SMGroup

The Cost of Hypoglycemia

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INTRODUCTION

Hypoglycemia is a common complication in diabetes treatment, and can causes major complications as well as morbidity and mortality.

There are varying degrees of severity for hypoglycemia according to the need or not for a third person.

Hypoglycemia is defined as non severe if the person can manage the event alone.

Severe hypoglycaemia is an event requiring the intervention of another party to actively administer carbohydrates, glucagon, or take other corrective actions [1]. It's generally associated with insulin therapy and represents a major problem in the management of diabetic patients.

Hypoglycemia has a considerable impact on the lives of diabetic patients including depression, heightened anxiety, impairment of the ability to drive, work and function in ways that are important for quality of life [2].

It can become a major barrier for initiating or intensifying antihyperglycemic therapy and obtaining a better metabolic control.

It's also an important source of falls [3], accidents [4], diabetic shock or coma , dementia [5], and it's associated with increase in the risk of mortality particularly in patients type 2 diabetics with known cardiovascular diseases [6].

In addition to the clinical consequences, treatment of severe hypoglycemic episodes requires substantial health care resources, such as Emergency Room **(ER)** visits and hospitalizations.

Despite the fact that the European Association for the Study of Diabetes and the American Diabetes Association emphasize that education on the recognition and management of hypoglycemia is an important part of diabetes therapy, the effective doctor-patient communication about hypoglycemia is not well established [7].

Hypoglycemia occurs more frequently in insulin-deficient states Type 1 Diabetes Mellitus **(T1DM)** but is also a concern in Type 2 Diabetes Mellitus **(T2DM)** [8].

These last years, many clinical trials illustrated the high frequency of the severe hypoglycemia in T1DM but also in T2DM.

Indeed in the ACCORD, ADVANCE and VADT trials, sets out to determine the effect of the lowering of glucose to near-normal levels on cardiovascular risk in type 2 diabetes showed incidence rates for severe hypoglycemia in intensive insulin group ranging from 0,7 to 12 events/100 person-years.

The DCCT and UKPDS trials demonstrated that the risk of hypoglycaemia increases as glycemic control improves [9,10].

The UKPDS has shown that there is no significant difference in the frequency of severe hypoglycemia in T2DM treated by sulfonyl ureas or insulin less than 2 years; however the frequency increases after 5 years of insulin therapy. What is particularly interesting to note is the higher incidence of severe hypoglycemia in T1DM treated by insulin compared to T2DM. Moreover, this trial reported incidence rates of severe hypoglycemia of 110 and 320 events per 100 patient-years for individuals with T1DM treated by insulin for less than 5years or more than 15years, respectively. However, the determination of the prevalence of hypoglycemia in « real-life » is too complicated and the most available data are from small prospective studies or larger retrospective studies [11,12].

In France a study was carried out to determine the frequency of hypoglycemia in « real-life » setting. DIALOG was a national wide observational study to evaluate the incidence of severe and non-severe confirmed hypoglycemia in a real-life setting among patients T1DM and insulin-treated T2DM and to define the predictive factors for hypoglycaemia.

This study showed that 13.4% of T1DM and 6.4% of T2DM treated by insulin present at least one episode of severe hypoglycemia during one month only of follow up [13].

Otherwise, the increase in the prevalence of diabetes may also create problems for healthcare systems as hypoglycemia can have a direct and indirect economic impact [14].

COSTS OF HYPOGLYCEMIA

Hypoglycemia is an acute complication of diabetes, its costs is considerable because it occurs frequently, affects seriously the daily life and can be a cause of morbidity and mortality.

Hypoglycemia is a considerable cost burden to healthcare systems and society , William *et al.* reported that patients with confirmed hypoglycemia had a 71% ($p \leq 0.001$) increase in diabetes-related healthcare costs during a 12-month period compared to patients with no hypoglycemia [15]. Moreover Hypoglycemia is responsible for the hospitalization of 8% of the diabetic patients and involves an increase the length of hospital stay and mortality [16,17].

Turchin *et al*. demonstrated that for each day of hypoglycemia, the length of hospital stay increased by 2.5 days and the risk of death increased by 85.3% during the hospitalization and by 65.8% after one year [17]. In addition, many reports estimated that 4 to 10% of deaths of patients with type 1 diabetes were due to hypoglycemia [1,18]. In a study of 1013 adults with type 1 and type 2 diabetes, self-reports of severe hypoglycemia, after 5years, were associated with a 3.4-fold increased risk of death compared with those who reported mild or no hypoglycemia episodes [19].

A study on more than 100.000 hospitalized patients with diabetes demonstrated that patients whose average blood glucose was <70mg/dl had higher total charges (38.9%), longer lengths of stay (3 days) and higher mortality than patients who not had low blood glucose levels [20].

Calculating the cost of hypoglycemia is a complex issue because it depends on the frequency and the severity of the hypoglycemic episode and also on the difference of healthcare system from country to country based on the quality of service and the extent of treatment.

The costs of hypoglycemia include direct, indirect and intangible costs.

The Direct Medical Costs

It include costs for the medical treatment of hypoglycemia, it depends on the severity of the event.

Severe hypoglycemia may require hospitalization, the moderate episode may require emergency care, and consultation by a doctor, and mild forms may need only a glucagon injection.

The Indirect Costs

- A number of diabetes patients may not be able to continue working or work as effectively as they could before the onset of their condition.
- A loss of productivity due to sickness, absence, disability, premature retirement or premature mortality [21].
- However loss of productivity is seldom significant, because most severe hypoglycemia episode do not happen while patients are at work [22].

- Moreover, in long-term, the recurring episodes of hypoglycemia require a reinforcement of the glycemic self-monitoring and a follow-up by a physician or a nurse, it's also a contributor to clinical inertia in intensifying therapy, impacting maintenance of euglycemia, and leading to increase of the risk of diabetes complications [23].

Intangible Costs

- Pain, anxiety, inconvenience and other factors which decrease quality of life [21].
- The constant fear of developing hypoglycemia that some patients experience after one severe hypoglycemia event may lead to behavioral changes to manage hypoglycemia symptoms and cause sub-optimal insulin therapy and poor glycemic control [24].
- These last years, some medico-economic studies, mainly from anglosaxons and scandinavian countries have allowed to evaluate the costs of hypoglycemia [25-27].
- The results are different between studies because it depends on several factors: the country of study, the type of costs considered, data collection methodologies used, and there is a lack of consensus of classification of hypoglycemia across studies.
- Furthermore, studies have focused on the evaluation of the impact of severe hypoglycemia, the economic and clinical implications of non severe hypoglycemia were examined by few studies including the Brod *et al* paper [28].

Direct and indirect costs of hypoglycemia

Hypoglycemia represents a considerable burden in terms of healthcare systems and has a substantial negative impact on health and patient quality of life [29] (figure1).

In some cases, hypoglycemia can leads to hospitalization, especially in elderly patients. In fact, oral hypoglycemic agents and insulin were responsible, respectively, for 10.7% and 13.9% of the emergency hospitalization for adverse drug events in US elderly patients (>65) from 2007 through 2009 [30].

A large retrospective study realized in a major university hospital in North America reported that hypoglycemia was responsible for 7.7% of admissions [17].

Lipska *et al*, noted that during the period from 1999 to 2011, the rates of hospital admissions for hypoglycemia have risen by 11.7% among older adults in the United States, and hypoglycemia rates were 2-fold higher for older patients (≥75 years) [31].

Although the economic aspects of hypoglycemia management are experiencing a rise in interest [32], only few studies tried to determine the cost of hypoglycemia [33].

An Italian retrospective study estimated the mean hospitalization cost at €5137 per admission and the average cost per each SHE at €1911. The yearly total cost of severe hypoglycemia in patients with diabetes in Italy was estimated to be approximately €23 million, mostly due to hospital admission [34].

On the basis of a validated hypoglycemic model, a recent publication estimated the US economic impact of hypoglycemic events to be approximately $900 million per year and the direct costs for severe episodes requiring assistance from a healthcare practitioner to be $1161 per episode [35].

Comparatively, in a retrospective analysis of 320 severe hypoglycemic events in patients with diabetes in an emergency department in Korea from 2006 to 2009, the largest medical cost was $1.385 per event [36].

In a retrospective observational study conducted in Andalusia Autonomous Region during 2012, all hypoglycemic emergency calls that requested medical assistance were registered, the total estimated annual costs were €6 093 507, and the mean direct cost per episode was €702±565 much higher for the episodes requiring emergency hospital care (€1677±304) [37]. However Farmer *et al* [38], estimated the average cost per hypoglycemic emergency call of only €363, which is considerably much lower than the cost found in Barranco *et al* study. This is because Farmer *et al* did not include some costs such as the distance between transfers or the use of a helicopter.

A recent survey (n=30710) estimated that the cost of hypoglycemia-related hospitalization was high €10,258 and it was a direct consequence of the length of stay noticed in hypoglycemic patients [39].

Ward *et al* reported that the annual cost of hypoglycemia event was €16.478, € 1311, €176 when requiring respectively a hospitalization, emergency department visit and glucagon injection [27].

A European survey has estimated both direct and indirect costs of treatment and follow up for Severe Hypoglycaemic Events **(SHEs)** in diabetes patients receiving insulin in Germany, Spain and the UK [25].

The average cost per SHEs was similar in the three countries for patients with type 2 diabetes (Germany €533, Spain €691, UK €537). Otherwise, the costs per SHE for type 2 patients were higher than type 1 diabetes patients (Germany €441, Spain €577, UK €236) [25].

The highest costs per event were for hospitalized patients and were estimated at €3023-3298 in Germany and only €1400 in Spain and €1300 in UK, this higher cost observed in Germany were due to a longer duration of hospital stay.

This cost estimation in German is a little lower than that found in a swedish study of type 2 diabetes patients which reported a total costs of €3918 per severe hypoglycemic event including direct costs €2807 and indirect costs €1111 [40]. The total cost of hypoglycemia was estimated to be €4,250,000 (€14 per patient with Type 2 diabetes) per year of which moderate episodes contributed the largest proportion [40].

Similarly, a french study estimated that the average cost of hospitalization for hypoglycemia was FF14,000 per event (2133 euros 2000; 2836 euros 2014) in 1992, with a length of stay in hospital of 6.6days [41].

A prospective study over 12 months period conducted in Tayside, Scotland has estimated the total direct cost of emergency treatment of severe hypoglycemia to £92.078 in one year, and based on the prevalence statistics for diabetes in Tayside, the autors estimated that severe hypoglycaemia could cost to the health service ≤ £13 million a year [42].

In a french analysis collecting all cases of severe hypoglycemia occurring in Grenoble during 2010, the mean cost per episode was €4977 and the total yearly cost was €522.648. Extrapolating this results to the whole of France, the authors estimated the national total cost to >125 millions € per year [43].

Another french national multicenter study HYPO15 estimated the mean cost of severe hypoglycemia to €2000 per event and the total cost to > €40 million per year [44].

Despite the comparison between the studies is difficult according to the differences in health services, it is obvious that severe hypoglycemia poses significant burdens to each healthcare system and society.

Considering that most episodes of severe hypoglycemia are treated at home without the intervention of emergency medical services, cases of hypoglycemia requiring an emergency department are considered to be the « tip of the iceberg ».

A recent US analysis reported that mild hypoglycemia episode may incur similar annual direct medical costs to severe hypoglycemia [32,35].

In addition, recent evidence suggests that the average cost of non severe hypoglycemic events is approximately $127 per person per event [45].

A recent study, estimated that lost productivity ranged from $15.26 to $93.47 per non severe hypoglycemia event representing 8.3-15.9 hours of lost work time per month, 18.3% missed work for a mean duration of 9.9 hours. Among those who reported having a non-severe hypoglycemic episode outside working hours, 22.7% were either late for work or missed a whole day. Nocturnal hypoglycemia was associated with the highest cost for lost productivity with an average of 14.7 working hours lost [28].

Moreover this study demonstrated that the week following a non severe hypoglycemic event, patients monitor their blood glucose test frequently and, consequently, they require an average of 5.6 extra tests. Monthly out-of-pocket costs for test strips and lancets were estimated at $17.23± $19.51 [28].

Intangible costs of hypoglycemia

Hypoglycemia has a large impact on patient lives in terms of physical, mental, and social functioning; it can disrupt many everyday activities such as driving, travel, work performance and leisure pursuits [46]. In addition, hypoglycemia is associated with a significant impact on Health Related Quality of Life **(HR QoL)** in both short and long term [47].

Short term implications relate to the actual episodes and include unpleasant symptoms [48] and negative effects on mood and emotions [49], but the major risk of hypoglycemia occurs in dangerous situations, for example if neuroglucopenia occurs when driving, it can causes motor vehicle accidents [50].

Hypoglycemia can also interfere with balance, coordination; vision and level of consciousness and lead to falls and injury, such as fractures and joint dislocations. Hypoglycemia can cause coma, seizure and may precipitate a stroke [51].

Long-term consequences of hypoglycemia relate to negative social and emotional sequelae, including change in behavior and self-management and fear of future episodes.

Numerous studies demonstrate the adverse effects of hypoglycemia on HR QoL and it appears that patients suffering hypoglycemic episodes are more at risk of developing anxiety and panic attacks [24,52].

Marrett *et al* assessed HRQoL using the EuroQol- 5D Questionnaire **[EQ-5D]** US-weighted summary score [utility] and Worry subscale of the Hypoglycemia Fear Survey **[HFS]**) to evaluate the impact of the severity and frequency of hypoglycemia on quality of life. Severity was classified as mild, moderate, severe and very severe. After adjusting for age, gender, weight gain, HbA1c, microvascular complications and selected cardiovascular conditions, it was seen that the utility decrement was 0.045 (by level of severity: 0.009, 0.055, 0.131, 0.208), and the HFS increase was 9.6 (by severity: 5.3, 12.4, 17.6, 23.2). HRQoL further decreased with greater frequency of hypoglycemic episodes [8]. Alvarez-Guisasola *et al*, evaluated patient-reported hypoglycemic symptoms with ratings of their HRQoL state (EuroQol visual analogue scale, EQ- 5D VAS), and patient-reported adverse events. It was seen that patients reporting hypoglycemic symptoms had significantly lower EQ-5D VAS scores, indicating worse patient-reported quality of life. Patients with severe symptoms of hypoglycemia had lower EQ-5D VAS scores compared with patients with moderate, mild, or no symptoms [53].

In a Swedish survey of 309 patients with type 2 diabetes, 37% reported (n=115) reported symptoms of hypoglycemia in the past month. Health-related utility measured via the EQ-5D was considerably lower in patients with hypoglycemic symptoms (0.7) than those with no hypoglycemic symptoms (0.77) (p=0.006) [54].

A study demonstrated that patients reporting hypoglycemia symptoms were significantly more likely to have lower HRQoL in several parameters including limitations on mobility (OR=1.93,

p<0.0001) and usual activities (OR=1.78, p<0.0001), increased pain/discomfort (OR=2.00, p<0.0001), and anxiety/depression (OR=2.31, p<0.0001) [55]. Even minor hypoglycemia symptoms (e.g., sweating, hunger, anxiety) can reduce QoL [56,57].

Davis *et al* demonstrated- using a retrospective survey (n=861) and generic utility estimates (EQ-5D and SF-36)- that mean health-related utility decreased as the severity of hypoglycemia increased and that nocturnal hypoglycemia had less of an effect on HRQoL during the 3 months before undertaking the survey [58]. Solli *et al* showed that ischemic heart disease and social limitations had a greater negative impact on HRQoL in patients with type 1 diabetes, while fear of hypoglycemia and work limitations had a greater impact on patients with type 2 diabetes [59].

Elderly patients are at an increased risk for geriatric syndromes (i.e., depression and falls), pharmacotherapy-related hypoglycemia, and diabetes complications which further complicates care management. Care planning is also complicated because of limited life expectancy and high rates of co morbidity and functional disability. Laiteerapong *et al* have demonstrated that geriatric syndromes [-5.3 (95% CI -5.8 to -4.8), p < 0.001] and diabetes complications [-3.5 (-4.0 to -2.9), p < 0.001] were associated with lower physical HRQoL. Hypoglycemia was associated with lower mental HRQoL [-4.0 (-7.0 to -1.1), p = 0.008] [60].

The negative consequences and unpleasant symptoms associated with hypoglycemia can provoke significant anxiety or fear of hypoglycemia in patients with diabetes [24].

The constants threat of hypoglycemia can be associated with chronic anxiety which can disturb normal sleep and cause marital disharmony and affect personal relationships.

Nocturnal hypoglycemia is particularly feared, because symptoms are absent during sleep and blood glucose monitoring is rarely performed during the night [61].

The Hypoglycemic Fear Survey **(HFS)** was developed to quantify fear of hypoglycemia experienced by patients and their families and it is the most widely measure used [62].

This scale is divided into behavior and worry subscale; the behavior subscale includes items describing diabetes self-management and the worry subscale uses items relating to anxiety provoking aspects of hypoglycemia [24].

It has been proved that high scores on the HFS behavior scale were positively associated with increased frequency of history of hypoglycemia and high levels of the HFS worry scale were reported by patients with a lower mean daily blood glucose level and higher mean blood glucose level variability [63].

Another study found that patients with type 1 diabetes reported an increased fear of hypoglycemia with increased frequency of severe hypoglycemic episodes, and patients with type 2 diabetes reported increased fear of hypoglycaemia as the number of both mild/moderate and severe events increased [64].

These studies suggest that the magnitude of fear of hypoglycemia is associated with the severity and frequency of previous hypoglycemic episodes.

Fear of hypoglycemia has also been found to be associated with personality traits as anxiety. Polonsky *et al* observed that in patients with both type 1 and type 2 diabetes, there was a correlation between higher scores on the worry scale of the HFS and higher levels of trait anxiety and fear. In patients with type 1 diabetes, higher scores on the worry scale were also associated with difficulty in discriminating between anxiety and hypoglycemia symptoms [65].

The alteration of the ability to discriminate between anxiety and hypoglycemia could prevent patient from managing correctly hypoglycemia and lead to severe hypoglycemic episode.

Fear of hypoglycemia not only increases psychological distress, but it is also thought to have a behavioral impact on diabetes management and metabolic control. In order to avoid symptoms of past hypoglycemia episodes, patients who have fear of hypoglycemia can decrease or omit insulin, resulting in poor glycemic control and an increased risk of serious health consequences [24].

A self-administered survey of 202 patients with type 1 and 133 patients with type 2 diabetes has shown that following a mild or moderate hypoglycemic episode, 37.8% of type 1 and 29.9% of type 2 diabetes patients reported increased fear of future episodes; and 74.1% and 43.3%, respectively, reported modifying their insulin dose. Additionally, they demonstrated that following a severe hypoglycemic episode the majority of patients; 63.6% type 1 and 84.2% type 2 reported increased fear of future episodes and 78.2% and 57.9%, respectively, reported modifying their insulin dose [66].

Fear of hypoglycemia affects also the parents of children with diabetes [67] has a negative impact on both parental health and quality of life. The Patton 2008 study showed that mothers experienced greater fear of hypoglycemia than fathers of young children [68]. Scores on the behavior scale of the HFS, particularly of mothers, suggest that they may maintain slightly higher than optimal glucose levels in their children in order to avoid hypoglycemia [68,69] and this hypoglycemia avoidance behavior in parents may lead to poor glycemic control.

PREVENTION OF HYPOGLYCEMIA

Since hypoglycemia constitutes a barrier to diabetes management and metabolic control and a substantial burden to healthcare systems, prevention is indispensable. Prevention of hypoglycemic episodes should be achieved through patient-centered process. The establishment of an appropriate glycemic target for each patient is essential. An individualized target range should be identified after a thorough appraisal of a patient's medical history considering age, life expectancy, duration of disease, presence or absence of co morbidities and diabetes complications, previous history of hypoglycemia, and psychosocioeconomic characteristics [70]. Less stringent targets are recommended for patients at higher risk of hypoglycemia [71,72].

Effective education of patients (and their relatives) is fundamental in the treatment of diabetes mellitus. Clinicians should review the signs and symptoms of hypoglycemia regularly with patients and to make sure that patients have indeed assimilated the quantity of glucose needed to correct hypoglycemic episode as well as when to retest. Moreover, patients should receive dietary counseling with special highlight on dietary missteps and practical advice about physical exercise.

A detailed analysis of the ACCORD trial has shown that approximately half of all severe hypoglycemic episodes were preceded by delayed or missed meals or low carbohydrate consumption in the preceding meal [73].

It's generally accepted that Self-monitoring of Blood Glucose **(SMBG)** is useful in insulin treated patients but the role of SMBG in self-management of glycemia is not clearly established for patients using non insulin therapies [74]. However, experts agree that SMBG plays a fundamental role in the identification and prevention of hypoglycemia [71,75].

In certain circumstances, the use of a CGM device may help to assess glycemia in diabetes patients and identify hypoglycemia [76]. It has been shown that real-time CGM has a beneficial in preventing severe hypoglycemia in people with impaired awareness of hypoglycemia [77] and might be one of the major methods by which the risk of hypoglycemia can be considerably diminished.

Continuous subcutaneous insulin infusion with external insulin pumps reduces the risk of severe hypoglycemia in children and adults with T1DM [78] and seems to be most effective in people receiving multiple insulin injection therapy who have a high frequency of hypoglycemia [79].

In addition, to facilitate an appropriate glycemic control with lower risk of hypoglycemia, progress in the field of research of insulin treatment, have been defined, by the near upcoming availability of degludec insulin. This is a new ultra-long acting basal insulin (half-life: about 25 h), which forms soluble multi-hexamers, when injected subcutaneously, determining a deposit from where the degludec insulin is absorbed continuously and slowly in the circulation, leading to a uniform and stable hypoglycemic effect.

Degludec insulin shows an intra-patient day to day variability in glucose-lowering effect four times lower compared to insulin glargine [80].

In spite of the development-in the past 30 years -of many types of insulin, formulations and new approach of delivery comprising the introduction of human insulin and insulin analogues, the frequency of hypoglycemia has not changed in adults with T1DM [81]. In patients with T2DM, the increase use of aggressive insulin therapy might be associated with an increased risk of hypoglycemia. Short-acting insulin analogues do not influence the frequency of severe hypoglycemia [82] but the long-acting analogues seem to have modest effect in lowering the risk of nocturnal events in insulin-treated patients [83].

Wherever possible, pharmacologic therapy for T2DM should preferably employ therapeutic agents that exhibit a low risk for producing hypoglycemia.

Obviously sulphonyl ureas and other insulin secret agogues for treating T2DM are recognized to cause hypoglycemia, but all glucose-lowering drugs can potentially cause hypoglycemia.

Nevertheless, the frequencies of hypoglycemia with new classes of oral and injectable glucose-lowering drugs such as the incretin mimetics (GLP 1 receptor agonists and DPP 4 inhibitors) and the SGLT2 inhibitors, are very low [84].

The increasing use of these agents rather than sulphonylureas should help to reduce the risk of hypoglycemia and its consequences especially in vulnerable groups such as elderly individuals.

CONCLUSION

Hypoglycemia has a substantial adverse impact on mortality, morbidity and quality of life and it causes a tremendous economic burden to the healthcare systems in the emerging epidemic of type 2 diabetes. It is important for clinicians to be attentive to hypoglycemia when managing patients with diabetes. Because of the risk of hypoglycemia it's fundamental to use realistic and safe glycemic targets especially in vulnerable group such as people with coronary heart disease, very young children and the frail elderly. Treatment selection, as well as glycemic targets, should be also customized based on each patient's individual risk of hypoglycemia. This measures designed to reduce the incidence of hypoglycemic events have the potential to save considerable healthcare costs, while greatly improving the quality of life of patients with diabetes.

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