Long-Term Sulfonylurea Use and Impaired Awareness of Hypoglycemia Among Patients With Type 2 Diabetes in Taiwan

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ABSTRACT

PURPOSE We undertook a study to investigate the relationship between duration of medication use and prevalence of impaired awareness of hypoglycemia (IAH) among patients with insulin-treated or sulfonylurea-treated type 2 diabetes in Taiwan.

METHODS A total of 898 patients (41.0% insulin users, 65.1% sulfonylurea users; mean [SD] age = 59.9 [12.3] years, 50.7% female) were enrolled in pharmacies, clinics, and health bureaus of Tainan City, Taiwan. Presence of IAH was determined with Chinese versions of the Gold questionnaire (Gold-TW) and Clarke questionnaire (Clarke-TW). Sociodemographics, disease and treatment histories, diabetes-related medical care, and health status were collected. We used multiple logistic regression models to assess the relationship between duration of medication use and IAH.

RESULTS Overall IAH prevalence was 41.0% (Gold-TW) and 28.2% (Clarke-TW) among insulin users, and 65.3% (Gold-TW) and 51.3% (Clarke-TW) among sulfonylurea users. Prevalence increased with the duration of sulfonylurea use, whereas it decreased with the duration of insulin use. After controlling for potential confounders, 5 or more years of sulfonylurea use was significantly associated with 3.50-fold (95% CI, 2.39-5.13) and 3.06-fold (95% CI, 2.11-4.44) increases in the odds of IAH based on the Gold-TW and Clarke-TW criteria, respectively. On the other hand, regular blood glucose testing and retinal examinations were associated with reduced odds in both insulin users and sulfonylurea users.

CONCLUSIONS The prevalence of IAH was high among patients using sulfonylureas long term, but the odds of this complication were attenuated for those who received regular diabetes-related medical care. Our study suggests that long-term sulfonylurea use and irregular follow-up increase risk for IAH. Further prospective studies are needed to confirm the observed associations.

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VISUAL ABSTRACT

INTRODUCTION

Hypoglycemia is a noteworthy problem in the glycemic control of type 2 diabetes. The annual prevalence of mild hypoglycemia is approximately 30% to 40% among patients with insulin-treated type 2 diabetes.[1] In a study across China, Korea, Malaysia, Thailand, and Taiwan, 35.8% of patients with type 2 diabetes using oral antihyperglycemic agents reported having hypoglycemic symptoms in the past 6 months.[2] The prevalence of hypoglycemia in patients with sulfonylurea-treated type 2 diabetes might be as high as 42.2% based on a Romanian study[3] and 50% based on an Argentinian study.[4] Hypoglycemia can lead to many complications, including severe cardiac arrhythmia, vascular injury, temporary focal deficits, impaired cognitive function, and death.[5,6] Recurrent hypoglycemic episodes also reduce patients' quality of life[2] and cause impaired awareness of hypoglycemia (IAH).[6]

Unfortunately, IAH can start a vicious cycle leading to recurrent hypoglycemia or severe hypoglycemia, which in turn can cause serious medical issues and death. IAH is also associated with relatively high risks of various adverse events, such as motor vehicle crashes and falls.[7,8]

Most prior studies have investigated the prevalence of IAH in patients with type 1 diabetes and have shown a moderate variation in the estimate (prevalence of 20%

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to 25%), probably because of differences in the measures used and diversity of the patient populations.[9] Given the increasing number of patients with type 2 diabetes using insulin or oral antihyperglycemic agents and the considerable incidence of hypoglycemia among this group, IAH in type 2 diabetes warrants more attention. Although research shows the prevalence of IAH to be approximately 5.93% to 22.9% in patients with insulin-treated type 2 diabetes,[10-14] there is limited information in patients whose diabetes is treated with oral antihyperglycemic agents.

The factors associated with IAH in type 2 diabetes included lower education,[15] nonpartnered status,[13] high body mass index,[13] diabetes-related comorbidities,[15] lower medication adherence,[15,16] use of complex insulin regimens,[13] higher frequency of hypoglycemia in the past 6 months, and severe hypoglycemia events in the past year.[12] Oral antihyperglycemic agents, especially sulfonylureas, carry high risk for hypoglycemia with long-term use.[16,17] Sulfonylureas use is also associated with IAH.[16] A study by van Meijel et al,[13] however, showed that among patients using insulin for type 2 diabetes, sulfonylurea use protected against IAH. The relationship between receipt of comprehensive medical care to avert diabetic complications and IAH was not considered.

In this study, we aimed to compare the association of duration of medication use with prevalence of IAH between patients with insulin-treated and patients with sulfonylurea-treated type 2 diabetes. The results may inform care strategies to increase patients' awareness of hypoglycemia while being treated for type 2 diabetes.

METHODS

Our study was approved by the Institutional Review Board of National Cheng Kung University Hospital (No. B-ER-109-088).

Study Design and Sample Size

This cross-sectional observational study included a convenience sample of patients with type 2 diabetes currently using insulin and/or a sulfonylurea. Presence of type 2 diabetes was based on the prescriptions refilled. On the basis of the estimated prevalence of IAH from previous studies,[9,13,14] we determined that a sample size of 385 patients would produce a 2-sided 95% CI with a width equal to 0.06 when the IAH prevalence was 10%, which is based on the binomial distribution where the possibility of IAH is the same for each replication. Given the same level of α error and CI precision, the required sample size increases to 897 at an IAH prevalence of 30%. We therefore decided to enroll at least 897 patients.

Patient Enrollment

Data collection was conducted between August and November in 2022. Potential participants were consecutively invited at 7 community pharmacies, 8 primary care clinics, and 4 local health bureaus in Tainan, a metropolis in southern Taiwan with nearly 2 million inhabitants. Thirty-three health care professionals, mostly pharmacists and nurses, identified potential participants. When patients presented their prescriptions for medication refill, the health care professionals verified their eligibility for inclusion. To be eligible, patients had to be aged 20 years or older, live in the metropolitan area of Tainan, and be currently using insulin injections or an oral sulfonylurea, regardless of use or nonuse of other antihyperglycemic agents. The type of insulin used was not collected.

Participation in this study and cooperation of these facilities was entirely voluntary. The health care professionals obtained written informed consent from patients and then conducted face-to-face interviews (lasting roughly 15 minutes) at the time of prescription refilling. A 60-minute training session was provided to the interviewers to standardize the structured interview.

Measures of IAH

Questionnaires developed by Clarke et al[18] and Gold et al[19] (hereafter referred to as the Clarke questionnaire and Gold questionnaire) can be used to determine IAH status in patients with diabetes.

The Clarke questionnaire has 8 questions, with response options to each of "aware" or "reduced awareness."[18] The highest possible total score is 7 "reduced awareness" responses. For the Clarke questionnaire, patients are defined as having IAH if they have 4 or more "reduced awareness" responses. The Gold questionnaire has only 1 question and uses a 7-point Likert scale to represent awareness of hypoglycemia (1 = "always aware" to 7 = "never aware").[19] For the Gold questionnaire, patients are defined as having IAH if they have a score of 4 or higher.

Both questionnaires have been commonly used in prior studies.[10,11] The Chinese versions of the Clarke and Gold questionnaires (Clarke-TW and Gold-TW, respectively) have been translated from the original questionnaires[20] and were used in this study to assess patients' experience of IAH through the interviews. The Clarke-TW and Gold-TW questionnaires have moderate test-retest reliability and satisfactory levels of convergent and discriminant validity.[20]

Measures of Potential Correlates

In addition to assessing IAH, we collected a number of potential correlates of IAH during the interview: (1) sociodemographic characteristics (age, sex, education, marital status, residence, occupation, and living arrangement); (2) disease and treatment histories (diabetes duration, medication category, and duration of antihyperglycemic agent use); (3) self-reported diabetes-related medical care (frequency of clinical visits for diabetes and blood glucose testing, most recent hemoglobin A_{1c} and fasting blood glucose levels, tests for urine microalbumin, and retina and foot examinations);

and (4) health status (perceived health and limitation in daily activities). The perceived health score is based on a validated questionnaire; it has a 100-point scale (scores are in increments of 10 points), and a higher score indicates better health.[21] Limited activity was defined based on the severity of activity limitation due to health problems in the past 6 months (not at all, mild, or severe).[21]

Statistical Analysis

We first used descriptive statistics to calculate mean (SD) values for continuous variables and numbers and percentages for categorical variables. Prevalences of IAH for various durations of insulin and sulfonylurea use were calculated based on results of both the Gold-TW and Clarke-TW questionnaires. The 95% CI of IAH prevalence was calculated with the normal approximation method.

We used a binary logistic regression model with a generalized estimation equation that accounted for the intercorrelation of data collected from the participants interviewed at the same pharmacy, clinic, or health bureau.[22] We generated multiple logistic regression models with sequential adjustment for potential confounders to assess the association of antihyperglycemic drug use for various durations with the likelihood of IAH. The strength of association between various measures and IAH was assessed with adjusted odds ratios. Sequential adjustment for sociodemographics, then disease history and medical care, and finally health status could add information and help ascertain which categories of potential confounders have greater influence on the relationship between duration of drug use and IAH.

All statistical analyses were conducted using the R package version 4.1.3 "gee" function (R Foundation for Statistical Computing).

RESULTS

We invited 1,095 patients aged 20 years or older who had type 2 diabetes and were currently using insulin and/or a sulfonylurea to participate in this study. A total of 898 patients gave informed consent and agreed to be interviewed, for a response rate of 82%.

Patient Characteristics

Table 1 shows the characteristics of the study patients. The cohort was equally divided by sex, and the majority of participants were aged 40 to 69 years. About one-third, 29.8%, had a highest education level of elementary education or less and 46.3% resided in rural areas. Most patients were married (75.2%) and living with others (88.4%), and 36.5% were not actively employed. Nearly 80% of study patients had had type 2 diabetes for at least 5 years, and the mean (SD) duration for all patients was 14.0 (9.8) years. The majority currently used only insulin injections (59.0%), fewer used only oral sulfonylureas (34.9%), and a small group used both (6.1%).

Fully 94.3% of the patients made an outpatient visit for diabetes care every 2 to 3 months, consistent with current guidance on routine care,[16] whereby patients with diabetes must refill their prescriptions every 3 months. Only 56.3% had received a blood glucose test in the past 3 months. Larger shares had received other tests/examinations: 80.1% had

Table 1. Characteristics of Study Patients (N = 898)

Characteristic	Value
Disease and treatment history	
Diabetes duration, No. (%)	
< 1 year	31 (3.5)
1-2 years	65 (7.2)
3-4 years	85 (9.5)
≥5 years	717 (79.8)
Diabetes duration, mean (SD), y	14.0 (9.8)
Current use of hypoglycemic agents, No. (%)	
Insulin only	530 (59.0)
Sulfonylurea only	313 (34.9)
Sulfonylurea and insulin	55 (6.1)
Duration of insulin use, No. (%)[a]	
< 1 year	103 (17.6)
1-2 years	142 (24.3)
3-4 years	106 (18.1)
≥5 years	234 (40.0)
Duration of sulfonylurea use, No. (%)[b]	
< 1 year	23 (6.3)
1-2 years	59 (16.1)
3-4 years	59 (16.1)
≥5 years	225 (61.5)
Sociodemographics	
Sex, No. (%)	
Male	443 (49.3)
Female	455 (50.7)
Age group, No. (%)	
20-39 years	61 (6.8)
40-69 years	643 (71.6)
70-89 years	194 (21.6)
Age, mean (SD), y	59.9 (12.3)
Highest education level, No. (%)	
Illiteracy/elementary	268 (29.8)
Junior high	170 (18.9)
Senior high	263 (29.3)
College and above	197 (21.9)
Marital status, No. (%)	
Married	675 (75.2)
Single	104 (11.6)
Widowed/divorced	119 (13.3)

continues

[a] Denominator is 585 insulin users.
[b] Denominator is 366 sulfonylurea users (2 of 368 had missing data).
[c] Government employees and teachers, agriculture, animal husbandry, forestry, fishing workers, technology workers.
[d] Scale is 1 to 100; a higher score indicates better perceived health.

Table 1. Characteristics of Study Patients (N = 898)
(continued)

Characteristic	Value
Disease and treatment history	
Residence, No. (%)	
Urban	482 (53.7)
Rural	416 (46.3)
Occupation, No. (%)	
Services workers	100 (11.1)
Housekeepers	152 (16.9)
Manufacturing, construction, sales	207 (23.1)
Not actively employed	328 (36.5)
Other[c]	111 (12.4)
Living arrangement, No. (%)	
Living alone	104 (11.6)
Living with others	794 (88.4)
Medical care	
Outpatient visit for diabetes care in past year, No. (%)	
Almost every month	4 (0.4)
Once every 2-3 months	847 (94.3)
Once every 4-6 months	34 (3.8)
Only once in 12 months	3 (0.3)
Irregular	10 (1.1)
Blood glucose test in past 3 months, No. (%)	
No	392 (43.7)
Yes	506 (56.3)
Urine microalbumin test in past year, No. (%)	
No	179 (19.9)
Yes	719 (80.1)
Retina examination in past year, No. (%)	
No	251 (30.0)
Yes	647 (70.0)
Foot examination in past year, No. (%)	
No	186 (20.7)
Yes	712 (79.3)
Health status	
Perceived health score, mean (SD)[d]	69.8 (13.2)
Limited daily activities for ≥6 months, No. (%)	
Not at all	704 (78.4)
Mild	181 (20.2)
Severe	13 (1.4)

[a] Denominator is 585 insulin users.
[b] Denominator is 366 sulfonylurea users. Two had missing data.
[c] Government employees and teachers, agriculture, animal husbandry, forestry, fishing workers, technology workers.
[d] Scale is 1 to 100; a higher score indicates better perceived health.

received a test for urine microalbumin, 70% a retina examination, and 79.3% a foot examination in the past year.

The patients had a mean (SD) perceived health score of 69.8 (13.2) on the 100-point scale. Few (1.4%) reported severe impairment of physical functioning in daily activities for more than 6 months.

IAH Prevalence

Among insulin users, the overall prevalence of IAH based on the Gold-TW and Clarke-TW criteria was 41.0% (95% CI, 37.0%-45.0%) and 28.2% (95% CI, 24.6%-31.8%), respectively (Table 2). IAH prevalence in patients using insulin for less than 1 year was consistently higher than that in patients using insulin for 5 or more years, regardless of whether Gold-TW or Clarke-TW criteria were used.

Among sulfonylurea users, the overall prevalence of IAH based on the Gold-TW and Clarke-TW criteria was 65.3% (95% CI, 60.4%-70.2%) and 51.3% (95% CI, 46.2%-56.4%), respectively (Table 2). In addition, the IAH prevalence in patients using sulfonylureas for 5 or more years was consistently higher than that in those using sulfonylureas for less than 1 year with both Gold-TW and Clarke-TW measurements.

Odds of IAH generally increased with duration of sulfonylurea use and were significantly elevated in patients using these drugs for at least 5 years compared with peers not using them at all (Supplemental Table 1 and Supplemental Table 2). Conversely, longer use of insulin was associated with reduced odds of IAH relative to no use. Regular receipt of certain diabetes-related medical care (blood glucose tests, retina examinations, and possibly urine microalbumin tests) was associated with lower odds of IAH in both sulfonylurea users and insulin users.

Independent Risk Factors for IAH

In multiple logistic regression analysis, based on Gold-TW criteria, sulfonylurea use for 1 to 2 years, 3 to 4 years, and 5 or more years was associated with increased odds of IAH (crude ORs = 2.68, 1.89, and 3.84, respectively) compared with no use (Table 3). After adjusting for sociodemographic factors, disease history and receipt of medical care, and health status, only use for 5 or more years remained significantly associated with an increased likelihood of IAH (adjusted OR = 3.56). In contrast, compared with no insulin use, insulin use for 1 year or longer was associated with significantly lower odds of IAH before and after adjustment for other factors; the reduction was most pronounced with 5 or more years of use (crude OR = 0.25; fully adjusted OR = 0.33).

Findings of the analysis using IAH prevalence measured instead by Clarke-TW criteria were largely the same (Table 4). In the fully adjusted model, compared with no use, 5 or more years of sulfonylurea use carried sharply higher odds of IAH (adjusted OR =3.06), whereas 5 or more years of insulin use vs none was associated with a roughly halving of the odds of this complication (adjusted OR = 0.52).

DISCUSSION

To the best of our knowledge, very few studies have investigated risk factors for IAH among people with insulin- or oral antihyperglycemic–treated type 2 diabetes, especially using 2 measurement tools simultaneously. We found that the

prevalence of IAH with sulfonylurea use for 5 or more years among patients with sulfonylurea-treated diabetes was higher than that with insulin use for 5 or more years among patients with insulin-treated diabetes based on both Gold-TW and Clarke-TW criteria. Longer sulfonylurea use was associated with higher odds of IAH, but longer insulin use was associated with lower odds. In addition, regular blood glucose tests and retina examinations were significantly associated with lower risk of IAH determined by both sets of criteria.

Findings in Context

In Asia, the prevalence of IAH determined by the Gold and Clarke questionnaires among people with insulin-treated type 2 diabetes collected from hospitals was 19.6% and 13.7%, respectively, in Singapore, but that from clinics was between 5.93% and 17.01% in Jordan.[11,12] Among people with insulin- and oral antihyperglycemic–treated type 2 diabetes, the prevalence of IAH based on the Clarke questionnaire was 25% in Spain[15] and 52.1% in the Kingdom of Saudi Arabia.[23] All of these studies showed that IAH prevalence was higher among patients treated with insulin, with or without oral antihyperglycemic agents, than among those treated with insulin only. Although sulfonylureas are older antihyperglycemic agents, studies investigating IAH prevalence among users are limited. Moreover, these studies have not investigated the relationship between the duration of use and IAH.

Table 2. Prevalence of Impaired Awareness of Hypoglycemia, by Duration of Antihyperglycemic Drug Use and Overall

Group and Duration of Use	Gold-TW Criteria[a]		Clarke-TW Criteria[b]	
	Score, Median (Range)	IAH Prevalence Rate (95% CI[c])	Score, Median (Range)	IAH Prevalence Rate (95% CI[c])
Insulin users (n = 585)				
Duration of use				
< 1 year	5 (1-7)	57.3 (47.7-66.9)	3 (0-5)	30.1 (21.2-39.0)
1-2 years	3 (1-7)	44.4 (36.2-52.6)	3 (0-5)	31.7 (24.0-39.4)
3-4 years	3 (1-7)	41.5 (32.1-50.9)	3 (0-5)	26.4 (18.0-34.8)
≥5 years	2 (1-7)	31.6 (25.6-37.6)	2.5 (0-6)	26.1 (20.5-31.7)
Overall	2 (1-7)	41.0 (37.0-45.0)	3 (0-6)	28.2 (24.6-31.8)
Sulfonylurea users (n = 366)				
Duration of use				
< 1 year	3 (1-7)	47.8 (27.4-68.2)	3 (0-4)	30.4 (11.6-49.2)
1-2 years	5 (1-7)	62.7 (50.4-75.0)	4 (1-5)	50.9 (38.1-63.7)
3-4 years	4 (1-7)	54.2 (41.5-66.9)	3 (0-5)	39.0 (26.6-51.4)
≥5 years	5 (1-7)	70.7 (64.8-76.6)	4 (0-5)	56.9 (50.4-63.4)
Overall	5 (1-7)	65.3 (60.4-70.2)	4 (0-5)	51.3 (46.2-56.4)

Clarke-TW = Chinese version of Clarke questionnaire; Gold-TW = Chinese version of Gold questionnaire; IAH = impaired awareness of hypoglycemia.

[a] Possible scores range from 1 to 7. A score of 4 or higher was defined as IAH.
[b] Possible scores range from 0 to 7. A score of 4 or more "reduced awareness" responses was defined as IAH.
[c] The 95% CI was calculated by the normal approximation method.

In our study, the prevalence of IAH among patients with sulfonylurea-treated type 2 diabetes, both overall and long term, as determined by Gold-TW and Clarke-TW criteria was higher than that among patients with insulin-treated type 2 diabetes. The inconsistent prevalence of IAH across studies might be explained by different populations, treatment regimens, and/or measurement tools. Rubin et al[24] showed that 32% of patients with type 1 diabetes were inconsistently classified by the 2 questionnaires, and the Clarke questionnaire was more likely than the Gold questionnaire to classify an individual as having IAH. Moreover, in contrast to the Gold-TW questionnaire with its single item, the Clarke-TW questionnaire with its 8 questions shows 2 discrete domains of IAH, namely, unawareness of a low blood glucose level and ignorance of hypoglycemia symptoms,[20] revealing the bifactorial nature of this questionnaire. The different IAH prevalences based on Gold-TW and Clarke-TW criteria could be due to dissimilar psychometric properties between the 2 questionnaires. The potential clinical implementation of these 2 questionnaire might depend on the prevalence of IAH as determined by their use. A questionnaire yielding higher prevalence might be better for screening, even given the possibility of a higher false-positive rate, which is potentially less concerning when the follow-up method is noninvasive.

Long-acting sulfonylureas are a type of insulin secretion–stimulating agent that have a higher risk of hypoglycemia than other oral antihyperglycemic agents. In a study by Jennings et al,[25] the prevalence of reported hypoglycemic symptoms largely declined after use of a sulfonylurea for more than 4 years, reflecting drug failure, sufficient knowledge to avoid hypoglycemia, and/or IAH. Sola et al[26] have pointed out that sulfonylurea use should be limited to 3 to 6 months in relatively young patients to avoid secondary failure. Secondary failure occurs after prolonged use, which directly stimulates beta cells and leads to their progressive dysfunction and reduced insulin secretion, ultimately worsening diabetes control.[26] C-peptide concentration has been shown to fall in patients using sulfonylureas long term; use for more than 5.7 years is associated with a significant decline from baseline.[27] Prolonged exposure to sulfonylureas, with repeated beta cell stimulation, likely causes recurrent hypoglycemia episodes, leading to an attenuated sympathoadrenal response and increased odds of IAH.[28] Our study revealed that patients with type 2 diabetes who used sulfonylureas for 5 or more years had higher odds of IAH based on Gold-TW and Clarke-TW criteria.

In addition, insulin use is thought to confer a high risk of hypoglycemia, and patients with a history of recurrent hypoglycemia might have greater risk of IAH.[29,30] We found an inverse

Table 3. Odds Ratios for Impaired Awareness of Hypoglycemia Assessed by Gold-TW Criteria, According to Duration of Insulin and Sulfonylurea Use

Drug and Duration of Use	Model 1 Crude OR (95% CI)	Model 2[a] Adjusted OR (95% CI)	Model 3[b] Adjusted OR (95% CI)	Model 4[c] Adjusted OR (95% CI)
Duration of insulin use				
No use	1.00	1.00	1.00	1.00
< 1 year	0.72 (0.46-1.13)	0.72 (0.45-1.15)	0.72 (0.42-1.23)	0.73 (0.42-1.26)
1-2 years	0.43 (0.28-0.64)	0.43 (0.28-0.65)	0.55 (0.35-0.88)	0.55 (0.35-0.88)
3-4 years	0.38 (0.24-0.60)	0.37 (0.23-0.59)	0.52 (0.31-0.87)	0.54 (0.32-0.92)
≥5 years	0.25 (0.17-0.35)	0.23 (0.16-0.33)	0.32 (0.21-0.48)	0.33 (0.22-0.49)
Duration of sulfonylurea use				
No use	1.00	1.00	1.00	1.00
< 1 year	1.46 (0.63-3.38)	1.46 (0.62-3.46)	0.43 (0.17-1.08)	0.42 (0.17-1.03)
1-2 years	2.68 (1.54-4.68)	2.92 (1.64-5.21)	1.11 (0.57-2.15)	1.09 (0.56-2.12)
3-4 years	1.89 (1.10-3.25)	1.91 (1.10-3.29)	1.11 (0.58-2.12)	1.06 (0.54-2.09)
≥5 years	3.84 (2.75-5.38)	3.91 (2.78-5.52)	3.56 (2.45-5.19)	3.50 (2.39-5.13)

Gold-TW = Chinese version of Gold questionnaire; OR = odds ratio.

Note: Multiple logistic regression models with sequential adjustment for potential confounders. The "no use" groups are the reference groups.

[a] Adjusted for sociodemographics: age, sex, highest education level, marital status, living area, occupation, living arrangement.
[b] Adjusted for sociodemographics and disease history and medical care: diabetes duration, outpatient visit for diabetes care in past year, blood glucose test in past 3 months, urine microalbumin test in past year, retina examination in past year, foot examination in past year.
[c] Adjusted for sociodemographics, disease history and medical care, and health status: perceived health, limited daily activities for ≥6 months.

Table 4. Odds Ratios for Impaired Awareness of Hypoglycemia Assessed by Clarke-TW Criteria, According to Duration of Insulin and Sulfonylurea Use

Drug and Duration of Use	Model 1 Crude OR (95% CI)	Model 2[a] Adjusted OR (95% CI)	Model 3[b] Adjusted OR (95% CI)	Model 4[c] Adjusted OR (95% CI)
Duration of insulin use				
No use	1.00	1.00	1.00	1.00
< 1 year	0.42 (0.26-0.67)	0.39 (0.24-0.63)	0.51 (0.29-0.87)	0.51 (0.30-0.88)
1-2 year	0.45 (0.30-0.68)	0.45 (0.29-0.69)	0.57 (0.35-0.93)	0.57 (0.35-0.92)
3-4 year	0.35 (0.21-0.57)	0.34 (0.20-0.56)	0.52 (0.30-0.91)	0.53 (0.30-0.93)
≥5 year	0.34 (0.24-0.49)	0.33 (0.23-0.48)	0.52 (0.35-0.78)	0.52 (0.34-0.78)
Duration of sulfonylurea use				
No use	1.00	1.00	1.00	1.00
< 1 year	1.27 (0.51-3.16)	1.33 (0.51-3.43)	0.57 (0.22-1.50)	0.54 (0.21-1.42)
1-2 years	3.01 (1.74-5.20)	3.27 (1.85-5.81)	0.99 (0.50-1.99)	1.05 (0.52-2.12)
3-4 years	1.86 (1.06-3.25)	2.03 (1.14-3.62)	0.99 (0.52-1.87)	0.98 (0.51-1.89)
≥5 years	3.84 (2.77-5.33)	3.84 (2.74-5.37)	3.04 (2.10-4.38)	3.06 (2.11-4.44)

Clarke-TW = Chinese version of Clarke questionnaire; OR = odds ratio.

Note: Multiple logistic regression models with sequential adjustment for potential confounders. The "no use" groups are the reference groups.

[a] Adjusted for sociodemographics: age, sex, highest education level, marital status, living area, occupation, living arrangement.
[b] Adjusted for sociodemographics and disease history and medical care: diabetes duration, outpatient visit for diabetes care in past year, blood glucose test in past 3 months, urine microalbumin test in past year, retina examination in past year, foot examination in past year.
[c] Adjusted for sociodemographics, disease history and medical care, and health status: perceived health, limited daily activities for ≥6 months.

relationship, however, between duration of insulin use and IAH. One possible explanation might be that clinicians provide good education about hypoglycemia risk and its prevention to patients starting insulin therapy. In addition, correct insulin use (eg, adequate injection skill, accurate injection of the intended dose, appropriate injection timing) may lower hypoglycemia risk. Therefore, education about correct insulin use among patients with type 2 diabetes is very important, in that it might decrease the risk of hypoglycemia and improve survival over time.[31] Although hypoglycemia has been implicated as a potential risk factor for IAH, this information was not collected in our study. It was not easy for patients to recall information on hypoglycemia, especially mild events. The reasons for the differential association of hypoglycemia history with IAH between insulin users and sulfonylurea users need more study.

Patients who reported receiving regular medical care to avert diabetes complications had a lower prevalence of IAH. Specifically, those with regular blood glucose tests and retina examinations were significantly less likely to experience IAH as determined by both Gold-TW and Clark-TW criteria. The risk of IAH among patients with longer use (≥5 years) of sulfonylureas declined after additional adjustment for medical care (regular outpatient visits and regular follow-up/screening examinations); with Gold-TW criteria, the adjusted OR fell from 3.91 to 3.56 (Table 3) and with Clarke-TW criteria, it fell from 3.84 to 3.04 (Table 4). Patients with a good physician-patient relationship tend to have a lower risk of nonadherence and better health care outcomes.[32] This implies that those who regularly receive follow-up care generally interact favorably with their physicians, leading to better prognosis, possibly including a lower risk of IAH.

Strengths and Limitations

This study has several strengths. First, considering that there is much less information on IAH prevalence in type 2 diabetes vs type I diabetes, and that the former needs more investigation, our findings make an additional contribution to the evidence base. Second, with a sufficient sample size, this study was able to generate antihyperglycemic agent duration-specific estimates of IAH prevalence

without compromising precision. Third, a response rate exceeding 80% leaves little room for selection bias. Fourth, both the Gold-TW questionnaire and Clarke-TW questionnaire have been tested for validity and reliability, thereby providing reassurance on patients' IAH classification. Fifth, the risk of residual confounding was considered small because we included a comprehensive list of potential correlates for IAH.

This study also has some limitations, however. First, generalizability of our findings is limited because we included only patients with type 2 diabetes who used insulin injections and/or sulfonylureas. Moreover, all study participants were residents of Tainan, which allowed them to refill prescriptions in person at community pharmacies, primary care clinics, or local health bureaus. Second, information on medical care relied solely on self-report in our study, and it was not possible to validate self-report against medical charts or electronic health records, which might lead to overreporting of medical care due to patients' desires to adhere to social norms and to please the interviewer. This limitation could be especially valid given that all of the interviewers were health care professionals.[33] Third, the findings should be interpreted with caution because the cross-sectional study design precludes causal inference of the study results.

CONCLUSIONS

Long-term sulfonylurea use was associated with a higher risk of IAH among patients with type 2 diabetes. Lower IAH risks were seen in patients receiving regular medical care, suggesting the potential beneficial influence of adherence to medical monitoring. This finding also suggests that patients with regular outpatient visits and physicians with firm arrangements for follow-up blood glucose testing and complication screening are important to reduce IAH risk in type 2 diabetes. Further studies such as clinical trials proving a causal effect of physician adjustment of therapeutic strategies on hypoglycemia risk are needed to identify interventions for improving hypoglycemia awareness in this population.

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Key words: hypoglycemia; type 2 diabetes; sulfonylurea; insulin; hypoglycemic agents; glycemic control; risk factors; diabetes complications; primary care

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Supplemental materials

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