Physician Perspective™
VIEWPOINT

Based on presentations from the International Diabetes Federation (IDF)
19th World Diabetes Congress

Cape Town, South Africa December 3-7, 2006

TREATING TYPE 2 DIABETES MELLITUS THROUGH INCRETIN ENHANCEMENT

INTRODUCTION

The global diabetes epidemic is predicted to grow over the next few decades, from 2.8% in 2000 to 4.4% in 2030 (Wild et al. *Diabetes Care* 2004;27(5):1047-53). The UK Prospective Diabetes Study (UKPDS) found that intensive therapy with sulphonylureas or insulin reduced microvascular complications in type 2 diabetes by 25% (*P*=0.0099) but not macrovascular complications such as myocardial infarction, which was non-significantly reduced by 16% (*P*=0.052) (*Lancet* 1998;352(9131): 837-53). Intensive blood glucose control resulted in more hypoglycemic episodes and weight gain than conventional therapy. Progressive hyperglycemia and deterioration in HbA_{1c} is characteristic of type 2 diabetes, yet studies of maximal conventional therapy, including sulphonylureas, metformin, rosiglitazone and the addition of acarbose to UKPDS monotherapy, have found a worrying pattern of initial improvement followed by gradual deterioration in glycemic control (Kahn et al. *N Engl J Med* 2006;355(23):2427-43, Cook et al. *Diabetes Care* 2005;28(5):995-1000, Holman et al. *Diabetes Care* 1999;22(6):960-4). This gradual deterioration appears to result from deteriorating ß-cell function rather than from declining insulin sensitivity (*Diabetes* 1995;44(11):1249-58, Kahn et al. *N Engl J Med* 2006; 355(23):2427-43). Therefore, current management of type 2 diabetes and its associated complications is inadequate and the challenge facing us is to find new therapies that maintain glucose levels without side effects, particularly hypoglycemia.

Reported by:
Jean-François Yale, MD, CSPQ (Endocrinology)

Director, Metabolic Day Centre
MUHC-Royal Victoria Hospital

Professor of Medicine
McGill University
Montreal, Quebec

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

ß-cells have four essential features that enable them to control blood glucose: the ability to make proinsulin, package insulin and secrete it; the ability to recognize signals and couple these signals to the secretion of insulin (stimulus-secretion coupling); the ability to communicate with other ß-cells; and the ability to adapt to both short-term (minute to minute) and longer-term metabolic demands that result from aging and lifestyle changes. In type 2 diabetes, normal ß-cell function is disturbed and the cells are less responsive to glucose levels, show abnormal oscillatory insulin release, increased proinsulin levels and loss of first-phase and abnormal second-phase insulin release (Buchanan TA. *Clin Ther* 2003;25(Suppl B):B32-B46). There is an associated reduction in ß-cell mass.

Type 2 diabetes arises from impaired ß-cell function in the face of insulin resistance. The ß-cell impairment in turn reflects a combination of reduced ß-cell mass and a specific defect in glucose-regulated insulin secretion. Dr. Philippe Halban, Professor, Department of Genetic Medicine and Development, University of Geneva, Switzerland, explained that our understanding of normal ß-cell function has led to the hypothesis that the highly differentiated state of this particular cell renders it unusually susceptible to biological stress, leading to impaired function as well as apoptosis. In type 2 diabetes, such stressful signals include hyperglycemia, possibly in combination with dyslipidemia (glucolipotoxicity). Glucolipotoxicity may damage islet cells via several synergistic pathways including cytokine-induced inflammation.

The reduction in ß-cell mass could be caused by increased cellular death, decreased cell regeneration or a combination of both. The relative contribution of each in type 2 diabetes is not clear. Equally poorly defined is whether self-replication of existing ß-cells or neogenesis from precursor cells occurs in adults *in vivo*. There is no non-invasive way of monitoring ß-cell mass and consequently, no way of documenting its decline as individuals progress towards overt diabetes, nor any possible reversal of this process with appropriate therapy.

Maintaining a functional ß-cell mass is a fundamental goal of diabetes management. However, conventional strategies aimed at improving ß-cell function by directly stimulating insulin secretion, regardless of the prevailing glucose level and without any impact on ß-cell mass (e.g. sulphonylureas), may be associated with the risk of hypoglycemia and may even further decrease ß-cell mass in the long term. The ß-cells are highly specialized but this degree of specialization becomes their undoing when environmental factors are out of the normal range. Any new medication for type 2 diabetes must ideally lead to the restoration of both ß-cell function and mass while maintaining physiological insulin levels without the risk of hypoglycemia. The incretin glucagon-like peptide 1 (GLP-1) mimetics and inhibitors of its degradation (the enzyme dipeptidyl-peptidase 4 [DPP-4] inhibitors) may offer these features.

THE ROLE OF INCRETINS

An oral glucose load leads to a higher insulin secretory response than does an intravenous glucose load. This difference is known as the incretin effect. In normal individuals, this incretin effect is responsible for half of the insulin secretory response after oral glucose and mixed meals. The two major incretins are glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. GIP is secreted by endocrine K-cells in the proximal gastrointestinal (GI) tract (duodenum and proximal jejunum) and GLP-1 is secreted by L-cells in the distal GI tract (ileum and colon). In the fasting state, levels of both incretins are low but they increase rapidly after eating a meal. Both are rapidly metabolized by the DPP-4 inhibitors and the metabolites are eliminated by the kidney (Drucker DJ, Nauck MA. *Lancet* 2006; 368(9548):1696-705).

Following secretion of GIP and GLP-1, both incretins stimulate glucose-dependent insulin release from ß-cells, while GLP-1 also suppresses hepatic glucose output by inhibiting glucagon response from alpha cells in a glucose-dependent manner. In animal and *in vitro* studies, both these incretins increase ß-cell replication and reduce apoptosis. GLP-1 also stimulates insulin gene transcription, enhances insulin biosynthesis and expands ß-cell mass in rodent and human islets (Drucker DJ, Nauck MA. *Lancet* 2006; 368(9548):1696-705). Other actions of GLP-1 include reduction of appetite and food intake by the action of GLP-1 on receptors in the hypothalamus and delayed gastric emptying.

As discussed by Dr. Michael Nauck, Diabetes Centre, Bad Lauterberg, Germany, the incretin effect is markedly reduced in type 2 diabetes, resulting in delayed and reduced insulin release following oral glucose administration. The effect of GIP on insulin release is also reduced in patients with type 2 diabetes, while the effect of GLP-1 is unchanged. It is likely that a failure of incretin-induced insulin secretion is one of the basic problems leading to impairments of postprandial insulin release in type 2 diabetes.

Intravenous GLP-1 normalizes and subcutaneous GLP-1 lowers plasma glucose in patients with type 2 diabetes. However, GLP-1 is rapidly broken down by DPP-4, resulting in a half-life of only one to two minutes and making routine clinical use unlikely. GLP-1 receptor agonists (incretin mimetics) such as exenatide and liraglutide, which are injectable peptides, offer an alternative. A further approach is to prevent the metabolism of GLP-1 and GIP using DPP-4 inhibitors (incretin enhancers) such as vildagliptin and sitagliptin, which are low molecular-weight agents in an oral formulation. Incretin mimetics and enhancers address the pathophysiological defects in the enteroinsular axis in patients with type 2 diabetes. Because incretins stimulate insulin in a strictly glucose-dependent manner,

the likelihood of hypoglycemic episodes is reduced (Table 1).

Table 1. Incretins as Pharmacologic Agents

	Incretin Mimetic		DPP-4 Inhibitors	
	Exenatide	Liraglutide	Vildagliptin	Sitagliptin
Administration	Injection		Tablet	
Insulin Secretion	Increased		Increased	
Glucagon Secretion	Decreased		Decreased	
HbA_{1c} Reduction	-0.8 to 2.0%	-0.8 to 2.0%	-0.5 to -1.5%	-0.5 to -1.5 %
Weight Reduction	Yes (-3 to 5 Kg)	Yes (-3 to 5 Kg)	No	No
Hypoglycemia	No	No	No	No
Nausea	Yes	Less	None	None

TREATING TYPE 2 DIABETES WITH SELECTIVE DPP-4 INHIBITORS

Sitagliptin and vildagliptin are two emerging DPP-4 inhibitors with promising clinical data. Unlike incretin mimetics, which also have potential for improving glucose metabolism by acting on the glucagon pathway, both sitagliptin and vildagliptin are orally active. In addition to previously published studies, a substantial amount of new clinical data with each of these agents was presented here during the scientific sessions.

One advantage of sitagliptin is its highly favourable pharmacokinetics. In clinical trials, this agent has enhanced GLP-1 and GIP levels for 24 hours following a single 100-mg dose, according to Dr. Peter Stein, Rahway, New Jersey. Reviewing both the monotherapy and combination regimen trials, Dr. Stein reported that sitagliptin has demonstrated significant improvement in glucose control whether used alone or with other active agents, such as metformin and pioglitazone.

In a series of double-blind monotherapy trials in patients with type 2 diabetes, sitagliptin reduced $HbA_{1C\,by}$ by nearly 1% relative to placebo over treatment periods ranging up to 24 weeks (Aschner et al. *Diabetes Care* 2006; 29(12):2632-7, Raz et al. *Diabetologica* 2006;49(11):2564-71). Important reductions in HbA_{1C} were observed even if the baseline value was mildly elevated, while the greatest reductions occurred in patients with high baseline levels. Consistent with the mechanism of action of DPP-4 inhibitors, several studies have demonstrated that patients not only improve HbA_{1C} but avoid the postprandial spikes in glucose observed in placebo patients after a standard meal challenge. The rates of hypoglycemia have been similar in patients on placebo vs. those on sitagliptin.

In a combination study of patients with type 2 diabetes taking metformin, patients were randomized to the addition of sitagliptin 100 mg or placebo in a 2:1 ratio (Charbonnel et al. *Diabetes Care* 2006;29(12):2638-43). After 24 weeks, patients in the treatment group had a 0.65% greater reduction in HbA_{1C} than patients randomized to placebo. In a similar study combining sitagliptin 100 mg or placebo to an existing pioglitazone (30 or 45 mg/day) regimen, the combination reduced HbA_{1C} by -0.70% (Rosenstock et al. *Diabetes* 2006;55(suppl 1):A132, Abstract 556-P). Importantly, twice as many patients reached a glycemic target of HbA_{1C} <7% when sitagliptin 100mg was added to existing therapy.

In a recent study, patients on either glimepiride or glimepiride and metformin (half the patients in each group) were followed through a long run-in period to ensure that they had a stable HbA_{1C} of 7.5 to 10%. Patients were then randomized to the addition of sitagliptin 100 mg/day or placebo in addition to existing medication. After 24 weeks, sitagliptin had reduced HbA_{1C} levels by -0.74% compared to placebo. When added to glimepiride, the reduction was -0.6% and when added to the combination of glimepiride and metformin, the reduction was -0.9% compared to placebo.

In one of several new studies presented here, six treatment groups were compared over 24 weeks: placebo (n=106), sitagliptin 100 mg/day (n=179), metformin 500 mg b.i.d. (n=182), metformin 1000 mg b.i.d. (n=182), sitagliptin 50 mg/metformin 500 mg b.i.d. (n=190), or sitagliptin 50 mg/metformin 1000 mg b.i.d. (n=192). According to the senior author of this randomized study, Dr. Deborah Williams-Herman, Rahway, New Jersey, the mean HbA_{1C} was 8.8% and mean FPG at baseline was 11.1 mmol/L.

After 24 weeks of therapy, the placebo-subtracted mean change in HbA_{1C} from baseline was: -0.8% for sitagliptin 100 mg/day; -1.0% for metformin 500 mg b.i.d.; -1.3% for metformin 1000 mg b.i.d.; -1.6% for sitagliptin 50 mg/metformin 500 mg b.i.d. (P<0.001); and -2.1% for sitagliptin 50 mg/metformin 1000 mg b.i.d. (P<0.001). The proportion of patients who achieved an HbA_{1C} <7.0% were: placebo 9%; sitagliptin 100 mg/day 20%; metformin 500 mg b.i.d 23%; metformin 1000 mg b.i.d. 38%; sitagliptin 50 mg/metformin 500 mg b.i.d. 43%; and sitagliptin 50 mg/metformin 1000 mg b.i.d 66%. Thus, 20% more patients using low-dose metformin combination therapy and 28% more patients using high-dose metformin combination therapy achieved the target HbA_{1C} of <7.0% than the equivalent dose of metformin monotherapy. Forty-four per cent of patients taking sitagliptin 50 mg/metformin 1000 mg b.i.d achieved an HbA_{1C} of <6.5%.

Hypoglycemia occurred in <1% of those on placebo, sitagliptin 100 mg/day and metformin 500 mg b.i.d., and in 1% of those on metformin 1000 mg b.i.d. or the combination sitagliptin/low-dose metformin. In the high-dose metformin/sitagliptin combination group, hypoglycemia occurred in 2%. Nausea occurred in 1% of those patients on placebo or sitagliptin alone, in 3% and 8% of those on low- and high-dose metformin alone and in 4% and 6% of those on low- and high-dose combination therapy. GI adverse events in combination therapy were similar to those found in metformin monotherapy. All groups, except for sitagliptin monotherapy, experienced similar mean reductions in body weight from baseline (-0.6 to -1.3 kg). The sitagliptin monotherapy group had no mean change in weight from baseline to week 24.

In another study discussed here, sitagliptin 100 mg was compared to the sulphonylurea glipizide in a non-

inferiority design over 52 weeks. At baseline, mean HbA_{1C} was 7.5%. Three-quarters of patients had an HbA_{1C} <8%. According to Dr. Williams-Herman, there was a similar reduction in both cohorts using an intention-to-treat analysis and a mild advantage to sitagliptin (-0.67%) using a per protocol analysis. Again, greater reductions were seen in patients with higher baseline HbA_{1C} levels. Although DPP-4 inhibitors are classically weight-neutral, which is a clear advantage, there was a 2.5 kg weight difference in this study between groups after one year, and those on sitagliptin lost a mean of 1.5 kg while those on glipizide gained a mean 1.1 kg from baseline. Waist circumference increased slightly in those on glipizide while it fell in those on sitagliptin. As predicted in the experimental setting, a significantly lower proportion of patients treated with sitagliptin experienced hypoglycemia (4.9%) than in the glipizide-treated group (32%).

Vildagliptin has also been studied as both monotherapy and in combination with other established glucose-lowering agents. Among published studies, vildagliptin monotherapy has been compared to both placebo (Pi-Sunyer et al. *Diabetes Res Clin Pract* 2007;Epub ahead of print) and rosiglitazone (*Diabetes Care* 2007;30(2):217-23). In the dose-ranging placebo study, the highest dose achieved a reduction in HbA_{1C} of about 0.9% vs. no change in the placebo group. There were no confirmed cases of hypoglycemia and treatment was well tolerated. In the rosiglitazone comparison, HbA_{1C} was reduced by 1.1% in the vildagliptin cohort and by 1.3% in the rosiglitazone arm (both $P<0.001$ vs. baseline) over 24 weeks. In a study population of 786 patients, there was one case of hypoglycemia in each arm.

In new data on vildagliptin presented here this week, one report collated data from four independent phase III monotherapy studies. As noted by Dr. R. Rebuli, Basel, Switzerland, one of the four studies was conducted over 12 weeks, two over 24 weeks and the fourth over 52 weeks. Again, vildagliptin reduced the HbA_{1C} by about 1% in most of the trials. In the 52-week study, vildagliptin was compared to metformin in 760 patients randomized in a 2:1 ratio. A sustained reduction in HbA_{1C} was achieved with both therapies, averaging 1% in the vildagliptin group and 1.4% in the metformin cohort. The authors noted that the rate of adverse events on vildagliptin, although not significantly lower than metformin, was numerically lower. Hypoglycemia occurred in fewer than 1% of patients in any of the study groups randomized to the DPP-4 inhibitor.

In another set of data reported by Dr. Rebuli, the efficacy and tolerability of vildagliptin was specifically assessed in patients with type 2 diabetes aged 65 years or older by comparing individuals in this age group to younger patients in two studies. Each study contained more than 500 patients. Dr. Rebuli reported that HbA_{1C} was reduced slightly but not significantly more in younger than older patients; however, tolerability was indistinguishable. The overall incidence of adverse events was 61.6% and 62.6%, respectively. The incidence of hypoglycemia was <1% in both subgroups.

Overall, data with both of the DPP-4 inhibitors appear promising. Reductions in HbA_{1C} have been robust when these agents are used alone or in combination with other active glucose-lowering agents. Moreover, these compounds have proven to have a high degree of tolerability with a low risk of hypoglycemia. Results to date provide a strong indication that these treatments will play an important role in type 2 diabetes management.

SUMMARY

Type 2 diabetes mellitus is rapidly increasing globally and is not optimally controlled on current standard therapy. The aim of type 2 diabetes management is to reduce insulin resistance, improve ß-cell functional mass and reduce excess hepatic glucose production. Not only is conventional therapy found wanting in reducing macrovascular complications of type 2 diabetes, but it has not addressed the progressive deterioration in ß-cell functional mass and is often associated with the unwanted complications of hypoglycemia and weight gain.

Increasing incretin levels, either directly with incretin mimetics or using an oral DPP-4 inhibitor, has opened a new opportunity to address these shortcomings of current management. Of the oral DPP-4 inhibitors, both sitagliptin and vildagliptin are progressing rapidly through the final stages of clinical testing and may eventually play a role in glucose control. In clinical trials, they have demonstrated efficacy as both monotherapy and in combination with agents such as metformin and glimepiride in reducing FPG and HbA_{1C}. The DPP-4 inhibitors have demonstrated a high degree of tolerability among both young and older patients and pose a low risk of hypogycemic episodes. Importantly, unlike some other glucose-lowering agents, they do not appear to lead to weight gain and may even produce a modest weight loss. In animal models, these agents also appear to benefit ß-cell functioning and perhaps prevent the loss of these cells or even increase their number. Further studies are needed to confirm these effects on ß-cell function and mass, a key factor in the progression and treatment of type 2 diabetes. □