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# Update on Serum Glucose and Metabolic Management of Clinical Nuclear Medicine Studies: Current Status and Proposed Future Directions

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**Management of a patient's blood glucose or metabolism in nuclear medicine studies has become an integral aspect of daily work primarily due to the increasing use of F-18 flurodeoxyglucose (FDG) positron emission tomography (PET). Newer tracers such as F-18 Fluciclovine and C-11 Choline, are in theory subject to metabolic shifts and changes based on patients' insulin levels, and also require attention to achieving optimum patient preparation. Metabolic derangements can also affect other studies, such as gastric emptying (GE), the results of which are dependent upon the patient's blood glucose level during the time of imaging.**

**The growing variety of diabetic medications has increased the complexity of the instructions which need to be given to patients. Current guidelines for patient preparation were developed in the past and have only slowly evolved with the introduction of newer oral medications. In addition to older insulin formulations newer formulations with different profiles of onset, duration, and consistency of action are being used.**

**The wide spectrum of newer drugs now in use for treating diabetes has not been accompanied by any updated consensus on how to manage these drugs for imaging studies which require blood glucose level management. In this article we review these newer diabetes medications primarily to raise awareness of the changing landscape. Our focus will be on suggestions to optimize patient preparation and management for these studies. For each scenario, our suggestions will be given as summary proposals for best patient management. Our hope is that this discussion will stimulate multicenter studies to provide data to support new practice guidelines for metabolically dependent nuclear medicine procedures.**

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## Review of Diabetes Medications

Diabetic medication effects are best understood when divided into two broad categories: insulin or insulin secretagogues/insulinogenic versus other antihyperglycemic agents/noninsulinogenic. This distinction is especially important when the patient has to be fasting (NPO) for a procedure as the latter group have a low risk of hypoglycemia and need not be stopped for fasting. A study looking at whether patients are given sufficient instructions to prepare for PET studies found that 99% were given inadequate instructions in at least one area of fasting, medication or blood glucose level (BGL) requirements prior to their procedure.[1] The standard of care is to hold all diabetes medication if NPO, except in specific cases.[2] Most antihyperglycemic agents would not be a problem if inadvertently taken right before the procedure. Conversely, insulin secretagogues do need to be discontinued as they interfere with the metabolic state at the time of the procedure. Hence, understanding the mechanisms of these new medications is important for proper patient preparation.

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## Insulins and Insulin Secretagogues

### Sulfonylureas

In the United States. sulfonylureas include glipizide (both regular and extended release forms), glimepiride, and glyburide. They have a similar mechanism of action but with differences in half-life, routes of elimination, absorption, and dosing. Their principal mechanism of action is to stimulate the sulfonylurea receptor on pancreatic beta cells thus stimulating insulin secretion.[3] If the patient is to be NPO, these agents should be held the morning of and up to two days prior to a study, depending upon their half-life (Table 2).

### Glinides or Meglitinides

These are also insulin secretagogues which attach to the sulfonylurea receptor. Repaglinide and nateglinide are available in the United States. They are rapidly absorbed and more rapidly eliminated than most sulfonylureas. They are typically given with meals. If the last dose is with supper the night before a procedure, they will have little effect the following morning and may be held the morning of the procedure if the patient is NPO.[4]

### Incretin pathway agents

These include dipeptidyl peptidase-4 inhibitors and Glucagon-Like Peptide receptor agonists (GLP-RA). The former oral agents inhibit the enzyme that degrades GLP-1 increasing levels of the peptide. Both improve glucose mediated insulin release and glucagon inhibition but GLP-RA's also slow GE and improve postprandial satiety. The GLP-1 receptor agonists are currently only available in subcutaneous (SC) formulation in pens given once or twice daily or weekly depending on the product. As any insulin release is only glucose mediated, these agents generally do not cause hypoglycemia. While these are generally held when a patient is NPO, they do not cause hypoglycemia, and if taken the procedure does not need to be cancelled for that reason.[5]

### Short Acting Insulin Analogs

These have more rapid onset and shorter duration of action than regular insulin. These include lispro, aspart, and glulisine. A newer version of aspart with the addition of a small amount of niacin to facilitate rapid absorption and L-arginine to stabilize the formulation is also available. These analogs have more predictable onsets and durations of action compared to regular insulin.

### Basal Insulin Analogs

Several more consistent, long acting basal insulins have also become available including glargine, detimir, and degludec insulins. These are available in different concentrations such as U-200 or U-300 pen formulations. The more concentrated formulation of glargine insulin may be associated with more consistent and longer action compared to the U-100 formulation. A highly concentrated U-500 regular insulin is also available via pen or vial, the latter with accompanying U-500 syringes. All other syringes for human use are U-100. If dosed correctly basal insulins should not result in hypoglycemia even if a patient is NPO. However, it is reasonable to reduce this dosage by 20%-40% prior to a NPO procedure to avoid the risk of hypoglycemia. This is in contrast to NPH insulin, which is typically reduced by 50%. Knowing the duration of action of these drugs is important in recommending whether to withhold a dose not only the morning of the nuclear medicine procedure but also at times adjusting the previous evening.[6]

### Intravenous Regular Insulin

In situations where rapid glucose control is necessary, regular insulin may be delivered intravenously (IV) preferably as an infusion rather than as boluses. When given IV, onset of action is very rapid, and the elimination half-life is around 6-8 minutes, resulting in a short duration of action.[7,8] IV administration of regular insulin should be under close medical supervision with monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia. It should be used at concentrations from 0.1 unit/mL to 1 unit/mL in infusion systems with the infusion fluid 0.9% sodium chloride using polyvinyl chloride infusion bags. A number of protocols are published elsewhere, and not covered here.[9–11]

To achieve proper glucose control, it may be necessary to administer IV insulin in a nuclear medicine setting. This requires adequately trained staff and appropriate monitoring as there is an increased risk of hypoglycemia. Some hospital based imaging centers may not allow IV insulin to be administered, as they are outside an intensive care unit. In some settings a physician may be the only person who is allowed to administer IV insulin, which can be a major logistical hurdle.

### SC Insulin

Human insulin (regular insulin), protaminated (NPH or N insulin), and partially protaminated "premixed" insulins, are effective and relatively inexpensive compared to newer formulations. For many patients they have been replaced by insulin analogs. Insulin use is divided into basal, prandial, and correction insulin to mimic pancreatic insulin secretion. Basal insulin requirement is generally 50% of total daily insulin need and prandial is the other 50%. Many people with diabetes are started on basal insulin along with other agents and are not on prandial or correction insulin. Newer SC insulin analogs can achieve glucose control more rapidly than older SC insulins, and closer to IV insulin.

### Insulin Pumps

Besides the new insulin formulations, there are new delivery devices such as pens and insulin pumps. Insulin pumps use rapid acting analogs, but are compatible with U-500 R insulin. They deliver basal insulin by using frequent small doses of rapid acting insulin subcutaneously. They can also give bolus doses by user direction. Most pumps can deliver a "temporary basal" rate programmed by the user for a NPO procedure. The adjustment would be similar to the recommendations for basal insulin analogs. Some new pumps adjust the basal infusion automatically based on continuous glucose monitor feedback. It is important to differentiate

Type 1 from Type 2 diabetes as the former must receive insulin even if NPO while the latter might not need this.[12]

### Inhaled Insulin

An inhaled rapid acting insulin is available, with time of onset within 12 minutes and duration 1.5-3 hours. In theory, this could have an interesting role in the preparation for Nuclear Medicine procedures. Caution should be used in patients with lung disease such as asthma and chronic obstructive pulmonary disease as its use may be associated with increased incidence of rhinitis, cough, and decline in lung function. It is unlikely to have any issues when administered for a single procedure, although it is not food and drug administration approved for acute glucose control. This should be held the morning of a procedure similar to other rapid acting insulins.[13]

## Approaches to Acute Insulin Dose Adjustments

Rapid acting insulins are used to lower elevated BGL where an acute correction is needed. A common formula used to determine dose is the 1700 rule. It was developed to determine the dose for Type 1 diabetes but also may apply to Type 2 diabetes. The total daily dose of insulin (or 0.4-0.5 unit/kg for those not on insulin) is divided into 1700 to derive the insulin sensitivity factor (ISF). The ISF is determined by rounding the result of the 1700 rule calculation to the closest ISF value. Table 1 shows a correction scale based on ISF. Each institution may have its own correction or "sliding scale."[14]

Table 1 is shown to assist in how to acutely normalize a patient's BGL using the 1700 rule. For example a patient on a total of 40 units of insulin per day (1700/40 = 42.5, which would be closest approximation to the Sensitive ISF column) with a BGL of 200-250 mg/dL, would require two units of insulin to reduce the blood sugar to 110-120 mg/dL. Usually if a patient is not already on insulin, the sensitive or average scale is used. Of note, the example ISF table is to assist in normalizing a patient's serum glucose, but since the desired target in FDG PET studies may be to just bring it down to <150-200 mg/dL, lower doses could be utilized.

A "carbohydrate ratio" can be calculated using the 450 rule to determine a needed SC insulin dose. One divides 450 by the total daily insulin dose or a calculated dose based on 0.4-0.5 units/kg. For example, if a patient is on 45 units of insulin per day, the carbohydrate ratio would be 450/45 = 10 g/unit insulin. If the patient is to be given a 50 g glucose load or eat 50 g of carbohydrate, the amount of rapid acting insulin to deliver subcutaneously to prevent a rise in glucose would be 5 units. If using aspart, lispro, or glulisine, this should be given 5-10 minutes prior to ingestion.[15]

## Other Antihyperglycemic Medications

### Metformin

This has been available in the United States since 1995 and appears to work primarily by reducing glucose production by the liver. Other mechanisms of action have been reported.[16,17] Since it does not stimulate insulin release, it is not associated with hypoglycemia. Although it is commonly withheld, a study can proceed without it being discontinued. Additional precautions need to be taken if IV iodinated contrast imaging will be performed, though these are for renal protective issues not related to glucose management.[18]

### Thiazoladinediones

Rosiglitazone and pioglitazone have been available since the late 1990's. These drugs work primarily by activating peroxisome proliferator-activated receptor-gamma and result in insulin sensitization.[19] They do not stimulate insulin release and thus do not result in hypoglycemia. They are safe even if taken on the morning of a procedure when patient is NPO.

### Sodium-Glucose Co-transporter Type 2 Inhibitors

These are among the most recent medications to become available for treatment of Type 2 diabetes. They act by inhibiting the reabsorption of glucose in the proximal tubule resulting in glycosuria. They do not result in hypoglycemia, but are associated with increased frequency of urination, and can result in prerenal azotemia if taken and patients are unable to have fluid intake.

### Miscellaneous

There are a number of lesser used drugs for treatment of Type 2 diabetes including α-glucosidase inhibitors, rapid release bromocriptine, colesovelam, and pramlintide. α-Glucosidase inhibitors result in carbohydrate malabsorption in the proximal small bowel.[20] Rapid release bromocriptine is a dopaminergic agent that appears to have a central effect on the brain and is administered early in the morning to duplicate the normal dopaminergic circadian peak.[21] Colesovelam is a bile acid sequestrant that lowers

**Table 1** This Table is an Example of a Scale Used at Temple University Hospital with ISF added

| Blood Sugar in mg/dL | Sensitive | Average | Resistant | Very Resistant |
|---|---|---|---|---|
| | ISF 50 | ISF 25 | ISF 16.67 | ISF 12.5 |
| >150 | 1 | 2 | 3 | 4 |
| >200 | 2 | 4 | 6 | 8 |
| >250 | 3 | 6 | 9 | 12 |
| >300 | 4 | 8 | 12 | 16 |
| >350 | 5 | 10 | 15 | 20 |
| >400 | 6 | 12 | 18 | 24 |

BGL.[22] Pramlintide works on the incretin pathway by slowing GE but does not stimulate insulin release. None of these agents cause hypoglycemia.[23]

Finally, oral agents may be delivered in different combinations, such as mixtures of metformin with a sulfonylurea. Such use of combination therapies will increase the complexity of instructions needed for patients.

## Patient Preparation for Nuclear Medicine PET Studies

While the patient preparation for various nuclear medicine exams have important differences between them, the majority of studies utilizing FDG and other metabolic tracers have one aspect in common: ideally, the patient arrives in a fasting state with euglycemia and low normal serum insulin level. Typically when patients with diabetes are NPO for a PET procedure all diabetic medications are held with the exception of basal insulin. If the patient received rapid acting insulin or an insulin secretagogue shortly before the planned procedure and blood sugar is on the low side, it may be best to reschedule the procedure.

Current recommendations for patient preparation have been published by various societies.[18,24–32] The following discussion is not an in depth review of the current guidelines nor meant to replace them, but rather to provide additional background and suggestions on how newer diabetic agents may affect patient preparation.

### FDG PET in Oncology and Neurology

In routine clinical practice, it is common to see patients who are sub-optimally prepared and present with poor glycemic control. Studies have examined the role of giving IV regular insulin to acutely control BGL with subsequent injection of FDG 60-90 minutes later. These show qualitatively normal biodistribution, and similar standardized uptake values compared to patients who present with acceptable BGL.[33–36]

While acute control of BGL with IV regular insulin may save patient rescheduling, it increases the complexity of the study due the need for careful BGL monitoring. Newer drugs do not offer a temporal benefit, taking the same or longer time to correct BGL, and are more expensive but potentially safer and requiring less intensive monitoring of BG. A study using SC rapid acting insulin found that the optimal scans required waiting >4 hours after glucose correction, whereas IV dosing could achieve adequate studies in 1 hour.[37,38] No studies have been done using inhaled insulin, but its rapid action may yield similar results. Another case report showed no qualitative effect after using a long acting insulin, glargine, within 3 hours prior to FDG injection.[39]

Other agents have also been studied with regards to their effects on FDG uptake. Rosiglitazone had no effect on the quality of FDG scans.[40] Pioglitazone actually induced increased FDG uptake in malignant lesions, but the study specifically looked at the effect of stimulating the peroxisome proliferator-activated receptor-gamma receptor in tumors, as opposed to optimizing image quality.[41]

Except for metformin, the other antihyperglycemic agents are unlikely to cause problems with image quality. Metformin has been demonstrated to cause diffuse colonic uptake. To avoid this it is recommended that metformin be discontinued up to 3 days prior to the scan. Alternative methods are needed to control BGL during that time period.[42–44]

In neurologic imaging, many centers are less strict about fasting or BGL control. This assumes that FDG metabolism of the brain is so high that changes in BGL are unlikely to affect the pattern of uptake. Current guidelines for patient preparation are the same as oncologic imaging and studies do show that the pattern of uptake could be affected by hyperglycemia.[45–47] In fact, it is well-known that patients who present for oncologic or infection/inflammatory PET imaging with severe hyperglycemia do have altered uptake in the brain. The newer agents have been studied in neurological diseases with FDG PET, again not for the purposes of optimizing imaging, but in the study of effects of clinical pathology.[48,49]

#### Summary Proposals

1) Patients who have 7) taken any rapid acting insulin or insulin secretagogues <4 hours prior to FDG injection should be rescheduled, or receive FDG injected >4 hours after the medication. Some drugs such as glyburide have a long half-life, and if taken before study, patients may need to be rescheduled to minimize risk of hypoglycemia.
2) Patients presenting with hyperglycemia who cannot be rescheduled may alternatively have their BGL controlled with the following:
   a Intravenous insulin, followed by FDG injection >30-90 minutes, or preferably as late as 4 hours post-IV insulin correction.
   b Rapid acting insulin analogues or inhaled insulin may both have rapid but sustained actions. FDG injection should be at least 4 hours after medication administration.
   c Insulin should be titrated using ISF doses (Table 1).
   d Check serial BGL levels to gauge insulin activity prior to tracer injection.
3) Metformin could be avoided in patients undergoing abdominal evaluations by temporarily switching them to another oral or insulin analogue regimen.
4) Oral agents should be discontinued, although the procedure can likely continue if a nonhypoglycemic/antihyperglycemic medication is inadvertently taken (Table 2).
5) Patients on basal insulin regimens or pumps need to have their rates adjusted appropriately for fasting (usually decreased by ~20%-40%) and the insulin pump infusion should not be discontinued for the exam. See previous discussion.

### FDG PET Imaging in Infection and Inflammation

The methodologies for imaging infectious and inflammatory diseases are generally the same as for oncologic imaging, as

**Table 2** The Onset and Duration of Action of Agents is Based on Package Insert and Various Sources but May Vary From Patient to Patient Based on a Number of Factors Including Renal Function

| Medication Class | Time to Effect | Duration of Action | Causes Hypoglycemia? | Adjust Prior to PET Metabolic Scans | Adjust Prior to Gastric Emptying |
|---|---|---|---|---|---|
| Insulinogenic | | | | | |
| Insulin (intermediate acting) | 1-3 h | 12-16 h | Yes | 50% if long acting (eg NPH) | No |
| Subcutaneous rapid insulin (short acting) | 30-60 mins | 5-6 h | Yes | Discontinue | ISF based |
| Basal Insulin analog (long acting) | >4 h | >18-42 h | Yes | Reduce by ~20%-40% | No |
| Insulin analog (rapid acting) | 15 mins | 3-5 h | Yes | Discontinue | ISF based |
| Insulin pumps (subcutaneous) | Dependent upon insulin used – short acting or continuous | Dependent upon insulin used – short acting or continuous | Yes | Reduce by ~20%-40% of basal rate | May reduce by ~20%-40% of basal rate, if at all |
| Intravenous insulin bolus | very rapid | 30 mins | Yes | N.A. | N.A. |
| Inhaled insulin | 12-15 mins | $1^1/_2$-3 h | Yes | Discontinue | No |
| Sulfonylureas[61] | >30 mins | 12-24 h | Yes | Discontinue (1-2 d) | No |
| Glinides or meglitinides | 15-20 mins | 3-6 h | Yes | Discontinue | No |
| DPP-4 | <1-2 h | ~24 h | **No** | No | No |
| GLP1-RA | <1-2 h | <1-7 d | **No** | **No** | **Yes** |
| **Medication Class** | **Time to Effect** | **Duration of Action** | **Causes Hypoglycemia?** | **Adjust Prior to PET Metabolic Scans** | **Adjust Prior to Gastric Emptying** |
| **Noninsulinogenic** | N.A. | N.A. | **No** | | **Often discontinued, but not mandatory** |
| Acarbose | N.A. | N.A. | No | For cardiac viability if oral glucose loading protocol is used | No |
| Colesovelam | N.A. | N.A. | No | For cardiac viability if oral glucose loading protocol is used | No |
| Metformin | N.A. | N.A. | No | Discontinue 2-3 days prior to FDG PET procedures, especially if evaluating bowel | No |
| Pramlintide | N.A. | N.A. | No | No | **Yes** |
| Thiazoladinediones | N.A. | N.A. | No | No | No |
| SGLT2 Inhibitors | N.A. | N.A. | No | Often discontinued, but not mandatory | No |

N.A., not applicable.

when evaluating fever of unknown origin, hardware infections, etc. In the cases for vasculitis and cardiac etiologies such as myocardial sarcoidosis, myocarditis, endocarditis, etc. the preparation is more extensive. For these studies, one has to achieve suppression of physiologic myocardial FDG uptake, for which prolonged fasting >6-12 hours, and instructions to follow a high protein/fat-low carbohydrate diet for at least 1 day prior to the study are recommended. Unfractionated IV heparin inhibits lipolysis to increase myocyte fatty acid uptake and reduce FDG uptake, and may also be utilized.[29] If a patient does present with hyperglycemia, care must be taken in using any insulin or insulin analog as a corrective measure as insulin will promote background myocardial FDG uptake.

## Summary Proposals

1) Patients with noncardiovascular infection/inflammation evaluation can follow the oncologic preparation guidelines and proposals.
2) For cardiac evaluation
   a Extra preparation such as extended fasting, low carbohydrate diet, and unfractionated heparin may be recommended to limit cardiovascular FDG uptake.
   b Patients presenting with hyperglycemia should be rescheduled unless it cannot be more optimally controlled. Acute glucose correction is in theory could be problematic, although no studies have evaluated this.
   c If insulin correction is considered, intravenous form may be preferable if possible due to its short duration of action. For SC insulin, use ISF factors (Table 1) on the conservative/lower side to estimate how much should be given. Serial glucose could be obtained to monitor when insulin effects may start wearing off before FDG injection.
   d Patients already on basal insulin or infusion pumps can have their rate adjusted until acceptable glucose levels are achieved. This should not enhance glucose myocardial uptake. A recommended decreased of 20%-40% from basal rate should be acceptable, provided that baseline BGL is under reasonable control.

e Metformin should be held, especially if the GI tract is a consideration for sources of infections, etc.

## FDG PET Cardiac Viability

Viability studies aim to achieve a euglycemic but hyperinsulinemic (fed) state so that there is increased glucose and suppressed fatty acid myocardial uptake prior to FDG injection. The initial preparation involves standard fasting immediately prior to the scan, and may involve a preparatory low carbohydrate diet 1-2 days prior to the study.

There have been various recommendations formulated over a decade ago, with few recent studies that have evaluated potential new options offered by newer drugs for insulin management. The options vary in complexity and efficacy. The most complex procedure is the euglycemic-hyperinsulinemic clamp, which involves on intravenous administrations of glucose and insulin. This method, however, is labor intensive and difficult to perform because of needed frequent titration. A less complex method involves IV glucose loading with IV insulin boluses. Simpler methods use oral glucose loading and relying on endogenous stimulation of insulin to cause myocardial FDG uptake. This may be supplemented with IV insulin boluses. Niacin with Aspirin, or Acipimox (outside the United States) have been used as they decrease serum free fatty acid levels, which in turn promotes cardiac glucose uptake and utilization.[29]

Rapid acting SC insulin analogues using the ISF scales to guide dosing offer an alternate to the standard IV insulin and have several theoretical advantages. Unlike SC regular insulin, lispro, aspart, and glulisine are more rapid acting, although not as rapid as IV regular insulin. Furthermore, they last for up to 3-5 hours. These agents may also require fewer repeat injections and are also less likely to cause severe hypoglycemia. Other rapid acting agents such as meglitinides might also have some utility.

Patients on basal insulin or insulin pumps should decrease their basal rate by 20%-40% when fasting, but during the viability procedure their rates could be readjusted, or just given exogenously based on ISF tables to achieve the necessary metabolic state. In theory, this could require less intensive monitoring than when administering other exogenous insulin to reduce the risk for hypoglycemia.

For a patient on Acarbose, an oral glucose loading protocol will be blunted and possibly not work. This is because inhibition of α-glucosidase in the proximal bowel significantly decreases glucose uptake into the serum, and decreasing the glucose loading phase of the procedure. For this, loading with alternate sugars (eg, maltose, lactose, etc) or similar caloric supplemental meal may be needed. One would also need to pay attention to the fat content of the meal since that could inhibit myocardial glucose uptake (MGU) despite the sugar loading. Other agents such as Colesovelam also decrease oral glucose availability for loading.

Studies have looked at the effects of FDG uptake of cardiac muscle with various agents but have not specifically looked at their ability to perform viability studies.[50] Administration of GLP-1 on MGU has shown that it is dependent on baseline MGU.[51,52] Other medications such as rosiglitazone also have the potential to raise MGU in patients with diabetes.[53] How this may affect a cardiac myocardial viability study needs further study.

### Summary Proposals

1) Oral hypoglycemic agents should be discontinued, but other oral agents need not be changed, although they are commonly held (Table 2).
2) As an alternative to intravenous insulin bolus or infusion clamp procedures, insulin analogues or inhaled insulin could be used, and are possibly preferable.
   a They are theoretically safer to perform, requiring less monitoring, and decrease the need for specialized staff.
   b Their longer duration of action could be advantageous promoting FDG uptake into the myocardium for increased time.
   c ISF values (Table 1) should be used to titrate doses for the insulin analogues.
3) GLP-RA and other agents as potential alternatives need further study.
4) As noted earlier, patients with diabetes already on long acting insulin analogues, basal insulin, or pumps need to have their rates adjusted appropriately for fasting (generally decreased by 20%-40%), but should not be completely discontinued for the exam.
5) Patients undergoing the oral glucose loading procedure should discontinue medications such as acarbose or colesovelam.
   a If the patient has taken acarbose, alternate sugar source (such as maltose, lactose, etc.) should be considered with avoidance of any fat in the meal. Although milk or similar meals may be less than optimal given its fat content, a good endogenous insulin response from the meal stimulation may still overcome any suppression from fatty acids.
   b Otherwise, consider using an alternate protocol using IV insulin or SC analogues (as above), or other options such as Niacin + Aspirin, etc.
6) Use of other oral medications (eg, rosiglitazone) may enhance myocardial FDG uptake but is a subject needing further study.

## PET in other Metabolite Imaging: Amino Acids, Choline, etc

PET imaging with amino acids and metabolites has recently come into use with the introduction of Fluciclovine and C11-Choline for prostate cancer. C11-Methionine PET imaging with limited availability has been around for several years. There are conflicting data in humans whether fasting versus preloading with amino acids affects imaging. Similarly data are lacking looking at optimizing metabolite imaging based on whether serum insulin and BGL can optimize amino acid uptake into target tissue.[54–56] Both serum amino acids and insulin levels appear to affect the regulation and expression of amino acid transporters.[57,58] Hence, amino acid

metabolism may be coupled to glucose metabolism and patient preparatory recommendations are similar to those for FDG imaging.[59] There is some evidence that choline uptake is also affected by insulin levels, although the extent is not known.[60] Conversely, other metabolites like 3′-deoxy-3′[(18)F]-fluorothymidine (FLT), [(124)I]-iododeoxyuridine (IUdR), etc are not known to need a specialized diet prior to tracer administration.

### Summary Proposals

1) Patients should be prepared with the appropriate diet and fasting as per current guidelines for amino acid, choline, and other metabolite scans.
2) Diabetic medications should be adjusted or discontinued for the study to plan for NPO status. This may also improve other metabolite uptake in target tissue since in theory it is influenced by insulin; however, there is no clinical evidence available supporting that claim as yet.
3) Effects of BGL and insulin use on metabolite imaging are currently unknown, although good control is suggested as a matter of good practice. Insulin levels should be near fasting levels to avoid increasing uptake into muscles or other tissues, but enough to keep BGL under control. It is unknown whether checking baseline BGL prior to the scan could be a useful surrogate to help determine whether scan quality may be affected.

## Gastric Emptying and Glycemic Control

The relationship of GE and BGL is complex and can differ in normal controls compared to patients with diabetes. There is a well-recognized relationship between BGL and its effect on the rate of GE. If GE is too fast and postprandial blood glucose increases there will be a slowing of GE.[62] Hypoglycemia will accelerate GE to increase BG.[63]

A recent systematic review has shown that acute, severe hyperglycemia (marked hyperglycemia with BGL of 16-20 mmol/L (288-360 mg/dL) delays GE in patients with type 1 diabetes.[64] Modest hyperglycemia (8 mmol/L (145 mg/dl)) also delays GE however the effect is small and not greater in type 1 diabetes than day-to-day variations in GE.[65] The effect of differing levels of hyperglycemia in patients without diabetes has not been well documented. Insulin-induced hypoglycemia has been shown to accelerate the GE of both solids and liquids in long standing type 1 diabetes.[66] Because hyperglycemia can slow GE, it has been recognized that BGL, especially in diabetic patients, should be controlled during a GE study.

### Blood Glucose Effects on Gastric Emptying

BGL is typically tightly regulated in normal subjects. Normally after a meal BGL rises and then returns to pre-meal levels as glucoregulatory mechanisms occur. In the fasting state, BGL is set by the rate that endogenous glucose is released into the circulation and the rate of glucose uptake in the body.[62,64] Glucagon secretion prevents a fall in BGL by stimulating hepatic glucose production while basal rates of insulin suppress hepatic glucose production and promote glucose uptake in peripheral tissues. In the fed state, the rate of GE helps to control delivery of nutrients into the GI tract. The rate of GE is controlled by many factors including not only the meal composition but also the motor activity of the stomach and duodenum, nutrient feedback from receptors in the small intestine and the secretion of GI hormones.[67] There is a relation between BGL and the rate of GE.[68] Neither insulin nor glucagon has a direct effect on the rate of GE.[69]

When nutrients are ingested, they also stimulate release of incretins. Incretin effects include: increased glucose dependent insulin secretion, inhibition of glucagon secretion, induction of satiety and slowing of gastric emptying.[70–72] K cells from the duodenum secrete glucose-dependent insulinotropic peptide (GIP). In the distal ileum and colon, L cells secrete glucagon-like peptide-1 (GLP-1). GLP-1 induces an inhibitory feedback effect, slowing GE.[70] Direct manometric recording of antral contractions performed with glucose clamping have shown antral contractions were nearly absent at serum glucose level of 250 mg/ml and markedly reduced at 175 -140 mg/dl with no effect seen at 120 mg/dl.[71] Brener et al using physiologic saline in the stomach and glucose infusions into the duodenum showed that delivery of glucose to the duodenum inhibited GE.[72]

Horowitz et al using a liquid only glucose meal in normal volunteers showed that elevated plasma glucose levels at 120 minutes correlated with slowing of GE.[73] His group also showed selective slowing of the liquid component of a mixed solid and liquid meal with mean hyperglycemia levels of > 15 mmol/ L (> 270 mg/dl) compared to those with a mean < 15 mmol/L (< 270 mg/dl).[74] Fraser et al also demonstrated that hyperglycemia during glucose clamping with a blood glucose range 16-20 mmol/L (288- 360 mg/dl) slowed GE for both solid and liquid in a mixed meal in patients with Type 1 diabetes.[75]

In healthy individuals Barnett and Owyang showed a slowing of GE even when glucose was raised only to 140 mg/dL (7.8 mmol/L) which is just at the upper end of normal, physiologic postprandial plasma glucose.[71] Schvarcz et al showed more "physiologic" levels of hyperglycemia (blood glucose concentration of 8 vs 4 mmol/L(145 vs 72 mg/dL) also delayed GE in type 1 diabetes and normals.[76] Nowak et al found that fasting hyperglycemia at the start of a GE study in type 1 diabetes using a radiolabeled, solid meal had no correlation with GE half time. In that study the shortest GE half time was seen in the patient who had the highest blood glucose values.[77] Another study in type 2 diabetes showed no overall relationship of hyperglycemia to GE of solids but did slow emptying of liquids and increased the duration of the lag phase of GE.[78] A reduction in BGL below normal fasting levels has been shown to accelerate GE. Russo et al showed that insulin-induced hypoglycemia in patients with diabetes accelerated GE.[79]

It is always important to study nondiabetic controls vs diabetic responses. Fraser et al showed that with low physiologic BGL of 4 mmol/L (72 mg/dl) GE rates were the same. However, when plasma glucose was elevated to 8 mmol/L (145 mg/dL) there was a slowing of GE in the normal controls but GE was

more rapid in the patient with diabetes.[76] Bharucha et al recently showed that a group of patients with poorly controlled type 2 diabetes had rapid GE with elevated BGL.[80]

One might hypothesize that normal subjects might show less of an effect of varying BGL on GE rate than those with diabetes. This hypothesis however is not supported by the results of Schvarez et al. These authors used an insulin-glucose clamp to stabilize BGL and measured GE using a mixed solid (egg) and liquid meal similar to the currently recommended GE solid meal. For nondiabetics, gastric retention of the solid meal at 100 minutes was 55% at 8 mmol/L (145 mg/dL) versus 37% at 4 mmol/L (72 mg/dL) ($P$= 0.004) and in type 1 diabetes was 44% versus 36% ($P$= 0.004). The T1/2 for the liquid meal was 57 minutes at 8 mmol versus 32 at 4 mmol/L ($P$= 0.002) in normals and 41 minutes versus 29 minutes ($P$= 0.002) in type 1 diabetes. Thus changes in blood glucose within the normal postprandial range (145-72 mg/dL) had a significant impact on GE in both normal subjects and patients with type 1 diabetes.[76]

Ramzan et al utilized continuous glucose monitoring to compare post prandial BGL in patients who were normal or had type 2 diabetes both with and without gastroparesis, and patients with idiopathic gastroparesis during GE scintigraphy utilizing the current recommended liquid egg white meal. They found that those with diabetes with gastroparesis had similar peak postprandial BGL (231 ± 26 mg/dL) vs nongastroparetics (232 ± 18 mg/dL). However the 4 hour postprandial BGL was higher in those with gastroparesis (187 ± 25.6 vs 97 ± 10 mg/dL). Normal controls had a peak postprandial blood glucose of only 56.1 ± 10.2 mg/dL.[81]

## Current Recommendations on Glucose Control for Gastric Emptying Scintigraphy

The above studies all support the need for glucose control of patients referred for a GE study. The most recent society of nuclear medicine and molecular imaging (SNMMI) Guideline on GE recommends that the prestudy fasting BGL should be less than equal to 200 mg/dL.[82] A recent American Gastroenterological Association (AGA) practice guideline states "markedly uncontrolled (>200 mg/dL)" glucose levels may delay gastric emptying and aggravate symptoms of gastroparesis (strong recommendation, high level of evidence) and recommends deferring GE testing until relative euglycemia is achieved to obtain accurate GE results. The AGA guideline further states "Patients with diabetes should have blood glucose measured before starting the GE test and hyperglycemia treated with test started after blood glucose is <275 mg/dL (Strong recommendation, moderate-high level of evidence)".[83]

The following proposals include suggestions made to promote best management of patients with hyperglycemia sent for a GE study and to promote more dialogue on this subject.

### Summary Proposal - Prestudy General Instructions and Management of Blood Glucose Prior to a GE study

A All patients are instructed to be NPO after midnight the night prior to the GE study. All patients can take any nondiabetic, oral medications with a requisite amount of water at home prior to coming for their GE study. To avoid any medication questions, patients should bring all medications with them for review. Patients with diabetes should be reminded specifically to bring all oral diabetic drugs and/or injectable/insulin (s) in addition to any other medications.

B Diabetes patients should be scheduled preferably for an early start time (first or second case of the day).

C All patients should be told they will have a BGL test done prior to their GE study. It is recommended that patients with diabetes should bring their glucose monitoring device with them, if they have one.

### Summary Proposal - Pre-GE study glucose assessment

Most nuclear medicine departments currently do not check a prestudy BGL in normal or patients with diabetes. Prestudy BGL should be measured in all patients as unsuspected elevated baseline BGL needs to be excluded even in patients not previously diagnosed with diabetes. As there is a potential for inaccuracy in self-measurement of BGL, all BGL testing should be done by certified, point-of-care professional. As BGL testing for FDG PET/CT studies has become the standard of care, nuclear medicine imaging departments should have the ability to check a BGL prior to a GE study.

### Summary Proposal - Prestudy Glycemic control

*Normal Patients, or Those With Diabetes not on Medication.*

A These patients are instructed to be NPO after midnight on the evening before their study, and to remain fasting until they receive their GE meal. In the absence of any current guidelines this is likely to remain the recommendation for nondiabetic patients. There is, however, a growing problem that a large proportion of the population has either prediabetes or undiagnosed type 2 diabetes. Therefore, as above, a pre-GE study BGL check should be performed. If <200 mg/dL the study can proceed. If there is an elevated fasting BGL, this should be included in the study report with particular attention to the referring physician of the need for further formal testing for diabetes.

B If a prestudy glucose shows an unexpected blood glucose >200 mg/dL there are two options. First, the patient may be referred back to the ordering physician for diabetic work-up with a recommendation for the patient to return when BGL is under control. If there is an immediate clinical need to proceed with the study, rapid acting insulin may be given.[84]

*Patients with diabetes on oral agents.*

A As many oral agents in use today are antihyperglycemic and not hypoglycemic there is no reason to hold any of the noninsulinogenic oral agents from the standpoint of the study, although as previously stated, these are commonly held as a matter of general practice.

B If fasting blood sugar <275 mg/dL by AGA guideline, or close to <200 mg/dL by SNMMI guideline the site can make a determination to have the GE study proceed. Patient may take their normal oral diabetic medicine just before or after eating the GE test meal. No further monitoring is necessary.

C If prestudy BGL >200 mg/dL by SNMMI, or >275 mg/dL per AGA, the following options could be considered.
   a Study may be cancelled and patient rescheduled to return on another date with better control.
   b An option could be to continue despite poor control if the patient's BGL is chronically poorly controlled, as it might be useful to assess the patient's function at their usual baseline, and potentially compare it with another when the BGL can be better controlled.
   c Rapid acting insulins may be used for acute control, as they will peak at 1-1.5 hours. Wait to check a BGL at 0.5-1.0 hour and if appropriately controlled, proceed with GE test meal and imaging study.

D On sulfonylurea or meglitinide medication. These agents should be held for the morning of the GE test. If the pretest BGL is <200-275 mg/dL take their medication with the GE test meal and proceed. If >200-275 mg/dL take daily medication and give supplemental short acting insulin as above.

E For patients on GLP1 receptor analogs these will need to be discontinued as these slow GE. Many of these agents are taken once weekly, others once or twice daily. Ideally the GE study should be timed for at least 5-7 days after previous medication dose if weekly, and 24 hours after last dose if daily or twice a day. These patients may experience acute hyperglycemia off the agent and will need insulin to control BGL using insulin. Similarly, Pramlintide may also need to be discontinued and substituted given its effects on gastric emptying.

*Patients with diabetes on insulin.*

A Single basal insulin dose—if the patient is on a correct basal insulin dosage, there is no peak to the insulin effect and the dose needs no dose adjustment. If on glargine, detimir, or degludec one could consider that the GE test meal has less caloric value than the patient's typical breakfast and could then reduce the prior night or morning dose by 20%-40 % prior to the GE test.

B Basal and short acting insulin—since the caloric content of the test meal may be less than patient's typical breakfast it is suggested patient takes half usual short acting insulin with the GE meal. The dose reduction can be made by comparing the calories of the patient's typical breakfast to the current standard liquid egg white, two pieces white toast, and jam meal which contains approximately 220 calories and 45 g carbohydrate.

C NPH or Premix Insulins—while the use of these agents is decreasing some diabetes patients may still be on NPH or premix insulins. These patients can follow older recommendation to take half their long acting insulin dose before coming to nuclear medicine. The patient then checks BGL before the study and study proceeds if glucose <200-275 mg/dL. If BGL > 200-275 mg/dL, insulin for acute control should be considered. Patient may then check BGL at end of the 4 hour study and takes approximately half more of their long acting insulin depending on post-test glucose level.

D Insulin pump therapy—as above, depending on the patient's normal breakfast caloric content versus GE meal, suggest reducing the basal insulin dose by 20%-40 % starting the morning of the test by putting in a temporarily basal infusion rate to start at the time of ingestion of the GE test meal.

E Mixed insulin and oral medication—again as stated above, most oral medications, especially in this scenario, are likely to be antihyperglycemics as opposed to hypoglycemic agents. Thus, they need not be necessarily stopped, except to follow routine clinical practice. If there is a hypoglycemic agent, the instructions can follow as suggested before. Any insulins should likewise follow the options as above.

*Summary Proposal—Is There a Need for Glucose Control During the GE Study?* From the results described above by Ramzan et al utilizing continuous BGL monitoring during GE scintigraphy, there is no expected hyperglycemic peak that will slow GE in nondiabetic subjects.[81] There is therefore no expectation that any monitoring or active adjustment of BGL during the GE study is needed in nondiabetics. Diabetics both with and without gastroparesis, however, had a peak BGL > 200 mg/dL during the study. This raises concerns that maintaining euglycemic BGL after test meal ingestion might give different GE results. Currently there are no guidelines or studies with data to support the use of continuous BGL monitoring and active intervention during GE studies. This is an area of needed future research.

## Conclusion

In this article we have reviewed several scenarios for achieving optimum BGL using both older and newer diabetes medications. This is done in an attempt to increase awareness of the nuclear medicine community of the increasing complexity created by multiple new diabetes drugs. Some clinics have begun to incorporate updated instructions to patients into their practices. Few, however, are using protocols to specifically address patients on these newer diabetic medications. Currently, there are no formal consensus statements on how to best optimize use of these drugs. Formal recommendations will eventually need to take into account clinical efficacy, practical logistics, as well as costs of using the newer agents in favor of the older ones. For now, a practical approach is to work closely with one's local endocrinologist on recommendations for optimum glycemic control for preparation for nuclear medicine studies. More work will be

needed from future clinical trials to optimize protocols for glycemic control for the wide range of nuclear medicine imaging studies discussed in this review.

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