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A practical and evidence-based approach to management of inpatient diabetes in non-critically ill patients and special clinical populations

Aidar R. Gosmanov *

Endocrinology Section, Stratton VAMC, 113 Holland Avenue, Albany, NY 12208, USA

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ABSTRACT

Inpatient diabetes is a common medical problem encountered in up to 25–30% of hospitalized patients. Several prospective trials showed benefits of structured insulin therapy in managing inpatient hyperglycemia albeit in the expense of high hypoglycemia risk. These approaches, however, remain underutilized in hospital practice. In this review, we discuss clinical applications and limitations of current therapeutic strategies. Considerations for glycemic strategies in special clinical populations are also discussed. We suggest that given the complexity of inpatient glycemic control factors, the "one size fits all" approach should be modified to safe and less complex patient-centered evidence-based treatment strategies without compromising the treatment efficacy.

Introduction

About 25–30% of hospitalized patients have a known diagnosis of diabetes while additional 5–10% of patients will have the diagnosis discovered during admission for the first time [1–4]. Over the last decade, the inpatient diabetes prevalence remains steady as was reported by the same group of authors in 2002 and 2016 [3,5]. The Endocrine Society clinical practice guidelines suggest that, based on retrospective and observational evidence, inpatient random blood glucose (BG) levels below 180 mg/dL and fasting BG below 140 mg/dL are more likely to be associated with better clinical outcomes such as reduced risk of infections, less disability after hospital discharge, and improved perioperative complications in non-critically ill medical and surgical patients [1]. However, in prospective trials, the positive impact of BG goal-driven glycemic control in non-intensive care unit (non-ICU) setting was less evident [6] raising a question if intensive management of hyperglycemia in non-ICU setting is of targetable clinical benefit. Only one randomized controlled trial conducted in surgical patients on the floor showed that scheduled insulin therapy targeting recommended inpatient glycemic goals reduces incidence of infections and combined postoperative complication rate [7]. Interventional studies in medical patients with diabetes could not reproduce similar benefits [6]. It is important to recognize that to date there are no prospective trials that tested clinical efficacy and outcomes of targeting different inpatient BG goals in non-critically ill patients.

Insulin therapy is suggested as cornerstone treatment strategy in the management of inpatient diabetes [1,8]. Over the last 20 years of intensive clinical research, we witnessed a remarkable move away from the old approach of using insulin per "sliding scale" due to its poor glycemic efficacy and potential harms in the management of inpatient diabetes [9,10]. However, with the evolution of evidence supporting anti-hyperglycemic efficacy of basal-bolus insulin (BBI), high rates of hypoglycemia were reported suggesting that even in the hands of experienced endocrinologists conducting these trials, new insulin strategies may not be as harmless as originally thought [7,11–14]. While the clinical benefits from achieving proposed glycemic goals in non-critically ill patients with diabetes are yet to be determined at least in medical patients, insulin-induced hypoglycemia appears to be more of a concern during inpatient diabetes management [15]. Therefore, newer strategies utilizing non-insulin approaches in the management of inpatient hyperglycemia were proposed and recently studied in hospitalized patients with diabetes [16,17].

In addition to the risk of hypoglycemia due to intensive inpatient insulin regimens, some other factors may lessen current enthusiasm in the field and, most importantly, uptake of current anti-hyperglycemic strategies by non-endocrinologists. System-based issues, provider-related factors, and patient-specific presentation all cause unavoidable confusion among the hospital administrators and non-endocrinology providers in regard to how hyperglycemia should be managed in the non-ICU setting. In Fig. 1, we combined potential contributors to the low adherence to current glycemic management recommendations. Of note, it is very difficult to enforce

* Tel.: +1 518 626 5642; fax: +1 518 626 6464.
E-mail address: aidar.gosmanov@va.gov.
Abbreviations: BBI, basal-bolus insulin; BI, basal insulin; BG, blood glucose.

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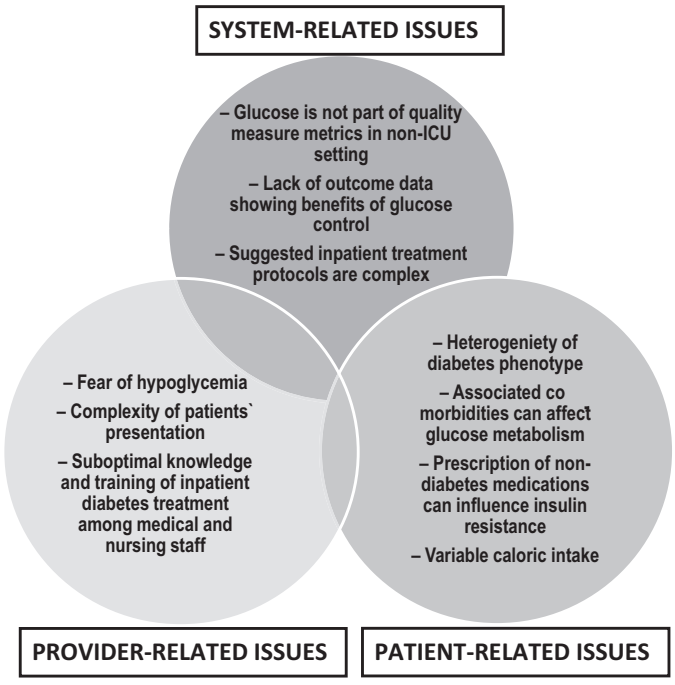

Figure 1. Barriers to achieving glycemic control in non-critically ill patients with diabetes.

hospital administration to implement hyperglycemia treatment strategies in non-critically ill patients unless the BG metric becomes one of the inpatient care goals or part of patient care bundles. A group of experts further delineated current problems in managing inpatient diabetes and drew a road map to overcome the problems [18].

Each patient with diabetes admitted to the medical or surgical ward is unique in his/her presentation. Underlying co-morbidities, admission BG level and hemoglobin A1c, presenting complaints, outpatient insulin use, diabetes duration, co-administration of steroids, and nutritional status are among those variables that should influence the decision-making process during evaluation for anti-hyperglycemic therapy. All this information is objectively difficult to ascertain during the admission by internal medicine providers. Therefore, it may still be tempting for non-endocrinologists to use a reactive approach in the management of hyperglycemia by initiating "sliding scale" insulin regimen in spite of the evidence that this strategy can not only be harmful but also does not address pathophysiology of glucose dysregulation in hospitalized diabetes patients.

In this review, we summarized the results of recent evidence from the interventional trials on diabetes control in non-critically ill patients. We will discuss unique aspects of diabetes care in special patient groups. Furthermore, we suggest potential pathways to address both efficacy and safety of diabetes treatment approaches in the hospital.

Glycemic management of hospitalized patient with diabetes

Patients admitted to the hospital should be evaluated for a history of diabetes, and if the diagnosis is confirmed, bedside glucose monitoring and a therapeutic plan to manage hyperglycemia should be initiated. Hemoglobin A1c measurement on admission will identify patients in whom optimization of outpatient diabetes treatment is indicated. It was recently shown that, in medical and surgical non-critically ill patients, an admission A1c >9.0% is associated with decreased likelihood of achieving optimal inpatient glucose control and higher insulin requirements [19]. Furthermore, an A1c >9.0% will help identify the individuals who may benefit from addition of insulin therapy on discharge [20]. Hospitalized patients without known history of diabetes should be strongly considered for diabetes screening. Measurement of A1c or random BG may offer benefits in identifying new diabetes diagnosis [4] though more prospective studies needed to fully understand cost-effectiveness of universal inpatient diabetes screening.

Patients with type 1 diabetes should be clearly identified and promptly treated using scheduled insulin therapy. In the absence of prospective trials in insulin-dependent diabetes patients, the starting total dose of basal and bolus insulin therapy should range between 0.3 and 0.5 units/kg/day. The 2014 inpatient diabetes national survey in the UK revealed that out of all registered diabetic ketoacidosis cases, 7.8% developed *de novo* in already hospitalized patients [21] suggesting the need for more vigilance in the care of insulin-dependent diabetes in the hospital. In type 2 diabetes patients, we have limited options for the management of hyperglycemia in the medical or surgical wards [22]. Insulin therapy is a treatment of choice that addresses pathophysiology of glucoregulation. The provision of basal insulin (BI) will target fasting hyperglycemia and help to alleviate stress hyperglycemia due to insulin resistance regardless of the patient's nutritional state. Administration of short-acting prandial insulin in eating patients will address abnormalities in post-prandial glucose control. For eating patients, this strategy is called a BBI regimen [13]. However, proof of concept studies showed that for some type 2 diabetes subjects BI plus correction insulin regimen could be another alternative in the management of inpatient hyperglycemia [11].

The important questions in hospital practice are to identify patients who will benefit from insulin prescription and how to start and tailor the insulin regimen. Prospective trials that compared efficacy of BBI therapy versus either sliding scale insulin or premixed insulin enrolled type 2 diabetes subjects with admission BG of 140–400 mg/dL and who had no clinical and biochemical evidence of organ failure, received no corticosteroid therapy, and had no indication for ICU transfer; patients had different baseline characteristics [7,12–14,23]. Further analyses demonstrate that while there were similarities in the average admission A1c of 8–9% and BG of 200–230 mg/dL among the studies, the end of study insulin requirements were discordant. Average final total daily insulin dose was 30–40 units/day or 0.3–0.4 units/kg/day for those patients who had diabetes duration <10 years and were mostly treated with diet and/or non-insulin agents before admission [7,11,13]. In contrast, in the trials that enrolled patients who had type 2 diabetes for >10 years and preadmission insulin usage was recorded in >50% of the subjects, the mean effective daily insulin dose ranged between 0.5 and 0.6 units/kg/day [12,14,23,24]. The evidence guiding initial management of diabetes in patients who are euglycemic on presentation, admitted with severe non-ketotic hyperglycemia, may require glucocorticosteroids and/or exhibit signs and symptoms of organ failure is limited.

Following the initiation of therapy, insulin titration strategies are less well defined as they were not formally tested in prospective trials. One should keep in mind that the risks and benefits of aggressive BG lowering are unknown while the risk of hypoglycemia in hospitalized non-critically ill patients is considerable and associated with adverse clinical outcomes [25,26]. With known inter- and intra-individual variations of pharmacokinetics and unique mechanism of appearance in the systemic circulation of basal insulin analogs glargine and detemir [27,28], large and frequent changes in insulin prescription should be avoided to reduce the risk of hypoglycemia. As was emphasized by the Endocrine Society clinical practice recommendations [1], insulin therapy can be increased by 10–20% if BG level is above the target; similarly, 10–20% reduction in insulin prescription should be considered if BG is below 100 mg/dL during the hospitalization.