

Systematic Review Research Proposal

Health Care Resource Use and Costs for Adult Patients Presenting to Emergency Departments with Acute DM-Associated Hypoglycemia: a Systematic Review

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1 Introduction/Background

Hypoglycemia is a condition characterized by abnormally low levels of blood glucose. Clinically relevant episodes of this condition are mainly associated with both Type 1 and Type 2 Diabetes Mellitus (DM) and are a consequence of treatment of the disease; low blood glucose results from failure to adjust antihyperglycemic therapy to unexpected reduction in nutritional intake (2,3). The most important effect of hypoglycemia is impairment of function due to a deficiency of glucose in the brain. Mild cases are transient and can be reversed with a simple oral supplementation while moderate and severe cases can result in seizures and coma. Hypoglycemia is also linked to higher rates of adverse cardiovascular events (1).

Although DM-associated hypoglycemia presentations to emergency departments (ED) are infrequent, severe hypoglycemic episodes often result in ED presentation. These presentations are usually preceded by pre-hospital care by emergency medical services (EMS). Treatment approaches in both the pre-hospital and ED settings are not well standardized. For example, a recently published review of 11 Canadian sites enrolling 1039 DM cases found that 84% arrived by ambulance and hypoglycemic patients with type 1 DM were less frequently admitted to hospital than those with type 2 DM (1). Additionally, relapse rates can be high, especially for patients with type 2 DM who present more frequently and have higher rates of comorbidities. Clearly, hypoglycemic presentations result in considerable costs in the form of investigations, prolonged ED stay, and hospital admission (1).

The economic burden of DM in several countries is well understood. In Canada, according to the Canadian Diabetes Association, the direct cost of the disease accounts for approximately 3.5% of public healthcare spending with an economic burden estimated at \$12.2 billion in 2010, rising by \$4.7 billion by 2020 (4). In the USA, the total cost of diabetes was estimated by the American Diabetes Association to be \$245 billion in 2012, an increase of 41% from \$174 billion in 2007 (5). Data specific to the cost of DM-associated hypoglycemia, however, is lacking.

2 Rationale

An understanding of the health care resource use and accompanying costs for patients presenting to EDs with DM-associated hypoglycemia is likely to provide valuable information regarding the economic consequences of these events. This information will serve to encourage administrators, clinicians and manufacturers to improve the detection, treatment and prevention of the condition.

3 Objective

To conduct a systematic literature review regarding health care use and economic evaluations of adult patients presenting to the ED or requiring hospitalization with DM-associated hypoglycemia.

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4 Methods

4.1 Question

In adult patients with diabetes mellitus (Population) presenting to the ED (Setting), what are the health costs (Outcomes) associated with moderate to severe acute hypoglycemia (Exposure)?

4.2 Characteristics of Studies

Studies will be included if they are primary studies that report direct and/or indirect costs of DM-associated hypoglycemia presenting to the ED or requiring hospitalization. A wide range of study designs will be eligible including prospective and retrospective cohort studies, administrative database studies, and controlled clinical trials. The patients in the studies will be adults, or mostly adults, who presented to an ED with a primary or secondary diagnosis of hypoglycemia.

4.3 Search Methods

A systematic search of published literature databases for relevant articles will be conducted with the aid of a medical librarian and expert searcher. The following databases will be searched: MEDLINE, EMBASE, CINAHL, Global Health, SCOPUS, EconLit, EBMALL, several of the EBM Reviews, ProQuest Dissertations and Theses Global, Conference Proceedings Citation Index - Science (CPCI-S) -- 1990-present, Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH) -- 1990-present, and OCLC PapersFirst. Searches will employ both controlled vocabulary (e.g. MeSH and Emtree) and text words to identify the concepts "hypoglycemia" and "economics". In the primary databases (MEDLINE, EMBASE, and CINAHL), pediatric and animal studies will be excluded. Reference lists from included studies will also be searched. Restrictions of language and publication period will not be applied. Foreign language articles will be translated using Google Translate. The draft search query, below, was designed for use on MEDLINE and will be adapted for the other databases.

Draft search query:

- 1 Diabetic Coma/ or exp Hypoglycemia/ or (hypoglycemia or hypoglycaemia or "low blood sugar").ti,ab. (38464)
- 2 (hypoglyc?emic adj1 (emergenc* or event* or shock or coma or comas or incident or incidents or severe or hospitalization* or accident* or condition or conditions)).ti,ab. (2202)
- 3 1 or 2 (39031)
- 4 exp *Economics/ or exp *Models, Economic/ (266594)
- 5 economics.fs. (340830)
- 6 (fiscal* or financ* or income* or revenue* or charges or "out of pocket" or levy or levies or cost or costs or costing or economic* or fee or fees or price or prices or priced or pricing or budget* or afford* or cost or costs or costing or money or monetary or payment* or outlay or "burden of illness" or "lost days of work" or "length of stay").m_titl. (164532)
- 7 4 or 5 or 6 (528790)
- 8 3 and 7 (394)
- 9 limit 8 to "all child (0 to 18 years)" (74)
- 10 limit 9 to "all adult (19 plus years)" (40)

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- 11 8 not 9 (320)
- 12 10 or 11 (360)
- 13 limit 12 to animals (11)
- 14 12 not 13 (349)

4.4 Selection Method

Studies will be independently assessed in two steps by two reviewers (CA, SK). In the first step, the title, abstract, and keywords/descriptors of each study will be assessed and relevant studies will be selected for full review. In the second step of the assessment, the full text of each study will be assessed and relevant studies will be selected for inclusion in the systematic review. Agreement among the reviewers regarding inclusion of studies in the systematic review will be measured using the Kappa (κ) statistic. Disagreements between the two reviewers will be resolved by a third individual (BHR or SEJ) and reasons for exclusion of a study will be documented.

4.5 Study Quality Assessment

The Newcastle-Ottawa scale (NOS) will be used for assessing the quality of included studies. This scale was designed for assessing the quality of nonrandomized studies to be used in a systematic review (6). It employs a 'star system' that is applied on three perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. The NOS was determined by Deeks et al to be suitable for use in a systematic review (6).

4.6 Analysis

Costs will mainly be reported descriptively. If there is a reasonable quantity of homogeneous costs reported across studies, data pooling and calculation of descriptive statistics (mean with standard deviation or median with interquartile range, as necessary) will be performed. Descriptive statistics may be calculated for cost of hypoglycemia episodes overall and for purposes of comparison between subgroups such as costs for patients with DM type 1 vs type 2 and costs for patients who are discharged vs admitted.

5 Budget

This project is being completed with support from: 1) the Emergency Medicine Research Group (EMeRG), Department of Emergency Medicine, University of Alberta; 2) Merck Inc, Montreal, PQ. Dr. Rowe is supported through the Canadian Institutes of Health Research (CIHR) as a Tier I Canada Research Chair in Evidence-based Emergency Medicine from the Government of Canada. The funders have no control over the content of the review.

6 Dissemination Plan

The results will be submitted to a peer-review journal and presented at the Canadian Association of Emergency Physicians Annual Scientific Meeting in Edmonton, AB in June 2015.

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7 Timeline

This protocol will be submitted in March 2015 to the Health Research Ethics Board (HREB) of the University of Alberta. Literature search and selection for systematic review is expected to begin February 1, 2015 and end June 2015.

8 References

1. Rowe, B. H., Singh, M., Villa-Roel, C., Leiter, L. A., Hramiak, I., Edmonds, M. L., et al. (2015). Acute management and outcomes of patients with diabetes mellitus presenting to Canadian emergency departments with hypoglycemia. *Canadian Journal of Diabetes*, 39(1), 55-64.
2. Morales, J., & Schneider, D. (2014). Hypoglycemia. *The American Journal of Medicine*, 127(10 Suppl), S17-24.
3. Cornish, W. (2014). Safe and appropriate use of insulin and other antihyperglycemic agents in hospital. *Canadian Journal of Diabetes*, 38(2), 94-100
4. Economic tsunami: The cost of diabetes in Canada (2009). Canadian Diabetes Association.
5. American Diabetes Association. (2013). Economic costs of diabetes in the U.S. in 2012. *Diabetes Care*, 36(4), 1033-1046.
6. Deeks, J. J., Dinnes, J., D'amico, R., Sowden, A., Sakarovitch, C., Song, F., et al. (2003). Evaluating non-randomised intervention studies. *Health Technology Assessment*, 7(27), 1-179.

9 Appendices

Appendix 1: Motivation

The reference below served as key motivation for this systematic review. It comprised a Canada-wide retrospective chart audit of diabetic patients who presented with hypoglycemia to Canadian EDs between 2008 and 2010. With this systematic review, we seek to provide an economic perspective to complement the clinical perspective.

Rowe, B. H., Singh, M., Villa-Roel, C., Leiter, L. A., Hramiak, I., Edmonds, M. L., et al. (2015). Acute management and outcomes of patients with diabetes mellitus presenting to Canadian emergency departments with hypoglycemia. *Canadian Journal of Diabetes*, 39(1), 55-64.

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Appendix 2: **Table 1. Description of studies (Template).**

RefID	Lead Author	Year	Country	Currency	Study Design	Format	DM Type Studied	Cost Type Reported

Appendix 3:

Table 2. Cost of DM-associated hypoglycemia episode (non-specific/overall basis; Template).

Study		Cost							Notes
RefID	Lead Author	Year	Currency	Mean	SD	95% CI		Range	Median
						Lower	Upper	Lower	Upper

Appendix 4: **Table 3. Cost of DM-associated hypoglycemia episode by medical setting (Template).**

Study		Costs by Main Medical Settings												
Lead Author	Year	Currency	ED				Outpatient				Inpatient (Hospitalization)			
			Mean	SD	95% CI	Median	Mean	SD	95% CI	Median	Mean	SD	95% CI	Median

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Appendix 5: Systematic Review Study Eligibility Form

Reviewer: _____ Date: _____ Study ID: _____
YYYY-MM-DD

Inclusion Criteria	Yes	No	Unsure/ Maybe
Study Design			
Is this a primary research study?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Study Population			
Are all or most patients adults?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do patients have diabetes mellitus (either of type 1 or 2)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do patients have hypoglycemia and/or other complications of diabetes mellitus?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Study Outcomes			
Does the study report costs of DM-associated hypoglycemia incurred in an acute care setting? (Acute care setting e.g. ED, outpatient, inpatient.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Non-English report requiring translation	<input type="checkbox"/>	Language: _____	
Reviewer's Decision:			
Include	<input type="checkbox"/>	Exclude	<input type="checkbox"/>
		Unsure	<input type="checkbox"/>
Final Decision:			
Include	<input type="checkbox"/>	Exclude	<input type="checkbox"/>
		Unsure	<input type="checkbox"/>