Association of Antidiabetic Therapies to Glycemic Control and to Body Weight in Type 2 Diabetes: A German Multicenter Analysis on 9.294 Patients

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Key words
• diabetes treatment
• obesity
• glycemic control
• quality management

Abstract
Glycemic and body weight control are two outstanding goals in the treatment of patients with type 2 diabetes that often are not appropriately achieved. This observational study evaluates whether treatment by quality controlled diabetes centers generates an improvement in this regard and focuses on associations with different therapies. Data of 9.294 type 2 diabetic patients (mean age 66.9±11.6 years, mean diabetes duration 12.4±9.2 years) from 103 German diabetes centers were assessed by a standardized, prospective, computer-based diabetes care and outcome documentation system (DPV-Wiss-database). Therapeutic concepts included lifestyle intervention (n=1.813), oral antidiabetics (OAD, n=1.536), insulin (n=4.504) and insulin plus OAD (n=1.441). HbA1c and body weight were compared before and after a stable therapeutical period of 1.07±0.3 years. Change in HbA1c (%): all patients 7.4±1.6–7.0±1.3, lifestyle intervention 7.5±1.9–6.9±1.5, OAD 6.7±1.1–6.5±1.0, insulin 7.6±1.6–7.2±1.4, insulin plus OAD 7.5±1.5–7.2±1.3; each p<0.05. Change in body weight (kg): all patients +0.08±0.7, n.s.; lifestyle intervention –0.28±0.20, OAD –0.56±0.13, each p<0.05 [metformin –0.77±0.21, sulfonylurea drugs –0.75±0.34, each p<0.05; glitazones +0.62±0.70, α-glucosidase inhibitors –0.22±0.76, each n.s.], insulin +0.27±0.10, insulin plus OAD +0.63±0.14, each n.s. In summary, lifestyle, metformin or sulfonylurea drug treatment resulted in HbA1c-values below 7.0% plus a significant weight reduction. Insulin treatment-associated concepts resulted in HbA1c-values slightly above 7.0% without body weight alterations. These “real life” data underline that a specialised and quality controlled diabetes care is able to achieve significant treatment results even in patients with disease progression and a high proportion of insulin therapies.

Introduction
The incidence of type 2 diabetes (T2DM) has increased dramatically in recent years. Obesity and weight gain are the main risk factors for the development of T2DM, and almost 90% of newly diagnosed T2DM patients are considered overweight or obese (Buchwald et al., 2009; Rosen and speigelman 2006). Since T2DM patients exhibit a number of serious cardiovascular risk factors that are associated with increased morbidity and mortality (Narayan et al., 2003; Schramm et al., 2008; Howard et al., 2006), antidiabetic therapy should focus on the combined vascular and metabolic factors that may lead to a cardiovascular event. There is growing evidence on visceral adipose tissue as a complex and highly active metabolic and endocrine organ and on the presence of excess visceral fat as a central component of cardiovascular risk. Thus, abdominal obesity often is associated with insulin resistance, hyperglycemia, dyslipidemia, hypertension, and prothrombotic and proinflammatory states (Whitlock et al., 2009; McGill et al., 2002; Fontaine et al., 2003; Després et al., 2001). Weight loss intervention should therefore represent an important tool in the therapy for patients with T2DM in order to improve glycemic control and to reduce cardiovascular risk factors. However, several recent studies demonstrate that patients treated for T2DM frequently stay obese or even gain weight (Barnett et al., 2007; UK Prospective Diabetes Study, 1998; Gerstein et al., 2008; Patel et al., 2008).

An inadequate consideration of weight control might also have played a role in recent randomised controlled trials investigating the effect
of an intensive glucose-lowering regimen on death and cardiovascular outcomes compared with a standard regimen. A meta-analysis of these studies revealed that a mean reduction of 0.9% HbA1c was associated with a 17% reduction of non-fatal myocardial infarctions and a 15% reduction of coronary heart disease events, but had no effect on stroke and all-cause mortality (Ray et al., 2009). The initial patient BMI of 30 kg/m² (Ray et al., 2009) was, however, not addressed and even increased by the glucose-lowering regimens (UK Prospective Diabetes Study, 1998; Gerstein et al., 2008; Patel et al., 2008). On the other side, several other studies primarily representing routine medical care and/or primary care data demonstrated an insufficient glucose control of patients with T2DM, and that particularly patients with a disease progression require more intensive and complex treatment (Saaddine et al., 2006; Harris SB et al., 2006; Liebl et al., 2001; Rihi et al., 2002; Huppertz et al., 2009).

In the present observational study we analysed data of specialised diabetes centers that make use of an electronic diabetes documentation and quality management system. In detail, we studied anonymised data of patients that were regularly transferred from specialised German diabetes centers to the DPV-Wiss-database, a central computer-based database for documentation of diabetes care and outcome. One objective of this analysis was to provide representative “real life” data from such quality controlled diabetes centers concerning clinical key parameters such as age, duration of diabetes and treatment modality. Furthermore, we focused on associations of different stable, antidiabetic, center-controlled therapies with both, glycemic control and body weight.

**Patients and Methods**

**Description of the database**

The DPV-Wiss-database is a standardized, prospective, multicenter, computer-based documentation of diabetes care and outcome that has been approved by the ethics committee of the university of Ulm, Germany. Data are recorded locally at the participating centers and transferred for central analysis after anonymisation. Inconsistent data are reported back to the centers every 6 months for correction.

**Study design and description of patients**

By September 2009, 9,294 patients with T2DM treated by 103 qualified diabetes treatment centers were selected from the database as described (Fig. 1). For each patient, the current HbA1c-value and body weight were compared with data directly before starting the respective therapy representing a stable therapeutic period without any alterations for at least 6 months. Based on local reference ranges, HbA1c values were mathematically adjusted to the DCCT reference range (4.05 – 6.05 %; DCCT, 1993) using the MOM (multiple of the mean) method. In the beginning of the analysed treatment period the mean age of the patients was 65.8 ± 11.6 years, the mean duration of diabetes was 11.4 ± 9.2 years and the mean body mass index (BMI) was 25.5 ± 7.6 kg/m² (Table 1). The mean gender distribution was balanced (52.2% male). Treatment was classified either as lifestyle intervention (n = 1,813, mean duration of treatment period 1.0 ± 0.3 years, mean duration of diabetes 8.8 ± 8.7 years, mean HbA1c 7.5 ± 1.9%), oral antidiabetic therapy (n = 1,536, mean duration of treatment period 1.1 ± 0.3 years, mean duration of diabetes 6.5 ± 6.5 years, mean HbA1c 6.7 ± 1.1%), metformin 73.0%, long-acting sulfonylurea drugs 39.7%, glitazones 14.4%, short-acting sulfonylurea drugs 12.2%, α-glucosidase inhibitors 6.5%, insulin treatment (n = 4,504, mean duration of treatment period 1.1 ± 0.3 years, mean duration of diabetes 14.0 ± 9.6 years, mean HbA1c 7.6 ± 1.6%), rapid acting insulin analogues 32.5%, long acting insulin analogues 26.0%) or treatment with oral antidiabetics plus insulin (n = 1,441, mean duration of treatment period 1.1 ± 0.3 years, mean duration of diabetes 11.7 ± 7.8 years, mean HbA1c 7.5 ± 1.5%), rapid acting insulin analogues 38.9%, long acting insulin analogues 43.7%, metformin 80.2%, long-acting sulfonylurea drugs 20.9%, short-acting sulfonylurea drugs 9.4%, glitazones 8.7%, α-glucosidase inhibitors 4.4%).

**Statistical analyses**

Data were adjusted for age, sex, duration of diabetes, initial weight, initial HbA1c-value and change of HbA1c. The SAS 9.1 statistical software package (SAS Institute Inc., Cary, NC, USA) based on a mixed hierarchical model using SAS procedure GLIMMIX with cluster adjustment (treatment center as random variable) was used for data analysis with weight change as the dependent variable, and antidiabetic therapy, age, diabetes duration, observation period, initial BMI, initial HbA1c and change in HbA1c during the intervention as fixed effects. Adjusted means based on observed marginal frequencies were calculated for visualisation, and p-values for multiple comparisons among treatment groups were adjusted according to Kramer-Tukey. P < 0.05 was considered significant.

**Results**

**Treatment-related alterations of glycemic control**

Within a mean stable therapeutic period of 1.1 ± 0.3 years, every antidiabetic concept was associated with a significant improvement of glycemic control resulting in a reduction of the mean DCCT adjusted HbA1c-value from 7.4 ± 1.6 to 7.0 ± 1.3%. Mean HbA1c-values below 7.0% were only reached in the group of...
**Table 1** Clinical characterisation of all patients and treatment subgroups in the beginning of the observation period.

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Number (n; % of total)</th>
<th>Age (years ± SD)</th>
<th>Diabetes Duration (years ± SD)</th>
<th>Observation Period (years ± SD)</th>
<th>HbA1c (% ± SD)</th>
<th>BMI (kg/m² ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>9,294 (100)</td>
<td>65.8 ± 11.6</td>
<td>11.4 ± 9.2</td>
<td>1.1 ± 0.3</td>
<td>7.4 ± 1.6</td>
<td>30.5 ± 5.7</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>1,813 (19.5)</td>
<td>64.4 ± 12.2</td>
<td>8.8 ± 8.7</td>
<td>1.0 ± 0.3</td>
<td>7.5 ± 1.9</td>
<td>29.7 ± 5.5</td>
</tr>
<tr>
<td>OAD</td>
<td>1,536 (16.5)</td>
<td>64.5 ± 12.1</td>
<td>6.5 ± 6.5</td>
<td>1.1 ± 0.3</td>
<td>6.7 ± 1.1</td>
<td>30.5 ± 5.7</td>
</tr>
<tr>
<td>Insulin</td>
<td>4,504 (48.5)</td>
<td>67.5 ± 11.2</td>
<td>14.0 ± 9.6</td>
<td>1.1 ± 0.3</td>
<td>7.6 ± 1.6</td>
<td>30.2 ± 5.6</td>
</tr>
<tr>
<td>Insulin plus OAD</td>
<td>1,441 (15.5)</td>
<td>63.9 ± 10.9</td>
<td>11.7 ± 7.8</td>
<td>1.1 ± 0.3</td>
<td>7.5 ± 1.5</td>
<td>32.5 ± 6.0</td>
</tr>
</tbody>
</table>

Shown are the mean and the respective standard deviation (SD) of the data. Based on local reference ranges, HbA1c-values were mathematically adjusted to the DCCT reference using the MOM (multiple of the mean) method. OAD represents the oral antidiabetics metformin, sulfonylurea drugs, glitazones and α-glucosidase-inhibitors.

non-insulin treated patients (Fig. 2). The highest amount of HbA1c-reduction was achieved in the group of patients treated with lifestyle interventions only (HbA1c-reduction in treatment groups: lifestyle −0.6%, oral antidiabetics −0.2%, insulin −0.4%, oral antidiabetics and insulin −0.3%). At the beginning of the treatment period approximately 30% of all patients presented with a HbA1c level below 6.5%. This percentage was increased at the end of the treatment period to approximately 40% of all patients. The highest percentage of patients reaching a HbA1c level below 6.5% was achieved in the group of patients treated by OAD, whereas insulin treated patients had the lowest percentage in excellent control (change in percentage of patients achieving HbA1c levels below 6.5%: all patients 30.7±0.5 to 40.7±0.5, lifestyle intervention 36.6±1.2 to 48.3±1.3, OAD 48.7±1.3 to 58.2±1.3, insulin 24.7±0.7 to 33.9±0.7, insulin plus OAD 23.1±1.1 to 33.8±1.3).

Treatment-related alterations of body weight

The mean BMI for all patients in the beginning of the analysed treatment period was 30.5±5.7 kg/m² and demonstrates that this cohort of patients with T2DM was predominantly overweight or obese. During the treatment period the overall weight effect was neutral (+0.08±0.07 kg; p>0.05). Patients treated with lifestyle interventions or with oral antidiabetics significantly reduced weight, while all other treatment concepts had no significant effect on body weight (body weight alterations adjusted for age, sex, duration of therapy, initial weight, initial HbA1c-value, change of HbA1c-value and mathematically adjusted to the DCCT reference. Shown are the mean and the respective standard deviation of the data. OAD represents the oral antidiabetics metformin, sulfonylurea drugs, glitazones and α-glucosidase-inhibitors.

A subgroup analysis of patients treated with oral antidiabetics revealed that only patients treated with metformin and/or sulfonylurea drugs reduced weight, while patients treated with glitazones or α-glucosidase inhibitors showed no significant weight effect (adjusted body weight change: metformin −0.77±0.21 kg, sulfonylurea drugs −0.75±0.34 kg; p>0.05, respectively; insulin +0.27±0.10 kg, insulin plus oral antidiabetics +0.63±0.14 kg; p>0.05, respectively; Fig. 3).

There was no significant difference between the body weight of patients treated either with normal or with analogue insulin (adjusted body weight alterations: prandial analogue insulin +0.31±0.26 kg, long acting analogue insulin −0.04±0.27 kg; p>0.05, respectively). Whereas patients treated with insulin plus oral antidiabetics showed a non-significant weight gain, patients treated with insulin and metformin tended to reduce body weight (adjusted body weight alteration: −0.53±0.5 kg; p>0.05, respectively).

HbA1c reduction and body weight change

Adjusted for age, sex, duration of therapy, initial weight and initial HbA1c-value, reduction in HbA1c was significantly related to
the body weight change in the group of all treated patients (-0.38±0.06 kg/1 unit of HbA1c improvement), lifestyle treated patients (-0.78±0.16 kg/1 unit of HbA1c improvement), OAD treated patients (-1.07±0.22 kg/1 unit of HbA1c improvement) and insulin treated patients (-0.27±0.09 kg/1 unit of HbA1c improvement). In the group of patients treated with OAD plus insulin we found a small increase of 0.14±0.15 kg body weight/1 unit of HbA1c improvement, that was not significant in the tested model.

Discussion

In the present analysis of data from 9,294 T2DM patients selected from the DPV-Wiss-database, each antidiabetic, center-controlled therapeutic concept resulted in a significant improvement of glycemic control during a stable one year therapeutic period. Based on HbA1c-values mathematically adjusted to the DCCT reference, the patients had a mean initial HbA1c of 7.4% and a final HbA1c of 7.0%. According to national and international practice guidelines that recommend glycosylated blood glucose levels below 6.5% (IDF Clinical Guidelines Task Force, 2005) or less than 7.0% (American Diabetes Association, 2007), the goal of glycemic control was not completely reached in our study. Thus, in the end of the treatment period, approximately 40% of all patients achieved a HbA1c level below 6.5% and approximately 60% a HbA1c level below 7.0% (data not shown). It must, however, be argued, that these data are superior to those of other studies primarily representing routine medical care and/or primary care data. Data from the “National Health and Nutrition Examination Survey” (NHANES) 1999–2002 & “Behavioral Factors Surveillance System” (BFSS) 2002, USA, revealed a mean level of 7.7% for patients with diabetes (Saaddine et al., 2006). The Canadian “Practice Diabetes Management Study” revealed a mean HbA1c of 7.7% for T2DM patients (Harris SB et al., 2006). In the German arm of the “Costs of Diabetes in Europe – Type 2” study (CODE-2), patients with T2DM had a mean HbA1c of 7.5% including 26% of patients with an HbA1c below 6.5% (Liebl et al., 2001). An analysis of a primary care cohort of 4,575 German T2DM patients (IRIS-study) revealed a proportion of 16% of patients reaching a HbA1c target below 6.5% and 32% of patients reaching a HbA1c target below 7.0% (Rihl et al., 2002). Patients treated by lifestyle intervention had a mean HbA1c of 6.54%, orally treated of 7.54% and insulin treated patients of 7.99% (Rihl et al., 2002). Such a decline of metabolic control associated with a therapeutic escalation was also seen in a recent epidemiological study of German primary care, the “Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment” study (DETECT; Huppertz et al., 2009). In this study 8,188 patients with T2DM had a mean HbA1c of 6.89% including 38.8% of T2DM patients with an HbA1c ≥7.0%. The quality of glycemic control clearly decreased when treatment needed to become more intensive and people had a plus-10-year history of diabetes (Huppertz et al., 2009). In our analysis of effects of antidiabetic therapies conducted by specialised diabetes centers, the patients were characterized by a mean diabetes duration of 11.4 years, a mean age of 65.8 years and a proportion of more than 60% on insulin. According to these characteristics of patients with a predominant disease progression, the glycemic control of our cohort of people with T2DM was superior compared to evaluations of cohorts treated by routine medical/primary care physicians.

Regarding the outstanding endocrine and metabolic function of fat tissue, weight loss intervention is important in the therapy of obese patients with T2DM in order to improve glycemic control and to reduce cardiovascular risk factors. In our observational study of obese T2DM patients, the decrease of HbA1c from 7.4 to 7.0% over a time period of approximately one year was paralleled by a stable body weight. This result differs from other recent studies that commonly resulted in a significant weight gain by multiple glucose-lowering treatment concepts (Barnett et al., 2007; UK Prospective Diabetes Study, 1998; Gerstein et al., 2008; Patel et al., 2008). In detail, patients treated with insulin or insulin plus oral antidiabetics showed only a tendency towards weight gain, whereas patients treated with lifestyle interventions or oral antidiabetics significantly reduced body weight by 0.28±0.2 and 0.56±0.13 kg, respectively. These data are influenced by a fraction of patients treated with metformin solely or in combination with other diabetes medications. 73.0% of all patients treated with oral antidiabetics (n=1,536) and 80.2% of all patients treated with insulin plus oral antidiabetics (n=1,441) received metformin, representing approximately 25% of all patients in this observational study. It appears, that metformin mitigates the adverse effects of insulinotropic drugs or insulin on body weight. Thus, patients treated with insulin plus oral antidiabetics showed a tendency to gain weight (+0.63±0.14 kg), whereas the subgroup of patients with insulin plus metformin more often reduced weight (-0.53±0.5 kg) without reaching a significant effect. Weight-neutral or weight-sparing effects of metformin have been reported in several previous studies (Golay, 2008) and clearly constitute a therapeutic advantage in diabetes management. This advantage is underlined by the result of a recent meta-analysis that only treatment with metformin was associated with a decreased risk of cardiovascular mortality compared with any other oral diabetes agent or placebo (Selvin et al., 2008).

The result of a general neutral development of body weight in this observational study is, however, surprising, since most of the patients received treatments including insulinotropic drugs or insulin. These treatments that usually promote clinically significant weight gain represented more than 70% of all patients. It must, however, be argued that the HbA1c-related body weight effects differed between the treatment groups. In the adjusted
model for the whole group, one unit reduction of HbA1c was related to a weight reduction of 0.38 kg (at the observed HbA1c reduction of −0.4% this amounts to −0.15 kg). This effect was more pronounced in patients on lifestyle intervention only (−0.78 kg per unit reduction in HbA1c) and in patients on OAD alone (−1.07 kg) compared to patients treated with insulin alone (−0.27 kg) or the combination of insulin with oral drugs (+0.14 kg). It remains unexpected, that, in the OAD subgroup analysis, patients treated with sulfonylurea drugs achieved a significant and clear weight reduction. This result might have been influenced by patients receiving combinations of sulfonylurea drugs with metformin and/or short-acting sulfonylurea drugs. It also has to be considered that the present data are taken from a quality management database of specialised diabetes centers. Firstly, qualified diabetes centers provide a broad and regular self-management training that, among other effects, has been shown to be effective on glycemic and weight control, especially if patient collaboration is involved (Norris et al., 2001). Secondly, it appears advantageous for the treatment outcome, if the diabetes unit regularly receives detailed information concerning treatment trends and quality (benchmarking reports).

It has to be considered that our analysis of patients with T2DM also included a certain proportion of elderly patients and that the prognostic importance of overweight and obesity in elderly persons is controversial. On the one hand, Harris et al. demonstrated in a cohort of 4954 people aged ≥65 years that heavier weight was associated with cardiovascular disease and cardiovascular risk factors (Harris TB et al., 1997). On the other hand, a recent systematic review of published studies concerning the association between BMI and mortality in elderly persons revealed that the optimum BMI tended to be higher for the elderly compared to young and middle-aged populations (Heiat et al., 2001). Although these studies did not explicitly focus on patients with T2DM, it has to be noted that the definition of weight goals in elderly patients could differ from general guidelines and, even more, should consider the individual body composition and general health status. In summary, this database analysis on the effects of antidiabetic therapies in patients with T2DM, disease progression and a high proportion of insulin therapies demonstrates that treatment by specialised diabetes centers, that make use of a diabetes documentation and quality management system, enables an optimalization of glycemic and weight control, especially if patient collaboration is involved (Norris et al., 2001). In this regard, new glucose-lowering pharmaceutical concepts that also support a weight reduction as well as weight loss programs and/or the establishment of obesity programs could be helpful in a cardiovascular-orientated treatment of T2DM.

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Conflict of Interest: None.

References


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