Comparing Current Therapies, Incretins and Incretin Mimetics in Type 2 diabetes Management

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ABSTRACT

The benefits of tight glycaemic control in landmark clinical trials in conjunction with aggressive blood pressure and lipid control in preventing / postponing diabetic complications have now been well established. In view of the complex and progressive nature of the disease, only 15-25% of type 2 diabetic subjects are able to maintain a target haemoglobin A1c of less than 7% that too at the cost of hypoglycaemia and weight gain. Further, type 2 diabetic patients have often lost 50% of -cell function at the time of diagnosis of the disease and glycaemic deterioration occurs over ensuing years regardless of therapy.

Glucose-dependent insulinotropic polypeptide stimulated by oral nutrient ingestion represents potent insulin secretagogues responsible for the augmentation of insulin release. The observation that the patients with type 2 diabetes exhibit a significant reduction in the magnitude of meal-stimulated insulin release underlies the interest in determining whether defective incretin release or resistance to incretin action contributed to the -cell dysfunction in diabetic subjects. Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, apart from the potent glucose lowering properties also have remarkable effects on -cell proliferation and cytoprotection and may be helpful in preventing progression to -cell failure in diabetic subjects. GLP-1R agonists and DPP-IV inhibitors in ongoing clinical trials suggest that one or both classes of agents may ultimately be approved for the treatment of type 2 diabetes. Furthermore, there remains intense interest in developing GLP-1 secretagogues or GLP-1 receptor activators. Strategies focused on enhancing incretin action are likely to receive increasing attention if the first generation of GLP-1R agonists and DPP-IV inhibitors are approved for the treatment of type 2 diabetes.

INTRODUCTION

Recognition of the benefits of strict glycaemic control in type 1 diabetes[1] and the landmark United Kingdom Prospective Diabetes Study (UKPDS)[2,3] and the Kumamoto Study[4] have clearly shown that glycaemic control matters not only in type 1, but also in type 2 diabetes. Diabetic complications can be prevented by improved glycaemic control and in conjunction with adequate control of blood pressure and lipids. Since type 2 diabetes has a long asymptomatic phase, it is not uncommon to observe minimal or overt complications at the time of diagnosis.[5] The "ticking clock" hypothesis of Haffner et al[6] that macrovascular coronary artery disease precedes the onset of type 2 diabetes while microvascular complications accompany the diagnosis of type 2 diabetes has put the onus of early recognition of abnormal glucose tolerance on individuals at risk to develop diabetes. Our ability, however, to reach the rather low long-term glycaemic targets is, at best, limited in view of the complex and progressive nature of the disease and with hitherto available therapeutic strategies, only 15-25% are able to achieve a good glycaemic control.[7]

Type 2 diabetes is characterized by insulin resistance and impaired β-cell secretory function.[8] Loss of acute insulin response to a carbohydrate load occurs when fasting plasma glucose levels reach 115 mg/dl[9] and by the time it reaches to 140mg/dl, 75% of β-cell function is lost. The deposition of amyloid has been associated with progressive loss of β-cell function and mass.[10] Insulin resistance in the hepatocyte and peripheral tissues leads to unrestrained hepatic glucose production (HGP) and diminished glucose uptake and utilization.[8,11] It could be due to defects in insulin receptor binding, decreased numbers of receptors or post-receptor attenuation of insulin action.[8] In addition, the high circulating free fatty acid levels further aggravate insulin resistance and adversely affect β-cell secretion, a phenomenon known as lipotoxicity.[12]

Type 2 diabetes may be present 9 to 12 yrs before diagnosis[13] and a study in Pima Indians indicates that defects in both insulin secretion and action occurs early in the course of the disease[14] and also predicts the transition from normal to IGT and from IGT to diabetes.[15] Because of its progressive nature, in UKPDS study, it was clearly shown that the percentage of patients who achieved a HbA_{1c} level lower than 7% with diet alone or monotherapy with insulin, a sulfonylurea or metformin decreased from 50% at 3 yrs to less than 25% at 9 yrs of follow-up.[16] Further, patients

with Type 2 diabetes have often lost 50% of β-cell function at diagnosis of diabetes[17] and over ensuing years is associated with glycaemic deterioration regardless of therapy.[18] The difficulty in maintaining HbA_{1c} at target levels may be related to several behavioral factors (e.g. lack of adherence to diet, exercise, medication) but primarily reflects the underlying progressive decline in β-cell function.[17]

The newer drugs already in use, or in the process of being developed for management of type 2 diabetes are classified into (1) insulin secretagogues (2) insulin sensitizers (3) drugs delaying gastrointestinal glucose absorption (4) drug acting on intermediary metabolism to reduce hepatic glucose output and (5) insulin mimetic drugs (Table 1).

Table 1 : Target drug therapy for type 2 DM

Functional Class*	Drugs
1. Insulin secretagogues	Sulfonylureas Meglitinide derivatives (Repaglinide, Nateglinide) GLP-1 Amylin antagonists
2. Insulin sensitizers	Metformin Thiazolidinediones (Troglitazone, Rosiglitazone, Pioglitazone) Anti-obesity drugs
3. Inhibitors of GI glucose absorption	α-glucosidase inhibitors (Acarbose, Miglitol) Amylin analogue (Pramlintide)
4. Inhibitors of intermediary metabolism	Antilipolytic and Antihyperlipidemic agents Fatty acid oxidation inhibitors
5. Insulin-mimetic drugs	Insulin analogues IGF-1 Vanadium salts

* Functional class 1,4 and 5 have hypoglycemic, while 2 and 3 have anti hyperglycemic mode of response.

A comparative evaluation of various oral drugs used in treatment of type 2 diabetes mellitus is shown in Table 2.

WHAT IS THE OPTIMAL TREATMENT REGIMEN?

Initial therapy is shifting from secretagogues and α-glucosidase inhibitors, which effectively lower only plasma glucose concentrations, to insulin sensitizers-drugs that lower plasma glucose levels while also reducing cardiac risk factors - that it is hoped will lead to a decrease in the incidence of cardiac events. Metformin acts as insulin sensitizer by inducing weight loss through decreasing appetite and, perhaps, by increasing the mobilization of glucose transporters in the muscle, however, the sensitizing effects of metformin are much weaker than those of TZDs.[20]

TREATMENT WITH INSULIN SENSITIZERS

TZDs

TZDs shift adipocytes from the peritoneum to subcutaneous space[21,22] reduce circulating free fatty acids (FFA) levels and increase FFA storage in the subcutaneous adipocytes[23] and produce an improvement in the profile of cardiac risk factors associated with insulin resistance.[24-28] Besides TZDs therapy have been shown to be associated with decrease in the thickness of tunica media and intima of carotid arteries and decrease in the incidence of restenosis of the coronary arteries following angioplasty.[29-31]

TZDs and β-Cell Function

The most compelling reason to use TZDs in type 2 diabetic subjects is its ability to preserve or improve β-cell function. In the β-cell, increased triglyceride levels due to defective activity of leptin[32] leads to an increase in intracellular FFAs which increase the activity of nitric oxide synthase and thus raise nitric oxide levels accelerating β-cell apoptosis.[33] TZD therapy provide β-cell stabilization or even rejuvenation [34] and decrease proinsulin-to-insulin ratio.[35] It also increases endogenous insulin levels[36] and in the Troglitazone In Prevention of Diabetes (TRIPOD) study, troglitazone treatment resulted in >50% decrease in the development of diabetes.[37] The characteristics of TZD-induced fluid retention and its mechanism remain poorly defined[38] but may be due to the potentiation of insulin effects on sodium and water retention. The fluid retention should not necessarily be equated with worsening HF,[38] and these patients should not

Table 2 : Comparison of different oral drugs used in management of type 2 diabetes

	Sulfonylureas	Repaglinide	Metformin	Thiazolidinediones	Acarbose
Decrease in FPG(mg/dl)	60-70		60-70	35-40	20-30
Decrease in HbA_{1c}(%)	1.5-2.0		1.5-2.0	0.5-1.0	0.7-1.0
Triglycerides	No effect or mild ↓		↓	↓	↓
HDL-C	No effect		↑	↑	No effect
LDL-C	No effect		↓	↑	No effect
Body weight	↑		→	↑	No effect
Plasma insulin	↑		↓	↓	No effect
Adverse Events	Hypoglycemia, Wt. gain		GI intolerance, Lactic acidosis	Wt. gain, Fluid retention, Hepatotoxicity	GI intolerance

necessarily be deprived of its usefulness as long as they are being closely monitored for weight gain, fluid retention, and other signs and symptoms of decompensated HF.[38]

Metformin and TZD Combination Therapy

Even though the United Kingdom Prospective Diabetes Study (UKPDS) showed a decrease in the incidence of cardiac events with metformin use in overweight patients with type 2 diabetes, metformin is a weak insulin sensitizer when compared with a TZD.[20] The combination therapy of metformin and TZD in small doses increases the efficacy, minimize side effects, improve compliance and save costs compared with a large dose of one drug.[40] Increased efficacy results from the action of metformin on the liver complementing the actions of the TZD and stabilizing or rejuvenating pancreatic β-cell. Metformin is however, contraindicated in all patients with heart failure as its use is associated with an increased risk of potentially lethal lactic acidosis.[41]

However, the major advantage of using an insulin sensitizer alone or in combination with another sensitizer is the absence of severe or even moderate degree of hypoglycemia and better glycemic control. A lower level of HbA_{1c} has been shown to be associated with reduced cardiac mortality and total mortality.[42-45] If once-daily combination of metformin and TZD does not achieve the target level of HbA_{1c}, the insulin sensitizers should be administered twice daily. If building up to a maximum twice-daily regimen does not achieve the desired glycemic goals, then a secretagogue (i.e., a sulfonylurea, repaglinide, or nateglinide) should be added.

Triple Oral Therapy

First described in 1998, triple oral therapy consisting of metformin, a TZD, and a sulfonylurea has achieved target HbA_{1c} levels provided that a third agent was not added when the difference between the current and target HbA_{1c} values was >1.5%.[46] During the 6 months after troglitazone was replaced with rosiglitazone in a group of patients receiving triple therapy, 24% had their secretagogue dose reduced or stopped, 7% discontinued suggesting a continued improvement in β-cell function,[47] and at 3-year 70% maintained HbA_{1c} of 6.9% with significant increase in endogenous insulin production.[48] At 5-year 62% of these patients continued to have an average HbA_{1c} of 7.1%.[36] A double-blind study of therapy failure with metformin and sulfonylurea showed that patients randomized to the addition of rosiglitazone had a return of first-phase insulin response, an effect that did not occur in patients randomized to the addition of insulin.[49]

-GLUCOSIDASE INHIBITORS

Because α-glucosidase inhibitors lower only postprandial[50] and not fasting plasma glucose levels, the efficacy of these agents is limited to a 0.5% to 1.0% decrease in HbA_{1c} value.[51,52] The acarbose has been associated with a significant reduction in the risk of cardiovascular disease and hypertension[53] (STOP-NIDD Trial). Side effects such as excess flatulence due to undigested carbohydrate fermented by bacteria in the large bowel are troublesome to most patients. However, patients who are renally compromised can attain a 5-times higher peak plasma drug concentration, possibly leading to hepatotoxicity.[53,54] Therefore, in patients whose serum creatinine concentration is >2.0 mg/dL, α-glucosidase inhibitors should not be used.

SECRETAGOGUES

All secretagogues cause the release of more insulin at any given plasma glucose level by closing the energy-sensitive potassium channel in the cell membrane of the β-cells. This leads to β-cell depolarization and an influx of calcium, resulting in increased exocytosis and release of insulin.[56,57] The first-and second-generation sulfonylureas have a more prolonged attachment to the sulfonylurea receptor, causing a more prolonged release of insulin, and are more likely to be associated with hypoglycemia.[57] In addition, glyburide has been shown to decrease the counter-regulatory release of both glucagon from the pancreas and growth hormone from the pituitary gland, which further increases the risk of hypoglycemia.[58]

Another problem with first- and second-generation sulfonylureas is the closing of energy-sensitive potassium channels not only in the all-membrane of pancreatic β-cell but also in cardiomyocytes. The process of ischaemic preconditioning during myocardial ischaemia does not occur when potassium-adenosine triphosphate (k.ATP) are blocked with the result the ischaemia is sustained and risk of myocardial damage increases, when it may have been averted.[55] At the Mayo Clinic, coronary angioplasty after acute MI was found to be associated with increased 48-hour mortality in patients with diabetes who were treated with sulfonylurea.[59] Another study showed a decrease in the ejection fraction of ischaemic myocardium with glyburide but not with insulin.[60] The results of these studies confirm that ischaemic preconditioning is blocked in both non-diabetic and diabetic myocardium by glyburide but not the third-generation glimepiride.[61,62]

A recent retrospective study[63] suggested that attenuation of electrocardiographic ST-segment elevation during moderate-sized acute MI occurs in diabetic patients treated with sulfonylurea drugs. During acute MI with creatinine phosphokinase (CPK) levels between 500 and 1,000 mg/dL, those patients treated with sulfonylurea drugs were found to have a reduced magnitude of ST elevation as compared with subjects with diabetes who were not treated with sulfonylurea drugs. These patients were less likely to meet the standard ECG criteria for thrombolytic therapy. Large-scale evaluations are necessary to further clarify the impact of sulfonylurea treatment and evaluation of acute MI in this population.[63]

MAINTAINING GLYCEMIC CONTROL WITH EXOGENOUS INSULIN

When triple therapy fails, the addition of a subcutaneous insulin injection is needed to regain glycemic control. A premixed insulin, preferably of rapid-acting insulin with a compatible intermediate-acting insulin (e.g., insulin analogue lispro 75/25 or aspart 70/30 mix), may be administered with the evening meal, or the long-acting insulin glargine may be injected at bedtime. To maximize the potential of these insulins, start with a small dose (0.2 per kg or 10 IU) and titrate by 20% increments at intervals of 2 to 3 days until either the fasting plasma glucose value is ≤ 110 mg/dL or nocturnal or early morning hypoglycemia occurs.

If daytime glycemic control cannot be maintained by means of oral agents and a single injection of insulin, options include

Table 3 : Exploring New therapies in Diabetes-Incretin mimetics.

GLP-1 Receptor Agonists	
▪ GLP-1 Analogues	
- NN 2211	Liraglutide
- CJC-1131	DAC-GLP-1
▪ Extendin Analogues	
- AC 2993	Exendin-4 (Exenatide)
- AC 2993	Exendin-4 Long acting
- ZP-10	
DPP-IV Inhibitors	
▪ LAF 237	
▪ MK 0431	

expanding the regimen to two injections of a premixed insulin or administering a preprandial dose of short-acting insulin 1 to 3 times daily in addition to glargine at bedtime.[64] At the same time, discontinuation of the secretagogue is suggested and maintenance of a single or dual insulin-sensitizer regimen is recommended; insulin therapy for type 2 diabetes, especially in obese patients, offers better glycemic control when combined with an insulin sensitizer than when administered as monotherapy.[65]

EXPLORING NEW THERAPIES IN DIABETES - INCRETIN MIMETICS

The observation that food ingestion or enteral glucose administration provoked a greater stimulation of insulin release compared with similar amounts of energy (glucose) infused intraveously[66,67] led to the development of the incretin concept. Hence, it was postulated that gut-derived signals stimulated by oral nutrient ingestion represent potent insulin secretagogues responsible for the augmentation of insulin release when energy is administered via the gut versus the parenteral route. Although several neurotransmitters and gut hormones posses incretin-like activity, the considerable evidence from immunoneutralization, antagonist and knockout studies suggest that glucagon-like peptide (GLP-1) represent the dominant peptides responsible for the majority of nutrient-stimulated insulin secretion.

Incretin : Synthesis, Secretion and degradation

Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 are members of the glucagons peptide superfamily. Ingestion of a mixed meal or a meal enriched with specific fats and complex carbohydrates is particularly effective in stimulating GIP and GLP-1 release in human subjects. Circulating levels of GIP (1-42) are normal or slightly increased in type 2 diabetic subjects in the basal or postprandial state.[69] In contrast, subjects with diabetes or impaired glucose tolerance exhibit modest but significant reductions in levels of meal stimulated circulating GLP-1.[69,70] Furthermore, meal-induced increase in GIP and GLP-1 secretions are inversely correlated with the extent of insulin resistance detected in human subjects.[71]

Biological actions of GLP-1

- Stimulate insulin secretion and suppresses glucagons secretion
- Slows gastric emptying and reduces food intake

Table 4 : Properties and biological actions of GIP and GLP-1

GIP	GLP-1
42-amino acid peptide	30/31-amino acid peptide
Released from duodenum	Released from distal small bowel and colon
NH_2-terminal inactivation by DPP-IV	NH_2-terminal inactivation by DPP-IV
Stimulates insulin secretion	Stimulates insulin secretion
Minimal effect on gastric emptying	Inhibits gastric emptying
No effect on glucagon secretion	Inhibits glucagon secretion
No regulation of satiety and body weight	Inhibits food intake and weight gain
Promotes expansion of β-cell mass	Promotes expansion of β-cell mass
Normal GIP secretion in diabetic subjects	↓ed GLP-1 secretion in diabetic subjects
Defective GIP response in type 2 diabetes	Preserved GLP-1 response in type 2 diabetes

- Increases β-cell mass and maintains β-cell function
- Improves insulin sensitivity and enhances glucose disposal

Single or repeated subcutaneous injection of native GLP-1 decrease blood glucose in human subjects[72,73] and the glucose lowering effect is no longer evident 1-2 h after peptide injection.[74,75] Continuous IV or subcutaneous infusion of GLP-1 has been shown to be highly effective in lowering blood glucose in diabetic subjects[72-79] when compared with peptide infusion for 16 hrs[76] however, rapid degradation and clearance of native and exogenously administered GLP-1 have spurred the clinical development of degradation resistant GLP-1 analogues with longer duration of action in vivo.

Exendin-4, a naturally occurring 39-aminoacid GLP-1 agonist isolated from the salivary gland venom of the lizard *Heloderma suspectum*,[81] exhibits 53% aminoacid identity to mammalian GLP-1.[81,82] Intravenous infusion of exendin-4 lowered fasting and postprandial blood glucose in normal healthy volunteers and was associated with a 19% reduction in caloric consumption.[83] It exerted a similar effects on insulin secretion after IV infusion in diabetic subjects,[84] and subcutaneous daily administration in type 2 diabetic subjects reduced HbA_{1c} from 9.1 to 8.3% over a 1-month treatment period.[85] Exendin-4 has been evaluated in eight phase 2 trials in 323 type 2 diabetes subjects receiving dosages of 0.05-2.0 μg/kg subcutaneously. Nausea and vomiting were the principal side effects observed.[86]

Exendin-4 treatment (0.08 μg/kg s.c., b.i.d. or t.i.d.) over one month in 109 patients treated with sulfonylurea or metformin, alone or in combination resulted in significant reduction in levels of serum fructosamine, HbA_{1c}, and mean postprandial glucose.[87] Currently it is being evaluated for the treatment of type 2 diabetes in phase 3 trials.

NN2211 (liraglutide) is a fatty acid linked DPP-IV resistant derivative of GLP-1, has been shown to reduce fasting and postprandial glycaemia in diabetic subjects after a single 10 μg/kg subcutaneous injection at 11:00 p.m., in association with

Table 5 : Characteristics of DPP-IV inhibitors and GLP-1R agonists

DPP-IV inhibitors	GLP-1R agonists
Orally available	Injectable
Multiple targets	Single known GPCR target
GLP-1 PK favorable	Higher levels of GLP-1 achievable, but narrow PK profile
Short-versus long-acting	Longer acting- days to weeks
Less potent agents	More potent glucose lowering
Drug overdose nontoxic	Drug overdose problematic
No central nervous system side effects	Nausea and vomiting
Less defined side effect profile	Well-described and tolerable side effect profile

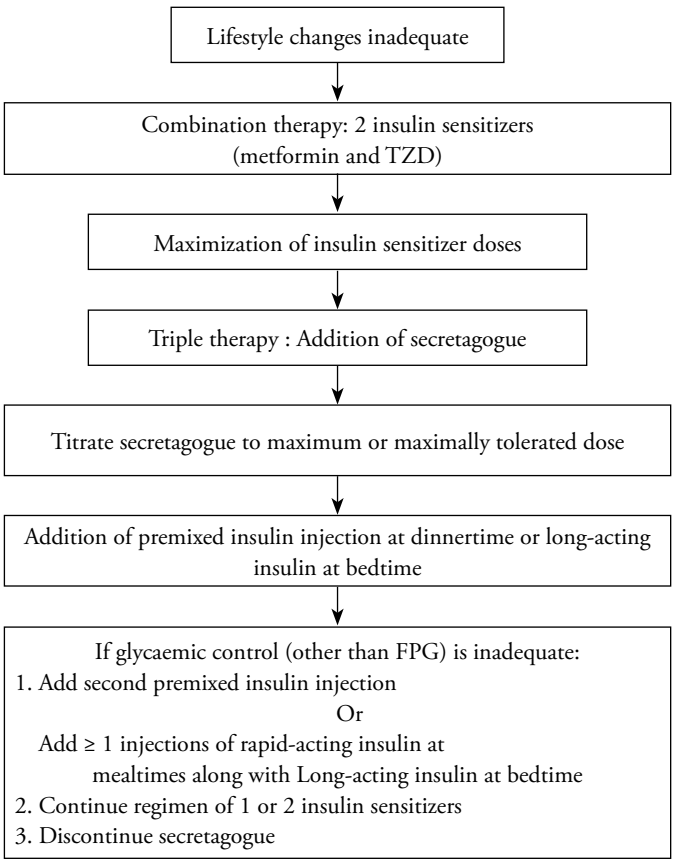

Fig. 1 : The proposed treatment regimen for Type 2 diabetes

inhibition of gastric emptying and reduced levels of circulating glucagons.[89] NN2211 has been tested in phase 2 clinical trials.

Inhibition of DPP-IV for the treatment of type 2 diabetes

DPP-IV, the principal enzyme responsible for incretin inactivation,[90,91] in a single-dose escalation study of P32/98 in healthy male volunteers improved oral glucose tolerance with increase levels of GLP-I. A 4-week trial of NUP DPP 728 in type 2 diabetic subjects (mean entry HbA_{1c} of ~ 7.6%) produced significant glucose lowering in mean HbA_{1c} to 6.9%[92] DPP-IV

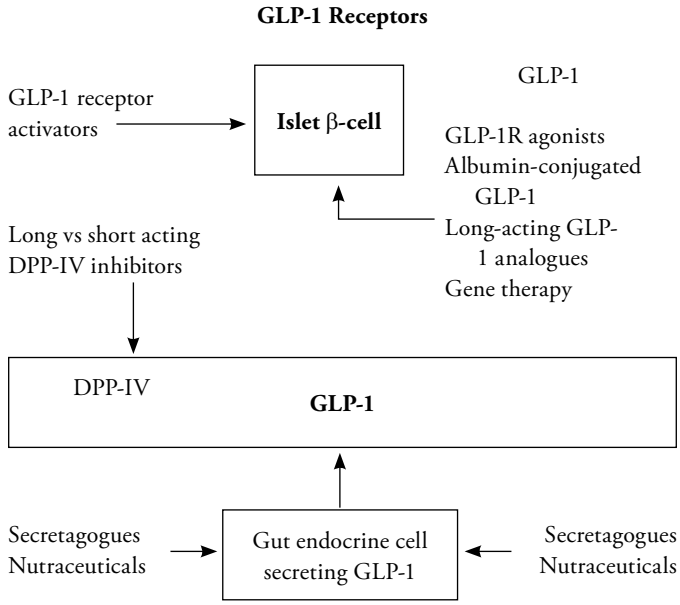

Fig. 2 : Potentiation of incretin action for the treatment of Type 2 diabetes

inhibitor, LAF237, is currently in phase 2 clinical trials. DPP-IV also exhibits catalytic activity against a number of peptide substrates[90,93] and hence, the long-term safety of sustained DPP-IV inhibition merits careful scrutiny.

GLP-1R agonists and DPP-IV inhibitors: Unanswered questions

GLP-1 exhibits several distinct advantages desirable in a therapeutic agent for treating type 2 diabetes (Table 4). GLP-1 R agonists produce remarkable effects on β-cell proliferation and cytoprotection and therefore its potential to prevent progression to β-cell failure in diabetic subjects is intriguing, but largely undocumented.

DPP-IV inhibitors will be able to achieve the same pharmacological elevation in levels of circulating GLP-1 (Figure 2) compared with injectable GLP-1 based drugs, and are likely to be less potent compared with injectable GLP-1 R agonists (Table 5).

REFERENCES

1. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Eng J Med* 1993;329:977-986.
2. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS34) [Published correction appears in *Lancet* 1998; 352:1557]. *Lancet* 1998; 352:854-865.
3. UK Prospective Diabetes Study(UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [Published correction appears in *Lancet* 1999; 354:602]. *Lancet* 1998; 352:837-853.
4. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with NIDDM: a randomized prospective 6 yr study. *Diabetes Res Clin Pract* 1995;28: 103-117.
5. UK Prospective Diabetes Study Group (UKPDS VIII). Study design, progress and Performance. *Diabetologia* 1991; 34:877-890.

6. Haffner SM, Stern MP, Hazuda HP, et al. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes. *J Am Med Assoc* 1990;263:2893-2898.
7. DeFronzo. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131:281-303.
8. Kahn SE, Porte D Jr. The pathophysiology of Type II (non-insulin dependent) diabetes mellitus: implications for treatment. In: Porte D Jr., Sherwin RS, eds. Ellenberg and Rifkin's Diabetes mellitus. 5th ed. Stamford. Conn. Appleton and Lange; 1997:487-512.
9. Porte D Jr. Banting Lecturer 1990: β-cells in type 2 diabetes mellitus. *Diabetes* 1991;40:166-180.
10. Porte D Jr. Kohn SE. β-cell dysfunction and failure in type 2 diabetes: potential mechanisms. *Diabetes* 2001;50(Suppl 1): S 160-S 163.
11. DeFronzo RA, Bonadonna RC, Ferranini E. Pathogenesis of NIDDM: a balanced overview. *Diabetes Care* 1992;15:318-368.
12. Le Roith D. Beta-cell dysfunction and insulin resistance in type 2 diabetes: role of metabolic and genetic abnormalities. *Am J Med* 2002; 113(Suppl 6A):3S-11S.
13. Harris MI, Klein R, Welborn TA, Kmiman M.W. Onset of NIDDM occurs at least 4-7 yr. before clinical diagnosis. *Diabetes Care* 1992;15:815-819.
14. Weyer C, Bogardus C, Moh DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999;104:787-794.
15. Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care* 2001;24:89-94.
16. Turner RC, Cull CA, Frighi V, Holman RR, UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999;281:2005-2012.
17. UK Prospective Diabetes Study Group, UK Prospective Diabetes Study 16: Overview of 6 years therapy of type 2 diabetes: a progressive disease [Published correction appears in *Diabetes* 1996; 45:655]. *Diabetes* 1995; 44:1249-1258.
18. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [Published correction appears in *Lancet* 1999;354:602]. *Lancet* 1998;352:837-853.
19. American Diabetes Association Consensus statement, The pharmacological treatment of hyperglycemia of NIDDM. *Diabetes Care* 1995;18:1510-1518.
20. Chu NV, Kong AP, Kim DD, et al. Differential effects of metformin and troglitazone on cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Care* 2002;25:542-549.
21. Olesky JM. Treatment of insulin resistance with peroxisome proliferator-activated receptor γ agonists. *J Clin Invest* 2000;106:467-472.
22. Okuno A, Tamemoto H, Tobe K, et al. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J Clin Invest* 1998;101:1354-1361.
23. Guan HP, Li Y, Jensen MV, et al. A futile metabolic cycle activated in adipocytes by antidiabetic agents. *Nat Med* 2002;8:1122-1128.
24. Haffner SM, Greenberg AS, Weston WM, et al. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation* 2002;106:679-684.
25. Parulkar AA, Pendergrass ML, Granda-Ayala R, et al. Non-hypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001;134:61-71.
26. Kelly IE, Han TS, Walsh K, Lean ME. Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. *Diabetes Care* 1999;22:288-293.
27. Frohlich M, Imhof A, Berg G, et al. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care* 2000;23:1835-1839.
28. Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interieukin-6 with metabolic syndrome X. *Diabetologia* 1997;40: 1286-1292.
29. Law RE, Goetze S, Xi XP, et al. Expression and function of PPARγ in rat and human vascular smooth muscle cells. *Circulation* 2000;101:1311-1318.
30. Takagi T, Akasaka T, Yamamuro A, et al. Troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with non-insulin dependent diabetes mellitus: a serial intravascular ultrasound study. *J Am Coll Cardiol* 2003;36:1529-1535.
31. Minamikawa J, Tanaka S, Yamauchi M. et al. Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 1998;83:1818-1820.
32. Shimabukuro M, Koyama K, Chen G, et al. Direct antidiabetic effect of leptin through triglyceride depletion of tissues. *Proc Natl Acad Sci* USA 1997;94:4637-4641.
33. Shimabukuro M, Ohneda M, Lee Y, Unger RH. Role of nitric oxide in obesity-induced β cell disease. *J Clin Invest* 1997;100:290-295.
34. Finegood DT, McArthur MD, Kojwang D, et al. β-cell mass dynamics in Zucker diabetic fatty rats: rosiglitazone prevents the rise in net cell death. *Diabetes* 2001;50:1021-1029.
35. Porter LE, Freed MI, Jones MP, Biswas N. Rosiglitazone improves β cell mass dynamic in Zucker diabetic fatty rats: rosiglitazone prevents the rise in net cell death. *Diabetes* 2000;49:A122.
36. Ovalle F, Bell DS. Clinical evidence of thiazolidinedione-induced improvement of pancreatic β cell function in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2002;4:56-59.
37. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 2002;51:2796-2803.
38. Tang WH, Francis GS, Hoogwerf BJ, Yong JB. Fluid retention after initiation of thiazolidinedione therapy in diabetic patients with established chronic heart failure. *J Am Coll Cardiol* 2003;41:1394-1398.
39. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care* 2003;26:2433-2441.
40. Bell DS. Why I initiate therapy with two insulin sensitizers in the type 2 diabetic patient. *Endocr Pract* 2003;9:98-100.
41. Masoudi FA, Wang Y, Inzucchi SE, et al. Metformin and thiazolidinedione use in Medicare patients with heart failure. *JAMA* 2003;290:81-85.
42. Stratton IM, Adler Al, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2diabetes (UKPDS 35): prospective observational study. *BMJ* 2003;321:405-412.
43. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ* 2001;322:15-18.
44. American Diabetes Association, Reducing cardiac mortality in patients with diabetes: perspectives from the 59th Scientific Sessions of the American Diabetes Association. American Diabetes Association, Baylor College of Medicine; Dallas, TX; 1999.
45. Geiss LS, Herman WH, Smith PJ, Mortality in non-insulin dependent diabetes. In: National Diabetes Data Group, ed. Diabetes in America. 2nd ed. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, 1995:233-257. NIH publication 95-1468.
46. Ovalle F, Bell DS. Triple oral antidiabetic therapy in type 2 diabetes mellitus. *Endocr Pract* 1998;4:146-147.
47. Bell DS, Ovalle F, Shadmany S. Conversion from troglitazone to rosiglitazone. *Endocr Pract* 2001;7:326.
48. Bell DS, Ovalle F. Long-term efficacy of triple oral therapy for type 2 diabetes mellitus. *Endocr Pract* 2002;8:271-275.
49. Ovalle F, Bell DS. The effect of rosiglitazone versus insulin on the pancreatic beta-cell functions of patients with type-2 diabetes mellitus. *Diabetes* (In press).
50. Lebovitz HE. A new oral therapy for diabetes management: α-glucosidase inhibition with acarbose. *Clin Diabetes* 1995;13:99-103.
51. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus: a multicenter controlled clinical trial. *Ann Intern Med* 1994;121:928-935.
52. Segal P, Feig PU, Schernthaner G, et al. The efficacy and safety of miglitol therapy compared with glibenclamide in patients with NIDDM inadequately controlled by diet alone. *Diabetes Care* 1997;20:687-691.

53. Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;290:486-494.
54. Precose (acarbose tablets) [prescribing information]; West Haven, CT: Bayer Pharmaceuticals Corp; 2003.
55. Bell DS. Déjà vu all over again? University Group Diabetes Program. *Endocr Pract* 1998;4:64-65.
56. Perfetti R, Ahmad A. Novel sulfonylurea and non-sulfonylurea drugs to promote the secretion of insulin. *Trends Endocrinol Metab* 2000;11: 218-223.
57. Bell DSH, Yumuk V. Frequency of severe hypoglycemia in patients with non-insulin-dependent diabetes mellitus treated with sulfonylureas or insulin. *Endocr Pract* 1997;3:281-283.
58. ter Braak EW, Appeiman AM, van der Tweel I, et al. The sulfonylurea glyburide induces impairment of glucagons and growth hormone responses during mild insulin-induced hypoglycemia. *Diabetes Care* 2002;25:107-112.
59. Garratt KN, Brady PA, Hassinger NL, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1999;33:119-124.
60. Scognamiglio R, Avogaro A, Vigili DK, et al. Effects of treatment with sulfonylurea drugs or insulin on ischemia-induced myocardial dysfunction in type 2 diabetes. *Diabetes* 2002;51:808-812.
61. Klepzig H, Kober G, Matter C, et al. Sulfonylureas and ischaemic preconditioning: a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999;20:439-446.
62. Lee TM, Chou TF. Impairment of myocardial protection in type 2 diabetic patients. *J Clin Endocrinol Metab* 2003;88:531-537.
63. Huizar JF, Gonzalez LA, Alderman J, Smith HS, Sulfonylureas attenuate electrocardiographic ST-segment elevation during an acute myocardial infarction in diabetics. *J Am Coll Cardiol* 2003;42:1017-1021.
64. Yki-Jarvinen H, Dressler A, Ziemen M, for the HOE 901/3002Study Group. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 2000;23:1130-1136.
65. Aviles-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 Diabetes Mellitus: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999;131:182-188.
66. Elrick H, Stinoruler L. Hlad CJ, Arai Y. Plasma insulin response to oral and intravenous glucose administration. *J Clin Endocrinol Metab* 1964; 24:1076-1082.
67. Mclntyre N, Holdsworth CD, Turner DS. Intestinal factors in the combol of insulin secretion. *J Clin Endocrinol Metab* 1965;25:1317-1324.
68. Dupre J, Beck JC. Stimulation of release of insulin by an extract of intestinal mucosa. *Diabetes* 1966;15:555-559.
69. Vilsboll T, Krarup T, Ocean CF, Madsbad S, Holst JJ. Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. *Diabetes* 2001;50:609-613.
70. Lugari R, Dei Cas A, Ugolotti D, Finardi L, Barilli A L, et al. Evidence for early impairment of glucagon like peptide 1-induced insulin secretion in human type 2 (non-insulin dependent) diabetes. *Hormo Metab Res* 2002; 34:150-154.
71. Rask E, Olsson T, Soderberg S, Johnson O, Seckl J, Ahren B. Impaired incretin response after a mixed meal is associated with insulin resistance in non-diabetic men. *Diabetes Care* 2001;24:1640-1645.
72. Nauck MA, Wollschlager D, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Willms B. Effects of subcutaneous glucagon-like peptide 1 (GLP-1[7-36 amide]) in patients with NIDDM. *Diabetologia* 1996;39:1546-1553.
73. Junti-Berggren L, Pigon J, Karpe F, Hamsten A, Gutniak M, Vignati L, Effendic S. The antidiabetogenic effect of GLP-1 is maintained during a 7-day treatment period and improves diabetic dyslipoproteinemia in NIDDM patients. *Diabetes Care* 1996;19:1200-1206.
74. Gutniak MK, Linde B, Holst JJ, Efendic S. Subcutaneous injection of the incretin hormone glucagon-like peptide 1 abolishes postprandial glycemia in NIDDM. *Diabetes Care* 1994;17:1039-1044.
75. Ritzel R, Orskov C, Holst JJ, Nauck MA. Pharmacokinetic, insulinotropic, and glucagonostatic properties of GLP-1 [7-36 amide] after subcutaneous injection in healthy volunteers: dose-response relationship. *Diabetologia* 1995;38:720-725.
76. Larsen J, Hylleberg B, Ng K, Damsbo P. Glucagon-like peptide-1 infusion must be maintained for 24 h/day to obtain acceptable glycemia in type 2 diabetic patients who are poorly controlled on sulphonylurea treatment. *Diabetes Care* 2001;24:1416-1421.
77. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 2002;359: 824-830.
78. Rachman J, Barrow BA, Levy JC, Turner RC. Near normalization of diurnal glucose concentrations by continuous administration of glucagon-like peptide 1 (GLP-1) in subjects with NIDDM. *Diabetologia* 1997,40: 205-211.
79. Todd JF, Wilding JP, Edwards CM, Ghatei MA, Bloom SR. Glucagon-like peptide-1 (GLP-1): a trial of treatment in non-insulin-dependent diabetes mellitus. *Eur J Clin Invest* 1997;27:533-536.
80. Deacon CF, Johnsen AH, Holst JJ. Degradation of glucagon-like peptide-1 by human plasma in vitro yields an N-terminally truncated peptide that is a major endogenous metabolite in vivo. *J Clin Endocrinol Metab* 1995; 80:952-957.
81. Eng J, Kleinman WA, Singh L, Singh G, Raufman JP. Isolation and characterization of exendin 4, an exendin 3 analogue from Heloderma suspectum venom. *J. Biol Chem* 1992;267:7402-7405.
82. Chen YE, Drucker DJ. Tissue-specific expression of unique mRNAs that encode proglucagon-derived peptides or exendin 4 in the lizard. *J Biol Chem* 1997;72:4108-4115.
83. Edwards CM, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, Ghatei MA, Bloom SR. Exendin-4 reduces fasting and postprandial glucose and decrease energy intake in healthy volunteers. *Am J Physiol* 2001;281: E155-E161.
84. Egan JM, Clocquet AR, Elahi D. The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. *J Clin Endocrinol Metab* 2002;87:1282-1290.
85. Egan JM, Meneilly GS, Elahi D. Effects of one month bolus subcutaneous administration of exendin-4 in type 2 diabetes. *Am J Physiol Endocrinol Metab* 2003;34:E1072-E1079.
86. Nielsen LL, Baron AD. Pharmacology of exenatide (synthetic exendin-4) for the treatment of type 2 diabetes. *Curr Opin Investig Drug* 2003;4: 401-405.
87. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim DW, Baron AD. Effect on glycemic control of synthetic exendin-4 (AC2993) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 2003;26:2370-2377.
88. Agerso H, Jensen LB, Elbrond B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1derivative, in healthy men. *Diabetologia* 2002; 45:195-202.
89. Juhl CB, Hollingdal M, Sturis J, Jakobsen G, Agerso H, Veldhuis J, Porksen N, Schmitz O. Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. *Diabetes* 2002;51:424-429.
90. Drucker DJ. Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes. *Expert Opin Investig Drugs* 2003;12: 87-100.
91. Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. *Diabetes* 1998;47:1663-1670.
92. Ahren B, Simonsson E, Larsson H, Landin-Olsson M, Torgeirsson H, Hansson PA, Sandqvist M, Bavenholm P, Efendic S, Eriksson JW, Dickinson S, Holmes D. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. *Diabetes Care* 2002; 25:869-875.
93. Mentlein R. Dipeptidyl-peptidase IV (CD26): role in the inactivation of regulatory peptides. *Regul Pept* 1999;85:9-24.