What Every Practitioner Should Know About Incretin Hormones: Evolving Treatment Strategies for Type 2 Diabetes

Learning Objectives

• Discuss the pathophysiology and management of type 2 diabetes, including updates on incretin hormones and combination therapies.
• Identify 2 newer approaches to achieve long-term glycemic control and A1c targeted goals in patients with type 2 diabetes.

Faculty

Frank Lavernia, MD
Founder, North Broward Diabetes Center
Private Practice
Internal Medicine and Diabetes
Coconut Creek, Florida

Dr Frank Lavernia (known to his patients as Dr Frank), has been a practicing diabetologist for 25 years in South Florida. He was the founder of the North Broward Diabetes Center, at the North Broward Medical Center, in Pompano Beach, Florida. This center has been accredited by the American Diabetes Association since 1991.

Dr Frank is on various national faculties including the National Diabetes Education Initiative (a think tank for type 2 diabetes and insulin resistance), the Vascular Biology Working Group, and the Coalition for the Advancement of Cardiovascular Health. He is also on numerous national speaking bureaus within the pharmaceutical industry and lectures around the country.

His private office has been accredited with the Certificate of Recognition for Diabetes Care by the American Diabetes Association for the last 6 years. His most recent project has been the development of Dr Frank’s Diabetes Workshops to teach and empower people with diabetes.

Charles Burant, MD, PhD
Professor of Internal Medicine, and Molecular and Integrative Physiology
University of Michigan
Ann Arbor, Michigan

Charles F. Burant, MD, PhD, is professor of internal medicine, and molecular and integrative physiology, at the University of Michigan in Ann Arbor. He also holds the Robert C. and Veronic Atkins Chair in Metabolism and is the director of the University of Michigan Metabolomics and Obesity Center. He is board certified by the American Board of Internal Medicine with subspecialty certification in endocrinology, diabetes and metabolism.

Dr Burant earned both his medical degree and doctorate of philosophy in molecular and cellular biology from the Medical University of South Carolina in Charleston. Internship and residency both were served at the University of California in San Francisco, and Dr Burant completed his fellowship in the Department of Medicine, Endocrinology Section at the University of Chicago.
Dr Burant has held several memberships and offices in professional societies, including the American Diabetes Association, Central Society for Clinical Investigation, the American College of Physicians, and the American Association of Clinical Endocrinology. He is editor or the American Diabetes Association’s Guide to the Medical Management of Type 2 Diabetes.

Dr Burant is a recipient of many awards, including both the American Diabetes Association’s and the American Medical Association’s Award for Outstanding Research, and the Medical Scientist Training Program Award. He also has been elected to the Central Society for Clinical Research and serves on the Advisory Board for the National Diabetes Education Initiative.

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The presenting faculty reported the following:

Dr Lavernia has no relationship to disclose.
Dr Burant receives monetary compensation as a scientific advisor from Takeda Pharmaceuticals North America, Inc.

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- Content validation by external topic expert and internal Pri-Med Institute clinical editorial staff

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**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td>metformin</td>
<td>Glucophage, Glucophage XR</td>
</tr>
<tr>
<td>sitagliptin + metformin</td>
<td>Janumet</td>
</tr>
<tr>
<td>exenatide</td>
<td>Byetta</td>
</tr>
<tr>
<td>pramlintide</td>
<td>Symlin</td>
</tr>
<tr>
<td>nateglinide</td>
<td>Starlix</td>
</tr>
<tr>
<td>repaglinide</td>
<td>Prandin</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>rosiglitazone</td>
<td>Avandia</td>
</tr>
<tr>
<td>glimepiride</td>
<td>Amaryl</td>
</tr>
<tr>
<td>glipizide</td>
<td>Glucotrol</td>
</tr>
<tr>
<td>glyburide</td>
<td>DiaBeta/ Micronase/Glynase</td>
</tr>
</tbody>
</table>
Investigational
liraglutide
saxagliptin
alogliptin
vildagliptin			Galvus

Suggested Reading List


Creutzfeldt W. The incretin concept today. Diabetologia. 1979;16(2):75-85.


What Every Practitioner Should Know About Incretin Hormones

Evolving Treatment Strategies for Type 2 Diabetes

What are incretins?

1. Pituitary factors that control glucagon secretion
2. Gastrointestinal hormones that affect insulin secretion
3. Pancreatic factors that influence GI motility
4. Plant-derived sterols that influence appetite
5. Animal-derived venoms

Incretins have been shown to:

1. Increase gastric emptying
2. Delay first-phase insulin secretion
3. Reduce postprandial hyperglucagonemia
4. Increase beta cell mass in patients with type 2 diabetes
5. Improve erectile dysfunction

Which incretin-based therapies do you currently use in your practice?

1. Sitagliptin
2. Exenatide
3. Both sitagliptin and exenatide
4. I do not use incretin-based therapies

Approved combination therapies include:

1. Sitagliptin + exenatide
2. Sitagliptin + insulin
3. Sitagliptin + metformin
4. Exenatide + insulin
5. Glitazones + pramlintide

Prevalence of Diabetes and Impaired Fasting Glucose in Adults in the U.S. Population

National Health and Nutrition Examination Survey 1999–2002

73 million Americans with or at risk for diabetes
YOUR treatment goals for patients with T2DM are:

1. A1C < 6%
2. A1C ≤ 6.5%
3. A1C < 7%
4. A1C < 8%

What percentage of YOUR patients have achieved the ADA recommended minimal target of A1C < 7%?

1. < 25%
2. 25 to 50%
3. 50 to 75%
4. > 75%

ADA Recommended Goals for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C*</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>70-130 mg/dL</td>
</tr>
<tr>
<td>Postprandial capillary plasma glucose</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt;100 mg/dL (&lt;70 mg/dL) 1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol (♂)</td>
<td>&gt;40 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol (♀)</td>
<td>&gt;60 mg/dL</td>
</tr>
</tbody>
</table>

* Therefore, the A1C goal for selected individual patients is as close to normal (< 6%) as possible without significant hypoglycemia 1

ADA Goals

A1C ≥ 7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level as close to the non-diabetic range as possible or, at a minimum, decreasing the A1C < 7%. 1

Therefore, the A1C goal for selected individual patients is as close to normal (< 6%) as possible without significant hypoglycemia. 1

ADA/EASD Global Treatment Strategy

“The ADA, EASD consensus treatment algorithm emphasizes the need for rapid addition (2 to 3 months) of medication and transition to new regimens when target glycemic goals are not achieved or sustained” 2

Case 1

- 37-year-old Hispanic woman who works as a high school teacher presents with a 3-year history of type 2 diabetes treated with metformin 1000 mg b.i.d.
  - A1C initially improved from 8.5% at diagnosis to 6.2%
  - A1C has been increasing, and at most recent visit was 7.4%
  - On review, A1C has been above 7 for approximately 10 months
  - Lipid and blood pressure guidelines are maintained with a statin and ACE inhibitor
  - BMI 31 kg/m²

How would you manage her increasing A1C?

1. Reinforce lifestyle modification
2. Increase metformin to 3 g
3. Add a sulfonylurea
4. Add nateglinide or repaglinide
5. Add a glitazone (TZD)
6. Add sitagliptin
7. Add exenatide
8. Add basal insulin
9. Add alpha glucosidase inhibitor
10. Reassure patient

This is the Problem

Bewildering treatment options due to the complex pathophysiology

The pathophysiology of T2DM includes three main defects

1. Insulin deficiency
2. Excess glucose output
3. Insulin resistance

Progressive Impairment in β-cell Function

- Diminished insulin
- Hyperglycemia
- Liver
- Muscle and fat

Anti-Hyperglycemic Agents in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Expected decrease in A1c (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Initial lifestyle to decrease weight and increase activity</td>
<td>1-2</td>
<td>Low costs, many benefits</td>
<td>Fails for most in first year</td>
</tr>
<tr>
<td>Metformin</td>
<td>Weight neutral, inexpensive</td>
<td>GI side effects, rare lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Step 2: Additional therapy insulin</td>
<td>1.5-3.5</td>
<td>No dose limit, inexpensive, improved lipid profile</td>
<td>Injections, monitoring, hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1-2</td>
<td>Improved lipid profile</td>
<td>Weight gain, hypoglycemia*</td>
</tr>
<tr>
<td>Thiazolidinediones (glitazones)</td>
<td>0.5-1.4</td>
<td>Potential decreased risk of MI</td>
<td>Fluid retention, two-fold increase risk of CHF, potential increased risk of MI‡, atherogenic lipid profile, weight gain, expensive</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Frequent GI side effects, three times/day dosing, expensive</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5-1.0</td>
<td>Weight loss</td>
<td>Injections, frequent GI side effects, little experience</td>
</tr>
<tr>
<td>Glinides</td>
<td>1-1.5§</td>
<td>Short duration</td>
<td>Three times/day dosing, expensive, hypoglycemia</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5-1.0</td>
<td>Weight loss</td>
<td>Injections, three times/day dosing, frequent GI side effects, expensive, little experience</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Little experience, expensive</td>
</tr>
</tbody>
</table>

Discussion:

Anti-Hyperglycemic Agents in Type 2 Diabetes

*Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (e.g. chlorpropamide and glibenclamide, glyburide) are more likely to cause hypoglycemia than glipizide, extended-release glipizide, glimepiride, or gliclazide. †Pioglitazone. ‡Rosiglitazone. §Repaglinide is more effective at lowering A1C than nateglinide. GI, gastrointestinal; MI, myocardial infarction.

Characteristics of Incretins

- Gastrointestinal hormones (GLP-1 and GIP)
- Secreted in response to food ingestion
- Stimulate glucose-dependent insulin secretion
- Account for up to 60% of the insulin response in healthy subjects
- Suppress glucagon and may have effects on appetite and gastric emptying
- Short half-life (~2 minutes) due to rapid enzymatic degradation by DPP-4

GLP-1 = glucagon-like peptide 1
GIP = glucose-dependent insulinotropic polypeptide
DPP-4 = dipeptidyl peptidase 4

Modulation of Insulin and Glucagon Levels: The Enteroinsular Axis

Incretin effect in T2DM

Decreased Postprandial Levels of GLP-1 in Type 2 Diabetes

Let’s take a closer look at how incretins affect this pathophysiology
Case 1: Review

- 37-year-old Hispanic female, high school teacher presents with a 3-year history of type 2 diabetes treated with metformin 1000 mg b.i.d.
  - A1C initially improved to 6.2% from 8.5% at initial presentation
  - A1C has been increasing, and at most recent visit was 7.4%
  - Lipid and blood pressure values are consistent with guidelines and maintained with a statin and an ACE inhibitor
  - BMI 31 kg/m²

How would you NOW manage her increasing A1C?

1. Reinforce lifestyle modification
2. Increase metformin to 3 g
3. Add a sulfonylurea
4. Add nateglinide or repaglinide
5. Add a glitazone (TZD)
6. Add sitagliptin
7. Add exenatide
8. Add basal insulin
9. Add alpha glucosidase inhibitor
10. Do nothing

Classification of Incretin-Related Therapies

- GLP-1 Mimetics (injectable)
  - Exenatide
  - Exenatide LAR*
- GLP-1 Analogs (injectable)
  - Liraglutide*
- Incretin enhancers (DPP-4 inhibitors) (oral)
  - Sitagliptin
  - Vildagliptin*
  - Saxagliptin*
  - Alogliptin* *

Overview of Incretin-Related Therapies

Summary of Clinical Trial Data: Exenatide in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Duration</th>
<th>N (µg)</th>
<th>A1C (%)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ SU/MET</td>
<td>30 weeks</td>
<td>241</td>
<td>-1.0</td>
</tr>
<tr>
<td>+ SU</td>
<td>30 weeks</td>
<td>129</td>
<td>-1.0</td>
</tr>
<tr>
<td>+ MET</td>
<td>30 weeks</td>
<td>113</td>
<td>-0.9</td>
</tr>
<tr>
<td>+ TZD</td>
<td>16 weeks</td>
<td>75</td>
<td>-0.9%</td>
</tr>
<tr>
<td>Monotherapy*</td>
<td>28 days</td>
<td>8</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

*Not FDA-approved indication

Exenatide: Weight: 3-Year Completers

Exenatide: Change in A1C and Weight After 3 Years


Classification of Incretin-Related Therapies

- GLP-1 Mimetics (injectable)
  - Exenatide
  - Exenatide LAR*
- GLP-1 Analogs (injectable)
  - Liraglutide*
- Incretin enhancers (DPP-4 inhibitors) (oral)
  - Sitagliptin
  - Vildagliptin*
  - Saxagliptin*
  - Alogliptin*  * Not currently approved

Incretin Secretion and Metabolism

DPP-IV = dipeptidyl peptidase-IV

Incretin Actions

GLP-1(7-36)
Active
Plasma
DPP-IV
Renal Clearance
Active
Incretins
Inactive
Incretins

Sitagliptin Indications:
Monotherapy, + Metformin, + Glitazone, + SU

All at 100 mg po qd for 24 weeks

Initial Combination With Sitagliptin Plus Metformin Study Design

Initial Combination Therapy With Sitagliptin Plus Metformin Compared to Monotherapy

Mean A1C = 8.8%

- Sitagliptin 50 mg + metformin 1,000 mg bid
- Metformin 1,000 mg bid
- Sitagliptin 100 mg qd
- Sitagliptin 50 mg + metformin 500 mg bid
- Metformin 500 mg bid

LSM A1C Change From Baseline, %

-3.5  -3.0  -2.5  -2.0  -1.5  -1.0  -0.5  0.0  0.5  1.0  1.5  2.0  2.5  3.0  3.5  4.0

*LSM change from baseline without adjustment for placebo; qd=once a day; bid=twice a day.


24-Week Placebo-Adjusted Results

Monotherapy Combination


Initial Combination Therapy With Sitagliptin Plus Metformin Study

Percentage of Patients Achieving ≤7% A1C at 24 Weeks

- Sitagliptin 50 mg + metformin 1,000 mg bid
- Metformin 1,000 mg bid
- Sitagliptin 100 mg qd
- Sitagliptin 50 mg + metformin 500 mg bid
- Metformin 500 mg bid
- Placebo

A1C <6.5% A1C <7%

To Goal, %

0 10 20 30 40 50 60 70 80 90

178 177 183 178 175 n=165 183 178 175 177 183 178

aLSM change from baseline without adjustment for placebo; qd=once a day; bid=twice a day.


Sitagliptin Plus Metformin Study

Change in Body Weight


Glipizide-Controlled Sitagliptin Add-on to Metformin Noninferiority Study Weight Change and Incidence of Hypoglycemia

Incidence of Hypoglycemia at 52 Weeks

Incidence, %

0 10 20 30 40 50 60 70 80 90

6 12 18 24 30 36 42 48 52

52 11 9

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

LSM=least squares mean.

Adapted from Hecox et al. Diabetes Obes Metab. 2007;9:194–205.

Sitagliptin: Insulin Synthesis and Release 24-Week Monotherapy Study

Proinsulin/insulin

Placebo (n=235) Sitagliptin 100 mg (n=210)

Week 24 Baseline

HOMA-β

Placebo (n=220) Sitagliptin 100 mg (n=218)

Week 24 Baseline

P ≤ 0.01*

P ≤ 0.01*

HOMA-β = homeostasis model assessment of beta-cell function.

Least-squares mean change from baseline vs placebo.


Do we need to adjust the dose of sitagliptin for patients with impaired renal function?
Sitagliptin AUC Increases With Decreasing Creatinine Clearance

Case 2
- 55-year-old Caucasian female postal worker, 15-year history of diabetes, on metformin 1000 mg b.i.d. and glyburide 5 mg b.i.d.
  - A1C has increased over the years to 8.2%
  - Evidence of early microvascular complications (nonproliferative diabetic retinopathy)
  - History of coronary artery disease, but no CHF
  - Lipids, blood pressure and weight are well controlled

How would you manage her increasing A1C?
1. Reinforce lifestyle modification
2. Increase glyburide to 10 mg b.i.d.
3. Add a glitazone (TZD)
4. Add sitagliptin
5. Add exenatide
6. Add basal insulin

Discussion: How would you manage her increasing A1C?

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinforce lifestyle</td>
<td>It is never too late to reinforce lifestyle modification. However, it is not likely that this alone would get the patient to goal.</td>
</tr>
<tr>
<td>modification</td>
<td></td>
</tr>
<tr>
<td>Increase glyburide to 10</td>
<td>Wrong SU, Wrong dose</td>
</tr>
<tr>
<td>mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>Add a glitazone (TZD);</td>
<td>CVB concerns, Fluid retention, Weight gain, Associated with decreased bone density</td>
</tr>
<tr>
<td>Add sitagliptin</td>
<td>Well tolerated, Weight neutral, No long-term safety data, Reports of hypersensitivity</td>
</tr>
<tr>
<td>Add exenatide</td>
<td>WEIGHT LOSS, Injectible, Initial GI side effects, Pancreatitis, Expensive</td>
</tr>
<tr>
<td>Add basal insulin</td>
<td>Greatest A1C-lowering potential, Hypoglycemia, Weight gain</td>
</tr>
</tbody>
</table>

Shared Decision Making
- Customize therapy based on the following:
  - Risk of hypoglycemia
  - Cardiovascular status
  - Renal status
  - Weight
  - A1C
  - Cost
  - Adherence
  - Route of administration

Earlier and More Aggressive Intervention May Improve Patients’ Chances of Reaching Goal

Published Conceptual Approach
What are incretins?

1. Pituitary factors that control glucagon secretion
2. Gastrointestinal hormones that affect insulin secretion
3. Pancreatic factors that influence GI motility
4. Plant-derived sterols that influence appetite
5. Animal-derived venoms

Incretins have been shown to:

1. Increase gastric emptying
2. Delay first-phase insulin secretion
3. Reduce postprandial hyperglucagonemia
4. Increase beta cell mass in patients with type 2 diabetes
5. Improve erectile dysfunction

Approved combination therapies include:

1. Sitagliptin + exenatide
2. Sitagliptin + insulin
3. Sitagliptin + metformin
4. Exenatide + insulin
5. Glitazones + pramlintide

Conclusion

• Type 2 diabetes is a progressive disease characterized by ongoing beta cell failure
• Most patients with type 2 diabetes should be able to achieve an A1C goal of < 7% with the broad range of antihyperglycemic agents available

Conclusion

• Early pharmacological intervention, combination therapy and persistent titration are often required to achieve these goals
• Incretin-based therapy can be used early and as a component of combination therapy
• DPP-4 inhibitors are well tolerated, weight neutral and not associated with hypoglycemia when used alone or in combination with metformin or TZDs