The association of hypoglycemia severity and economic outcomes among patients with type 2 diabetes mellitus using basal insulin

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INTRODUCTION

- Diabetes is a chronic, progressive, lifelong condition estimated to have affected 415 million adults worldwide in 2015. The prevalence of diabetes is predicted to rise by over 50% by 2040, and the economic burden of the disease, estimated at $320 billion in the US alone in 2015, is likely to rise as a consequence.[1]
- The treatment goal for people with diabetes is to achieve and maintain plasma glucose concentrations within a target range, avoiding periods of hyper- and hypoglycaemia.[2]
- Basal insulin (BI) therapy is an integral component of the management strategy for type 2 diabetes mellitus (T2DM),[2] although many patients reduce their insulin dose or omit injections in response to hypoglycemic episodes, and physicians cite concerns regarding hypoglycemia as a barrier to optimal BI use.[3]
- In addition to being a barrier to achieving glycemic control, hypoglycemia is costly in terms of healthcare utilization; the direct cost of an episode requiring assistance from a healthcare practitioner was estimated at $1161 in the US.[4]
- Although a number of real-world database studies (using data from claims and electronic medical records) have reported the costs of severe hypoglycemia, the direct and indirect burden of non-severe hypoglycemia is rarely captured.

OBJECTIVE

To assess whether economic outcomes (productivity, healthcare utilization and costs – both direct and indirect) differed by hypoglycemia severity among patients with T2DM receiving BI in the US.

METHODS

- This study used the US National Health and Wellness Survey (NHWS), which is an annual self-administered internet-based survey of a demographically representative segment of the US adult (aged ≥18 years) population.
  - Data were obtained from the 2011–2013 diabetes patient datasets, which had a total sample size of 17,676 uniquely identified patients with T2DM. For patients who participated in multiple survey years, only their most recent data were kept for analyses. Participants provided informed consent.
  - This analysis used data from eligible respondents who had T2DM and were using BI.
- Patients were categorized as having no hypoglycemia, non-severe hypoglycemia (episodes not requiring third-party intervention) or severe hypoglycemia (episodes requiring third-party intervention) in the preceding 3 months. The timing of the hypoglycemic event (nocturnal or daytime) was also collected.
- Patient characteristics included in the survey: demographic information, HbA1c medical history (e.g. Charlson Comorbidity Index (CCI) scores and diabetes-related complications) and treatment received (covering both general and diabetes-related conditions).
- Economic outcomes:
  - Work productivity and activity impairment was measured using the 6-item Work Productivity and Activity Impairment (WPAI) questionnaire.[5] Only respondents who reported being in full-time or part-time employment provided data for absenteeism (hours missed in the last week because of ill health), presenteeism (hours missed in the last week because of health impairment while at work) and overall work impairment. All respondents provided data for impairment in activities of daily living, such as shopping, cleaning, gardening etc.
  - Healthcare utilization was defined by the number of healthcare provider visits, emergency room visits and hospitalizations in the past 6 months.
  - Direct and indirect costs were estimated from the 2012 Medical Expenditure Panel Survey (MEPS; mean values) and the US Bureau of Labor Statistics (BLS), respectively. Data were adjusted to give annualized estimates; indirect costs were only estimated for employed respondents.

- Subgroup analyses were performed to evaluate the effect of potential confounders, such as patients with macrovascular (congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease) and/or microvascular disease (retinopathy, kidney disease), on any observed differences in outcomes according to hypoglycemia severity.
- Multivariable generalized linear models were employed for group comparisons, with adjustment for covariates (e.g. age, HbA1c, any diabetes complications).
- WPAI, healthcare utilization and costs had skewed distributions, and were therefore analyzed specifying a negative binomial distribution with logarithm linkage models; least square (LS) means along with corresponding p-values were reported.

RESULTS

Study population:

- A total of 2423 patients were included (patient characteristics are shown in **Table 1**).
  - Overall, glycemic control was suboptimal; of those patients who reported an HbA1c level, 64.0% had a value ≥7.0%.
- 61.3% (1485/2423) of surveyed patients had experienced hypoglycemia in the 3 months prior to the time of the survey.
  - Non-severe hypoglycemia was reported by 55.1% (1335/2423) of patients and severe hypoglycemia by 6.2% (150/2423).
  - For both non-severe and severe events, one-third of patients reported their hypoglycemic episode as nocturnal.

Patient characteristics by hypoglycemia severity:

- Patients who experienced severe hypoglycemia were younger than those who experienced non-severe or no hypoglycemia (both p<0.001; **Table 1**).
- Those with severe hypoglycemia had a higher mean HbA1c than those with non-severe hypoglycemia (p=0.001). However, those with non-severe events tended to have lower HbA1c values than those with no hypoglycemia (p=0.002; **Table 1**).
- Those with any hypoglycemia had higher CCI scores and were more likely to have microvascular comorbidities than those with no hypoglycemia (all p<0.05). Patients with severe hypoglycemia were more likely to have macrovascular comorbidities than those with no hypoglycemia (p=0.034). In addition, patients with severe hypoglycemia had higher CCI scores than those with non-severe hypoglycemia (p=0.001; **Table 1**).

Work productivity and activity impairment:

- Patients who experienced severe hypoglycemia reported greater overall work productivity impairment than those who experienced non-severe or no hypoglycemia (adjusted LS means: 36.6% vs 21.3% and 18.0%, respectively, both p<0.05) and greater activity impairment (54.4% vs 41.1% and 38.8%, respectively, both p<0.001) (**Figure 1A**).

Healthcare utilization and impact on costs:

- After adjusting for patient demographics and clinical characteristics, patients with severe hypoglycemia had a greater number of doctor visits in the past 6 months compared with patients with non-severe and no hypoglycemia (10.28 vs 7.73 and 6.97, respectively, both p≤0.001). A similar pattern emerged with the number of emergency room visits (0.93 vs 0.31 and 0.30, respectively, both p<0.001), and hospitalizations (0.56 vs 0.19 and 0.23, respectively, both p<0.001) in the past 6 months (**Figure 1B**).
- As a result of greater work productivity impairment and resource use, patients with severe hypoglycemia, compared with patients with non-severe and no hypoglycemia, incurred higher adjusted annual direct ($58,887 vs $30,728 and $30,273, both p<0.001) and total costs ($60,194 vs $34,142 and $32,643, both p<0.001) in the past 6 months (**Figure 1C**).
- Patients with non-severe hypoglycemia had greater numbers of doctor's visits and higher indirect costs compared with those without hypoglycemia, after controlling for observed confounders (both p<0.05; **Figures 1B** and **1C**).

Table 1: Patient characteristics by hypoglycemia severity among patients with T2DM using basal insulin

| Patient characteristics	No hypoglycemia in the past 3 months (n=938)	Non-severe hypoglycemia in the past 3 months (n=1335)	Severe hypoglycemia in the past 3 months (n=150)	Non-severe vs no	Severe vs no	Severe vs non-severe
General characteristics						
Age, years	60.8 (11.0)	61.0 (10.5)	55.3 (13.0)	0.602	<0.001	<0.001
Gender (female), n (%)	352 (37.5)	518 (38.8)	58 (38.7)	0.538	0.789	0.974
BMI category, n (%)						
Overweight (≥25 to <30 kg/m²)	179 (19.1)	303 (22.7)	38 (25.3)	0.038	0.075	0.467
Obese (≥30 kg/m²)	683 (72.8)	928 (69.5)	100 (66.7)	0.088	0.120	0.474
Duration of diabetes, years	16.28 (9.43)	17.14 (8.87)	15.55 (9.38)	0.270	0.374	0.038
Duration of BI use, years	8.17 (7.44)	9.27 (7.51)	9.09 (9.67)	0.0006	0.2669	0.8257
HbA1c, %	7.51 (1.46)	7.31 (1.29)	7.78 (1.84)	0.002	0.106	0.001
HbA1c category, %						
<7.0%	23.2	30.5	18.7	<0.001	0.214	0.003
≥7.0%	47.2	48.8	44.0	0.449	0.462	0.261
Don't know	29.5	20.7	37.3	<0.001	0.054	<0.001
Hypoglycemia during preceding 3 months, %						
Daytime	N/A	66.7	66.7	N/A	N/A	1.0
Nocturnal	N/A	33.3	33.3	N/A	N/A	1.0
Comorbidities						
CCI score excluding diabetes	0.88 (1.38)	1.05 (1.56)	1.51 (1.80)	0.008	<0.001	0.001
Microvascular comorbidities, %	16.2	20.7	27.3	0.006	0.001	0.062
Macrovascular comorbidities, %	24.5	26.7	32.7	0.279	0.034	0.118
Concomitant medication, %						
Insulin sensitizers (metformin or thiazolidinediones)	53.7	52.3	49.3	0.496	0.316	0.493
GLP-1 receptor agonists	5.7	6.3	2.7	0.527	0.128	0.075
Secretagogues (sulfonylureas or meglitinides)	24.3	27.4	32.0	0.097	0.044	0.235
DPPIV inhibitors	10.8	7.7	10.7	0.012	0.970	0.207
Rapid/pre-mix insulin	47.7	62.2	56.0	<0.001	0.058	0.141

Data are mean (SD) unless otherwise indicated. 75% of patients responded to the question of "Any hypoglycemia episodes in the past 3 months?". Non-severe hypoglycemia refers to self-managed events; severe hypoglycemia refers to events that required third-party assistance.
BI, basal insulin; BMI, body mass index; CCI, Charlson Comorbidity Index; DPPIV, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide-1; SD, standard deviation

Economic outcomes stratified by macrovascular and microvascular disease:

- After adjusting for covariates, results obtained when evaluating patients with macrovascular and/or microvascular disease were generally consistent with the overall population (data not shown).
  - Of note, among patients with macrovascular and/or microvascular disease, non-severe hypoglycemia was associated with a greater frequency of both doctor visits and emergency room visits compared with those reporting no hypoglycemia.

Figure 1

Figure 1: (A) Work productivity and activity impairment, (B) healthcare resource utilization and (C) costs by hypoglycemia severity among patients with T2DM using basal insulin (adjusted for covariates)

All generalized linear models adjusted for the following covariates: age, gender (females vs males), ethnicity (non-Hispanic black, Hispanic, other vs non-Hispanic white), income (<$50K, declined to answer vs >$50K), insurance (don't have vs have), presence of diabetes complications (have any vs none), HbA1c (don't know; uncontrolled vs controlled), years diagnosed with diabetes, number of oral antihyperglycemic drugs, Charlson Comorbidity Index (CCI; excluded diabetes and diabetes-related complications), body mass index (overweight, obese, unknown vs underweight/normal weight), and exercise (≥1 times vs 0 times in past month). Non-severe hypoglycemia refers to self-managed events; severe hypoglycemia refers to events that required third-party assistance. Absenteeism, presenteeism, overall work impairment and direct costs calculated only for employed respondents. Total costs for unemployed respondents do not include indirect costs. ER, emergency room; ns, not significant; LS, least squares

STRENGTHS AND LIMITATIONS

- The study was able to capture non-severe and nocturnal hypoglycemic events. This contrasts with typical real-world databases based on health insurance claims or electronic medical records, which tend to capture only the more severe events resulting in healthcare encounters.
- The study is potentially limited owing to the self-reported nature of the data – information was not verified by patients' medical charts or other objective data.
- The data are cross-sectional in nature and do not allow for causal explanations to be generated.
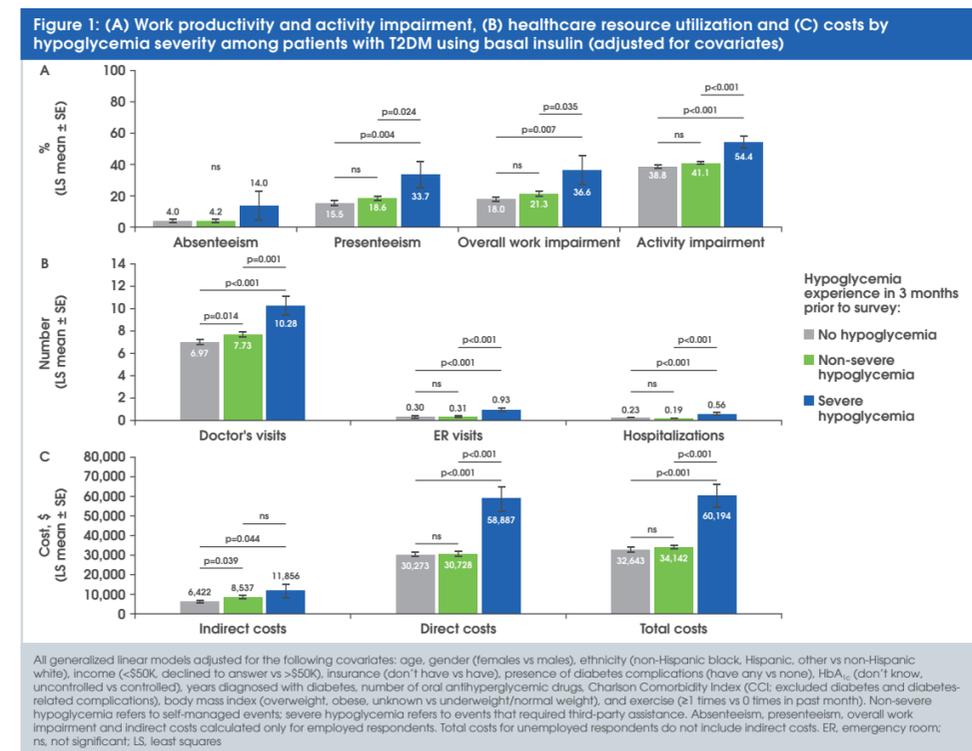
SUMMARY

- Although patients with no hypoglycemia had higher HbA1c values than those with non-severe hypoglycemia; patients with severe events had higher HbA1c levels than those with non-severe events. Experience of severe events may have been a barrier to driving towards glycemic targets.
- Individuals with severe hypoglycemia, compared with those with non-severe or no hypoglycemia, experienced greater activity and work productivity impairment, utilized healthcare resources to a greater extent and incurred higher associated costs.
- Non-severe events are frequently under-reported in database analyses; however, they should not be overlooked when assessing the overall burden of hypoglycemia, because such events occur far more frequently than severe events. In this analysis, non-severe hypoglycemia was associated with significantly more doctor visits and indirect costs versus no hypoglycemia, after accounting for patient characteristics.

CONCLUSION

Although the elevated economic burden seen in patients with hypoglycemia may be multifactorial, these findings highlight the need for treatment options with better hypoglycemic profiles in patients with T2DM receiving basal insulin.