Randomized Study of Two Different Target Levels of Glycemic Control Within the Acceptable Range in Type 2 Diabetes

Effects on well-being at 1 year

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OBJECTIVE — A randomized trial with 1-year follow-up was conducted in 23 general practices to study the relationship between target values for glycemic control and well-being in type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 176 patients with type 2 diabetes, aged 40–75 years, were included. General practitioners were encouraged to make decisions according to a standardized step-up regimen until the target level of glycemic control was reached. The random allocation to a strict or a less strict target level of glycemic control (fasting capillary glucose <6.5 or <8.5 mmol/l), change in HbA_{1c} and fasting glucose, and initiating insulin or treatment with oral hypoglycemic agents were studied as putative determinants of scores on a type 2 diabetes symptom checklist, a profile of mood states, an affect balance scale, and general well-being. Adjustments were made for baseline scores on the outcome at issue.

RESULTS — Positive affect (an odds ratio [OR] [95% CI] of 0.39 [0.19–0.83]) and perceived treatment burden (OR 0.48 [0.23–0.98]) were unfavorably altered in the group randomly allocated to stricter target levels (fasting capillary glucose <6.5 mmol/l). Patients who had a decrease in HbA_{1c} of 1% or more tended to have comparatively favorable mood (OR displeasure score 0.35 [0.13–0.94]) and general well-being scores at 1 year (ORs of having unfavorable scores ranged from 0.4 to 0.5, NS).

CONCLUSIONS — Perceived treatment burden and positive effect are unfavorably affected by random allocation to a strict target level for glycemic control. Improved glycemic control is associated with favorable mood and possibly general well-being in type 2 diabetes.

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Sustained improvement in health is recognized as an important goal in diabetes care. Among the primary objectives of treatment are relief of symptoms and improvement of quality of life (1,2). In practical diabetes care, a trade-off often has to be made between beneficial and adverse effects of strict glycemic control. Prevention of chronic complications requires glycemic levels as close to normal as possible (3). However, if hypoglycemic episodes occur, and if the treatment regimen is experienced as burdensome, quality of life could be improved by less strict glycemic control.

The objective of the present study was to establish the relationship between target level of glycemic control, glycemic improvement, and other aspects of treatment on the one hand, and several measures of well-being on the other hand, in type 2 diabetes. The study was designed as a randomized clinical trial, comparing the effects of a strict glycemic target level with a less strict target level, within the same management protocol, situated in general practice. Although this design did not yield a meaningful glycemic contrast, it did allow us to study the effects of allocation to strict target levels on well-being experimentally. The influence of changing glycemic levels on well-being, given the absence of an experimental glycemic contrast at 1 year, could be studied prospectively by analysis of within-subject changes in the study cohort as a whole.

Based on previous research at our institution, we anticipated a beneficial effect of good glycemic control on both physical symptoms and emotional well-being (as long as no unacceptable hypoglycemic episodes occur) (4). However, if improvement of glycemic control requires initiation of more intensive modes of treatment (such as taking oral hypoglycemic agents [OHAs] instead of only lifestyle measures, or injecting insulin instead of only taking OHAs), we would logically expect this to hamper well-being, as was found by Jacobson et al. (5). Other studies, some reporting only in passing on this issue, remain inconclusive (6–11).

Differences in study populations and methods of assessment may be held accountable for inconsistent results of previous studies on glycemic control, treatment modality, and quality of life in type 2 diabetes. Using only a general, albeit multidimensional, quality-of-life instrument (and often only including men), other studies in this field have not provided conclusive results as to the relationship between improvement of glycemic control and well-being (6,12–14). Acknowledging the necessity for a multidimensional approach and expecting subtle changes over time in a relatively healthy population, we have

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Abbreviations: ABS, affect balance scale; DSC, diabetes symptom checklist; GP, general practitioner; OHA, oral hypoglycemic agent; OR, odds ratio; POMS, profile of mood states.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

chosen to measure the various aspects of subjective well-being using as specific and sensitive instruments as possible. We addressed symptoms related to diabetes, emotional well-being, positive as well as negative affect, and overall evaluations of well-being and satisfaction.

RESEARCH DESIGN AND METHODS

— A randomized trial was performed, allocating participants to either group 6 or group 8. For patients in group 6, the glycemic target level was a fasting capillary glucose <6.5 mmol/l; for patients in group 8, the target level was <8.5 mmol/l. The treatment itself did not differ between these groups; the only difference was the fasting glucose level below which no glucose-lowering measures were to be taken by the participating general practitioners (GPs). Because the Dutch treatment standard exclusively considered fasting glucose values for daily practice, we informed the GPs that corresponding targets for HbA_{1c} in groups 6 and 8 should be about 6 and 8%, respectively. All GPs were encouraged to make treatment decisions according to a standardized step-up regimen based on a widely used treatment standard of the Netherlands College of General Practitioners (15). Additional features of the regimen were a stepwise protocol for initiation of insulin therapy by the GP and the direct availability to the GP of education facilities for insulin therapy. The regimen had the usual buildup: tablets were to be prescribed, if necessary, considering the fasting glucose target value, and dosages increased up to their usual maximum before other glucose-lowering agents were added. In patients with a BMI >27 kg/m^2, metformin was the first step. If the assigned glucose target value was not reached, a sulfonylurea (either glibenclamide, gliclazide, or glipizide) was to be added. In patients with a BMI <27 kg/m^2, metformin was not considered indicated, so a sulfonylurea was the first step. If the assigned target value was not reached on tablets alone, bedtime intermediate-acting insulin was added (and metformin, if any, discontinued). If the target value was not reached with this combination therapy, a sulfonylurea was to be discontinued and twice-daily injections of a mixture of short- and intermediate-acting insulin was to be started.

At the study center, glycemic control was assessed three times a month. Both fasting glucose and HbA_{1c} were reported to the GP. All patients were requested to contact their GP 2 weeks after each visit to the study center for obtaining therapeutic advice according to the step-up regimen. The duration of follow-up was 1 year. The ethics committee of our university approved the study protocol.

Patients

Assessment of eligibility of potential participants was done by an initial file survey and by subsequently including incident cases between June 1992 and February 1994 in 23 practices (27 GPs) out of a total of 26 general practices in Hoorn, the Netherlands. GPs were asked to identify all their patients with type 2 diabetes aged between 40 and 75 years and of Caucasian ethnicity. A total of 347 patients were identified. Of these, 51 met one of the following exclusion criteria: no established diagnosis of diabetes according to World Health Organization criteria in the absence of glucose-lowering medication (n = 4); carcinoma (n = 6); other comorbidity preventing three monthly visits to the study center (n = 17) or seriously impairing well-being (n = 8); language problems (n = 5); GP objected to participation of patient because of psychological problems (n = 11).

Thus, 296 potential participants—86% of all Caucasian patients with type 2 diabetes within the eligible age range—were invited. Of these, 229 (77%) gave written informed consent. Thirty people (13%) not treated with blood glucose–lowering medication and with a fasting capillary glucose <6.7 mmol/l and an HbA_{1c} ≤6.1% at baseline were regarded as probably nondiabetic and excluded from the study, because they were not expected to contribute to our experimental contrast at 1-year follow-up. Thus, 199 patients were randomized to either group 6 (n = 101) or group 8 (n = 98), of whom 176 had sufficient data to be analyzed at 1 year.

Methods

Determinants and potential confounders. HbA_{1c} (reference 4.3–6.1%) was determined by ion-exchange high-performance liquid chromatography. Capillary whole blood glucose level was assessed with a portable blood glucose monitor (One Touch II; LifeScan, Milpitas, CA). The same devices were used in all participating practices. At each visit, the use of blood glucose–lowering drugs was recorded, and weight was measured.

In a previous cross-sectional analysis, the relationship between glycemic control and well-being often was apparent only in patients with lower neuroticism scores (i.e., more adequate patients). In this study, the Netherlands Personality Questionnaire was administered (16). Its neuroticism scale consists of 21 items reflecting tendencies toward vague fears, vague physical signs, depressed mood, and feelings of insufficiency, resulting in a score with a theoretical range from 0 to 42. People with high scores on this scale are known to report more symptoms and can be described as generally emotional, tense, insecure, or gloomy. Tested in various populations, the neuroticism scale was shown to have an average internal consistency coefficient (α) of 0.86 and a test-retest reliability between 0.77 and 0.86 (16). It was not feasible to assess personality before the start of the study. Forced by the length of the questionnaire and the possibility of mutual interference of the personality and well-being assessments, we chose to postpone the personality assessment, more stable as a concept and as a questionnaire, until 6 months into the study.

A cardiovascular history was considered to be present if the patient reported a myocardial infarction or a stroke to have taken place at any time in the past; if angina pectoris had been confirmed by a cardiologist; if a transient ischemic attack had been diagnosed by a GP or a neurologist; or if typical intermittent claudication, according to a standard questionnaire (17), was present.

Assessment of well-being. The following questionnaires concerning well-being were administered during the baseline and 1-year visits to the study center. We used the type 2 diabetes symptom checklist (DSC-type 2) (18) to measure the presence and perceived burden of diabetes-related symptoms. The DSC-type 2 refers to the month preceding the visit. It consists of 34 items divided over eight scales: hyperglycemic, hypoglycemic, neuropathic pain symptoms, sensibility symptoms, fatigue, cognitive distress, cardiovascular, and ophthalmological. Each item is scored on a frequency scale and, if a symptom is present, also on a discomfort scale. Multiplication of frequency by its corresponding discomfort score yields weighted scores for each scale. In this analysis, weighted scores were used.

The Dutch shortened version of the profile of mood states (POMS) (19) was used to measure emotional well-being. The POMS (32 items) consists of four negative scales (depression, anger, tension, fatigue) and one positive scale (vigor), referring to "the past few days, including today." From these scales, an aggregate mood score can

be calculated. A more accurate measure of mood state, assumed to be less influenced by physical fatigue, is the displeasure scale, which was computed as the sum of the depression, anger, and tension scores.

In addition to the POMS, which predominantly measures negative affect, the widely used affect balance scale (ABS) was administered. The ABS is a 10-item scale that measures happiness, covering both positive and negative aspects (20). In our study, it referred to the previous 3 weeks. All scores on DSC-type 2, POMS, and ABS were transformed to a 0–10 scale, with lower scores indicating higher levels of well-being.

Referring to the previous 3 months, subjects were asked to score their perceived health ("How would you describe your current state of health?") and to give two overall evaluations of their quality of life ("How did you feel, all things considered?" "How satisfied were you, all things considered, with your life?") on a 5-point Likert scale. In addition, patients were asked to indicate on a 4-point Likert scale the perceived burden of their diabetes treatment. All questionnaires were introduced to the patients by the first author and completed by the patients themselves at the study center.

At each visit to the study center, referring to the previous 3 months, patients were asked if they had experienced any episodes of sweating, weakness, hungriness, dizziness, etc. If these symptoms had disappeared shortly upon taking carbohydrate in any form, they were taken to indicate an episode of hypoglycemia. Hypoglycemia was recorded if the episodes did not occur just before a planned meal or in connection with unusual physical exertion (grade 2) and if help from others had been necessary to regain normoglycemia (grade 3).

Statistical analysis. Because of skewed distributions of most outcome measures and/or a substantial proportion of 0 scores, linear regression analysis could not be performed (not even after log transformation of scores), as judged from the distribution of the residuals. Therefore, the 1-year levels of all well-being scores were made dichotomous, so that logistic regression analyses could be performed. This dichotomization generally took place at the median value of the levels at baseline (where 0 indicates a score below the median, and 1 indicates a score above the median). The four overall subjective evaluations were dichotomized between the two most commonly encountered categories. In logistic regression analysis, the influence of a determinant can be expressed as the odds ratio (OR), adjusting for confounding by all the other determinants in the model (21). The SEMs of the regression coefficients and, if necessary, covariances were used to obtain the 95% CIs of the ORs.

The baseline level of each outcome measure and neuroticism was found to be strongly (and independently) related to the level of almost all outcome measures. Therefore, these variables were included as standard control variables in all subsequent analyses.

Initially, we considered the associations between all outcome measures and the randomization group (group 6/group 8; intention-to-treat analysis). Subsequently, while the randomization group remained included as an additional standard variable in all analyses, the strengths of the following potential determinants of well-being were investigated separately: a decrease in HbA_{1c} by ≥1% (HbA_{1c} decrease, yes/no); a decrease in glucose level by ≥1.5 mmol/l (glucose decrease, yes/no); and initiation of a more intensive treatment modality (tablets started, yes/no; insulin started, yes/no). Finally, we included both an HbA_{1c} decrease and initiation of a more intensive treatment modality in the same logistic model to investigate their mutually independent relationships with the outcome measures.

As potential confounders, sex, age, duration of diabetes, and cardiovascular history (yes/no) were included in all models one by one and retained in the model if confounding was considered to be present (i.e., if the magnitude of the OR of a primary determinant was changed by >20% upon inclusion of the variable) or if inclusion yielded smaller SEMs of the coefficients of the primary determinants. Product terms of an HbA_{1c} decrease with age, sex, baseline HbA_{1c}, and neuroticism were statistically tested one by one (at the 95% CI) to investigate the relationship between an HbA_{1c} decrease and all outcomes at different levels of these potential determinants (effect modification). Before calculating product terms, the component variables were centered whenever necessary to prevent collinearity. While testing the significance of the product terms, the component variables were retained in the models.

RESULTS — Follow-up was completed by 183 out of 199 participants (92%). Eight patients dropped out of the study because they found it too burdensome to make three-monthly visits to the study center (not because of particularly bad glycemic control). Six patients were lost to follow-up because they moved out of the area or stopped showing up because of illness unrelated to diabetes, and two patients died. In total, 176 (96%) patients had sufficient data to be included in the analyses. We additionally had to exclude two subjects from the analyses: at the baseline or 1-year visit, major life events had influenced their quality of life such that inclusion would disturb many analyses. For those who completed follow-up, attendance at follow-up visits at the study center was virtually 100%. Compliance with our encouragement to visit the GP after each of the study visits was probably less satisfying, which is discussed in a companion manuscript (F.E.E.v.d.D., J.N.D.d.N., R.J.H., J.H. Dekker, L.M.B., unpublished observations).

At 1 year of follow-up, treatment had been intensified more in group 6 than in group 8. In group 6, 53% of patients had taken one or more treatment steps, compared with 40% in group 8 (P = 0.001, adjusted for baseline glycemic level). In spite of this, no significant difference in glycemic level between groups 6 and 8 had been established. In group 6 (n = 93), mean (± SD) HbA_{1c} and fasting glucose decreased nonsignificantly from 7.2 ± 1.5 to 7.1 ± 1.2% (P = 0.15) and from 7.8 ± 2.1 to 7.4 ± 1.8 mmol/l (P = 0.06), respectively. In group 8 (n = 81), HbA_{1c} and glucose values were already higher than those in group 6 at baseline (P = 0.04 and 0.02, respectively) and decreased significantly from 7.8 ± 2.0 to 7.4 ± 1.5% (P = 0.005) and from 8.7 ± 2.8 to 7.3 ± 2.1 mmol/l (P < 0.001), respectively.

Table 1 shows baseline characteristics and changes during follow-up of the total population as well as for those who experienced an HbA_{1c} decrease of ≥1% compared with those who did not. In addition, the same data are presented for the subgroup of the total population in whom insulin treatment was started during follow-up. The cut-off level of an HbA_{1c} decrease of ≥1% is depicted in Fig. 1 (- - - -), which shows the HbA_{1c} change for all patients, stratified for treatment modality initiated during follow-up. As can be seen in Table 1, patients with a ≥1% HbA_{1c} decrease, compared with those without, were in less favorable glycemic control (P < 0.001) and less intensively treated at baseline. In the subgroup of the study population in which insulin treatment was initiated (n = 15), a

Table 1—*Baseline characteristics and follow-up experience of the total population, of the population divided by two levels of an HbA_{1c} decrease, and of the subgroup in whom insulin treatment was started during follow-up*

	Total	HbA_{1c} decrease of <1.0%	HbA_{1c} decrease of ≥1.0%	Insulin started
n	174	132	42	15
% Male	44.8	44.7	45.2	26.7
Age (years)	63.6 ± 8.3	63.9 ± 8.2	62.7 ± 8.7	63.4 ± 8.5
Diabetes duration (years)	4.0 (2.0–8.4)	3.4 (1.9–8.0)	5.3 (2.6–8.7)	5.3 (2.6–13.3)
Neuroticism >75th percentile (%)	24.7	23.5	28.6	33.3
Baseline treatment (%)				
Diet only	26.4	24.2	33.3	0.0
OHA	55.8	57.6	50.0	100.0
OHA + insulin	17.8	18.2	16.7	0.0
Treatment at 1 year (%)				
Diet only	16.7	19.7	7.1	0.0
OHA	57.5	56.1	61.9	0.0
OHA + insulin	25.9	24.2	31.0	100.0
Baseline HbA_{1c} (%)	7.5 ± 1.8	6.9 ± 1.2	9.5 ± 1.8	9.4 ± 2.0
Δ HbA_{1c} (%)	−0.3 ± 1.1	+0.2 ± 0.7	−1.8 ± 0.8	−0.7 ± 1.3
Baseline fasting capillary glucose (mmol/l)	8.2 ± 2.4	7.5 ± 1.8	10.4 ± 2.9	10.7 ± 3.0
Δ Glucose (mmol/l)	−0.9 ± 2.3	−0.3 ± 1.9	−2.6 ± 2.8	−3.3 ± 2.9
Baseline BMI (kg/m²)	28.3 ± 3.8	28.0 ± 3.7	29.4 ± 4.0	30.9 ± 4.3
Δ BMI (kg/m²)	+0.1 ± 1.3	+0.1 ± 1.2	+0.0 ± 1.5	+1.1 ± 1.3
Hypoglycemia (grade 2) (%)				
3 months preceding baseline	8.0	9.8	2.4	0.0
3 months preceding visit at 1 year	7.5	6.8	9.5	6.7
Cardiovascular history (%)	21.3	20.4	23.8	26.7

Data are means ± SD, median (interquartile range [i.e., between the 25th and 75th percentiles]), %, or *n*. For hypoglycemia, grade 3 (help from others necessary to regain normoglycemia) did not occur. A cardiovascular history included myocardial infarction, angina pectoris, stroke, transient ischemic attack, or intermittent claudication. Δ, change during follow-up.

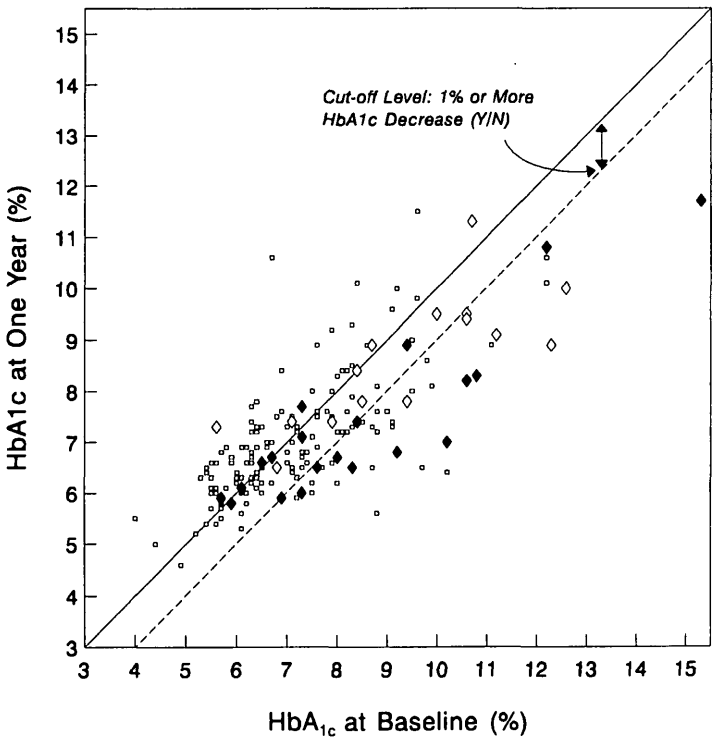

Figure 1—*HbA_{1c} at baseline and at 1 year. - - - -, the cut-off level between an HbA_{1c} decrease of ≥1% and no decrease, as used in the analyses. In the reference group, treatment with neither OHAs nor insulin was started. Y/N, yes/no.* ◆, *Tablets started;* ◇, *insulin started;* □, *reference.*

substantial decrease in fasting glucose (P = 0.001) and HbA_{1c} values (P = 0.05) was attained (Table 1, right column). As expected, these patients, on average, gained some weight during follow-up (P = 0.007). No hypoglycemic complaints more severe than grade 2 were reported at baseline or during follow-up.

In Table 2, baseline and follow-up data on selected outcome measures are given for the same groups as in Table 1. In this relatively healthy study population, median scores at baseline on the three questionnaires (first six rows) were low, indicating that many patients reported satisfactory well-being. Although mean changes of these scores during follow-up are also small, the reported SDs indicate that substantial changes did take place. Scoring percentages on the four separate items after follow-up, as compared with baseline, seem to be consistent with the changes on the three questionnaires.

By calculating rank-correlations between neuroticism and well-being scores at baseline, it was confirmed that people with high neuroticism scores tend to report more symptoms (r = 0.47 for DSC total, P <

Table 2—*Baseline levels and mean change during follow-up of selected measures of well-being for the total population, for the population divided by two levels of an HbA_{1c} decrease, and for the subgroup in whom insulin treatment was started during follow-up*

	Total	HbA_{1c} decrease of <1.0%	HbA_{1c} decrease of ≥1.0%	Insulin started
DSC-type 2, hyperglycemic score				
At baseline	0.6 (0.0–2.5)	0.6 (0.0–2.3)	0.6 (0.0–4.4)	1.0 (0.4–3.8)
Change over 1 year	−0.2 ± 1.8	+0.0 ± 1.6	−0.8 ± 2.1	−0.9 ± 3.0
POMS, displeasure score				
At baseline	0.7 (0.2–1.4)	0.7 (0.1–1.4)	0.8 (0.4–1.7)	1.5 (0.4–3.2)
Change over 1 year	+0.1 ± 1.1	+0.2 ± 1.1	−0.1 ± 1.3	+0.8 ± 1.4
ABS, total score				
At baseline	2 (1–3)	2 (1–3)	2 (1–3)	3 (2–4)
Change over 1 year	−0.2 ± 2.0	−0.1 ± 1.9	−0.5 ± 2.2	+0.1 ± 3.0
How did you feel . . . ? (% "good" or better)				
At baseline	73.1	76.9	61.0	53.3
At 1 year	74.7	73.1	80.0	40.0
How would you describe . . . health . . . ? (% "good" or better)				
At baseline	64.9	69.9	51.2	33.3
At 1 year	71.9	70.2	77.5	46.7
How satisfied were you with your life . . . ? (% "satisfied" or more)				
At baseline	83.0	84.6	78.0	66.7
At 1 year	79.5	77.1	87.5	60.0
How burdensome . . . treatment . . . diabetes? (% more than "not burdensome")				
At baseline	39.2	42.3	29.2	60.0
At 1 year	38.6	40.5	32.5	53.4

Data are means ± SD, median (interquartile range), or proportions. All scores on the questionnaires were transformed to a 0–10 scale, where higher scores are unfavorable.

0.001). As expected, high scores were also associated with worse emotional well-being ($r = 0.57$ for POMS displeasure, $P < 0.001$), general well-being ($r = 0.28$, $P < 0.001$), satisfaction ($r = 0.21$, $P = 0.006$), and perceived health ($r = 0.24$, $P = 0.002$).

Logistic regression analyses

ORs >1.00 indicate that the determinant (allocation to group 8, HbA_{1c} decrease, or insulin started) is associated with unfavorable well-being; ORs <1.00 indicate the opposite. CIs not including 1.00 are statistically significant at the 5% level. In our analysis of the randomization group, allocation to group 8 (i.e., a less strict glycemic target level) was significantly more favorable than allocation to group 6 with regard to whether the treatment was experienced as burdensome (OR [95% CI] 0.48 [0.23–0.98]) and with regard to the positive scale of the ABS (OR 0.39 [0.19–0.83]). In addition, there were trends toward a favorable effect of allocation to a less strict glycemic target in the overall subjective evaluations of general well-being (OR 0.51 [0.23–1.15]) and perceived health (OR 0.46 [0.21–1.04]). Additional adjustment for baseline HbA_{1c}—considered necessary because of the 0.6% difference at baseline between the randomization groups—did not affect these results. We found no effects of the randomly allocated target value with regard to scores on POMS or DSC-type 2.

Table 3 shows relationships, expressed as ORs (with 95% CIs) adjusted for baseline level of the outcome, neuroticism, and randomization group, of an HbA_{1c} decrease and of insulin being started with all outcome measures. Focusing on psychological well-being (POMS, ABS, and overall evaluations of well-being), almost all ORs associated with an HbA_{1c} decrease are <1.00, while almost all ORs associated with insulin being started are >1.00. Considered separately, however, few ORs are significant in statistical terms. Furthermore, the 95% CIs of the ORs associated with insulin being started, are wide, which is related to the small number of insulin starters ($n = 15$). Tablets being started did not significantly affect any outcome measure in our study (data not shown), despite a mean improvement in HbA_{1c} of 1.2% ($P < 0.001$) in that subgroup. The relationships of the glucose decrease with the outcome measures hinted in the same direction as was found for the HbA_{1c} decrease, only to a statistically less significant degree (data not shown).

Overall, none of the DSC-type 2 scales is influenced by an HbA_{1c} decrease, except for a relative increase in neuropathic sensibility symptoms (Table 3). However, statistically significant product terms for an HbA_{1c} decrease and age ≥70 years (yes/no) showed that associations of the HbA_{1c} decrease with the hyperglycemic and the cardiovascular scales of the DSC-type 2 were different for people ≥70 years of age compared with the rest of the population. In the older age-group ($n = 48$), there were beneficial relationships between the HbA_{1c} decrease on the one hand and cardiovascular score (OR 0.18 [0.06–0.55]) and hyperglycemic score (OR 0.20 [0.06–0.64]) on the other hand, whereas in the rest of the population, no relationships were found (OR 1.68 [0.59–4.80] and OR 1.41 [0.51–3.89], respectively). Considering the fact that the hypoglycemic scale of the DSC-

Table 3—*Overall relationships of an HbA_{1c} decrease (≥1%; yes/no) and initiation of insulin treatment (yes/no) during follow-up with all outcome measures*

	HbA_{1c} decrease	Insulin started
DSC-type 2		
Fatigue	1.17 (0.46–2.98)	1.27 (0.27–5.96)
Hyperglycemic	0.84 (0.35–2.01)	0.36 (0.09–1.51)
Neuropathic sensibility symptoms	2.37 (1.05–5.37)	4.43 (1.17–16.7)
Neuropathic pain symptoms	0.71 (0.28–1.77)	2.72 (0.70–10.6)
Ophthalmological	0.88 (0.39–2.00)	0.78 (0.22–2.73)
Cardiovascular	0.96 (0.39–2.38)	1.06 (0.25–4.42)
Cognitive distress	1.40 (0.54–3.64)	2.80 (0.59–13.2)
Hypoglycemic	0.69 (0.29–1.63)	3.13 (0.82–11.9)
POMS		
Depression	1.13 (0.45–2.85)	4.14 (0.88–19.6)
Anger	0.46 (0.18–1.14)	1.56 (0.37–6.50)
Tension	0.77 (0.31–1.91)	3.82 (0.75–19.4)
Subtotal: displeasure score	0.35 (0.13–0.94)	1.25 (0.26–6.06)
Vigor	1.45 (0.65–3.24)	4.12 (1.08–15.7)
Fatigue	0.71 (0.28–1.81)	0.96 (0.21–4.34)
Total	1.02 (0.38–2.74)	2.10 (0.40–10.9)
ABS		
Positive	0.53 (0.22–1.28)	1.31 (0.38–4.46)
Negative	0.52 (0.17–1.61)	0.56 (0.10–3.09)
Total	0.49 (0.19–1.24)	1.17 (0.31–4.43)
General well-being		
How did you feel . . . ?	0.54 (0.19–1.49)	3.73 (1.00–14.0)
How satisfied were you with your life . . . ?	0.39 (0.12–1.23)	1.49 (0.37–5.99)
How would you describe . . . health . . . ?	0.51 (0.19–1.37)	1.72 (0.46–6.37)
How burdensome . . . treatment . . . diabetes?	0.83 (0.36–1.94)	1.62 (0.47–5.64)

Data are OR (95% CI). ORs >1.00 indicate unfavorable well-being; ORs <1.00 indicate favorable well-being; dichotomization took place at the median of the baseline values. All ORs are adjusted for baseline level of the outcome measure at issue, neuroticism, and randomization group.

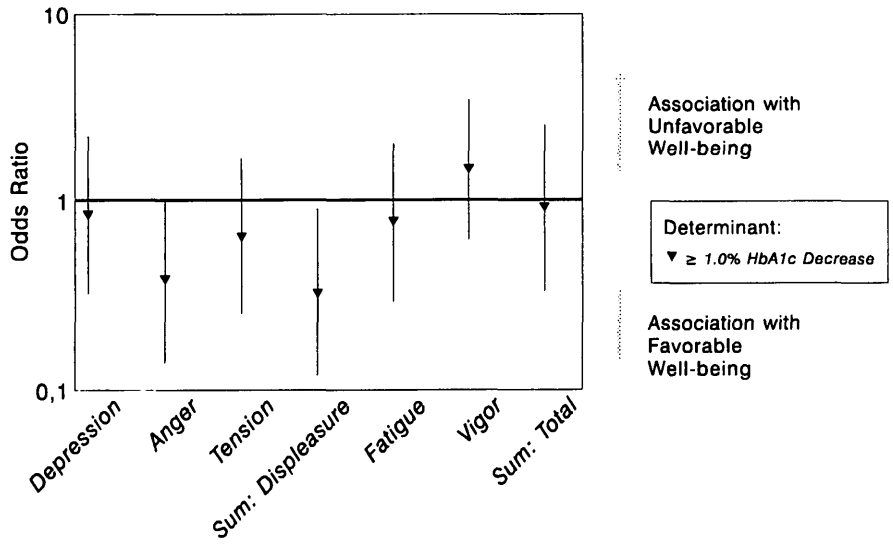

Figure 2—*Associations between an HbA_{1c} decrease and the scores on the POMS at 1 year. ORs with 95% CIs were adjusted for the effects of changes in treatment modality, baseline level of the outcome measure at issue, neuroticism, and randomization group. Outcome measures were dichotomized at the baseline median value.*

type 2 contains no real physical signs, we also performed logistic regression analysis with self-reported hypoglycemic complaints in the 3 months preceding the 1-year visit as the outcome measure. This analysis yielded no significant findings. The frequency of hypoglycemia was, however, low (Table 1).

In Fig. 2, ORs and 95% CIs are shown for the associations between an HbA_{1c} decrease and the scores on the POMS, independent of (i.e., adjusted for the effects of) changes in treatment modality. An HbA_{1c} decrease is associated with favorable scores on the displeasure scale (OR <1.00), while the (statistically nonsignificant) associations with scores on the three components of this scale (depression, anger, and tension) at least exhibit the same direction. The product term for an HbA_{1c} decrease and gender proved to be statistically significant in the model of the tension scale of the POMS: for men, no relation was found between an HbA_{1c} decrease and tension (OR 1.77 [0.48–6.6]); for women with an HbA_{1c} decrease, however, there tended to be a concordant decrease in tension score (OR 0.29 [0.08–1.05]).

Adjusted ORs and 95% CIs for associations between the HbA_{1c} decrease on the one hand and the ABS and the four separate questions on general well-being on the other hand, are presented in Fig. 3. In these general well-being scores, trends consistent with the findings in the POMS displeasure scale are apparent.

The associations between an HbA_{1c} decrease, tablets being started, and insulin being started on the one hand and the measures of well-being on the other were not substantially influenced by mutual adjustment of the determinants. For the HbA_{1c} decrease, this can be seen by comparison of the ORs in Table 3, left column, and the mutually adjusted ORs in Figs. 2 and 3. Apart from the interactions described above, no effect modifications by age, gender, baseline HbA_{1c}, or neuroticism were identified. Additional adjustments for confounding were not necessary. Our results did not change substantially as a result of dichotomization of the outcome measures at the 75th percentile instead of the median.

The larger number of items in the displeasure score of the POMS—which we consider to be our most accurate measure of mood state—and the accompanying smoother distribution of values made it possible to perform the more accurate and powerful method of linear regression analysis for this particular score, which lacks the neces-

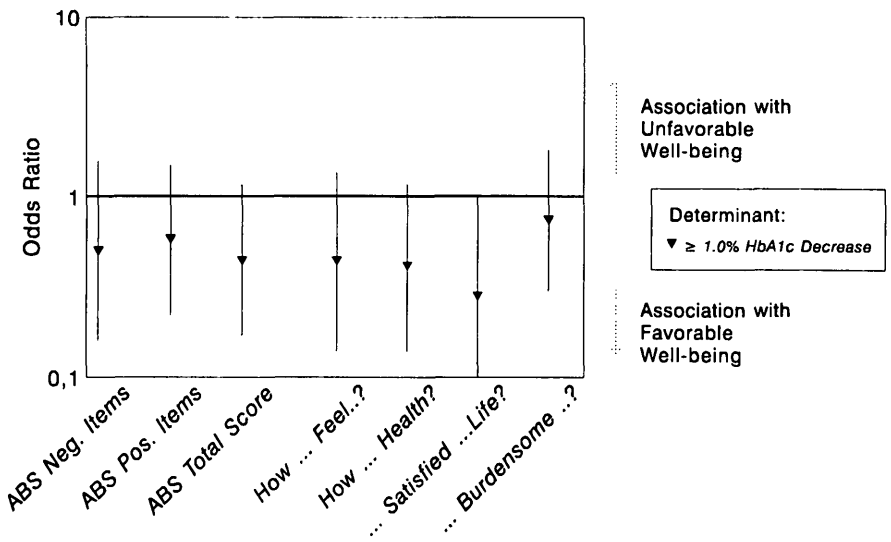

Figure 3—*Associations between the HbA_{1c} decrease and scores on the ABS and overall evaluations of well-being at 1 year. ORs with 95% CIs were adjusted for change in treatment modality, baseline level of the outcome measure at issue, neuroticism, and randomization group. Outcome measures were dichotomized at the baseline median value (ABS) or between the two most commonly encountered responses (overall evaluations).*

sity of collapsing the outcome by dichotomization. As expected, the association of an HbA_{1c} decrease with mood was confirmed by this linear regression analysis (P = 0.01); an HbA_{1c} decrease explained 2.4% of the variation in the displeasure scores that remained after adjustment for baseline levels. Adjusted displeasure scores of patients with an HbA_{1c} decrease were 15% (95% CI: 4–26%) lower than those of patients without, while adjusted scores of patients who started insulin were 29% (7–57%) higher than the scores of those who did not. Again, the contribution of tablets being started was nonsignificant (P = 0.9).

CONCLUSIONS — This experiment involved random allocation to a stringent or a less stringent target for fasting glucose in type 2 diabetic patients. Random allocation to the more stringent target level (fasting glucose <6.5 mmol/l, group 6), as opposed to accepting somewhat higher glucose levels (group 8), appeared to be associated with a greater perceived burden of treatment and less positive affect. By design, and despite better glycemic control at baseline, treatment was intensified in significantly more patients in group 6 compared with group 8. However, the proportion of patients with glucose values below the target value rose only slightly from 28 to 31% in group 6, while in group 8, this percentage rose from 59 to 80% (data not shown). We assume that our study design led to a more rigid adherence to treatment goals, which implies that allocation to a strict target value would be more frustrating, probably to both patient and doctor. Therefore, it might be postulated that the adverse effect of target levels is attributable only to patients who were not able to reach their assigned target level during follow-up. On post hoc stratified analysis, this appeared to be the case for positive affect but not for perceived burden of treatment (data not shown). This suggests that reaching strict target levels may diminish unhappiness but does not necessarily make patients perceive the treatment as less burdensome.

A relevant difference in HbA_{1c} between groups 6 and 8 could have provided additional trial data on the relation between glycemic control and well-being. In the absence of such a contrast, we have had to settle for the next-best solution regarding this issue: cohort analysis of within-subject changes in glycemic control as a determinant of well-being, which had already been planned for the analysis of changes in treatment modality.

Despite the above-described experimental results showing possible side effects of setting stringent glycemic targets, these further analyses suggest that in a population with relatively well-controlled type 2 diabetes recruited from general practice, further improvement in glycemic control (independent of the effects of the random target level) is generally accompanied by a more favorable mood, overall satisfaction, and well-being, but that the size of these effects is not large. The relationship between HbA_{1c} and well-being we reported earlier, based on cross-sectional data, is confirmed by this prospective study (4).

Only in the prospective setting could the psychological impact of initiating more intensive treatment modalities (taking tablets instead of diet alone, or starting daily insulin injections) have been determined. However, during 1 year of follow-up of this study population, insulin was initiated in only a small number of patients, so that the estimates of the effects did not turn out to be precise enough to allow any conclusions on this issue. At first glance, the initiation of insulin treatment seems associated with unfavorable well-being, albeit not significantly so in statistical terms: almost all of the ORs in the right column of Table 3 are >1. Upon closer inspection of the crude values of the 15 patients who initiated insulin treatment, it appeared that the majority of these patients reported no dramatic changes in measures of well-being. For example, the association we found between insulin being started and general well-being (OR 3.73 [1.00–14.0], Table 3) appeared to have come about through 3 people reporting worse, 1 person reporting better, and 11 people reporting an equal score on this scale. In addition, the OR is a relative measure, which means that an allegedly unfavorable effect may be just an expression of a lack of favorable effect relative to the rest of the population.

Note that in this small subgroup, baseline well-being was already worse (P = 0.05 for general well-being) than in the population as a whole (Table 2). Although our results were adjusted for baseline level, it should be interesting to investigate in a future study whether people with adverse well-being react differently to initiation of insulin treatment, as compared with people with favorable well-being. Further longer-term studies are required to assess whether short-term adverse effects, if any, are temporary. Interestingly, the step from dietary measures alone to tablet treatment did not have a favorable or unfavorable effect on any well-being score used in our study.

Although the glycemic changes in our already intensively treated population seem small, one should keep in mind that the natural history of type 2 diabetes probably would have led to slightly higher HbA_{1c} lev-

els after 1 year, instead of slightly lower ones (26). A general problem posed by repeating self-administered questionnaires after an intervention is a possible change of the internal standard of measurement during follow-up, creating so-called response shift bias (22). This does have a role to play in interpreting changes in well-being scores in the total population, but it does not prevent comparison of changes between groups.

The association we found between the HbA_{1c} decrease and the neuropathic sensibility symptom score is interesting with respect to the often-cited clinical observation that neuropathic pain can increase paradoxically upon institution of good glycemic control, possibly attributable to structural repair (23). In our population, neuropathic pain symptoms were, however, scarcer than sensibility symptoms. Moreover, the sensibility scale of the DSC-type 2 has been found to correlate with clinical and neurophysiological assessments in known diabetic neuropathy, while the neuropathic pain scale did not correlate with these measures (24). The absence of an association between the HbA_{1c} decrease and the fatigue and vigor scales of the POMS is consistent with a similar absence for the fatigue scale of the DSC-type 2 (Fig. 2 and Table 3).

By force, the results concerning the HbA_{1c} decrease were based on within-subject changes and not on a contrast attained through randomization. Our observations regarding the causes of the absence of a difference in glycemia at follow-up between groups 6 and 8 are the subject of an as yet unpublished study (F.E.E.v.d.D., J.N.D.d.N., R.J.H., J.H. Dekker, L.M.B., unpublished observations). Although the results of this follow-up study are more convincing in combination with our earlier cross-sectional findings (4), this issue could be further explored by establishing experimental contrasts, as is being done in studies currently under way (25,26). There are some plausible explanations for discrepancies between study results in this field, apart from the fact that the alleged relation is simply not a strong one and therefore inherently difficult to confirm. Studies that found a relationship between glycemic control and perceived health (i.e., our study and a study by Nerenz et al. [12]) included both men and women. Previous negative studies included only men (6,13,14). In our view, these negative results could be attributable to floor effects, especially in men, in whom scores are generally lower than in women (27). Furthermore, discrepancies between studies might be attributable to differences in severity of disease characteristics and complications. For example, in an analysis similar to the present, no relation was found within a population where insulin use and multiple diabetic complications were much more prevalent (6). Finally, to our knowledge, there are no other studies that have been able to adjust for neuroticism, which is a major determinant of well-being scores.

Of course, it is far from ideal that personality was assessed after 6 months instead of at the beginning. We have found no indication that neuroticism scores were differentially affected by study participation: mean neuroticism scores in groups 6 and 8 were equal (12.0 vs. 13.2 on a 0–42 scale; $P = 0.4$).

Our findings are in accordance with the idea that as to well-being, modest short-term benefits of improved glycemic control exist but may be paid for by less positive feelings and/or an increased perceived burden of treatment in some of the patients allocated to strict target values for glycemic control. This finding, although principally not speaking against intensification of treatment whenever considered necessary, would call for individual stepwise target setting to avoid frustration. No unacceptable hypoglycemic episodes occurred during our study, reconfirming the relative safety of intensification of treatment in type 2 diabetes. For the assessment of long-term effects of changes in glycemic level, more research is necessary not only on well-being in the longer term but also on the onset of late complications in type 2 diabetes (3).

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