Gender-specific Effects of Treatment with Lifestyle, Metformin or Sulfonylurea on Glycemic Control and Body Weight: A German Multicenter Analysis on 9108 Patients

Abstract

Effects of diabetes treatment are strongly connected to individual factors, but the relevant role of gender has not been addressed so far. This observational study evaluates whether monotherapy with lifestyle, metformin or sulfonylurea has gender-specific effects on glycemic control and/or body weight. Data of 9108 patients with type 2 diabetes from 129 German diabetes centers were assessed by a standardized, prospective, computer-based diabetes care and outcome documentation system (DPV-Wiss-database; age 63.1 ± 12.8 years, diabetes duration 5.7 ± 7.4 years, HbA1c 55.7 ± 17.7 mmol/mol [7.2 ± 1.6%], BMI 30.6 ± 6.1 kg/m², 49.3% female patients). Antidiabetic concepts included lifestyle intervention (n = 5,787), metformin (n = 2,180), sulfonylurea (n = 943) or other antidiabetic drugs (n = 198), respectively. HbA1c and body weight were compared before and after a stable monotherapeutic period of 0.8 ± 0.4 years. Women had a significantly higher reduction of body weight after treatment with lifestyle (women -0.8 ± 0.1 vs. men -0.2 ± 0.1 kg; p < 0.05), metformin (women -1.8 ± 0.2 vs. men -1.2 ± 0.2 kg; p < 0.05) or sulfonylurea drugs (women -0.9 ± 0.2 vs. men -0.1 ± 0.2 kg; p < 0.05), whereas men displayed significantly higher HbA1c-reductions after treatment with lifestyle (men -6.9 ± 0.2 mmol/mol [-0.6 ± 0.02%] vs. men -7.5 ± 0.2 mmol/mol [0.7 ± 0.02%]; p < 0.05) and metformin only (women -6.3 ± 0.3 mmol/mol [-0.6 ± 0.03%] vs. men -7.4 ± 0.3 mmol/mol [-0.7 ± 0.03%]; p < 0.05). No differences were seen for sulfonylurea monotherapy concerning the HbA1c-reduction (women -5.6 ± 0.5 mmol/mol [-0.5 ± 0.05%] vs. men -6.4 ± 0.4 mmol/mol [-0.6 ± 0.04%]; p = 0.196). In summary, antidiabetic treatment concepts might result in gender-specific effects on body weight and HbA1c. Gender might therefore represent another important factor in the context of an individualized treatment management of type 2 diabetes.

Introduction

Individualisation of treatment has been identified as a key principle for successful diabetes management. It has been recommended to consider diverse factors in this process, but the potential role of gender in the response to antidiabetic treatment remains unknown [1]. Furthermore, enrolment of women in randomized clinical trials remains low relative to their overall representation in disease populations [2,3]. Gender differences were identified for several adipokines and hormones that are involved in the regulation of glucose metabolism, body weight and appetite [4]. Besides biological aspects, gender differences also involve psychosocial factors and self-assessment of quality of life. Furthermore, gender influences health behavior, as well as diabetes treatment strategies and outcome [5,6]. Gender appears particularly important in the interaction between type 2 diabetes and heart disease since women with diabetes have a higher cardiovascular risk than men with diabetes [7-9]. It is also known from health services research, that women with diabetes received less treatment for diverse coronary heart disease risk factors than men with diabetes and that women were less likely than men to have a HbA1c < 53 mmol/mol/7.0% [5,9,10]. Differences concerning medical care are not known except single drug side effects (e.g. bone loss with thiazolidinediones or genital infections due to SGLT2 inhibitor treatment) [11-13]. On the other hand, metabolic disorders have a specific gender-based pathophysiology that also might influence the result of diabetes treatment.
In the present observational study we analysed data of specialized German diabetes centers that were regularly transferred to the DPV- (Diabetes Documentation and Quality Management System) database and compared effects of treatment with lifestyle, metformin or sulfonylurea monotherapy on glycemic control and/or body weight between women and men.

Patients and Methods

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, and meets the ethical standards of the WMA Declaration of Helsinki. 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 [14].

By September 2013, 9108 patients treated at 129 qualified diabetes treatment centers were selected from 197,596 patients with type 2 diabetes by the following criteria: age ≥18 years, documentation of clinical data within a 3–12 month period, exclusion of patients with medical combination therapy, treatment change within the reported period, and beta cell antibody positivity overall. The gender distribution was balanced (49.3% female). The patient group was characterized by an average age of 63.1 ± 12.9 years, diabetes duration of 5.7 ± 7.4 years, body weight of 87.1 ± 19.4 kg, BMI of 30.6 ± 6.1 kg/m² and Hba1c of 55 ± 17.7 mmol/mol [7.2 ± 1.6%] at the beginning of the stable monotherapeutical period of 0.8 ± 0.4 years. Monotherapeutic regimen were classified as "lifestyle intervention" (n=5787), "metformin" (2180), short- and long-acting "sulfonylurea" (n=943) or "other oral antidiabetic drugs" (n=198; glitazones, α-glucosidase inhibitors, incretin-based therapy). Since the subgroup "other antidiabetic drugs" included only a small number of patients, and since these antidiabetic drugs are known to induce divergent effects on body weight, we excluded this subgroup from further analyses.

The basic characteristics of patients in the 3 major subgroups prior to the respective antidiabetic therapy are shown in Table 1. As expected, most patients were treated by a "lifestyle intervention" concept followed by "metformin" treatment. A smaller amount of patients were treated by "sulfonylurea", most likely because of metformin incompatibility, contraindications for metformin or following the national treatment recommendation pathway. The gender distribution and the duration of the stable monotherapeutical period were balanced between the subgroups. Patients with "sulfonylurea" were the oldest and had the lowest BMI, whereas "metformin" patients were characterized by the shortest diabetes duration, lowest Hba1c and highest BMI, respectively (Table 1).

For each patient, the Hba1c-value and body weight/BMI were compared with data directly before starting the respective therapy representing a stable monotherapeutical period without any drug changes for 3–12 months. Based on local reference ranges, Hba1c values were mathematically adjusted to the DCCT reference range (4.05–6.05%; DCCT, 1993) using the MMM (multiple of the mean) method [15]. The BMI was calculated as body weight in kilogram divided by the square of height in meters.

Data were adjusted for age, duration of diabetes, initial Hba1c-value and the observational period. The SAS 9.1 statistical software package (SAS Institute Inc., Cary, NC, USA) based on a

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Basic characteristics of patients in the 3 major subgroups prior to the respective antidiabetic therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>group</td>
<td>number</td>
</tr>
<tr>
<td>lifestyle intervention</td>
<td>5787</td>
</tr>
<tr>
<td>metformin</td>
<td>2180</td>
</tr>
<tr>
<td>sulfonylurea</td>
<td>943</td>
</tr>
</tbody>
</table>

Schött M et al. Effects of Gender on Diabetes Treatment... Exp Clin Endocrinol Diabetes 2015; 123: 622–628
mixed hierarchical model implemented with SAS procedure GLIMMIX with cluster adjustment (treatment center as random variable) was used for data analysis. To compare groups, non-parametric statistics (Wilcoxon) were used, and to correct for multiple comparisons the Bonferroni step-down method (Holm) was used [16]. P-values for multiple comparisons among female and male patient subgroups were adjusted according to Tukey-Kramer. P < 0.05 was considered significant.

Results

Analysis of the whole study population without adjustment demonstrated an overall reduction of the HbA1c from 55±17.5 (7.2±1.6%) to 48±13.1 mmol/mol (6.5±1.2%) and a body weight reduction from 87.1±19.4 to 86.4±19.1 kg or BMI reduction from 30.6±6.1 kg/m² to 30.4±6.0 kg/m² during the observational period of 0.8±0.4 months.

Data for the subgroups of women and men were adjusted to age, diabetes duration, baseline HbA1c and observational treatment period. After these adjustments, women had a significantly higher reduction of body weight after lifestyle intervention (women 8.0±0.1 vs. men 0.2±0.1 kg), metformin (women 1.8±0.2 vs. men 1.2±0.2 kg) or sulfonylurea monotherapies (women 0.9±0.2 vs. men 0.1±0.2 kg). Highest body weight reductions were clearly seen in women treated with metformin. It is worth noting that women treated by sulfonylurea drugs reduced body weight to a similar extent as seen in the lifestyle group. Men had a stable body weight during lifestyle or sulfonylurea treatment and also reached a clear body weight reduction during metformin treatment (© Fig. 1). In contrast to these body weight data, men developed significant higher HbA1c-reductions after treatment with lifestyle (women 6.9±0.2 mmol/mol [-0.6±0.02%] vs. men 7.5±0.2 mmol/mol [0.7±0.02%]) and metformin (women 6.3±0.3 mmol/mol [-0.6±0.03%] vs. men 7.4±0.3 mmol/mol [0.7±0.03%]), respectively (each p<0.05, adjustment for multiple comparisons), while no differences were seen for sulfonylurea drug treatment (women 5.6±0.5 mmol/mol [-0.5±0.05%] vs. men 6.4±0.4 mmol/mol [-0.6±0.04%]; p=0.196; © Fig. 2).

Further analysis revealed a strong correlation between body weight and HbA1c alterations for treatment with metformin and to a lesser extend for lifestyle intervention, whereas treatment with sulfonylurea showed no such correlation (Spearman correlation coefficients, data not shown). These results were not different between women and men, respectively.

Discussion

Both, glycemic and body weight control are important aims in the treatment of patients with type 2 diabetes. In the present analysis of data from 9108 patients with type 2 diabetes selected from the DPV-Wiss-database, we demonstrated that antidiabetic treatment concepts have different effects on body weight and HbA1c between women and men. Beyond that, body weight and HbA1c differences were inverse, namely women developed higher body weight reductions during lifestyle, metformin or sulfonylurea treatment, while men showed higher HbA1c reductions during lifestyle or metformin treatment. Lifestyle intervention and metformin clearly constitute a therapeutic advantage in diabetes management and remain the first steps in type 2 diabetes treatment for women and men [1,17]. Nonetheless, the knowledge of gender-specific treatment effects might be important for the process of defining individualized treatment goals and for the assessment of treatment results. Lifestyle intervention has been shown to improve glycemic and body weight control particularly in the beginning of the disease supported by lifestyle counseling and/or self-management training [18,19]. The present data taken from a quality management database of specialised diabetes centers confirm these results. Furthermore, they also point to gender-based differences. Our finding that women developed higher body weight reductions but men higher HbA1c reductions was unexpected. It is well known that women are more often obese and less physically active, but may even have greater benefit from increased physical activity than males [20,21]. We have no information whether
women in our database predominantly lost more visceral fat (representing a prominent cardiometabolic risk factor particu-
larly in women) or mainly enhanced physical activity. It is also
not clear, whether women or men predominantly improved
their fasting or postprandial hyperglycemia that might be rele-
vant for HbA1c alterations [22]. Other studies have shown that
postprandial hyperglycemia is more common in females, espe-
cially in postmenopausal women, whereas males are often char-
acterised by fasting hyperglycemia [9, 23, 24]. Hormone
replacement therapy that might affect insulin sensitivity has not
been analysed.
Metformin usually represents the first oral drug in diabetes
treatment initiated in parallel or shortly after lifestyle interven-
tion. Accordingly, the majority of antidiabetic drug treated
patients in our database received metformin. It is assumed that
patients with metformin were treated by both, lifestyle inter-
vention plus metformin. Therefore it was not possible to clearly
distinguish between lifestyle intervention only and metformin
only effects. In any case, metformin treatment resulted in even
higher body weight reductions in women and men as compared
with lifestyle intervention only, while HbA1c reductions were
similar in both groups. Furthermore, the same gender differ-
ences that were detected in the lifestyle intervention only group,
namely higher body weight reductions in women and higher
HbA1c reductions in men, were also seen in the metformin
group. It appears, that metformin clearly strengthened the body
weight reduction effect of lifestyle intervention in both, women
and men, but did not further improve the HbA1c reduction.
A current study by Zhou et al. was conducted to investigate a
potential genetic role concerning the variation noted in patients’
glycaemic response to metformin. They found that the glyca-
emic response to metformin in patients with type 2 diabetes is
partially heritable and represents underlying biological differ-
ences between individuals, whereas additional gender differ-
ences were not proven [25]. The objective of another recent
study was to assess whether metformin’s effect on glycaemic con-
duct differs by race-ethnicity. On the basis of a large health sys-
tem database it was figured out that in comparison with
European Americans metformin use was associated with lower
HbA1c levels in African American individuals. Gender differ-
ences were not investigated [26].
Another important outcome of metformin treatment in trials of
oral diabetes medications is a decreased risk of cardiovascular
mortality [27]. This effect might be connected to other molecular
modes of action beyond glucose metabolism [28] and it is not
known, whether gender differences might also play a role in this
respect. A recent study by Lyons et al. suggests a gender-specific
impact on myocardial metabolism by metformin. In this small
study of 78 patients with type 2 diabetes, metformin treatment
over a period of 3 months resulted in decreased fatty acid clear-
ance, which was linked to increased plasma fatty acid levels, myo-
cardial fatty acid utilization and oxidation, and lower myocardial
lipid utilization in men but not women [29]. Gender differences
may therefore also exist in the cardiovascular effects of metformin
that probably are related to the findings of the current study.
Reductions of body weight and HbA1c were approximately simi-
lar in patients treated with sulfonylurea drugs as compared with
lifestyle intervention patients. In detail, only women were able
to clearly reduce body weight, whereas the HbA1c reduction
showed no gender difference. It has to be noted, that patients in
the sulfonylurea group were characterised by older age, longer
diabetes duration and a lower BMI. It remains unexpected, that
patients in this subgroup did not gain weight or rather reduced
weight (women). Besides parallel lifestyle intervention treat-
ment, this result might have been influenced by the broad and
regular self-management training provided by the specialised
diabetes centers that participate in this diabetes care and out-
come documentation system. Furthermore, it appears advanta-
geous for the treatment outcome, if the diabetes unit regularly
receives detailed information concerning treatment trends and
quality (benchmarking reports).
Overall, different therapeutic regimens for type 2 diabetes might
influence glucose control and body weight in a gender-specific
manner. This suggests that gender should be taken into account
when designing and evaluating a patient’s diabetes treatment.
Further studies are needed in order to improve the treatment
outcome especially in females with diabetes and to understand
gender differences in action, pharmacokinetics and side effects
of antidiabetic therapy.

Acknowledgments

Financial support for the development of the DPV software was
provided by the Kompetenznetz Diabetes (BMBF FKZ 01GI1106),
Kompetenznetz Adipositas (FKZ 01GI1130), Bundesministerium
für Gesundheit, Deutsche Diabetes-Stiftung, Bürger-Büsing-Stif-
tung, Deutsche Forschungsgemeinschaft, European Foundation
for the Study of Diabetes.
We acknowledge the participating diabetes centres listed in the
succeeding texts: Aachen – Innere Klinik RWTH; Ailddingen Praxisge-
meinschaft; Altenötting-Burghausen Innere Medizin; Asbach
Kamillus-Klinik Innere; Augsburg Innere; Bad Aibling Internis-
tische Praxis; Bad Driburg/Bad Hermsborn Innere; Bad
Reichenshell Kreisklinik Innere Med.; Bad Säckingen Hochreih-
linik Innere; Bayreuth Innere Medizin; Berchtesgaden MVZ
Innere Med.; Berlin Klinik St. Hedwig Innere; Berlin Oskar Zieten
Krankenhaus Innere; Berlin Schlosspark-Klinik Innere; Berlin St.
Josephskrankenhaus Innere; Berlin Vivantes Hellersdorf Innere;
Bottrop Knappschafskrankenhaus Innere; Bremen-Mitte Innere;
Chemnitz-Hartmannsdorf Innere Medizin – DIATOMED-1; Darm-
stadt Innere Medizin; Deggendorf Medizinische Klinik II; Dort-
mund Knappschafskrankenhaus Innere; Dortmund Medizinische
Kliniken Nord; Dortmund-Homburk Marienhospital; Dort-
mund-St. Josefshospital Innere; Duisburg Evangelisches und
Johanniter Krankenhaus Innere; Duisburg Malteser St. Anna
Innere; Duisburg Malteser St. Johannes; Duisburg-Huckingen;
Duisburg-St.Johannes Heilico; Eberswalde Klinikum Barnim
Werner Forssmann – Innere; Eisleben Lutherstadt Heilico-Innere;
Erlangen Uni Innere Medizin; Essen Diabetes-Schwerpunkt-
praxis; Eutin St.-Elisabeth Innere; Forchheim Diabeteszentrum
SPF; Frankfurt Diabeteszentrum Rhein-Main-Erwachsenendia-
betologie (Bürgerspital); Freiburg Uni Innere; Friedberg
Innere Klinik; Fulda Innere Medizin; Gießen Klinik Hellens-
stein Innere; Gelnhausen Innere; Gießen Ev. Krankenhaus Mitt-
telhessen; Güstrow Innere; Halle-Delitz Sädtische Kinderklinik;
Hamburg Endokrinologikum; Hanau St. Vincentz – Innere; Han-
over Henriettensift – Innere; Heidelberg Uni-Kinderklinik;
Heidelberg Arztpraxis Allgemeinmedizin; Heilbronn Innere
Klinik; Herford Innere Med I; Herne Evangelisches Krankenhaus
Innere; Herten St. Elisabeth Innere Medizin; Hinrichseg-
Brückmühl Diabetikerklinikhaus; Idar Oberstein Innere; Ingol-
stadt Klinikum Innere; Iselroth Innere Medizin; Jena
Uni-Kinderklinik; Kamen Hellmig-Krankenhaus; Karlsruhe
Conflict of interest: There are no competing interests to declare.

References

