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ORIGINAL RESEARCH

Gender-associated Differences in Weight Gain, Insulin Requirement and Metabolic Control in Newly Insulin-treated Type 2 Diabetic Patients with Secondary Sulfonylurea Failure—a One-year Observation

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Abstract

Objective: The aim of the present study was to determine differences between male and female type 2 diabetic patients concerning body weight, metabolic control, insulin requirement and prevalence of vascular diseases during the first year insulin therapy.

Patients and Methods: We investigated 102 newly insulin-treated type 2 diabetic patients (60 female) with secondary sulfonylurea failure. Observation period was the first year insulin therapy. We compared BMI, HbA1c, lipids and insulin requirement at the begin and after one year, C-peptide and prevalence of vascular diseases at the start of insulin therapy.

Results: At the start of insulin substitution, omen had a higher BMI (27 + 3 versus 25 + 3; $p < 0.05$). Women also required a higher insulin dose than did men (28 + 6 versus 24 + 6 IU/day) Mean HbA1c and cholesterol levels were similar in both groups whereas triglycerides were higher in women (244 + 88 versus 203 + 76 mg/dl; $p < 0.05$). Both groups achieved a similar gain in body weight after one year (+2.5% versus +2.6%; NS). HbA1c decreased from 9.2 + 1.1 to 7.4% + 0.9% (−19%) in women and from 9.4 + 1.1 to 7.5% + 1.0% (−20%) in men. The prevalence of vascular diseases was not significantly different in both groups.

Conclusions: At the start of insulin therapy female type 2 diabetic patients showed a significant higher BMI and a higher insulin requirement than male patients. The metabolic control was similar in men and women, only the triglycerides were higher in the female patients. Weight gain and increase of needed insulin as well as prevalence of macroangiopathy were the same in both groups.

Keywords: gender, type 2 diabetes, insulin therapy

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Introduction

Male and female diabetic patients differ in respect of biological, social, as well as behavioral factors, frequently depending on age.[1] From the published literature we know that gender differences in adherence to diet and diabetes treatment may be attributed, in part, to gender differences in symptoms among young type 1 diabetics from urban environments with poor metabolic control.[2] Interventions targeting these symptoms may be necessary to improve adherence and HbA1c control in male as well as female patients. A recent study reported a gender-associated difference in basal insulin requirements among type 1 diabetes patients using insulin pump.[3] In the literature there are few published data concerning gender-specific differences in the development of type 2 diabetes and cardiovascular disease. The waist-to-height ratio has been described as an independent parameter for the development of type 2 diabetes in Chinese type 2 diabetic women but not in men.[4] In a recent study it was discussed that adherence to dietary recommendations may differ between women and men with type 2 diabetes.[5] Specific differences in pathophysiology, traditional and psychosocial risk factors may be responsible for this phenomenon.[6]

In type 2 diabetes patients, the first year of insulin therapy following secondary sulfonylurea failure is usually associated with weight gain and increased insulin requirements. Published data concerning gender-dependent differences in body weight, C-peptide levels, insulin requirements and metabolic control as well as weight gain and increased insulin requirement under insulin therapy are scarce.[7]

We hypothesized that significant gender-dependent differences are also present in the first year of insulin therapy of type 2 diabetes. The aim of the study was to determine differences in BMI, C-peptide, insulin requirement and metabolic control between men and women during the first year of insulin therapy. In addition, we assessed the prevalence of vascular diseases in both patient groups.

Patients and Methods

Only type 2 diabetic patients with new insulin-treatment due to sulfonylurea failure were included in the study. The duration of follow-up was one year. Only patients whose data of 12 months were completely available, were evaluated in this study. We retrospectively investigated consecutively insulin-treated type 2 diabetic patients, of whom 42 were male and 60 were female. Secondary sulfonylurea failure was defined as repeatedly high HbA1c (>8%) under the maximum sulfonylurea dose (6 mg glimepiride or 240 mg cliclazid daily). Two HbA1c measurements were performed at 8-week interval in the outpatient care unit. At the start of insulin substitution the patients were admitted to the hospital for one week. All patients received the same diet, which included 140 g of carbohydrates per day. All subjects were educated in estimating the carbohydrate content and caloric intake of their diet.

The patients also participated in a 5-day diabetes teaching program within four weeks after the start of insulin therapy. All patients were well educated in respect of the diabetes diet and insulin therapy and performed self blood-sugar monitoring at least three times a day. After being discharged from the hospital the patients underwent control investigations at the outpatient care unit, usually at 3- to 6-month intervals. The blood samples were taken off by a nurse in the morning, the patients were in a fasting condition.

The insulin regimen was similar in both groups. Intensified insulin therapy (3 × daily prandial insulin) was used by 68% of women and 64% of men while conventional (1–2 × daily a long-acting or mixed insulin) treatment was given to the remaining patients. Those who switched to functional insulin substitution (basal bolus insulin therapy) during the observation period were excluded from the study (n = 12, female 6). Male and female patients were investigated separately to determine gender-associated differences in body weight, insulin requirement and metabolic control.

All investigations, especially all blood measurements were performed routinely according to the recommendations of the National and International Diabetes Associations. Baseline data of the two groups are summarized in Table 1. In both groups we compared body weight, BMI, diabetes duration, HbA1c (photometric method Biorad, Vienna), C-peptide (ELISA test), cholesterol and triglycerides (Hitachi Autoanalyzer, Laboratory Kits, Roche Company, Vienna) as well as the prevalence of vascular diseases

Table 1. Baseline data of the type 2 diabetic patients at the start of insulin therapy.

	Female	Male
Number (n)	60	42
Age (years) x ± SD	58 ± 14	60 ± 12
BMI x ± SD	27 ± 3*	25 ± 3*
Diabetes duration (years) x ± SD	11 ± 7	10 ± 6
C-peptide basal (ng/ml) x + SD	2.2 ± 0.9*	1.8 ± 0.8*
HbA1c (%) x ± SD	9.2 ± 1.1	9.4 ± 1.1
Systolic pressure (mm Hg) x ± SD	136 ± 15	135 ± 14
Diastolic pressure (mm Hg) x ± SD	84 ± 9	82 ± 9
Cholesterol (mg/dl) x ± SD	212 ± 46	222 ± 48
HDL-cholsterol (mg/dl) x + SD	41 ± 7	45 ± 8
Triglycerides (mg/dl) x ± SD	244 ± 88*	203 ± 76*
Smokers (%)	28	29
Insulin requirement (IU/day)** x ± SD	28 ± 6*	24 ± 6*
Insulin requirement (IU/kg/day) x + S	0.34 + 0.07	0.31 + 0.07
Insulin therapy regimen (%)		
Conventional	68	64
Prandial	32	36
Additional metformin therapy (%)	28	23

*$p < 0.05$, **Insulin dose 4 weeks after the start of insulin substitution.

and vascular complications in the patient's history at the start of insulin therapy. The insulin requirement was calculated after four weeks of insulin substitution. In addition, we evaluated weight gain, increase in insulin requirement and improvement of metabolic parameters during twelve months of insulin therapy. The insulin requirement was defined as the insulin dose needed to achieve a significant reduction in HbA1c levels. The prevalence of vascular diseases was evaluated at the begin of insulin therapy: cerebrovascular disease (CVD) was defined as stroke grade III–IV in history and/or carotid artery stenos >80% in the Duplex sonography. Coronary artery disease (CAD) was defined as angina pectoris and/or ST deviation on the electrocardiogram and/or myocardial infarction in history. Peripheral artery disease (PAD) was diagnosed in case of claudicatio intermittens and/or ankle/brachial index <7 in the Doppler sonography as well as amputation in history (with and without intervention).

Statistical Analysis

Statistical analysis was performed using SPSS for Windows. Statistical methods included the paired Student's t-test to compare differences within groups and the unpaired Student's t-test to compare data between groups. For comparison of differences between groups in respect of not normally distributed data we used the Wilcoxon and the Man-Whitney U-test as non-parametric tests. A p-value < 0.05 was considered statistically significant.

Results

The mean duration of diabetes was 10 ± 6 years in men and 11 ± 7 years in women. At the start of insulin therapy women had a higher BMI (28 ± 3 versus 25 ± 3; $p < 0.05$). Prior to the start of insulin substitution, both groups had similar mean HbA1c and cholesterol levels; only triglycerides were higher in women (244 ± 88 versus 203 ± 76 mg/dl; $p < 0.05$).

In addition, C-peptide levels were significantly higher in women (2.2 ± 0.9 versus 1.8 ± 0.8 ng/ml; $p < 0.05$). After one year of insulin therapy the women's body weight increased from 80 ± 9 kg to 82 ± 11 kg (+2.5%) while the men's body weight increased from 76 ± 12 kg to 78 ± 9 kg (+2.6%). During this period, the insulin requirement increased from 28 ± 6 to 30 ± 8 IU/day (+7%) in women and from 24 ± 6 to 26 ± 7 IU/day (+8%) in men. The insulin requirement in IU/kg body weight daily was 0.34 versus 0.31 in both groups.

HbA1c deceased from 0.2 ± 1.1 to 7.4% ± 0.9% (–19%) in women and from 9.4 ± 1.1 to 7.5% ± 1.0% (–20%) in men (NS). Mean cholesterol and HDL cholesterol as well as the triglyceride levels dropped, but not significantly, in both groups. The data are summarized in Table 2.

Table 2. Weight gain, increase in insulin requirement, and metabolic control after twelve months of insulin therapy.

	Female	Male
Weight gain (%)	+2.5	+2.6
Increase in needed insulin (%)	+7	+8
HbA1c (%) x + SD	7.4 + 0.9*	7.5 + 1.0*
Cholesterol (mg/dl) x + SD	195 + 64	205 + 66
HDL-cholesterol (mg/dl) x + SD	44 + 7	47 + 7
Triglycerides (mg/dl) x + SD	194 + 62	174 + 56
Decrease of HbA1c (%)	–17	–20
Decrease of cholesterol (%)	–8	–8
Increase of HDL cholesterol (%)	+7	+4
Decrease of triglycerides (%)	–22	–14
Systolic pressure (mm Hg) x + SD	138 + 16	136 + 14
Diastolic pressure (mm Hg) x + SD	85 + 9	83 + 8

*$p < 0.01$ (in comparison to baseline data).

Table 3. Prevalence of cerebrovacular disease (CVD), coronary artery disease (CAD), peripheral artery disease (PAD) and vascular complications in the patients' history as well as prevalence of diabetic nephropathy and retinopathy.

	Female	Male
Vascular diseases (n/%)		
CVD	14 (23%)	10 (24%)
CAD	14 (23%)	10 (24%)
PAD	13 (22%)	9 (21%)
Vascular complications in history (n/%)		
Stroke	5 (8%)	3 (7%)
Myocardial infarction	5 (8%)	7 (17%)
Leg amputation	5 (8%)	3 (7%)
Diabetic nephropathy (n/%)		
with macroproteinuria	5 (8%)	3 (7%)
with microalbuminuria	10 (16%)	6 (14%)
Diabetic retinopathy (%)	23	26

The prevalence of vascular diseases was similar in men and women (23% versus 24%). However, the frequency of myocardial infarction in the patient's history was more common in diabetic men (8 versus 17%), but the difference was not significant. The prevalence of diabetic retinopathy and nephropathy was identical in both groups. The data are presented in Table 3.

Discussion

In poorly controlled type 1 diabetic patients, gender differences in adherence to diet and metabolic control were described in the literature.[2] Interventions targeting mental health symptoms may be required to improve adherence to diet and HbA1c levels in male as well as female patients. There are few studies dealing with type 1 diabetes and gender-specific differences in the metabolic control.[3] In type 2 diabetes there are several data in the literature, concerning gender-specific differences in the development of type 2 diabetes and cardiovascular disease in type 2 diabetic patients.[4,7] In a recent study it was discussed that adherence to dietary recommendations may differ between women and men with type 2 diabetes.[4] After a period of 10 years, secondary gender-associated differences were observed at the beginning of insulin substitution; body weight and insulin requirement as well as mean basal C-peptide levels were significantly higher among women.[5] Specific differences in pathophysiology, traditional, and psychosocial risk factors may be responsible for this phenomenon.[6] Our data confirm the results in the literature. It may be assumed that insulin resistance was the reason for the higher BMI and C-peptide and the higher insulin requirement in women. The high BMI and C-peptide levels in our female patients also may have been due to non-compliance. However, our patients were intensively educated in diabetes-oriented dietary regulations. At the start of insulin therapy the patients were under strict control of their carbohydrate and caloric intake.

The relative increase in body weight was the same in both groups (2.5% and 2.6%, respectively) although the baseline BMI was higher in women. With regard to the higher mean C-peptide levels, it may

be assumed that insulin resistance was significantly higher in this group. However, insulin sensitivity was only measured in few cases (HOMA index), and the insulin requirement, when calculating in IU/kg body weight, was not significantly different in both groups.

The main reason for weight gain was the high energy intake over decades in both genders.[1] However, weight gain probably does not occur due to food intake alone.[9,10] In our study, diabetic women had a significantly higher BMI, which is indicative of different dietary habits in the two groups. The similar weight gain in our insulin-treated diabetic patients is in agreement with published data. Similar changes in weight changes have been described in non-diabetic men and women.[4] In our study, both groups achieved a similar degree of metabolic control after one year of insulin substitution. The incidence of hypoglycemia was approximately the same among women and men.

Several studies have reported gender differences in cardiovascular disease, which is associated with higher morbidity and mortality in diabetic women than in men.[6–8]

However, the topics of the women protection against cardiovascular diseases as well as the presence of insulin resistance are lacking. In our study the prevalence vascular diseases was similar in both groups. Myocardial infarction in the patients' history was more common in male type 2 diabetic patients but not significantly. The prevalence of stroke and amputations as well as vascular risk factors were similar in both groups. It may be assumed that in the diabetic women higher body weight and hyperinsulinemia as well as hypertriglyceridemia and loss of hormonal balance may have contributed to the similar high prevalence of coronary artery disease as registered in our male patients. Gender differences in cardiovascular mortality among elderly patients have been reported in the literature.

Especially in obese elderly patients, the body mass index is a major determinant of left ventricular mass in women, but not in men.[11] Women are also reported to have a more severe type of dyslipidemia than men, characterized by low levels of high-density lipoprotein cholesterol (HDL), small particle size of low-density lipoprotein cholesterol, and high levels of triglycerides. These risk factors for cardiovascular diseases have a stronger influence in women. Oxidative stress may increase the risk of cardiovascular disease for women with diabetes more than for men with diabetes.[12,13] In our study, HDL levels were only measured in patients with >200 mg/dl total cholesterol. In these cases, the mean HDL in women (n = 32) was slightly higher than in men (n = 24) with 41 ± 7 versus 45 ± 8 mg/dl. Triglycerides were significantly higher in our women.

Conclusion

Among new insulin-treated type 2 diabetes, women had a significantly higher BMI and required higher doses of insulin than did men. Additionally, C-peptide and triglyceride levels were higher in the female patients. After one year of insulin therapy, men and women achieved a similar improvement of their metabolic control. The prevalence of vascular diseases was the same in both groups whereas myocardial infarction in the patient's history was more common among men (NS). Although women started insulin substitution with a higher BMI than did men, both genders achieved a similar weight gain.

Disclosures

The authors report no conflict of interest.

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