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Male Patients with Longstanding Type 2 Diabetes Have a Higher Incidence of Hypoglycemia Compared with Female Patients

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ABSTRACT

Introduction: To explore whether there was a gender difference in the risk of hypoglycemia during intensive insulin therapy in patients with longstanding type 2 diabetes (T2D). This was a post hoc analysis of a single-center, open-label and prospective trial.
Methods: All subjects were admitted as inpatients, underwent a standard bread meal test at baseline and received a 7-day continuous subcutaneous insulin infusion (CSII) therapy for achieving glycemic control. Patients then were randomized 1:1 to two groups receiving (1) 4 days of Novo Mix 30 followed by 2 days of Humalog Mix 50; (2) 4 days of Humalog Mix 50 followed by 2 days of Novo Mix 30. All patients were subjected to 4-day retrospective continuous glucose monitoring (CGM) during the last 4 days in this study. The primary outcome was the incidences of hypoglycemia monitored by CGM at the end point.
Results: A total of 102 patients met the inclusion criteria and completed the study. Our data revealed that 29 patients (28%) experienced hypoglycemia as detected by CGM at the end point. Binary logistic stepwise regression analysis showed that only gender significantly correlated with hypoglycemia ($B = 1.17$, $p = 0.017$). Importantly, male patients had a significantly higher incidence of hypoglycemia than female patients (male = 20/52, female = 9/50, $p = 0.022$), although male patients required significantly lower insulin doses to maintain glycemic control than female patient ($p = 0.00$).
Conclusion: Male patients with longstanding T2D had a higher incidence of hypoglycemia than female patients during intensive insulin therapy.
Trial registration: ClinicalTrials.gov identifier, ChiCTR-IPR-15007340.

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INTRODUCTION

Several studies indicate that gender differences play a role in risk, progression, prevention and glucose-lowering therapy for type 2 diabetes (T2D) [1–3]. We conducted a retrospective study using continuous glucose monitoring (CGM) showing that older males with newly diagnosed T2D have a higher risk of nocturnal hypoglycemia during intensive insulin therapy compared with older females [4]. Therefore, a better understanding of gender-sensitive clinical approaches is imperative [5].

Continuous subcutaneous insulin infusion (CSII) is an effective therapeutic for treating hyperglycemia when conventional therapies are no longer sufficient to maintain glycemic control in T2D patients [6, 7]. Early administration of a CSII therapy leads to a significant improvement in beta cell function and prolonged remission in newly diagnosed T2D patients [8–11]. Even in longstanding T2D patients, CSII therapy is still able to further decrease the A1c levels [12]. Using CGM, we also observed that CSII provided a greater improvement in glycemic variations in both newly diagnosed T2D and longstanding T2DM patients [6].

However, hypoglycemia, especially nocturnal hypoglycemia, is a side effect of intensive insulin therapy [13], which may be an important barrier for patients with diabetes trying to achieve better glucose control as it may result in sudden death in severe cases [14]. Nearly 20% of patients using insulin pump therapy and one-fifth of patients had symptomless nocturnal hypoglycemia [15]. Studies further highlighted that older patients had high incidences of hypoglycemia [16, 17], although we observed that newly diagnosed male and female T2D patients required similar insulin doses to maintain glycemic control [18]. The gender differences in insulin doses required to maintain euglycemic control in patients with longstanding T2D remain largely unknown.

In this study, we tried to clarify whether there was a gender difference in hypoglycemia during intensive insulin therapy in patients with longstanding T2D.

METHODS

This was a post hoc analysis of a single-center, open-label and prospective trial, which focused on patients with T2D to determine whether patients would benefit from premixed insulin therapy after CSII for achieving glycemic control (ClinicalTrials.gov, no. ChiCTR-IPR-15007340). The study protocol and patient consent forms were approved by the Institutional Ethics Committee of Nanjing First Hospital, Nanjing Medical University. All procedures were in accordance with the ethical standards of Nanjing First Hospital and with the Helsinki Declaration of 1964 as revised in 2013. Informed consent was obtained from all patients recruited in the study.

Between February 2013 and December 2014, we recruited a total of 118 patients with T2D who failed oral antihyperglycemic agents in Nanjing First Hospital, Nanjing Medical University. The inclusion criteria were (1) patients aged between 18 and 80 years; (2) 7.5% $\leq$ HbA1c $\leq$ 12%. Patients were excluded from analysis if they were positive for antiglutamic acid decarboxylase antibody or if they had maturity onset diabetes in the young (MODY) or mitochondrial diabetes mellitus [7].

At baseline, all subjects were admitted as inpatients and underwent a standard bread meal test (100 g) [19]. Serum samples were obtained at 0, 30 and 120 min after meal loading. Serum C-peptide and glucose concentrations were measured centrally at the central laboratory in Nanjing First Hospital, Nanjing Medical University. Then, recruited subjects received 7-day CSII therapy to achieve glycemic control. CSII therapy was provided with aspart (Novo Nordisk, Bagsvaerd, Denmark) using a Medtronic insulin pump (Northridge, CA) as previously described [6, 18, 20]. After subjects achieved glycemic control, defined as a fasting and 2-h post prandial capillary blood glucose concentration between 6.1 and 8.0 mmol/l [21], patients were randomized 1:1 to two groups receiving: (1) 4 days of Novo Mix 30 (Novo Nordisk, Bagsværd, Denmark) followed by 2 days of Humalog Mix 50 (humalog® Mix50™, Eli Lilly and Co., Indianapolis, IN, USA); (2)

4 days of Humalog Mix 50 followed by 2 days of Novo Mix 30. Initial premixed insulin doses were calculated as 0.4–0.5 IU/kg, and doses were subsequently adapted according to capillary glucose values obtained by self-monitoring during the first 2 days of the premixed insulin titration period. Investigators titrated insulin doses on an individual patient basis with the titration algorithm (if the blood glucose level was < 4.4 mmol/l, the basal insulin dose was reduced 2 units; if the blood glucose level was within 4.4–6.1 mmol/l, the basal insulin dose was unchanged; if the blood glucose level was within 6.2–7.8, 7.9–10.0 and > 10.0 mmol/l, the basal insulin dose was increased subsequently by 2, 4 and 6 units, respectively), as described previously [6, 22]. Therapy was then unchanged for another 4 days, including 2 days of Humalog Mix 50 and 2 days of Novo Mix 30 after glycemic control had been achieved. During the premixed insulin treatment period, patients did not take any oral antihyperglycemic agents.

All patients were subjected to 4-day retrospective CGM (Sof-sensor, CGMS-Gold, Medtronic Incorp., Northridge, CA, USA) at the last 4 days in this study [18, 23]. All subjects were instructed to maintain moderate physical activity and received breakfast (0700), lunch (1100) and dinner (1700). The total daily caloric intake and percentages of carbohydrate, proteins and fats of each meal were the same as previously described [24].

We analyzed the day 2 and day 4 CGM data to compare the glycemic profiles between the two premixed insulin groups in this study. Because of the premixed insulin cross-over design, at least a 24-h washout period was needed [25]. The 24-h mean glucose concentrations (MGs), 24-h mean amplitude of glycemic excursions (MAGE), percentage time duration (%) of hyperglycemia (defined as glucose concentration > 10.0 mmol/l) and hypoglycemia (defined as glucose concentration < 3.9 mmol/l) [4, 22], incremental area under the curve (AUC) of hyperglycemia and incremental area over the curve (AOC) were calculated by software from Medtronic Incorp. (USA), and the hypoglycemic episodes were also recorded. β-Cell function was assessed by homoeostasis

model assessment B (HOMA-B), the insulin sensitivity was indicated by the homoeostasis model assessment insulin resistance (HOMA-IR) [7, 26], and the Matsuda Index was calculated as previously described [27, 28]. The insulin doses of the CSII and Novo Mix 30 therapy period were recorded, respectively.

The primary outcome was the incidences of hypoglycemia at the end point. The secondary end points were the differences in insulin doses and glycemic profiles between the two groups.

Statistical Analysis

All data are presented as the means ± SD. Statistical analysis was performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA). Shapiro-Wilk test was used to assess the distribution of data. A chi-squared test was performed comparing the ratio differences between the two groups. The mixed ANOVA model (2×2) test was used to compare differences between groups. A two-way ANOVA was used for repeated measurements for the group comparisons followed by the Bonferroni-Dunn post hoc test. We used correlation and binary logistic stepwise regression analyses to examine the interrelationships between gender and hypoglycemia. P values were two tailed with a significance level of 5%.

RESULTS

A total of 118 patients were recruited into this study. Seven patients who had glucose levels > 22.2 mmol/l during the CGM period were excluded as the CGM sensor used in this study was unable to monitor glucose concentrations > 22.2 mmol/l, and 9 patients did not meet the inclusion criteria (Fig. 1). The 102 patients who completed the study with age 59.4 ± 11.8 years, body mass index (BMI) 23.0 ± 7.3 kg/m², HbA$_{1c}$ values 9.8 ± 2.6% and course of disease 9.4 ± 5.7 years were analyzed.

We analyzed the incidence of hypoglycemia between groups at the end point. Our data revealed that 29 (28%) patients experienced hypoglycemia as detected by CGM. Correlation analysis showed that BMI, age, course of disease,
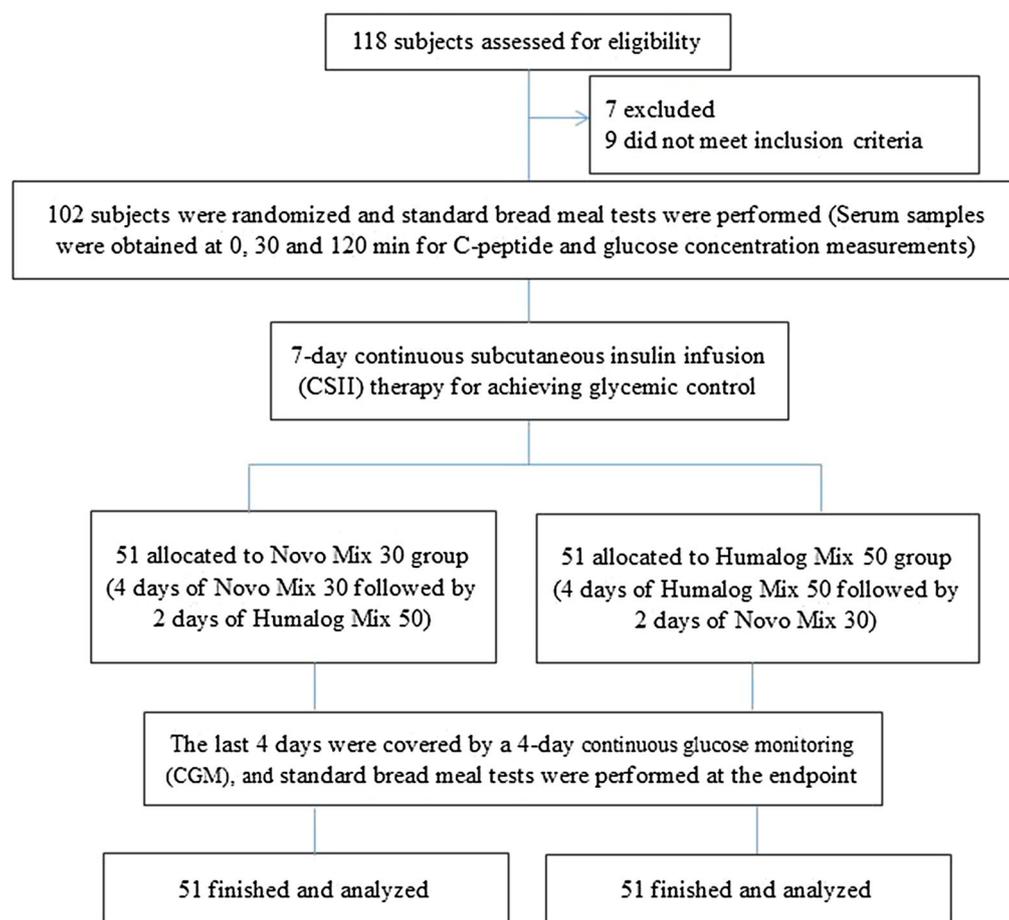
Fig. 1 Study flow chart

HbA1c values and gender were correlated with hypoglycemia, respectively. We performed a binary logistic stepwise regression analysis, controlling for BMI, age, course of disease, HbA1c values and gender, to identify which factors contributed to the increased incidences of hypoglycemia. Interestingly, only gender was the independent factor for hypoglycemia ($B = 1.17$, $p = 0.017$). Furthermore, a chi-squared test was performed to compare the hypoglycemic ratio differences between patients in the male and female groups. Our data indicated that males had a higher incidence of hypoglycemia compared with females (males = 20/52, females = 9/50; $p = 0.022$).

We therefore analyzed the gender differences in glycemic variations at the end point. We did not observe any difference in hourly blood glucose concentrations between the male and

female patients (Fig. 2). Our CGM data showed that male and female patients had similar 24-h MG, SDBG, MAGE, percentage of time duration (%) of hyperglycemia and hypoglycemia, incremental AUC of hyperglycemia and the incremental AOC of hypoglycemia (Table 1).

There were no differences in the mean values of various measurements between male and female groups, such as age ($p = 0.47$), BMI ($p = 0.76$), waistline ($p = 0.64$), waist-to-hip ratio ($p = 0.55$), course of disease ($p = 0.63$) and HbA1c values ($p = 0.99$) (Table 2).

Male and female patients took similar time to achieve glycemic control during CSII therapy (6.1 ± 3.7 vs. 6.6 ± 3.7 days, $p = 0.52$). Our results surprisingly showed lower total, basal and bolus insulin doses ($p < 0.01$, respectively) in the male than female patient group during the CSII period. We also analyzed the insulin
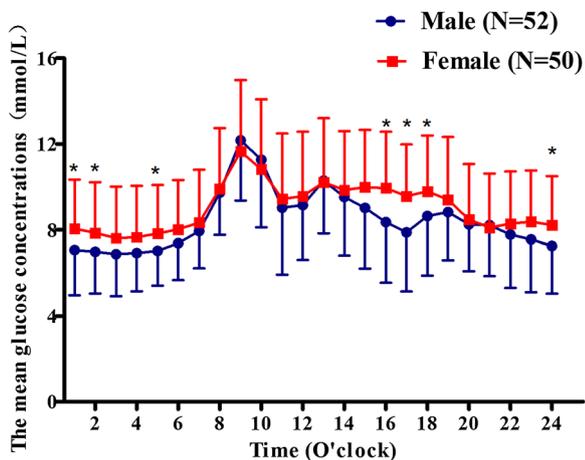
Fig. 2 Hourly glucose concentrations in male and female patients

doses required by patients between the two groups at the end point. Our data showed that male patients required significantly lower premixed insulin doses ($p = 0.00$), with a significant reduction in breakfast ($p = 0.01$), lunch ($p = 0.02$) and dinner insulin doses ($p = 0.00$) to maintain glycemic control at the end point than female patients (Table 3).

Table 2 Baseline of male and female patients with type 2 diabetes

Items	Male group	Female group	p value
Number	52	50	–
Age (years)	58.6 ± 11.7	60.3 ± 12.0	0.47
Duration	6.2 ± 6.3	7.0 ± 6.2	0.63
BMI	22.8 ± 6.4	23.3 ± 8.2	0.76
HbA1c	9.8 ± 3.0	9.8 ± 2.1	0.99
Waistline	78.7 ± 26.8	75.9 ± 32.6	0.64
Waist-to-hip ratio	0.8 ± 0.3	0.8 ± 0.3	0.55

Data are presented as means ± SD
*$p < 0.05$. Age (years); Duration (years): duration of T2D; BMI: body mass index (kg/m^2), HbA1c: glycated hemoglobin (%); waistline (cm); waist-to-hip ratio

To analyze the mechanism underlying the different insulin dose required to maintain glycemic control for male and female patients, we compared β cell function and insulin resistance between the two groups using the HOMA-B and

Table 1 Glycemic variations in male and female patients with type 2 diabetes

Items	Male group	Female group	p value
Number	52	50	/
24-h MG	8.5 ± 1.5	9.0 ± 1.8	0.08
SDMG	2.3 ± 0.8	2.2 ± 0.7	0.58
MAGE	5.8 ± 2.2	5.3 ± 2.2	0.28
Duration above	27.1 ± 22.0	34.4 ± 24.5	0.12
Duration below	3.2 ± 5.4	0.9 ± 2.8	0.01
AUC > 10.0 mmol/l	0.6 ± 0.7	0.8 ± 0.8	0.17
AUC < 3.9 mmol/l	0.1 ± 0.0	0.0 ± 0.0	0.17

Data are presented as means ± SD
24-h MG 24-h mean glucose concentrations (mmol/l), *SDMG* 24-h standard deviation of mean glucose concentrations (mmol/l), *MAGE* 24-h mean amplitude of glycemic excursions (mmol/l), *Duration above* duration > 10 mmol/l (%), *Duration below* duration < 3.9 mmol/l (%), *AUC > 10.0 mmol/l* incremental AUC of glucose level > 10.0 mmol/l (mmol/l day), *AUC < 3.9 mmol/l* the incremental AUC of glucose < 3.9 mmol/l (mmol/l day)
*$p < 0.05$

Table 3 Insulin doses and glycemic variations in male and female patients with type 2 diabetes

Items	Male group	Female group	p value
TDD1	0.55 ± 0.22	0.73 ± 0.26	0.00^*
Basal	0.26 ± 0.11	0.37 ± 0.16	0.00^*
Bolus	0.29 ± 0.11	0.37 ± 0.16	0.01^*
TDD2	0.54 ± 0.22	0.70 ± 0.25	0.00^*
BI	0.22 ± 0.10	0.27 ± 0.09	0.01^*
LI	0.15 ± 0.07	0.19 ± 0.09	0.02^*
DI	0.17 ± 0.08	0.24 ± 0.10	0.00^*

Data are presented as means $\pm$ SD
TDD1 CSII total daily dose (IU/kg/day), *Basal* CSII basal insulin dose (IU/kg/day), *Bolus* CSII bolus insulin dose (IU/kg/day), *TDD2* thrice-daily total daily dose (IU/kg/day), *BI* breakfast insulin dose (IU/kg), *LI* lunch insulin dose (IU/kg), *DI* dinner insulin dose (IU/kg)
$^*p < 0.05$

Table 4 The β-cell function and insulin sensitivity in male and female patients at baseline

Items	Male group	Female group	p value
C-peptide 0	2.0 ± 1.0	2.1 ± 1.0	0.60
C-peptide 30	2.7 ± 1.5	3.3 ± 2.1	0.62
C-peptide 120	4.9 ± 2.9	5.1 ± 2.8	0.28
HOMA-B	19.7 ± 15.1	22.5 ± 23.4	0.14
HOMA-IR	2.6 ± 1.6	3.4 ± 2.6	0.04^*
Mastuda Index	104.3 ± 87.4	91.7 ± 63.3	0.04^*

Data were presented as means $\pm$ SD
C-peptide 0 C-peptide 0 min (ng/ml), *C-peptide 30* C-peptide 30 min (ng/ml), *C-peptide 120* C-peptide 120 min (ng/ml), *HOMA-B* homoeostasis model assessment B, *HOMA-IR* homoeostasis model assessment IR
$^*p < 0.05$

Matsuda indices. Our data showed that male and female patients had similar C-peptide concentrations at 0 min ($p = 0.60$), 30 min ($p = 0.62$) and 120 min ($p = 0.28$) after bread load (Table 4). We also analyzed the β-cell function and insulin sensitivity between male and female patients at baseline. Our data showed that male and female patients had similar HOMA-B values ($p = 0.14$). However, male patients had significant increases in the Matsuda Index ($p = 0.04$) and decreases in the HOMA-IR ($p = 0.04$) compared with female patients (Table 4).

DISCUSSION

In this study, we observed that the incidence of hypoglycemia as monitored by CGM was 28% in patients receiving intensive insulin therapy. Binary logistic stepwise regression analysis showed that only gender was significantly correlated with hypoglycemia. Importantly, our data indicated that male patients had a significantly higher hypoglycemic ratio than female patients, although we observed that male patients with T2D required significantly lower insulin doses to achieve glycemic control and

significant pre-mixed insulin analog doses to maintain glycemic control compared with female patients in this study. Our data indicated that attention should be paid to preventing hypoglycemia in male patients receiving intensive insulin therapy even at lower insulin doses than in female patients.

Achieving the optimal HbA1c level in patients with T2D is the main target for physicians when choosing glucose-lowering therapies [29]. HbA1c is generated by the exposure of overall blood profiles for the long term, which does not necessarily reflect daily plasma glucose variations over the entire day [30, 31]. CGM provides a unique opportunity to examine the 24-h glucose glycemic excursions in patients with T2D, which might be the best tool to determine the overall blood glucose profiles [4]. Intensive insulin therapy has been used to treat patients with T2D in China [7]. Intensive insulin therapy consists of CSII using an insulin pump and multiple daily injections (MDIs) [32]. Some patients with longstanding type 2 diabetes mellitus respond well to intensive treatment [33] and are able to maintain euglycemia with minimal treatment for a long period [34]. Indeed, patients' response to intensive insulin therapy is quite variable, mirroring the heterogeneity of diabetes [33]. Reports have

highlighted the importance of hypoglycemia in intensive insulin therapy compared with conventional therapy with or without the use of an insulin pump [13].

Why male patients had a higher incidence of hypoglycemia during intensive insulin therapy is not known. However, this highlights that more careful blood glucose monitoring may be necessary in patients receiving intensive insulin therapy, especially males, to prevent the occurrence of hypoglycemia. The number of older patients with diabetes started on intensive insulin treatment has been increasing in recent years [35]. This has mainly been in T1D. Very few studies have used CSII in older patients with T2D. A relatively large study did highlight the increased risk of hypoglycemia in the older patients [16, 17]. We further demonstrated that male patients were prone to having hypoglycemia monitored by CGM during intensive insulin therapy [4]. In this study, the men and women had the similar ages, courses of disease, BMIs, waistlines, waist-to-hip ratios and HbA$_{1c}$ values. We could not exclude that other factors might affect the insulin doses in patients with T2D in maintaining glycemic control, such as the age, course of T2D, BMI, HbA1c, waistline, waist-to-hip ratio, HOMA-B, HOMA-IR and Mastuda Index. However, multivariate analysis, controlling for all the above-mentioned factors, showed that gender still was an independent factor affecting the incidence of hypoglycemia between the two groups.

Our data indicated that, as expected, male and female patients had similar pancreatic β cell function (HOMA-B). In this study, the BMI of the recruited patients was relatively low $(24.37 \pm 4.69 \text{ kg/m}^2)$. This was in agreement with Ntuk et al. who reported that Chinese women with BMI 24.0 kg/m^2 and Chinese men with BMI 26.0 kg/m^2 have equivalent prevalences of diabetes at BMI 30 kg/m^2 as white participants [36]. Interestingly, female patients had an insignificant increase in BMI compared with male patients in this study. Thus, we inferred the trend of a decrease in body weight might be the reason for the increased insulin sensitivity, because body fat weight is associated with a decreased Matsuda Index and increased HOMA-IR [28]. The increased insulin sensitivity

in male patients compared with female patients indicated that the body fat weight might be related to the Matsuda Index and HOMA-IR. Future studies are needed to identify the differences in insulin resistance between male and female patients.

Our study has other limitations. First, the study only observed a single city in Northern China, and the situation might not be the same in other cities. Second, the sample size was relatively small. Third, our observations were not carried out for a long time period.

CONCLUSIONS

In conclusion, our data suggested that male patients with T2D required lower insulin doses to maintain glycemic control. Our outcome indicated that increased attention should be paid to preventing hypoglycemia in male patients receiving intensive insulin therapy.

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the data analysis. Feng-fei Li contributed to writing the manuscript and its final approval.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability. The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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