Hyperglycemia in hospitalized patients is associated with increased morbidity, mortality, and length of hospital stay. Insulin counteracts the damaging processes caused by hyperglycemia and is therefore a logical choice in treating inpatient hyperglycemia. This article emphasizes the importance of using a physiological (basal-bolus) insulin regimen for noncritically ill hospitalized patients, discusses protocols for initiating and titrating insulin doses and for transitioning from insulin infusion to a subcutaneous regimen, and recommends insulin teaching as part of discharge planning for patients who were not on insulin before admission.

Management of Inpatient Hyperglycemia in Noncritically Ill Patients

Hyperglycemia in hospitalized patients is a common, serious, and costly health care problem with profound medical consequences. This article attempts to synthesize the data on hyperglycemia and outcomes in noncritically ill hospitalized patients, the proposed mechanisms behind these associations, and management issues as these patients are transitioned from the critical care units to the regular hospital units and then to home.

Association Between Hyperglycemia and Outcomes

Increasing evidence indicates that the development of hyperglycemia during acute medical or surgical illness is not a physiological or benign condition, but rather is a marker of poor clinical outcome and mortality. Evidence from observational studies indicates that development of hyperglycemia in critical illness is associated with an increased risk of complications and mortality, a longer hospital stay, a higher admission rate to the intensive care unit (ICU), and a higher likelihood that transitional or nursing home care after hospital discharge will be required. In a retrospective study of 1,886 patients admitted to a community hospital, mortality in the general floors was significantly higher in patients with newly diagnosed hyperglycemia and those with known diabetes than in those who were normoglycemic (10, 1.7, and 0.8%, respectively; \( P \text{ < } 0.01 \)). Admission hyperglycemia has also been linked to worse outcomes in patients with community-acquired pneumonia.

In a prospective cohort multicenter study of 2,471 patients, those with admission glucose levels of > 198 mg/dl had a greater risk of mortality and complications than those with lower glucose levels. The risk of in-hospital complications increased 3% for each 18 mg/dl increase in admission glucose. In a retrospective study of 348 patients with chronic obstructive pulmonary disease and respiratory tract infection, the relative risk of death was 2.10 in those with a blood glucose of 126–160 mg/dl and 3.42 for those with a blood glucose > 160 mg/dl.
Biological Basis for Risks of Hyperglycemia and Benefits of Insulin Treatment

Hyperglycemia is a frequent manifestation of critical illness, resulting from the acute metabolic and hormonal changes associated with the response to injury and stress. The counterregulatory response results in a number of alterations in carbohydrate metabolism, including insulin resistance, increased hepatic glucose production, impaired peripheral glucose utilization, and relative insulin deficiency. Hyperglycemia induces key pro-inflammatory transcription factors, such as intra-nuclear factor κB (NFκB) binding and activator protein-1 binding. Increases of these transcription factors are associated with increased expression of genes that encode numerous proteins that can mediate inflammation, platelet aggregation, apoptosis, and endothelial dysfunction.

Hyperglycemia is also associated with an increase in the generation of reactive oxygen species and an increase in p47phox expression, which is indicative of an increase in nicotinamide adenine dinucleotide phosphate oxidase activity. The increased oxidative load observed with hyperglycemia is associated with damage to lipids, proteins, and DNA. Production of superoxide and its reaction with nitric oxide (NO) in these conditions results in production of peroxynitrite, nitration of proteins, and activation of NFκB if euglycemia is not reestablished.

Insulin administration can prevent many of the adverse outcomes associated with hyperglycemia. The biological effects of insulin on inflammatory factors are likely to be responsible for some of the observed benefits. Insulin suppresses the pro-inflammatory transcription factors NFκB and early growth response factor 1, and studies have demonstrated that insulin administration is associated with a decrease in the concentration of compounds whose gene transcription is modulated by these factors, including tissue factor, plasminogen activator inhibitor-1, intercellular cell adhesion molecule-1, monocyte chemotactic protein-1, matrix metalloproteinase-1, and matrix metalloproteinase-9.

Administration of insulin may cause suppression of the generation of reactive oxygen species. In addition, insulin may also induce vasodilatation, inhibition of lipolysis, and reduction in free fatty acids, platelet aggregation, and inflammatory response. The vasodilatation that accompanies insulin administration may be attributed to its ability to stimulate NO release and induce the expression of endothelial NO synthase. Therefore, the administration of insulin is key in preventing the risks associated with hyperglycemia in the hospital.

Goals of Glycemic Control in the Hospital

A recent position statement of the American College of Endocrinology and the American Diabetes Association recommended glycemic targets between 80 and 110 mg/dl for critically ill patients in the ICU. For patients with noncritical illness, preprandial blood glucose levels < 110 mg/dl and random blood glucose levels < 180 mg/dl were recommended.

Recently, several groups have raised concerns about these recommendations, and higher target glucose levels have been recommended. Because of concerns of hypoglycemia and its effect on hospital morbidity and mortality reported in recent randomized clinical trials, more conservative glucose targets have been recommended in the ICU. Based on an extensive review of published clinical trials in critically and noncritically ill patients, advisable in-hospital targets are to maintain fasting and preprandial glucose levels between 90 and 140 mg/dl and random glucose levels < 180 mg/dl.

Treatment Modalities

Despite the increasing evidence in support of intensive glycemic control in hospitalized patients, blood glucose control continues to be deficient and is frequently overlooked in general medicine and surgery services. Many factors could explain physicians’ inactivity in addressing in-hospital hyperglycemia. First, hyperglycemia is rarely the focus of care during the hospital stay because the overwhelming majority of hospitalizations in patients with hyperglycemia occur for comorbid conditions. Second, fear of hypoglycemia is a major barrier to efforts to improve glycemic control in hospitalized subjects, especially in patients with poor caloric intake.

Third, practitioners frequently do not administer insulin until blood glucose levels exceed 180–200 mg/dl, based on the misconception that mild elevations are not deleterious. Finally, and perhaps more importantly, in the presence of altered nutrition and associated medical illness, physicians frequently hold their patients’ previous outpatient antidiabetic regimen and initiate sliding-scale coverage with regular insulin.

Potential advantages of sliding-scale insulin (SSI) are convenience, simplicity, and promptness of treatment. The regimen is easy to implement in general surgical and medicine areas and does not depend on locating an attending physician or a house staff officer concerning the necessary insulin dosage. The use of SSI as the sole treatment for inpatient hyperglycemia, however, has been shown to be ineffective and associated with several problems. The regimen treats hyperglycemia after it has already occurred instead of pre-
vent its occurrence. This “reactive” approach can lead to rapid changes in blood glucose levels, exacerbating both hyperglycemia and hypoglycemia, and can lead to iatrogenic diabetic ketoacidosis.\textsuperscript{4,30,36}

Insulin is a common source of medication error, and health care professionals should know how to effectively prescribe it. Insulin therapy must provide both basal and nutritional components to achieve blood glucose targets. Hospitalized patients often require high insulin doses to achieve target glucose levels because of increased insulin resistance; thus, in addition to basal and nutritional insulin requirements, patients often require supplemental or correction insulin for the treatment of hyperglycemia.

As discussed above, use of SSI alone is discouraged. We recently reported the results of a prospective, randomized multicenter trial comparing the efficacy and safety of a physiological (basal-bolus) insulin regimen with glargine and glulisine and SSI with regular insulin in patients with type 2 diabetes admitted to general medicine wards.\textsuperscript{37} Among 130 insulin-naïve patients with an admission blood glucose level between 140 and 400 mg/dl (mean admission blood glucose: 229 ± 6 mg/dl, A1C: 8.8 ± 2 %), the use of basal-bolus insulin yielded greater improvement in blood glucose control than SSI alone. Subjects had a known history of diabetes for at least 3 months. Oral diabetes agents were discontinued on admission. A blood glucose target of < 140 mg/dl was achieved in 66% of patients in the basal-bolus group and 38% in the SSI group. One-fifth of patients treated with SSI without a basal component had persistently elevated blood glucose levels > 240 mg/dl during the hospital stay. There was no difference in length of hospital stay or mortality between groups. Thus, similar improvement in glycemic control can be achieved with either detemir/aspart or NPH/regular regimens in medical inpatients with type 2 diabetes.

In a smaller pilot study designed to determine if a premixed insulin algorithm provided better glycemic control than traditional SSI, 10 subjects were given a 70/30 premixed formulation according to a titration algorithm, and 10 patients received SSI. Subjects were hospitalized adults with type 2 diabetes.\textsuperscript{38} Titration for the morning dose of the premixed insulin was based on blood glucose measurements taken at 4:00 p.m. the day before, and titration for the evening dose was based on blood glucose levels measured at 7:00 a.m. that day. The 70/30 group achieved a lower mean glucose than the SSI group (151.3 vs. 171.6 mg/dl, P = 0.042). There was no significant difference in the number of insulin units given per glucose concentration per day. None of the subjects had a glucose level < 60 mg/dl in either group.

**Status of Glycemic Control in Hospitals**

The dearth of outcome studies on glycemic control in general hospital wards possibly contributes to the inertia in managing diabetes in noncritically ill patients. However, when systematically analyzed in one institution, the leading cause of hyperglycemia was “lack of ownership” of diabetes, i.e., the hospital staff did not actively try to manage diabetes because this was not the reason for patients’ admission.\textsuperscript{43} In a large teaching institution, inertia for intensifying diabetes management in a hospitalist-run general medicine service was evident.\textsuperscript{30} Basal insulin was ordered in only 43% of patients with either known diabetes or inpatient hyperglycemia, with only 4% of patients placed on scheduled short- or rapid-acting insulin. In fact, in 65% of patients who had at least one episode of hyperglycemia or hypoglycemia, no change was made to insulin orders in the first 5 days of hospitalization. In another study from the same institution, a retrospective analysis of over 3,613 patients admitted to non-ICU wards and who were not on insulin infusion showed that intensification of antidiabetic treatment was done in only 22% of the hyperglycemic days.\textsuperscript{41}

In another academic institution, data were analyzed from 2,916 patients with diabetes or inpatient hyperglycemia and not admitted to the ICU.\textsuperscript{42} Seventy-two percent of patients received some form of subcutaneous insulin during their hospital stay. Among those who used insulin, 58% received “bolus-only” or SSI, 42% received basal-bolus, and 1% received only basal injections. When divided according to tertiles of mean glucose levels, 65% of those patients in the highest tertile received an increase in insulin dose, but 31% actually had a decrease in insulin doses despite a lower frequency of glucose levels < 70 mg/dl (1.2 values per 100 measurements per person).

**Educational Efforts**

Just as clinical trials are difficult on the general floors, education of hospital staff on proper management of hyperglycemia has been a challenge. At one institution where order entry was not available and the use of protocols for dosing basal-bolus insulin was not mandatory, re-education was attempted through lectures to physicians, mid-level providers, and nursing staff and through implementation of a pre-printed order sheet incorporating basal and bolus insulin for some general hospital services. Prescription practices for hyperglycemia management were compared between a cohort of 100 patients in 2002 and 100 patients in 2006.\textsuperscript{41} Although SSI remained as the most common initial treatment, subsequent management using basal insulin with or without bolus insulin increased significantly from 33 to 47%, whereas the use of sole SSI decreased significantly from 67 to 53%. The percentage of patients with known diabetes and newly diagnosed hyperglycemia who were left untreated significantly decreased
Table 1. Examples of Orders for Using Long-Acting and Rapid-Acting Insulin

- Basal insulin: glargine and detemir
- Bolus or prandial insulin: lispro, aspart, glulisine

1. Patients treated with diet or oral agents before admission:
- Hold oral antidiabetic drugs on admission.
- Starting total daily insulin dose:
  - 0.4 units/kg of body weight/day when blood glucose concentration is between 140 and 200 mg/dl
  - 0.5 units/kg of body weight/day when blood glucose concentration is between 201 and 400 mg/dl
- Lower insulin doses (0.3 units/kg of body weight/day) should be given to elderly patients or those with renal failure (glomerular filtration rate < 60 ml/min)
- Half of total daily dose will be given as basal insulin and half as rapid-acting insulin.
- Give basal insulin once daily, at the same time of day.
- Rapid-acting insulin should be given in three equally divided doses before each meal. Hold rapid-acting insulin if a patient is not able to eat to prevent hypoglycemia.

2. Patients treated with insulin before admission:
- Insulin-treated patients should be started at the same amount as their outpatient insulin dose.
- Half of total daily dose will be given as basal insulin and half as rapid-acting insulin.
- Basal insulin should be given once daily, at the same time of day.
- Rapid-acting insulin should be given in three equally divided doses before each meal. Hold rapid-acting insulin if a patient is not able to eat to prevent hypoglycemia.

3. Supplemental insulin:
Supplemental doses of rapid-acting insulin are given in addition to the mealtime insulin to correct hyperglycemia (Table 3).
- If patients are able and expected to eat all or most of their meals, supplemental rapid-acting insulin is given before each meal and at bedtime following the “usual” column in Table 3.
- If a patient is not able to eat, supplemental rapid-acting insulin is given every 6 hours (Example: 6:00 a.m., noon, 6:00 p.m., and midnight) following the “insulin sensitive” column in Table 3.

4. Insulin adjustment:
- If fasting and premeal blood glucose is < 140 mg/dl (in the absence of hypoglycemia): no change
- If fasting and premeal blood glucose is between 140 and 180 mg/dl (in the absence of hypoglycemia): increase basal insulin by 10% every day
- If fasting and premeal blood glucose is > 180 mg/dl (in the absence of hypoglycemia): increase basal insulin dose by 20%
- If a patient develops hypoglycemia (< 70 mg/dl): decrease total daily insulin dose by 20%

5. Blood glucose monitoring:
Blood glucose will be measured before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucose meter. In addition, blood glucose will be measured at any time if a patient experiences symptoms of hypoglycemia.

from 8 to 0% and from 50 to 36%, respectively.

To re-educate the house staff and eliminate the use of SSI, one interventional study involved an endocrinologist making rounds with two residents twice a day for 2-week blocks. At the end of the 8-week study, 16 residents had participated. Residents took care of 88 patients who were included in the study group. These subjects were patients admitted to the medical service and with either known diabetes or new hyperglycemia. Residents were taught how to prescribe either oral agents or a combination of NPH and regular insulin without the use of SSI to the study subjects. The study subjects were then compared to a historical control of 98 subjects. The control group had received SSI with or without NPH/regular insulin or oral agents. The mean blood glucose was lower for study patients compared to control subjects (150 ± 37 vs. 200 ± 51 mg/dl, P < 0.01). The frequency of glucose levels < 60 mg/dl was greater in the study patients compared to control subjects (3.6 vs. 1.4%, P = 0.01).

To further enhance the use of scheduled insulin (as opposed to SSI), several institutions have protocols for dosing. Examples are seen in Tables 1–3, which are protocols used at the senior author’s institution. The availability of protocols, however, does not necessarily translate into high adherence. In one institution, the opportunity to improve glycemic control on the general medicine floors was offered using a protocol developed by a multidisciplinary team. The residents agreed to use the protocol for only 56% of the patients. Although basal insulin and nutritional insulin were prescribed significantly more often in the pilot group compared to a previously studied control group (basal 64 vs. 49%; nutritional 13 vs. 0%), the numbers reflected suboptimal adherence to the protocol. The use of a standard SSI algorithm from a computerized order set was similar between groups (90 vs. 93%).

Because of the difficulty in changing house staff practice for managing inpatient hyperglycemia, one study assessed baseline knowledge of medical subinterns (4th year medical students) on inpatient diabetes to find out whether the problem already existed at that stage of training. Through a pretest using hypothetical
inpatient scenarios, as well as multiple-choice and matching questions given before a didactic lecture on inpatient diabetes, it was found that subinterns were able to give an appropriate initial plan for diabetes only 67% of the time, whereas they were able to address chest pain, hypertension, obesity, and renal dysfunction 84–100% of the time. SSI was prescribed as initial treatment for hypothetical case scenarios by 28 of 52 students (56%). In a follow-up study using either traditional teaching methods or a website for subinterns, the same authors found

<table>
<thead>
<tr>
<th>Table 2. Regimen of NPH Insulin Twice Daily Plus Supplemental Regular Insulin</th>
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</table>

1. **Patients treated with diet or oral agents (insulin naïve) before admission:**
   - Hold oral antidiabetic drugs on admission.
   - Starting total daily insulin dose:
     - 0.4 units/kg of body weight/day when the admission or mean blood glucose concentration is between 140 and 200 mg/dl
     - 0.5 units/kg of body weight/day when the admission or mean blood glucose concentration is between 201 and 400 mg/dl
   - Two-thirds of the total daily dose is given in the morning before breakfast, and 1/3 is given in the evening before dinner as a split-mixed regimen.
   - The insulin dose will be given as 2/3 NPH and 1/3 regular insulin.
   - Hold regular insulin if a patient is not able to eat to prevent hypoglycemia. (Decreasing the morning NPH to 2/3 of the usual dose is also recommended.)

2. **Patients treated with insulin before admission:**
   - Subjects receiving NPH plus regular insulin will continue to receive the same outpatient insulin schedule and dosage.
   - Two-thirds of the total daily dose is given in the morning and 1/3 in the evening as a split-mixed regimen.
   - The insulin dose will be given as 2/3 NPH and 1/3 regular insulin.
   - Hold regular insulin if a patient is not able to eat to prevent hypoglycemia. (Decreasing the morning NPH to 2/3 of the usual dose is also recommended.)

3. **Supplemental insulin:**
   - Regular insulin is given before each meal and at bedtime following the “usual” column in Table 3.
   - If a patient is not able to eat, supplemental regular insulin is given every 6 hours (for example, 6:00 a.m., noon, 6:00 p.m., and midnight) following the “insulin sensitive” column in Table 3.

4. **Insulin adjustment:**
   - If the fasting and premeal blood glucose is < 140 mg/dl (in the absence of hypoglycemia): no change
   - If the fasting and premeal blood glucose is between 140 and 180 mg/dl (in the absence of hypoglycemia): increase total insulin dose by 10% every day
   - If the fasting and premeal blood glucose is > 180 mg/dl (in the absence of hypoglycemia): increase total insulin dose by 20%
   - If a patient develops hypoglycemia (< 70 mg/dl): decrease total daily insulin dose by 20%

4. **Blood glucose monitoring:**
   - Blood glucose will be measured before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucose meter. In addition, blood glucose will be measured at any time if a patient experiences symptoms of hypoglycemia.

<table>
<thead>
<tr>
<th>Table 3. Supplemental Insulin Protocol</th>
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<table>
<thead>
<tr>
<th>Blood Glucose* (mg/dl)</th>
<th>Insulin Sensitive</th>
<th>Usual</th>
<th>Insulin Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 141–180</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>181–220</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>221–260</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>261–300</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>301–350</td>
<td>10</td>
<td>12</td>
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</tr>
<tr>
<td>351–400</td>
<td>12</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>&gt; 400</td>
<td>14</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>

*Check appropriate column and cross out other columns.
that focused teaching was associated with decreased frequency of prescribing SSI as sole initial treatment when the subinterns’ medical progress notes were reviewed (M.C.L., unpublished observations).

Adjusting Care From the Critical to the Noncritical Care Setting
Patients who have been on an IV insulin infusion in the critical care unit most often do not need to continue on this when transferred to a step-down unit or a regular floor. Although interventional studies of IV insulin infusion in the ICU have used various methods of administering insulin once patients are transferred out of the unit (such as the use of multiple daily doses of scheduled subcutaneous insulin for intensive control or simply conventional diabetes treatment), it stands to reason that control of hyperglycemia should be maintained during this transition. Protocols for transitioning make use of fairly easy calculations and often result in a slightly lower total daily dose of scheduled subcutaneous insulin compared to the same patient’s dose while on the insulin infusion. This is in anticipation of the patient’s improving clinical condition.

An example of a transitioning scheme can be seen in Table 4. The premise is that the last 6 hours of insulin infusion requirement probably best reflects the current, and presumably improved, clinical state of the patient and decreases the chance of hypoglycemia compared to computing a total daily dose based on the entire previous 24-hour insulin requirement.

Summary
The management of hyperglycemia in noncritically ill hospitalized patients is undergoing transformation from the rampant use of SSI to the more physiologically sound method of giving scheduled insulin to cover basal and prandial needs. The demonstration that protocols help achieve target glycemic goals is another step in the right direction. There is vast opportunity for outcomes research focusing on improved length of stay, lower costs of hospital stays, and improvements in morbidity and mortality as potential benefits of improved glycemic control in this population of patients.

References

Table 4. Example of Orders for Transitioning From IV to Subcutaneous Insulin

<table>
<thead>
<tr>
<th>Basal-Bolus Insulin Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Subcutaneous insulin should be given 2 hours before discontinuation of insulin infusion.</td>
</tr>
<tr>
<td>• Diabetic subjects who are clinically stable can be transitioned to subcutaneous insulin according to the following formula: total daily insulin dose: rate of insulin (units/hour) during the last 6 hours multiplied by 4. For example, if insulin infusion rate is 2 units/hour for the last 6 hours, the total daily dose of insulin = 2 × 6 × 4 = 48 units.</td>
</tr>
<tr>
<td>• Half of the total daily dose will be given as basal insulin and half as rapid-acting insulin.</td>
</tr>
<tr>
<td>• Give basal insulin (glargine or detemir) once daily, at the same time of day.</td>
</tr>
<tr>
<td>• Rapid-acting insulin (lispro, aspart, glulisine) should be given in three equally divided doses before each meal.</td>
</tr>
<tr>
<td>Hold rapid-acting insulin if a patient is not able to eat to prevent hypoglycemia.</td>
</tr>
<tr>
<td>Hold scheduled or bedtime insulin and call MD to clarify insulin regimen.</td>
</tr>
</tbody>
</table>

1. Give glargine/detemir ________ units subcutaneously at ________ every day.
2. Give lispro/aspart/glulisine ________ units subcutaneously before each meal.
3. Check blood glucose before meals and at bedtime if patient is taking nutrition by mouth.
4. Check blood glucose every 6 hours if patient is having nothing by mouth.
5. Supplement with rapid-acting insulin using “Supplement Scale” shown in Table 3.
6. For blood glucose < 70 mg/dl, follow these Hypoglycemic Orders:
   • If patient is alert and can tolerate oral intake, give 20 g of fast-acting carbohydrate (6 oz. fruit juice or regular soda, crackers)
   • If patient is not alert and cannot tolerate oral intake, give 1 ampule (50 ml) of D50 by IV push.
   • Check fingerstick blood glucose every 15 minutes and repeat above treatment (1 or 2) until blood glucose is > 100 mg/dl.
   • Once blood glucose is > 100 mg/dl, repeat fingerstick blood glucose 1 hour later and treat as follows:
     o If blood glucose is < 70 mg/dl, call MD and start Hypoglycemia Orders at the beginning again.
     o If blood glucose is 70–100 mg/dl, give snack/scheduled meal and recheck blood glucose every 1 hour until blood glucose is > 100 mg/dl.
     o If blood glucose is > 100 mg/dl, no further treatment is needed.
   • Hold scheduled or bedtime insulin and call MD to clarify insulin regimen.

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