

# What Will be Covered

- Background
- Methodology
- Key Beta-Cell Concepts
- Key Concept Assessment:
  - Medical Literature & CMEs
  - Guidelines
  - Professional Communications
- Summary & Conclusions

# PCP Knowledge of T2D Pathophysiology

- “Awareness of pathophysiological concepts of type 2 diabetes – a survey in 847 physicians”; Busse, Benti, Stumvoll (2006)
  - Objective: Determine physicians’ knowledge of specific concepts generally implicated in the pathophysiology of T2D
- Key terms were “highly familiar” to the following percentage of PCPs:
  - Insulin resistance – 60% (vs. 80% SPCs)
  - Pancreatic beta-cells – 40% (vs. ~79% SPCs)
  - Beta-cell dysfunction – 40% (vs. ~75% SPCs)
  - Pancreatic alpha-cells – 19% (vs. ~50% SPCs)
  - Incretin hormone – 2% (vs. 30% SPCs)
- 47% (blended PCPs & SCPs) agreed that “beta-cell dysfunction is a key determinant of T2D onset”
  - 57% agreed with “beta-cell dysfunction being a key determinant of T2D progression”
- Conclusions:
  - Pathogenetic role of beta-cell dysfunction in onset and progression of T2D does not seem well established
  - “Insulin resistance” was a well known concept even among PCPs, while “hepatic glucose output”, “pancreatic alpha cells” and “glucagon” were not
  - Incretin hormones and GLP-1 were not widely known
  - This may effect prescribing behaviour and how well an individual’s therapy is based on pathophysiology

Source: Awareness of pathophysiological concepts of type 2ndiabetes—A survey in 847 physicians Franziska P. Busse a, Veronica Denti b, Michael Stumvoll a,\* a Clinic and Policlinic for Internal Medicine, University of Leipzig, Philipp-Rosenthal Str. 27, D-04103 Leipzig, Germany

# How PCPs Choose Medications to Treat T2D

- “How Doctors Choose Medications to Treat Type 2 Diabetes”; Grant, Wexler, Watson, Lester, Cagliero, Campbell, Nathan (2007)
- Objective: Study the means by which physicians (academic generalists & specialists) choose medications for patients with Type 2 Diabetes
- Major prescribing considerations included overall assessment of patient’s health/comorbidity; A1C level; patient’s adherence behavior... but NOT expert guidelines/hospital algorithms or patient age
- Conclusions:
  - Physicians considered a wide range of qualitative and quantitative factors when making choices for hyperglycemia management
  - The apparent complexity of the medication choice process contrasts with current evidence-based treatment guidelines

Source: How Doctors Choose Medications to Treat Type 2 Diabetes Richard Grant, Deborah Wexler, Alice Watson, William Lester, Enrico Cagliero, Eric Campbell, David Nathan; Diabetes Care, Volume 30, Number 6, June 2007

# Purpose of Analysis



Assess what has been and is being communicated to primary care physicians about new insights into beta and islet cell physiology and its implications to the progression of T2D

# Methodology

- Identify and assess a sample of recent literature, CMEs, guidelines and industry information targeted to PCPs for coverage of key concepts on beta and islet cell physiology
  - Relevant literature from Pubmed and select primary care and high-impact general medicine journals
    - Primary care: American Family Physician, Archives of Internal Medicine, Annals of Internal Medicine
    - General medicine: NEJM, JAMA, Lancet
  - Leading online and association CME sources
    - Medscape, MedPage Today, Primed, NDEI, DO CME Online, Caring for Diabetes.com, ADA, ACP
  - Current guidelines
    - ADA/EASD consensus algorithm, ADA, AACE
  - Recent industry communications such as detail aids and professional web sites
    - Actos, Avandia, Januvia, Janumet, Byetta

# Methodology (cont.)

- Evaluate to what extent key concepts on beta and islet cell physiology are being addressed:
  - Beta-Cell dysfunction as key driver of T2D
    - Pathogenic discussion on biology of pancreatic  $\beta$ - and islet-cells; function and mass
  - Beta-Cell failure begins early and is progressive
    - Function; rate of decline; reversibility
  - Role of incretin pathway and abnormalities in T2D
    - Role of incretin hormones in glucose regulation; “incretin effect”; effect of GLP-1 impairment on T2D; impaired first phase response
  - Role of GLP-1 in glucose regulation ( $\beta$ - &  $\alpha$ -cells)
    - Multiple glucoregulatory effects through coordinated secretion of insulin and glucagon by beta and alpha cells; effect on  $\beta$ -cell function and mass
  - Incretin therapies in relation to drivers
    - Linkage of incretins and causal pathway of islet-cell dysfunction; benefits of restoration of native GLP-1
  - Differentiation in MOA between incretin classes
    - GLP-1 receptor agonists and DPP-4 inhibitors; when incretin therapies should be used

# Executive Summary: Key Concept Assessment by Coverage in Recent Literature and CMEs

CONCEPT	QUALITY AVAILABLE	QUANTITY AVAILABLE
$\beta$ -cell dysfunction as key driver	Good	Good
$\beta$ -cell failure begins early & is progressive	Good	Poor
Role of incretin pathway & abnormalities in T2D	Good	Fair
Role of GLP-1 in glucose regulation ( $\beta$ - & $\alpha$ -cells)	Good	Fair
Incretin therapies in relation to drivers	Good	Poor
Differentiation in MOA between incretin classes	Good	Fair

**Quality:** Good = At least one article and one CME define concept well

**Quantity:** Good = > 2/3 of articles and CMES include concept

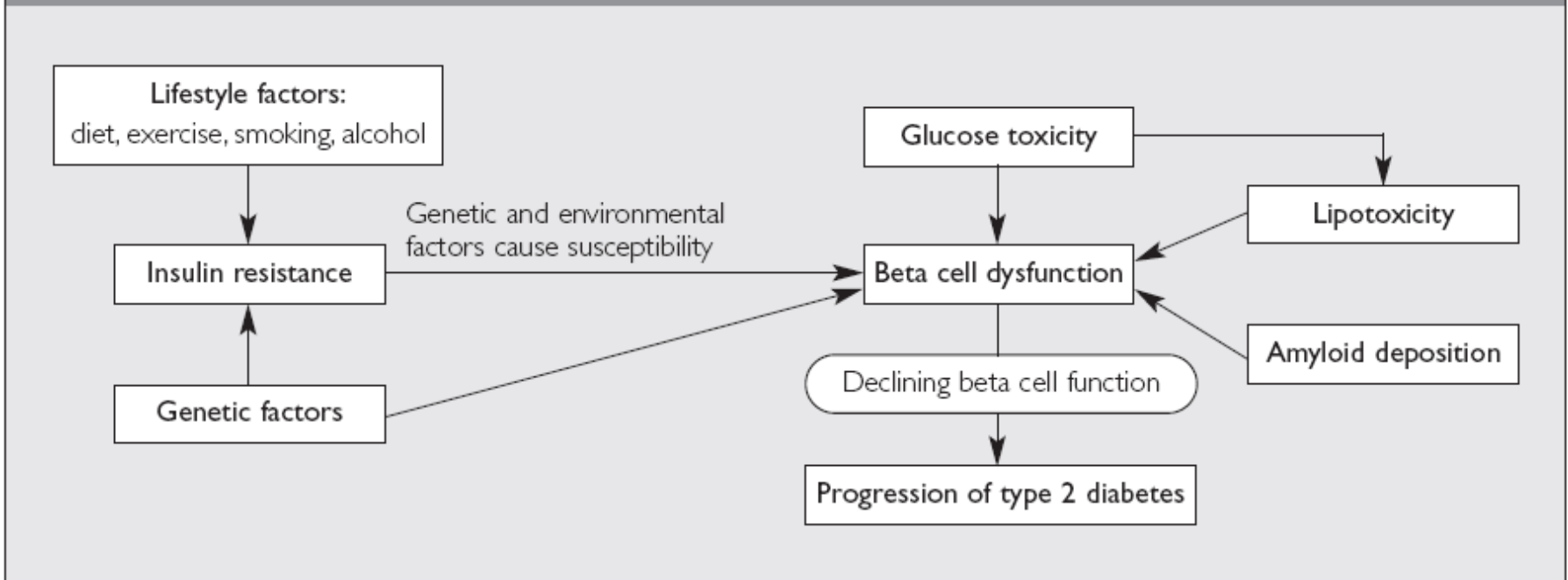
Poor = < 1/3 of articles and CMES include concept

# Summary of Literature

- High quality (but few) review articles exist reflecting current knowledge around beta and islet cell physiology
- Most articles cover pathophysiology of islet cells only as backdrop to new incretin-based therapies, not a principal focus of article
  - Conceptual context for incretin therapies is only recently being developed in primary care literature
- Recent articles present new view of  $\beta$ -cells as precipitating factor in disease onset and progression; few describe as paradigm shift
  - Details of underlying susceptibility of  $\beta$ -cells and relative roles of  $\beta$ -cell function and mass are not clearly explained
- Many articles mention progressive nature of  $\beta$ -cell decline
  - However, few articles point out that decline begins earlier than previously thought and continues despite treatment with traditional therapies
- Overview of incretin system in glucose regulation is often provided
  - How GLP-1 coordinates the secretion of insulin and glucagon, through signaling of  $\beta$ - and  $\alpha$ -cells respectively, is only described in the best review articles
- Majority of literature deals with introduction of new incretin therapies
  - Most articles do not strongly link to treatment of key disease driver
  - Many articles touch on differing mechanisms of actions between GLP-1 receptor agonists and DPP-4 inhibitors
  - When to use is not well delineated

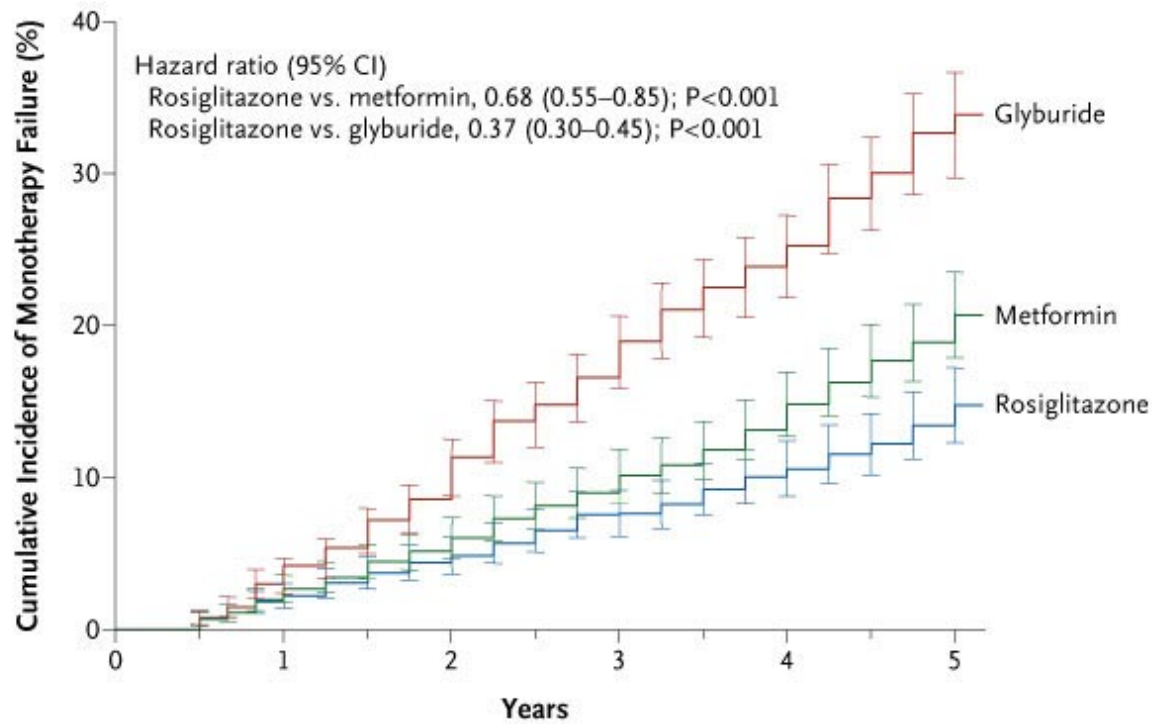


**Figure 1. Overview of factors influencing stages from insulin resistance to progression of type 2 diabetes**

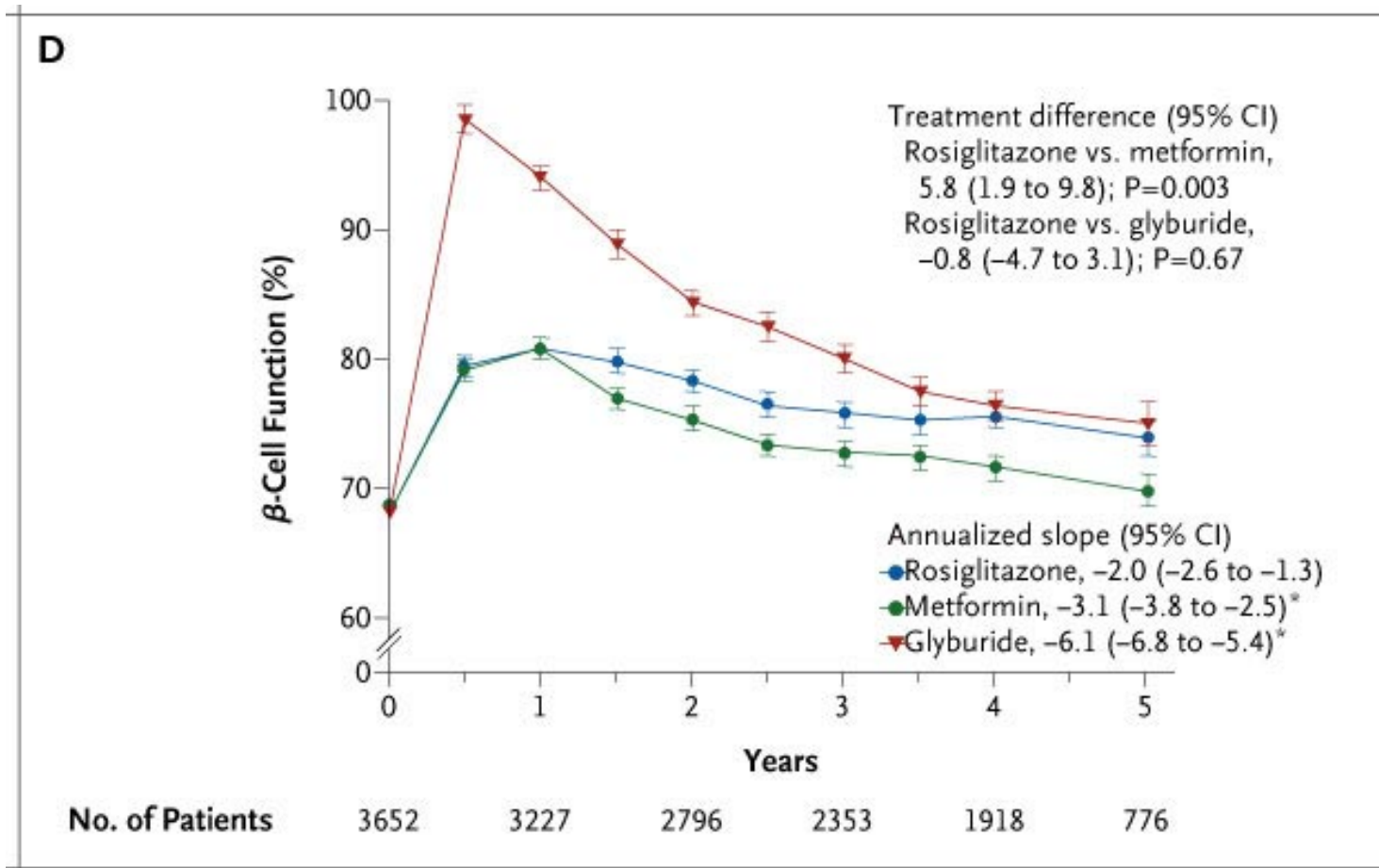


**Table 1. Potential for beta cell preservation of currently available antihyperglycemic agents according to dysfunction hypotheses criteria**

<b>Class/agent</b>	<b>↓ BG (Glucose toxicity)</b>	<b>↓ FFA (Lipotoxicity)</b>	<b>Rests beta cell?</b>	<b>Amyloid deposition (stimulates endogenous insulin secretion)</b>
Sulfonylureas	++	+?	--	Yes
Metformin	++	++	++	-
Meglitinides	++	+?	-	Yes
Acarbose	+	-	+	-
TZDs	++	++	++	-
Insulin	++(+)	+	++	-



No. at Risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218



During the first 6 months, levels of  $\beta$ -cell function (as determined by HOMA) increased more in the glyburide group (mean ratio of 6-month value to baseline value, 1.45; 95% CI, 1.42 to 1.48) than in either the rosiglitazone group (1.17; 95% CI, 1.15 to 1.19) or the metformin group (1.16; 95% CI, 1.14 to 1.19) (Figure 4D). Thereafter, levels of  $\beta$ -cell function declined in all three groups. The annual rate of decline after 6 months was greatest in the glyburide group (a decrease of 6.1%), intermediate in the metformin group (a decrease of 3.1%), and least in the rosiglitazone group (a decrease of 2.0%) (P<0.001 for the comparison of the rosiglitazone group and the glyburide group and P=0.02 for the comparison of the rosiglitazone group and the metformin group).

# Summary of CMEs

- A few excellent CMEs targeted to PCPs reflecting current knowledge around beta and islet cell physiology are available
- However, most CMEs focus on emerging role of incretin therapies, as opposed to detailed understanding of pathophysiology of disease
  - Conceptual context for new therapies is often not well developed
- Role of  $\beta$ -cells as key driver of disease onset and progression is noted
  - Not presented as a change in perspective
  - Details of underlying physiologic roles of  $\beta$ - and islet cells often lacks depth of available literature
  - Minimal highlighting of early and progressive  $\beta$ -cell failure
- Ability of GLP-1 to restore incretin response is often mentioned
  - Details of incretin pathway and abnormalities appear somewhat less well covered than in literature
- Emphasis is on availability of new incretin classes
  - Gaps include linkage to disease drivers, differing MOAs and implications
  - Minimal descriptions of when to use; use of case scenarios largely absent

# Summary of Guidelines

- $\beta$ - and islet cells are mentioned as part of disease context, but not identified as a key treatment target
  - Focus is reaching glycemic targets (A1c)
  - No mention of momentum in research around key role of  $\beta$ - and  $\alpha$ -cells
- ADA's/EASD's consensus algorithm:
  - Insulin secretory capacity is considered in recommendations, as one of several nonglycemic effects
  - No mention of role of  $\beta$ -cell as key disease driver; of early and progressive failure; and of impacts of various therapies on  $\beta$ -cell function
- ADA's guidelines:
  - No mention of  $\beta$ -cell dysfunction as a key disease driver or treatment target
- AACE's guidelines:
  - Briefly discusses decline in pancreatic insulin secretion as one of several causal elements
  - Notes that 50% of  $\beta$ -cell functioning is lost by time of diagnosis
  - Mentions impact of therapies on  $\beta$ -cell function:
    - TZDs noted as helping to preserve  $\beta$ -cell function
    - Incretins noted as having potential to preserve  $\beta$ -cell function and to regenerate  $\beta$ -cell mass

Sources: AACE. Endocr Pract. May/June 2007;13(Suppl 1):3-68. ADA. Diabetes Care. Jan. 2008;31(Supplement 1);S12-S54. Nathan, et al. Diabetes Care 2008;31(12):1-11.

*Translational Working Group on Islet and Beta Cell Dysfunction*

# Summary of Professional Communications

- Communications targeted to practicing physicians are behind the science discussed in medical literature, but are somewhat consistent with guidelines
- Gap in translating scientific learnings to education and practice
  - Beta-cell dysfunction is often mentioned as a core defect, along with or secondary to insulin resistance, in T2D
  - Increasing mention of GLP-1 improving glucose regulation ( $\beta$ - and  $\alpha$ -cells) – primarily in DPP-4 and exenatide communications
  - Limited discussion of early  $\beta$ -cell failure and progression; incretin pathway and abnormalities; incretin therapies in relation to drivers; differentiation between incretin classes
- Note – Industry information sources are oriented towards education about and promoting their class

# Summary of Professional Communications (cont.)

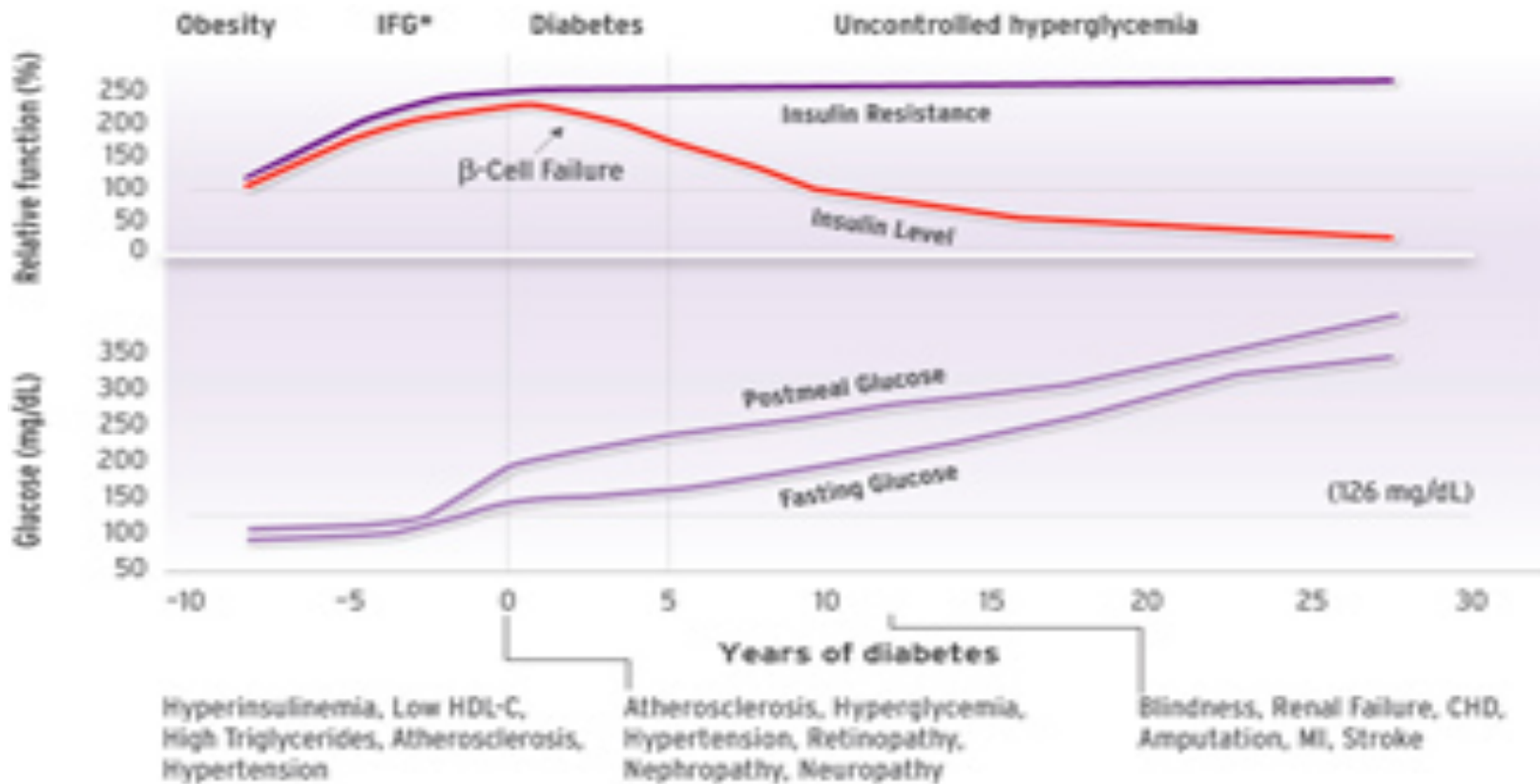
Brand	Main HCP Message	Sample Beta-Cell Emphasis & Message Points
Actos	Target the defects... Treat the disease	<ul style="list-style-type: none"> <li>• Two core defects central to T2D development: insulin resistance &amp; <math>\beta</math>-cell dysfunction (which therapy targets &amp; addresses, in addition to hepatic glucose output)</li> <li>• Some markers may be sign of deeper problem:               <ul style="list-style-type: none"> <li>• Presence of IR is often associated with abnormalities and over time can lead to insufficient <math>\beta</math>-cell function</li> <li>• IR likely to be present up to 12 years before diagnosis</li> <li>• <math>\beta</math>-cell function typically declines by an average of 50% by dx</li> </ul> </li> </ul>
Januvia	Powerful efficacy to help more patients reach A1C treatment goals	<ul style="list-style-type: none"> <li>• Targets two key defects of T2D: offers glucose-dependent mechanism which targets insulin release and hepatic glucose production</li> <li>• Inhibits DPP-4 enzymes, increasing levels of active incretins:               <ul style="list-style-type: none"> <li>• Increases production &amp; release of insulin from <math>\beta</math>-cells in pancreas</li> <li>• Reduces secretion of glucagon from <math>\alpha</math>-cells in pancreas which lowers glucose production in the liver</li> </ul> </li> </ul>
Byetta	Addresses fundamental treatment challenges of A1C, weight & hypoglycemia	<ul style="list-style-type: none"> <li>• T2D = Insulin Resistance + reduced <math>\beta</math>-cell response</li> <li>• Incretin hormones have important glucose-regulatory effects</li> <li>• GLP-1 enhances glucose-dependent insulin secretion and suppresses inappropriate glucagon secretion</li> </ul>



# Professional Communications Examples



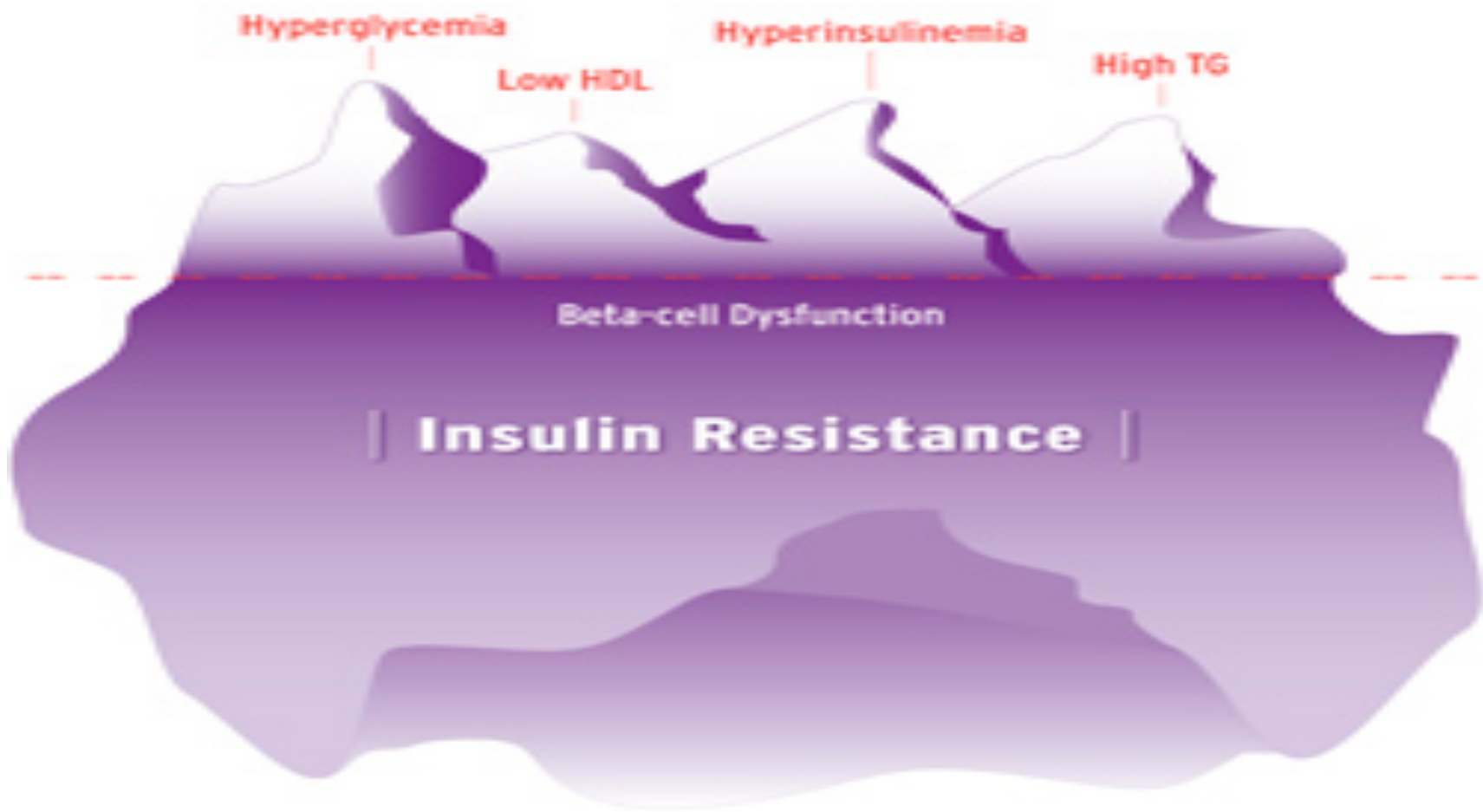
# Actos Professional Site and Detail Aid: T2D is a Result of Chronic Insulin Resistance and Beta-Cell Failure



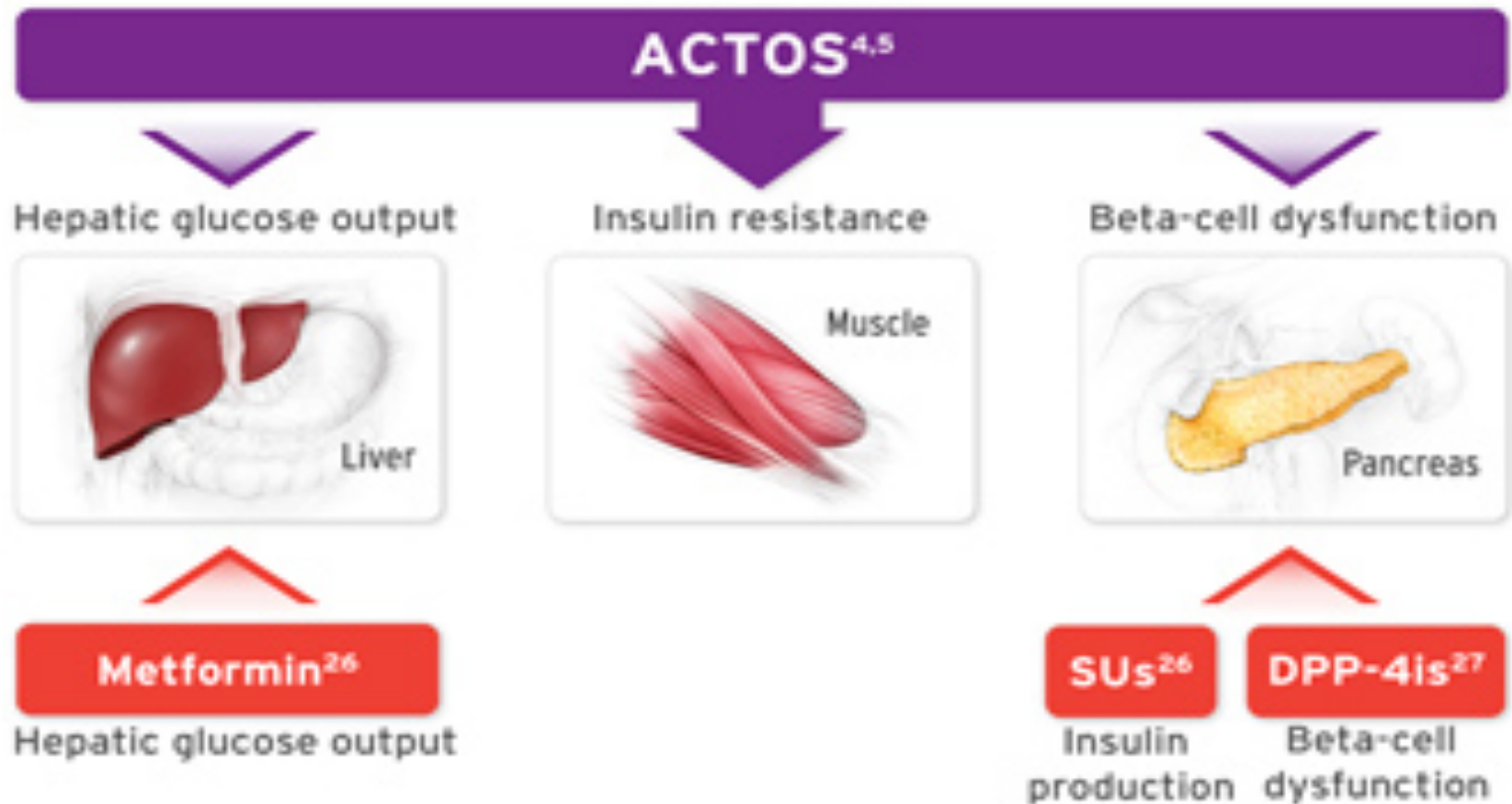
\*IFG—Impaired Fasting Glucose.

©2003 International Diabetes Center, Minneapolis, MN. All rights reserved.

# Actos Professional Site and Detail Aid: The “Iceberg Effect” – Some Markers May be a Sign of a Deeper Problem



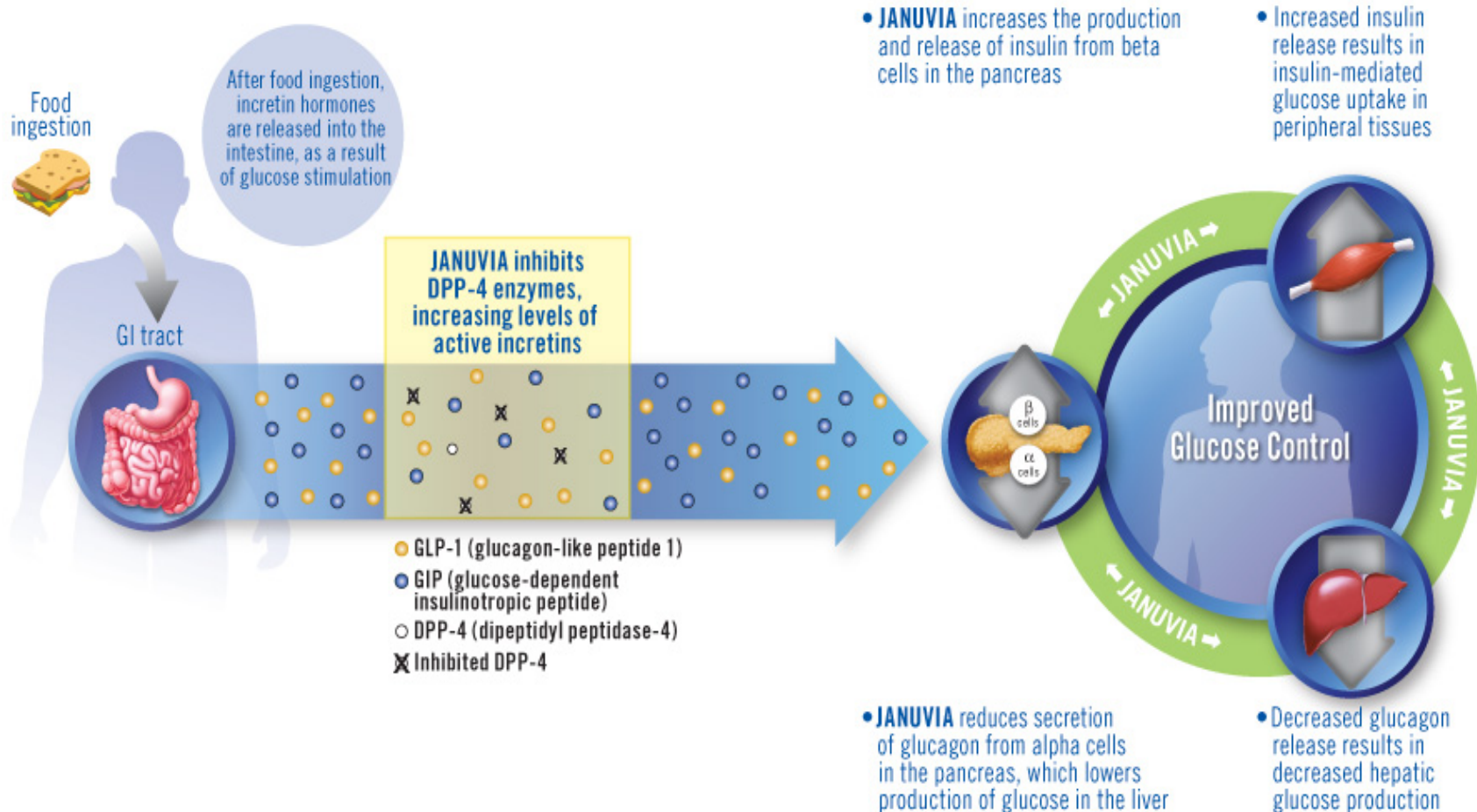
# Actos Professional Site and Detail Aid: Actos Targets Three Defects of T2D



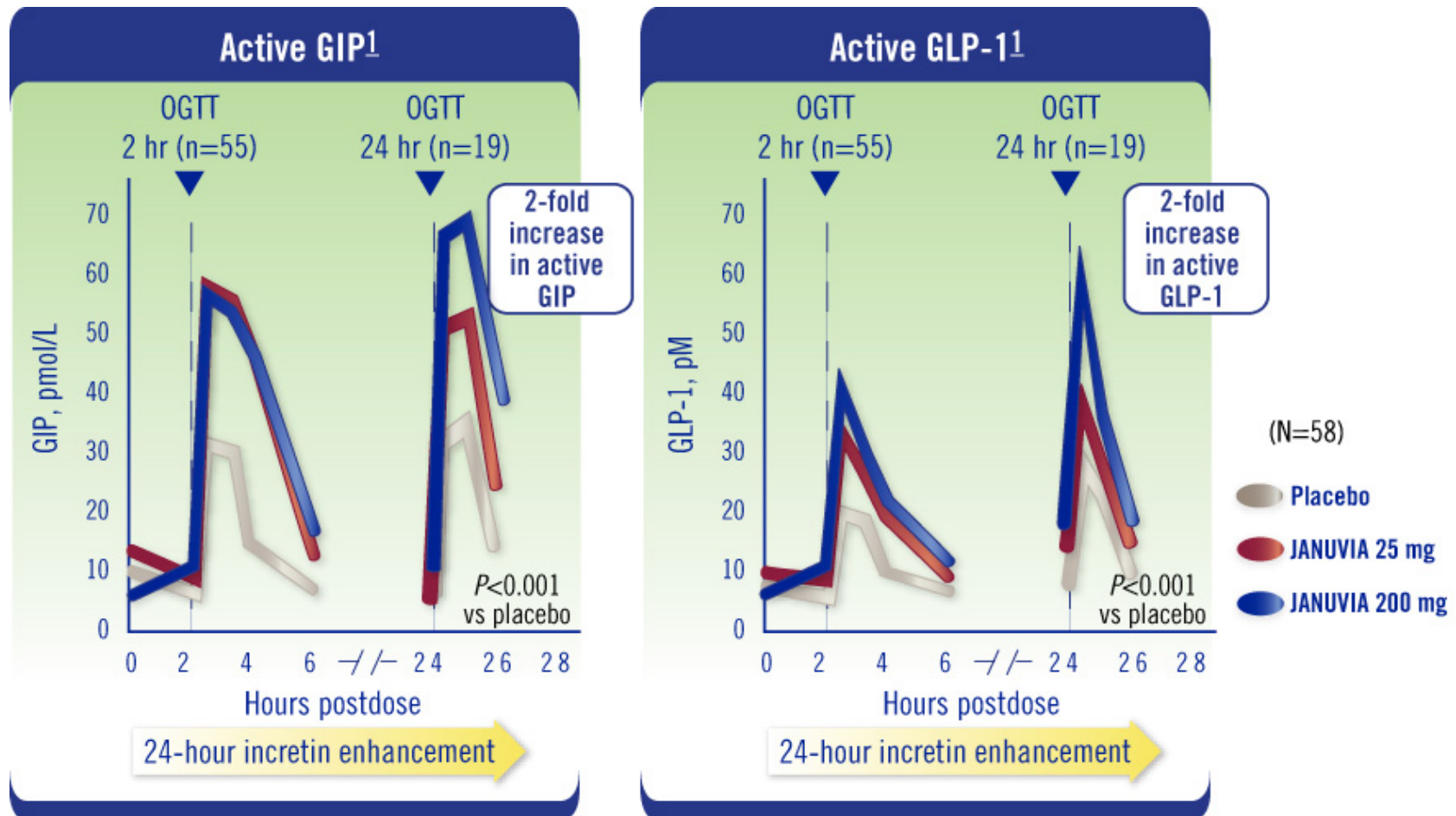
# Actos Professional Site and Detail Aid: Actos Targets Insulin Resistance and Beta-Cell Function to Help Improve Glycemic Control



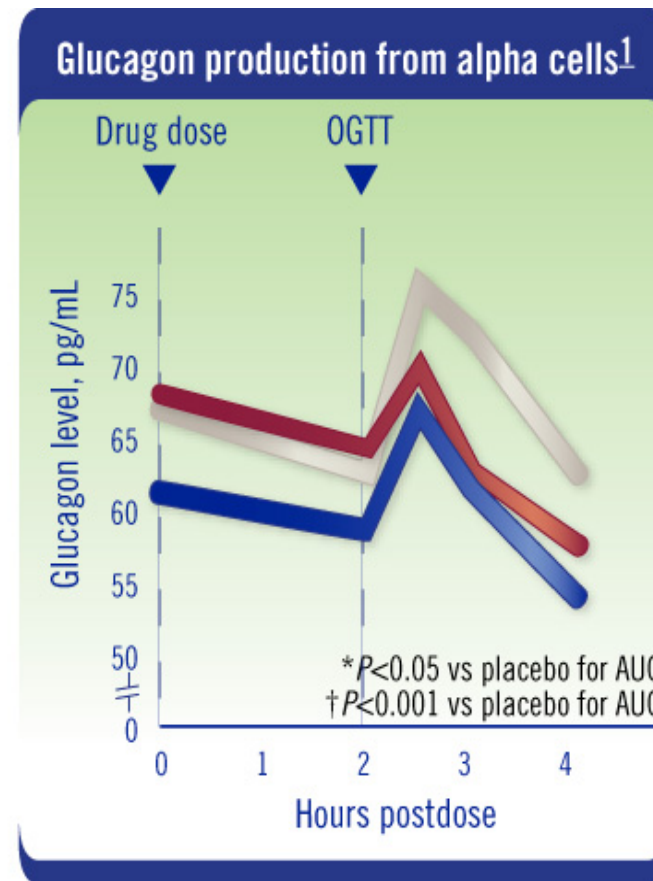
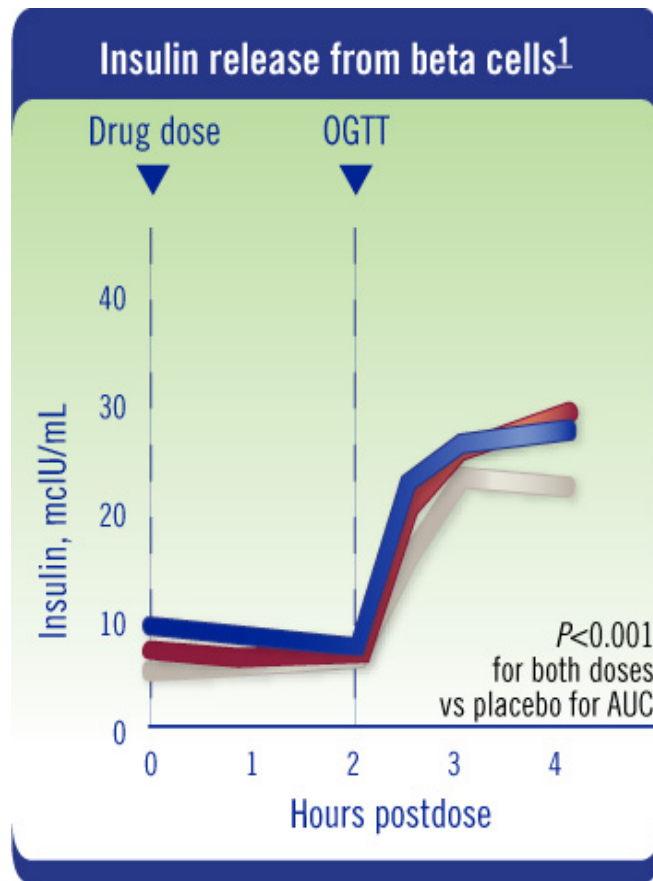
# Januvia/Janumet Professional Site Content: Increases Insulin Synthesis and Release and Decreases Glucagon to Help Improve Glycemic Control



# Januvia/Janumet Professional Site: Regulates Glucose by Increasing Beta-Cell Insulin Synthesis and Release and Inhibiting Alpha-Cell Glucagon Release



# Januvia/Janumet Professional Site: Januvia Improves Key Measures of Alpha-Cell and Beta-Cell Responsiveness to Glucose



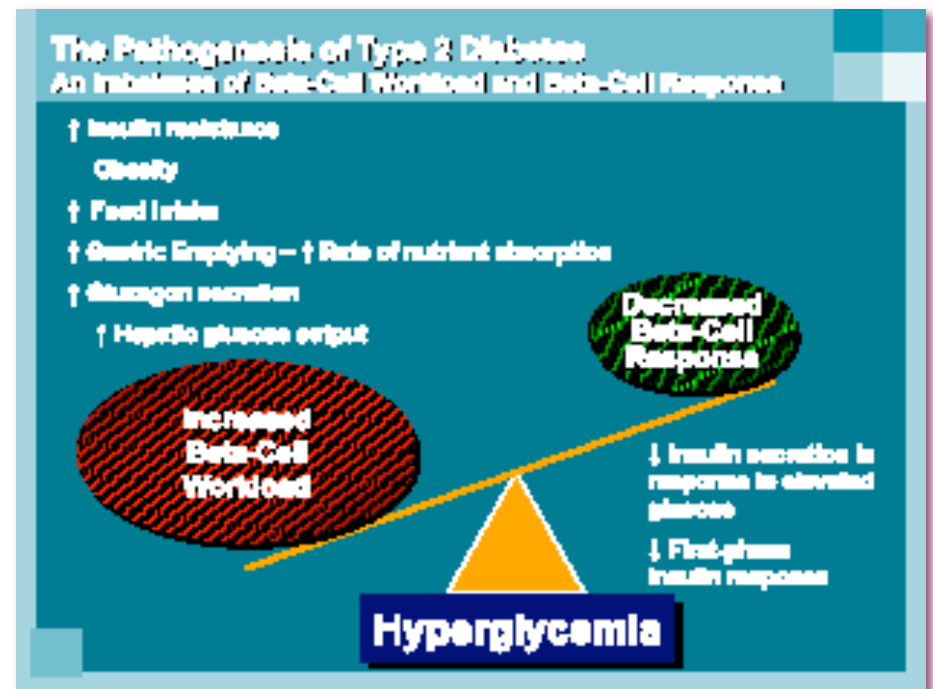
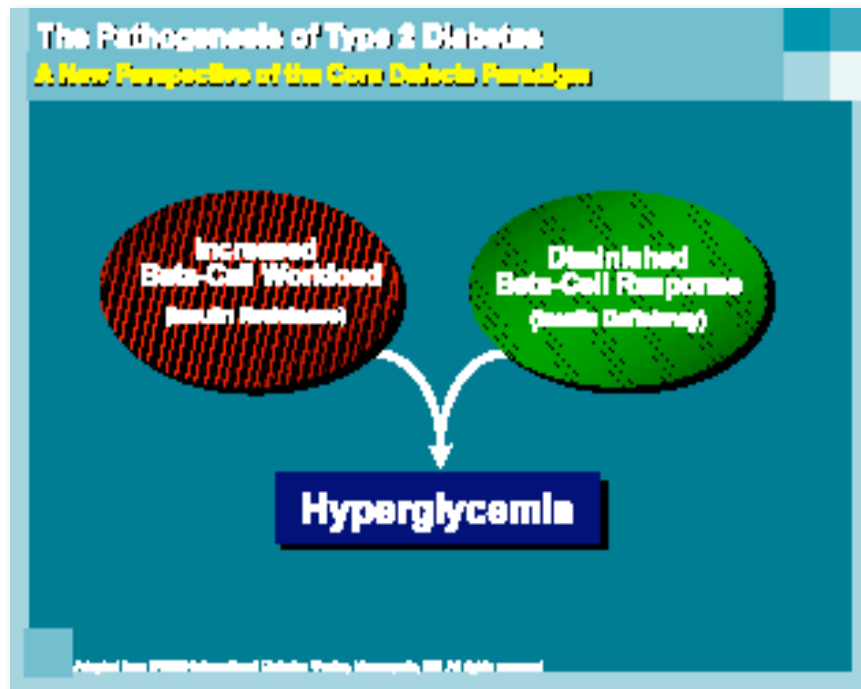
(N=58)

- Placebo
- JANUVIA 25 mg
- JANUVIA 200 mg



# BYETTA Physician Slides: The First Incretin Mimetic – An Overview

Carlos Campos, MD, MPH



# BYETTA Physician Slides: The First Incretin Mimetic – An Overview Carlos Campos, MD, MPH

### GLP-1 Effects in Humans

Understanding the Natural Role of Incretins

GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

Beta-cell workload

Alpha cells: Pancreatic (incretin) secretion

Liver: Increases insulin hepatic glucose uptake

Stomach: Helps regulate gastric emptying

Beta cells: Chronic glucose-dependent insulin secretion

Increases beta-cell response

Source: Holman GD, et al. N Engl J Med. 2006;354:2213-21. Copyright © 2006, American Medical Association. All rights reserved.

### Beta-Cell Workload and Beta-Cell Response

BYETTA Helps Restore Self-Regulating Glycemic Control

Decreases Beta-Cell Workload

Improves Beta-Cell Response

↓ Food intake and weight

↓ Glucagon secretion

↓ Hepatic glucose output

Regulates gastric emptying

↓ Rate of nutrient absorption

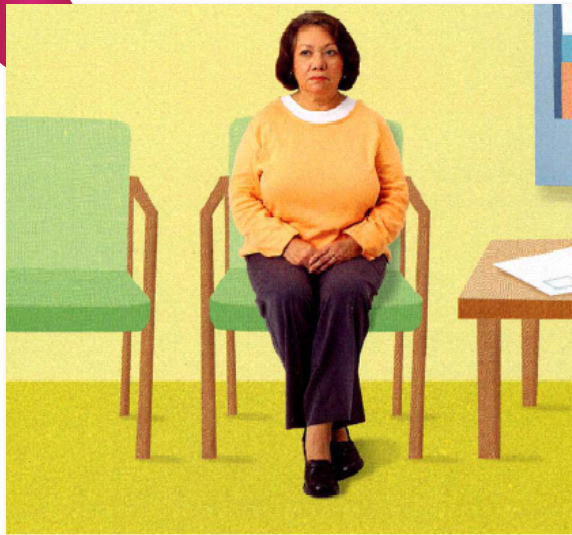
↑ Glucose-dependent insulin secretion

Restores first-phase insulin response

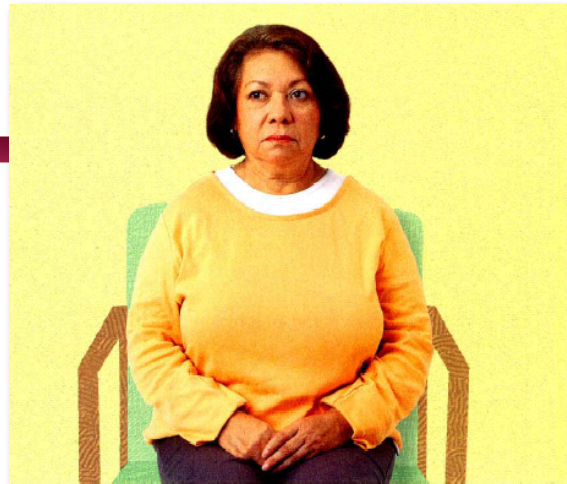
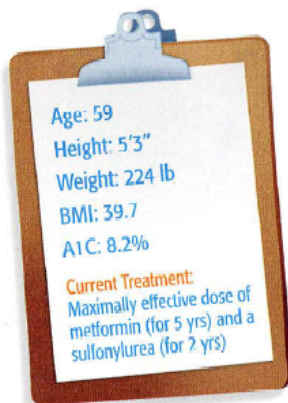
Byetta  
Liraglutide

Source: Holman GD, et al. N Engl J Med. 2006;354:2213-21. Copyright © 2006, American Medical Association. All rights reserved.

# 2006 BYETTA Sales Aid - Visual



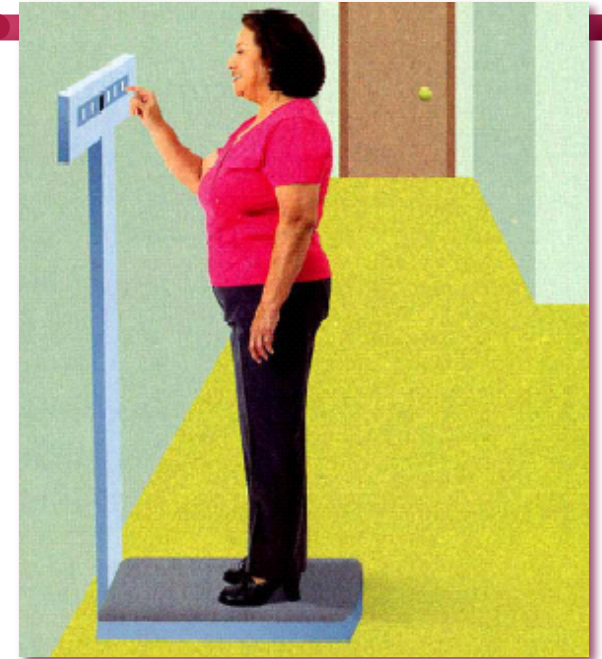
Is Doris in your waiting room?



Clinical trials of BYETTA included patients like Doris



BYETTA improves acute beta-cell responsiveness in your patients like Doris by providing self-regulating glycemc control



# Summary and Conclusions

- Medical literature reflects current thinking on key concepts around beta and islet cell physiology... quality is high but quantity remains quite limited
- CMEs are beginning to include many of the key concepts as part of their programs and enduring materials
- Guidelines mention  $\beta$ - and islet cells as part of disease concept but not as a treatment target
- Industry communications around education primarily reflect commercial interests, therefore information on  $\beta$ - and islet cell physiology is limited
- Opportunity to further the science and begin to translate to practice

# Appendix



# Literature and CME Review: Beta-Cell Dysfunction As Key Driver in Disease Onset and Progression

- Context: Pathogenic elements are most often mentioned in background sections of materials on incretin therapies
- Insulin resistance (IR) and  $\beta$ -cell dysfunction are often noted as the two major pathogenic factors
  - Dual roles of genetic and environmental factors are often mentioned, but not elaborated on
- Older literature emphasizes insulin resistance (IR) as precipitating factor for T2D
  - Mechanism: IR places high demand on  $\beta$ -cells, leading to  $\beta$ -cell exhaustion, “burn out”, and eventual failure
- Recent materials identify  $\beta$ -cells as primary defect and precipitating factor in disease progression
  - Very little discussion of “susceptible” vs. healthy  $\beta$ -cells
- Little discussion of underlying biology of pancreatic  $\beta$ - and islet-cells or of how  $\beta$ -cell function and mass are regulated
- Lack of clarity around relative importance and distinction between  $\beta$ -cell function and mass

# Literature and CME Review: Beta-Cell Failure Begins Early and Is Progressive

- Materials seldom highlight that  $\beta$ -cell decline begins earlier than originally thought
  - Estimate is not well highlighted that  $\sim 50\%$  of  $\beta$ -cell functioning is lost by time of diagnosis
  - Biphasic rate of decline in  $\beta$ -cell functioning is not mentioned
    - Decay rates accelerate from  $\sim 2\%/yr$  to  $\sim 18\%/yr$  after compensatory threshold is crossed, approximately at time of symptoms and diagnosis
- Some materials mention that  $\beta$ -cell decline is relentlessly progressive
  - However, most materials do not mention that  $\beta$ -cell functioning continues to decline, despite treatment with traditional therapies
  - Very few materials suggest that  $\beta$ -cell loss (especially functional loss) appears to be reversible in early stages

# Literature and CME Review: Incretin Pathway and Abnormalities in T2D

- Incretin pathway is most often mentioned as a prelude to discussion of new incretin therapies
- Role that incretin hormones play in glucose regulation is increasingly beginning to be outlined in materials
  - What incretin hormones are usually mentioned
  - Concept of “incretin effect” is often briefly described
  - Glucoregulatory role of GLP-1 is also mentioned, but not amplified
- How GLP-1 impairment manifests in T2D is usually not richly described
  - Details and terminology of what is impaired in T2D is uneven—some confusion around concept of “GLP-1 deficiency”
  - Specific mention of impaired first phase (or acute phase) response is occasionally mentioned



# Literature and CME Review: GLP-1 Improves Glucose Regulation Through Mediation of Beta- and Alpha-Cells

- GLP-1's multiple glucoregulatory effects, through the coordinated secretion of insulin and glucagon by  $\beta$ - and  $\alpha$ -cells, is most often not well described
  - Role of islet  $\beta$ -cells to stimulate insulin secretion is often mentioned
  - However, role of islet  $\alpha$ -cells to suppress glucagon secretion is seldom described
  - Resulting physiologic balance (i.e., regulation of insulin in a glucose-dependent manner or glucose homeostasis) is mentioned, but mechanism isn't often explained
- Improves  $\beta$ -cell function in humans and increases  $\beta$ -cell mass in animal models

# Literature and CME Review: Incretin Therapies in Relation to Disease Drivers

- Vast majority of published material (addressing  $\beta$ -cells and targeted to PCPs) focuses on the availability of new incretin therapies
- Few materials suggest a paradigm shift vis-à-vis disease drivers
  - Most do not draw distinction between old view of focusing on acquired defects (insulin resistance) and new view of targeting underlying disease drivers ( $\beta$ - and  $\alpha$ -cell dysfunction)
- While many materials describe incretins, most do not make clear linkage to causal pathway of islet-cell dysfunction
- Most explain value of restoring impaired GLP-1 response (GLP-1 deficiency) in terms of glucose regulation
  - Most do not mention benefit in terms of restoration native GLP-1, with its multiple benefits

# Literature and CME Review: Differentiation Between Incretin Therapies

- Of increasing volume in incretin therapy materials, most provide overview of key differences between GLP-1 receptor agonists and DPP-4 inhibitors
  - Most touch on principal difference in mechanism of action
  - Many mention potential beneficial effect on  $\beta$ -cells
  - Few highlight differences in efficacy; many charts showing similar efficacy
  - Many identify differences in weight loss benefit and side effects
  - Most do not delineate between sub-categories of GLP-1 analogs, i.e., human GLP-1 analogs and exendin-based products
- Shortcoming: Few materials specify when in disease stage incretin therapies should most appropriately be used
  - A few articles present case scenarios to illustrate decision-making
  - Guidelines are not clear on this point
- Most materials conclude with tone of great promise
  - Caveat: Need for longer term data to confirm sustainability of effect is noted—particularly with regards to improvements in  $\beta$ -cell functioning and possibility of control/reversal of disease progression

# References for Literature & CME Search

- Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. JAMA. July 11, 2007;298(2):194-206.
- Boyle PJ., Freeman JS. Application of incretin mimetics and dipeptidyl peptidase IV inhibitors in managing type 2 diabetes mellitus. Journal of the American Osteopathic Association. May 2007; Suppl 3;107(5):S10-S16. [http://www.jaoa.org/cgi/reprint/107/suppl\\_3/S10?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=diabetes+incretins&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT](http://www.jaoa.org/cgi/reprint/107/suppl_3/S10?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=diabetes+incretins&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT)
- Cobble ME. How to implement incretin therapy. The Journal of Family Practice. Sept. 2008; Suppl; 57(9):S26-S32.
- Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696-1705.
- Exanatide for Type 2 Diabetes, Annals of Internal Medicine, CME, April 2007, [http://cme.annals.org/cgi/hierarchy/annintcme\\_course;M05-1582](http://cme.annals.org/cgi/hierarchy/annintcme_course;M05-1582)
- Freeman JS. The pathophysiologic role of incretins. Journal of the American Osteopathic Association. May 2007; Suppl 3;107(5):S6-S9. [http://www.jaoa.org/cgi/reprint/107/suppl\\_3/S6?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=diabetes+incretins&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT](http://www.jaoa.org/cgi/reprint/107/suppl_3/S6?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=diabetes+incretins&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT)
- Freeman JS, Unger J. Why and when to implement incretin therapy. The Journal of Family Practice. Sept. 2008; Suppl;57(9):S19-S25.
- Freeman J, A Comprehensive Review of Incretin Therapies, February 2008, [http://www.docmeonline.com/ce-bin/owa/pkg\\_disclaimer\\_html.display?ip\\_cookie=29511029&ip\\_mode=secure&ip\\_test\\_id=12408&ip\\_company\\_code=AOAM](http://www.docmeonline.com/ce-bin/owa/pkg_disclaimer_html.display?ip_cookie=29511029&ip_mode=secure&ip_test_id=12408&ip_company_code=AOAM)
- Garber AJ., Spann SJ. An overview of incretin clinical trials. The Journal of Family Practice. Sept. 2008; Suppl;57(9):S10-S18.

# References for Literature & CME Search

- Garber A, Lovshin J, D'Alessio D, Advances in Glucagon-like Peptides in the Treatment of Type 2 Diabetes, Vol 1 August 2008, Vol 2 November 2008 <http://cme.medscape.com/viewprogram/17806>
- Henry R, Burant C, Drucker D, Meredith M, Resurrecting the Beta Cell in Type 2 Diabetes: Examining Tomorrow's Breakthroughs Today, November 2006, <http://cme.medscape.com/viewprogram/6013>
- Holst JJ. An overview of incretin hormones. The Journal of Family Practice. Sept. 2008; Suppl; 57(9):S4-S9.
- Joy S, Focus on New and Emerging Therapies, clinical review, <http://www.pri-med.com/PMO/Activity.aspx?activity=121718>
- Langer ES. A new generation of agents for treating patients with type 2 diabetes mellitus. Journal of the American Osteopathic Association. May 2007; Suppl 3;107(5):Cov2-S1. [http://www.jaoa.org/cgi/content/full/107/suppl\\_3/Cov2?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=diabetes+incretins&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT](http://www.jaoa.org/cgi/content/full/107/suppl_3/Cov2?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=diabetes+incretins&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT)
- Leahy J, Pathogenesis of Type 2 Diabetes Mellitus. Archives of Medical Research. 2005; 36:197-209.
- Leahy J, Garber A, Pratley R, The Evolution and Role of Incretin-based Therapeutics, April 2008, <http://www.medpagetoday.com/webcast?SciMed4/?mptts+20081216025116>
- Leahy J, Weissman P, Type 2 Diabetes—Restoring Glucose Homeostasis with Incretin Therapy: New Perspectives on Old Challenges, March 2008, <http://www.medscape.com/viewprogram/8870>
- Leahy J, Fonseca V, Vilsboll T, Ready for Primetime: Incretin Based Therapies Play a Novel Role in the Treatment of Type 2 Diabetes, August 2008, <http://cme.medscape.com/viewprogram/17009>
- LeRoith D, Pi-Sunyar F X, Type 2 Diabetes: Pathophysiologic Challenges, Incretin Solutions, <http://www.caringfordiabetes.com/glp1>

# References for Literature & CME Search

- Logtenberg SJ, Kleefstra N, Ubink-Veltmaat LJ, et al. Intensification of therapy and no increase in body mass index with longer disease duration in type 2 diabetes mellitus (ZODIAC-5). *Family Practice*. Dec. 2007;24(6):529-531.
- Munro N, Levy J, El-Gayar H, et al. New therapies for diabetes. *Diabetes and Primary Care*. Summer 2007. [http://findarticles.com/p/articles/mi\\_m0MDP/is\\_/ai\\_n27280960?tag=artBody;col1](http://findarticles.com/p/articles/mi_m0MDP/is_/ai_n27280960?tag=artBody;col1)
- Nauck M, Seeley R, Marchetti P, D'Alessio D, Deacon C, Wysham C. Incretin Mimetics and Their Future in the Treatment of Diabetes [http://www.diabetesconnect.org/storetemplate/08CE\\_Lectures.aspx](http://www.diabetesconnect.org/storetemplate/08CE_Lectures.aspx)
- Nauck M, Leahy J. The Unraveling of Incretin Biology: New Dimensions in the Treatment of Type 2 Diabetes. Aug 2008. <http://cme.medscape.com/viewprogram/15689>
- Review: Incretin Therapy Improves Glycemic Control More than Placebo in Patients with Type 2 Diabetes, ACP Journal Club, <http://diabetes.acponline.org/clinician/CL-CT-DT.html>
- Spellman CW. Islet Cell Dysfunction in Progression to Diabetes Mellitus. *Journal of the American Osteopathic Association*. May 2007; Suppl ; 107(5):S1-S5. [http://www.jaoa.org/cgi/reprint/107/suppl\\_3/S1?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=diabetes+incretins&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT](http://www.jaoa.org/cgi/reprint/107/suppl_3/S1?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=diabetes+incretins&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT)
- Stolar M, Inzucchi S, Laveria F. The Role of Incretin Therapy in Your Practice, December 2007, [http://www.ndei.org/v2/website/content/index.cfm?misccontent\\_id=981](http://www.ndei.org/v2/website/content/index.cfm?misccontent_id=981)
- Unger J. Diabetes Management in Primary Care. (Chapter 12: Amylin, Glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-IV (DPP-IV) Inhibitors as Novel Treatments for Diabetes.) Published by Lippincott Williams & Wilkins. 2007
- Unger J. Diagnosis and management of type 2 diabetes and prediabetes. *Primary Care*. Dec. 2007;34(4):731-759.
- Unger J, Moriarty C. Preventing type 2 diabetes. *Primary Care*. Dec. 2008;35(4):645-662.

Thank you



*Translational Working Group on Islet and Beta Cell Dysfunction*

