Lipodystrophy: Metabolic and Clinical Aspects

Resource Room Slide Series
Current Thinking About the Diagnosis and Treatment of the Insulin-Resistant State: How to Use Insulin Therapy

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Disclosures

- Grants: Sanofi
- Consulting: Abbott Pharmaceuticals, Johnson & Johnson, Roche, and Valeritas
Learning Objectives

- Define the major syndromic and non-syndromic forms of insulin resistance to distinguish them in clinical practice
- Identify appropriate and inappropriate uses of currently available human and analogue insulin, based on pharmacokinetics, to guide therapy in severely insulin resistant patients
- Describe an appropriate algorithm for diagnosis and treatment of patients with severe insulin resistance to prioritize clinical decision-making
Traditional Treatment of Insulin Resistance: U-500 Insulin

- Main reason in early 1950s was for high insulin requirements in type 1 diabetes because high levels of insulin antibodies developed from other animal insulins
  - Also used for severely insulin-resistant patients with type 2 diabetes
  - Only developed as a regular insulin
- Beef U-500 replaced by pork U-500 regular insulin in 1980
- Replaced by human U-500 regular insulin in 1997
Why Do We Need Different Insulin Concentrations?

- Late 1970s: Decision to phase out U-40 and U-80 insulins to make all insulin U-100
  - “It represents a single, understandable strength”
  - Reduces errors in syringe measurement using different insulin concentrations
Obesity* by County, United States, 2009

*Age-adjusted percentage of adults ≥20 years of age

Source: www.cdc.gov/diabetes
Diagnosed Diabetes by County, United States, 2009

*Age-adjusted percentage of adults ≥20 years of age

Source: www.cdc.gov/diabetes
Algorithm for Treatment of Severe Insulin Resistance?

- No consensus
- Appropriate to first determine etiology (syndromic insulin resistance?)
Why the Need for More *Concentrated* Insulins?

- For more-resistant patients, U-100 insulin both impractical and inconvenient
  - When >100 units (1 mL) are required at one time, would need more than one injection
  - Large volume of insulin more painful
  - Large depot of insulin impedes absorption, making it unpredictable (more concentrated insulin should be more predictable at these doses)
Before Moving to U-500 Insulin, What “Pearls” Should Be Considered Regarding U-100 Insulin?
Glucose Infusion Rates (GIRs) for Different Glargine Doses Injected into Abdomen

1.0, 1.5, and 2.0 units/kg greater GIR than 0.5 units/kg, but not greater than each other!

Teaching Point 1:

Although it is possible that duration of insulin action is prolonged with increasing doses of glargine, there is no difference in insulin action for the 24 hours after injection once the dose is >1.0 unit/kg.
U-100 Pearl 2: What Do We Know About Large Depots of Insulin?

- The larger the depot, the more variable the absorption.
- What would happen if NPH was given as two injections?
  - $n = 15$: one site (A1C = 10.0%, 240 units NPH)
  - $n = 16$: two sites (A1C = 10.3%, 254 units NPH)
  - At 12 months, A1C = 8.8% vs. 10.4% favoring two sites ($P < 0.05$)

Teaching Point 2:

Large depots of NPH insulin appear to be more efficacious when split into two depots. Although this may be true for basal insulin analogues, the expense of these doses of insulin and low risk of hypoglycemia make NPH insulin preferred in this situation.
Is it possible that NPH insulin, which has a “peak,” could, despite more unpredictable absorption than glargine and detemir, improve overall glycemic control?

Case report:
- 52-year-old man; type 2 diabetes
- Glargine, 80 units twice daily; lispro, 60 units three times daily
- A1C = 9.5%
- After 3 months of NPH/lispro, A1C = 6.1%; after 7 months, A1C = 6.8%. No change in insulin dose (1.48 units/kg) or weight (108 kg)

“NPH insulin might be superior to the long-acting analogue glargine in cases of severe insulin resistance, but randomized studies are needed to confirm our findings and clarify the involved mechanisms. NPH insulin also provides a significant cost reduction.”

More Concentrated Basal Insulins in Development

- U-300 insulin glargine
- U-200 insulin degludec

The hope is that more concentrated preparations of these long-acting basal analogues will result in smaller insulin depots and more consistent absorption with the larger doses required in severely insulin-resistant patients.
These patients also require prandial insulin. What about large doses of rapid-acting analogues? Should we substitute regular insulin like we currently do with NPH?

The best way to treat mealtime hyperglycemic spikes is with a rapid-acting analogue, but even this is far from perfect.
Rapid-Acting Analogues: Are They Really “Rapid” at Higher Doses?

How Long Can a Really Big Dose of Insulin Last?

- An 80-year-old nondiabetic man with a suicide attempt
  - 10,000 units of human regular insulin
  - 6,000 units of human NPH insulin
  - Intravenous dextrose required to maintain glucose >100 mg/dL for more than 13 days (more than 312 hours!)

What About Adding GLP-1 for These Patients?

- $n = 13$ patients receiving $>200$ units/day of insulin for 13 months
- Add liraglutide

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<th>A1C (%)</th>
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<td>2.3</td>
<td>8.9</td>
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<tr>
<td>After liraglutide</td>
<td>126</td>
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Chukwu JF, Hirsch IB, Trence D. Presented at ENDO 2012, the 94th annual meeting of the Endocrine Society, Houston, Texas, June 2012.
Clinical Algorithm: Where to Start?

History and physical exam:
• Consider endocrinopathy
  – Cushing’s syndrome, acromegly, glucagonoma, pheochromocytoma
• Lipodystrophy
  – Congenital or acquired
• Type B insulin resistance syndrome (IRS)
• Mitochondrial diabetes
  – Maternally inherited diabetes and deafness (MIDD)
Algorithm: Insulin-Resistant Type 2 Diabetes

Endocrinopathy

Lipodystrophy

Type B IRS

MIDD

Metreleptin?  

Determine etiology

Syndromic insulin resistance

yes

Treat the cause

>1 units/kg basal insulin analogue

no

>2 units/kg/day or 200 units/day and A1C >8%

Metreleptin?

GLP-1 analogue?

NPH twice daily (1 or 2 sites)

AND

Continue rapid-acting analogue with increased lag time

>2 units/kg/day or 200 units/day and A1C >8%
Fundamental Question

Does the use of a more concentrated insulin (U-500) improve glycemic control compared to a standard-concentration insulin despite the fact that U-500 is only available in a regular insulin preparation?
U-100 Versus U-500 Insulin

- No randomized, controlled trials
- In one review of the eight reports in the literature ($n = 160$ patients), weighted mean A1C dropped from 10.0 to 8.4% ($P < 0.001$) with a nonsignificant increase in insulin dose of 286 to 317 units (11% increase, $P = \text{NS}$) and a weight increase of 4.2 kg ($P = 0.002$).

Pharmacokinetics and Pharmacodynamics of U-500 Insulin

- $n = 24$, age = 40 years, weight = 98 kg, BMI = 34.4 m/kg$^2$
- Euglycemic clamp studies performed after injection of 50 and 100 units of U-100 regular and U-500 regular
- U-500 peak concentration ($C_{\text{max}}$) was significantly lower than that for U-100 at both doses ($P < 0.05$).
- Time to peak concentration was significantly longer for U-500 than for U-100 at the 100-unit dose ($P < 0.05$).
- Both formulations have long durations of action (18.3-21.5 hours).
- The overall effect (amount of glucose infused, $G_{\text{tot}}$) for U-500 was similar to U-100 at both doses.

Pharmacodynamics of U-500 and U-100 Regular Human Insulin in Obese Patients With Type 2 Diabetes

As with most insulin management, what we do with U-500 is generally anecdotal. The good news: these patients generally do not get hypoglycemic!
So, Is U-500 Regular Insulin a Basal or a Prandial Insulin?

- It is both! (U-100 regular insulin, especially at these doses, is also both.)
- Lag times have never been studied, but it only makes sense that, when U-500 is used as mealtime insulin, the timing between injection and eating is even more important than with U-100 regular (or analogue) insulin.
- The main secret for success with U-500 insulin:
  - FREQUENT self-monitoring of blood glucose (SMBG)!
Communicating U-500 Dosing

- Two ways: “units” on a U-100 insulin syringe or volume (mL) on a tuberculin syringe
- Ideally, would be nice if everyone used both; most patients will discuss this in units
- A compromise with patients and in charting: always note U-500 with either volume or U-100 equivalent (5 units U-500, 0.05 mL, 25 units U-100)
A patient is taking 10 units of U-500 insulin (the equivalent of 50 units of U-100 regular) at breakfast, and it is decided to increase the dose to 14 units U-500.

- Tell the patient to increase the dose to 14 units U-500 in his U-100 syringe.
- Chart that the dose was increased to 14 units of U-500 (which is 70 units of U-100 regular and 0.14 mL).
Inpatient Issues with U-500 Insulin

- Major concern for error
  - “units” or mL?
- Many hospitals use both
  - “Give 10 units U-500 (0.10 mL) 30 minutes before breakfast.”
Implementing U-500 Insulin

• 150-300 units/day
  – U-500 has been shown to be effective with or without traditional basal insulin.
  – Without basal insulin, U-500 can be split into premeal breakfast and dinner shots (60/40%) or premeal shots three times daily (40/30/30 or 40/35/20%).
  – Many patients continue basal insulin, especially during the transition from U-100 insulin.
  – For continuous subcutaneous insulin infusion (CSII), I usually start 40% as basal using the total daily dose from the multiple daily injection regimen as a guide.
U-500 Insulin with CSII

- $n = 21$, $BMI = 39.4 \text{ kg/m}^2$, insulin dose = 196 units/day, $A1C = 8.6\%$

The problem with the U-500 data: no prospective trials with appropriate control groups

What About Cost?

(For reference, the rate of inflation for the past 5 years is 10.6% and for the past 7 years is 17.5%.)

- U-500: 1 vial = $720 per 20-mL vial (400% increase in past 6 years)
- U-100 Humulin regular and Novolin NPH insulin: $71 per vial (114% increase in the past 7 years)
- Lispro and glargine: $138 and $119 per vial (134% and 116% increase in past 7 years, respectively)
- Aspart FlexPens (15 mL) = $257 for a 5-pen box (117% increase in past 7 years)

How We Use U-500 Insulin
Case Study 1

- A 35-year-old woman with partial congenital lipodystrophy
- Takes 5-8 units of U-500 based on meal size
- Corrects with insulin lispro, which she mixes with the U-500 (insulin sensitively factor: 1 unit for every 5 mg/dL >150 mg/dL)
- Uses insulin glargine as basal insulin at 50 units at bedtime
- A1C = 5.9-6.4%
- Hypoglycemia: cannot recall ever having a blood glucose level <60 mg/dL
Case Study 1, Summary

- The relatively large volumes of prandial insulin required made U-500 insulin a better choice for this patient.
- She does well using traditional basal insulin at bedtime, although many of these patients do just as well with U-500 insulin at bedtime.
Case Study 2

• A 42-year-old woman with congenital lipodystrophy
• Receives 25-30 units of U-500 insulin before meals three times daily
• Misses many of her scheduled insulin doses; tried to use correction doses with U-500, but performed SMBG infrequently
• Receives 100 units of glargine twice daily
• A1C usually 8-10%, but when careful with diet has been as low as 6.2%
• Teaching point: these large doses of insulin can be effective, but because of poor adherence, her diabetes is poorly controlled.
Case Study 3

- A 34-year-old woman with gestational diabetes presents with type 1 diabetes 6 months after pregnancy
- Blood glucose never well controlled, A1C 9-10%
- Insulin requirements progressed to 1.5 units/kg with poor control on CSII
- Developed rheumatoid arthritis and proteinuria and required hearing aids at age 40
- At age 45, diagnosed with coronary artery disease, required stenting two times, did not tolerate statins
- Started U-500 in 2008
- A1Cs now mostly in low-7% range
Case Study 3: What Is Her Diagnosis?

• MIDD (maternally inherited diabetes and deafness), a mitochondrial form of diabetes associated with severe insulin resistance

• Teaching point: always be on the look out for rare syndromes when treating patients with severe insulin resistance!
Case Study 4

- A 19-year-old man with cystic fibrosis–related diabetes, recently diagnosed with idiopathic diabetes incipidus, (magnetic resonance imaging was normal) with good response to intranasal vasopressin
- Insulin requirements went extremely high during the next 6 months, to the point where he had severe pain with the large doses of insulin aspart he required for meals (>50 units)
- Transitioned to U-500 insulin
Case Study 4, cont.

- Took 8-12 units of U-500 before meals three times daily with no basal insulin
- Correction dose aspart for blood glucose levels >150 mg/dL at mealtimes and >200 mg/dL at bedtime
- Bedtime blood glucose levels were mostly <180 but >120 mg/dL
- Most fasting blood glucose levels were 90-150 mg/dL
- Two nocturnal hypoglycemic seizures
- Why the seizures, and what is the etiology of his insulin resistance?
- Central nervous system Nocardia infection
Conclusion

• The primary objective when encountering a patient with severe insulin resistance is to determine the etiology.
  – Syndromic forms of insulin resistance can often be improved with specific therapies.
• There are novel ways to think about our current U-100 insulins when managing patients with severe insulin resistance.
• There are many situations in which more concentrated insulins appear to help this growing population.