes, the fasting blood glucose had to be greater than or equal to 6 7 mmol/l on two or more occasions.

intake (29). Patients (n=106) answered followed-up questions 4 years after the initial study. Reasons for missing data on energy and fat intake were that the patients died (n=8), moved to an unknown address (n=4), had another reason or an unknown reason for not responding (n=5), or refused to fill out food frequency questionnaire (n=21). However, 3 of those patients still provided data on body weight and eating behaviour. For the present study, complete data on body weight and energy intake at follow up (the dependent variables in this study) were available for 46 males and 51 females. Relevant baseline characteristics of those who did not participate at the 4-year follow-up did not differ significantly from the subjects whose 4-year measurements were not missing (Appendix A). This study was performed according to the standards of ethical conduct, and all patients gave written informed consent.[2]

Treatment

All patients received regular care from their general practitioner. This included a referral to a registered dietician just after diagnosis. In two visits with the dietician, individually tailored advice was given, according to current guidelines. Generally, this implied a reduction in energy and fat consumption.

Measurements

Measurements took place at diagnosis, 8 weeks after diagnosis, and 4 years after diagnosis. The following measurements were included.

Body weight and height were measured without shoes and with light clothing. In every practice, the same balance was used for subsequent measurements. Body mass index (BMI) was calculated as follows: Weight in kilograms was divided by height squared.

To assess the *fat and energy consumption,* we used a food frequency questionnaire (FFQ). In this questionnaire, the frequency of consumption of 104 food items is scored retrospectively. The reference period was 1 month and common festivities such as birthday visits and parties were considered to be part of the habitual food pattern. The FFQ was completed by the patient and checked for major errors by the investigator; if necessary, the patient was contacted for clarification. Total energy intake (MJ/day) and total fat (expressed as the percentage of energy intake) were calculated using software designed especially for the questionnaire (30). For the 4-year measurement, an updated version of the questionnaire was used (31), and calculations were done using updated software (32). In a validation study, the FFQ showed results similar tot those from dietary history (Pearson correlation coefficients for energy intake and total fat were .83 and .78, respectively (33)). The FFQ has been shown to

[2] This study was performed in accordance with the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects The protocol for the 8-week study was approved by the Central Medical Committee for Studies in General Practice. The Local Ethics Committee of the Radboud University Nijmegen Medical Centre approved the protocol for the 4-year study.

have good reproducibility over 2 months (Pearson correlation coefficients for energy intake and total fat were .97 and .87, respectively (34)).

Dietary restraint and overeating-tendency were measured with the Dutch Eating Behaviour Questionnaire (DEBQ (35, 36)). This questionnaire has a scale on restrained eating (e.g., "Do you try to eat less at mealtimes than you would like to eat?") and two separate scales on overeating tendency: emotional eating (e.g., "Do you have a desire to eat when you are irritated?") and external eating (e.g., "If food smell and looks good, do you eat more than usual?"). Each of these two aspects of overeating tendency corresponds with a major theory on the aetiology of overeating, that is psychosomatic theory (23) and externality theory (35-37). Information on their construct, concurrent, and predictive validity has been published previously (36, 38, 39).[3] Cronbach's alpha coefficients of the scales as obtained at diagnosis and at follow up in the present study can be found in Table 3.3.1.

Data on *use of medication* were derived from the patients' record and provided by the general practitioner. In addition, the use of anti-diabetic and cholesterol-lowering medication during the interval was registered.

Physical activity was measured by another questionnaire with nine equally weighted yes-or-no questions. Patients were asked whether they had the following regular activities: playing sports, bicycling, gardening, walking, doing odd jobs, climbing stairs, doing household activities, doing daily food shopping, and working (either paid or unpaid (42)). Thus, a score ranging from 0 (*no exercise*) to 9 (*maximum amount of exercise*) was calculated.

Other variables such as smoking, age, and level of education were assessed by a short questionnaire.

Strategy for analyses

First, descriptive analyses were conducted to gather information about the means, standard deviations, and intercorrelations of the model variables. Because of sex differences in life style and body composition (43), these analyses were conducted separately for males and females. To assess the change between scores at diagnosis

[3] Stice, Fischer and Lowe (40) questioned the validity of the DEBQ restraint scale on the basis of outcomes of studies using unobtrusive measures for food intake, but this conclusion has been refuted by Van Strien, et al (39). A major problem with the study by Stice et al (40), is that food intake was measured only at one moment in time, and this is at variance with both the fundamentals of valid dietary assessment and the concept of restraint as a trait. In nutritional science, single eating episodes are regarded as inappropriate for assessing chronic dietary intake: A minimum time window of 24 hours is normally recommended (41). Moreover, we know of at least three experimental taste-test studies where the positive association between restraint and food consumption disappeared or even became negative when tendency toward overeating was controlled for (7, 8, 21) In the studies by Stice et al. (40), the tendency to overeat was not partialed out of the relation between restraint and food intake. A problem with all validity studies is that the objective measures may not reflect restriction of food intake, that is, eating less than desired In theory, people may eat more than required (in terms of physical activity and body weight) and still be restrained eaters insofar as (owing to dietary restraint) they eat less than they would otherwise be inclined to eat.

and at the 4-year follow up, we calculated effect sizes (*d*) by dividing the difference between the means by the standard deviation at diagnosis. Effect sizes between 0.2 and 0.5 reflect a small effect, between 0.5 and 0.8 a moderate effect, and above 0.8 a large effect (44).

Next, for the whole sample, an hierarchical regression analysis was conducted to determine whether restrained eating, overeating tendency (emotional and external eating), and their interaction at diagnosis, in addition to change in restrained eating and overeating tendency (emotional and external eating) after 4 years, accounted for a significant amount of variance in BMI at 4 years, over and above that accounted for by BMI at diagnosis, sex, and smoking at 4 years.[4] Of special interest was the significance of the change in explained variance associated with the variables at each step in the analysis.

A similar procedure was followed in the analyses with *energy intake* at 4 years as dependent variable. However, here we corrected for sex, body weight, and physical activity[5] by forcing these variables into the first step of the analysis.

Unfortunately, data for smoking or physical activity were missing in 2.5% of the records for the 97 subjects in the main analyses. It turned out that missing values were randomly distributed. Little's missing completely at random test yielded a chi-square of 90.246 with 71 degrees of freedom (n=97, p=.060). So missing values could be estimated by the expectation-maximization algorithm, which preserves correlations between the independent variables as well as possible (see SPSS Missing Value Analysis, Version 7.5). It is stressed that the dependent variables (BMI and intake of energy, both measured 4 years after diagnosis) are not involved in this imputation procedure.

Results

Descriptive analyses

At diagnosis, the 46 males had a mean age of 58.7 years (SD=6.9), a mean body weight of 87.1 kg (SD=14.2), and a mean BMI of 28.0 kg/m^2 (SD=4.0). Most patients were living together with a partner (87%) and 67% had primary or basic vocational education only. After 8 weeks, 34 men showed weight loss (M=–3.4 kg, SD=2.4) and 5 gained weight (M=1.5 kg, SD=1.4); for 7 patients, change in weight was unknown.

[4] Sulphonylurea (e.g., tolbutamide, glibenclamide) and insulin therapy may increase body weight by increasing the level of circulating insulin. Other medication for Type 2 diabetes is weight neutral. Because there was no variation in use of medicine in the subjects (as all subjects used either insulin or sulphonylurea), this variable was left out of the analysis.
Age, level of education, physical activity at diagnosis or at follow up, smoking at diagnosis, or change in smoking did not, in preliminary analysis, affect change in BMI. Therefore, we did not control for these variables at Step 1.

[5] Body weight and physical activity were forced at Step 1, to account for the fact that the individual energy requirements depend largely on body weight and physical activity.

The mean weight change between diagnosis and after 4 years was a gain of 1.3 kg (SD=5.4). Nineteen men showed weight loss or maintenance of body weight in relation to their body weight at diagnosis (mean weight loss=3.3 kg, SD=3.8), and 27 men showed weight gain in relation to their body weight at diagnosis (mean weight gain=4.6 kg, SD=3.7).

At diagnosis, the 51 women had a mean age of 58.6 years (SD=8.1), a mean body weight of 81.9 kg (SD=17.7), and a BMI of 30.7 kg/m^2 (SD=5.6). After 8 weeks, 40 women showed weight loss (M=–3.1 kg, SD=2.0); for 11 patients, change in weight was unknown. Four years after diagnosis, only a few women had maintained this weight loss. The mean weight change compared with weight at diagnosis was –1.1 kilograms (SD=5.0). Thirty women showed weight loss or maintenance of body weight in relation to body weight at diagnosis (mean weight loss=–4.4 kg, SD=3.8), and 21 women showed weight gain in relation to body weight at diagnosis (mean weight gain=3.5 kg, SD=2.0).

Results on energy intake, fat intake, and the three types of eating behaviour are shown in Tables 3.3.1 and 3.3.2. Both men and women reported lower intakes of energy at the 4-year follow-up, compared with their intakes at diagnosis: For men, $t(45)=4.544$, $p<.000$, $d=–0.607$; for women, $t(50)=4.650$, $p<.000$, $d=–0.555$. In men, there were no differences in total fat intake, $t(45)=1.398$ *ns*, $d=–0.302$, whereas in women a lower total fat intake was reported, $t(50)=3.646$, $p<.000$, $d=–0.564$. Further, for both the men and women, the change in bodyweight at the 4-year follow-up compared with diagnosis was not significant: For men, $t(44)=–1.600$, *ns*, $d=0.103$; for women, $t(50)=1.517$, *ns*, d=–0.071. In both men and women, an increase in restrained eating was found: For men, $t(45)=3.061$, $p<.005$, $d=0.465$; for women, $t(50)=3.989$, p<.000, d=0.488. In men, scores on external and emotional eating did not change: For external eating, t(45)=–1.375, *ns*, $d=–0.164$; for emotional eating, $t(45)=1.041$, *ns*, d=0.119. In women, scores on external eating showed a statistically significant decrease, t(50)=–2.091, $p=.042$, $d=–0.200$, whereas scores on emotional eating did not change, $t(50)=.822$, *ns*, $d=0.106$.

Correlations between model variables

The correlation matrix and the Cronbach's alphas of the three types of eating behaviour at diagnosis and at 4 years, is shown in Table 3.3.1. In Table 3.3.2, the correlation matrix and the Cronbach's alphas of eating behaviour, and energy and fat consumption and BMI are shown.

For each of the three types of eating behaviour, high and statistically significant test-retest correlations were found, ranging from .51 to .68 in men and from .61 to .73 in women. So it seems that assessment of eating behaviour, particularly when this involves emotional or external eating, pertains a trait like construct with fair temporal stability rather than a temporary state. In both men and women, emotional and external eating were significantly correlated at diagnosis and after 4-year follow-up.

In men, there were no significant correlations between any of the types of eating behaviour and intake of energy or fat. However, when we controlled for body weight and physical activity in partial correlation analyses, the correlation between restrained eating and energy intake at diagnosis became borderline significant, r=–.304, p=.06, and the correlation between restrained eating at follow-up and intake of fat became significant, r=–.360, p=.024. The correlation between external eating and energy intake at follow-up became borderline significant, r=304, p=.060.

In women, both types of eating behaviour at diagnosis were significantly correlated with energy intake at diagnosis. Emotional eating at diagnosis was also associated with energy intake at the 4-year follow up. Further, there were significant negative correlations between restrained eating and fat intake at diagnosis and between restrained eating and fat intake at the 4-year follow up.

Table 3.3.1. Pearson Correlation Coefficients, Descriptive Statistics and Cronbach's Alpha of Restrained, Emotional and External Eating at Baseline and at 4 years for males and females (in parentheses)

	1	2	3	4	5	6
1. Restrained eating[a]		23 (.29*)	20 (.26)	51** (61**)	41** (36*)	38* (.14)
2. Emotional eating[a]			.54** (.49*)	18 (12)	.68** (.73**)	.55** (.43**)
3 External eating[a]				37* (.29*)	50** (.47**)	.64** (.73**)
4. Restrained eating[b]					29 (34*)	.21 (.20)
5. Emotional eating[b]						.76** (.57**)
6 External eating[b]						
Mean	2.21 (.2.63)	1.54 (1.99)	2 37 (2 27)	2 61 (3.04)	1 61 (2.06)	2.26 (2.16)
SD	.86 (.84)	.59 (.66)	.67 (.55)	.91 (84)	.61 (.63)	62 (.49)
Cronbach's α	.92 (.89)	.95 (.89)	.85 (.79)	84 (.92)	.94 (.91)	.86 (.74)

* P<.05, ** P<.01

[a]Baseline; [b]Four-year follow-up

Hierarchical regression analyses

BMI at 4 years. Change in restrained, emotional and external eating (the significant increase in explained variance associated with restrained, emotional, and external eating at follow-up over and above restrained, emotional and external eating at diagnosis) did not significantly explain variations in BMI at 4 years. Also, none of the

interaction terms between restrained eating and emotional eating and restrained eating and external eating were significant, so only the outcomes of the first three steps of the regression analyses are reported here (Table 3.3.3). Only tendency toward overeating (emotional and external eating, Step 3) at diagnosis led to a significant increase in explained variance of BMI 4 years after diagnosis, beyond that accounted by sex, BMI at diagnosis, smoking and use of medicine, F_{change} (2, 90)=3.841, p=.025.

Table 3.3.2. Pearson Correlation Coefficients and Descriptive Statistics of the Three Types of Eating Behaviour, Intake of Energy, and Total Fat at Baseline and at 4 years, and of Body Mass Index (BMI) at Baseline and Change in BMI (Diagnosis to 4 years) for Men and Women (in parentheses)

	Energy[a] (KJ/day)	Total fat[a] (Energy%)	BMI[a] (Kg/m^2)	Energy[b] (KJ/day)	Total fat[b] (Energy%)	BMI-Change (Kg/m^2)
Restrained eating[a]	-.22 (-.11)	.12 (-.30*)	- 04 (.21)	.08 (.-.24)	09 (- 23)	-.12 (- 02)
Emotional eating[a]	.14 (.31*)	.17 (-.14)	.13 (.31*)	.09 (.29*)	-.04 (-.11)	-.04 (-.13)
External eating[a]	22 (40**)	01 (.01)	24 (.32*)	18 (.24)	.15 (.01)	.12 (.18)
Restrained eating[b]				.26 (-.16)	-.19 (-.32*)	.03 (-.02)
Emotional eating[b]				17 (.22)	-.06 (.02)	-.03 (- 14)
External eating[b]				25 (.27)	17 (.21)	.13 (.09)
Mean	11806 (9683)	40.3 (41.0)	28.0 (30.7)	9506 (8206)	38.3 (36.6)	.42 (-.40)
SD	3788 (2663)	6.9 (7.8)	4.1 (5.6)	2827 (2384)	7 8 (8 1)	1 76 (1 89)

* p<.05; ** p< 01
[a]Baseline; [b]Four-year follow-up

Intake of energy. Only tendency toward overeating at diagnosis (emotional and external eating, Step 3) led to a significant increase in explained variance of intake of energy 4 years after diagnosis, F_{change} (2, 90)=3.330, p=.040. When simultaneously entered into the model, neither emotional nor external eating was significantly associated with intake of energy at 4 years (see Table 3.3.4). Additional analyses showed that emotional eating significantly explained variance in energy intake at follow-up when entered into the model without external eating, F_{change} (2, 90)=4.184, p=.044. Similarly, external eating significantly explained variance in energy intake at follow-up when entered into the model without emotional eating, F_{change} (2, 90)=5.067, p=.027. This suggests that the overlapping variance of emotional and external eating is significantly associated with intake of energy at follow-up, although the types of eating behaviour separately only explained a small amount of variance (4%).

Table 3.3.3. Hierarchical Multiple Regression Analyses with Body Mass Index (BMI) at 4 Years After Diagnosis in 97 Patients With type 2 Diabetes

		BMI	
		β[a]	ΔR^2
Step 1			.98**
	BMI at diagnosis	.92**	
	Sex	-.01	
	Smoking at 4-years	.08*	
Step 2			.00
	Restrained eating at diagnosis	-.03	
Step 3			.01*
	Emotional eating at diagnosis	-.08	
	External eating at diagnosis	.115*	

*p<.05, **p<.0001
[a]Betas in the last step

Table 3.3.4. Hierarchical Multiple Regression Analyses With Energy Intake at 4 Years After Diagnosis in 97 Patients With type 2 Diabetes

		Energy intake	
		β[a]	ΔR^2
Step 1			.06
	Sex	-.276*	
	Body weight at follow up	-.109	
	Physical activity at follow up	-.028	
Step 2			.00
	Restrained eating at diagnosis	-.148	
Step 3			.06*
	Emotional eating at diagnosis	.160	
	External eating at diagnosis	.189	

*p<.05
[a]Betas in the last step

Discussion

Four years after diagnosis of type 2 diabetes, all patients showed lower mean intakes of energy per day in comparison to their intakes at diagnosis. The women also showed lower mean intakes of total fat (as a percentage of energy). Yet, although most patients showed weight loss immediately after the dietary consultations, about half of the patients ended up weighing even more at the 4-year follow-up then they did at diagnosis. Although this result is in close correspondence with most follow-up results

of weight loss programs (45), it is a rather undesirable outcome of the treatment of type 2 diabetes (46). This raises the question of how this weight gain can be explained, especially in the view of the reported lower energy intake and higher levels of dietary restraint. First, it is recognized that lowering energy intake does not unequivocally lead to weight loss. Restrained eating, for instance, may alter metabolic functioning in the direction of anabolism (47-50). Increased metabolic efficiency in response to repeated efforts at dieting may increase the difficulty of losing weight and may even cause weight gain in the long run (2). Indeed, it may be necessary for dietary restraint to increase over time if one is to lose weight in the long run (51, 52). Other explanations of altered metabolism or weight gain might be in the use of anti-diabetic medication with weight gaining properties or in the secular trend that has shown an increase in body weight over the last decades.

Second, the level of dietary restraint does not seem to be a plausible explanation for the weight gain either, because in the analysis no relationship was found between restrained eating behaviour and change in BMI at diagnosis or at follow-up, even when this relation was corrected for variables such as smoking. Increased metabolic efficiency may correspond, however, with the observation that dietary restraint, despite its increase, also was not related to weight loss. In this line of thought, the increase in dietary restraint may have been insufficient to counteract any anabolism to achieve the outcome of weight loss.

Third, a candidate for explaining weight gain is tendency toward overeating that seems so frequently associated with restricted eating. In the present study, support for this possibility was obtained by the finding that tendency toward overeating at diagnosis (emotional and external eating) explained a significant (although small) amount of variance in BMI change, a finding substantiated by the positive relationships between tendency toward overeating and intake of energy at the 4-year follow-up.

The suggestion that the weight gain in this study could be best explained by the tendency toward overeating is in line with other studies where the tendency toward overeating was found to be a better predictor of food consumption than was restraint (7, 8, 21, 22, 53). Although this finding seems a tautology at first sight, it is not in light of the dieting dilemma, because it suggests that the dieting dilemma could be resolved when the question Should we put a moratorium on dieting, yes or no, was reformulated into the question Who can be expected to have a good response to a dietary intervention and who should be treated differently?

Towards matched treatment of patients with type 2 diabetes

The present results fit well with research that suggests that the success of a dietary intervention may be predicted by a subject's tendency toward overeating (54, 55). This opens the possibility that the long-term effect of dietary consultations – for example, for patients with type 2 diabetes – may be enhanced by matching specific treatments to specific patients (56-58). Matched treatment may be based on a distinction between

type 2 diabetes patients with potentially good responses to dietary advises and those patients who do not have such positive responses. Patients with a low tendency toward overeating (emotional and/or external eating) may be expected to have good responses to the dietary consultations. It has been shown in an experimental setting that persons with a low tendency to overeat were not tempted to overeat when faced with delicious ice cream, or appetizing cookies (7, 8, 21). Moreover, they may be more likely to have a stable body weight in real life (59-62). Patients with a tendency to overeating (emotional and/or external eating) are less likely to benefit from dietary advice unless their overeating tendency is addressed. In their case, treatment should additionally target their overeating tendency (56): their sensitivity to food cues (in the case of external eating) or their low interoceptive awareness (in the case of emotionally induced overeating (36, 63)).

Limitations and strengths

A possible drawback of the study was the method of measuring food intake, which may have been subject to recall bias. However, it must be noted that all available instruments to measure food intake are subject to this bias and, therefore, a real gold standard does not exist. A drawback of record keeping or self-monitoring is its reactivity: For this precise reason, this method is a vital component of behaviour modification and treatment (64). A serious drawback of the unobtrusive measures that Stice, Fisher & Lowe (40) used in their validation study of measures for dietary restraint was that food intake was only assessed at one moment in time, and this is at variance with the fundamentals of valid dietary assessment, where a minimum time window of 24 hours is required (39, 41).

The small number of subjects may have affected the power of the study. Nevertheless, its strength is that the results all pointed at the same direction. The main strengths of our study were that it provided follow-up data (a) of sufficient length; (b) in a cohort of patients newly diagnosed with type 2 diabetes (subjects in whom we may assume high motivation for weight loss); (c) with satisfactory long-term participation rate; and (d) that were rooted in general practice, which means that the results correspond with normal daily life rather than with an experimental setting. A further strength of the study is that body weight and height, which were central to the outcome variable BMI change, were not based on self-reports but had been actually measured.

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Appendix A

Descriptive statistics at baseline of dropouts versus subjects

	Dropouts (n=47)		Subjects (n=97)		
	mean	SD	mean	SD	T
Sex	1.51	.50	1.52	.50	-.169 (ns)
Age	57.74	9.74	57.79	7.54	-.033 (ns)
Education	2.34	1.80	2.54	1.76	-.638 (ns)
Body weight	85.68	17.53	84.36	16.33	.413 (ns)
Energy	10469.87	3401.42	10689.59	3399.34	-.364 (ns)
Total fat	41.23	7.36	40.67	7.33	.432 (ns)
Smoking	1.79	.41	1.75	.44	.616 (ns)
Physical activity	5.60	1.36	5.95	1.39	-1.380 (ns)
Restrained eating	2.48	.91	2.44	.88	.263(ns)
Emotional eating	1.79	.80	1.76	.68	.221 (ns)
External eating	2.38	.81	2.31	.61	.484 (ns)

Chapter 4.1

Is acarbose equivalent to tolbutamide as first treatment for newly diagnosed type 2 diabetes in general practice? A randomised controlled trial

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Abstract

We performed a double blind randomised controlled trial in General Practice to assess equivalence between tolbutamide and acarbose with respect to the effect on mean HbA_{1c} in newly diagnosed patients with type 2 diabetes. Secondary objectives were to compare the effects of both treatments on fasting and post-load blood glucose and insulin levels, lipids, and adverse events. Patients were randomised to receive acarbose, dosed step-wise to a maximum of 100 mg three times daily (n=48) or Tolbutamide, similarly dosed to a maximum of 2000 mg in three doses (n=48). The two treatments were considered equivalent if the two-sided 90% confidence interval (CI) for the difference in mean HbA_{1c} levels was within the range –0.4% to 0.4%. Results were analysed on an intention-to-treat, per-protocol and on worst-case basis. Both agents reduced the HbA_{1c} percentage and fasting blood glucose levels. The difference in mean decrease of HbA_{1c} was 0.6% in favour of tolbutamide (90% CI 0.3,0.9; 95% CI 0.2,1.0). A worst-case analysis, assuming no change in HbA_{1c} for dropouts, yielded a difference in mean decrease of 0.9% (90% CI 0.6,1.2) in favour of tolbutamide. The difference in mean decrease of fasting blood glucose was 1.0 mmol/l in favour of tolbutamide (95% CI 0.3,1.7). There were no significant differences in post-load blood glucose, fasting and post-load insulin levels, or lipids. In the acarbose group significantly more patients (15 versus 3) discontinued therapy because of adverse effects, mostly of gastrointestinal origin. We conclude that the results of this study favour tolbutamide over acarbose as first treatment for patients with newly diagnosed type 2 diabetes.

Introduction

Currently, sulfonylureas are the most frequently used and recommended medication for type 2 diabetes in general practice. The Dutch guidelines for general practitioners are the most explicit (1), recommending as first choice a sulfonylurea in non-obese patients, when diet therapy has failed. Metformin is the first choice in obese patients, and if neither is sufficient alone, the two should be combined. Acarbose is indicated if the combination of both sulfonylurea and metformin fails, or in case of contraindications to, or adverse effects from tolbutamide or metformin. In contrast to other guidelines (2), the Dutch guidelines do not recommend the use of more than two different blood glucose lowering agents.

Worldwide, most experience has been gained with tolbutamide, a first-generation sulfonylurea. The results of the controversial University Group Diabetes Program, in which increased cardiovascular morbidity was associated with the use of tolbutamide, are now not considered of clinical importance (3). Tolbutamide causes relatively few hypoglycaemic events compared to other sulfonylureas and there is no convincing evidence that second-generation sulfonylureas are to be preferred over tolbutamide (4).

Acarbose, an inhibitor of alpha-glucosidase of the small intestine brush border, has a beneficial effect on postprandial bloodglucose and HbA_{1c} levels. It is well established in placebo-controlled trials as both first-line treatment (5) and as an adjunct to other oral agents (6, 7). An additional advantage of acarbose may be a beneficial effect on hyperinsulinaemia, a risk factor for cardiovascular disease (8).

In view of its capacity to lower postprandial blood glucose and insulin levels, acarbose might be the preferred first-line agent, provided that its glucose-lowering potential equals that of the sulfonylureas.

The results of studies comparing the glucose-lowering capacities of acarbose and a sulfonylurea are contradictory. Two trials showed a 0.4% advantage for the sulfonylurea in decreasing HbA_{1c} levels ($p=0.03$ (9) and $p=0.068$ (10)), one showed a 0.2% ($p=0.07$) advantage for acarbose (11), and two more showed no difference at all (p-value not reported) (12, 13). None of these studies were designed as equivalence trials. In addition, postprandial insulin levels were measured in three of these studies, and acarbose treatment resulted in statistically significantly lower levels compared to sulfonylurea (9-11). None of these studies was carried out in a primary care setting or in newly diagnosed diabetic patients.

Because of these contradictory results, we conducted a study in newly diagnosed type 2 diabetic patients in primary care to asses equivalence in the capacity of lowering HbA_{1c} levels between acarbose and tolbutamide. Secondary objectives were to compare the effects of both treatments on fasting and post-load blood glucose and insulin levels, plasma lipids, and tolerability.

Methods

Patient selection

The study took place from April 1995 to July 1998. Forty-six general practitioners working in general practices spread throughout the Netherlands recruited patients. Not all physicians participated for the entire period of three years. The physicians were asked to select patients either with complaints suggestive of diabetes mellitus and a capillary fasting blood glucose (FBG) ≥6.7 mmol/l or patients in whom a raised blood glucose level was found coincidentally. For patients without symptoms more than one abnormal fasting blood glucose was needed (14).

Patients were eligible for the trial if their FBG levels were between 6.7-20.0 mmol/l after an 8-week dietary treatment period (see below), and they met the following criteria: age between 40 and 70 years; and sufficient understanding of spoken Dutch to follow instructions.

Exclusion criteria were: any significant disease or condition likely to prevent patients from completing the study; uncorrected endocrine disturbances; pregnancy or breastfeeding; women of childbearing age not using contraceptives; diseases with abnormal gut motility or altered absorption of nutrients, or use of medications for such conditions; use of systemic glucocorticoids; hypersensitivity or other contraindications to acarbose or tolbutamide; habitual use of drugs or an alcohol intake >10 units daily; lactose intolerance; participation in another experimental study; serum cholesterol >10 mmol/l or a serum triglyceride >4 mmol/l; use of lipid lowering agents containing ionic-substitution resins (e.g. colestipol); aspartate aminotransferase (AST) >50 U/l, alanine aminotransferase (ALT) >50 U/l, Gamma GT >150 U/l; creatinine >150 µmol/l; myocardial infarction within the last 6 months.

All patients gave their written informed consent and the study protocol was approved by a central review board on medical ethics and was conducted in accordance with the Declaration of Helsinki.

Study Design

All selected patients entered an 8-week dietary treatment period. Dietary advice tailored to individual food habits and to serum levels of HbA_{1c} and lipids was given by a registered dietician. This was given at two visits and followed current recommendations for type 2 diabetes mellitus. All patients who still had a FBG between 6.7 and 20 mmol/l at the end of the diet phase were randomised into the tolbutamide or the acarbose group. During the 30 weeks trial period patients visited their general practitioner seven times. At each visit the FBG was measured, and compliance, concomitant diseases or medication, and adverse events were checked. Post-load glucose, fasting and post-load insulin, lipids, and liver and kidney functions were measured one week before randomisation and in week 29. HbA_{1c} was measured before randomisation and in weeks 22 and 29.

In the first 6 weeks after randomisation patients received an individually titrated step-up dose of tolbutamide or acarbose. As long as the FBG exceeded 6.7 mmol/l the physician increased the dosage of the double-blind medication at two, four and/or six weeks. The maximum dosage schedule at week 0, 2, 4 and 6 was for acarbose (milligrams, morning – afternoon – evening): 50 – 0 – 0, 50 – 0 – 50, 50 – 50 – 50 and 100 – 100 – 100 respectively. Similarly, for tolbutamide the scheme was 500 – 0 – 0, 500 – 0 – 500, 500 – 500 – 500 and 1000 – 500 – 500 respectively. Otherwise medication dosage was continued to the end of the trial. If FBG was >20 mmol/l at the end of the sixth trial week patients were excluded from the study.

Randomisation and blinding

Patients entering the trial received a code provided by a computer program generating random numbers at the trial centre. Each code corresponded to one of the treatments. The clinical quality assurance manager kept the allocation schedule in a central study file not accessible to the participating general practitioners. The code was sent to the general practitioner in a sealed radio-opaque envelope that was only to be broken in case of a medical emergency. At the end of the study the envelope had to be returned unopened.

Because of the different sizes of the actual tablets it was necessary to use the so-called 'double dummy' technique to ensure blinding. All patients received two sets of pills, apparently acarbose and tolbutamide, but only one set contained an active substance.

Measurements

Post-load blood samples for glucose and insulin were taken one hour after ingestion of 75 g glucose in 300 ml water. Patients were instructed to take the morning study medication after the test was completed. We chose the option of the post-load glucose test, using it as a measure of severity of the insulin-resistance syndrome. Insulin was measured by a radioimmunoassay technique (Pharmacia, Uppsala, Sweden). HbA_{1c} measurements were done by HPLC (Perkin Elmer, series 4, reference range 4.5-6.0%, assay DCCT aligned). For cholesterol and HDL-cholesterol estimation the CHOD-PAP method on Hitachi 717 (Boehringer Mannheim, Almere, The Netherlands) was used, and for triglycerides the Peridochrom triglycerid GPO-PAP method on the same machine. Fasting and one-hour post-load glucose measurements were performed on the spot using a calibrated glucometer for capillary samples. Reference ranges for the safety parameters were: AST 8-32 U/l, ALT 8-32 U/l, Gamma GT 8-28 U/l and creatinine 56-125 µmol/l (females) and 39-103 µmol/l (males). Drug compliance was checked by pill counting, and adverse effects were assessed by history taking and, if necessary, physical examination.

Statistical analysis

The number of participants was calculated by the formula for the power of the two-sample t-test for equivalence (15). Given a beta value of 20%, the formula yielded a sample size of 70 patients per treatment group.

The efficacy analysis was performed on an intention-to-treat (ITT) basis and as a per-protocol analysis (PP). ITT analysis included all randomised patients, including those who were included in the trial in error, those with low compliance, and patients whose data were missing. Missing data were handled according to the last-observation-carried-forward principle. Patients without baseline or without both post-baseline HbA_{1c} measurements were excluded from ITT analysis. In the event of significant differences in drop-out rates, a worst-case-analysis was carried out assuming that HbA_{1c} values for drop-outs did not change from baseline values. The PP analysis included all patients who completed the protocol without any violation.

Analysis for safety was carried out for all patients who received at least one dose of the study medication.

The primary efficacy measure was defined as the decrease in HbA_{1c} levels at the end of treatment, analysed by means of covariance (ANCOVA) with the baseline values as covariates. Therapeutic equivalence was assumed if the two-sided 90% confidence interval for the difference in mean HbA_{1c} levels between the two treatments was entirely within the range from –0.4% to 0.4%. In addition a second analysis was performed assessing the difference in proportion of patients with a reduction of HbA_{1c} $\geq$0.8%, taking this difference as a cut-off level for successful treatment. The decrease of 0.8% was based on expected effects of both agents as described in a recent literature overview (16).

Secondary efficacy measures were the fasting and one-hour post-load blood glucose levels; fasting and one-hour post-load insulin levels; total cholesterol, triglycerides, and HDL-cholesterol; and adverse events. Glucose, insulin, and lipid levels in the two treatment groups were also compared, by means of analysis of covariance, with baseline values as covariates. For each measure the 95% confidence interval for the difference in mean level was computed.

Differences in the occurrence of adverse events were assessed by the Cochrane-Mantel-Haenszel-chi-square test.

In the case of withdrawals before week 22, no post-baseline HbA_{1c} measurements were available. Therefore, to estimate the possible influence of withdrawal on trial results, we analysed fasting blood glucose levels in all randomised patients. Missing values were handled according to the last-observation-carried-forward principle.

Results

Patient flow

We recruited 144 subjects with newly diagnosed type 2 diabetes. Forty-eight patients did not enter randomisation because of the following reasons: FBG <6.7 mmol/l (n=33), high liver enzymes (n=5), consent withdrawn (n=6), FBG >20 mmol/l (n=1), protocol violation (n=1), falsely included (n=2). Of 96 patients that were eligible for randomisation, 48 were randomised to acarbose and 48 to tolbutamide (Figure 4.1.1). In the acarbose group, 15 patients discontinued the study due to side effects: gastrointestinal adverse events like flatulence, diarrhoea, abdominal pain or nausea (n=13), headache (n=1), not reported (n=1). One patient discontinued for other, unknown, reasons. In the tolbutamide group five patients discontinued, three because of respectively eructation, nausea and flatulence. For two patients the reason was not known. The difference between the two groups was statistically significant (p=0.007).

Due to protocol deviations we excluded for the PP analysis six patients in the acarbose group (insufficient data on compliance n=2, myocardial infarction n=1, single FBG <6.7 mmol/l before randomisation n=1, low compliance and duodenal ulcer n=1, breast carcinoma n=1), and five patients in the tolbutamide group (insufficient data on compliance n=1, myocardial infarction n=1, cholecystitis and pancreatitis n=1, randomisation code broken n=2). There were no significant differences in baseline characteristics between the groups (Table 4.1.1).

In the acarbose group, 5, 4, 7, and 17 patients used 50, 100, 150 and 300 mg of acarbose respectively in the tolbutamide group, 8, 8, 7, and 20 patients used 500, 1000, 1500, and 2000 mg respectively.

Efficacy

In both groups the primary efficacy measure, HbA_{1c} percentage, decreased significantly. The decrease of HbA_{1c} levels was more pronounced with tolbutamide than with acarbose. The calculated difference in mean decrease was 0.6% (90% CI 0.3,0.9, 95% CI 0.2,1.0) (Table 4.1.2). By definition, equivalence would have been established if the confidence interval of the difference in mean decrease in HbA_{1c} concentration was between –0.4% and 0.4%. Thus, these results do not demonstrate equivalence between acarbose and tolbutamide. However, equivalence cannot be ruled out on the basis of these results, as 0.4%, the predefined lower limit of equivalence, lies within the confidence interval.

The worst-case-analysis, assuming no change in HbA_{1c} for dropouts, yielded a difference of 0.9% (90% CI 0.6,1.2) between acarbose and tolbutamide in favour of tolbutamide. The proportion of patients with a reduction of HbA_{1c} ≥0.8% was 17/48 (35.4%) in the acarbose group and 35/48 (72.9%) in the tolbutamide group. Drop-outs were considered to have a reduction <0.8%. This difference was statistically significant (p<0.001).

Table 4.1.1. Baseline characteristics in all randomized patients, intention-to-treat and per-protocol analysis groups

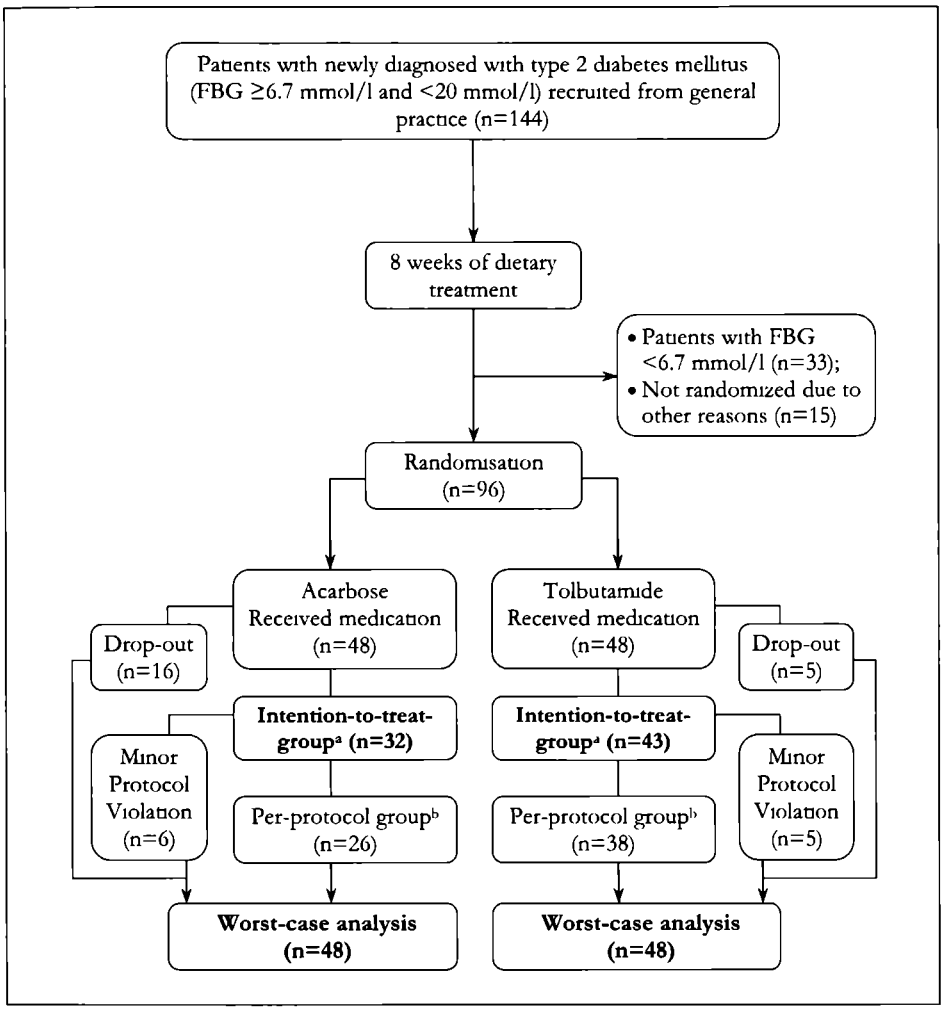
	Acarbose			Tolbutamide		
	Randomized	ITT	PP	Randomized	ITT	PP
Sex (male/female)	25/23	16/16	14/12	25/23	23/20	21/17
Mean age (years)	59.3 (7.5)	58.6 (7.7)	59.0 (7.9)	57.8 (7.3)	58.6 (7.1)	58.8 (7.2)
BMI (kg/m^2)	29.1 (4.6)	29.1 (5.0)	29.0 (4.8)	28.8 (5.5)	28.7 (5.6)	28.1 (5.0)
HbA_{1c} (%)	8.1 (1.8)	7.9 (1.8)	8.0 (1.5)	8.1 (1.6)	8.2 (1.7)	8.2 (1.7)
Fasting blood glucose (mmol/l)	10.0 (2.7)	9.8 (2.5)	9.9 (1.9)	10.2 (2.7)	10.3 (2.8)	10.3 (2.8)
Glucose 1 hour post-load (mmol/l)	18.8 (4.3)	18.5 (4.4)	18.8 (3.6)	18.8 (3.7)	18.8 (3.9)	18.7 (4.0)
Fasting insulin (pmol/l)	138 (64)	138 (72)	137 (65)	147 (99)	152 (103)	142 (74)
Insulin 1 hour post-load (pmol/l)	405 (219)	390 (230)	379 (198)	507 (313)	515 (324)	491 (303)
Triglyceride (mmol/l)	2.4 (2.0)	2.4 (2.4)	2.5 (2.6)	2.6 (2.2)	2.7 (2.3)	2.7 (2.5)
Total cholesterol (mmol/l)	5.8 (1.0)	5.7 (1.1)	5.7 (1.2)	5.9 (1.1)	5.9 (1.7)	6.0 (1.2)
LDL cholesterol (mmol/l)	3.7 (0.8)	3.6 (0.9)	3.7 (0.9)	3.7 (0.9)	3.7 (1.0)	3.8 (0.9)
HDL cholesterol (mmol/l)	1.0 (0.2)	1.0 (0.3)	1.0 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)

Randomized: (n=96): All randomized patients who took study medication
Intention-to-treat group (n=75): All randomized patients with at least one post-baseline HbA_{1c} measurement
Per-protocol group (n=64): All randomized patients who completed the protocol without any violations
Values are mean (standard deviation)

Table 4.1.2. Secondary efficacy measures. ITT analysis (n=75)

	Acarbose			Tolbutamide				
	Baseline (SD)	Endpoint (SD)	Change (n; SD, 95% CI)	Baseline (SD)	Endpoint (SD)	Change (n, SD, 95% CI)	Point Estimate†	95% CI
HbA_{1c} (%)	7.9 (1.7)	6.8 (1.3)	-1.1 (32; 1.0; -1.4,-0.7)	8.2 (1.7)	6.4 (1.0)	-1.8 (43, 1 3, -2.2,-1.4)	0.57	0 3,0 9*
FBG (mmol/l)	9.8 (2.5)	8.3 (2.5)	-1 5 (32; 2.1; -2.2,-0.7)	10.3 (2.8)	7.4 (1.7)	-2.9 (43; 2.6; -3.7,-2.1)	1 15	0 3,2 0
BG 1 hour Post-load (mmol/l)	18.1 (4.1)	16.9 (3.7)	-1 2 (29, 3.9; -2.7,0.3)	18.8 (3.9)	16 4 (3.4)	-2.2 (41; 2.8; -3.0,-1.3)	0 7	-0.6,2.1
Fasting insulin (pmol/l)	139 5 (59 3)	134.8 (56.8)	-4.7 (28, 56.0, -26.4,17.0)	154.9 (107.8)	151.7 (123 2)	-3.2 (35, 96.1; -36.2,29.9)	-6.0	-45 3,33.3
Insulin 1 hour Post-load (pmol/l)	385.4 (192.3)	392.9 (208 7)	7.5 (25; 136.5; -48.9,63 8)	494 3 (324.1)	520.7 (301.2)	26.4 (35; 282 2, -70.5,123.4)	-61.5	-172.8,49.9
Triglycerides (mmol/l)	2.5 (2.5)	2.2 (1.2)	-0.3 (28; 1.6; -0.9,0.3)	2.7 (2.4)	2.4 (1.9)	-0 4 (39; 2 1; -1.0,0 3)	-0.1	-0.7,0.6
Total cholesterol (mmol/l)	5.5 (0.9)	5 7 (1.0)	0.1 (28, 0.5, -0.1,0.3)	6.0 (1.1)	6 0 (1 2)	0.0 (39, 0.7, -0.2,0.2)	0.1	-0.2,0.4
LDL-Cholesterol (mmol/l)	3.5 (0.6)	3.6 (0.8)	0.1 (27, 0.4; -0.1,0.3)	3.8 (1 0)	3.7 (0.8)	-0.1 (38; 0.7, -0 3,0.2)	0.1	-0.2,0.4
HDL-Cholesterol (mmol/l)	1.0 (0.2)	1.1 (0.3)	0.1 (28, 0 2, 0.0,0.2)	1.1 (3 1)	1.2 (0.3)	0.1 (38; 0.4; 0.0,0.2)	-0 1	-0.2,0 1

† Calculated by Analysis of Covariance (ANCOVA) with baseline values as covariates
* 90% CI, 95% CI 0 2,1 0
Values are mean (standard deviation)



[a] Patients with at least one post-baseline HbA_{1c} measurement
[b] Patients who completed the protocol without deviations

Figure 4.1.1. Study design and patient flow

Except for fasting blood glucose, all secondary measures of efficacy, including post-load insulin levels, did not differ significantly. The results from analysis on a PP basis did not differ from the results of the ITT analysis (data not displayed).

To estimate the effect of premature withdrawals, the mean difference in FBG levels in all randomised patients was calculated. The point estimate (acarbose-tolbutamide) was 1.01 mmol/l (0.29,1.73). This result was similar to that of the ITT and PP analysis.

Safety and adverse drug reactions

Of the 96 patients who received at least one dose of the study medication, 22 (46%) patients in the acarbose treatment group and 12 (25%) patients in the tolbutamide treatment group reported 39 and 27 drug-related adverse events, respectively. The most frequently occurring drug-related adverse events were flatulence, diarrhoea, and abdominal pain or nausea. Except for the expected higher rate of flatulence in the acarbose treatment group (acarbose 27%; tolbutamide 2%), the two treatment groups had similar profiles of drug-related adverse events. There were no hypoglycaemic events reported in both treatment groups.

No patients had to be excluded due to FBG >20 mmol/l during the treatment period.

Discussion

Equivalence between acarbose and tolbutamide could not be established in this trial. Rather, this trial provides evidence that, when taking all aspects of treatment and side effects into account, the effects of acarbose are inferior. The result of the worst-case analysis and the more pronounced reduction of FBG values among tolbutamide users underpin this.

Further, this study shows no difference in post-load insulin levels and a statistically and clinically significant difference in adverse effects in favour of tolbutamide.

With respect to the primary efficacy measure the results of this study are in line with the results of Coniff (9) and Salman (10). Statistical significance, however, was only established in the study of Coniff et al., which was also the only trial with tolbutamide as the sulphonylurea. The studies that report no differences or an advantage for acarbose were performed earlier and all conducted by the same group (11-13).

We found no differences in post-load insulin levels. This was surprising because such evidence as is available indicates an advantage for acarbose (9-11). This conflicting result might be because we did not conduct full meal tolerance tests, but instead we measured post-load insulin after ingestion of 75 g glucose, without previous ingestion of the study medication. Because acarbose does not affect the absorption of simple carbohydrates like glucose, ingestion of acarbose prior to a glucose tolerance test would not have influenced the normal insulin rise. We also found no evidence that treatment with acarbose offers advantages over tolbutamide with respect to glucose tolerance, fasting insulin levels, and insulin response.

In contrast to previous studies, adverse effects were a major cause for discontinuation, especially in the acarbose group. One of the reasons for this remarkable discrepancy might be the increase in dosage from 150 to 300 mg, which could be too rapid. Also, the setting of the study may have been contributed to the large number of dropouts. Comparable studies were performed in hospitals or specialised diabetes centres with more opportunities to monitor and motivate participating patients. The general practitioners who treated patients in our study probably had only limited time to motivate patients who experienced adverse gastrointestinal effects. Although the high number of withdrawals is disappointing for the investigators, it demonstrates everyday practice and is therefore a valuable outcome, which hampers the long-term treatment of at least one in every three patients. By calculating the outcome for fasting blood glucose in all randomised patients we showed that it is unlikely that these withdrawals affected the primary endpoint.

We could not achieve the number of patients required by the power calculation. To estimate the influence of insufficient power, we recalculated the difference in mean HbA_{1c} using 70 patients per treatment group, assuming the same statistical distribution. This resulted in a 90% confidence interval of 0.3,0.8. Thus, even if the patient numbers called for by the power calculation had been met, a statistically significant outcome was not sure. This was also true for the secondary efficacy measures.

Because about 75% of all type 2 diabetic patients in the Netherlands are treated by general practitioners, our findings represent the main patient population treated for diabetes mellitus. To our knowledge there is no previous study conducted in a similar setting: this makes comparison with other reports insecure. The literature does not provide unequivocal results that allow drawing unambiguous conclusions. Nevertheless, this study may be a guide to judging the usefullness of acarbose in general practice by its true merits.

To conclude, we found no evidence to challenge the current policy of giving a sulfonylurea as the first treatment of choice for type 2 diabetes in general practice. The relatively low cost of sulphonylureas compared to acarbose together with a favourable safety profile, underlines this policy. Acarbose remains a rational alternative, however, when a sulfonylurea fails, or as an addition to other drug therapy.

For a definite answer to our primary question, we strongly recommend a meta-analysis of our results together with those of previous studies.

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Chapter 4.2

Alpha-glucosidase inhibitors for patients with type 2 diabetes mellitus: results from a Cochrane systematic review and meta-analysis

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Chin J Evid-based Med 2006;6(5):335-351

Abstract

Objective. To review the effects of monotherapy with alpha-glucosidase inhibitors (AGIs) for patient with type 2 diabetes, with respect to mortality, morbidity, glycemic control, insulin levels, plasma lipids, body weight and side effects.
Methods. We systematically searched the Cochrane Central register of Controlled Trials, MEDLINE, EMBASE, Current Contents, LILACS, databases of ongoing trials, reference lists and we contacted experts and manufacturers. Inclusion criteria were randomized controlled trials of at least 12-weeks duration, AGI monotherapy compared with any intervention, and one of the following outcome measures: mortality, morbidity, GHb, blood glucose, lipids, insulin levels, body weight, or side effects. Two independent reviewers assessed all abstracts, extracted all data, and assessed quality. We contacted all authors for data clarification. Continuous data were expressed as weighted mean differences and analyzed with a random-effects model. Possible influences of study characteristics and quality were assessed in sensitivity and meta-regression analyses.
Results. Forty-one studies were included in the review (acarbose 30, miglitol 7, voglibose 1, and combined 3), and heterogeneity was limited. We found no evidence for an effect on mortality or morbidity. Compared with placebo, AGIs had a beneficial effect on GHb (acarbose –0.77%, miglitol –0.68%), fasting and postload blood glucose and postload insulin. With acarbose dosages higher than 50 mg t.i.d., the effect on GHb was the same, but the occurrence of side effects increased. Acarbose decreased the BMI by 0.17 kg/m^2 (95% CI 0.08 to 0.26). None of the AGIs had an effect on plasma lipids. Compared with sulphonylurea, AGIs seemed inferior with respect to glycemic control, but they reduced fasting and postload insulin levels. For comparisons with other agents, little data were available.
Conclusions. We found no evidence for an effect on mortality or morbidity. AGIs have clear beneficial effects on glycemic control and postload insulin levels but not on plasma lipids. There is no need for dosages higher than 50 mg acarbose t.i.d.

Abstract (Chinese)

摘要

背景：α-葡萄糖苷酶抑制剂，比如阿卡波糖或 miglitol，有可能提高 2 型糖尿病患者的糖控？特别是与糖尿病死亡率和发病率相关的这些作用的实际效果，还未进行过系统文献评价和 meta-分析。

目的：评价 α-葡萄糖苷酶抑制剂在治疗 2 型糖尿病患者中的作用。

检索方法：我们检索了 Cochrane Library, MEDLINE, EMBASE, Current Contents, LILACS，正在进行的试验数据，以 α-葡萄糖苷酶抑制剂为主题的相关评价目录，并与其他试验的专家与实施者取得联系。最近检索的数据有 Current Contents（2003 年 12 月）其他数据库（2003 年 4 月）。

纳入标准：持续至少 12 周的 α-葡萄糖苷酶抑制剂单独治疗与其他干预治疗 2 型糖尿病的随机对照试验，至少包括一项下列结果：死亡率、发病率、生命质量，糖控？血脂，胰岛素水平、体重、副作用。

数据收集与分析：两名评价者阅读所有摘要，评价质量，独立提取数据，不一致性可以通过第三方进行一致性评价或判断进行解决。对所有数据库中提取的数据，进行统计学核对，并尽可能与所有作者取得联系并核实数据。

主要结果：纳入 41 个试验（8130 名病人），30 例研究了阿卡波糖，七例使用 miglitol 一例实验 voglibose 和三例区别与 α-葡萄糖苷酶抑制剂的对照试验？绝大多数研究持续了 24 周，只有两个研究持续时间超过一年，几乎无有关死亡率、发病率、生命质量的数据报道。阿卡波糖相对于安慰剂有明显的糖控作用。糖化血红蛋白-0 8% [95% CI（ -0 9 to -0 7)], 禁食血糖 -1.1 mmol/L [95% CI（ -1 4 to -0 9）], 后负荷血糖 -2 3 mmol/L [95% CI（ -2.7 to -1.9）]，阿卡波糖对血红蛋白的作用呈非剂量依赖。而对后负荷胰岛素水平，非临床相关作用血脂和体重则有减低作用。副作用主要是胃肠道器官并有剂量依赖。相对于磺脲，阿卡波糖分别将禁食和后负荷胰岛素水平从-24.8 pmol/L [95% CI（ -43.3 to –6.3）]降低到-133.2 pmol/L [95% CI（ -184.5 to -81.8）]，但是阿卡波糖引起的副作用也更多。

评价者结论：关于 α-葡萄糖苷酶抑制剂是否影响 2 型糖尿病患者的死亡率和发病率仍不清楚。相反，其对糖控或胰岛素水平却作用明显，对血脂和体重的作用无明显统计学差异。这些作用在 α-葡萄糖苷酶抑制剂长期维持治疗时仍不确定。阿卡波糖剂量超过 50 mg TID 时对糖化血红蛋白的作用无增加，但副作用却更加明显，相对于磺脲，α-葡萄糖苷酶抑制剂降低了禁食和后负荷胰岛素水平，但在糖控和副作用方面亦存在不利影响。

Introduction

Alpha-glucosidase inhibitors (AGIs: acarbose, miglitol, voglibose) are widely used in the treatment of patients with type 2 diabetes. AGIs delay the absorption of carbohydrates from the small intestine and thus have a lowering effect on postprandial blood glucose and insulin levels.

In modern medicine, the efficacy of an intervention should be investigated in well-designed randomized trials. Results from the trials should be collected in a high quality systematic review, if possible with a meta-analysis. And finally, the evidence should have its repercussions on practice guidelines.

How does this apply for AGIs? Recommendations on when to use AGIs and the evidence used for these recommendations appear to be different in various guidelines. For example, the guideline by the European Diabetes Policy Group (1) and a consensus statement by the American Diabetes Association (2) are not very specific. They mention the possible use of AGIs as first-line agent or in combination with other antihyperglycemic drugs, but they don't offer a more precise judgment, and literature references are not given. The Dutch guidelines are more explicit about the use of AGIs. They advise using acarbose only when other agents are contraindicated, and references are provided with this advice (3). The guidelines of the Royal College of General Practitioners in the U.K. reach similar recommendation as the Dutch. These guidelines are based on a systematic review of the literature. For AGIs the advice is based on one review article and 17 additional trials, with acarbose both as monotherapy and as additional therapy (4).

In recent years literature reviews focused exclusively on acarbose or miglitol. Voglibose has not been subject to a literature review. It is difficult to value the results of these reviews because all have methodological weaknesses: no description of search strategy and inclusion criteria (5-7), no report of search results (5-9), and either lack or have an unclear quality assessment of the included studies (5-9). In general, all reviews reported beneficial effects on glycemic control. One review reported results from a meta-analysis by calculating the mean effect from 13 trials with acarbose (GHb –0.90%, fasting blood glucose –1.3 mmol/l, postprandial blood glucose –3.0 mmol/l) (7). Although generally assumed, the existence of a dose dependency of the effect could not be concluded from these reviews.

A review on the effect of oral antihyperglycemic agents on serum lipids in patients with type 2 diabetes found beneficial effects of acarbose on HDL and LDL cholesterol and a decreasing effect of voglibose on triglycerides (10). However, a meta-analysis was not performed. Another study of very recent date concluded from a meta-analysis of seven trials that acarbose reduces the incidence of myocardial infarctions in patients with type 2 diabetes (11). However, this study was subject to publication bias, heterogeneity, detection bias and confounding (12).

We conducted a systematic literature review and meta-analyses within the framework of the Metabolic and Endocrine Disorders Review Group of the Cochrane

Collaboration Our main research focused on the effects of AGIs versus placebo (or any other intervention) with respect to: 1) mortality and (diabetes-related) morbidity; 2) glycemic control, plasma lipids, insulin levels, and body weight; and 3) side effects.

Methods

We searched the Cochrane Central register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Current Contents, LILACS, reference lists of reviews on the topic, and we contacted manufacturers and experts for additional (unpublished) trials. In addition, we searched databases of ongoing trials on the Internet. The last systematic search was in December 2003 for Current Contents and April 2003 for the other databases.

For MEDLINE, we combined the search strategies for "type 2 diabetes mellitus" and "randomized controlled trials" that we adapted from the Review Group (13) and combined these with a combination of the Medical Subject Headings key word "acarbose" and all different spellings for AGIs and their brand names. This strategy had to be slightly adapted for EMBASE and Current Contents, making the search more sensitive. For the other databases we searched with the words for AGIs only, because these databases already included controlled trials only (CENTRAL, databases of ongoing trials) or because its browser didn't allow complex searches (LILACS).

Studies had to meet five inclusion criteria: 1) inclusion of patients with type 2 diabetes that received no other antidiabetic medication (when both patients with and without additional antidiabetic medication were included, the results for the latter (sub)group should be well presented); 2) a duration of at least 12 weeks; 3) intervention with an AGI; 4) random allocation to the comparison groups; 5) at least one of the following outcome measures: mortality, morbidity, quality of life, glycemic control, insulin or C-peptide levels, lipids, body weight, or adverse effects.

When a study could not be excluded on basis of title or abstract alone, it was included and retrieved for further scrutiny. Two independent reviewers read all titles and abstracts. Interrater agreement was calculated by kappa statistics.

Data extraction and quality assessment

The same two independent reviewers extracted all data and assessed quality. For data-extraction we used an adapted version of a form provided by the Review Group. We extracted the following aspects: general items (e.g., setting, sponsoring, ethical approval), design (parallel or cross-over, method of randomization, blinding), participants (e.g., diagnostic criteria, inclusion and exclusion criteria), interventions (e.g., dietary reinforcement, dosage schedules), baseline characteristics (e.g., age, sex, GHb), and outcomes (e.g., occurrence of mortality, changes in blood glucose and measures of variance). We attempted to contact authors in the case of missing

information or uncertainties. If necessary, we also extracted data from graphical figures.

Differences in opinion between the reviewers were resolved by consensus, by referring back to the original data, or by consulting a third reviewer in case of persisting disagreement.

We assessed and scored the following quality items being adequate or inadequate/unclear (14, 15): randomization and allocation concealment (referring to selection bias), blinding (performance bias) and handling of drop-outs (attrition bias). For studies that had morbidity or quality of life as main endpoints, the method of blinding outcome assessment was also assessed (detection bias).

Data analysis

Available data of sufficient quality were summarized statistically and used for meta-analyses. We first divided the data into all possible comparisons (e.g., acarbose versus placebo, voglibose versus sulphonylurea) and then subdivided them into all possible outcomes (e.g., death, glycated hemoglobin). Finally, within the outcomes we made subgroups for the different dosages. Outcomes were calculated per subgroup and for all subgroups together.

Dichotomous data were expressed as odds ratios and continuous data as weighted mean differences; the overall results were calculated with the random effects model. The measures of effect for all continuous variables were the differences from baseline to endpoint. When the SDs for these differences were missing, we first contacted the authors for these additional data. If these data were not provided we calculated the SD of the difference with the following formula (14):

$$SD_{paireddifference} = \sqrt{((SD_{pre\text{-}treatmentvalue})^2 + (SD_{post\ treatmentvalue})^2 - 2 \times r \times SD_{pre\text{-}treatmentvalue} \times SD_{post\text{-}treatmentvalue})}.$$

We used a conservative correlation coefficient (r) of 0.4.

Heterogeneity was assessed by a visual inspection of the forest plots first. In addition, we used Z score and Chi square statistics. We also used funnel plots to test for possible small study bias. Sensitivity analyses were performed to investigate the possible influence of the predefined quality criteria (14, 15), language of publication, country, source of funding and statistical model (random versus fixed effects models). Further, we performed subgroup and meta-regression analyses for baseline GHb, mean age, sex, duration of diabetes, duration of intervention, use of a step-up dosage schedule, and use of a fixed dose versus an individually titrated scheme.

We used Revman 4.2.3 (2003, The Cochrane Collaboration, Oxford, U.K.) for all analyses, except for meta-regression analyses, which were done with in SAS proc Mixed (version 8.0).

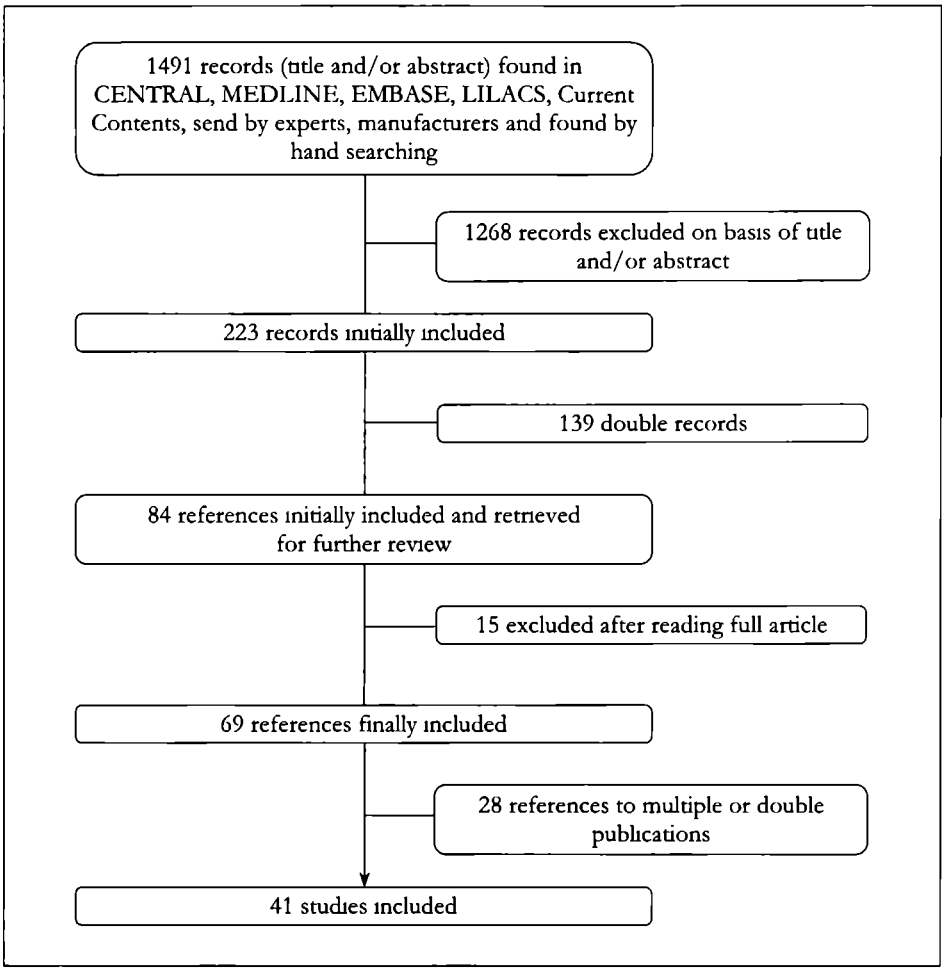

Figure 4.2.1. Study flow diagram

Results

Interrater kappa for agreement on inclusion read by the two reviewers was 0.74 (95% CI 0.67 to 0.81). All differences in opinion were resolved by consensus. We included 41 studies in the systematic review (Figure 4.2.1) (16-56). Fifteen studies were excluded after reading the full article. Eleven studies investigated the use of AGI in addition to other antidiabetic therapy, and there was no clear report of a diet-only subgroup (57-67). Two studies had a duration less than 12 weeks (68, 69), one study was not randomized (70) and one study included patients with impaired glucose tolerance (71). In addition, we found three trials in registers of ongoing trials (72-74), but we were not able to obtain published or unpublished reports.

The main study characteristics are listed in Table 4.2.1. All but three studies (33, 36, 38) showed one or more deficiencies or insufficient reporting of the main quality criteria. Pharmaceutical companies sponsored 33 studies, 2 studies were sponsored by another fund, 1 study was not sponsored, and possible sponsoring was unclear for 5 studies. We attempted to contact all authors for data clarification, which led to additional data for 22 studies.

Effects on mortality and morbidity

Three studies reported mortality and found no differences between treatment groups (24, 37, 40). The trial performed within the United Kingdom Prospective Diabetes Study (UKPDS) reported prospectively collected data concerning "any diabetes-related endpoint" and microvascular disease. The relative risks for acarbose compared with placebo were 1.00 (95% CI 0.81 to 1.23) and 0.91 (95% CI 0.61 to 1.35), respectively. Another study with miglitol found statistically significant less cardiovascular events in the miglitol-treated patients than in patients treated with glyburide (17 vs. 29%), but these outcomes were derived from the safety data and not collected in a well defined and prospective way (40).

Meta-analyses

Most data for meta-analyses were available from studies with acarbose. The main overall results are summarized in Table 4.2.2.

Glycemic control

Compared with placebo acarbose decreased GHb by 0.77% (95% CI 0.64 to 0.90) (Appendix A) and miglitol by 0.68% (95% CI 0.44 to 0.93), respectively. For voglibose, only one study was available, which yielded a difference of 0.47% in favour of voglibose (95% CI 0.31 to 0.63) (43). With respect to GHb, we found no evidence for a dose dependency for acarbose in the range from 50 mg t.i.d. to 300 mg t.i.d.. The

subgroup analyses for acarbose 50 mg, 100 mg, 200 mg and 300 mg t.i.d. showed a decrease in GHb of 0.90%, 0.76%, 0.77% and 0.78% respectively (Appendix A). In contrast, for miglitol such a dose dependency seemed to be present; miglitol 25 mg, 50 mg, 100 mg and 200 mg t.i.d. decreased GHb by 0.46, 0.58, 0.79 and 1.26%, respectively. However, the results from this meta-analysis are based on seven comparisons, of which four were derived from one (multi-arm) trial (28).

In the subgroup analysis and meta-regression analyses, we found a tendency towards a larger effect on GHb of acarbose at higher baseline levels for GHb. The subgroup analyses for studies with baseline GHb <7%, 7-9% and >9% yielded a decrease in GHb of 0.56% (95% CI 0.36 to 0.76), 0.78% (95% CI 0.63 to 0.93) and 0.93 (95% CI 0.53 to 1.33), respectively. In the meta-regression analysis with effect on GHb as dependent and baseline GHb as independent variable, we found a regression coefficient of –0.12 (95% CI –0.26 to 0.03), indicating an extra 0.12% GHb decrease for every 1% higher baseline GHb.

The subgroup-analysis for study duration yielded that long-term studies (more than 24 weeks) showed less effect on GHb. The decrease in GHb for studies with a duration of less than 24 weeks, equal to 24 weeks and more than 24 weeks was 0.77 (95% CI 0.61 to 0.93), 0.82 (95% CI 0.63 to 1.01), and 0.53 (95% CI 0.20 to 0.87) respectively. This was mostly due to the data from the UKPDS study (duration 156 weeks) in which a decrease of only 0.19% on GHb was found (95% CI –0.29 to 0.67) (37).

In the subgroup and meta-regression analyses, we also found that the application of a fixed dosage scheme and the absence of a step-up dosage scheme, increased the effect on glycemic control, but also increased the occurrence of side effects (data not shown).

For acarbose fasting blood glucose decreased by 1.09 mmol/l (28 comparisons; 95% CI 0.83 to 1.36), for miglitol by 0.52 mmol/l (2 comparisons; 95% CI 0.16 to 0.88), and for voglibose by 0.60 mmol/l (1 comparison; 95% CI 0.23 to 0.97). One hour postload glucose decreased by 2.32 mmol/l (acarbose; 22 comparisons; 95% CI 1.92 to 2.73), 2.70 mmol/l (miglitol; 2 comparisons' 95% CI –0.14 to 5.54) and 2.40 mmol/l (voglibose; 1 comparison; 95% CI 1.83 to 2.97). In contrast to the outcome for GHb, acarbose showed a dose-dependent decrease of postload glucose. Acarbose 50 mg, 100 mg, 200 mg, and 300 mg t.i.d. reduced postload glucose by 1.63, 2.26, 2.78, and 3.62 mmol/l, respectively (Appendix B).

Data from studies that compared AGI with other blood glucose lowering interventions were scarce. Pooling of results was only possible for the comparison acarbose with sulphonylurea. The overall comparison of acarbose with sulphonylurea yielded a non-significant advantage for sulphonylurea with respect to overall GHb of 0.38% (Appendix C). However, seven of the studies in the meta-analyses used unequal comparators, because they compared a fixed dose of acarbose with individually adjusted dosages of sulphonylurea (24, 30, 35, 44, 47, 49) or a usual dose of acarbose with a very low dose of glibenclamide (32). The results for the subgroup "acarbose 100 mg versus glibenclamide 3.5 mg" were not consistent with the other comparisons.

Table 4.2.1. Characteristics of 41 randomized controlled trials of at least 12 weeks duration, comparing AGIs with any other intervention

Ref.	Design*, location, setting	Duration (weeks)	Randomization†	Allocation concealment†	Blinding†	Handling of drop-outs†	Patients randomized (n)	Mean age (years)	Female (%)	Mean duration diabetes (months)	Interventions
(16)	Germany, GP	24	B	B	A	B	152	60.5‡	41.9‡	16.5‡	ACA 100 mg t.i.d., PLA
(17)	Scotland, OP	16	B	B	B	B	28	58.7‡	30.0‡	48.0‡	ACA max. 200-100-200 mg (decreased with intolerance), PLA
(18)	Spain, OP	16	B	B	A	B	40	ND	ND	ND	ACA 100 mg t.i.d., PLA
(19)	United Kingdom, GP	156	A	B	A	B	789	62.0‡	34.9‡	38.1‡	ACA 50 mg t.i.d., ACA 100 mg t.i.d., PLA
(20)	Asia, OP	24	B	B	A	A	126	53.4	49.2	28.8	ACA 100 mg t.i.d., PLA
(21)	Canada, OP	52	B	B	B	B	77§	57.2	37.7	62.4	ACA max 200 mg t.i.d. (titrated), PLA
(22)	Canada, OP	36	B	B	A	A	324	58.1	25.9	55.0	MIG 100 mg t.i.d., metformin 500 mg t.i.d., PLA, (combination of MIG and metformin)
(23)	USA, OP	24	A	A	A	A	212	55.8‡	50‡	65.5‡	ACA max 300 mg t.i.d (titrated), PLA
(24)	USA, OP	24	A	A	A	A	290	56.5	51‡	70.9	ACA 200 mg t.i.d., tolbutamide max 1000 mg t.i.d. (titrated), PLA, (combination ACA and tolbutamide)
(25)	USA, OP	16	A	A	A	B	290	55.4	43	66	ACA 100 mg t.i.d., ACA 200 mg t.i.d., ACA 300 mg t.i.d., PLA
(26)	Russia, OP	24	B	B	B	B	180	51.0‡	62.1‡	ND	ACA 100 mg t.i.d., PLA
(27)	Switzerland, OP	16	B	B	B	B	17	ND	30.0	26	ACA 50 mg b.i.d., PLA
(28)	The Netherlands, GP/"Study centres"	24	B	A	A	B	599	63.4‡	45.1‡	40.0‡	MIG 25 mg t.i.d., MIG 50 mg t.i.d., MIG 100 mg t.i.d., MIG 200 mg t.i.d., PLA

Table 4.2.1 continued

(29)	Europe, OP	24	A	A	A	B	495	56 6‡	47 1‡	21 7‡	ACA 25 mg t.i.d., ACA 50 mg t.i.d., ACA 100 mg t i d., ACA 200 mg t i d , PLA
(30)	No blinding, Germany, OP	24	A	B	-	A	96	61.5	58.9	26 5	ACA 100 mg t.i d , glibenclamide max 3 5 mg t.i d. (titrated)
(31)	Cross-over study, Italy, OP	12	B	B	B	B	76	ND	76.7	110 4	ACA 100 mg t i d , PLA
(32)	Germany, OP	16	B	B	B	B	77	58.7	48.1	80 0	ACA 100 mg t i d , glibenclamide 1 mg t i d , PLA
(33)	Germany, OP	24	A	A	A	A	100	59.5‡	48 9‡	59 5‡	ACA 100 mg t i d., PLA
(34)	Cross-over, Germany, OP	12	B	B	B	B	18	ND	ND	ND	ACA 200 mg b i d., MIG 200 mg b i d , glibenclamide 7 mg q d.
(35)	Single-blind (for glibenclamide), Germany, OP	24	A	A	A	B	96	58 5‡	55 3‡	14.0‡	ACA 100 mg t.i d., glibenclamide max 3.5 mg t i d (titrated)
(36)	Single-blind (for metformin), Germany, OP	24	A	A	A	A	96	58.4‡	66 0‡	35.1‡	ACA 100 mg t.i d., metformin 850 mg b.i.d., PLA
(37)	England, OP	156	A	A	A	B	256§	60 5	28.9	87.2	ACA 100 mg t i d (decreased in case of intolerance), PLA
(38)	Germany/France/Spain, OP	24	A	A	A	A	179	62.4	35.2	58.5	ACA 100 mg t i d (decreased in case of intolerance), nateglinide 120 mg t i d.
(39)	Japan, OP	24	B	A	A	B	40	48.9‡	24.3‡	56.4‡	ACA 100 mg t.i.d., PLA
(40)	USA, OP	56	B	B	A	A	411	67.8‡	32.4‡	64.4‡	MIG 25 mg t i.d., MIG 50 mg t i d , glyburide max 20 mg q d. (titrated), PLA
(41)	USA, OP	52	B	B	B	B	69§	ND	ND	ND	MIG max. 200 mg t.i.d. (decreased in case of intolerance), PLA
(42)	USA, OP	28	B	B	B	A	45§	56 6‡	42.2‡	49.6‡	MIG 100 mg t i d (decreased in case of intolerance), PLA
(43)	Japan, setting unclear	12	B	B	B	B	445	ND	ND	ND	MIG 50 mg t.i.d , VOG 0 2 mg t.i d , PLA
(44)	Single-blind (for glibenclamide), OP	24	B	A	A	A	102	57 8	53 9	54	ACA 100 mg t i d , glibenclamide max 3.5 mg t.i d (titrated), PLA
(45)	Canada, OP	52	B	B	B	A	192	70 0	34 9	63.4	ACA max 100 mg t i d (titrated), PLA
(46)	Canada, OP	24	B	A	A	A	100	58 0‡	40 6‡	71 8‡	MIG 100 mg t.i.d., glibenclamide mg b i d (+ 1 PLA)

Table 4.2.1 continued

(47)	No blinding, Germany, GP	24	A	B	-	B	76	57 5	ND	27.7	ACA 100 mg t.i.d , glibenclamide max. 10.5 mg in 2 dose (titrated)
(48)	Europe, setting unclear	24	B	B	B	B	603	ND	ND	ND	ACA 100 mg t.i.d., MIG 50 mg t.i.d., MIG 100 mg t.i.d., PLA
(49)	No blinding, Turkey, OP	24	A	A	-	B	72	54.4‡	42.1‡	53.6‡	ACA max. 100 mg t.i.d (may be reduced), gliclazide 80 mg b i d (in general, max. dose not recommended)
(50)	Italy, OP	16	A	B	B	B	84	55.8‡	35.9‡	51 5‡	ACA 50 mg t i.d., ACA 100 mg t.i.d., PLA
(51)	New-Zealand/Australia, OP	16	B	A	A	B	105	56.5	36	23.5	ACA 100 mg (t.i.d.) (decreased in case of intolerance), PLA
(52)	Europe, OP	24	B	B	A	B	201	58.7‡	42‡	ND	MIG 100 mg t i d., glibenclamide 3.5 mg q.d. (or b i d. when hypoglycemia was unacceptable)
(53)	No blinding, Germany, OP	24	A	B	-	B	72	59.5‡	60‡	ND	ACA 100 mg t i d., glibenclamide max. 3.5 mg (titrated)
(54)	No blinding, Japan, OP	12	B	B	-	B	36	50.5	28‡	0	VOG 0.3 mg t.i.d., glyburide 1.25 mg q.d., diet therapy
(55)	The Netherlands, GP	30	A	A	A	B	96	58 6	48	0	ACA max. 100 mg t.i.d. (titrated), tolbutamide max 2000 mg in 3 doses (titrated)
(56)	China, OP	24	B	B	B	A	77	49 3	48	49.8	ACA 100 mg t i.d., PLA

*Except when indicated, all studies were parallel and double blind. †A, adequate, B, inadequate, unclear. ‡All values except these are based on all randomized patients. §subgroup of patients treated with diet only. ||Based on proportion of patients in analysis, number of patients randomized in diet-only group not reported
ACA, acarbose; GP, general practice; MIG, miglitol; ND, No available data; OP, outpatient; PLA, placebo, VOG, voglibose

This discrepancy remained unexplained. Leaving this subgroup out of the meta-analysis yielded an overall effect of 0.63% (95% CI 0.26 to 1.00) in favour of sulphonylurea. In the same comparison, outcomes for the meta-analyses for fasting and 1-h postload blood glucose were 0.69 mmol/l in favour of sulphonylurea (95% CI 0.16 to 1.23) and 0.10 mmol/l in favour of acarbose (95% CI –0.43 to 0.22) (37).

Insulin levels

Compared to placebo, acarbose had no effect on fasting insulin levels and a lowering effect on 1-h postload insulin levels of 40.8 pmol/l (95% CI 21.0 to 50.6). For miglitol and voglibose, only a limited number of comparisons were available, and no statistically significant effects were found (Table 4.2.2).

Compared with sulphonylurea, acarbose had a statistically significant decreasing effect on fasting insulin of 24.8 pmol/l (7 comparisons; 486 participants, 95% CI 6.3 to 43.3) and 1-h postload insulin of 133.2 pmol/l (7 comparisons; 483 participants, 95% CI 81.8 to 184.5) (Table 4.2.2).

Plasma lipids

Meta-analyses were only possible for studies with acarbose. We found a small effect of –0.09 mmol/l for acarbose on triglycerides that was borderline statistically significant (95% CI –0.18 to 0.00; p=0.06). The effect on triglycerides became smaller and lost statistical significance in the sensitivity analysis excluding studies with inadequate randomization and the analyses excluding studies with high total and selective dropout rates. No other effects on other lipids were found.

Body weight

We found that acarbose had a statistically significant decreasing effect on BMI of 0.17, but the effect on the outcome "body weight" was not statistically significant (Table 4.2.2). We found no beneficial effects on body weight for acarbose compared with sulphonylurea.

Adverse events

We used the total number of patients that experienced at least one adverse event. Most studies reported that gastrointestinal events occurred most frequently. But for most reports, the definitions were insufficiently similar to be used for meta-analysis.

Compared with placebo, patients treated with acarbose had significantly more side effects (OR 3.37; RR 1.43) (Table 4.2.2). There was a dose-dependent increase in adverse events in the range 25-200 mg t.i.d. This relationship was even more clear when the subgroup of studies that applied a fixed dose (in contrast to an individually titrated dose) was analyzed (ORs of 1.95, 4.12, 6.97, and 8.31 for 50, 100, 200, and 300

Table 4.2.2. Results of overall meta-analysis for the comparison of acarbose and miglitol versus placebo and sulphonylurea

	Placebo controlled studies						Sulphonylurea controlled studies					
	Acarbose			Miglitol			Acarbose			Miglitol		
Outcome	Comp, part*	Effect Size†	95% CI	Comp, part*	Effect Size†	95% CI	Comp, part*	Effect Size†	95% CI	Comp, part*	Effect Size†	95% CI
GHb (%)	28, 2831	-0.77	-0.90, -0 64	7, 1088	-0.68	-0.93, -0.44	8, 596	0.38	-0.02, 0.77	1, 90	0 40	-0.16, 0.96
Fasting blood glucose (mmol/l)	28, 2838	-1.09	-1 36, -0 83	2, 398	-0.52	-0.88, -0.16	8, 596	0.69	0.16, 1.23	1, 90	0.27	-0.74, 1.28
1-h postload blood glucose (mmol/l)	22, 2238	-2.32	-2.73, -1.92	2, 398	-2.70	-5.54, 0.14	8, 591	-0.10	-0.43, 0 22	1, 88	-0.60	-3.43, 2.23
Fasting insulin (pmol/l)	15, 1264	-0.5	-7.9, 6.9	1, 162	-18.2	-57.0, 20.6	7, 486	-24.8	-43 3, 6 3	1, 90	-44 8	-53.7, -35.8
1-hour postload insulin (pmol/l)	13, 1050	-40.8	-60.6, -21.0	2, 398	-16 6	-39.2, 6.0	7, 483	-133.2	-184.5, -81.8	ND	ND	ND
Total cholesterol (mmol/l)	23, 2133	0.00	-0.10, 0.09	ND	ND	ND	7, 499	-0.09	-0 23, 0 05	1, 88	0 08	-0.29, 0.45
HDL cholesterol (mmol/l)	14, 924	0.00	-0.04, 0.04	ND	ND	ND	7, 485	0.02	-0 02, 0 06	1, 86	-0.01	-0.26, 0.24
LDL cholesterol (mmol/l)	4, 402	-0.08	-0.41, 0.25	ND	ND	ND	4, 312	0.10	-0.07, 0.27	ND	ND	ND
Triglycerides (mmol/l)	21, 1969	-0.09	-0.18, 0.00	ND	ND	ND	8, 591	0 01	-0.18, 0.20	1, 89	-0.04	-0.40, 0.32
Body weight (kg)	16, 1451	-0.13	-0.46, 0.20	1, 162	0.27	-0.50, 1.04	5, 397	-1.90	-4.01, 0.21	1, 90	0 46	-0.48, 1.40
BMI (kg/m^2)	14, 1430	-0.17	-0.25, -0.08	ND	ND	ND	4, 230	-0.39	-0 83, 0.05	ND	ND	ND
Occurrence of any side effect	23, 3819	3.37	2.60, 4.36	7, 1304	4 01	1.69, 9.52	7, 607	3.95	2.00, 7.80	2, 232	1.29	0.69, 2.41

Continuous data are expressed as weighted mean differences; occurrence of side effects is expressed as odds ratio Results are calculated with a random effects model.
*Number of comparisons (comp), participants (part). † A negative value indicates an advantage for acarbose or miglitol. ND, No available data

mg acarbose TID respectively). Results for miglitol were similar (OR 4.01) (Table 4.2.2).

Sensitivity analyses were performed for the comparison acarbose versus placebo only. As for the other comparisons, the number of included studies was too low. In the sensitivity analyses, we found very few statistically significant results. Studies with inadequate or unclear randomization showed, in contrast to studies with adequate randomization, a statistically significant beneficial effect on total cholesterol: –0.25 (95% CI –0.47 to –0.03) vs. 0.04 (95% CI –0.06 to 0.14). Studies with a high dropout rate showed no statistically significant effect on postload insulin levels. Non-European studies showed a more profound effect on postload glucose levels. Repeating the analyses with a fixed effects model yielded a statistically significant decrease in fasting insulin and body weight.

Discussion

In this systematic review of 41 randomized studies on the efficacy of AGIs, we have found no evidence for a beneficial effect on morbidity or mortality. In meta-analyses we found statistically significant effects on GHb and fasting blood glucose (acarbose and miglitol), postload glucose and insulin levels, and BMI (acarbose). The effect on GHb was more profound in studies with higher baseline values for GHb, and we found evidence that this effect was less in studies that lasted longer than 6 months. We found no effects on fasting insulin levels and lipids and only minor effects on body weight. There was no increase in effect on GHb for acarbose dosages higher than 50 mg t.i.d. In general, most evidence and best results were found for acarbose. Comparisons with other drugs were limited and mostly hampered by unequal comparators.

With respect to the effect on glycemic control, the results from our review are roughly in line with previous reviews. But there are significant differences and additional findings. First, we found evidence for a dose-dependent effect on fasting and postload blood glucose but not for GHb. This remarkable finding might be explained by a lower compliance of patients that received higher dosages. After all, occurrence of side effects increased with higher dosages, and the effect of a lower compliance will probably hardly affect fasting and postload blood glucose as patients will not "forget" their medication before a study visit. Secondly, we could not find an effect on plasma lipids in a meta-analysis. However, the conclusions from previous reviews were not based on a meta-analysis but on the results from single studies. Third, we could not confirm the optimistic view on side effects in the previous reviews. Although, due to differences in reporting, we were only able to perform a meta-analysis for the occurrence of "all adverse events", it was obvious from all reports that gastro-intestinal events (flatulence, diarrhoea, stomach-ache) were the

most frequent occurring. Finally, we could not affirm the optimistic view about the efficacy of AGIs compared with other agents. Only for the comparison acarbose versus sulphonylurea were sufficient data available, and these comparisons point in the direction of inferior effects on glycemic control and side effects but a clear superior effect on fasting and postload insulin levels

This systematic review included a high number of trials. Because of the strict inclusion criteria, studies were similar with respect to key items: all were randomized, included patients with type 2 diabetes, and applied AGI monotherapy. Heterogeneity by other crucial factors such as comparison drug and different dosages was addressed by using different (sub)groups for the meta-analyses. The residual heterogeneity seamed to be limited in this review, because visual inspection of the forest plots of the main outcomes showed consistent outcomes. Further sensitivity, subgroup, and meta-regression analyses for a number of possible confounders, including quality items, only yielded few significant results. AGIs given as a fixed dose and without a step-up scheme have the largest positive effect on GHb but also a worsening effect on side effects.

One of the main limitations of our study was that not all data in the original studies were available in a way appropriate for a meta-analysis. This was especially striking for one study of long duration and with a high number of participants; data from this trial could not be used because the main outcome measure was the time until patients with good control on diet alone needed additional medication (19). At least 33 studies were sponsored by a pharmaceutical company. Research funded by pharmaceutical companies is more likely to produce results favouring the tested drug, which is mostly due to publication bias or inappropriate comparators (75). The risk for publication bias is limited since we have done every possible effort to find published and unpublished studies. However, inappropriate comparators were obvious in the studies comparing acarbose with sulphonylurea.

Clinical applicability and implications for research

The place of AGIs in the treatment of patients with type 2 diabetes cannot be determined from the results of this review alone. Developers of guidelines should weigh the best available evidence, preferably from high quality systematic reviews, evaluating other drugs in the first line treatment of diabetes. The exact place for AGIs also depends on the priorities in diabetes treatment. For example: how important is a reduction of (post-load) insulin levels?

Studies with AGI monotherapy investigating surrogate endpoints such as GHb or insulin levels are redundant. Therefore, future research should aim at assessing effects on endpoints that are directly relevant to patients, such as mortality or morbidity, instead of focusing on surrogate parameters. At least, such endpoints should be included in all trials with patients with chronic diseases. Even if the study is underpowered for such an endpoint, such data might be useful for a meta-analysis.

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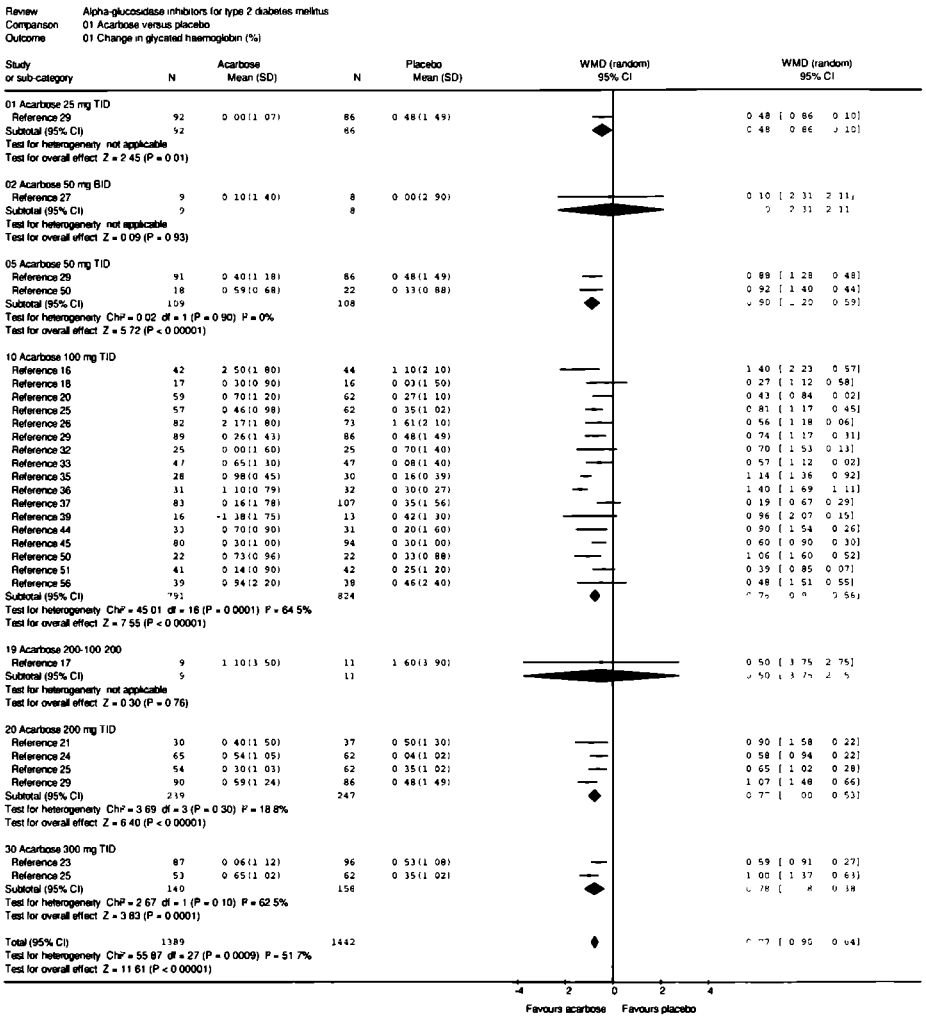
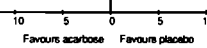
Appendix A


Review: Alpha-glucosidase inhibitors for type 2 diabetes mellitus
Comparison: 01 Acarbose versus placebo
Outcome: 01 Change in glycated haemoglobin (%)
Study or sub-category
Acarbose N Mean (SD)
Placebo N Mean (SD)
WMD (random) 95% CI
WMD (random) 95% CI
01 Acarbose 25 mg TID
Reference 29 92 0 00 (1 07) 86 0 48 (1 49) 0 48 [0 86 0 10]
Subtotal (95% CI) 92 66 0 48 [0 86 0 10]
Test for heterogeneity not applicable
Test for overall effect Z = 2 45 (P = 0 01)
02 Acarbose 50 mg BID
Reference 27 9 0 10 (1 40) 8 0 00 (2 90) 0 10 [2 31 2 11]
Subtotal (95% CI) 9 8 [2 31 2 11]
Test for heterogeneity not applicable
Test for overall effect Z = 0 09 (P = 0 93)
05 Acarbose 50 mg TID
Reference 29 91 0 40 (1 18) 86 0 48 (1 49) 0 88 [1 28 0 48]
Reference 50 18 0 59 (0 68) 22 0 33 (0 88) 0 92 [1 40 0 44]
Subtotal (95% CI) 109 108 0 90 [1 20 0 59]
Test for heterogeneity Chi² = 0 02 df = 1 (P = 0 90) I² = 0%
Test for overall effect Z = 5 72 (P < 0 00001)
10 Acarbose 100 mg TID
Reference 16 42 2 50 (1 80) 44 1 10 (2 10) 1 40 [2 23 0 57]
Reference 18 17 0 30 (0 90) 16 0 03 (1 50) 0 27 [1 12 0 58]
Reference 20 59 0 70 (1 20) 62 0 27 (1 10) 0 43 [0 84 0 02]
Reference 25 57 0 46 (0 98) 62 0 35 (1 02) 0 81 [1 17 0 45]
Reference 26 82 2 17 (1 80) 73 1 61 (2 10) 0 56 [1 18 0 06]
Reference 29 89 0 26 (1 43) 86 0 48 (1 49) 0 74 [1 17 0 31]
Reference 32 25 0 00 (1 60) 25 0 70 (1 40) 0 70 [1 53 0 13]
Reference 33 47 0 65 (1 10) 47 0 08 (1 40) 0 57 [1 12 0 02]
Reference 35 28 0 98 (0 45) 30 0 16 (0 39) 1 14 [1 36 0 92]
Reference 36 31 1 10 (0 79) 32 0 30 (0 27) 1 40 [1 69 1 11]
Reference 37 83 0 16 (1 78) 107 0 35 (1 56) 0 19 [0 67 0 29]
Reference 39 16 -1 38 (1 75) 13 0 42 (1 30) 0 96 [2 07 0 15]
Reference 44 33 0 70 (0 90) 31 0 20 (1 60) 0 90 [1 54 0 26]
Reference 45 80 0 30 (1 00) 94 0 30 (1 00) 0 60 [0 90 0 30]
Reference 50 22 0 73 (0 96) 22 0 33 (0 88) 1 06 [1 60 0 52]
Reference 51 41 0 14 (0 90) 42 0 25 (1 20) 0 39 [0 85 0 07]
Reference 56 39 0 94 (2 20) 38 0 46 (2 40) 0 48 [1 51 0 55]
Subtotal (95% CI) 791 824 0 75 [0 9 0 56]
Test for heterogeneity Chi² = 45 01 df = 16 (P = 0 0001) I² = 64 5%
Test for overall effect Z = 7 55 (P < 0 00001)
19 Acarbose 200-100 200
Reference 17 9 1 10 (3 50) 11 1 60 (3 90) 0 50 [3 75 2 75]
Subtotal (95% CI) 9 11 0 50 [3 75 2 75]
Test for heterogeneity not applicable
Test for overall effect Z = 0 30 (P = 0 76)
20 Acarbose 200 mg TID
Reference 21 30 0 40 (1 50) 37 0 50 (1 30) 0 90 [1 58 0 22]
Reference 24 65 0 54 (1 05) 62 0 04 (1 02) 0 58 [0 94 0 22]
Reference 25 54 0 30 (1 03) 62 0 35 (1 02) 0 65 [1 02 0 28]
Reference 29 90 0 59 (1 24) 86 0 48 (1 49) 1 07 [1 48 0 66]
Subtotal (95% CI) 239 247 0 77 [1 00 0 53]
Test for heterogeneity Chi² = 3 69 df = 3 (P = 0 30) I² = 18 8%
Test for overall effect Z = 6 40 (P < 0 00001)
30 Acarbose 300 mg TID
Reference 23 87 0 06 (1 12) 96 0 53 (1 08) 0 59 [0 91 0 27]
Reference 25 53 0 65 (1 02) 62 0 35 (1 02) 1 00 [1 37 0 63]
Subtotal (95% CI) 140 158 0 78 [1 8 0 38]
Test for heterogeneity Chi² = 2 67 df = 1 (P = 0 10) I² = 62 5%
Test for overall effect Z = 3 83 (P = 0 0001)
Total (95% CI) 1389 1442 0 77 [0 95 0 64]
Test for heterogeneity Chi² = 55 87 df = 27 (P = 0 0009) I² = 51 7%
Test for overall effect Z = 11 61 (P < 0 00001)
-4 -2 0 2 4
Favours acarbose
Favours placebo

Appendix B

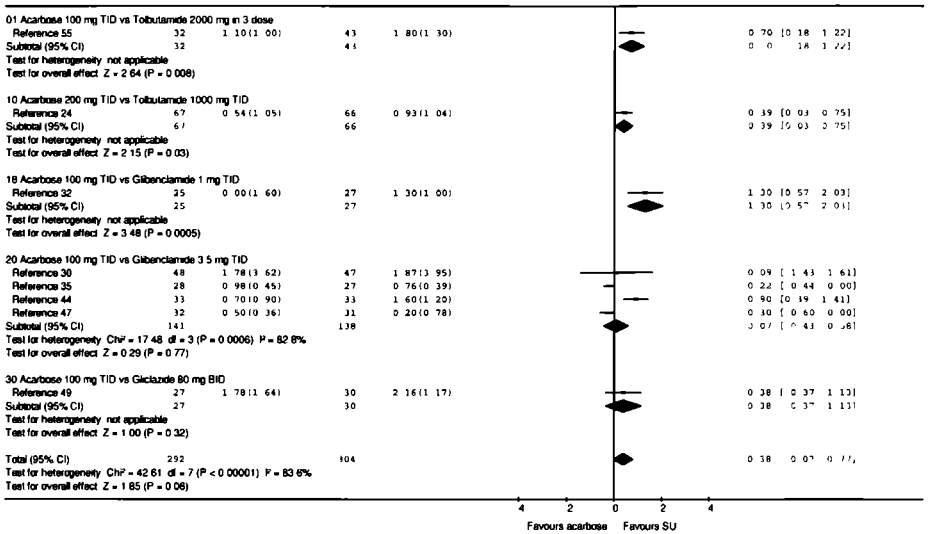
Review: Alpha-glucosidase inhibitors for type 2 diabetes mellitus
Comparison: 01 Acarbose versus placebo
Outcome: 03 Change in post load blood glucose (mmol/l)

Study or sub-category	Acarbose N	Acarbose Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (random) 95% CI	WMD (random) 95% CI
01 Acarbose 25 mg TID						
Reference 29	89	1 34 (2 55)	87	0 02 (2 74)		1 36 [2 14 0 58]
Subtotal (95% CI)	89		87			1 36 [2 14 0 58]
Test for heterogeneity not applicable						
Test for overall effect Z = 3 41 (P = 0 0007)						
02 Acarbose 50 mg BID						
Reference 27	9	1 50 (1 60)	8	0 30 (1 40)		1 80 [3 23 0 37]
Subtotal (95% CI)	9		8			1 80 [3 23 0 37]
Test for heterogeneity not applicable						
Test for overall effect Z = 2 47 (P = 0 01)						
05 Acarbose 50 mg TID						
Reference 29	92	1 71 (2 86)	87	0 02 (2 74)		1 73 [2 55 0 91]
Reference 50	18	0 80 (3 50)	22	0 20 (3 20)		1 00 [3 10 1 10]
Subtotal (95% CI)	110		109			1 43 [2 40 0 87]
Test for heterogeneity Chi² = 0 40 df = 1 (P = 0 53) I² = 0%						
Test for overall effect Z = 4 19 (P < 0 0001)						
10 Acarbose 100 mg TID						
Reference 16	42	3 20 (2 50)	44	1 40 (2 50)		1 80 [2 86 0 74]
Reference 20	59	0 77 (2 60)	62	0 65 (2 90)		1 42 [2 40 0 44]
Reference 25	51	2 31 (3 31)	56	1 36 (3 39)		3 67 [4 94 2 40]
Reference 26	82	3 20 (2 20)	73	2 50 (2 00)		0 70 [1 36 0 04]
Reference 29	87	1 48 (2 69)	87	0 02 (2 74)		1 50 [2 31 0 69]
Reference 32	25	2 40 (6 40)	25	0 10 (7 40)		2 30 [6 14 1 54]
Reference 33	47	3 70 (2 30)	47	0 80 (2 60)		2 90 [3 89 1 91]
Reference 35	28	1 80 (0 74)	30	0 03 (1 01)		1 83 [2 28 1 38]
Reference 36	31	2 36 (0 74)	32	0 01 (0 36)		2 37 [2 66 2 08]
Reference 39	16	2 69 (3 22)	15	0 21 (2 93)		2 48 [4 65 0 31]
Reference 44	33	4 70 (3 70)	31	1 70 (4 20)		3 00 [4 94 1 06]
Reference 50	22	2 00 (3 00)	22	0 20 (3 20		2 20 [4 03 0 37]
Reference 56	39	5 82 (3 60)	38	0 40 (3 50)		5 42 [7 01 3 83]
Subtotal (95% CI)	562		562			2 26 [2 79 1 73]
Test for heterogeneity Chi² = 52 37 df = 12 (P < 0 00001) I² = 77 1%						
Test for overall effect Z = 8 35 (P < 0 00001)						
20 Acarbose 200 mg TID						
Reference 24	67	2 82 (3 71)	62	0 61 (3 93)		2 21 [3 53 0 89]
Reference 25	51	2 50 (3 39)	56	1 36 (3 39)		3 86 [5 15 2 57]
Reference 29	88	2 40 (2 96)	87	0 02 (2 74)		2 42 [3 26 1 58]
Subtotal (95% CI)	206		205			2 78 [3 72 1 85]
Test for heterogeneity Chi² = 4 07 df = 2 (P = 0 13) I² = 50 9%						
Test for overall effect Z = 5 83 (P < 0 00001)						
30 Acarbose 300 mg TID						
Reference 23	90	1 70 (3 70)	95	1 07 (3 91)		2 77 [3 87 1 67]
Reference 25	50	3 17 (3 31)	56	1 36 (3 39)		4 53 [5 81 3 25]
Subtotal (95% CI)	140		151			3 62 [5 34 1 89]
Test for heterogeneity Chi² = 4 20 df = 1 (P = 0 04) I² = 76 2%						
Test for overall effect Z = 4 11 (P < 0 0001)						
Total (95% CI)	1116		1122			2 32 [2 73 1 92]
Test for heterogeneity Chi² = 80 59 df = 21 (P < 0 00001) I² = 73 9%						
Test for overall effect Z = 11 28 (P < 0 00001)						



Appendix C

Review: Alpha glucosidase inhibitors for type 2 diabetes mellitus
Comparison: 02 Acarbose versus sulphonylurea (SU)
Outcome: 01 Change in glycated haemoglobin (%)



Chapter 4.3.1

Letter to the Editor and authors' response:

No evidence for a reduction of myocardial infarctions by acarbose

Floris A. van de Laar, Peter L.B.J. Lucassen

Radboud University Nijmegen Medical Centre, Department of General Practice, Nijmegen, The Netherlands

Meta-analysis of long-term studies to assess the effect of acarbose on cardiovascular risk reduction – scientifically credible: Reply

Markolf Hanefeld

Technical University Dresden, Centre for Clinical Studies, Science and Technology Transfer, Dresden, Germany

Eur Heart J 2004;25(13):1179-1180

No evidence for a reduction of myocardial infarctions by acarbose

With great interest we read the article of Hanefeld et al., in which a meta-analysis of seven randomised controlled trials was presented. This meta-analysis compared acarbose with placebo in patients with type 2 diabetes with respect to the incidence of cardiovascular events (1). The conclusion that acarbose can prevent myocardial infarctions surprised us because, currently finishing a Cochrane systematic review on the topic (2), we found only scarce outcomes regarding diabetes-related morbidity so far. Moreover, we were very disappointed that the design and conduct of this study was not critically discussed at all, even more so because they suggest major flaws that seriously undermine the conclusions.

The criteria for the selection of these seven long-term randomised controlled trials are not clear. Studies that are included in meta-analyses should be the result of an extensive and systematic search strategy. Failing to do so could result in selection bias, affecting the outcome significantly, usually in the direction of the desired outcome (3). Also, the results from the largest included study were never published as a journal article and thus not subject to the peer-review process, and two studies were not published at all. The inclusion of unpublished studies is a virtue, but the reasons why a study has not been published should be made clear because this might reflect methodological flaws or conflicting interests.

Heterogeneity should not be investigated solely by statistical methods, but firstly with a visual inspection of the main study characteristics of each trial. In this meta-analysis clinical heterogeneity is obvious. For example, different kinds of co-interventions were used. We also have concerns about the way the main outcome data were collected and handled. The authors use the so-called safety data from the original studies, an idea that is creative in a fashion. However, safety-data were not collected following the rigorous methods as required in controlled trials.

Possible other causes for a reduction of myocardial infarctions should be investigated carefully. First, it should be made clear which study contributes most to the results. This might lead to possible other factors related to study design that also might explain the results. Secondly, special attention should be paid to the possible contribution in each study of additional medication and lifestyle factors. And thirdly, the data should be analysed accounting for the intervention that was actually received. Since the authors used data from the safety group, an unknown number of patients did not actually use acarbose. Usually, dropouts receive some other form of anti-diabetic treatment and thus it cannot be excluded that the measured effect on cardiovascular events is merely the result of anti-diabetic treatment in general, rather than the effect of acarbose. Finally, we wonder if the outcome 'any cardiovascular event' would still be significant if myocardial infarctions were excluded. If so, the conclusion that acarbose has shown preventive effects on 'any cardiovascular event' is not logical.

In summary, this meta-analysis is subject to publication bias, heterogeneity, detection bias and confounding factors. The conclusion that there is evidence for a reduction of myocardial infarctions by acarbose is not justified.

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Meta-analysis of long-term studies to assess the effect of acarbose on cardiovascular risk reduction – scientifically credible: Reply

The authors criticised our meta-analysis of seven long-term studies to assess the effect of acarbose on cardiovascular risk reduction. Two different approaches are generally accepted as standard procedures for meta-analyses (1). These are systematic literature reviews or meta-analyses of all randomised controlled trials. Our meta-analysis is based on the latter approach. As clearly stated in our article, data from all randomised, double-blind, placebo-controlled clinical trials with a minimum treatment duration of 52 weeks were included. The source was the Bayer Acarbose clinical database. As a consequence, publication and selection bias (regarded as substantial risks in the situation of systematic literature review) (2) can be excluded.

Whilst it is true that two studies included in the analyses were not formally published and therefore not subject to peer review, both studies were part of the New Drug Application for acarbose. Although we highly respect the quality and rigour of the science journal peer review procedure, we doubt that the drug approval process is any less strict (3). The study by Bachmann et al., has in the meanwhile recently been published.

We agree with Dr. van de Laar et al., that heterogeneity should not be investigated by statistical testing alone. We consider only heterogeneity in the treatment effect to be problematic for statistical analysis (in accordance with CPMP). Some deviations concerning other characteristics could be seen as an advantage for increasing its generalisation and external validity (2, 4). This said, co-intervention was balanced between acarbose and placebo because of the randomisation. It should be mentioned that in addition to formal statistical testing, graphical and descriptive methods were also employed to confirm homogeneity of treatment effect.

The use of individual patient data has the advantage of enabling a common outcome variable to be defined across studies (4). Therefore it seems straightforward to use safety data to define an outcome based on cardiovascular events. Indeed, we are surprised to note the concerns of Dr. van de Laar et al., regarding the safety data collection procedure. As a matter of fact, in clinical trials performed according to Good Clinical Practice the occurrence of adverse events is monitored carefully and recorded in detail during the trial.

We would like to point out that in the Cox Proportional Hazards model, patients contribute only for the time that they are observed under treatment and only to the corresponding treatment group. Moreover, not only the actual number of events under treatment and placebo contribute to the analysis, but also the event free times in both groups.

Finally, the 'any cardiovascular event' outcome is indeed still significant, even after exclusion of myocardial infarction from the cardiovascular events (HR=0.69, 95% CI: 0.50-0.95).

In summary, our meta-analysis was conducted based on scientifically sound and credible principles. Thus the data published in the European Heart Journal suggest that acarbose, in addition to its effect on glycemic control, could have a beneficial effect on cardiovascular complications in patients with established type 2 diabetes. These results are in line with the beneficial effect of acarbose on cardiovascular events, as found in the STOP-NIDDM trial (5).

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Chapter 4.3.2

Letter to the Editor and authors' response:

Alpha-Glucosidase Inhibitors for Patients With Type 2 Diabetes: Response to Van de Laar et al.

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Alpha-glucosidase Inhibitors for Patients With Type 2 Diabetes: Response to Hanefeld et al.

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Diabetes Care 2005;28(7):1840-1841

Alpha-Glucosidase Inhibitors for Patients With Type 2 Diabetes: Response to Van de Laar et al.

The authors of the Cochrane systematic review carefully analyzed all available studies that fulfilled the criteria of randomized clinical trials of at least 12 weeks' duration (1). With the exception of one study (2), all registered mortality and morbidity as secondary objectives. Glycemic control was the primary objective in 40 of 41 of these trials. Thus, the major legitimate conclusion of this careful analysis was that "AGIs [Alpha-glucosidase inhibitors] have clear beneficial effects on glycemic control" mainly through their dose-dependent effect on postprandial hyperglycemia.

However, the authors also state as one of their main conclusions that they "found no evidence for an effect on mortality or morbidity." Although this statement may be mathematically correct, it is misleading as it purports to be based on a solid analysis of the data from the 41 studies. This is not the case in their meta-analysis. Most of the selected trials had a treatment period of ≤24 weeks; many were of 3-month duration only and were therefore not designed and powered to investigate hard clinical end points such as morbidity or mortality. This is well reflected by the fact that, as reported by the authors, information on morbidity or mortality could only be retrieved in 3 of the 41 trials. While one study showed a significant treatment effect regarding cardiovascular events, the others presented only general statements without providing any detail. It is well known that sample sizes of individual clinical trials are often too small to detect clinically important effects reliably and that this is one of the reasons why meta-analysis is employed (3, 4). However, hard end points such as cardiovascular mortality are going to be very rare in short-term duration studies unless compensated for by a huge population sample. Therefore, including short-term duration studies in their meta-analysis dilutes the cases of cardiovascular mortality. That biases the interpretation of the data analyzed.

The MERIA (MEta-analysis of Risk Improvement under Acarbose) analysis of seven placebo-controlled, long-term, randomized studies examining the effect of acarbose on cardiovascular-related mortality and morbidity showed a reduction of cardiovascular events in patients with type 2 diabetes (5). This analysis is based on all available acarbose studies with a minimum treatment duration of 52 weeks from a database including individual patient data. Because of this, publication and selection bias were already ruled out, as discussed in the response (6) to the criticism raised by van de Laar and Lucassen. Unfortunately, the same criticism voiced previously is repeated in their meta-analysis without taking the detailed response into consideration. In summary, the MERIA analysis showed a beneficial effect on cardiovascular complications in patients with established type 2 diabetes, a finding which is in accordance with the results from the STOP-NIDDM trial in subjects with impaired glucose tolerance (7).

We fully agree with the authors' statement that prospective trials with the primary objective of investigating cardiovascular events and mortality are required to confirm

the beneficial effect of acarbose on cardiovascular events in these high-risk populations. However, the combined data from the STOP-NIDDM trial and the MERIA meta-analysis are highly suggestive of the preventive effects of acarbose on cardiovascular complications in subjects with glucose intolerance.

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Alpha-glucosidase Inhibitors for Patients With Type 2 Diabetes: Response to Hanefeld et al.

Hanefeld et al. (1) assert that the conclusion ("no evidence for an effect on mortality or morbidity") from our systematic review on the effects of alpha-glucosidase inhibitors (AGIs) for patients with type 2 diabetes was biased. Furthermore, they claim to have found evidence for such an effect based on their own meta-analysis. We disagree with both statements.

First, we would like to underline that the solid basis of our results is a systematic review and that meta-analyses were only applied when this was methodologically sound. The extensive search for all possible trials investigating AGI monotherapy yielded only one study with prospectively collected data on morbidity or mortality (2), so a meta-analysis could not be done with these end points; therefore, we concluded that no evidence for an effect on mortality and morbidity could be found (which is essentially different from "evidence for no effect"). In the above-mentioned study, it was reported that for the entire treatment group (AGIs given both as monotherapy and as additional therapy), no effects of acarbose on cardiovascular end points were found.

This makes it quite remarkable that this particular study (2) was not included in the MERIA (MEta-analysis of Risk Improvement under Acarbose) study (3). Hanefeld et al. assert that this meta-analysis shows a beneficial effect of acarbose on the occurrence of myocardial infarctions. If it had been included in the MERIA study, it would have been the study with the second longest duration, it would have nearby doubled the number of patients, and it would have been the only study with a sound method of collecting end points. This points to the fact that the sole use of a manufacturer's database is not a reliable method for the selection of studies for a meta-analysis and that an extensive systematic review is necessary to reduce the risk of selection bias.

Other differences between the conclusions of MERIA and our Cochrane review can be explained by differences in inclusion and methodological robustness. Three of the seven studies in MERIA were also included in our Cochrane review, but no reliable data on cardiovascular outcomes could be obtained. The four other publications were excluded from our review, mainly because no data on AGI monotherapy were available or accessible. Moreover, it should be noted that there was no quality assessment of the studies included in MERIA. Other serious concerns about the MERIA study were expressed in our previous letter and remain largely unresolved (4).

In conclusion, there is currently no evidence for an effect on cardiovascular morbidity and mortality of monotherapy with AGIs in patients with type 2 diabetes. In the near future, indirect evidence may be derived from another Cochrane review on the effects of AGIs for patients with glucose intolerance (5). We are pleased that the authors of the main studies in this field already have assured their cooperation.

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Chapter 5

Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose

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Extended data are available from the published version of this chapter

Cochrane Database Syst Rev 2006;(4):CD005061

Abstract

Background. Alpha-glucosidase inhibitors (AGIs) reduce blood glucose levels and may thus prevent type 2 diabetes and cardiovascular disease in patients with impaired glucose tolerance. These possible effects, and the effects on quality of life, plasma lipids and body weight, have never been investigated in a systematic literature review and meta-analysis.

Objectives. To assess the effects of alpha-glucosidase inhibitors in patients with impaired glucose tolerance (IGT) or impaired fasting blood glucose (IFBG), or both.

Search strategy. We searched The Cochrane Library (Clinical Trials database, formerly known as CENTRAL), PUBMED, EMBASE, Web of Science, LILACS, databases of ongoing trials, reference lists of relevant reviews, and we contacted experts and manufacturers. Date of last search was February 2006.

Selection criteria. Randomised controlled trials of at least one-year duration in patients with IGT or IFBG, or both, comparing AGI monotherapy with any other intervention.

Data collection and analysis. Two reviewers read all abstracts, assessed quality and extracted data independently. Discrepancies were resolved by consensus or by the judgement of a third reviewer.

Main results. We included five trials (2360 participants), all investigating acarbose, that included patients with IGT or patients 'at increased risk for diabetes' (n=1). Study duration was one, three (n=2), five and six years. One study was at low risk of bias and four studies at high risk of bias. Except for the outcome incidence of type 2 diabetes in acarbose versus no treatment (two studies), meta-analyses were not possible. Data from the study at low risk of bias suggests that acarbose decreases the occurrence of type 2 diabetes (NNT=10), cardiovascular events (NNT=50, based on 47 events, study not initially powered for this outcome), post-load blood glucose (–0.6 mmol/l, 95% CI –1.0 to –0.3) and body mass index (–0.3 kg/m^2, 95% CI –0.5 to –0.1). No statistically significant effects were observed on mortality, other morbidity, glycated haemoglobin, fasting blood glucose, lipids and blood pressure. The effects on the incidence of type 2 diabetes were confirmed in two studies at high risk of bias (OR 0.2, 95% CI 0.1 to 0.6). Adverse effects were mostly of gastro-intestinal origin (OR 3.5, 95% CI 2.7 to 4.4).

Conclusions. There is evidence that acarbose reduces the incidence of type 2 diabetes in patients with IGT. However, it is unclear whether this should be seen as prevention, delay or masking of diabetes. Acarbose may prevent the occurrence of cardiovascular events, but this finding needs to be confirmed in more studies.

Introduction

Impaired glucose tolerance (IGT) and impaired fasting blood glucose (IFBG) are generally recognised as an expression of abnormal glucose homeostasis that is not severe enough to meet the criteria for type 2 diabetes mellitus (DM2). The term IGT was introduced in 1979. In the past IGT has been called a 'pre-state' of diabetes or 'prediabetes'. The term IFBG (sometimes referred to as impaired fasting glycaemia) has been introduced much later (2). IGT and IFBG represent different pathophysiological mechanisms: IGT is seen as a characteristic of peripheral insulin resistance and IFBG is seen as an expression of raised hepatic glucose output and a defect in early insulin secretion. On the other hand, there are many similarities, as both IGT and IFBG are associated with an increased risk of diabetes and the development of (diabetes related) complications such as cardiovascular disease (3). Currently, the criteria for IGT and IFBG are as follows (plasma venous glucose concentrations). IGT: fasting blood glucose <7.0 mmol/l and 2-hours post-load blood glucose 7.8-11.0 mmol/l; IFBG: fasting blood glucose 6.1-6.9 mmol/l (2-hours post-load blood glucose <7.8 mmol/l, if measured) (4, 5). In 2003, the ADA recommended to change these criteria to 5.6-6.9 mmol/l (6).

IGT and IFBG cause no symptoms and the condition should be seen as a risk factor more than a disease itself. It is closely related to other risk factors of type 2 diabetes such as obesity and overweight, unfavourable dietary habits and a shortage of exercise. People with IGT or IFBG are at increased risk of developing DM2 and cardiovascular disease (even before the onset of diabetes). Thus, the question arises whether an intervention in patients with IGT or IFBG could prevent the development of DM2 and cardiovascular complications. Lifestyle interventions consisting of exercise or diet, or both, showed that the incidence of diabetes might be reduced (relative risk reduction) in up to 58% of cases (7-9). In addition, pharmacological interventions have been investigated in patients with IGT. Especially drugs that claim to intervene with insulin resistance seem appropriate: biguanides (metformin: decreases hepatic glucose output and increases insulin action) (7), thiazolidinediones (rosiglitazone, pioglitazone: increase insulin sensitivity by increasing glucose utilization in muscle and liver) (10) and alpha-glucosidase inhibitors (see further).

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs) are reversible inhibitors of alpha-glucosidase, an enzyme present in the brush border of the small intestine. Currently, three AGIs exist: acarbose, miglitol and voglibose. Emiglitate, a fourth AGI, is currently not available on the market. AGIs delay absorption of complex carbohydrates and thus inhibit postprandial glucose peaks and consequently lower postprandial insulin levels. In the treatment of DM2, AGIs have been proven to have beneficial effects on glycaemic control and post-load insulin levels but there is no evidence for a reduction of mortality or morbidity (11).

Potential side-effects are of special importance in the use of medication in persons with IGT or IFBG for two reasons. First, IGT and IFBG are asymptomatic, so people will, in contrast to potential side-effects, not notice any direct benefits from the medication. Second, because of the chronic and long-lasting character of IGT and IFBG, medication will have to be used for a long period of time. Therefore, long-term safety is very important. AGIs cause unfavourable dose-dependent side-effects, mostly flatulence and other gastro-intestinal side-effects, when compared to placebo or sulphonylurea. But there is no evidence for long-term detrimental effects of AGIs (11).

Existing evidence

More recently, AGIs have been put into a new light as a result of a study on the efficacy of acarbose in patients with IGT (12, 13). This study showed that acarbose could prevent or delay the development of IGT into DM2. Moreover, it showed a reduced risk of cardiovascular disease and hypertension in the acarbose treated group. However, the conclusions of this study are heavily debated (14-16). We have found no systematic review that focuses exclusively on the efficacy of AGIs for patients with IGT or IFBG.

Objectives

To assess the effects of alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials with a minimum duration of one year. Because the common adverse effects of AGIs make true blinding difficult, both blinded and non-blinded studies were included. Studies published in any language and all identified trials, published or unpublished, were investigated.

Types of participants

Patients referred to as having a prediabetic state, i.e. IGT or IFBG, or both, existing or newly diagnosed. Changes in diagnostic criteria, both for IGT or IFBG, or both, or diabetes mellitus type 2 (1-5, 17, 18) may have produced variability in the clinical characteristics of the patients included as well as in the results obtained. We planned to explore these differences in a sensitivity analysis.

Types of interventions

Monotherapy with AGIs (acarbose, miglitol or voglibose) compared with:

1. Placebo;
2. A non-pharmacological intervention (for example: diet therapy, exercise);
3. Biguanides (for example, metformin);
4. Thiazolidinediones (for example, pioglitazone);
5. Sulphonylurea (for example, glibenclamide);
6. Meglitinide (for example, nateglinide);
7. Any other pharmacological intervention.

Types of outcome measures

Primary outcomes

1. Incidence of DM2: diagnosed with criteria prevailing at the time of the diagnosis (1, 2, 4, 5, 17, 18);
2. Morbidity related to impaired glucose metabolism, the metabolic syndrome or DM2: vascular complications (angina pectoris, myocardial infarction, stroke, peripheral vascular disease, amputation), neuropathy, retinopathy, nephropathy, erectile dysfunction, and hyperosmolar nonketotic dysregulation;
3. Mortality: Total mortality, mortality related to impaired glucose metabolism, the metabolic syndrome or DM2 (death from myocardial infarction, stroke, renal disease, or sudden death, death from hyperosmolar nonketotic coma);

Secondary outcomes

4. Glycaemic control: glycated haemoglobin levels, fasting and post-load blood glucose levels;
5. Plasma lipids (triglycerides, total-, high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol);
6. Blood pressure: diastolic and systolic blood pressure;
7. Fasting and post-load insulin and C-peptide levels;
8. Body weight (or body mass index);
9. Adverse effects (e.g. diarrhoea, stomachache, flatulence);
10. Quality of life, assessed with a validated instrument;
11. Costs;

Specific patient covariates, effect modifiers, confounders

12. Compliance.

Timing of outcome assessment (length of intervention)

We assessed a possible influence of treatment duration in a sensitivity analysis.

Search strategy for identification of studies

Electronic searches

We used the following sources for the identification of trials:

- The Cochrane Library (2006, issue 1);
- PUBMED (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) (contains MEDLINE and a number of additional life science journals, 1966 - February 2006);
- EMBASE (1974 - October 2005);
- LILACS (www.bireme.br/bvs/I/ibd.htm) from 1986 to March 2006;
- Web of Science (contains: Science Citation Index Expanded 1945 - February 2006; Social Sciences Citation Index 1956 - February 2006; Arts and Humanities Citation Index 1975 - February 2006).

Databases of ongoing trials (latest access March 2006):

- Current Controlled Trials (http://www.controlled-trials.com - with links to other databases of ongoing trials);
- UK National Research Register (http://www.update-software.com/National/nrr-frame.html);
- USA - CenterWatch Clinical Trials Listing Service (http://www.CenterWatch.com/);
- USA - National Institutes of Health (http://clinicalstudies.info.nih.gov/);
- Dutch Trial Register (Nederlands Trial Register) (http://www.trialregister.nl/).

The described search strategy (see below) was used for PUBMED. For use with EMBASE and Web of Science the strategy was slightly adapted because these databases have different interfaces. The necessary changes in the search string were done in such a way that the search became more sensitive (i.e. yields a higher number of 'hits'). In The Cochrane Library, LILACS and the databases of ongoing trials we searched with the various text words for the AGIs and their brand names.

Search strategy

We combined three different search strategies (see: Appendix A):

1. for alpha-glucosidase inhibitors we used a strategy used for a recent systematic review on AGIs (11);
2. for controlled trials we used a sensitive validated search strategy (19);
3. for IGT and IFBG we developed a search strategy combining keywords (MeSH headings) and text words. We extensively tested it by running the search and subsequently investigated whether known key-studies were not included, we then adjusted the model until we didn't find any relevant study that was not found by the search string.

Handsearching

We searched reference lists of relevant trials and AGI reviews and selected possible references that were already in our own files.

Other search strategies

Authors of relevant identified studies and other experts were contacted by mail in order to obtain additional references, unpublished trials, and ongoing trials or to obtain missing data not reported in the original trials. Similarly, manufacturers and patent holders (Bayer AG, Sanofi-Synthelabo, Pfizer, Takeda) were contacted in order to retrieve information on AGIs trials, published and unpublished.

Methods reviewing process

Selection of studies

Two reviewers (FVDL and PL) independently checked the titles, abstract sections and keywords of every record retrieved. Full articles were retrieved for further assessment when the information given suggested that the study: (1) included patients with IGT or IFBG; (2) compared AGIs with placebo or any other control; (3) assessed one or more relevant predefined clinical outcomes; (4) used random allocation to the comparison groups. In case of any doubt regarding these criteria from the information given by the title and abstract, the full article was retrieved for clarification. Interrater agreement for study selection was assessed using the kappa statistic (20). A third party (EVDL) resolved differences in opinions between the two reviewers. If resolving disagreement was not possible, the article was added to those 'awaiting assessment' and the authors were contacted for clarification. If no clarification was provided, we planned to consult the review group editorial base.

Quality assessment of trials

The two reviewers (FVDL and PL) assessed each trial independently. Possible disagreement was resolved with consensus, or with consultation of a third reviewer (EVDL) in case of disagreement. We assessed the following quality items:

Minimisation of selection bias

- Randomisation procedure: the randomisation procedure was scored 'adequate' if the resulting sequences were unpredictable (e.g. computer generated schemes, tables of random numbers, coin tossing);
- Allocation concealment: allocation concealment was scored 'adequate' if participating patients and investigators could not foresee the assignment (e.g. by central randomisation remote from trial site, sequentially numbered and sealed radio-opaque envelopes).

Minimisation of performance bias

- Method of blinding: blinding was scored 'adequate' if the two (or more) drugs / pills were similar in size, colour and shape or when a double-dummy method was applied. Because of the sometimes-obvious adverse effects of AGIs, true blinding is difficult. For trials that reported blinding of patients for medications, we also investigate whether blinding was checked (for example by asking patient and investigator afterwards about the medication they suspected to have been supplied with).

Minimisation of attrition bias

- Handling of drop-outs: handling of drop-outs was considered 'adequate' when studies reported a complete description of all patients failing to participate until the end of the trial and if the data were analysed on intention-to-treat (ITT) basis, that means with all randomised patients included;
- Quantity of dropouts: overall dropout rate less than 15% was considered 'adequate';
- Selective dropout: a difference in dropout rates between the main treatment groups less than 10% was considered 'adequate'.

Minimisation of detection bias

- Method of blinding outcome-assessment: outcome assessment was considered 'adequate' if the outcome assessors were completely blind for the intervention. This item was considered less relevant for studies with laboratory data or death as main outcomes;
- Method of blinding of analysis: this was considered 'adequate' if the outcome assessors (investigators, statisticians) were completely blind for the intervention up to the point that all analyses were completed. Blinding of analyses is to date not a common practice in the conduct of randomised trials. Therefore we only planned to explore possible influences of blinded analyses in a sensitivity analysis and we did not plan to use this item for the overall quality assessment.

Following these criteria, studies were broadly subdivided into the following three categories using an adapted version of the Cochrane Handbook criteria:

A. All quality criteria met (1. adequate randomisation and allocation concealment, 2. adequate blinding, 3. adequate ITT analysis or both drop-out rate less than 15% or selective drop-out less than 10%, or both 4. adequate blinding outcome-assessment): low risk of bias.
B. One or more quality criteria only partially met (1. inadequate randomisation or inadequate allocation concealment, 2. mentioning of blinding but exact method unclear, 3. inadequate/unclear ITT analysis but drop-out less than

15% or selective drop-out less than 10%, 4. mention of blinding outcome-assessment but exact method unclear): moderate risk of bias.

C. One or more quality criteria not met (1. inadequate randomisation and allocation concealment, 2. inadequate or no blinding, 3. inadequate ITT and drop-out rate equal to or greater than 15% and selective drop-out equal to or greater than 10%, 4. inadequate blinding outcome-assessment): high risk of bias.

We explored the influence of individual quality criteria in a sensitivity analysis (see under 'sensitivity analyses'). The two reviewers discussed all quality items. In cases of disagreement, a third reviewer was planned to be consulted (EVDL).

Data extraction and management

Two reviewers extracted data on intervention and outcomes independently, using a pre-tested data extraction form that was adapted from a standard form provided by the review group. The data extraction form included the following items:
General information: author, type of publication (including the existence of duplicate or multiple publications), year of publication, language, country where the study was conducted, setting (general practice, hospital or outpatient / rural, city, developed / developing world / single or multi-centre), the stated aim of the study published, sponsor(s), ethics approval;
Study characteristics: parallel or cross-over, type of control groups (placebo, other medication etc.), existence of run-in or wash-out period, or both, description of possible carry-over effect (for cross-over studies), method, type and quality of randomisation, method and quality of allocation concealment, method and quality of blinding, information about handling of drop-outs, withdrawals and losses to follow-up, numbers of and reasons for drop-out, method and quality of blinding of outcome assessment (if applicable), method and quality of blinding of analyses, existence of possible sub-groups, method of assessment of compliance;
Participants: description of diagnostic criteria for IGT or IFBG, or both, and diabetes mellitus type 2, inclusion and exclusion criteria;
Interventions: specification of possible lifestyle co-intervention, the nature, dose and regimen of AGI(s) and control interventions, duration of intervention and follow-up;
Baseline characteristics and measurements: numbers of patients, sex, age, ethnicity, socio-economic status and duration of diabetes, other risk factors for DM2 or macrovascular disease (familiar disposition, history of gestational diabetes, exercise, smoking) existence of significant differences at baseline, baseline glycated haemoglobin, fasting and post-load blood glucose, plasma lipids (triglycerides, total-, HDL- and LDL-cholesterol), height, weight and body mass index (BMI), fasting and post-load insulin and C-peptide (standard deviations if applicable), specifications (including reference ranges) of all laboratory measurements, type of post-load test, time between fasting and post-load measurements, centralisation of laboratory

measurements, assessment of health-status, definitions of health outcomes (e.g. myocardial infarction, heart failure, renal failure);
Outcomes: total and disease specific deaths and morbidity, quality of life (including method of assessment), mean changes (standard deviation, SD) of the following values: glycated haemoglobin, fasting and post-load blood glucose, lipids, fasting and post-load insulin / C-peptide, body weight, BMI, occurrence of adverse events (total and gastro-intestinal), compliance, costs.
Differences in data extraction were resolved by consensus, referring back to the original article. If necessary, information was sought from the authors of the original studies. If necessary, we also planned to extract data from graphical figures: two reviewers (FVDL and PL) would calculate the data independently and if both outcomes were not similar, a third reviewer (EVDL) would recalculate the data. A statistician checked all extracted data for errors, after transfer to the database.

Data analysis

The table of comparisons was divided in all possible comparisons first (e.g. acarbose versus placebo), then sub-divided into all possible outcomes (e.g. death, glycated haemoglobin, adverse events) and finally, within the outcome sub-groups were made for the different dosages. Outcomes were calculated per sub-group and for all sub-groups together.

Dichotomous data were expressed as relative risks (RR). We calculated the risk difference (RD) and we converted the RD into the number needed to treat (NNT) or the number needed to harm (NNH) taking into account the time of follow-up.

Continuous data were expressed as weighted mean differences (WMD) and an overall WMD was calculated. We used the differences from baseline to endpoint as the actual measure of effect of all continuous variables. The standard deviations of these differences are essential for the data to be included in the meta-analysis. If the standard deviation (SD) of the difference were not reported, we first asked the authors to provide these data. If the SDs were not provided we estimated the SD of the difference with the following formula:

$$SD_{paireddifference} = \sqrt{[(SD_1)^2 + (SD_2)^2 - 2 \times r \times SD_1 \times SD_2]}$$

$SD_{paireddifference}$=standard deviation of the difference (pre- / post-treatment) SD_1=Standard deviation of the pre-treatment value, SD_2=Standard deviation of the post-treatment value, r=correlation coefficient. We used a conservative correlation coefficient of 0.4.

Overall results were calculated based on the random effects model. Heterogeneity was statistically tested by using the Z score and the Chi^2 statistic with significance set at

P<0.10. Quantification of the effect of heterogeneity was assessed by means of I^2, ranging from 0-100% including its 95% confidence interval (21). I^2 demonstrates the percentage of total variation across studies due to heterogeneity and was used to judge the consistency of evidence. Possible sources of heterogeneity were (planned to be) assessed by subgroup, sensitivity and meta-regression analyses as described below.

The analyses were done with Review Manager (RevMan 4.2).

Subgroup analyses

We planned to investigate main outcome measures by subgroup analyses in order to explore differences in effect as follows:

1. Glycated haemoglobin level at baseline (subdivided into groups, based on data);
2. Age (subdivided into groups, based on data);
3. Gender (subdivided into groups, based on data);
4. Body mass index (BMI) (subdivided into groups, based on data);
5. Different kinds of lifestyle co-interventions used (i.e. dietary advice, exercise, help with smoking cessation, combined interventions);
6. Duration of intervention (subdivided into groups, based on data);
7. Use of an individually titrated versus fixed dose of AGI;
8. Use of a step-up dose versus administering the full dose immediately.

Sensitivity analyses

We planned to perform sensitivity analyses for a number of factors by comparing the results of the meta-analysis for studies with and without certain characteristics. Data from a minimum of five studies had to be available for both groups to be considered.

The following factors were planned to be investigated:

1. Comparing published and unpublished studies;
2. Comparing studies with and without (or with unknown) quality characteristics: adequate randomisation, adequate allocation concealment, adequate method of blinding, adequate ITT analyses, adequate blinding of outcome-assessment (if applicable), adequate method of blinding of analyses. Further, comparing studies with an overall drop-out rate of more than or equal to 15% and less than 15%, differences in drop-out rates less than 10% and more than or equal to 10% between the main treatment groups. In addition, the overall score for quality based on the Cochrane criteria was used (studies with score A and B compared to studies with C);
3. Repeating the analyses excluding trials using the following filters: diagnostic criteria (patients with IGT / IFBG / both), language of publication, source of funding (industry versus other or no sponsoring) or country;

4. Repeating the analyses using different measures of effect size (relative risk, risk difference) and different statistical models (fixed and random effects models);
5. Repeating the analyses excluding large studies or studies with a long duration (based on data) to establish how much they dominate the results;
6. Repeating the analyses excluding studies in which other risk factors for the development of DM2 or macrovascular disease were not equally distributed between treatment groups.

Meta-regression analyses

We planned to use meta-regression analyses (in SAS proc MIXED, version 8.0) to explore the influence of characteristics of study population and study design on the outcomes. We planned to examine all dependent variables for which sufficient studies are available; the minimal number of studies would need to be 10 to gain sufficient power. The independent variables were similar to the pre-defined sub-groups. The weight of each trial would be equal to the inverse sum of the within trial variance and the residual between trial variance, in order to perform a random effects analysis.

Assessment of small study bias

Small study bias was planned to be tested by using the funnel plot or other corrective analytical methods depending on the number of clinical trials included in the systematic review (22-24).

Results

Description of studies

Trials identified (see Figure 5.1)

PUBMED: 224 records were retrieved and assessed on basis of title or abstract, or both (until March 22nd 2006), 13 records were initially included for further reading and 12 were included in the final review.

EMBASE: 551 records were retrieved and assessed on basis of title or abstract, or both (until October 21st 2005), 20 records were initially included for further reading and 19 were included in the final review.

Cochrane Library: 432 records were retrieved and assessed on basis of title or abstract, or both (issue 1 2006), 10 records were initially included for further reading. All of those records remained included in the final review.

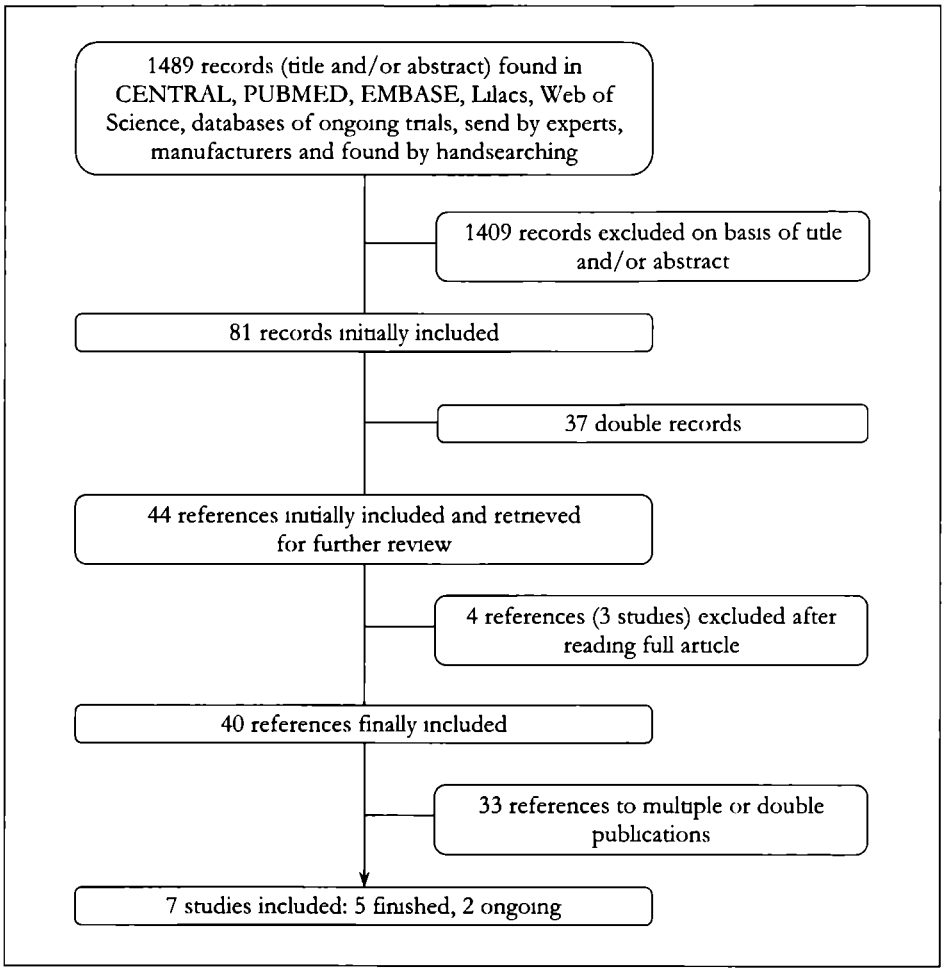

Figure 5.1. Study flow diagram

Web of Science: 117 records were retrieved and assessed on basis of title or abstract, or both (until February 7th 2006); eight records were initially included for further reading. All of those records remained included in the final review.
LILACS: 95 records were retrieved and assessed on basis of title or abstract, or both (until February 7th 2006). None of these references were initially included.

Experts: We obtained two references by corresponding with experts or authors. One of those references referred to a study that was included in the final review (25).

Manufacturers: Bayer is the developer of acarbose and miglitol and Takeda the developer of voglibose. Sanofi-Synthelabo is patent holder of miglitol. Bayer send us four references, four were initially included and three were finally included in the review. Takeda and Sanofi did not reply to our letters.

Handsearching (checking references of existing reviews, browsing on the Internet, posters on congress etc.): Twenty-one references found by handsearching seemed possibly interesting based on title or abstract, or both. Nineteen references were finally included.

Databases for ongoing trials: we retrieved 43 records, four of which were initially included (last search March 22nd 2006). Thus far, we did not receive any (un)published data that gave cause to exclude those studies for the review. Two of those studies were finished by the time of retrieval (26, 27) and two other studies were started in 2005 and will be completed in 2009 (28) and 2013 (29) (Table 5.1).

Interrater agreement

Interrater kappa for agreement on inclusion, calculated on basis of the first 1210 titles or abstracts, or both, read by the two reviewers (FVDL and PL) was 0.77 (95% confidence interval 0.65 to 0.90). All differences in opinion were resolved by consensus.

Missing data

We contacted all authors for data clarification and missing data. This was successful for one study (12). The corresponding author of the DAISI study (27) sent us the full statistical report with the restriction that we were not allowed to use the data before their manuscript was accepted for publication. The authors of the EDIT (26) study promised us to sent more details once their manuscript was in the galley-proof stage. For the other two studies the authors did not reply to our letters and mails (30, 31).

Table 5.1. Characteristics of ongoing studies

Study	Trial name or title	Participants	Interventions	Outcomes	Date
ABC-Study (28)	Alpha-Glucosidase-Inhibitor Blocks Cardiac Events in Patients With Myocardial Infarction and IGT (ABC Study)	Patients with IGT and old myocardial infarction.	Acarbose versus standard diet and exercise treatment	Primary outcomes: 1 cardiovascular mortality; 2 hospitalisation due to cardiovascular events; Secondary outcomes: 1 all cause mortality, 2 hospitalisation due to coronary artery disease; 3 progression of IGT to diabetes, 4 development or deterioration of either hypertension or hyperlipidaemia, 5 deterioration of renal function, 6 hospitalisation due to cerebrovascular disease; 7 hospitalisation due to heart failure	April 2005, last follow-up April 2009
Tamita (29)	Acarbose and Secondary Prevention After Coronary Stenting	Patients with abnormal glucose tolerance and coronary artery disease	Acarbose versus standard lifestyle modification	Primary outcome cardiovascular event free survival time. Secondary outcomes: 1 conversion of abnormal glucose tolerance to type 2 diabetes, 2 all cause of death, 3 occurrence of every cardiovascular event, 4 occurrence of in-stent restenosis, 5 regression of intimal plus medial complex of the carotid artery; 6 change in fasting, 2-hour blood glucose and insulin level; 7 change in homeostasis model assessment of insulin resistance; 8 change in HbA1c; 9 change in lipid profile	May 2005; last follow-up April 2013

Excluded studies

Three studies were initially included but excluded after reading the full article. Two studies turned out to be not randomised (32, 33) and one study included patients with DM2 (34).

Included studies

Five studies with 2360 participants, described in 36 articles, abstracts or web sites were finally included in the review. Data and information from the STOP-NIDDM study was obtained from 26 references (12, 13, 16, 35-57), for the DAISI study from two references (27, 58), for the EDIT study from eight references (25, 26, 59-64), and for the studies from Fang et al. (30) and Wang et al. (31) one reference was available. Details are given in the Table 5.2.

Publication type

Three studies were (predominantly) published as journal articles (12, 30, 31). For the STOP-NIDDM study (12) we also considered correspondence and debate articles as a result of the main publications. The other two studies were published on a web site or as abstracts, or both (26, 27).

Participants

Three studies included patients with IGT according to the WHO criteria of 1985 (27, 30, 31). One study included participants with IGT according to the WHO criteria of 1999 in addition to a fasting BG $\geq$5.6 and <7.8 mmol/l (12) and one study included participants at increased risk for DM2' with a fasting BG 5.5-7.7 mmol/l (26). In the STOP-NIDDM study (12) patients were (mainly) recruited through screening of high-risk patients and followed as outpatients in study-centres. In the EDIT study (26) the patients were 'self-referred' but the exact setting was unclear. Setting and recruitment for the other studies remained unclear, thus far.

Trial design

All studies had a parallel design. One study had a double-blind 2x2 factorial design (26). Two studies were blinded (12, 27) and two studies were not blinded (30, 31). All studies investigated acarbose as the alpha-glucosidase inhibitor and compared it to placebo (12, 26, 27), metformin (26, 30), diet and exercise (30) or treatment, or both (30, 31). Thus far, we found no completed studies with miglitol or voglibose. Study duration was six years (26), five years (30), three years (12, 27) and one year (31). In one study the treatment duration was followed by a three months wash-out period in which both groups were given placebo (12). In all other cases treatment duration was similar to the follow-up duration.

Table 5.2. Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
DAISI (27), Netherlands	Randomised controlled double blind trial; Duration: 3 years (treatment and follow-up) Allocation	SETTING: unclear; RECRUITMENT: unclear; DIAGNOSIS: 2-hour post-load BG >8.6 mmol/l and <11.1 mmol/l after 2 OGTTs (WHO 1985) NUMBER. AGI: included 61, completed 27, ITT 60, PP 32; C included 60, completed 33, ITT 58, PP 39, SEX: 'sex ratio nearly 1:1', AGE (YEARS (MEDIAN))· AGI 61; C 56 BMI: ND, GHB ND	Diet: unclear AGI: acarbose, week 1 50 mg OD; week 2 50 mg BID; week 3 - endpoint 30 mg TID C: placebo, dosing schedule not described	Incidence of type 2 diabetes and 'conversion to' normal glucose tolerance, fasting venous glucose; total- and HDL-cholesterol, triglycerides; β-cell function and insulin sensitivity	Sponsor Bayer Author contacted: statistical report received, not allowed to use data before acceptance for publication Source· databases of ongoing studies, handsearching
EDIT (26), United Kingdom	Randomised controlled, double blind, 2x2 factorial trial, patients randomised for both acarbose and metformin versus placebo Duration 6 years (treatment and follow-up)	SETTING: unclear; RECRUITMENT: unclear, 'self-referred'; DIAGNOSIS: Patients 'at risk' for developing diabetes, Fasting BG 5.5-7.7 mmol/l NUMBER: recruited 671, randomised 631; SEX: 51% Female, 49% Male, AGE (YEARS (MEAN (SD)): randomised patients 52,1 (10,0), BMI (KG/M2 (MEAN (SD)): randomised patients 28,6 (4,5), GHB (% (MEAN (SD))· all randomised patients 5 9 (0 5)	Diet: unclear 2X2 Factorial design, four possible treatments· AGI· acarbose 50 mg TID + placebo TID C1 placebo TID + placebo TID C2. metformin 500 mg TID + placebo TID C3: metformin 500 mg TID + acarbose 50 mg TID	Progression to type 2 diabetes, Quality of life; fasting BG, 'lipid profiles'; β-cell function and insulin sensitivity; body weight	Outcomes for the combination group (acarbose + metformin) not considered Sponsor· Bayer and Merck-Lipha Author contacted: data will be made available when accepted for publication Source· databases of ongoing studies, handsearching, experts

Table 5.2 continued

Study	Methods	Participants	Interventions	Outcomes	Notes
Fang (30), China	Randomised controlled trial, Duration: 5 years (treatment and follow-up)	SETTING: unclear; RECRUITMENT: selected volunteers, details missing; DIAGNOSIS: IGT according to WHO 1985, NUMBER: 549 volunteers screened, 178 cases of IGT included· AGI 50, C1 40, C2 48, C3 40, analysed AGI 45, C1 35, C2 44, C3 36; SEX (F/M): AGI 22/28, C1 18/22, C2 22/26, C3 22/18, AGE (YEARS (MEAN (SD)): analysed patients: AGI 50 (7), C1 47 (14), C2 50 (7), C3 49 (6), BMI (KG/M2 (MEAN (SD)) analysed patients· AGI 24.9 (2.1), C1 24.8 (2.5), C2 25.2 (2.8), C3 25.3 (1.9); GHB· ND	Diet: unclear AGI: acarbose 25-50 mg TID C1: no treatment (common diabetes prevention education) C2: flumamine (=metformin) 125-250 mg TID C3 Diet and exercise: Education and dietary advice and exercise based on personal situation	Incidence of type 2 diabetes, fasting and 2-hours post-prandial blood glucose, total cholesterol and triglycerides; BMI, systolic and diastolic blood pressure	Sponsor: unclear Author contacted no reply Source· EMBASE
STOP-NIDDM (12), Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel, Spain	Randomised controlled double blind trial; Duration: mean 3.3 years (SD 1 5) treatment period, followed by a three months wash out period	SETTING: Outpatients, RECRUITMENT: screening high-risk populations, particularly first degree relatives of diabetic patients, DIAGNOSIS IGT (WHO 1999)· 2 hour BG ≥7.8 and <11.1 mmol/l and fasting BG ≥5.6 and <7.8 mmol/l, NUMBER randomised 1429, analysed 1368 (AGI 682, C 686), medication discontinuation, AGI 230/682, C 130/686, SEX (F/M): analysed group AGI 353/329, C 342/344; AGE (YEARS (MEAN (SD)) analysed group: AGI 54.3 (7.9), C 54.6 (7 9), BMI (KG/M2 (MEAN (SD)): analysed patients: AGI 31.0 (4 3), C 30.9 (4 2), GHB (% (MEAN (SD)): analysed patients: AGI 5 24 (0.74), C 5.24 (0.78)	Diet· instructions about weight-reduction and exercise reinforced each visit AGI: acabose, from 50 mg (once daily) uptitrated to 100 mg TID or maximum tolerated dose. Mean daily dose 194 mg (SD 87) C: placebo, similarly dised as AGI, 'mean daily dose' was 238 mg (SD^2)	Mortality, incidence of diabetes and cardiovascular events, GHB, fasting and post-load blood glucose; total-, HDL and LDL-cholesterol, triglycerides; fasting and post-load insulin; body weight, BMI, diastolic and systolic blood pressure, occurrence of hypertension, adverse effects: yes	Sponsor. Bayer, manufacturer of acarbose Author contacted· additional data sent by author Source: PUBMED, CENTRAL, EMBASE, WOS, Handsearch, manufacturer

Table 5.2 continued

Study	Methods	Participants	Interventions	Outcomes	Notes
Wang (31), China	Randomised controlled trial, Duration: 1 year (treatment and follow-up)	SETTING: unclear, RECRUITMENT: unclear; DIAGNOSIS: IGT according to WHO 1985, NUMBER: randomised AGI 31, C 30; analysed AGI 30, C 30; SEX (F/M): AGI 15/16, C 14/16; AGE (YEARS (MEAN (SD)). AGI 64.0 (8.7), C 63.0 (7.0); BMI (KG/M2 (MEAN (SD)): AGI 22.7 (3.4), C 21 0 (3 0); GHB: ND	Diet: 5 hours dietary training AGI: acarbose 50 mg TID C no treatment	Incidence of type 2 diabetes, adverse effects	Sponsor: unclear Author contacted: yes, no reply Source: CENTRAL

AGI=Alpha-glucosidase inhibitor; BG=Blood Glucose; BID=Bis In Die (twice daily); BMI=Body Mass Index; C=Control ; GHB=Glycated Hemoglobin , IGT=Impaired Glucose Tolerance; ITT=Intention To Treat Population, ND=No Data, OD=once daily; OGTT=Oral Glucose Tolerance Test, PP=Per Protocol Population; TID=Ter In Die (three times a day)

Outcome measures
All studies reported occurrence of DM2 as a primary outcome. Data on cardiovascular morbidity and mortality was available for the STOP-NIDDM study (12) only. For two studies additional data for glycaemic control, lipids, blood pressure and body weight were available (12, 30). The DAISI (27) and EDIT (26) studies reported that they investigated a number of additional outcomes (e.g. plasma glucose, lipids) but these data were not accessible for us thus far.

Methodological quality (see Table 5.3)

With respect to selection bias only one study had both an adequate randomisation and allocation concealment (12). The risk of attrition bias was low in three studies. However, no study had adequate intention-to-treat analysis. Blinding (performance bias) was adequate in one study (12) and for two studies information was lacking about precise methods of blinding (26, 27). In one study outcomes were adequately assessed in a blinded fashion (12).

The overall quality was roughly assessed on a three-point scale according to the Cochrane handbook: one study scored A (low risk of bias) and four studies scored C (high risk of bias).

Heterogeneity

Because not more than a maximum of two studies could be included per (statistical) comparison, formal testing of heterogeneity was not performed. The studies were reasonably homogeneous with respect to a number of important items:

- All trials used acarbose as the alpha-glucosidase inhibitor (all with a dosage of 50 mg TID, except for the STOP-NIDDM study (12) in which a dosage of 100 mg TID was given);
- All trials focused on patients with IGT (instead IFBG), except for the EDIT study (26) which included patients 'at risk' for developing diabetes (with a fasting blood glucose 5.5-7.7 mmol/l);
- In all trials the number of included females and males were almost similar, ranging from 47% females (30) to 51% females (12);
- All trials included patients with a similar age, ranging from a mean of 49.1 years (30) to 63.5 years (31).

The following items could cause possible heterogeneity:

- Two studies were performed in an Asian population (30, 31). The effects of alpha-glucosidase inhibitors may be different from European or American

populations (the other trials) due to differences in amount and type of carbohydrate in the regular diet;
- The mean BMI ranged from a normal BMI (31) to overweight (26, 30) or obesity (12). It was unknown for the DAISI study (27);
- Baseline glycated haemoglobin was below 6.0% in two studies (12, 26), but unknown for the other studies;
- In two trials, all participants received additional advice on diet and lifestyle (12, 31) but for the other trials this information was missing.

Effect of the intervention

With exception of the outcome 'incidence of DM2' in the comparison 'acarbose versus no treatment' in which data from two studies were available (30, 31), we were unable to perform meta-analyses in this review because for none of the other comparisons data were available from more than one study.

Acarbose versus placebo

Three studies compared acarbose with placebo (12, 26, 27). However, only for one study sufficient data were available to allow statistical comparison (12). For the other two studies most of the data are not yet available (26, 27).

Mortality, incidence of DM2 and cardiovascular disease

No significant effects on total mortality and mortality due to cardiovascular causes were found (12). Data for the other two studies were missing (26, 27).

Acarbose reduced the incidence of (conversion to) DM2 in the acarbose group: RR 0.78 (95% CI: 0.68 to 0.90), Risk difference (RD) 0.09 (95% CI 0.04 to 0.14), Number Needed to Treat (NNT) =10 (12). The NNT indicates that 10 patients have to be treated for three years with acarbose in order to prevent one case of DM2. Also, in the EDIT-study (26) it was reported that the use of acarbose had a preventive effect on the incidence of DM2: RR 0.66 (P=0.046).

In the STOP-NIDDM study (12) a decreasing effect for acarbose on the incidence of cardiovascular disease as a combined endpoint (myocardial infarction, angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular events and peripheral vascular disease) was found: RR 0.47 (95% CI 0.26 to 0.86). Also, a decreasing effect on myocardial infarctions (RR 0.08 (95% CI 0.01 to 0.64) was found. The RDs were 0.02 (95% CI 0.01 to 0.04; NNT=50) and 0.02 (95% CI 0.01 to 0.03; NNT=50) respectively. No significant differences in the incidence of angina pectoris, revascularization procedures, congestive heart failure, cerebrovascular events or peripheral vascular events were found. In total, 47 events took place in the whole study population and the study was not initially powered for

Table 5.3. Quality of Studies

Study	Randomisation*	Allocation Concealment*	Treatment Blinding†	ITT analysis‡	Quantity drop-out+	Selective drop-out#	Blind outcome assessment†	Analyses Blinding†	Overall Quality$
DAISI (27)	B	B	B	C	B	A	B	B	C
EDIT (26)	B	B	B	C	B	B	B	B	C
Fang (30)	A	B	C	B	A	A	B	B	C
STOP-NIDDM (12)	A	A	A	B	A	A	A	B	A
Wang (31)	B	B	C	B	A	A	B	B	C

* A=adequate, B=not adequate / unclear
† A=adequate, B=mentioning of blinding but exact method unclear, C=non-blinded, inadequate or unknown
‡ A=adequate, B=ITT inadequate, C=Unclear or no reported data on drop-out / loss-to-follow-up
+ A<15%, B≥15% or unknown
# A=difference in drop-out rate in main groups <10%, B≥10% or unknown
$ A=all quality criteria met; B=one or more quality criteria only partially met, C=one or more quality criteria not met

this outcome. Thus far, we found no data on cardiovascular morbidity from the EDIT (26) and DAISI (27) studies.

Glycaemic control
Acarbose decreased post-load glucose by 0.61 mmol/l (95% CI 0.27 to 0.95). No significant effects on glycated haemoglobin and fasting blood glucose were observed (12).

In the EDIT study (26) acarbose decreased fasting blood glucose by 0.1 mmol/l (P=0.0043) and post-load blood glucose by 0.4 mmol/l (P=0.0075).

Plasma lipids
No significant effects on lipids were found (12) or no data were available (26, 27).

Blood pressure
In our analysis, we found no significant effects on diastolic and systolic blood pressure (Comparison 1, outcomes 41 and 42). However, in one study the authors reported a beneficial effect on the incidence of new cases of hypertension (which was not an outcome in our review) (12). In the acarbose and placebo groups 78 and 115 patients developed hypertension respectively (hazard ratio 0.66, 95% CI 0.49-0.89). Hypertension was defined as a blood pressure greater than 140/90 mmHg on two visits or if the family physician added antihypertensive medication. It is remarkable that at baseline almost half of all patients were already diagnosed with hypertension (acarbose 357/682, placebo 345/686), but these participants were kept in the analysis for the development of hypertension. No data on blood pressure was available for the other studies with the comparison acarbose-placebo (26, 27).

Fasting and post-load insulin and C-peptide
No significant effects on fasting and post-load insulin levels were found (12) or no data were available (26, 27).

Body weight
Acarbose decreased body weight by 1.2 kg (95% CI 0.5 to 1.8) and BMI by 0.3 kg/m^2 (95% CI 0.1 to 0.5). For the other studies (26, 27), no data were available.

Adverse events
Acarbose caused more gastro-intestinal side effects compared to placebo: RR 1.40 (95% CI 1.31 to 1.50) and RD 0.24 (95% CI 0.20 to 0.29; Number Needed to Harm (NNH) =4). For the other studies, no data were available.

Quality of life
We found no data for 'quality of life', although it was stated for the EDIT study (26) that this outcome would be measured.

Costs / compliance
Resource consumption data were not systematically collected in the STOP-NIDDM study (12). A cost-effectiveness study was published in which the likely consumption of healthcare resources were estimated and used for analyses. It was reported that compliance was assessed by pill counting but we found no outcome data in the published articles. We failed to ask for those data in our correspondence with the authors.

Adjustment for high discontinuation rate in the STOP-NIDDM study (12)
One of the main criticisms on the STOP-NIDDM study (12) was that the discontinuation rate in the acarbose group was higher than in the placebo group (acarbose 31% versus placebo 19%). Despite the fact that discontinuing patients remained in the ITT analyses, it was suggested that those patients were not followed-up regularly every three months and thus possible occurrence of diabetes or a cardiovascular event was less likely to be discovered (16).

In order to investigate the possible influence of differences in the frequency of follow-up, we re-analysed the data with the following adjustments: first we requested for the mean number of study visits for both treatment groups. Next, we divided the number of visits of the placebo group by the number of visits in the acarbose group. We used this outcome as correction factor for the number of events in the acarbose group (occurrence of cardiovascular morbidity and DM2).

The authors of the STOP-NIDDM study (12) reported that the mean numbers of study visit in the acarbose (n=682) and in the placebo group (n=686) were 13.3 (SD=5.4) and 14.6 (SD=4.3) respectively. The calculated correction factor was: 14.6/13.3=1.1. The effects sizes (Odds Ratios) of the outcomes for incidence of DM2 and occurrence of any cardiovascular disease became smaller after the correction but remained statistically significant. The (statistically significant) effects size for myocardial infarctions did not change (due to the fact that there was only one case in the acarbose group). The other outcomes remained statistically not significant after correction.

Acarbose versus metformin

One study investigated both agents in a 2x2 factorial design (26). From this study no data on the comparison acarbose versus metformin is available thus far.

Another study directly compared acarbose with metformin (30). Acarbose showed a decreasing effect on post-load blood glucose compared to metformin: 1.40 mmol/l (95% CI 0.55 to 2.25). Metformin showed a statistically significant decreasing effect on total cholesterol (0.90 mmol/l, 95% CI 0.19 to 1.61) and diastolic blood pressure (6 mmHg, 95% CI 2.81 to 9.19) compared to acarbose. No significant effects for acarbose or metformin were found for the effect on incidence of DM2, fasting blood glucose, triglycerides, BMI or systolic blood pressure. Data for cardiovascular events,

quality of life, insulin or C-peptide levels, costs, compliance or adverse events were not found.

Acarbose versus diet and exercise

One study investigated the comparison acarbose versus diet and exercise (30). In this study a beneficial effect of acarbose compared to diet and exercise was found on the incidence of DM2: RR 0.40 (95% CI: 0.17 to 0.96), Risk difference (RD) 0.20 (95% CI 0.02 to 0.38, NNT=5).

Further, acarbose significantly reduced fasting blood glucose (–1.37 mmol/l, 95% CI –0.50 to –2.24) and post-load blood glucose (–2.79 mmol/l, 95% CI –1.79 to –3.79). Effects on total cholesterol, triglycerides, body weight and BMI were not statistically significant. Data for cardiovascular events, quality of life, insulin or C-peptide levels, costs, adverse events or compliance were not found.

Acarbose versus no treatment

Two studies compared acarbose with no treatment (30, 31).

Mortality, incidence of DM2 and cardiovascular disease

The combined results of the two studies indicated that acarbose reduced the incidence of DM2: RR 0.31 (95% CI: 0.14 to 0.69), Risk difference (RD) 0.17 (95% CI –0.09 to 0.43, NS). We found no data for effects on mortality or cardiovascular morbidity.

Glycaemic control

One study reported data for the effects on fasting and post-load blood glucose. Compared to patients who were given no treatment, acarbose significantly reduced fasting blood glucose (–1.39 mmol/l, 95% CI –0.54 to –2.24) and post-load blood glucose (–4.53 mmol/l, 95% CI –3.54 to –5.52) (30).

Plasma lipids

One study reported data for the effects on total cholesterol and triglycerides. Compared to patients who were given no treatment, acarbose significantly reduced total cholesterol (–1.00 mmol/l, 95% CI –0.194 to –1.81) (30).

Blood pressure

One study reported data for the effects of acarbose on diastolic and systolic blood pressure: no significant effects were found (30).

Fasting and post-load insulin and C-peptide

No data were found for insulin or C-peptide levels.

Body weight
Data were available from one study: compared to patients with no treatment acarbose showed a non-significant effect on BMI (–1.1 kg/m^2, 95% CI –2.2 to 0, P=0.05) (30).

Adverse events
One study reported data on adverse effects (31). Two patients in the acarbose group and no patients who received no treatment reported adverse effects. The difference was not statistically significant.

Quality of life
We found no data for effects on quality of life.

Costs, compliance
No data were found for these outcomes.

Sensitivity analyses, sub-group analyses, meta-regression analyses, small study bias

Due to the low number of included studies no further analyses could be performed.

Discussion

Summary for main results

In this systematic review we found evidence from one large study of high quality (12) that acarbose compared to placebo reduces the incidence of DM2 and myocardial infarctions in patients with impaired glucose tolerance. These findings could not be confirmed nor refuted by two other (but highly similar) studies because most data were not available thus far (26, 27). Two smaller studies of low quality comparing acarbose with no treatment or exercise, confirmed the capacity of acarbose to reduce the incidence of DM2. Effects on cardiovascular morbidity could not be confirmed in other comparisons. Moreover it should be noted that the effects on cardiovascular morbidity in the STOP-NIDDM study (12) were based on a limited number of events and the study was not initially powered for this outcome. Compared to placebo, acarbose induces more gastro-intestinal side-effects (NNH=4).

Decrease in incidence of DM2

We found evidence from several studies that acarbose reduces the incidence of DM2 (12, 30, 31). A firm effect on the incidence of DM2 is not surprising. After all, acarbose has a clear effect on glycaemic control in patients with DM2 (11). Such a drug will have large effects on the 'incidence' of diabetes for people who are at the

border of fulfilling the criteria for DM2. So, the question is whether acarbose prevents, delays or even masks DM2. The authors of the STOP-NIDDM study (12) are undecided, as they sometimes speak of 'prevention' (in the title) and sometimes of 'delay' (in the summary) (12). Critics of the STOP-NIDDM study (12) suggested that acarbose masks DM2 since 15.4% of the patients on acarbose compared to 10,6% (placebo) converted to diabetes during a three months wash-out phase (15).

To assess the value of acarbose with respect to the effects on the development of DM2, it is probably more straightforward to look at the effects on glycaemic control. After all, IGT refers to an intermediate state between normal glucose homeostasis and DM2. In the STOP-NIDDM study (12) these effects are disappointing: no significant effect on glycated haemoglobin and fasting blood glucose, and a small effect on post-load blood glucose (–0.61 mmol/l, 95% CI –0.95 to –0.27) were found. Those effects are smaller than obtained in a Cochrane review on alpha-glucosidase inhibitors for patients with DM2 (11). This may be explained by the fact that in the before mentioned review it was found that the effects on glycaemic control were less strong with lower baseline values of glycaemia and longer study duration. Further, most trials in the Cochrane review studied post-load glucose with a full meal tolerance test, and not an oral glucose tolerance test (OGTT) as has been done in the STOP-NIDDM study (12). Acarbose has no direct effects on an OGTT as alpha-glucosidase inhibitors only delay the breakdown of complex polysaccharides (and not monosaccharide such as glucose). In this light, the decreasing effect of acarbose on a 2 hours OGTT is positive because it indicates a beneficial effect of insulin resistance.

Another argument in the question whether an effect of acarbose on the incidence of DM2 is relevant or important, is the desirability of a drug intervention in people at high risk for DM2. It is well recognized that the increase in the number of patients with DM2 is in lifestyle factors such as a shortage of exercise and an unhealthy diet. Focussing on drugs as the solution of the problem may distract people from the issues that are truly important: eat less and exercise more.

Finally the question arises whether true (primary) prevention of DM2 with a single drug is possible at all. DM2 is a very complex disease in which many pathophysiological mechanisms are involved (e.g. insulin sensitivity, blood pressure regulation). Only when one predominant mechanism would be identified, primary prevention by a drug targeting this mechanism would be feasible. Currently, it seems not likely that this will be the case for DM2 in the near future. In the mean while, drug interventions for IGT or IFBG should be regarded as secondary or tertiary prevention.

Decrease in incidence of cardiovascular disease

The observed beneficial effects on the occurrence of cardiovascular morbidity (12) are very interesting. However, these results should be interpreted with great prudence. This is underlined by the authors who sensibly stated that because effects on

cardiovascular morbidity were secondary objectives and the number of events relatively small, they should be seen as hypothesis generating (53).

Critics mentioned the skewed discontinuation rate as another explanation for the observed effects, other than an effect of acarbose (16). Because more patients in the acarbose group stopped taking their medication (mostly due to side-effects), the patients in the acarbose group were not followed-up as regular as the patients in the placebo group and could have had therefore less chance to be 'detected' in case a cardiovascular event had taken place. We re-analysed the data accounting for differences in follow-up rate and found that the odds ratios for the occurrence of any cardiovascular event became less strong, but remained statistically significant.

Another explanation could be in the existence of (unknown) confounding factors. Clues for differences in treatment groups were reported in the cost-effectiveness sub-study of the STOP-NIDDM trial (43). Baseline risk profiles were determined with a formula for the identification of high risk for DM2 (65) or cardiovascular risk (66). Based on these risk scores, it was stated that '... more placebo patients than acarbose-treated patients were represented in the high-risk subgroups...'. So, patients in the placebo group could have had a higher a-priori risk than patients on acarbose.

We conclude that the observed effects of acarbose on cardiovascular disease may be due to a treatment effect or to (unknown) confounding factors, or both. The results from the ongoing studies are needed to confirm or refute the observed effects in the STOP-NIDDM study (28, 29).

Effects on incidence of hypertension

We could not confirm the beneficial effects on hypertension observed in the STOP-NIDDM study (12), in which hypertension was studied as a clinical outcome (blood pressure greater than 140/90 mmHg on two or more occasions). Instead we studied the differences in diastolic and systolic blood pressure. These outcomes yielded no statistically significant effects of acarbose compared to placebo (12), and a detrimental effect of acarbose on diastolic blood pressure compared to metformin in one study of low quality and with a low number of participants (6 mmHg (95% CI 3 to 9)) (30).

Comparison with existing literature

As far as we are aware of, no systematic review has been done with an exclusive focus on alpha-glucosidase inhibitors for people with IGT of IFBG. Nevertheless, alpha-glucosidase inhibitors have been studied as part of a recent systematic review on all kind of drug therapy to delay or prevent DM2 (67). In that review two studies on acarbose were included: the STOP-NIDDM study (12), and a non-randomised study (32) (excluded for the current review). It was concluded that acarbose reduced the incidence of DM2 compared with placebo but that it could not definitively be recommended for diabetes prevention. Similar conclusions were drawn for metformin, troglitazone and orlistat (a weight reducing agent). Further, inconclusive results for a decrease in the incidence of DM2 were reported for cholesterol lowering

agents (fibrates and statins), antihypertensive agents and oestrogens. A systematic review on the efficacy of lifestyle education concluded that lifestyle education was clearly effective for reducing 2-hour plasma glucose (0.84 mmol/l, 95% CI 0.39 to 1.29) and the incidence of DM2 over one year (RR 0.55, 95% CI 0.44 to 0.69), and should thus be recommended for patients with patients at high risk for DM2 (68).

Strengths and limitations of the review

One of the main strengths of this review is the rigourness and completeness of the search. It is remarkable that only one trial (12) was listed in the database that is mostly used by clinicians all over the world (PUBMED), and that the other studies were retrieved from less well-known databases (EMBASE or The Cochrane Library), in databases of ongoing trials or by handsearching. Second, the a priori decision to include randomised trials only with a duration of at least one year ensured a 'minimum level' of quality. Third, we assessed many different outcomes in the review which enables the readers to judge by themselves what matters most for their own particular question. Finally, we think that the tables and figures and the extensive provision of all outcome data and information related to quality and heterogeneity, makes the review transparent.

It is clear that the main limitations are the missing data, especially from the EDIT (26) and DAISI (27) studies. The authors have kindly promised their help once their manuscripts are accepted for publication, but it is remarkable that these important studies have not been accepted for publication to date (July 2007). This points to a possible time lag bias: a kind of reporting bias in which studies may be published rapidly or delayed depending on the nature and direction of the results. Of course we will use upcoming data from these studies, and from the studies that are still going on in future updates of our review. Another limitation is the external validity of the results. Only for one study the recruitment of the participants was clearly described. It is important to know how selection took place in order to be able to generalize the results to other clinical settings. For example, were the participants volunteers recruited with a newspaper advertisement (and thus highly motivated), or were they recruited from the files of general practitioners (and maybe less motivated). Further, we only found studies with acarbose as the AGI. The question whether the results may be extrapolated to miglitol or voglibose depends on the existence of a possible group effect for AGIs. The answer to this question is not known, although in the Cochrane review on AGIs for DM2 comparable results for acarbose and miglitol were obtained for most outcomes (11).

Reviewers' conclusions

Implications for practice

In patients with impaired glucose tolerance the use of acarbose reduces the incidence of DM2, but the effects on glycaemic control are limited. Acarbose has a possible effect on cardiovascular morbidity, which has to be confirmed in other studies. Lifestyle interventions remain the cornerstone of treatment for patients at risk for DM2. If physicians and patients feel that an active treatment for impaired glucose tolerance is needed, they should consider this evidence together with evidence for other interventions, especially lifestyle interventions.

Implications for research

First, the disclosure of the finished - but unpublished - studies is needed in order to confirm or refute the possible effects on cardiovascular morbidity. If the evidence remains inconclusive after these data have been incorporated in the systematic review, the results from two ongoing long-term intervention studies on the effects of alpha-glucosidase inhibitors for patients with IGT or IFBG may be awaited. Otherwise, new long-term studies with a similar focus could be initiated.

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Appendix A

Unless otherwise stated, search terms are free text terms, MesH=Medical subject heading (Medline medical index term), exp=exploded MeSH, the asterisk (*) stands for any character(s), tw=text word, pt=publication type, sh=MeSH, adj=adjacent

#1 Alpha glucosidase inhibitors (11)
"Acarbose"[MeSH] OR acarbos* [tw] OR bayg5421 OR bay 5421 [tw] OR glucobay [tw] OR precos* [tw] OR prandas* [tw] OR akarbos* [tw] OR miglitol [tw] OR glyset [tw] OR diastabol [tw] OR baym1099 [tw] OR bay 1099 [tw] OR voglibos* [tw] OR (basen NOT basen [au]) OR emiglitat* [tw] OR alpha-glucosidase inhibitor [tw] OR glucosidase inhibitor [tw] OR alpha glucosidase inhibitors [tw] OR glucosidase inhibitors [tw]

#2 Controlled trials (19)
(Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (clinical trial [tw]) OR ((singl*[tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (latin square [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])

#3 Impaired Glucose Tolerance or Impaired Fasting Blood Glucose
"Glucose Intolerance"[MeSH] OR "Diabetes Mellitus, Type II/prevention and control"[MeSH] OR "Glucose Tolerance Test"[MeSH] OR "Insulin Resistance/drug effects"[MeSH] OR "Metabolic Syndrome X"[MeSH] OR "impaired fasting glucose" [tw] OR "impaired fasting blood glucose" [tw] OR "impaired fasting bloodglucose" [tw] OR "impaired fasting glycaemia" [tw] OR "impaired fasting glycemia" [tw] OR impaired glucose toleran* [tw] OR impaired glucose stat* [tw] OR impaired glucose respons* [tw] OR impaired glucose control* [tw] OR IGT [tw] OR glucose intoleran* [tw] OR impaired glucose regul* [tw] OR impaired glucose metab* [tw] OR impaired glucose homeost* [tw] OR reduced glucose metabolism* [tw] OR reduced glucose toleran* [tw] OR glucose intolerant* [tw] OR glucose tolerance test* [tw] OR prediabet* [tw] OR praediabet* [tw] OR "pre diabetes" [tw] OR "prae diabetes" [tw] OR "pre diabetic" [tw] OR "prae diabetic" [tw] OR "pre diabetics" [tw] OR "prae diabetics" [tw] OR metabolic syndr* [tw] OR "syndrome X" [tw] OR borderline diabet* [tw] OR mild diabet* [tw] OR insulin resistan* [tw] OR impaired insulin secret* [tw] OR reduced insulin secret* [tw]
Whole search #1 AND #2 AND #3

These searches can be cut and pasted into PubMed (www ncbi nlm nih gov/entrez/query fcgi)

Chapter 6

General discussion

General discussion

In this thesis we assessed the evidence base for diet and alpha-glucosidase inhibition in the treatment for patients with type 2 diabetes mellitus (DM2) and/or impaired glucose tolerance. We also focused on dietary patterns of patients with DM2, and eating behaviour as a predictor of success or failure in dietary treatment. In this chapter, the main conclusions are discussed and suggestions for future research and advices for (guidelines for) diabetes care are given. Finally, some reflections are made about this thesis in the light of primary care research.

Diet in type 2 diabetes mellitus

The evidence base for diet therapy in DM2: lessons from systematic reviews

In order to assess the highest levels of evidence for diet for DM2, we reviewed all currently available systematic reviews on this topic (*chapter 2*). Our rigorous approach, based on Cochrane analysis guidelines, yielded six systematic reviews. Data from these reviews appeared to be mostly inconclusive.

Four out of six reviews aimed at studying a very broad topic (e.g., all dietary supplements, diet in general for DM2). As a consequence many authors limited the inclusion to long-term randomised trials, leaving only a small number of studies on which conclusions are based (e.g., Moore et al. (1)), others included a large number of heterogeneous studies and therefore were not able to draw conclusions beyond the sum of the original studies with implications for daily practice (2, 3). Therefore, we argued that new reviews should apply a more focussed research question and at the same time use broader inclusion criteria (e.g., the inclusion of non-randomised trials).

The question emerges how a systematic review on diet should ideally be done. It should first be recognized that it is difficult to look at 'diet' as a single intervention. Doctors and nurses may tend to look at diet as simply one aspect of lifestyle, but eating is far more complex. Eating behaviour is inextricably bound up with its psychological, social, cultural and economical context (4), all of which can serve as confounder or effect modifier. Those factors will inevitably affect outcomes of studies and will also be an important obstacle when it comes to generalizing the results to other populations, especially when the possible confounders are not reported or unknown.

To formulate a research question for a new systematic review in the field of diet and DM2, we made a distinction between efficacy, effectiveness and efficiency. The efficacy – does an intervention bring about effects under ideal circumstances – of dietary interventions should be investigated first in highly controlled experimental studies. Such studies will usually be of short duration, due to practical and financial reasons. This way, it is possible to investigate for example effects on body weight, blood lipids and glucose or blood pressure. However, it is almost impossible to look at

rare, but important, endpoints such as mortality or morbidity under these rigorous scientific conditions. To get data for these endpoints, increasing power with a meta-analysis of multiple studies, or the application of observational research, such as cohort or case-control studies, seem to be the alternatives. Although observational studies might be as credible as randomised trials, in the case of health effects of lifestyles that people take up because of health concerns, it may be notoriously difficult (5). The reason for this is that the exposure allocation (e.g., fat consumption) is not totally unrelated to the prognosis (e.g., as reflected by severity of disease). This might lead to an underestimation of the effects of, for example, diet: people at high risk will make more efforts to comply but have a worse outcome. So paradoxically, observational studies on the effects of diet could better be done in people who are all at low risk of (complications of) disease.

The effectiveness – does an intervention work in real-life – of diet depends not only on its efficacy, but to a large extent on adherence to dietary recommendations and other biological, psychosocial, cultural and economical factors that determine our food choices. Although randomisation could account for such confounders and effect modifiers, randomised trials are not suited for the study of long term (>10 years) effects of diet. Moreover, randomisation may account for confounding and effect-modification, but mechanisms by which psychological and cultural aspects, for example, interact with outcomes remain unrevealed. Therefore, research should focus on other topics in the behavioural science field (6) like the environmental factors related to obesity, theoretical constructs promoting long-term adherence, and understanding of motivation.

Finally, the efficiency – is an intervention worth its costs to an individual or society – of dietary interventions should be researched in cost-effectiveness or economic evaluation studies. Of course, proven efficacy and effectiveness is a prerequisite when investigating cost-effectiveness.

The enormous bulk of evidence from short-term experimental studies, randomised trials, observational studies, or economic evaluation studies may be assessed in multiple systematic reviews, all with their own specific focus. Systematic reviews should not aim to collect, summarize and analyze all evidence for one disease or treatment modality together because this is contradictory to basic scientific principles of having a limited and answerable research question.

Another lesson from our review of systematic reviews is that external validity is an underexposed topic in most reviews. At least, studies provided insufficient data to judge to whom the results of the study apply. Especially in the topic of diet, which is highly interwoven with cultural and economical factors, this may look surprising. However, there is evidence for the neglect of consideration of external validity (7). For example, there are no accepted guidelines on how external validity of RCTs should be assessed, funding agencies, ethics committees and drug licensing bodies hardly mention the importance of external validity in their guidelines and existing guidelines on the reporting of RCTs, and systematic reviews give very little space to external

validity. Still, it is encouraging that recently a checklist for the evaluation of clinical studies with a particular focus on external validity has been published (8).

Dietary habits of patients with DM2

In our cohort study of 144 patients newly diagnosed patients with DM2 we, found that even after four years of usual care, patients still had favourable energy and fat intake compared to diagnosis (*chapter 3.1*). We conclude that pessimism with respect to the willingness of patients to change their diet persistently, seems not justified. On the other hand, our results give rise to some concerns. Although the proportion of patients who comply with the recommendation of consuming less than 10 energy percents of saturated fat increases by a fourfold, four years after diagnosis about 73% of patient still do not meet this recommendation. This finding is all the more important, because this treatment goal has been sharpened recently to a limit of less than 7 energy percents of saturated fat for all patients with DM2. Of course, there will undoubtedly be room for improvement in the dietary treatment of patients (see *chapters 3.2 and 3.3*). But it is questionable whether such strict recommendations are realistic, especially for people living in a Western society like the Netherlands from which our cohort was recruited. What is the use of treatment goals that are so strict that meeting them seems an utopia for the individual?

Would it not be more reasonable to simply encourage patients to eat as less saturated fat as possible without referring to specific goals? Otherwise, patients, on the one hand, might get frustrated when confronted with goals that seem impossible to achieve, and care-providers, on the other hand, might neglect dietary aspects of treatment for diabetes and give priority to other more feasible goals. It is also important to emphasize that eating habits are, to a certain extent, a characteristic of a society as a whole and that also attention should be paid to dietary 'interventions' on societal level. Governmental policies and health promotion campaigns directed to the general public should be aimed at eating less, but more healthy food.

Eating behaviour as a predictor for short- and long term dietary changes

In *chapters 3.2 and 3.3*, we showed that patients with newly diagnosed DM2 do not differ from subjects in the general population with respect to restrained, emotional, and external eating behaviour. Moreover, we found that restrained eating predicts low energy consumption, and showed not to be a detrimental factor in itself, as has been advocated in previous research. Instead, emotional and external eating, also described as tendency towards overeating, were associated with weight gain and high energy intake four years after diagnosis. We also found clues that especially women with high scores for emotional eating have problems with initial beneficial dietary changes.

The results from the present study have only limited implications for daily practice. First, replication of our study in a larger sample size might learn whether or not eating behaviour also predicts long-term adherence to dietary recommendations, or whether eating behaviour also predicts energy consumption in men.

Second, disturbed eating behaviour deserves more detailed investigation in particular whether it is a cause in itself of unfavourable dietary changes, or a consequence of psychological mechanisms leading to low dietary adherence and weight gain. For example, depression, alexithymia and impulsivity are known to (partially) explain emotional eating behaviour and are related to body weight and energy and fat consumption. Especially depression or impulsivity may offer a promising therapeutic possibility to treat patients for their disability to change their diet.

If our findings can be reproduced one might argue that targeted dietary advice recognizing patients' specific type of eating behaviour and/or its underlying mechanisms is more effective than standard dietary consultation alone. However, it seems logical that such strategies will only be cost-effective if it is integrated in the whole package of diabetes treatment. After all, dietary modification has to compete with other priorities in diabetes treatment such as exercise, eye and foot care, and medication compliance (9). So, if a dietary advice targeted to specific eating behaviour is effective, it should be first offered to patients who are to be expected to benefit most. These patients will probably be those who have extreme high scores for emotional or external eating behaviour, who have enough room for improvement in energy and fat consumption or body weight, and who have a high motivation.

Alpha-glucosidase inhibitors for treatment of type 2 diabetes mellitus

Alpha-glucosidase inhibitors (AGIs) represent one of the six classes of oral drugs for the treatment of DM2 (10). AGIs reversibly inhibit a number of alpha-glucosidase enzymes (e.g., glucoamalyse, sucrase, maltase), consequently delaying the absorption of sugars from the gut (11). In a recent study among healthy subjects it was suggested that the therapeutic effects of AGIs are not only based on a delayed digestion of complex carbohydrates, but also on metabolic effects of colonic starch fermentation (12). Acarbose (Glucobay®) is the only AGI available on the Dutch market. The other AGIs are miglitol (Glyset®) and voglibose (Volix®, Basen®). AGIs might be a reasonable option as first-line drug in the treatment of patients with DM2 as it specifically targets postprandial hyperglycemia, a possible independent risk factor for cardiovascular complications (13). Moreover, AGIs are expected to have no dangerous side effects and cause no weight gain.

The effectiveness of AGIs in DM2

In a randomised controlled trial set up to investigate whether acarbose and tolbutamide were equivalent with respect to the effects on HbA_{1c}, we could not confirm, nor rule out clinical equivalence based on predefined criteria (*chapter 4.1*). Because acarbose showed a significantly less lowering effect on fasting blood glucose and a disadvantageous number of patients who dropped-out mostly because of side

effects, we concluded that tolbutamide is to be preferred above acarbose in patients newly diagnosed with DM2. In a Cochrane systematic review on all AGIs we found no evidence for beneficial effects on mortality or (cardiovascular) morbidity (*chapter 4.2*). This finding was not due to 'biased interpretation' as suggested by Hanefeld et al. (14, 15), but largely because long-term studies with solid data on morbidity and mortality were missing (*chapter 4.3.2*). Still, we found statistically and clinically significant effects for acarbose on HbA_{1c} (0.8% decrease), fasting (1.1 mmol/l decrease) and post-load (2.3 mmol/l decrease) blood glucose and BMI (0.2 kg/m^2 decrease) compared with placebo. Compared with sulphonylurea, acarbose was inferior with respect to its effect on fasting blood glucose and the occurrence of side-effects, but superior with respect to its effect on body weight and post-load insulin. Too few comparisons with metformin were available to make a fair judgment.

The place of AGIs in current therapeutic strategies. A comparison with the other oral blood glucose lowering drugs

In 2006, the American Diabetes Association and European Association for the Study of Diabetes together published a 'consensus statement' on the management of hyperglycemia. For all patients, metformin in combination with a lifestyle intervention is advised, followed by the addition of either a thiazolidinedione (TZD), a sulphonylurea, or insulin when HbA_{1c} remains ≥7%. AGIs are not included in the treatment algorithm, but is stated to be an "appropriate choice in selected patients" (16).

The guideline of the British National Institute for Clinical Excellence (2002) states that oral medication has to be initiated when lifestyle intervention alone fails. Metformin is therapy of first choice and sulphonylurea should be given in case of contra-indications for metformin, or should be added when therapy with metformin alone fails. TZDs are recommended to be added in case of contraindications for metformin, or if the combination of metformin and sulphonylurea fails. AGIs may be considered as an alternative glucose-lowering therapy in people unable to use other oral drugs (17).

The guidelines of the Dutch College of General Practitioners (DCGP) have changed during the course of our studies. At the time our studies were conducted, acarbose was recommended as a drug for the treatment of DM2 when sulphonylurea and/or metformin failed, or in case of contra-indications for one of these drugs (18). In the current Dutch guideline, however, the only AGI that is available in the Netherlands, acarbose, is no longer recommended (19). Instead, TZDs are introduced in the guideline to be used when metformin fails in obese patients (BMI ≥27 kg/m^2) with existing cardiovascular disease without an increased risk for heart failure. The low ranking of AGIs in all of these guidelines suggests that unequivocal evidence proving the superiority of the other oral drugs is available.

The case for metformin seems to be strong: metformin showed to have beneficial effects on diabetes-related morbidity (20). Moreover, in meta-analyses metformin

compared to placebo showed to decrease HbA_{1c} by 0.9% (21) or 1.0% (22). However, the cases for sulphonylurea and TZDs are less strong. The beneficial effects on microvascular complications that have been observed in sulphonylurea and insulin treated patients, are most likely due to the effects of tight glycemic control and not due to direct effects of sulphonylurea (23). Moreover, no beneficial effects on diabetes related mortality and macrovascular morbidity has been found thus far for sulphonylurea. On the contrary, although the results of the University Group Diabetes Program suggesting an increased risk of cardiovascular morbidity with the use of tolbutamide were heavily criticized (24), sulphonylurea remained under the suspicion of unfavourable effects on cardiovascular disease up to now (25, 26). In addition, sulphonylureas carry the risk of inducing life threatening hypoglycaemic events.

TZDs are becoming more popular; this is reflected by the increased expenses of these drugs in the Netherlands: from 2 million Euros in 2001 to almost 24 million Euros in 2005 (27). The PROACTIVE-study found a statistically significant effect for pioglitazone compared to placebo in addition to regular treatment in obese patients with DM2 and known cardiovascular morbidity on a secondary composite endpoint consisting of total mortality, non-fatal myocardial infarction and cerebrovasular accident resulting in a NNT of 50 patients (treatment duration three years) (28). However, in a recent Cochrane systematic review with 22 trials on the efficacy of pioglitazone, it was concluded that thus far no convincing evidence for effects on mortality and morbidity exist and that the previously mentioned result of the PROACTIVE-study are hypotheses generating and need reconfirmation (29). This precautious approach is underlined by results of a meta-analysis on another TZD, rosiglitazone, that showed an increased risk on myocardial infarctions and death from cardiovascular disease (30). Moreover, it is important to realise that TZDs cause fluid retention and are therefore contra-indicated in patients with or at increased risk for heart failure.

Compared with the evidence for the currently recommended therapy (metformin, sulphunylurea, TZDs) as described above, the results of AGI-treatment as studied in this thesis, are less unfavourable than could be concluded from the low ranking of AGIs in the current guidelines. The effect of AGIs on HbA_{1c} is on average only 0.1 to 0.2% less compared to metformin and TZDs. Moreover, its effect on post-load glucose may be superior, although this is based on one comparison only (31) and no data from meta-analyses are available. AGIs have a decreasing effect on the Body Mass Index, and the safety profile is favourable as there is no evidence for dangerous side effects. Most important, there are clues that AGI may prevent cardiovascular events in patients with impaired glucose tolerance in the STOP-NIDDM study (32). However, this study is heavily debated and the results deserve re-confirmation (33, 34). In our view, 'evidence' from a study that reported beneficial effects of acarbose on myocardial infarctions in patients with DM2 has to be neglected because of publication bias, heterogeneity, detection bias and confounding (*chapter 4.3.1*). The results of three recently performed trials are underway with mortality and morbidity endpoints in patients with abnormal glucose tolerance (35, 36) and early diabetes (37).

The gastro-intestinal side effects of AGIs are clinically relevant and may affect compliance. In this respect, it is of interest that we found evidence that acarbose in a low dose (50 mg TID) has similar effects on HbA_{1c} and less side effects compared to the double dose (100 mg TID) (see: *chapter 4.2*).

Altogether, AGIs appear to be a serious therapeutic option in the treatment of DM2 as it is has a comparable effect on glycemic control compared to metformin, it poses no risk for harmful adverse events, decreases Body Mass Index, it possibly reduces the risk for cardiovascular disease and the side-effects may be reduced by administering a lower dose without influencing its effect on glycemic control. AGIs are not necessarily a drug in the form of a pill as it may also be given as 'smart food' or as a food supplement. For example, a soy-bean derived touchi extract, a traditional Chinese food in the form of a paste, has shown to have alpha-glucosidase inhibiting properties and reduce blood glucose levels (38).

The effectiveness of alpha-glucosidase inhibitors in patients with impaired glucose tolerance or impaired fasting blood glucose

In order to investigate whether AGIs are able to prevent diabetes and its related morbidity and mortality, we performed another Cochrane systematic review investigating AGIs for people with IFBG or IGT. We found evidence that acarbose reduces the incidence of DM2 in patients with IGT. However, it remains unclear whether this should be seen as prevention, delay or masking of diabetes. We also found a preventive effect on combined cardiovascular endpoints (RR 0.46, 95% CI 0.26-0.86, NNT=50) on the occurrence of cardiovascular events, but this finding needs to be confirmed in more studies since it is based on only 47 events and the study was not originally powered for this goal (*chapter 5*). In the coming years, more data will be available from studies that have already been finished but yet unreported, and from studies that are currently ongoing. All together, the results of our review are likely not to appear in the advertisements of the manufacturers of AGIs. Thus far, lifestyle interventions are still much more effective in reducing the incidence of DM2 than AGIs (39-41).

Nevertheless, regardless of data from our review or other studies, the question arises whether drug interventions in people with no disease and who do not even feel ill is desirable. General Practitioners (GPs) are often confronted with the medical consequences of societal problems such as the massive adoption of sedentary lifestyles or loneliness and social isolation. But, just like a banker will talk money when confronted to problems, a doctor will most likely 'talk medicine' even when confronted with non-medical problems. This issue of medicalisation, raised in the seventies of the twentieth century, is to date still actual and even more complicated than before (42, 43). In a focus group study with Welsh doctors and practice nurses unnecessary medicalisation was a major concern with respect to preventive treatments

for DM2 (44). This thesis does not provide the answers to the question were the border should be between the medical domain and the responsibility of society as a whole, governments, schools and, last but not least, the individual himself. But asking the question in this philosophical and ethical issue is probably more important than any possible answer.

Final reflections: this thesis in the light of primary care research

This thesis has dealt with a number of topics related to the treatment of newly diagnosed patients with DM2 and its precursors (impaired glucose tolerance and impaired fasting blood glucose). One chapter was based on a randomized clinical trial, performed in general practice, the other chapters were based on observational research of a cohort and critical appraisal of published and unpublished studies. The main focus on the analysis of existing data and the sparse use of experimental design, could be considered a metaphor for general practice. For the majority of problems, the existing knowledge about (patho)physiology and epidemiology in combination with the patient's history, physical examination and context will lead to a diagnosis; the GP will sparsely use additional tests.

In this context, we feel that systematic reviews deserve special attention in both primary care research and the practice of primary care. In research, high quality systematic reviews should be the starting point of new research projects, as this is the best way to show how new research questions arise from the current state of evidence. Systematic reviews should be regularly updated so that new evidence is integrated in what is already known. It is important that systematic reviews meet the highest methodological standards. This includes that evidence from high quality studies is given more weight than results from low quality studies. As a consequence, researchers of the primary studies will be encouraged to apply and report sound scientific methods.

In the practice of primary care, systematic reviews may offer an information-dense way to keep up-to-date on a certain topic, on the condition that reviews are accessible and presented in a logical and comprehensive way. Therefore, the promotion of quality, quantity, dissemination, readability and the accessibility of systematic reviews relevant to people who work in primary care should be high on the primary care research agenda. It is no coincidence that this is exactly the mission statement of the renewed Cochrane Primary Health Care Field (45).

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Chapter 7.1

Summary

Summary

In ***chapter 1*** a short introduction about diabetes mellitus type 2 (DM2) and its treatment in general practice is given. The focus of the thesis is the evidence base of two interventions in the treatment and prevention of DM2. In the first part of the thesis, the evidence for the usefulness of dietary treatment was assessed. We focused on dietary patterns of patients with DM2, and on factors that determine patients' motivation to change their diet. In the second part of this thesis, we assessed the effectiveness of alpha-glucosidase inhibitors in the treatment and prevention of DM2.

In ***chapter 2***, the currently available evidence for the effectiveness of a dietary intervention in DM2 was assessed by investigating systematic reviews. A systematic review is an appraised method to summarize research in a concise and transparent way, and it may enable to draw conclusions beyond the sum of results of separate studies. We performed an umbrella systematic review to assess the results, quality and external validity of the available systematic reviews on diet in DM2. Six systematic reviews met the inclusion criteria. Those reviews investigated dietary interventions that were not prespecified (n=3), chromium supplementation (n=1), fish oil (n=1), or herbs and nutrition supplements (n=1). In the reviews with only minimal/minor quality flaws (4 out of 6), we found beneficial effects of very-low-calorie diets and fish oil supplements. However, the external validity could not be judged, due to absence of relevant data. In addition, we found that the systematic reviews largely failed to produce knowledge beyond the sum of the original studies. The quality and usefulness of systematic reviews of dietary intervention could possibly improve by application of more focused research questions, together with broader inclusion criteria (e.g. the use of observational studies).

The first step in treatment of DM2 is life style modification in the form of exercise and diet. If life-style modification fails to control blood glucose levels sufficiently, oral medication is prescribed. In *chapter 3* we describe our studies on a dietary intervention in newly diagnosed type 2 diabetic patients.

We performed a prospective cohort study in general practice in patients with newly diagnosed DM2 in order to investigate dietary habits, dietary changes (*chapter 3.1*), eating behaviour and adherence to diet (*chapters 3.2 and 3.3*). In 46 general practices throughout the Netherlands, 144 patients with newly diagnosed DM2 were recruited to be assessed for baseline measurements. In accordance with current guidelines, all patients were referred to a registered dietician who offered dietary advice tailored to individual needs, in the first weeks after diagnosis. Patients were re-assessed eight weeks and four years after diagnosis.

Although treatment targets for the consumption of dietary fat are well accepted, little is known about the actual fat consumption by newly diagnosed patients or the dietary adjustments that they make in the following years. In ***chapter 3.1***, the results of

measurements of fat intake in the above-described study population are given. Fat consumption was assessed with a 104-item food frequency questionnaire (FFQ), reference values were obtained from an age-matched sample of a population-based survey. At diagnosis the patients with DM2 had an unfavourable dietary intake compared tot the general population with respect to the mean total energy intake, cholesterol intake, total fat consumption and the proportion of saturated fat. After eight weeks, all levels decreased to values comparable to, or lower than, those measured in the general population. After four years, energy and the energy % of saturated fat were unchanged, there was a slight increase in the mean intake of total fat, and cholesterol consumption had further decreased, compared to eight weeks. However, after four years the treatment only 17% and 27% of participating patients respectively met the targets regarding consumption of total and saturated fat . We concluded that patients with DM2 are able to adapt a more favourable diet after diagnosis under regular care, and that they are able to sustain this improvement over four years. Still, recommendations with respect to the consumption of total and saturated fat are not met.

It is recognized that life style changes, including diet, may be difficult to implement and maintain. Therefore, it is important to identify potential obstacles or supportive factors. We investigated the relation between eating behaviour and energy and fat consumption and subsequent changes in the previously described cohort of patients with DM2 (***chapter 3.2***). In this study population, energy and fat consumption was measured as described above. Eating behaviour was assessed at diagnosis and after 4 years with the validated Dutch Eating Behaviour Questionnaire (DEBQ); a comparable sample of the general population served as a reference. The DEBQ distinguishes three types of eating behaviour: (1) emotional eating, that means eating more when experiencing negative emotions; (2) external eating behaviour, i.e. easily responding to food-related stimuli such as good smells or the look of attractive food; (3) restrained eating behaviour, when someone is fixed on losing weight. The distribution of the three types of eating behaviour was similar in patients newly diagnosed with DM2 and the general population. At diagnosis, external and emotional eating behaviour were associated with high energy intake and fat intake, and restrained eating behaviour with low energy intake. In women, a high level of external eating behaviour significantly related to a decrease in energy intake after eight weeks, whereas emotional eating showed not to be related. However, after four years no significant correlation was found between changes in energy and fat consumption and the three types of eating behaviour. We concluded that patients newly diagnosed with DM2 have a similar eating behaviour compared with the general population. Further, eating behaviour seems to be related more to the quantity (calorie intake), than to the quality (e.g., energy % fat) of food consumed. Finally, we concluded that women with high scores for emotional eating seem to be less able to make initial dietary changes after being diagnosed and having received dietary advice.

Dieting is generally considered to lead to weight loss, but it is often suggested that it may have the opposite effect. In ***chapter 3.3***, this 'dieting dilemma' was addressed: does dieting suppress or promote excessive food intake and weight gain? In the same cohort we performed an analysis in which results of the DEBQ at diagnosis and after four years were studied in relation to weight gain, change in body mass index, and energy intake (FFQ). If the dieting dilemma were true, we would hypothesize that restrained eating behaviour was the strongest predictor for weight gain or high energy intake four years after diagnosis of DM2.

We found strong correlations between eating behaviour at diagnosis and after four years. This suggests that eating behaviour is an individual trait, and that it remains stable over the years. Next, we found that tendency toward overeating (i.e., emotional or external eating behaviour) at diagnosis was associated with weight gain and energy intake 4 years after diagnosis. In contrast, restrained eating showed no correlation with weight loss or gain. These findings suggest that not dietary restraint but emotional and external eating behaviour may predict the possible failure of a dietary intervention.

In *chapter 4* we describe the effectiveness of alpha-glucosidase inhibitors (AGI) in the treatment of type 2 diabetes mellitus.

In the previously described cohort we performed a randomized controlled trial (***chapter 4.1***) that was designed to assess equivalence between tolbutamide and acarbose with respect to the effect on mean HbA_{1c} in newly diagnosed patients with DM2. Secondary objectives were to compare the effects of both treatments on fasting and post-load blood glucose and insulin levels, lipids and adverse events. Patients who still had a fasting blood glucose between 6.7 and 20 mmol/l eight weeks after diagnosis were randomized to treatment with tolbutamide (n=48) or acarbose (n=48) during 30 weeks. Patients received acarbose (titrated step-wise to a maximum of 100 mg t.i.d.) or tolbutamide (titrated step-wise to a maximum of 2000 mg in three doses) in a double-dummy double blind fashion. The two treatments were considered equivalent if the two-sided 90% confidence interval (CI) for the difference in HbA_{1c} levels would be within the range of -0.4 to 0.4%. We found that both agents reduced the HbA_{1c} and fasting blood glucose levels. The difference in mean HbA_{1c} decrease was 0.6% in favour of tolbutamide (90% CI 0.3-0.9, 95% CI 0.2-1.0). There were no significant differences in postload glucose, fasting and post load insulin levels, or lipids. In the acarbose group, significantly more patients discontinued treatment because of side effects, mostly of gastro-intestinal origin. We concluded that these results do not show equivalence but favour tolbutamide over acarbose as first medical treatment for patients with DM2 in general practice.

AGIs (acarbose, miglitol, voglibose) are widely used in the treatment of DM2, but the recommendations on when to use AGIs and the evidence used for these recommendations appear to be different in various (inter)national guidelines. We conducted a systematic literature review and meta-analysis focusing on the effects of

AGIs versus placebo (or any other intervention) with respect to mortality and (diabetes-related) morbidity, glycemic control, plasma lipids, insulin levels and body weight and side effects (***chapter 4.2***). In total, 41 studies were included (30 acarbose, 7 miglitol, 1 voglibose, 3 combinations). There was no evidence for an effect on mortality or morbidity. Compared with placebo, AGIs had a beneficial effect on HbA_{1c} (acarbose -0.8%, 95% CI 0.6-0.9; miglitol -0.7%, 95% CI 0.4-0.9), fasting and postload blood glucose and insulin levels. None of the AGIs had an effect on plasma lipids. Body mass index decreased by 0.2 kg/m^2 (95% CI 0.1-0.3), compared to placebo. When compared with sulfonylurea, AGIs showed inferior glycemic control, but more decrease of fasting and postload insulin levels. Side effects of AGIs treatment were predominantly gastro-intestinal. When the dose exceeded 50 mg t.i.d., the side effects increased, the blood post-load glucose levels showed more decrease, but the beneficial effect on HbA_{1c} did not increase. Although this effect is probably due to lower compliance in the higher dosage ranges, we concluded that there is no need for dosages higher than 50 mg acarbose t.i.d.

The results of our systematic review on AGIs (especially the lack of reported effects on morbidity and mortality), prompted us to react on an article by Hanefeld et al. (Eur Heart J 2004;25:10-6) in which they suggest that acarbose can prevent myocardial infarctions. Their conclusion was based on a meta-analysis of seven randomized controlled trials. We commented on their approach, concerning the publication bias, heterogeneity, detection bias and confounding factors which are evidently linked to this meta-analysis. In ***chapter 4.3.1*** the controversy is given by means of our letter-to-the-editor and the author's response. ***Chapter 4.3.2*** contains the correspondence on the same topic, but now initiated by Hanefeld et al. in reply to the publication of a synopsis of our Cochrane analysis in Diabetes Care.

Two risk factors for the development of DM2 (and cardiovascular disease) are impaired glucose tolerance (IGT) or impaired fasting blood glucose (IFBG). Both are generally recognized as an expression of abnormal glucose homeostasis that is not (yet) severe enough to meet the criteria for DM2. We investigated the current available evidence for the effect of AGIs in patients with IGT, IFBG or both by a systematic review (***chapter 5***). We searched for randomized controlled trials of at least one-year duration, comparing AGI monotherapy with any other intervention. In total, five trials were included (2360 participants). Only one study was at low risk of bias, the others were at high risk. Meta-analyses were not possible because of the limited data. Data from the first-mentioned study suggest that acarbose decreases the occurrence of DM2 (number needed to treat 10) and cardiovascular events (NNT 50, based on 47 events). However, the study was not initially powered for the latter outcome and this finding needs confirmation in more studies. We concluded that the reduced incidence of DM2 in patients with IGT/IFBG treated with acarbose is obvious, but it remains unclear whether this should be regarded as prevention, delay or masking of diabetes.

In ***chapter 6***, the main conclusions are discussed and suggestions for future research and advices for (guidelines for) diabetes care are given. Also, some reflections are given about this thesis in the light of primary care research.

Chapter 7.2

Samenvatting

Samenvatting

Dit proefschrift is gericht op de wetenschappelijke onderbouwing van twee aspecten van de behandeling en preventie van diabetes mellitus type 2 (DM2) in de huisartspraktijk: dieet en het gebruik van alpha-glucosidaseremmers (AGRs).

Hoofdstuk 1 omvat een korte inleiding over de behandeling van DM2 in de huisartspraktijk en de rol van AGRs en dieet.

In ***hoofdstuk 2*** onderzochten we het wetenschappelijke bewijs voor de effectiviteit van dieet interventies in DM2 aan de hand van systematische reviews. Een systematische review is een methode om divers wetenschappelijk onderzoek op een bondige en heldere manier samen te vatten zodanig dat conclusies kunnen worden getrokken die verder reiken dan de resultaten van de afzonderlijke studies. Wij deden een overkoepelende systematische review van de resultaten, kwaliteit en externe validiteit van bestaande systematische reviews naar dieet interventies voor DM2. Zes systematische reviews werden geïncludeerd met de volgende onderwerpen: dieet interventies zonder nadere specificatie (n=3), chroom suppletie (n=1), visolie (n=1), en kruiden en voedingssupplementen (n=1). In de methodologisch beste systematische reviews (4 van 6) vonden we gunstige effecten van vermageringsdiëten (caloriearme maaltijden) op lichaamsgewicht en visolie supplementen op LDL-cholesterol. Echter, een oordeel over de externe validiteit was niet mogelijk vanwege het ontbreken van belangrijke gegevens. De resultaten van de systematische reviews bleken weinig toe te voegen aan de in de originele studies gepresenteerde data. Wij concluderen dat de kwaliteit en de bruikbaarheid van deze systematische reviews verbeterd zou kunnen worden door de vraagstellingen aan te scherpen, en tegelijkertijd inclusiecriteria voor studies te verbreden.

De eerste stap in de behandeling van DM2 is leefstijladvies in de vorm van (meer) bewegen en dieetaanpassing. Indien deze maatregelen falen wordt medicatie voorgeschreven. In *hoofdstuk 3* rapporteren we onze studies naar dieetaanpassing in patiënten met een nieuw gediagnosticeerde DM2.

Wij deden een prospectief onderzoek in een groep nieuw gediagnosticeerde patiënten met DM2 in de huisartspraktijk. Het doel was om na te gaan hoe de dieetsamenstelling was ten tijde van de diagnose en of dit onder reguliere behandeling veranderde na acht weken en vier jaar (*hoofdstuk 3.1*). Verder keken we naar eetgedrag, en of dit voorspellend was voor veranderingen in dieet (*hoofdstukken 3.2 en 3.3*). In 46 Nederlandse huisartspraktijken werden 144 patiënten gerekruteerd. Na de diagnose en basismeting werden alle patiënten verwezen naar een diëtiste voor een voedingsadvies op maat volgens de vigerende richtlijnen. Acht weken en vier jaar later werden alle patiënten opnieuw bezocht om metingen te verrichten.

Hoewel er welomschreven richtlijnen bestaan over de inname van voedingsvetten voor patiënten met DM2 is maar weinig bekend over de eigenlijke vetconsumptie bij deze groep en of patiënten hun dieet aanpassen nadat de diagnose is gesteld. In ***hoofdstuk 3.1*** rapporteren we de vetconsumptie van de hierboven beschreven studiepopulatie. Vet- en energieconsumptie werd gemeten door middel van een voedselfrequentie vragenlijst met 104 items. Referentiewaarden voor de algemene bevolking kwamen van een bevolkingsonderzoek onder leeftijdsgenoten. Ten tijde van de diagnose hadden patiënten met DM2 gemiddeld een hogere inname van energie, cholesterol, totaal vet en verzadigde vetten vergeleken met de algemene bevolking. Na acht weken daalden deze waarden tot een vergelijkbaar of lager niveau. Na vier jaar bleef vervolgens de gemiddelde energie inname en de proportie verzadigd vet gelijk, steeg de inname van totaal vet licht, en daalde de inname van cholesterol nog verder. Aan de richtlijnen voor de consumptie van totaal en verzadigd vet werd echter maar voldaan in 17% (totaal vet) en 27% (verzadigd vet) van de gevallen. We concluderen dat patiënten met DM2 in staat zijn verbeteringen aan te brengen in hun voedingspatroon en dit vol te houden over meerdere jaren. De behandelrichtlijnen met betrekking tot de inname van totaal en verzadigd vet worden daarbij echter onvoldoende gehaald.

Het is lastig om leefstijlveranderingen, waaronder dieet, door te voeren en te behouden. Daarom is het belangrijk zicht te hebben op factoren die ondersteunend of belemmerend werken. Wij onderzochten eetgedrag in relatie tot de (verandering in) inname van energie en vet, in het eerder beschreven cohort patiënten met DM2 (***hoofdstuk 3.2***). Energie en vetconsumptie werd gemeten zoals hiervoor beschreven. Eetgedrag werd gemeten ten tijde van de diagnose en na vier jaar met de Nederlandse Vragenlijst voor Eetgedrag (NVE). Referentiecijfers werden verkregen van een vergelijkbare groep mensen uit de algemene populatie. In de NVE wordt onderscheid gemaakt tussen drie typen eetgedrag die in meer of mindere mate naast elkaar bestaan: (1) emotioneel eten, dit betekent dat men meer eet als men (negatieve) emoties ervaart; (2) extern eten, hierbij reageert men te laagdrempelig op voedingsgerelateerde prikkels zoals de reuk of aanblik van appetijtelijk eten; (3) lijngericht eten, als men gericht is op afvallen. De mate waarin deze drie typen eetgedrag aanwezig waren was gelijk in de patiënten met DM2 vergeleken met de algemene bevolking. Ten tijde van de diagnose waren emotioneel en extern eten geassocieerd met hoge energie en vet inname, en was lijngericht eten geassocieerd met een lage energie inname. Bij vrouwen was een hoge score voor extern eten, maar niet emotioneel eten, gerelateerd met een daling in energie inname na acht weken. Na vier jaar follow-up werden geen significante correlaties gevonden tussen veranderingen in energie en vetinname en de drie typen eetgedrag. Wij concluderen dat patiënten met nieuw gediagnosticeerde DM2 een eetgedrag hebben dat vergelijkbaar is met de algemene bevolking. Eetgedrag is sterker gerelateerd aan de kwantiteit (energie inname) dan aan de kwaliteit (bijv. percentage vet) van het eten. Tenslotte concluderen we dat vrouwen met hoge scores

voor emotioneel eten minder in staat lijken hun voedingsgewoonten te verbeteren na de diagnose DM2.

Hoewel in het algemeen wordt aangenomen dat men van 'lijnen' afvalt, wordt ook wel beweerd dat het juist een tegenovergesteld effect kan hebben. In ***hoofdstuk 3.3*** onderzochten we dit zogenaamde 'dieting dilemma': zorgt 'lijnen' voor een verbetering of verslechtering van overmatige voedselinname en gewichtsstijging? In het voornoemde cohort analyseerden we de relatie tussen de uitkomsten van de NVE (bij diagnose en na vier jaar) en veranderingen in Body Mass Index (BMI) en energie inname. Indien 'lijnen' inderdaad een negatieve invloed op energie inname en lichaamsgewicht zou hebben, zou lijngericht eten de sterkste voorspeller voor energie inname en BMI na vier jaar zijn.

We vonden sterke correlaties tussen eetgedrag ten tijde van de diagnose en na vier jaar. Dit laat zien dat eetgedrag een individueel kenmerk is dat weinig verandert in de loop van tijd. Vervolgens vonden we dat een neiging tot overeten (een combinatie van extern en emotioneel eten) ten tijde van de diagnose, geassocieerd was met gewichtsstijging en energie inname vier jaar later. We vonden geen relatie tussen lijngericht eten en gewichtsverandering. Deze resultaten suggereren dat niet lijngericht eetgedrag ('lijnen'), maar juist emotioneel en extern eetgedrag mogelijke voorspellers zijn voor succes van een diëtistische interventie.

In hoofdstuk 4 beschrijven we de effectiviteit van alpha-glucosidaseremmers (AGRs) in de behandeling van DM2.

In het eerder beschreven cohort van patiënten met nieuw gediagnosticeerde DM2 deden we een gerandomiseerd onderzoek (***hoofdstuk 4.1***) om na te gaan of acarbose (een AGR) en tolbutamide een gelijk effect hadden op het gemiddelde HbA_{1c}. Secundaire uitkomsten waren het effect van acarbose en tolbutamide op de nuchtere plasma bloedglucose en insuline, bloedglucose en insuline na een orale glucose tolerantietest (OGTT), plasma lipiden, en bijwerkingen. Patiënten die acht weken na de diagnose en dieetadvies nog een nuchtere bloedglucose tussen 6.7 en 20 mmol/l hadden, werden gerandomiseerd in een acarbose (n=48) of tolbutamide (n=48) behandelgroep voor een periode van 30 weken. Patiënten kregen dubbel-blind acarbose (stapsgewijs getitreerd tot maximaal 100 mg drie maal daags), of tolbutamide (stapsgewijs getitreerd tot maximaal 2000 mg in drie doses). De twee behandeling werden geacht gelijkwaardig te zijn als het tweezijdige 90% betrouwbaarheidsinterval (BI) voor het verschil in HbA_{1c} tussen -0.4% en 0.4% zou vallen. We vonden voor beide geneesmiddelen een daling in HbA_{1c} en nuchtere bloed glucose waarden. Het verschil in gemiddelde HbA_{1c} was 0.6% in het voordeel van tolbutamide (90% BI 0.3-0.9, 95% BI 0.2-1.0). Er waren geen significante verschillen in glucose na een OGTT, nuchtere insuline, insuline na een OGTT, en plasma lipiden. In de acarbose groep stopten significant meer patiënten met de behandeling vanwege bijwerkingen, veelal

van gastro-intestinale aard. Wij concluderen dat deze resultaten geen gelijkwaardigheid aantonen van acarbose en tolbutamide en eerder wijzen op een voorkeur voor tolbutamide in de initiële behandeling van patiënten met DM2 in de huisartspraktijk.

AGRs (acarbose, miglitol, voglibose) worden algemeen gebruikt in de behandeling van DM2, maar de aanbevelingen over in welk geval deze middelen te gebruiken en het wetenschappelijke bewijs waar deze aanbevelingen op gestoeld zijn varieert in verschillende (inter)nationale richtlijnen. Wij deden een systematische literatuurstudie en meta-analyse naar het effect van AGRs versus placebo (of enige andere interventie) met betrekking tot mortaliteit en (diabetes gerelateerde) morbiditeit, glykemische controle, plasma lipiden, plasma insuline, lichaamsgewicht en bijwerkingen (***hoofdstuk 4.2***). Wij includeerden 41 studies (30 acarbose, 7 miglitol, 1 voglibose, 3 combinaties) waarin wij geen bewijs vonden voor een effect op mortaliteit en morbiditeit. In vergelijking met placebo hadden AGRs een gunstig effect op het HbA_{1c} (acarbose -0.8%, 95% BI 0.6-0.9; miglitol -0.7%, 95% BI 0.4-0.9), nuchtere bloedglucose en postprandiale insuline en glucose. Geen van de AGRs had een effect op de plasma lipiden. BMI daalde met 0.2 kg/m^2 (95% BI 0.1-0.3) vergeleken met placebo. Vergeleken met sulphonylurea hadden AGRs een inferieur effect op glykemische controle, maar een groter effect op nuchtere en postprandiale insuline. De bijwerkingen van AGRs waren voornamelijk gastro-intestinaal. Bij een dosis hoger dan drie maal daags 50 mg namen de bijwerkingen toe, nam het effect op het postprandiale bloedglucose toe, maar werd het effect op het HbA_{1c} niet groter. Dit is mogelijk te verklaren door een slechtere therapietrouw in de hogere doseringen. We concluderen dat een acarbose dosering hoger dan 150 mg per dag niet zinvol is.

De resultaten van onze systematische literatuurstudie naar AGRs (met name met betrekking tot het ontbreken van bewijs voor effect op mortaliteit en morbiditeit), noodzaakten ons te reageren op een studie van Hanefeld et al. (Eur Heart J 2004;25:10-6) waarin beweerd werd dat acarbose hartinfarcten kan voorkómen. Hun bewering was gestoeld op een meta-analyse van zeven gerandomiseerde studies. Wij becommentarieerden hun studie met betrekking tot de publicatie bias, heterogeniteit, detectie bias en confounders die de resultaten vertekenden. In ***hoofdstuk 4.3.1*** wordt deze kritiek beschreven in een brief aan de redactie en het antwoord van de auteurs. ***Hoofdstuk 4.3.2*** behelst correspondentie over hetzelfde onderwerp, maar nu op initiatief van Hanefeld et al. die in een brief aan de redactie onze Cochrane review becommentariëren.

Gestoorde nuchtere glucose en gestoorde glucose tolerantie zijn risicofactoren voor het ontstaan van DM2 en hartvaatziekten. Beide worden gezien als een uiting van een gestoord glucose metabolisme dat (nog) niet ernstig genoeg is om te voldoen aan de criteria voor DM2. Wij onderzochten het effect van AGRs bij patiënten met gestoorde nuchtere glucose en/of gestoorde glucose tolerantie in een systematische

review (***hoofdstuk 5***). Wij zochten naar gerandomiseerde studies van minstens één jaar, waarin AGR monotherapie werd vergeleken met enige andere interventie. Vijf studies (2360 deelnemers) werden geïncludeerd. Slechts één studie had een laag risico op bias, de andere studies hadden een hoog risico op bias. Vanwege de beperkte hoeveelheid data kon geen meta-analyse gedaan worden. Data van de studie met laag risico op bias liet zien dat acarbose het risico op DM2 (Number-Needed-to-Treat (NNT) 10) en cardiovasculaire aandoeningen (NNT 50, gebaseerd op 47 gebeurtenissen) verminderde. Echter, deze studie had onvoldoende power om het effect op cardiovasculaire aandoeningen te bestuderen en daarom is bevestiging van deze uitkomst wenselijk in nieuwe studies. Wij concluderen dat AGRs de incidentie van DM2 bij patiënten met gestoorde nuchtere glucose en gestoorde glucose tolerantie weliswaar kan verminderen, maar dat het onduidelijk is of dit gezien moet worden als preventie, uitstel, of het maskeren van DM2.

In ***hoofdstuk 6*** bediscussiëren we de belangrijkste resultaten en bespreken we de implicaties voor de praktijk en toekomstig onderzoek. Daarnaast wordt dit proefschrift kort besproken in het licht van huisartsgeneeskundig onderzoek.

Dankwoord

Dankwoord

Het begon allemaal met een wetenschappelijke stage over het nut van neusseptumcorrecties. Met dit project(je) loodste mijn copromotor *Eloy van de Lisdonk* me in 1996 de afdeling binnen. Zijn prikkelende nieuwsgierigheid en enthousiasmerende werkstijl hebben mijn vuur voor huisartsgeneeskunde en onderzoek verder opgepookt. Ik ben dankbaar dat ik me steeds kon blijven verheugen in zijn opgewekte mentorschap. Met de start van het project wat leidde tot dit proefschrift werd ook *Peter Lucassen* mijn begeleider en copromotor. Van hem leerde ik de noodzakelijke lessen in geduld en nauwgezetheid en bovenal om bij alle (schijnbare) zekerheden vraagtekens te plaatsen. Bovendien zag ik bij hem dat het zijn van zowel huisarts als onderzoeker (en prins carnaval) kan leiden tot een organisch geheel.

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De onderkoelde humor van *Bernadette*, de slimme vragen van *Agnes*, de glupjes van *Anek*, de stijladviezen van *Marike*, het rookgordijn van *Antoinette*, de stoicijnse aanpak van *Karleen*, de centen van *Sacha* en het dirigentschap van *Marion* Zonder hen geen praktijk en al helemaal geen werkplezier.

Aan het einde van de dag en aan het einde van dit proefschrift kom ik thuis, in Zeeland en in Nijmegen.

Frans en Elly Meijer hebben, samen met *Tarzan*, *Floris*, *Rover* en *Nelson*, al sinds heugenis een bijzondere plaats. Ik heb me altijd met graagte gewenteld in hun gastvrijheid en onvermoeibare enthousiasme over studie, opleiding en werk. Hopelijk komen zij nog vaak ook in Nijmegen 'wentelen'.

Mijn vrienden zorgen er ook bij mij voor dat 'thirty-something' best dragelijk is, en het adagium 'never a dull moment' is sindsdien onverminderd van kracht gebleven (zie: Timmers, 2004) Ik vertrouw erop dat we elkaar niet uit het hart verliezen nu we richting 'almost-forty' gaan en onze kinderschare groeit.

Met *Gerard*, *Mieke* en *Fike Stikkelbroeck* deel ik niet alleen de liefde voor hun dochter en zus. Ik geniet van hun gezelschap en de gedeelte interesses voor alles wat mooi is.

Mijn *ouders* hebben altijd de juiste balans gevonden tussen actieve steun en me de ruimte geven. Door deze onvoorwaardelijke basis van liefde ben ik gekomen tot waar ik nu ben. De opdracht in dit boekje is een kleine blijk van waardering daarvoor Ook aan *Anneke* met haar *Jan-Hein* en *Jonne* wil ik dank zeggen voor hun niet aflatende steun en gezelligheid

Maar het allerlaatste woord is voor jou, lieve *Nike*. Het berglandschap van het promoveren is ons inderdaad niet vreemd. In de dalen konden we samen schuilen en je liep naast me als ik een moeilijk begaanbaar pad wilde ontdekken. Ik ben dankbaar en gelukkig om nu ook samen met onze dappere woudloper *Alex* onze weg te vervolgen.

Curriculum vitae

Curriculum vitae

Floris van de Laar werd geboren op 30 september 1971 in Beuningen. Later verhuisde hij naar Zeeland (Noord-Brabant) alwaar hij de lagere school volgde (opleider: zuster Odorica). Hij behaalde in 1988 het HAVO diploma en in 1990 het VWO diploma aan het Kruisheren Kollege te Uden. Vervolgens studeerde hij geneeskunde aan de Radboud Universiteit Nijmegen. Hij slaagde voor het doctoraal examen in 1995 en voor het arts examen in 1998. Daarna werkte hij als arts-assistent in het toenmalige Psychiatrisch Centrum Nijmegen tot de start van de huisartsopleiding in 1999. In 2000 startte hij met de gecombineerde opleiding tot huisarts en onderzoeker (AIOTHO). In 2003 voltooide hij de huisartsopleiding waarna hij onderzoekswerk combineerde met waarnemingen in huisartspraktijk en polikliniek GGZ. Vanaf 2005 werkt hij als huisarts en consultatiebureauarts voor Visveld (Lent) in het gezondheidscentrum Frans Huygen. Tevens werkt hij als docent en onderzoeker op de afdeling huisartsgeneeskunde van het UMC St Radboud en is hij coördinator van het Cochrane Primary Health Care Field.
Floris van de Laar is getrouwd met Nike Stikkelbroeck. Samen hebben zij een zoon, Alex.

Stellingen behorend bij het proefschrift

"Diet and alpha-glucosidase inhibition in the early treatment of type 2 diabetes mellitus"

1. Externe validiteit van wetenschappelijk onderzoek is een veelal onderbelicht onderwerp. *(dit proefschrift)*

2. Patienten met type 2 diabetes zijn in staat om na de diagnose blijvende gunstige aanpassingen in het dieet te maken. *(dit proefschrift)*

3. Patienten met type 2 diabetes hebben vergeleken met de algemene bevolking een niet afwijkend eetgedrag. *(dit proefschrift)*

4. Op grond van het beschikbare wetenschappelijke bewijs is het onterecht dat alpha-glucosidaseremmers geen plaats meer hebben in de laatste NHG-standaard. *(dit proefschrift)*

5 Een dosering van acarbose hoger dan drie maal daags 50 mg heeft weinig toegevoegde waarde. *(dit proefschrift)*

6. Alpha-glucosidaseremmers kunnen type 2 diabetes voorkómen. Het blijft echter onduidelijk of dit preventie, uitstel of maskering van de ziekte is. *(dit proefschrift)*

7. In de hedendaagse medische cultuur is het volstrekt logisch om lelijkheid een ziekte te noemen. *(Medisch Contact 2005;60(6):249)*

8. Ik rotzooi maar wat aan. *(Karel Appel)*

9. Als het logisch is, moet het kloppen. *(Henk van den Hoogen)*

10. Het ervaren van kunst maakt de geest ontvankelijk voor nieuwe ideeen

11. Samen leven is de hoeksteen van het gezin.

Floris van de Laar, 6 maart 2008