Guideline Title  Management of Hyperosmolar Hyperglycemic State

Summary:
Patients admitted to ICU (via ED) with HHS (Hyperosmolar Hyperglycemic State) will be monitored and managed appropriately.

Approved by:  ICU Director
Publication (Issue) Date:  March 2016
Next Review Date:  March 2019
Replaces Existing Guideline:  Management of Hyperosmolar Hyperglycemic State
Previous Review Dates:  2013

Background Information:
Hyperosmolar Hyperglycaemic State (HHS) is a diabetic emergency that although typically occurring in the elderly, is presenting in younger adults and teenagers, often as the initial presentation of type 2 diabetes mellitus (T2DM). Whilst DKA presents within hours of onset, HHS comes on over many days, and consequently the dehydration and metabolic disturbances are more extreme. The name changed from HONK (hyperosmolar non ketotic coma) to hyperosmolar hyperglycaemic state to allow for the fact that some patients may be extremely ill but not comatose and may also be mildly ketotic and acidotic. It has a higher mortality than DKA. Potential precipitants including infection/sepsis, myocardial infarction, stroke, alcohol excess, pancreatitis, trauma, medications (eg glucocorticoids) and insulin omission need to be identified and managed appropriately. HHS may be complicated by vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis. Seizures, cerebral oedema and central pontine myelinolysis (CPM) are uncommon but well-described complications of HHS.

1. Introduction contains:
The risk addressed by this policy:

<table>
<thead>
<tr>
<th>Risk Addressed by This Policy</th>
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</thead>
<tbody>
<tr>
<td>Patient Safety and correct management of patient with Hyperosmolar Hyperglycemic State (HHS).</td>
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</tbody>
</table>

The Aims / Expected Outcome of this policy:

<table>
<thead>
<tr>
<th>Aims / Expected Outcome</th>
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<tbody>
<tr>
<td>Staff caring for a patient with HHS will have the knowledge and skills required to provide effective and safe care of the patient in accordance with the recommendations of the ICU Medical team.</td>
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</tbody>
</table>

Related Standards or Legislation

- NSQHS Standard 1 Governance
2. **Policy Statement:**

- All care provided within Liverpool Hospital will be in accordance with infection prevention/control, manual handling and minimisation and management of aggression guidelines.

- A diagnosis of HHS is made by the Medical team based on the presence of marked hyperglycemia (BGL >30mmol/L) without significant hyperketonemia (serum ketones <3.0 mmol/L) or acidosis (pH > 7.3, HCO₃ > 15mmol/L) + high osmolality > 320 mosmol/kg + severe dehydration and hypovolemia.¹,²,³

- The BGL must be monitored by a blood glucose machine every 1 hour while the patient is receiving initial fluid replacement and while they remain on Intravenous Actrapid Insulin Infusion.

- Serum potassium must be measured on admission and repeated every 2 hours. Potassium should always be diluted and NEVER given undiluted through a peripheral line.⁶

- Arterial blood gas analysis, EUC, CMP, blood capillary ketone (bedside ketone test) and urine ketones and osmolality must be measured hourly for the first 6 hours and then 2nd hourly if the response is satisfactory, as indicated by a fall of osmolality of 3-8 mosmol/kg/hr¹,³.

- An arterial line should be inserted for repeated frequent blood sampling. In the absence of an arterial line, perform one initial arterial blood gas and then subsequent blood gas analysis can be with venous blood samples.

**Definition for HHS:**

A precise definition of HHS does not exist but there are characteristic features that differentiate it from other hyperglycemic states like DKA. These clinical features include:

<table>
<thead>
<tr>
<th>Diagnostic Criteria for DKA vs HHS¹,²,³</th>
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<tbody>
<tr>
<td><strong>DKA</strong></td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Plasma Glucose (mmol/L)</td>
</tr>
<tr>
<td>Arterial pH</td>
</tr>
<tr>
<td>Serum Bicarbonate (mEq/L)</td>
</tr>
<tr>
<td>Urine Ketones</td>
</tr>
<tr>
<td>Blood capillary ketones</td>
</tr>
</tbody>
</table>
Effective serum osmolality | Variable       | Variable       | Variable       | >320mOsm/kg
---|----------------|----------------|----------------|-----------------|
Alteration in sensorial or mental obtundation | Alert         | Alert / drowsy | Stupor / coma   | Stupor / coma  

3. Principles / Guidelines
Precipitants to HHS:
- Infection / sepsis.
- Discontinuation of insulin, inadequate insulin doses, missed insulin doses, non compliance (psycho-social factors)
- Acute major illnesses such as pancreatitis, myocardial infarction or cerebrovascular accidents.
- Drugs that affect carbohydrate metabolism, including glucocorticoids, higher dose thiazide diuretics, sympathomimetic agents (eg: dobutamine and terbutaline) and second generation antipsychotic agents.
- Underlying medical illness that provokes the release of counterregulatory hormones or compromises the access to water with resulting severe dehydration can precipitate HHS.
- Elderly patients (particularly residents of chronic care facilities) or individuals with known diabetes who become hyperglycaemic and are unaware of it or unable to take fluids.

Clinical Features of HHS:
HHS usually evolves over several days to weeks.
- Polyuria, polydypsia, weight loss.
- Vomiting, dehydration, weakness.
- Severe hypovolemia may manifest as tachycardia (HR>100bpm) and hypotension (SBP < 100mmHg).
- Mental status changes.
- Focal neurological signs (hemianopia and hemiparesis) and seizures (focal or generalised).
- Severe hypothermia if present is a poor prognostic sign.

Management of HHS:

Resolution of HHS:
- Target BGL is between 10 – 15mmol /L
- Complete normalisation of electrolytes and osmolality may take up to 72 hours.

Serum Osmolality:
2 x measured serum sodium + serum glucose + serum urea
Normal Serum osmolality is − 280 -300mmol/kg

Corrected Sodium:
Blood Glucose /3 + measured serum sodium
Treatment Goals\textsuperscript{1,2,3}

The goals of treatment are to provide frequent patient monitoring, to treat the underlying cause and to gradually and safely:

- Normalise the osmolality
- Replace fluid and electrolyte imbalances
- Normalise blood glucose levels

Prevention of:

- Arterial or venous thrombosis
- Potential complications such as cerebral edema / cerebral pontine myelinolysis
- Foot ulceration.

Normalise Osmolality\textsuperscript{1}

- Calculate (or measure) the osmolality (2 x serum sodium + BGL + serum urea) frequently to monitor response to treatment.
- A satisfactory fall in osmolality is 3-8mosmol/kg/hr in the first hour and 3mosmol/kg/hr after that.

Fluid Therapy\textsuperscript{1,3}

Assessment of volume status

- Fluid loss in HHS is estimated to be between 100-220ml/kg. For the average patient this is 8-10 litres.
- Despite severe electrolyte losses and total body volume depletion, the patient with HHS may not look as dehydrated as they are because the hypertonicity leads to movement of water from intracellular to extracellular space, thereby preserving intravascular volume. Severe hypovolemia may manifest as tachycardia and hypotension.
- Measuring osmolality is useful to both indicate the severity of HHS and to monitor the rate of change with treatment.

Fluid Management\textsuperscript{1,2,3}

- The goal of management is to expand intravascular and extravascular volume, without inducing cerebral edema due to too rapid reduction in plasma osmolality.
- The fluid of choice is 0.9% sodium chloride with potassium added as required. This fluid will replace the deficit, lower plasma osmolality (since it is still hypoosmotic to the patient) and reduce the serum glucose concentration by dilution and by increasing urinary losses as renal perfusion is increased.
- Fluid replacement alone (without insulin) will lower BGL and this will lower osmolality causing shift of water into the intracellular space. This results in a rise in serum sodium (a fall in BGL of 5.5mmol/L will result in a 2.4mmol/L rise in sodium). Thereafter the fall of serum sodium should not exceed 10mmol/L in 24 hours. The initial rise in serum sodium is expected and is not an indication to give hypotonic fluid. Rising sodium is only a concern if the osmolality is not declining concurrently.
- Only switch to 0.45% sodium chloride if osmolality is not declining despite adequate positive fluid balance.
- The aim of treatment should be to replace approximately 50% of estimated fluid loss within the first 12 hours and the remainder in the next 12 hours. This is determined by the initial severity, degree of renal impairment, and co-morbidities such as heart failure which may limit the speed of correction.
- Complete normalisation of electrolytes and osmolality may take up to 72 hours.

<table>
<thead>
<tr>
<th>Time</th>
<th>Fluid</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 60 minutes</td>
<td>0.9% NaCl – 1litre over 1 hour</td>
<td>Consider more rapid replacement if SBP &lt;90mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More cautious replacement in the elderly</td>
</tr>
<tr>
<td>60 minutes to 6 hours</td>
<td>0.9% NaCl – 0.5 -1L/hr Target is to achieve positive balance of 2-3L by 6 hours.</td>
<td>Depends on clinical assessment of dehydration</td>
</tr>
</tbody>
</table>
### 6 to 12 hours
- **Continue IV fluid replacement to achieve positive balance of 3-6 litres by 12 hours**
- **If BGL falls to <14mmol/L, commence 5% Glucose @ 125ml/hr AND continue 0.9% sodium chloride.**

### 12 to 24 hours
- **Continue IV fluid replacement to achieve remaining replacement of fluid losses within the next 12 hours**
- **Depends on initial degree of dehydration and response to therapy.**
- **Maintain accurate fluid balance, body weight, serum osmolality.**

### 24 hours to Day 3
- **Continue fluids till eating and drinking normally**
- **Assess for signs of fluid overload or cerebral edema.**

### Insulin Therapy

1. **If significant ketonaemia is present (capillary blood ketone > 1 mmol/L) insulin should be started at time zero once K+ confirmed to be >3.3 mmol/L.**
2. **If significant ketonaemia is not present (capillary blood ketone is less than 1 mmol/L) DO NOT initially start insulin. Fluid replacement alone will result in a fall in BGL.** Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse as water moves out of the intravascular space with resulting decrease in intravascular volume. Additionally, as most patients with HHS are insulin sensitive there is a risk of lowering the osmolality precipitously.
3. **Prepare Intravenous Actrapid infusion: Dilute 50units actrapid to 50mL sterile 0.9% Sodium Chloride, to give a concentration 1unit/mL.**
4. **Low dose insulin 0.05 units /kg/hr should only be commenced once the BGL is no longer falling with IV fluids alone OR immediately if there is significant ketonaemia (capillary blood ketone >1mmol/L).**
5. **The fall in BGL should be no more than 5mmol/L/hr. Measure hourly BGL.**

**Note:** If the patient is on an insulin infusion and being transferred to the general ward from either the Emergency Dept or the Intensive Care Unit the insulin infusion order must be written using the order suitable for the ward which is the Liverpool Hospital Intravenous Insulin/Glucose Infusion Order (CR132). Also refer to the Intravenous Insulin/ Intravenous Glucose Infusion Policy LH_PD2010_C03.37.

<table>
<thead>
<tr>
<th>Time</th>
<th>Insulin</th>
</tr>
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</table>
| 0 to 60 minutes | - BGL should initially fall with IV fluid replacement alone.  
- Insulin infusion should only be commenced @ 0.05units /kg/hr if there is significant ketonaemia (capillary blood ketone >1mmol/L ). Confirm K+ >3.3 mmol/L before commencing IV insulin. Otherwise delay insulin commencement- see box below for indications for commencing IV insulin. |
| 60 minutes to 6 hours | - When BGL is no longer falling with IV fluids alone, commence insulin infusion at 0.05 units/kg/hr (confirm K+ > 3.3 mmol/L before commencing IV insulin).  
- Target BGL is 10-15mmol/L but the fall in BGL should be no more than 5mmol/L/hr.  
- If BGL falls to <14mmol/L , continue IV insulin and commence 5% Glucose @ 125ml/hr AND continue 0.9% NaCl  
- Adjust IV insulin infusion in 1 unit/hr increments or decrements to achieve desired BGL. |
6 to 24 hours

- Target BGL is 10-15 mmol/L but the fall in BGL should be no more than 5 mmol/L/hr.
- If BGL falls to <14 mmol/L, continue IV insulin and commence 5% Glucose @ 125 ml/hr AND continue 0.9% NaCl.
- Adjust IV insulin infusion in 1 unit/hr increments or decrements to achieve desired BGL.
- After patient is initially stabilised, discuss with Intensivist or Endocrinology team regarding commencing daily subcutaneous long acting insulin (eg. Lantus) whilst patient is on the insulin infusion. This daily long acting insulin is to be used concurrently with the insulin infusion will facilitate the transition to subcutaneous therapy when the insulin infusion is ceased at a later time.

24 hours to Day 3

- When patient osmolality and BGL has stabilised and they are mentally alert and able to eat, consider converting IV insulin infusion to subcutaneous regime of insulin.

Subcutaneous Insulin Therapy\(^1,3,5\)

- When the patient is able to eat, a multiple dose schedule should be started that uses a combination of rapid acting insulin with meals and daily long acting insulin (eg. basal bolus QID regimen). This should be done in consultation with the endocrinology team.
- There must be an appropriate overlap between the intravenous insulin infusion and both the rapid acting and the long acting subcutaneous insulin doses. The intravenous insulin infusion should not be discontinued for at least 30 minutes after the administration of the rapid acting subcutaneous dose. This is critical for preventing worsened control and hyperglycemia. In addition, before ceasing the insulin infusion the long acting insulin must already have been commenced as a daily dose to provide ongoing background basal insulin therapy. Discuss with endocrinology team if unsure about the timing or dose of this daily long acting insulin therapy. (See the note above in Insulin Table (6-24hrs) regarding introducing the daily subcutaneous long acting insulin concurrently whilst on insulin infusion).
- If the patient prior to admission was not previously on insulin therapy estimating the initial Total Daily Dose (TDD) of insulin\(^5\) is based on patient’s sensitivity to insulin, degree of glycemic control, insulin resistance, weight and age.

\[
TDD = \text{Patients weight in kg} \times 0.5 \text{ to } 0.7 \text{ units}
\]

0.7 units is used for those thought to be more insulin resistant (teens, obese)

Eg: 72 kg patient TDD = 75 x 0.5 units = 36 units in 24hrs.

- The basal bolus QID regime for subcutaneous insulin: Give 50% of the TDD with the evening meal in the form of long acting insulin such as Lantus. Divide the remaining dose equally between pre-breakfast, pre-lunch and pre-evening meal in the form of rapid acting insulin.

Electrolyte Replacement – Potassium & Phosphate\(^1,2\).

Potassium:
- Maintain serum potassium (K\(^+\)) between 4-5 mmol/L.

<table>
<thead>
<tr>
<th>Serum K Aim to maintain</th>
<th>Potassium infusion rate if replacement via peripheral line</th>
<th>Potassium infusion rate if replacement via central access</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0-5.0 mmol/L</td>
<td>(40 mmol potassium chloride can be added to a)</td>
<td>(Potassium chloride can be drawn up undiluted in a 50ml)</td>
</tr>
</tbody>
</table>

Electrolyte Replacement – Potassium & Phosphate\(^1,2\).
1L bag of IV Fluid). syringe and administered via syringe driver

| K < 3.3 mmol/L | 20 mmol/hr | 30 mmol/hr |
| K 3.4 – 4.0 mmol/L | 10 - 20 mmol/hr | 20 mmol/hr |
| K 4.1 – 5.0 mmol/L | 10 mmol/hr | 10 mmol/hr |
| K 5.1 – 5.5 mmol/L | 5 - 10 mmol/hr | 5 - 10 mmol/hr |
| K > 5.5 mmol/L | Do not replace K, wait for next K result within 2 hours | Do not replace K, wait for next K result within 2 hours |

Note: If K+ < 3.3 mmol/L on patients initial bloods – Hold Insulin infusion. Replace K+ @ 20 mmol/hr (peripheral access) or 30 mmol/hr (central access) till K+ is > 3.3 mmol/L.

**Phosphate**

- Studies have failed to show any beneficial effect of phosphate replacement. However to avoid cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate administration may be indicated in patients with cardiac dysfunction, anemia or respiratory depression and in those with serum phosphate level < 0.32 mmol/L.
- Preparation: Potassium Di-Hydrogen phosphate – each ampoule of 10ml contains 10mmol potassium ions, 10mmol phosphate ions and 20mmol hydrogen ions.
- Add 20mmol Potassium Di-Hydrogen phosphate to the IV replacement fluid and monitor levels in those patients who require phosphate replacement.
- It is compatible with sodium chloride and glucose solutions. It is incompatible with compound sodium lactate solutions.

**Magnesium**

- Magnesium replacement has not been shown to be beneficial so only consider if the patient has symptomatic hypomagnesaemia or has symptomatic or significant hypocalcaemia.

**Clinical Issues**

- On admission:
  - Measure BGL with blood glucose meter. If the BGL is elevated off the meter send for urgent formal BGL from the lab.
  - Measure blood capillary ketones with a ketone meter.
  - Measure Arterial blood gas, EUC, CMP, FBC, serum lactate, LFT, HbA1C. If indicated attend blood cultures.
  - Test urine for glucose, ketones, nitrates. If indicated attend urine cultures and drug screen.
  - Perform other tests as clinically indicated, such as a septic screen, thyroid function tests, pregnancy test, troponin levels, amylase, lipase, CRP, ECG, Chest X-ray. Measure creatinine kinase levels if rhabdomylosis is suspected. (This is to aid in investigation for potential precipitants).
  - The BGL must be monitored by a blood glucose machine every 1 hour while patient receiving initial fluid replacement and while they remain on Intravenous Actrapid Insulin Infusion (If BGL remains above the upper limit of blood glucose machine, urgent formal glucose levels must be sent to the laboratory at least every 2 hours).
  - Serum potassium must be measured on admission and repeated every 2 hours. Potassium should always be diluted and NEVER given undiluted through a peripheral line.
  - Arterial blood gas analysis, EUC, CMP, blood capillary ketone (bedside ketone test) and osmolality must be measured hourly for the first 6 hours and then 2nd to 4th hourly if the response is satisfactory (a fall of osmolality of 3-8 mosmol/kg/hr).
In the absence of an arterial line, perform one initial arterial blood gas and then subsequent blood gas analysis can be with venous blood samples.

- An arterial line should be inserted for repeated frequent blood sampling.
- Vital signs are continuously monitored.
- Closely monitor patients level of consciousness and GCS – watch for signs of cerebral edema. Changes in mental status in HHS correlates with the severity of hyperosmolality – confusion being common with an osmolality > 330mOsmol/kg.
- Patient may be switched from intravenous to subcutaneous insulin once the HHS has resolved. This is indicated by the patient being mentally alert, serum osmolality < 315mosmol/L and they are able to eat normally.
- Biochemical and clinical evaluation must go hand in hand.
- The correction rate of metabolic changes need to take into account the physiological protective mechanisms induced by the metabolic decompensation.
- **Endocrine team should be involved for patient follow-up and education.**

**Antibiotic Therapy:**

- An infective source should be sought on clinical history and examination. Antibiotics should be given when there are clinical signs of infection or imaging / laboratory results suggest its presence.

**Anticoagulation:**

- DVT Prophylaxis is necessary for these patients as per the DVT Prophylaxis guideline.
- Consider extending prophylaxis beyond duration of admission in patients who are high risk.

**Foot Care:**

- These patients are at high risk of pressure ulcers.
- An initial and ongoing daily foot assessment should be performed.
- Protect heels by elevating them especially in those patients with neuropathy and peripheral vascular disease.

**Complications of HHS**

- **Cerebral Edema and Central Pontine Myelinolysis:** These are potentially fatal complication of HHS, caused by rapid shifts in osmolality which drives water into the central nervous system. This can be prevented by the gradual correction of glucose and serum osmolality. Clinically cerebral edema is characterised by deterioration in the level of consciousness, with lethargy, decrease in arousal and headache. Neurological deterioration may be rapid with seizures, pupilllary changes, bradycardia and respiratory arrest.

- **Pulmonary Edema:** This is rare complication. The cause and prevention strategies are the same as with cerebral edema. The elderly and those with impaired cardiac function are particularly at risk and fluid resuscitation should be carefully monitored in these patients using advanced hemodynamic monitoring.

- **Hypokalemia and hyperkalemia:** Serum potassium must be measured on admission and repeated every 2 hours. These are two life threatening complications that can be prevented by close monitoring of potassium levels.

- **Hypoglycemia:** this can result from excess administration of insulin. Hypoglycemia can cause cardiac arrhythmias and acute brain injury.

4. **Performance Measures**

All incidents are documented using the hospital electronic reporting system: IIMS and managed appropriately by the NUM and staff as directed.
5. References / Links


Author: ICU CNC, S.Shunker
Reviewers: ICU Medical Director, Staff specialists, ICU NM, NUMs, CNEs & CNSs, Endocrinology Staff Specialists
Endorsed by: ICU Medical Director: Prof. Michael Parr
HHS Definition:
- High serum osmolality, often > 320 mOsm/kg or more
- High BGL > 30mmol, without significant hyperketonemia (<3.0 mmol/L) or acidosis (pH > 7.3, HCO₃⁻ >15mmol/L).
- Severe dehydration, hypovolemia and unwell

Resolution of HHS:
Target BGL is between 10 – 15mmol/L
Complete normalisation of electrolytes and osmolality may take up to 72 hours.

Serum Osmolality:
\[ 2 \times \text{measured serum sodium} + \text{serum glucose} + \text{serum urea} \]

INSULIN

0-60mins
- BGL should fall with IV fluid replacement alone.
- Insulin infusion should only be commenced @ 0.05units /kg/hr if there is significant ketonaemia (capillary blood ketones >1mmol/L). Confirm K⁺ > 3.3mmol/L before commencing IV insulin. Otherwise delay IV insulin - see below.

60 mins – 6hrs:
- When BGL is no longer falling with IV fluids alone, commence insulin infusion at 0.05 units/kg/hr (confirm K⁺ > 3.3 mmol/L before commencing IV insulin).
- Target BGL is 10-15mmol/L, the fall in BGL should be no more than 5 mmol/L/hr.
- If BGL falls to <14mmol/L, continue IV insulin and commence 5% Glucose @ 125ml/hr AND continue 0.9% NaCl.
- Adjust IV insulin infusion in 1unit/hr increments or decrements to achieve desired BGL.

6hrs – 24hrs
- Aim to keep BGL 10-15mmol/L in first 24 hrs. Insulin management as per above 60mins – 6 hours.
- After patient is initially stabilised, discuss with Intensivist or endocrinology team regarding starting daily subcutaneous long acting insulin (eg. Lantus), whilst patient still on IV insulin infusion.

POTASSIUM

Potassium Note:
If K⁺ > 5.5mmol/L – Do not replace K, wait for the next K result within 2 hrs.

NB: If patient is to be transferred to the general ward on an insulin infusion, the ward “Intravenous Insulin/Glucose Infusion Order” (CR 132) must be used.

IV FLUIDS
- Assess volume status

0-60 mins:
- 0.9% NaCl – 1litre over 1 hour

60 mins – 6hrs:
- 0.9% NaCl – 0.5 to 1litre /1 hour
- Target is +ve balance of 2-3L by 6 hrs.

6hrs – 12hrs
- IV fluids to achieve +ve balance of 3-6 litres by 12 hrs
- If BGL falls to <14mmol/L commence 5% Glucose @ 125ml/hr AND continue 0.9% NaCl

12hrs – 24hrs
- Continue IV fluid replacement to achieve remaining replacement of fluid losses within the next 12 hrs.

IV Fluids Note:
- Aim for decrease in osmolality of 3-8mosmol/kg/hr in the first hour and 3mosmol/kg/hr after that.
- Only switch to 0.45%NaCl if osmolality is not declining despite adequate positive fluid balance.

24hrs – Day 3
- When patient osmolality and BGL has stabilised and they are mentally alert and able to eat, consider converting IV insulin infusion to subcutaneous regime of insulin.