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Malnutrition and Hypoglycemia Risk among Patients with Diabetes Mellitus

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Abstract

Hypoglycemia is associated with increased risk of morbidity and mortality, and is detrimental to patients regardless of Diabetes Mellitus (DM) status. Among patients with DM, hypoglycemia is considered a result of overtreatment of anti-diabetic agents (iatrogenic hypoglycemia). Among patients without DM, this condition is attributed to disease severity. Recently, high malnutrition risks, as well as other markers of malnutrition, were indicative of increased risk of hypoglycemia among hospitalized patients. In this review we focus on the relationship between hypoglycemia and malnutrition among patients with and without DM.

Keywords: Albumin; Diabetes mellitus; Hypoglycemia; Malnutrition; Nutrition

Introduction

Hypoglycemia can be defined as serum glucose level equal or under 70mg/dL (≤3.9mmol/L) [1,2]. Among patients with diabetes mellitus, and in accordance with the International Hypoglycemia Study Group guidelines, serum glucose under 54mg/dL (≤3.0mmol/L), is sufficiently low to indicate serious, clinically important hypoglycemia and thus should be routinely reported in clinical trials dealing with glucose-lowering agents [3]. For decades, it was assumed that serum glucose level is mostly regulated by two hormones-insulin and glucagon. Nowadays, it is well known that glucose homeostasis is regulated by various glucoregulatory hormones which effect multiple target tissues, such as muscle, brain, liver, and adipocyte [4,5].

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Classification of hypoglycemia

According to the report of the workgroup of the American Diabetes Association and The Endocrine Society, hypoglycemia can be classified as follows [6].

Severe hypoglycemia: Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Documented symptomatic hypoglycemia: Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70mg/dL (≤3.9mmol/L).

Asymptomatic hypoglycemia: Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70mg/dL (≤3.9mmol/L).

Probable symptomatic hypoglycemia: Probable symptomatic hypoglycemia is an event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70mg/dL (≤3.9mmol/L).

Pseudo-hypoglycemia*: Pseudo-hypoglycemia is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration >70mg/dL (>3.9mmol/L) but approaching that level.

*According to the previous report of the American Diabetes Association workgroup on hypoglycemia from 2004, this state was defined as "Relative hypoglycemia" [7].

Risk factors and prognosis associated with hypoglycemia

Risk factors for hypoglycemia among hospitalized patients include DM, older age, disease severity, renal insufficiency, septic shock, mechanical ventilation, tight glycemic control and increasing number of anti diabetic agents [8,9]. Iatrogenic hypoglycemia is associated with administration of insulin and insulin-secretagogues (sulfonylureas and meglitinides) [10].

Documented hypoglycemia is associated with poor short and long term prognosis among patients admitted to internal medicine departments regardless of Diabetes Mellitus (DM) status [11]. Among patients with DM, hypoglycemia was repeatedly shown to be associated with an increased length of hospital stay and decreased short and long term survival [9,11-13]. Moreover, hypoglycemia was found to be associated with an increased risk for dementia among older adults with DM [14-16]. Association between morbidity and hypoglycemia among patients without DM was documented as well [17-19]. While the prevalence of hypoglycemia is higher among DM patients, the

prognosis of patients with hypoglycemia is worse among patients without DM [20]. This raises the possibility that the etiology of hypoglycemia, rather than hypoglycemia per-se, is responsible for the poor outcome observed.

Spontaneous hypoglycemia

As described previously, hypoglycemia can also occur among hospitalized patients without DM. Unexpected severe (below 55mg/dL, 3mmol/L) hypoglycemia in non-diabetic patients outside the intensive care unit was 36 per 10,000 admissions (95% CI 24-64), and more than 90% of the patients were admitted as emergency cases [21]. Rate of hypoglycemia was higher among patients aged 65 and over. Hypoglycemia was more prevalent among patients with sepsis, kidney disease, alcohol dependence, pneumonia, liver disease, cancer, and self-harm with hypoglycemic agents. Spontaneous hypoglycemia may also occur among patients with DM, as was found among patients suffering from infection, with or without sepsis [22]. Postprandial (reactive) hypoglycemia may also be the cause of spontaneous hypoglycemia among patients with DM [23,24].

Hypoglycemia and malnutrition

Malnutrition is defined as an imbalance between consumption and expenditure of either energy, protein or any other nutrient that damages body function [25].

Several suggestions for classification of malnutrition were suggested over the years, mostly in infants and children in developing countries. In 1955, Gomez et al. [26], suggested a classification of malnutrition in infancy and childhood based on child's weight compared to that of a child in the 50th percentile of the same age. A later classification by Waterlow et al. [27], was based on z- Scores (SD) which took into account both weight and height of the child. The World Health Organization (WHO) classification is based on Waterlow's system with some modifications [28].

Two major clinical syndromes of malnutrition include kwashiorkor (almost normal weight for age, marked generalized edema) and marasmus (depletion of subcutaneous fat stores, muscle wasting, and absence of edema), though a mixed variant is also frequent [28].

Several types of malnutrition were described with different pathogeneses [29]. For example, malnutrition can be induced by reduced food intake due to diminished appetite, or as a result of impaired nutrient absorption [30]. Other causes include older age, socio-economic status and comorbidities [31]. In 2015, about 795 million people were undernourished worldwide [32]. Prevalence of malnutrition is high among inpatients as well. In a study including 504 newly hospitalized adult patients, 159 of them (31.5%) were identified as being at high risk for malnutrition according to the Nutrition Risk Score (NRS) 2002 [33,34]. Other studies showed that as many as 50% of all patients admitted to hospitals in western countries were malnourished or had an increased risk of malnutrition [35,36].

In the developing world, it has been demonstrated that patients with severe malnutrition (and hypoglycemia) may have Malnutrition-Related Diabetes Mellitus (MRDM), a rare type of diabetes associated with long term malnutrition [37,38]. Additionally, we showed recently that one of the risk factors for hypoglycemia among patients with and without DM was high risk for malnutrition as measured by the NRS2002 [39].

There are several surrogate markers for malnutrition that can be measured in the blood stream, serum albumin being the most frequently used. Albumin level was shown to be influenced by nutritional status [40], however, there is still a controversy whether albumin level is a marker of nutrition status [41], because it plays a major role in various medical conditions [42]. Interestingly, serum albumin is as accurate a predictor of outcome as the APACHE II Score among Intensive Care Unit (ICU) patients [43]. Low albumin level is associated with increased morbidity and mortality in many patient populations [44,45].

Other marker suggested as an indicator of malnutrition is serum prealbumin (i.e transthyretin). The major source of this protein is in the liver [46] and it has a half-life of two days [47]. Moreover, serum level of prealbumin is not altered by hydration status [48]. A reverse correlation was found between prealbumin level and mortality among hospitalized elderly patients with a decreased nutrient intake [49] and patients treated with hemodialysis and peritoneal dialysis [50]. On the other hand, among critically ill patients with inflammation, serum prealbumin level was not a sensitive marker for evaluating the adequacy of nutrition support. It was found that only change in CRP level was able to significantly predict changes in level of prealbumin, indicating that increase in prealbumin was as a result of improvement in inflammation, rather than nutrient intake [51].

Additional markers of nutritional status include serum cholesterol. It was shown that among patients with DM, both total and LDL cholesterol levels were lower in undernourished patients compared to well-nourished [52]. This was true regardless of treatment with insulin. In a recently published systematic review and meta-analysis regarding the association between blood biomarkers and risk of malnutrition in older adults, it was found that serum albumin, prealbumin and total cholesterol are useful biochemical indicators of malnutrition, even with the presence of chronic inflammation [53]. Recently we showed that serum albumin and cholesterol levels measured at hospital admission, predict hypoglycemia in patients admitted to general internal medicine units, regardless of DM status [54].

The mechanism responsible for hypoglycemia among malnourished patients is still unknown. A possible explanation might be a depletion of hepatic glycogen storage. Evidence to support the association of glycogen storage with hypoglycemia can be found in patients that suffer from Glycogen Storage Disorders (GSDs). These disorders are inborn errors of metabolism with abnormal storage or utilization of glycogen, with a cardinal presenting feature of hypoglycemia [55]. In spite of the different pathophysiology of both conditions, they may have the same clinical outcome, i.e., hypoglycemia. Other factors that may increase the likelihood of glycogen depletion include a shift towards anaerobic metabolism. Further research is warranted to determine the pathophysiology of hypoglycemia among malnourished patients.

Conclusion and Recommendations

In conclusion, hypoglycemia is associated with poor short and long-term prognosis and increased morbidity and mortality. Hypoglycemia is more common among patients with DM, probably as a result of anti-diabetic agents. However, it can occur among patients without DM as well. After diagnosis of hypoglycemia is established, a thorough evaluation of patient's nutritional status is recommended because of high risk for malnutrition. This is true regardless of

DM status. We recommend that nutritional assessment includes both laboratory tests as well as a referral to nutrition nurse, dietitian or expert clinician for further evaluation, including nutrition risk screening questionnaire and other nutritional and metabolic variables. A detailed care plan should be established following careful monitoring of outcomes.

Conflict of Interest

All the authors declare no conflict of interest.

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