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REVIEW

Incretin-based therapies: a new potential treatment approach to overcome clinical inertia in type 2 diabetes

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Abstract. Maintaining an adequate metabolic control is still a challenge in many patients with type 2 diabetes. Among the many factors advocated to explain the failure to achieve recommended goals, clinical inertia is increasingly recognised as a primary cause of poor glycaemic control. The existence of a "metabolic memory" strongly supports the adoption of a more aggressive treat-to-target approach, instead of waiting for treatment failure. This approach may be particularly important in the initial phases of the disease, to slow the progressive decline of beta-cell function and improve overall outcomes. The fear of hypoglycaemia and weight gain associated with most of the available treatments are among the main causes of clinical inertia, and strongly affect the attitudes of providers and patients toward therapy intensification. The incretin-based therapies represent a new potential goal-oriented treatment approach. Two classes of incretin-based drugs have been developed: GLP-1 mimetics (exenatide and liraglutide) and DPP-IV inhibitors (sitagliptin and vildagliptin). Incretino-mimetics have a peculiar mechanism of action that is associated with lack of hypoglycaemia and weight loss or neutrality; these characteristics may facilitate therapy intensification and help to attain established goals. Furthermore, they can induce benefits in terms of post-prandial hyperglicemia control and beta-cell function preservation. An early use of this class of drugs may show a positive impact on the disease progression and a delay in the need of insulin injections. (www.actabiomedica.it)

Key words: Type 2 diabetes, clinical inertia, incretins

The problem of clinical inertia

Targeting HbA1c levels below 7.0% is considered a primary goal of diabetes care, given its importance to obtain a sustained reduction in microvascular, and possibly macrovascular complications. However, maintaining an adequate metabolic control is still a challenge in many patients with type 2 diabetes (T2DM). Recent data from 114.000 patients in Italy suggest that over 50% of them fails to meet the <7.0% target, while approximately 30% has HbA1c >8.0%. Furthermore, only 5.5% achieves combined goals for HbA1c, blood pressure, and cholesterol (1).

Among the many factors advocated to explain the failure to achieve recommended goals, clinical inertia is increasingly recognised as a primary cause of poor glycemic control in T2DM (2-4). Clinical inertia may be defined as the failure to initiate or advance therapy in a patient who is not at the evidence-based therapeutic goal. The concept is well illustrated in a large, prospective study in patients who were members of the Kaiser Permanente Northwest. In this study, in patients on monotherapy with metformin or sulfonylurea a change in therapy was initiated only when HbA1c levels rose to 8.8% and 9.1%, respectively. The time required for therapy intensification ranged from 2 to 3 years, despite HbA1c levels above goal (5). Clinical inertia in T2DM has been confirmed in other studies, showing that patients are often left in a state of chronic hyperglycemia for long periods of

time, before treatment is intensified (3, 6, 7). Chronic hyperglycemia in turn increases the risk of complications and accelerates the decline in beta-cell function as a consequence of glucotoxicity.

The importance of an early, intensified approach to metabolic control has been clearly demonstrated by the long-term results of the UKPDS study, showing that the benefits of tight blood glucose control extended well beyond the end of the study and persisted after over 10 years (8). In fact, while between-group differences in HbA1c were lost one year after the end of the study, significant differences in favour of the tight metabolic control group were still present for microvascular and macrovascular complications, and a significant difference in overall mortality also emerged. These findings confirm the existence of a "metabolic memory" (9), initially described in the DCCT trial, and strongly support the adoption of a more aggressive treat-to-target approach, instead of waiting for treatment failure. This approach can be particularly important in the initial phases of the disease, to slow the progressive decline of beta-cell function and improve overall outcomes.

The causes of clinical inertia

The causes of clinical inertia are multifactorial, and include providers' attitudes and beliefs, the system of care, patients' preferences, and available treatments (10).

The primary responsibility lies with the providers, and reasons for clinical inertia may include uncertainty regarding the appropriate target in specific patient subgroups, lack of training in the treat-to-target approach, overestimation of adherence to guidelines.

Organizational factors, such as lack of sufficient time to address patient problems, or lack of shared care organization between the specialist and primary care may also contribute to clinical inertia.

Patients may also contribute by adopting unhealthy lifestyles and failing to adhere to prescribed medications.

Among the factors that strongly affect the choices of providers, as well those of patients, are the fear of hypoglycaemia and weight gain.

Hypoglycaemia

After the failure of monotherapy with metformin, clinicians are offered different options to intensify treatment, including sulfonylureas, glitazones, and insulin. However, all these classes of drugs show side effects that can limit their use.

Hypoglycaemia has a substantial impact in terms of mortality, morbidity, and quality of life (11). One out of four patients with T2DM treated with insulin for >5 years experiences at least one episode of severe hypoglycaemia, and the frequency of episodes increases with increasing age and diabetes duration.

Moreover sulfonylureas may cause hypoglycaemia, though at a lower rate than insulin. In a recent study, the frequency of moderate and severe episodes of hypoglycaemia were of 39% and 7%, respectively (12). Rates of hypoglycaemia defined by values <2.2 mmol/l for at least 20 minutes on continuous glucose monitoring were 14%. It should be underlined that the frequency of hypoglycaemic episodes is lower with the third-generation sulfonylureas (e.g. glimepiride, glipizide and gliclazide) and the metiglinides (e.g. repaglinide and nateglinide). Nevertheless, considering the elevate number of individuals treated with this class of drugs, even an event rate as low as 0.8% per annum for severe events translates into thousands of patients requiring emergency assistance (13).

The role of severe hypoglycaemia as a cardiovascular risk factor has been recently emphasized by the results of two large trials: the ACCORD and the VADT. Both trials were designed to determine the effect of the lowering of blood glucose to near-normal levels on cardiovascular risk. In the ACCORD trial, targeting a HbA1c level <6.0% was associated with a 22% excess mortality as compared with the standard-therapy group. In this trial, 27% of the patients allocated to the intensive therapy group experienced hypoglycaemia requiring assistance, and the high rate of hypoglycaemic episodes has been advocated as one of the possible causes of excess mortality (14). In the VADT trial, pursuing a strict metabolic target (HbA1c<6.5%) did not appreciably affect the risk of macrovascular complications and total mortality (15). Nevertheless, 21% of the patients in the intensive group and 10% in the control group had severe hypo-

glycaemia requiring medical assistance. The presence of a hypoglycaemic episode represented a strong predictor of major events in the following three months.

Weight gain

Despite the emphasis placed on weight loss in the management of type 2 diabetes, and the association of excess weight with poorer metabolic control and cardiovascular risk profile, many antidiabetic treatments are associated with weight gain (16). The fear of weight gain also represents one of the major barriers to the patient acceptance of treatment; this in turn may influence physician's decision to intensify the treatment. To this respect, the DAWN study has documented that 50-55% of the general practitioners and nurses tend to delay insulin therapy until absolutely necessary (17).

Insulin treatment in type 2 diabetes is typically associated with an average weight gain of 4 kg, but the increase in weight can reach 8-10 kg in some patients. Insulin detemir represents the only exception, as documented in several studies showing that this insulin has less effect on body weight than other insulins (18, 19). With the only exclusion of metformin and acarbose, also oral agents are responsible for weight gain. In the UKPDS, treatment with sulfonylureas was associated with a weight gain of about 5 Kg over 10 years (20). The effect on body weight is more prominent for first- and second-generation sulfonylureas compared to newer ones such as glimepiride and gliclazide (16).

The use of glitazones is also associated with weight gain, as documented in several clinical trials. Body weight was increased by 4 kg in three years with pioglitazone in the PROACTIVE study (21), while the use of rosiglitazone produced a weight gain of 5 kg in 5 years in the ADOPT study (22) and 2 kg in 3 years in the DREAM study (23).

More recently, the results of the ACCORD trial showed that intensive therapy aiming at a HbA1c target of <6.0% was associated with a weight gain of more than 10 kg in 27.8% of the patients (14).

In summary, once metformin therapy at the maximum tolerated dose fails to maintain an adequate metabolic control, physicians are faced with the choice of add-on treatments that are effective in reducing HbA1c levels, but also show important threats, represented by the risk of hypoglycaemia and weight gain. These represent important obstacles to therapy intensification and are often responsible for clinical inertia. Given this situation, the availability of new treatments that do not increase the risk of hypoglycaemia and have a positive or neutral effect on body weight could be of help in overcoming clinical inertia.

Incretin-based therapies

The incretin-based therapies represent a new potential goal-oriented treatment approach (10). These new drugs have a peculiar mechanism of action that can impact on several possible causes of clinical inertia. In fact, they are associated with lack of hypoglycaemia and weight loss or neutrality (24, 25). Therefore they may favour an early effective intervention against the diabetes progression.

Physiology of Incretin Hormones

Incretins are gastrointestinal hormones released during nutrient absorption to increase insulin secretion. The two gut peptides accounting for most of the incretin effect are

- GLP-1 (Glucagon-like peptide 1): it is synthesized in L-cells primarily found in the distal small bowel and colon.
- GIP (Glucose-dependent insulinotropic peptide): it is secreted by duodenal and proximal jejunal K cells.

Within some minutes of release from their intestinal sites, GIP and GLP-1 undergo rapid metabolism (proteolytic cleavage) to inactive metabolites by the enzyme dipeptidyl peptidase-IV (DPP-IV). The small amounts of active hormones that reach the pancreas act on receptor sites residing on beta-cells to stimulate insulin secretion in a glucose-dependent manner; furthermore, GLP-1 acts on alpha cells and inhibits the secretion of glucagon.

Incretins in the patophysiology of T2DM

Active GLP-1 levels after glucose administration are reduced in T2DM, even if its biological effect is

preserved. In contrast, plasma levels of GIP are normal or slightly increased in T2DM, while its activity is defective or absent. Thus, the blunted incretin response in T2DM is due to both impaired secretion of GLP-1 and defective activity of GIP.

Studies using continuous intravenous or subcutaneous infusions of GIP and GLP-1 in T2DM have documented that both GLP-1 and GIP produced a similar early insulin release, while later-phase insulin levels were much higher with GLP-1 than GIP infusion (26). Starting from these findings, only GLP-1 appeared to have potential useful clinical benefit in T2DM.

Actions, efficacy, and safety of incretino-mimetics

Two classes of compounds have been developed: GLP-1 mimetics, that have a longer duration of action than GLP-1 due to a higher stability in the presence of DPP-IV, and DPP-IV inhibitors, that delay endogenous degradation of GLP-1 and GIP, enabling higher plasma levels of the active hormones.

Incretino-mimetics, like endogenous hormones, act by stimulating the insulin secretion in a glucose-dependent manner and by inhibiting the glucagon release. They also have additional actions that make these compounds particularly interesting for the development of new optimized therapeutic strategies:

- *Hypoglycaemia:* differing from other secretagogue drugs, incretinomimetics do not induce hypoglycemia due to the induction of glucose-dependent insulin secretion
- *Effect on satiety and body weight:* GLP-1 is associated with enhanced satiety, reduced food intake, and weight loss or neutrality. It remains unclear whether the reason for the increased satiety is the slowed gastric emptying or a central mechanism.
- *Effect on beta-cell health:* GLP-1 preserves beta-cell morphology and function and reduces cellular apoptosis.
- *Effect on post-prandial hyperglycemia:* This parameter represents a new recognized target of diabetes therapy. While other oral agents and exogenous insulin are unable to prevent or minimize glucagon hypersecretion in T2DM, incretins can impact on this parameter through both the direct inhibition of the glucagon release and the paracrine inhibitory effect exerted by the increased insulin secretion. This double mechanism effectively reduces the post-prandial hyperglycemia and the glycaemic variability. The preservation of beta-cell function represents another factor that may contribute to the long-term control of post-prandial hyperglycemia.

GLP-1 mimetics are administered via subcutaneous injection and do not require the carbohydrates counting to estimate the most appropriate dose of drug. Therefore, also blood-glucose self-monitoring is not necessary, making the therapy simpler than that with insulin.

DPP-IV inhibitors are orally administered, thus offering a further advantage in terms of therapy compliance.

As for the efficacy of incretino-mimetics, a recent meta-analysis documented that, if compared with placebo, GLP-1 analogues lowered HbA1c by –0.97% (IC 95% –1.13%; –0.81%) and DPP-IV inhibitors by –0.74% (IC 95% –0.85%; –0.62%); their efficacy was similar to that of other hypoglycemic agents (27). In addition, GLP-analogues decreased body weight by 1.4 Kg in comparison with placebo and by 4.8 Kg in comparison with insulin; DPP-IV inhibitors showed a neutral effect on body weight. All the trials included in the meta-analysis had a duration of 30-weeks or shorter; therefore long-term efficacy and safety still need to be carefully evaluated.

As for the tolerability, GLP-1 analogues are associated with gastrointestinal side effects, that tend to attenuate after a few weeks; DPP-IV do not induce gastrointestinal side effects, but are associated with nasopharyngitis, upper respiratory infections, and headache.

Available compounds

Table 1 summarizes the main characteristics of the available incretin-mimetics.

Exenatide

Exenatide is approved and commercialized as adjunctive treatment in T2DM suboptimally controlled

Table 1. Characteristics of available incretins

Molecule	Brand name	Class	Administration	Indication in T2DM	Half-life (hours)	Daily dose	FDA/EMEA approval
Exenatide	Byetta	GLP-analogues	Subcutaneous	Association with metformin and/or sulfonylureas or TZDs	2,4	5 or 10 microg (twice daily)	Yes/yes
Liraglutide	-	GLP-analogues	Subcutaneous	-	10-14	0.6-1.8 mg	Revision/ Revision
Sitagliptin	Xelevia, Januvia, Tesavel	DPP-IV inhibitors	Oral	Monotherapy or in combination with metformin and/or sulfonylureas or TZDs	12	100 mg	Yes/yes
Vildagliptin	Galvus	DPP-IV inhibitors	Oral	Association with metformin and/or sulfonylureas or TZDs	1.5-4.5	25-200 mg	Revision/Yes

on maximum doses of metformin, sulfonylureas or both (10, 24, 25). More recently, the drug has been approved for use as add-on therapy in T2DM patients not adequately controlled on a TZD. Exenatide is twice daily administered within 60 minutes before breakfast and dinner by a pen prefilled with 5 or 10 micrograms.

Mild-to-moderate nausea occurs in about 40% of patients receiving twice-daily exenatide, with diarrhea and vomiting in less than 15%. However, nausea disappears within 4 weeks in most of the patients. Formation of antibodies to exenatide has been reported in up to 50% of the treated patients; although they neither seem affecting the drug efficacy nor having any clinical effect, the long-term relevance remains to be documented.

Recently, a FDA alert informed on 6 cases of hemorrhagic or necrotizing pancreatitis in patients taking Byetta, suggesting to promptly discontinue the treatment in case of suspected pancreatitis (28).

Exenatide LAR

A long-acting release (LAR) formulation of exenatide to be administered once weekly is currently under evaluation (29). Preliminary studies show that weekly doses of 2.0 mg reduced HbA1c by 1.7%, starting from baseline levels of 8.5%, and reduced body weight by 3.8 Kg after 15 weeks. This dose was more effective than 0.8 mg and placebo. Nausea occurred in 27% of patients treated with exenatide LAR and in 15% of patients treated with placebo.

Recent data suggest that, if compared with twice daily exenatide, one weekly administration of exenatide LAR is associated after 30 weeks with a higher likelihood to reach levels of HbA1c<7% (77% vs. 66% of patients), with an identical weight loss (about 4 Kg), and a lower frequency of nausea (26% vs. 35%), without any hypoglycemic episode (30).

Liraglutide

Liraglutide is a GLP-1 analogue with a 97% homology with the human native hormone. Its molecular properties determine a slow release from the injection site, while its binding to albumin protects liraglutide from the enzymatic activity of DPP-IV and reduces its renal clearance. Thanks to these characteristics, liraglutide has an half-life of about 12 hours, and may be administered once daily. LEAD 1-5 studies (31-35) have shown that this compound significantly reduces HbA1c levels in individuals with T2DM not

adequately controlled with diet and physical activity, or with other oral agents. The reduction of HbA1c levels is greater with higher baseline HbA1c, as observed with other drugs. Liraglutide also decreases body weight up to 3 kg, and weight loss is proportional to baseline BMI (36). A slight decrease in systolic blood pressure and an improvement in beta-cell function have also been documented (37,38).

Sitagliptin

Sitagliptin is indicated for the treatment of T2DM either as monotherapy or in combination with metformin and/or sulfonylureas or TZDs in patients poorly controlled on the maximum doses of these drugs. Monotherapy trials indicated that Sitagliptin produced placebo-subtracted HbA1c reductions of 0.6-0.8% from a baseline of about 8.0% (39,40). Sitagliptin in combination with metformin, glipizide, or pioglitazone yielded a HbA1c reduction of 0.6-0.7% when compared to placebo. The recommended dose in most patients is 100 mg once daily. The administration is independent of meals. Nasopharyngitis, upper respiratory infections, and headache occur in less than 3% of patients (10). Gastrointestinal disturbances are uncommon.

Vildagliptin

While FDA revision is ongoing, the drug has been approved by EMEA. Vildagliptin is a very selective DPP-IV inhibitor. When compared with other agents, its efficacy was similar to rosiglitazone and acarbose, but lower than metformin (40). It is used in combination with metformin, sulfonylureas, TZDs, or insulin, reducing HbA1c by 0.5% - 1.0% (40). Vildagliptin is well-tolerated; the most common side effects are urinary infections and headache (10).

Conclusions

After the failure of the maximum tolerated dose of metformin, therapy intensification requires the addition of other oral agents or insulin. All these drugs may have threats that limit their acceptance, particularly hypoglycaemia and weight gain. Furthermore, neither oral agents nor insulin effectively counter the progressive decline in pancreatic beta-cell function. Incretins minimize the risk of hypoglycaemia, are weight neutral (or promote weight loss in overweight patients), and significantly improve beta-cell function; they may thus greatly help in overcoming the barriers inducing to clinical inertia and delay the use of insulin.

Furthermore, all these compounds but exenatide may be independently administered from meals, and do not require self-monitoring, thus favoring the patient compliance. The development of extended release molecules that necessitate of less frequent administrations will further improve the acceptance of the treatment by the patient.

If the positive profile of efficacy and tolerability of incretins will be confirmed in long-term studies, this new class of drugs will represent an important tool to help overcoming clinical inertia, reduce the prevalence of treatment failure, and improve clinical outcomes.

References

1. Rossi MC, Nicolucci A, Arcangeli A, Cimino A, De Bigontina G, Giorda C, Meloncelli I, Pellegrini F, Valentini U, Vespasiani G; on behalf of the AMD Annals Study Group. Baseline quality of care data from a quality improvement program implemented by a network of diabetes outpatient clinics. *Diabetes Care* 2008 (in press).
2. Grant R, Adams AS, Trinacty CM, Zhang F, Kleinman K, Soumerai SB, et al. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. *Diabetes Care* 2007; 30: 807-12.
3. Ziemer DC, Miller CD, Rhee MK, Doyle JP, Watkins C Jr, Cook CB, et al. Clinical inertia contributes to poor diabetes control in a primary care setting. *Diabetes Educ* 2005; 31: 564-71.
4. Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? *Diabetes Care* 2005; 28: 600-6.
5. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes Care* 2004; 27: 1535-40.
6. Knecht LA, Gauthier SM, Castro JC, Schmidt RE, Whitaker MD, Zimmerman RS, et al. Diabetes care in the hospital: is there clinical inertia? *J Hosp Med* 2006; 1: 151-60.

7. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, et al. Clinical inertia. *Ann Intern Med* 2001; 135: 825-34.
8. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. *N Engl J Med* 2008 (in press)
9. Ihnat MA, Thorpe JE, Ceriello A. Hypothesis: the "metabolic memory", the new challenge of diabetes. *Diabet Med* 2007; 24: 582-6.
10. Triplitt C, McGill JB, Porte D Jr, Conner CS. The changing landscape of type 2 diabetes: the role of incretin-based therapies in managed care outcomes. *J Manag Care Pharm* 2007;13: S2-16.
11. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 diabetes. *Diabet Med* 2008; 25: 245-54.
12. UK Hypoglycaemia Study Group. Examining hypoglycaemic risk in diabetes: effect of treatment and type of diabetes. *Diabetologia* 2007; 50: 1140-7.
13. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, Frier BM, Morris AD; DARTS/MEMO Collaboration. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care* 2003; 26: 1176-80.
14. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545-59.
15. Studio VADT (Veterans Affairs Diabetes Trial). Press release: http://www.diabetes.org/for-media/pr-intense-blood-glucose-control-yields-no-significant-effect-on-cvd-reduction.jsp
16. Barnett A, Allsworth J, Jameson K, Mann R. A review of the effects of antihyperglycaemic agents on body weight: the potential of incretin targeted therapies. *Curr Med Res Opin* 2007; 23: 1493-507.
17. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, et al; The International DAWN Advisory Panel. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* 2005; 28: 2673-9.
18. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 2006; 29: 1269-74.
19. Raslová K, Bogoev M, Raz I, Leth G, Gall MA, Hâncu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract* 2004; 66: 193-201.
20. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837-53.
21. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366: 1279-89.
22. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; 355: 2427-43.
23. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006; 368: 1096-105.
24. 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: 1696-705.
25. Van Gaal LF, Gutkin SW, Nauck MA. Exploiting the antidiabetic properties of incretins to treat type 2 diabetes mellitus: glucagon-like peptide 1 receptor agonists or insulin for patients with inadequate glycemic control? *Eur J Endocrinol* 2008; 158: 773-84.
26. Vilsboll T, Krarup T, Madsbad S, Holst JJ. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. *Diabetologia* 2002; 45: 1111-9.
27. Amori RE, Lau J, Pittas AG. Efficacy and Safety of Incretin Therapy in Type 2 Diabetes Systematic Review and Meta-analysis. JAMA 2007; 298: 194-206.
28. U.S. Food and Drug Administration. Information for healthcare professionals. Exenatide (Byetta). Available at the website http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatide2008HCP.htm
29. Kim D, MacConell L, Zhuang D, Kothare PA, Trautmann M, Fineman M, et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. *Diabetes Care* 2007; 30: 1487-93.
30. Drucker DJ, Buse JB, Taylor K, Kendall B, Trautmann M, Zhuang D, et al. Exenatide once weekly results in significantly greater improvements in glycemic control compared to exenatide twice daily in patients with type 2 diabetes. *Diabetes* 2008; 57 (Suppl 1): A33.
31. Marre M, Shaw J, Brandle M, Wan Bebakar WM, Kamaruddin NA, Strand J, et al. Liraglutide added to a sulphonylurea (SU) offers significantly better glycaemic control and favourable weight change compared with rosiglitazone and SU combination therapy in T2D. *Diabetologia* 2008; 51 (Suppl. 1): P897.
32. Hermansenn K, Nauck MA, Frid A, Shah NS, Tankova T, Mitha IH, et al. Liraglutide, a once-daily human GLP-1 analogue, in type 2 diabetes provides similar glycemic control with reduced body weight compared with glimepiride when added to metformin. *Diabetologia* 2008; 51 (Suppl. 1): P895.

33. Garber A, Henry R, Ratner R, Garcia Hernandez P, Rodriguez Pattzi HM, Olvera-Alvarez I et al. Significantly better glycaemic control and weight reduction with liraglutide, a once-daily human GLP-1 analogue, compared with glimepiride: all as monotherapy in type 2 diabetes. *Diabetologia* 2008;51(Suppl. 1): P896.
34. Zinman B, Gerich J, Buse J, Lewin A, Schwartz SL, Raskin P, et al. Effect of the GLP-1 analogue liraglutide on glycaemic control and weight reduction in patients on metformin and rosiglitazone: a randomized double-blind placebo-controlled trial. *Diabetologia* 2008; 51 (Suppl. 1): P898.
35. Russel-Jones D, Vaag A, Schmitz O, Sethi B, Lalic NM, Antic S, et al. Significantly better glycaemic control/ weight reduction with human GLP-1 analogue liraglutide, than with insulin glargine: all as add-on to metformin + sulphonylurea in type 2 diabetes. *Diabetologia* 2008; 51 (Suppl. 1): OP148.
36. Schmitz O, Russel-Jones D, Shaw J, Brandle M, Matthews D, Frid A, et al. Liraglutide, a human GLP-1 analogue, reduces bodyweight in subjects with type 2 diabetes, irrespective of body mass index at baseline. *Diabetologia* 2008; 51 (Suppl. 1): P888
37. Colagiuri S, Frid A, Zdravkovic M, Le Thi TD, Vaag A, Garber A, et al. Liraglutide, a human GLP-1 analogue, reduces systolic blood pressure in subjects with type 2 diabetes. *Diabetologia* 2008; 51 Suppl 1: P899.
38. Matthews DR, Marre M, Le Thi TD, Zdravkovic M, Simo R, Garber A, et al. Liraglutide, a human GLP-1 analogue, significantly improves beta-cell function in subjects with type 2 diabetes. *Diabetologia* 2008;51 (Suppl. 1): P892
39. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE; Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2006; 29: 2632-7.
40. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; Sitagliptin Study 023 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia* 2006; 49: 2564-71.
41. Chia CW, Egan JM. Special Features: Incretin-Based Therapies in Type 2 Diabetes Mellitus. *J Clin Endocrinol Metab* 2008 (in press)

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