2nd National iNcretin Summit 2013

Proceedings From the Scientific Sessions
Do more than lower blood glucose. 

Grab diabetes by the roots.

Liraglutide injection

Once-daily Victoza® goes deep to impact many parts of type 2 diabetes, with significant and sustained‡:

- Reductions in HbA₁₀₀: up to 2.74% ‡
- Reductions in weight (mean): up to 2.8 kg²,³
- Reductions in systolic blood pressure (mean): up to 6.7 mm Hg²,³
- Improvements in beta-cell function²,⁴

The EASD and ADA recommend GLP-1 agonists as an option for early use after metformin.⁵

#Statistically significant results in the average patient population sustained up to 52 weeks. 1,2,3,4

1 Mean baseline HbA₁₀₀: >9.5% and n=16.¹

2 Victoza® in combination with metformin + rosiglitazone.¹

3 European Association for the Study of Diabetes 

Abbreviated prescribing information

Victoza (liraglutide)

Presentation: Prefilled, disposable pen containing 18 mg of liraglutide in 3 ml of solution. Indications: Victoza® is indicated for treatment of adults with type 2 diabetes. Dosage and administration: The starting dose is 0.6 mg once daily. After at least one week, the dose should be increased to 1.2 mg. Based on clinical response and after at least one week, the dose can be increased to 1.8 mg to further improve glycaemic control. Victoza® can currently not be recommended for use in patients with moderate/severe renal impairment or hepatic impairment. Victoza® is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, thigh, or upper arm. Victoza® should not be administered intravenously or intramuscularly. In combination with metformin or without a thiazolidinedione, no dose adjustment is required. When Victoza® is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia. Contraindications: Hypersensitivity to the active substance or any of the excipients.

Special warnings and precautions: Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Due to limited experience, Victoza® is not recommended in patients with inflammatory bowel disease or diabetic gastroparesis. There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and no experience in patients with NYHA class III-IV. Use of other GLP-1 analogues has been associated with the risk of pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, discontinuation of medical products should be considered. Thyroid adverse events, including increased blood calcitonin, goitre, and thyroid neoplasm, were reported in clinical trials, particularly in patients with preexisting thyroid disease. Pregnancy and lactation: Victoza® should not be used in women who are pregnant, who wish to become pregnant, or who are breast-feeding. Undesirable effects: The most frequently reported adverse reactions in patients treated with Victoza® are nausea and diarrhea. Less common adverse reactions include headache, vomiting, dyspepsia, upper abdominal pain, constipation, gastritis, flatulence, abdominal distension, gastrooesophageal reflux, bronchitis, nasopharyngitis, dizziness, fatigue, pyrexia, decreased appetite, and hypoglycaemia. Patients receiving Victoza® in combination with a sulphonylurea may have an increased risk of hypoglycaemia. The risk can be lowered by a reduction in the dose of sulphonylurea. Few cases (less than 0.1%) of acute pancreatitis have been reported during long-term clinical trials with Victoza®. A causal relationship between Victoza® and pancreatitis cannot be established nor be excluded. The full prescribing information can be obtained at no cost from Novo Nordisk.

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References:

Abbreviated prescribing information®Victoza® (liraglutide)

For the university of a registered medical practitioner or hospital or a laboratory

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<th>Full Form</th>
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<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
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<tr>
<td>AEs</td>
<td>Adverse Events</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>CV</td>
<td>Cardio Vascular</td>
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<tr>
<td>DPP-4</td>
<td>Dipeptidyl Peptidase-4</td>
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<tr>
<td>DTMS</td>
<td>Diabetes Tele Management System</td>
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<tr>
<td>EASD</td>
<td>European Association for the Study of Diabetes</td>
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<tr>
<td>FBG</td>
<td>Fasting Blood Glucose</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>GIP</td>
<td>Glucose-dependent Insulinotropic Peptide</td>
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<td>GLP-1</td>
<td>Glucagon-Like Peptide-1</td>
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<tr>
<td>GLP-1 RAs</td>
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<td>GLP-1 Rs</td>
<td>Glucagon-Like Peptide-1 Receptors</td>
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<tr>
<td>HbA1c</td>
<td>Glycated Haemoglobin</td>
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<tr>
<td>HOMA-B</td>
<td>Homeostasis Model Assessment- Beta cell Function</td>
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<td>HOMA-IR</td>
<td>Homeostasis Model Assessment-Insulin Resistance</td>
</tr>
<tr>
<td>IDet</td>
<td>Insulin Detemir</td>
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<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
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<tr>
<td>LEAD</td>
<td>Liraglutide Effect and Action in Diabetes</td>
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<tr>
<td>OHAs</td>
<td>Oral Hypoglycaemic Agents</td>
</tr>
<tr>
<td>PPBG</td>
<td>Post Prandial Blood Glucose</td>
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<tr>
<td>PPTG</td>
<td>Post Prandial Triglyceride</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<tr>
<td>SU</td>
<td>Sulphonylurea</td>
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<tr>
<td>T1DM</td>
<td>Type 1 Diabetes Mellitus</td>
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<td>T2DM</td>
<td>Type 2 Diabetes Mellitus</td>
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<tr>
<td>TZD</td>
<td>Thiazolidinedione</td>
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<tr>
<td>VLDL</td>
<td>Very Low Density Lipoprotein</td>
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Keynote Lecture: Is There a New Treatment Paradigm Evolving for Type 2 Diabetes?

Prof. (Dr.) V. Mohan

Dr. Viswanathan Mohan is the Chairman and Chief of Diabetology at Dr. Mohan’s Diabetes Specialities Centre which is a WHO collaborating centre for non-communicable diseases prevention and control and an IDF centre of education. He is also President and Director of the Madras Diabetes Research Foundation. Dr. Mohan has received numerous awards and fellowships. This includes the Padma Shri National Award by the Government of India for his accomplishments in the field of diabetology, Dr. B.C. Roy Award from the Medical Council of India and the Basanti Devi Amir Chand Prize from the Indian Council of Medical Research. Dr. Mohan has published over 760 papers including 130 chapters in text books.

Beta cell function in “early diabetes”

Conventionally, diabetes treatment is aimed at glycaemic control with lifestyle modification and monotherapy with oral hypoglycaemic agents (OHAs) and moved on to combinations of OHAs. When all combinations fail, insulin is initiated. Studies from the last decade found the importance of beta cell function in the progression of type 2 diabetes mellitus (T2DM). During the natural history of T2DM, beta cell function declines by almost 50% before the impaired glucose tolerance stage (50% loss) and this may extend to nearly 80% in pre-diabetes stage (Figure 1). Therefore, a shift in the treatment paradigm for T2DM to correct insulin resistance and preserve the beta cell function is required. An experimental study has clearly shown that beta cell function declines rapidly in Asian Indian patients with pre-diabetes as evident with decreased insulin secretion (measured as disposition index) and concomitant increase in insulin resistance (measured as Homeostasis Model of Assessment - Insulin Resistance, HOMA-IR). In true sense the presumed ‘Early Diabetes’ is already a ‘Late’ stage in the natural history of diabetes mellitus and needs promising therapies to preserve beta cell function.

How early should insulin be started?

Over a period of time, the glycated haemoglobin (HbA1c) level rises gradually in patients with T2DM, termed as ‘glycaemic burden’ and if this condition is left untreated for long, the result would be higher unavoidable burden. Therefore, to lower the unavoidable burden, starting therapy early after diagnosis and frequent check-up of blood sugar levels is needed to lower the impact of diabetic complications. It is the only way to keep blood sugar in good control and circumvent the unavoidable burden. The ICMR-INDIAB study, one of the largest epidemiological study on diabetes in India, estimated about 62.4 million people with diabetes and 77.2 million people with pre-diabetes. There are several diabetes related complications that affect them; nephropathy is the major concern with a prevalence of 17 million people. It is necessary that the huge number of people with pre-diabetes and diabetes are treated effectively at early stage to minimize the unavoidable burden.

Insulin therapy can be started at multiple stages of diabetes. Studies have shown that beta cell function can be preserved with early insulin therapy in T2DM. In a comparative study, patients newly diagnosed with diabetes were treated for 4 weeks with different agents: continuous subcutaneous (s.c.) insulin infusion (0.68 units/kg), multiple daily injections (0.74 units/kg) and oral agents (gliclazide 160 mg + metformin 1,500 mg). It was observed that patients given s.c. insulin infusion had significantly higher change in acute insulin response compared with other treatments. After 1 year follow-up, about 50% decline in insulin response was noted in patients given oral agents but the response was almost preserved in patients given s.c. insulin infusion, suggesting maximum benefit with insulin therapy early in diabetes.

Case study 1

Background

A 53-year-old person with 8 months duration of diabetes and central obesity presented with baseline fasting blood glucose (FBG), post prandial blood glucose (PPBG) and HbA1c of 217 mg/dL, 344 mg/dL and 11.4%, respectively. The patient was on treatment with gliclazide 80 mg b.i.d.
Intervention
The patient was started on insulin along with sitagliptin, gliclazide and metformin. After 1 month of combination therapy, insulin was stopped and OHAs were continued.

Results
A marked decrease in HbA1c (from 11.4 to 7.1%) and improvement in beta cell function was observed. Fasting C-peptide levels increased from 0.9 to 1.4 pmol/mL and stimulated C-peptide levels increased from 1.6 to 4.2 pmol/mL.

Conclusion
Insulin therapy for four weeks was effective in glycaemic control and preserving beta cell function, probably due to insulin initiation or continuation of sitagliptin or glycaemic control. Similarly, beta cell function was found to be preserved in long-term studies in newly diagnosed patients (HbA1c ≥ 8.5%) given intensive insulin therapy for 4 weeks, a probable treatment strategy for modifying the natural history of diabetes.8, 9

Alternative therapies to preserve beta cell function
GLP-1 based therapies
In addition to insulin therapy, sulphonylurea (SU) and thiazolidinedione (TZD) class of drugs are also available for treatment of T2DM. Although studies have shown the positive effect of these drugs on glycaemic control, over years their effect goes down.1 Incretin-therapy based with glucagon-like peptide-1 receptor agonists (GLP-1 RAs), (exenatide, liraglutide) and dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin) are potential lead candidates for treatment of T2DM. The GLP-1 RAs have multiple positive effects on beta cells including increasing beta cell function, first phase insulin secretion and maximum insulin secretory capacity. In addition, the beta cell mass is preserved by decreasing proinsulin:insulin ratio, glucagon secretion and beta cell apoptosis.3-5,6,7

One of the foremost reasons for preference of GLP-1 RAs in treatment of T2DM is the potential to induce weight loss. In an experimental study, treatment with liraglutide caused a significant reduction in the HbA1c with tremendous reduction in body weight (Data on file).

Case study 1
Back ground
A 39-year-old obese person with 10 years duration of diabetes with baseline HbA1c and body weight of 11.2% and 105.5 kg, respectively was on glicazide, metformin 500 mg BD and insulin (134 units in 3 divided doses).

Intervention
The patient was started on 0.65 mg s.c. liraglutide o.d. in the morning and i.v. Lantus o.d. (32 units) at bedtime with same doses of OHA.

Results
A marked reduction in HbA1c (from 11.2 to 7.4%) and body weight (from 105.5 to 90 kg) was observed.

Conclusion
Liraglutide treatment was effective in glycaemic control and weight reduction.

DPP-4 inhibitor based therapies
Treatment with different drugs of DPP-4 inhibitors class have also been reported to cause a significant reduction in HbA1c (0.5% to 0.8%) and being weight neutral in patients with T2DM from western countries.10-15. Reduction in HbA1c observed with sitagliptin was much higher (~1.36%) in Asian subjects with T2DM (from India and Korea) with baseline HBA1c of 8.74%, probably due to genetic makeup or insulin secretory defect.16, 17. Additionally, GLP-1 analogues and DPP-4 inhibitors also reduces beta cell death, alpha cell proliferation, blood pressure and cardiovascular (CV) risks.18-20. A new treatment algorithm for patients with T2DM has been suggested in Figure 2.

Summary
Combating T2DM requires multiple drugs used in combination to correct multiple pathophysiological defects. Since beta cell function(s) declines over time with disease progression, therapy must be started early not only to maintain glycaemic control but also to restore the beta cell function. Early insulin therapy has been shown to preserve beta cell function and correct glycaemic index for a longer period of time. Although incretin based therapies including GLP-1 analogues and DPP-4 inhibitors offers new avenues for therapy but long term studies are warranted.

Figure 2: New suggested treatment algorithm for the treatment of type 2 diabetes

Lifestyle + metformin
If patient can afford
If patient cannot afford, add low dose SU
If obese, add
liraglutide
If non-obese, add
DPP-4 inhibitor
If uncontrolled, consider insulin

HbA1c>7%
References


Session 1

Unravelling the Science of Incretin Biology
GLP-1 and the Beta Cell: A Long Lasting Relationship!

Dr. Ajay Kumar
Dr. Ajay Kumar is a consultant physician and diabetologist, and Director, Diabetes Care and Research Centre, Patna. In his illustrious career, Dr. Ajay Kumar has been an integral part of numerous clinical trials that have involved many of the recently approved drugs including liraglutide. He also holds a position at the University of Newcastle; Australia, where he teaches post graduate diabetologists using a problem-based learning method. He is a widely published author and also serves on the national advisory board of the prestigious Journal of the Association of Physicians of India. Dr. Kumar also has the distinction of delivering the Dr. M. Vishwanathan Oration at the annual conference of the RSSDI in 2011.

Introduction
In T2DM, pancreatic beta cells fail to produce sufficient insulin to meet physiological requirements, in part because of an acquired decrease in beta cell mass and function. In the aetiology of T2DM, decline of beta cell function is an important step, which might lead to further complications. With a change in the islet morphology, beta cell causes decreased insulin secretion and inappropriate glucagon secretion. Inadequate beta cell mass leads to hyperglycaemia which further creates a cascade of events culminating in loss of beta cell function. One of the major factors leading to decrease in beta cell mass in people with diabetes is increased apoptosis, even when other factors like new islet formation and beta cell replication seems to be normal.

Beta cell mass is increased in the pancreas by replication and differentiation from stem cells. Regeneration of beta cell mass can restore pulsatile insulin secretion and suppress glucagon secretion which in turn can reduce hepatic glucose output and insulin resistance in peripheral tissues. Therapeutic approaches designed to improve islet regeneration and arrest apoptosis could therefore be a significant step in the management of T2DM. Peptides, including GLP-1/exendin-4 have been reported to stimulate the regeneration of beta cells through differentiation and replication.

Beta cell and loss of incretin effect in T2DM
T2DM is characterised by a decreased beta cell mass, impaired insulin secretion in response to various stimuli, along with a variable extent of insulin resistance. GLP-1 and glucose-dependent insulinoctopic peptide (GIP) cause the incretin effect which accounts for a large part (two thirds) of insulin response to a meal. Studies have shown that the diminished incretin effect in patients with T2DM is correlated with increased FBG levels, a correlation which appears to be linked to the reduced maximum secretory capacity of beta cells and hyperglycaemia.

In addition, reduced expression of GIP receptors might cause decrease in GLP-1 secretion and hyperglycaemia, which may diminish the incretin effect in T2DM. GLP-1 not only stimulates insulin secretion in a glucose-dependent manner, but also induces a favourable beta cell gene expression profile, promoting restoration of glucose-sensing mechanisms and beta cell survival. A second set of actions of GLP-1 can produce changes in gene expression, which promote cellular programs favouring enhancement of insulin biosynthesis, cell proliferation, and resistance to apoptosis.

Effect of GLP-1 on insulin secretion
Among the incretin molecules, GLP-1 infusion (1 pmol) but not GIP (16 pmol) effectively increased both the early and late phases of insulin secretion (Figure 1). However, exogenous GLP-1 infusion at pharmacological levels restores insulin secretion in patients with T2DM. It is important to note that DPP-4 inhibitor therapy could also be a suitable therapeutic option in Asian population with T2DM. It was observed that maintenance of pharmacological concentration of GLP-1 for 24 hour duration was effective in maintaining glycaemic control. GLP-1 is known to induce glucose-dependent increase in insulin secretion and decrease in glucagon secretion, which is desirable in clinical practice to avoid hypoglycaemia in patients.

Studies have demonstrated that GLP-1 not only improves the
hypoglycaemia. If this can be achieved, even substantially if not only to achieve glycaemic control but also to restore the beta cell function. There is a need of medication at every stage not sustained improvement of these markers and its superiority over placebo and against a combination of oral hypoglycaemic agents (OHAs). Treatment with GLP-1 showed improvement in the first-phase insulin secretion as well as maximal beta cell secretory capacity (Figure 2). GLP-1 restored beta cell glucose sensitivity and effectively suppressed glucagon secretion, although not in hypoglycaemic conditions.

**Effect of incretin-based therapies on beta cell function**

Studies have shown the positive effect of GLP-1 RAs in particular liraglutide, on beta cell function in patients with T2DM. It showed significant improvement in HOMA beta cell function against placebo and against a combination of oral hypoglycaemic agents (OHAs). Treatment with GLP-1 showed improvement in the first-phase insulin secretion as well as maximal beta cell secretory capacity (Figure 2). GLP-1 restored beta cell glucose sensitivity and effectively suppressed glucagon secretion, although not in hypoglycaemic conditions. Additionally, 1 week of liraglutide treatment showed improvement in markers of beta cell function, % HOMA-B and proinsulin:insulin ratio against placebo. Liraglutide Effect and Action in Diabetes-6 (LEAD-6) trial (extension phase) showed sustained improvement of these markers and its superiority over exenatide in restoring beta cell function.

**Conclusion**

The aetiology of T2DM is marked by the loss of beta cell mass and function. There is a need of medication at every stage not only to achieve glycaemic control but also to restore the beta cell mass and function, to avoid cardiovascular and other long-term complications and side-effects like weight gain and hypoglycaemia. If this can be achieved, even substantially if not completely, it will redefine current treatment paradigms.


Dr. S. Venkataraman

Dr. Venkataraman is an eminent senior consultant diabetologist and physician at Apollo Hospitals, Chennai. In the past he has been the Professor of Diabetology at Madurai Medical College and Madras Medical College and a consultant diabetologist at the Rajaji Government Hospital, Madurai. Having rich experience in this field for around 35 years, he has been a postgraduate teacher in diabetology for 28 years. His key research interests are in the field of diabetes in pregnancy and metabolic syndrome. He has co-authored chapters in diabetes and is also a recipient of the IDF Award (1991, Washington) for his works on gestational diabetes mellitus.

Direct actions of GLP-1 on heart and other organs

Glucagon-like peptide-1 (GLP-1) is a gut-derived incretin hormone, which possesses several physiological properties that make it (and its analogues) a subject of intense investigation as a potential treatment for diabetes mellitus. GLP-1 acts directly on the pancreas, heart, stomach and brain and indirectly on liver and muscle. In addition to correction in physiologic glucose values, GLP-1 and its analogues offer beneficial effect on other comorbid conditions like hypertension, dyslipidaemia and vascular complications. GLP-1 increases insulin secretion, beta cell proliferation and decreases beta cell apoptosis and glucagon secretion in the islets of pancreas and in turn promotes insulin sensitivity in the muscles. It also increases cardio protection and cardiac output in the heart, inhibits acid secretion and reduces gastric emptying in the stomach, increases neuro protection, decreases food intake by increasing satiety in the brain, and decreases glucose production in the liver.

Indirect actions of GLP-1 on heart

Apart from its direct actions on the cardiomyocyte, GLP-1 may also influence cardiac function indirectly through its actions on pancreatic islet cells (Figure 1). Increase in insulin secretion and parallel decrease in glucagon secretion enhances glucose utilization and decreases dependency of cardiomyocytes on free fatty acids, thereby increasing short-term and long-term cardiac function.

Will incretin-based therapies modify the rates of macrovascular events?

GLP-1 appears to exert effects on many tissues via the GLP-1 receptor (GLP-1 R), which is expressed not only in the pancreatic islets, but also in intestine, endothelial cells, brain and smooth muscle cells. GLP-1 increases post-prandial insulin in a glucose-dependent manner which helps in physiological clearance of the chylomicron particles in the vascular endothelium. It decreases CD36 and reduces inflammation in peripheral macrophages. Since GLP-1 Rs are present in the endothelium, endothelial function is favourably altered by
increased production of reactive oxygen species. Consequently, it halts the progression of atherosclerotic plaque formation, thereby decreasing macrovascular complications. The evidence for GLP-1 action in cardiomyocytes, endomyocardium and vascular endothelium comes from the expression of GLP-1 Rs in these cells. In addition, GLP-1 and GLP-1 RAs are known to decrease systolic blood pressure (SBP), improve endothelial function, cardiac function and improve biomarkers of CV risk. Tight BP control has been demonstrated to significantly reduce the risk of CV events, death from CV disease by 18% and all-cause mortality. In a Phase II trial, liraglutide treatment (1.9 mg/day) for 14 weeks significantly reduced SBP level (by about 8 mmHg) than placebo regardless of the dose and decreased diastolic BP. In another study, treatment with liraglutide (for 3 weeks) significantly reduced SBP compared to placebo and the effect was sustained over a 26-week period. The same trend for liraglutide was further confirmed against all the regimens investigated in LEAD 1-6 trials (Figure 3). The reduction in SBP with liraglutide was greater in T2DM patients with higher baseline SBP and independent of concomitant antihypertensives.

Lowering of systolic blood pressure

Tight BP control has been demonstrated to significantly reduce the risk of CV events, death from CV disease by 18% and all-cause mortality. In a Phase II trial, liraglutide treatment (1.9 mg/day) for 14 weeks significantly reduced SBP level (by about 8 mmHg) than placebo regardless of the dose and decreased diastolic BP. In another study, treatment with liraglutide (for 3 weeks) significantly reduced SBP compared to placebo and the effect was sustained over a 26-week period. The same trend for liraglutide was further confirmed against all the regimens investigated in LEAD 1-6 trials (Figure 3). The reduction in SBP with liraglutide was greater in T2DM patients with higher baseline SBP and independent of concomitant antihypertensives.
understood. It has been postulated that GLP-1 RAs promote sodium excretion and increase urine volume in normal and obese patients\(^5\)\(^,\)\(^6\) which requires further investigation. A dose-dependent, biphasic action of native GLP-1 on BP was seen in animal models\(^7\). Although, GLP-1 increases diuresis in healthy and obese subjects, sodium excretion is seen in obese men\(^8\). In mice model system lacking GLP-1 Rs, the natriuretic response to exendin-4 was found to be blunted. Overall, GLP-1 induces basal\(^9\) and enhances acetylcholine-mediated vasodilation\(^10\) and improves endothelial function in patients with T2DM and coronary artery disease\(^1\).

**Cardio-protection and effects on CV biomarkers**

In a rat model of ischaemia, GLP-1 infusion was shown to limit the infarct size by activation of multiple pro-survival kinases whereas the protection was abolished by GLP-1 RA\(^1\). In a mouse model of myocardial infarction, a 7-day course of liraglutide (200 µg/kg b.i.d.) improved survival compared to placebo (80% vs. 40%, \(p=0.0001\)), reduced infarct size (21% vs. 29%, \(p=0.02\)), improved cardiac output\(^11\) and reversed cardiac dysfunction in a model of obesity\(^12\). Overall GLP-1 RA may contribute to Cardio protection by inhibiting fibrosis and inflammation\(^13\). In addition, GLP-1 RA therapy normalizes signalling, improves glucose, and lipid homeostasis as well as ER homeostasis\(^14\). Liraglutide use was also associated with improvements in CV biomarkers such as high-sensitivity C-reactive protein, brain natriuretic peptide, and plasminogen activator inhibitor-1\(^15\).

Liraglutide therapy may reduce CV risk through reduction in BMI and waist circumference with greater reduction in patients with high baseline values\(^16\).

**Evaluation of cardiovascular outcomes**

**Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)**

**Design**

A large multinational trial was designed to investigate the long-term effect of once daily liraglutide on heart disease and its risk factors in people with T2DM. Patients with high cardiovascular risk profile and uncontrolled hypertension are on standard care, with HbA1c<7% were randomised to liraglutide or placebo after a 2 week run-in period.

**Aim**

The primary endpoint of the study is a composite cardiovascular outcome to assess the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke from the time of randomisation. The secondary endpoints include time from randomisation to all cause death, time from randomization to first occurrence of an expanded composite cardiovascular outcome (primary endpoint + revascularisation, unstable angina or hospitalisation for chronic heart), and time from randomisation to each individual component of expanded composite cardiovascular outcome.

Subjects will be assessed frequently during the first six months of trial and every 6 months thereafter for 4.5 years. The study involves around 10,000 patients with T2DM from 30 countries. It started on 1st September 2010 and will run for approximately five years in 425 sites worldwide.

**Summary**

GLP-1-based therapies definitely hold promise of offering an edge over other resident anti-diabetic therapies in terms of CV protection by conferring actual CV benefits. Primarily, GLP-1 RA demonstrates its mechanistic action by controlling reduction of PPTG. The extent to which reduction in PPTG can modify the risk of diabetic complications remains unclear. GLP-1-based therapies also impart SBP control, promote sodium excretion and have positive impact on CV markers, which help them to confer actual CV protection. Results of on-going LEADER trial will not only determine the place of incretin-based therapies for CV benefits, but will also clarify many issues associated with long-term safety of GLP-1 analogues.

**References**


37. Zinman B, Colaguri S, Madisbal S, et al. The Human GLP-1 Analog, Liraglutide, Improves BMI and Waist Circumference in Patients with Type 2 Diabetes: Meta-Analysis of Six Phase 3 Trials. Presented at the 70th Scientific sessions (ADA) 2010, Orlando, USA.
Combining GLP-1 Receptor Agonists with Insulin: Therapeutic Rationales and Clinical Findings

Prof. J. Hans DeVries

Prof. J. Hans DeVries is lecturer and consultant in internal medicine and endocrinology at the academic medical centre at the University of Amsterdam, Netherlands. He obtained board licenses in internal medicine (1997) and endocrinology (2001) at the VU University Medical Centre, Amsterdam. He actively publishes in the field of clinical diabetes with now more than 130 publications in PubMed. He is a frequently invited speaker at international diabetes meetings, an editorial board member of Current Diabetes Reviews and Diabetes Technology & Therapeutics and a member of the clinical advisory board of the Journal of Diabetes Science and Technology. His research interests are insulin and GLP-1 therapies, continuous glucose monitoring, the artificial pancreas, glucose variability and glycaemia in hospitalized patients. He is scientific coordinator of AP@home and PCDIAB, consortia attempting to close the loop, funded under the Framework Program 7 of the European Commission.

Introduction

Diabetes mellitus is a multifactorial disease characterised by a progressive increase of glucose levels with parallel decline in beta cell mass and function. Beneficial effects of insulin in the management of diabetes have been shown in Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications trials. However, their follow-up trials have shown that insulin treatment is associated with increased weight gain and hypoglycaemia. Hence, there is an urgent need to design appropriate and timely anti-diabetic strategies to balance the benefits of insulin against its side effects.

GLP-1 RAs and insulin in T2DM

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) increase insulin release and suppress glucagon secretion in a glucose-dependent manner from the pancreatic islets, thus conferring glycaemic control with maintenance of residual beta cell function and low incidence of hypoglycaemia. GLP-1 RAs, unlike insulin therapy promote weight loss, which is an important concern in patients with T2DM. Treatment with insulin shows better efficacy in terms of FBG control whereas therapy with GLP-1 RAs control PPBG. However, the durability of their effectiveness is unknown and when compared with insulin, the anti-hyperglycaemic efficacy is limited. Therefore a combination of GLP-1 RA and insulin might offer complementary benefits for optimal glucose control, while overcoming the adverse effects typically associated with insulin treatment as suggested by the latest American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) position statement.

Insulin add-on to GLP-1 RAs in T2DM

Aim

To evaluate a novel treatment intensification sequence of addition of basal insulin to GLP-1 RA in patients with uncontrolled T2DM (HbA1c ≥7%) on metformin±SU.

Methods

Patients with sub-optimal glycaemic control on metformin±SU were given liraglutide 1.8 mg/day with discontinuation of SU in a run-in period of 12 weeks. Subsequently, those with HbA1c ≥7% were randomised to 26 weeks open-label addition of insulin detemir (IDet) to metformin + liraglutide or continuation without IDet and an extended phase of 26 weeks. Patients with HbA1c<7% after run-in period were also given 1.8 mg liraglutide with metformin (Observational group).

Results

After completing the run-in period (base line HbA1c=7.4%), at week 52, a significant reduction (p<0.0001) in HbA1c (0.5%) was observed in patients treated with liraglutide+IDet, whereas patients treated without IDet maintained HbA1c levels (Figure 1). Mean body weight decreased by more than 3 kg during the run-in period, probably due to the discontinuation of SU. Body weight further decreased significantly (p=0.04) in patients given liraglutide alone (1.02 kg), than patients receiving liraglutide+IDet (0.05 kg) at week 52 (Figure 2).

Figure 1: Addition of insulin detemir to liraglutide: mean HbA1c by week

Aim

To evaluate a novel treatment intensification sequence of addition of basal insulin to GLP-1 RA in patients with uncontrolled T2DM (HbA1c ≥7%) on metformin±SU.
The incidence of minor hypoglycaemia rates (episodes per patient year) over 52 weeks were minimal in patients receiving liraglutide alone compared with liraglutide+IDet (0.03 and 0.23, respectively). Addition of IDet to liraglutide regimen in this study showed at least 7 times fewer hypoglycaemic episodes per patient year than studies on addition of IDet with any other OHAs (1.6 to 3.67 episodes per patient year).

**Conclusion**

Addition of basal insulin to liraglutide therapy was well tolerated with good glycaemic control, weight reduction and an added advantage of very low hypoglycaemic episodes.

### GLP-1 RA add-on to insulin in T2DM

The beneficial effect of adding GLP-1 RA in patients failing to achieve optimal glycaemic control with insulin therapy has been demonstrated by Buse et al. 2011. In this study exenatide (10 µg, b.i.d.) was combined with insulin glargine (IGlar, given at minimum 20 U/day) and compared with placebo for 30 weeks and IGlar doses were titrated to achieve FBG<5.6 mmol/L. In another study (HARMONY-6), patients with poor glycaemic control on basal insulin+OHAs albiglutide (30 mg, o.w.) or insulin lispro (b.i.d.) was combined and administered with IGlar for 26 weeks. Additionally, in a 24 weeks study (GetGoal-L), s.c. lixisenatide (10-20 µg, o.d.) was combined with basal insulin (±metformin) and compared with placebo for 24 weeks in patients with insufficient glycaemic control with basal insulin (≥30 U/day). In all these studies, a marked decrease in HbA1c, body weight from baseline and hypoglycaemic episodes were observed indicating the positive effect of adding GLP-1 RA to existing insulin treatment.

Among the different GLP-1 RA molecules, treatment with exenatide showed more HbA1c lowering effects (-1.74% from baseline) compared to others. Very little benefit was observed with lixisenatide. Only 0.4% HbA1c reduction was observed in the placebo group, probably due to non-titration of insulin dose during trial. In HARMONY-6 study, albiglutide performed better than insulin lispro (given 3 shots a day, during meal time) in HbA1c lowering. The observed reduction in body weight and fewer hypoglycaemic rates in these trials further strengthened the case for the addition of GLP-1 RA in patients failing on insulin. Common side effects including nausea and vomiting were observed in smaller proportion of patients in all these studies.

**Conclusion**

The current ADA/EASD position statement recommends treatment intensification in patients failing to achieve HbA1c <7% with two-drug combination therapy including addition of insulin to GLP-1 RA plus metformin (Case 1) and addition of GLP-1 RA to insulin plus metformin (Case 2). In Case 1, a significant reduction in HbA1C, no increase in body weight and a low risk of hypoglycaemia was observed. Meanwhile in Case 2, a significant reduction in HbA1C and body weight was observed with no increased risk of hypoglycaemia.

### GLP-1 RA add-on to insulin in type 1 diabetes

Several investigators have demonstrated the effect of adding GLP-1 RA to existing insulin treatment in type 1 diabetes on glycaemic control. In a study GLP-1 (1.2 pmol/kg/min), saline, or GLP-1 RA, exendin 9-39 (300 pmol/kg/min) were administered to patients with type 1 diabetes mellitus (T1DM) with (T1D+) or without residual beta cell function (T1D-), and healthy controls. Infusion of GLP-1 before meals resulted in normalization of PPBG and glucagon levels as well as reduction of peak plasma glucose (by 45%) levels although meal time insulin levels were reduced by 50%. Slowing of gastric emptying (measured by delay in clearance of paracetamol) was observed in all groups. In another study, treatment of patients with T1DM using liraglutide for 1 week corrected glycaemic parameters with decrease in mean FBG (from 130±10 to 110±8 mg/dL, p<0.01) and overall blood glucose (137.5±20 to 115±12 mg/dL, p<0.01) levels. The decrease in blood glucose levels was observed with decreasing basal insulin (24.5±6 to 16.5±6 units, p<0.01) and bolus insulin (from 22.5±4 to 15.5±4 U, p<0.01) during the 1 week of trial.

The other study conducted in patients with T1DM using liraglutide for 4 weeks, exhibited significant lowering of HbA1c from the baseline in patients with and without residual beta cell function. This lowering effect was more pronounced in patients with T1D- (-0.47%) as compared to patients with T1D+ (-0.26%), probably due to the very low levels of activity of endogenous insulin in T1D+ group. Additionally, a significant reduction in insulin dose requirement (10-15 U/patient) and body weight (2-3 kg) was observed in patients with T1DM from both groups taking liraglutide treatment. Investigating these results in a large cohort of patients is necessary to establish better treatment strategies in patients with T1DM because of limited options available currently.

**Conclusion**

Data from several clinical studies support therapeutic potential of GLP-1 RA-insulin combination therapy, showing beneficial effects on glycaemic control, body weight with low incidence of hypoglycaemia. In T2DM, addition of insulin to GLP-1 RA is preferred due to lower hypoglycaemic episodes. The addition of GLP-1 RA to insulin seems promising in patients with T1DM.
References


Session 2

New Approaches to Old Challenges: Discovering the Role of Incretin Mimetics
GLP-1 Receptor Agonists in Type 2 Diabetes: The Clinician’s View

Dr. Ambrish Mithal

Dr. Ambrish Mithal is presently the Chairman and Head of Endocrinology and Diabetes division at Medanta, the Medicity, Gurgaon where he has established one of India’s premier diabetes and endocrinology centres. Dr. Mithal was the first DM in endocrinology from the All India Institute of Medical Sciences (1987), and subsequently served on the faculty at Sanjay Gandhi PGI, Lucknow (1988-1998) where he was instrumental in setting up the Department of Endocrinology. Dr. Mithal is immediate past president, Endocrine Society of India and the chairperson, Bone and Joint Decade-India. He is the founder, past president and currently chief advisor to the Indian Society for Bone and Mineral Research.

Introduction

The increased prevalence of T2DM warrants the appropriate use of therapeutic options and appropriate treatment intensification to ensure proper management of T2DM. Current treatment algorithms recommend metformin as the first-line agent, while advocating the addition of other OHAs or insulin to achieve the recommended levels of glycaemic control. In recent years, incretin-based therapies have gained attention in the context of being a component of initial combination therapy, given their potential beneficial effects on beta cell function with lowered risk of weight gain and hypoglycaemia. Exenatide, the first approved human GLP-1 analogue drug, has been extensively studied across all stages of T2DM treatment continuum.

Clinical experience with exenatide in obese North Indian patients with T2DM

Clinical use of exenatide has shown significant improvement in glycaemic control parameters like HbA1c (from 8.8 to 7.2%), FBG (from 177.6 to 126.0 mg/dL), PPBG (from 246.8 to 143.3%) and weight loss (from 97.7 to 89.3 kg) in obese patients with T2DM.

LEAD Studies: Liraglutide in the management of T2DM

Liraglutide (Victoza®), another drug from GLP-1 RA class was also extensively studied across the T2DM treatment continuum in LEAD 1-6 trials (Figure 1) and was approved for human use. Liraglutide is resistant to DPP-4 enzyme degradation, has long plasma half-life (t½=13 hours) and helps prevent beta cell apoptosis. The LEAD trials demonstrated that treatment with liraglutide (1.2 mg and/or 1.8 mg) significantly reduced HbA1c, from baseline over comparator drugs in patients with T2DM. In addition, greater reduction in body weight was observed in patients with T2DM taking liraglutide 1.8 mg than patients given insulin glargine or placebo. The quantum of reduction in body weight was greater in patients with higher BMI. Also, liraglutide can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy with no need of dose adjustments and self-monitoring of blood glucose.

Medanta Medicity - Who is treated with liraglutide?

With these benefits, liraglutide was being prescribed to patients attending the Medanta, the Medicity in Gurgaon with obesity and uncontrolled hyperglycaemia (preferably postprandial), to patients in whom prior use of DPP-4 inhibitors or current use of basal insulin was not contraindicated, able to afford and willing to take treatment after understanding the possible gastro intestinal (GI) side effects.

Liraglutide: Initial Medanta Medicity experience

Aim

To assess the efficacy and safety of liraglutide o.d. in patients with obesity and uncontrolled hyperglycaemia on multiple OHAs and/or insulin shots, attending the Medanta, the Medicity.

Intervention

Liraglutide o.d. was prescribed to all eligible patients (N=196) for 3 months with or without other medications.
Results
After 12 weeks of follow-up, significant improvement in mean HbA1c (from 9.2 to 7.7%, p<0.001), FBG (from 173.7 to 115.5 mg/dL, p<0.001), PPBG (from 252.5 to 177.1 mg/dL, p=0.007) and weight loss (from 100.1 to 96.0 kg, p<0.001) was observed. The incidence of adverse events was low with nausea, burping and belching being more frequent (n=17). Hypoglycaemia was reported in five patients on SU or insulin.

Conclusion
Treatment with liraglutide o.d. was effective in reducing the glycaemic index and body weight and was well tolerated with acceptable hypoglycaemic episodes.

In addition, post-marketing surveillance data of liraglutide from India demonstrated the efficacy and safety of once daily liraglutide in glycaemic and extra glycaemic parameters.

Case study 1
Background
A 38-year-old male (who had T2DM for 3 years prior to the current visit) with body weight of 97 kg and a high BMI was presented. The patient was on metformin 1 g b.i.d. plus sitagliptin 100 mg. The baseline HbA1c, FBG and PPBG were 8.2%, 169 mg/dL and 216 mg/dL, respectively.

Question
Participants’ response on choice of treatment a) advice regarding lifestyle modification alone, b) addition of SU, c) addition of glitazone, and d) addition of SU was recorded.

Intervention
In addition to the advice on diet/exercise, subcutaneous liraglutide 0.6 mg, daily for 1 week and subsequently 1.2 mg was advised apart from the current dose of metformin; sitagliptin was discontinued.

Results
At 6 months, a significant reduction in HbA1c (8.2% to 6.8 %), FBG (169 to 121 mg/dL), PPBG (216 to 157 mg/dL) and weight (97 to 89 kg) were observed without notable hypoglycaemia.

Conclusion
Liraglutide was effective in correcting HbA1c, BMI and weight.

Case study 2
Background
A 49-year-old obese woman presented with a 7-year long history of diabetes with hypertension and dyslipidaemia. The patient was on 100 mg sitagliptin daily, 6 (4+2) mg glimepiride daily and 1 g metformin b.i.d. The baseline weight, BMI, FBG, PPBG and HbA1c were 89 kg, 33 kg/m², 190 mg/dL, 270 mg/dL and 10.2%, respectively. Patient was leading sedentary lifestyle and was not willing to take insulin.

Question
Participants’ response on choice of treatment a) lifestyle modification alone (meal timings, exercise), b) modify the dose of SU, c) addition of glitazone, and d) convince her about insulin was recorded.

Intervention
Counselling on lifestyle modification, addition of subcutaneous liraglutide 0.6 mg, daily for 1 week and subsequently 1.2 mg, reduction of glimepiride to 4 mg daily and discontinuation of sitagliptin was prescribed.

Results
At 6 months, significant decline in FBG (from 190 to 121 mg/dL), PPBG (from 270 to 157 mg/dL) and HbA1c (from 10.2...
Conclusion
Liraglutide at 6 months and 1 year proved effective in correcting glycaemic parameters and in decreasing weight.

Case study 3

Background
A 54-year-old male presented with a 15-year long diabetes history, hypertension and dyslipidaemia. The patient was on 4 mg glimepiride b.i.d., 1 g metformin b.i.d. plus glargine (20 units daily). The baseline weight, BMI and HbA1c were 110 kg, 42 kg/m² and 8.6%, respectively. He was concerned about his cardiac problems and was suggested by his doctors to lose weight and avoid hypoglycaemia.

Question
Participants’ response on choice of treatment a) intensify insulin therapy b) add DPP-4 inhibitor c) addition of glitazone and d) bariatric surgery was recorded.

Intervention
Since patient was unwilling to undergo bariatric surgery, continuation of metformin, addition of subcutaneous liraglutide 0.6 mg, daily for 1 week and subsequently to 1.2 mg, increase of glargine by 4 units and reduction of glimepiride to 4 mg o.d. was prescribed.

Results
At 1 year decline in FBPG (from 140 to 122 mg/dL), PPBG (from 240 to 127) and HbA1c (from 8.6 to 6.9%) was observed. A 11 kg drop in weight was also observed.

Conclusion
Liraglutide was effective in correcting the glycaemic inconsistencies and reduced weight.

Case study 4

Background
A 52-year-old male presented with 16-year long T2DM history. The patient was on 3 mg glimepiride b.i.d., 15 mg pioglitazone daily, 1 g metformin b.i.d. plus premixed insulin. The patient was obese with pedal oedema and his baseline weight, BMI and HbA1c were 89 kg, 31 kg/m², and 9.2%, respectively.

Question
Participants’ response on choice of treatment a) increase dose of glitazone b) add DPP-4 inhibitor, c) increase premix dose and d) basal-bolus regimen was recorded.

Intervention
In addition to the advice on diet/exercise, continuation of metformin, adjustment of insulin dose, addition of subcutaneous liraglutide 0.6 mg, daily for 1 week and subsequently to 1.2 mg was prescribed. Following liraglutide addition, vildagliptin was discontinued.

Results
At 6 months, decline in HbA1c (from 10.5% to 7.3 %) along with a 2-kg drop in weight was observed.

Conclusion
With liraglutide, better glycaemic control and reduction in body weight was observed probably due to reduction in bolus insulin and shift to basal insulin + liraglutide.

Key clinical points from these cases
From the case studies it can be noted that liraglutide can be started at any stage of T2DM treatment continuum. The GI side effects are common in initial stages of treatment. These can be managed with slow increase in liraglutide dose, or withdrawal and reintroduction of liraglutide, or with proton pump inhibitors and prokinetics. With addition of liraglutide, maximum weight loss was observed in patients taking only metformin and comparatively less in those taking insulin or SU.

Summary
From the clinician’s perspective, long-term satisfaction was observed in patients using liraglutide. Apart from glycaemic control, the major motivation for use of liraglutide was weight loss. However, since GLP-1 RAs limits food intake, some patients experience nausea. Choosing the right patient and counselling are key to starting liraglutide therapy in patients with T2DM.
References


Achieving a Composite Outcome with Liraglutide: Clinical Insights from an Indian Experience

Dr. Jothydev Kesavadev

Dr. Jothydev Kesavadev is the CEO and Director of Jothydev’s Diabetes Research Centre, at Trivandrum. He is an alumnus of the prestigious Government Medical College, Trivandrum and Mayo Clinic, USA. He has several national and international presentations and publications to his credit in the field of diabetes, incretin therapy and enhancing patient education. He has been a speaker twice at ADA and IDF conferences and is also a reviewer of more than a dozen indexed journals. Interestingly, he has completed 451 diabetes awareness and detection camps across the state of Kerala. He is also the editor of JDC Gems, a monthly diabetes internet journal. He has more than 2000 television programs to his credit and also does diabetes education via YouTube on a regular basis. Dr. Jothydev effectively dedicates his time for diabetes clinical research, mass education and community work. His research mainly focuses on telemedicine, insulin pumps and continuous glucose monitoring systems.

Introduction

Type 2 diabetes mellitus is a progressive disease characterised by decline in beta cell function and insulin resistance. Liraglutide is a GLP-1 RA which has been shown in clinical studies to be an effective drug with beneficial effects on beta cell function and improved glycaemic control, without the side effects of weight gain and hypoglycaemia. According to one estimate, about 50% of patients rely on liraglutide for achieving glycaemic control while the rest discontinue or are on follow-up (data on file).

When to start GLP-1 RA treatment

Treatment with drugs of GLP-1 RA class can be initiated in patients with T2DM in combination with metformin as per the ADA/EASD position statement. In addition, liraglutide is initiated in some special situations at Jothydev’s Diabetes Research Centre, Trivandrum including:

i. Patients with T2DM with obesity

ii. Patients newly diagnosed with T2DM with HbA1c ≥ 6.5% and BMI ≥ 30 kg/m²

iii. Those patients regularly on follow up via telemedicine (Diabetes Tele Management System: DTMS®) with proven compliance

iv. Patient or caretaker’s able to afford therapy

v. Patients highly motivated and educated about treatment

Despite challenges, liraglutide is widely prescribed to patients with T2DM due to several attributes like considerable improvements in the outcomes of >80% patients, profound reduction in body weight and dose of concomitant medications, and improvement in CV factors.

Case study 1

A patient presented with T2DM and was started on liraglutide. The patient’s family doctor had previously suggested him to stop liraglutide due to the risk of thyroid and pancreatic cancers. After 2 years the patient was reinitiated on liraglutide. The patient found considerable improvement in glycaemic and non-glycaemic parameters, and is satisfied.

In an experimental study, patients with T2DM from India treated with liraglutide for 12 weeks, showed a significant decline in HbA1c (from 8.0% to 7.2%), FBG (from 170.7 to 114.6 mg/dL), body weight (5%) and BMI. This study suggests that liraglutide o.d. is an effective and well tolerated GLP-1 RA that improves glycaemic control with weight reduction.

A retrospective cohort study using DTMS was conducted in Jothydev’s Diabetes Research Centre, Trivandrum on patients who monitored their own blood glucose. The DTMS, based on telemedicine follow-up and multidisciplinary care was found to be safe and cost-effective method for treatment of T2DM, including patients prescribed with liraglutide without any serious co-morbidities. Liraglutide when combined with insulin has also been shown to possess an additive effect on mean glucose infusion rate (AUC<sub>GIR</sub>).

Case study 2

Background

A 70 year old person presented with 22-year long T2DM. He was on Novomix (20-10-10), glycozide metformin (1-1-1), janumet 50/500 (1-0-0) and metformin XR 500 mg (0-0-1). The baseline values of HbA1c, and weight were 8.4% and 112.5 kg, respectively.

In another case, an obese subject with 26-year long duration of T2DM, with HbA1c of 7.1% was presented.
Liraglutide (1.8 mg) was given for 6 months along with Novomix. In the obese subject, liraglutide was prescribed along with insulin pump for 6 months.

Addition of liraglutide markedly reduced body weight (from 112.5 to 105.8 kg) and HbA1c (from 8.4 to 7.2%) with concomitant reduction in doses of Novomix (from 20-10-20 to 2-0-2).

In the obese subject, addition of liraglutide markedly decreased the body weight (from 91 kg to 87.2 kg) and HbA1c (from 7.1 to 6.8%) along with a 12% reduction in total daily dose of Aspart in insulin pump.

Addition of liraglutide to insulin/insulin pump shows an additive effect, not only in reducing body weight and HbA1c, but also in reducing concomitant doses of insulin.

### Efficacy and safety of liraglutide in 195 patients with T2DM in India: A retrospective analysis

Treatment with liraglutide in real-life clinical practice, significantly reduced the systolic and diastolic blood pressure (p<0.01) along with total daily dose of antihypertensive drugs (p<0.05)\(^4\). A retrospective analysis of safety and efficacy data of liraglutide therapy in 195 patients with T2DM from India revealed that liraglutide significantly reduced glycaemic (HbA1c-from 8.1 to 7.0% %, FBG-from 163.8 to 111.6 mg/dL) and non-glycaemic parameters (body weight-from 86.4 to 82.4 kg, SBP-from 129.3 to 120 mmHg, DBP-from 76.2 to 70.9 mmHg, serum cholesterol-from 166.7 to 124.9 mg/dL) with mild to moderate adverse events (3.1%). Overall, ~50% patients with T2DM, achieved HbA1c<7.0% and 38% achieved HbA1c<6.5%\(^5\).

Although, newer therapies in diabetes are promising and show clinical benefits, affordability of the same to all people with T2DM has to be achieved for larger societal benefits.

### Case study 3

#### Background

A 42-year-old person with newly diagnosed T2DM (2 weeks) presented to the clinic. The patient was on metformin 850 mg. His baseline weight and HbA1c were 91.2 kg and 11.6%, respectively.

#### Intervention

Liraglutide (1.2 mg) was given for 6 months.

#### Results

Liraglutide treatment significantly reduced weight (from 91.2 to 82.2 kg), BMI (from 27.8 to 25.1 kg/m\(^2\)) and HbA1c (from 11.6 to 5.1%) with concomitant reduction in doses of metformin.

### Conclusion

Liraglutide is effective in reducing HbA1c, BMI and weight in newly diagnosed T2DM.

Liraglutide therapy beyond glycaemic control: An observational study in Indian patients with type 2 diabetes in real world setting\(^6\)

#### Aim

To assess efficacy and safety of liraglutide in Indian patients with T2DM who were overweight and obese.

#### Methods

Liraglutide injection, 0.6 mg/day for 3 days followed by 1.2 mg for next 10 days and finally 1.8 mg/day for 22 weeks was prescribed to patients (N=14) in whom it was clinically warranted.

#### Results

Liraglutide therapy reduced mean FBG (from 147.6 to 99.1 mg/dL, p=0.002) and PPBG (from 167.6 to 100.9 mg/dL, p=0.004) over 24 weeks. In addition significant reduction in HbA1c (from 7.9 to 5.5%, p<0.001), body weight (from 90.7 to 82.1 kg, p<0.001), BMI (from 33.5 to 30.2 kg/m\(^2\), p<0.001), was observed over 24 weeks for each parameter. Systolic blood pressure was reduced by 15.15 mm Hg (p=0.004). Also a significant improvement in low-density lipoprotein, total cholesterol, triglycerides, and serum creatinine was noted.

#### Conclusion

Liraglutide o.d. not only improved glycaemic control but was well tolerated with clinically significant reduction in body weight and improvement in lipid profile. Liraglutide therapy results in probable remission of newly diagnosed T2DM.

### Case study 4

#### Background

A 69-year old presented with 25-year long T2DM. The patient was on levemir 10 mg, novorapid (12-8-6), metformin SR 500 mg (1-1-1) and glimepiride 1 mg (1-1-1). Her baseline HbA1c and weight were 7.0% and 67.2 kg, respectively.

#### Intervention

Liraglutide 1.2 mg was given for 6 months.

#### Results

Liraglutide treatment significantly reduced weight (from 67.2 to 58.4 kg), and HbA1c (from 7.0 to 5.9%) with concomitant reduction in doses of levemir (from 10 to 8 mg) and metformin (from 1-1-1 to 1-1-1/2 mg dosage). Liraglutide treatment decreased blood glucose levels (measured by continuous glucose monitoring system) to normal range within a month.

#### Conclusion

Liraglutide together with insulin is effective in reducing HbA1c and weight in patients with T2DM.
Liraglutide is an effective and well tolerated therapeutic option in a majority of patients with T2DM. It is of particular importance to patients requiring profound weight reduction or reduction in total daily dose of insulin or remission from diabetes. However, some patients suffer from severe GI discomfort (about 2%) and approximately 7% patients do not show a reduction in HbA1c and weight. Tolerability is directly proportional to the titration methodology, so initial dose fixation and subsequent adjustment should be conducted in consultation with patients. Customization of dosage is necessary to achieve desired glycaemic and non-glycaemic benefits. In clinical practice, the benefits of liraglutide cannot be denied to eligible candidates.

References
Session 3
GLP-1 Receptor Agonists in the Treatment of Diabetes: Progress and Promise
Differentiating Liraglutide from Other Incretin-based Therapies for T2DM

Dr. Subhash K. Wangnoo

Dr. Subhash K Wangnoo is currently working as a senior consultant endocrinologist at the Indraprastha Apollo Hospital, New Delhi. He specialises in endocrinology with special interests in diabetes and metabolic medicine, reproductive endocrinology and thyroid disorders & disorders of growth in children. He has served as the principal investigator in a number of multinational clinical trials. He has several international publications to his credit. He is also the founder of the Apollo Centre for Obesity and Diabetes. He has been awarded WHO fellowship on ’NUTRITION & GOITRE’ for South East Asian Countries in 1988. He is also Honorary endocrinologist to his Excellency – President of India.

Introduction

Glucagon-like peptide-1 (GLP-1) is a gut derived incretin hormone with the ability to stimulate glucose-dependent insulin secretion, inhibit glucagon secretion, delay gastric emptying, promote satiety and decrease appetite. It has therefore been explored as a novel treatment for T2DM. However, GLP-1 is rapidly degraded by the enzyme DPP-4 which results in a short half-life of the active form of GLP-1 (<2 min). Therapeutic strategies that inhibit the enzyme DPP-4 and prolong the half-life of endogenously released GLP-1 or use GLP-1 RAs in pharmacological doses that are resistant to degradation by DPP-4 enzyme are employed.

The two types of incretin-based therapies are currently available GLP-1 RA (liraglutide o.d., exenatide o.d. and o.w.) and DPP-4 inhibitors (o.d. doses of sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin and teneligliptin). Table 1 summarizes the differences between GLP-1 RAs and DPP-4 inhibitors.

<table>
<thead>
<tr>
<th>DPP-4 inhibitors</th>
<th>GLP-1 RAs</th>
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<tr>
<td>Orally available</td>
<td>Injectable</td>
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<tr>
<td>Increase levels of GLP-1 to physiological range</td>
<td>Given in pharmacological range</td>
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<td>Limited by endogenous incretin secretion</td>
<td>Not limited by endogenous incretin secretion</td>
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<tr>
<td>Moderate efficacy</td>
<td>Enhanced efficacy</td>
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<td>Weight neutral</td>
<td>Associated with weight loss</td>
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<tr>
<td>Well-tolerated</td>
<td>GI side effects and antibody formation</td>
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Table 1. Comparing DPP-4 inhibitors with GLP-1

GLP-1 RAs vs. DPP-4 inhibitors

Liraglutide o.d. vs. Sitagliptin o.d.1-3

Aim

This randomised, parallel-group, open-label study compared the efficacy and safety of liraglutide o.d. versus sitagliptin o.d. each added to metformin, over 52 weeks in patients with T2DM.

Methods

Patients uncontrolled on metformin were randomised to 1.2 mg or 1.8 mg subcutaneous liraglutide o.d. or 100 mg oral sitagliptin o.d. for 26 weeks (main study). The same treatment was continued for patients for 26 weeks. In a further 26-week extension, sitagliptin-treated patients were randomly allocated to liraglutide at either 1.2 or 1.8 mg/day, while participants originally randomised to receive liraglutide remained unchanged.

Results

Liraglutide (1.2 or 1.8 mg) was superior to sitagliptin in reducing HbA1c below 7% within 12 weeks from baseline and sustaining the decrease up to 52 weeks. Although 52 weeks of sitagliptin changed HbA1c by -0.9% from baseline, further reduction occurred after switching to liraglutide (52-78 weeks) (1.2 mg/day, -0.2%, p<0.01; 1.8 mg/day, -0.5%, p<0.0001). Overall, liraglutide (at both doses) was significantly more effective than sitagliptin in allowing patients to reach target HbA1c <7% (ADA target) or 6.5% (American Association of Clinical Endocrinologists target) after 52 weeks of treatment (Figure 1).

At week 52, weight loss was greater with liraglutide 1.2 mg (-2.78 kg) and 1.8 mg (-3.68 kg) than sitagliptin (-1.16 kg) (both p<0.0001). After switching from sitagliptin to liraglutide (52-78 weeks), further weight loss was observed in patients.
switching to both liraglutide 1.2 mg/day (-1.6 kg), p<0.0001) and liraglutide 1.8 mg/day (-2.5 kg, p<0.0001)\(^3\). Proportions of patients reporting adverse events (nausea) during 52 weeks were comparable with minor hypoglycaemia reported in 8.1%, 8.3% and 6.4% of patients given liraglutide 1.2 mg, 1.8 mg and sitagliptin, respectively. Gastrointestinal side-effects, mainly nausea, initially occurred more frequently with liraglutide, but declined after 12 weeks.

**Conclusion**

Liraglutide treatment offered sustained and more effective reductions in HbA1c and body weight compared with sitagliptin over 52 weeks with similar rates of hypoglycaemia albeit with a transient increase in gastrointestinal reactions. Switching from sitagliptin to liraglutide resulted in further reduction in HbA1c and body weight.

**GLP-1 RA head-to-head trials**

**Liraglutide o.d. vs. Exenatide b.i.d. (LEAD-6)**\(^4,5\)

**Aim**

The LEAD-6 was a 26-week randomised parallel-group, multinational, open-label study designed to compare the efficacy and safety of liraglutide o.d. with exenatide b.i.d in patients with T2DM.

**Methods**

Patients with T2DM inadequately controlled on maximally tolerated doses of metformin, SU, or both were randomly assigned to receive additional 1.8 mg s.c. liraglutide o.d. or 10 \(\mu\)g exenatide b.i.d. In the 14-week extension of LEAD-6, patients switched from exenatide to liraglutide or continued liraglutide.

**Results**

The mean HbA1c reduction was more in patients receiving liraglutide than exenatide\(^6\). Switching from exenatide to liraglutide lead to further reduction in HbA1c from 7.2% at week 26 to 6.9% at week 40 (p<0.0001)\(^7\) (Figure 2).

Both drugs were well tolerated but nausea was less persistent with liraglutide than exenatide (3% vs. 9%). One major hypoglycaemic episode occurred in liraglutide arm\(^6\).

**Conclusion**

Liraglutide provided greater reduction in HbA1c and FBG than exenatide and showed comparable weight reduction with lower rates of hypoglycaemia and less persistent nausea. Switching from exenatide to liraglutide was well-tolerated and provided additional glycaemic control. Continuation of liraglutide treatment sustained improvements in glycaemic control, body weight and SBP.

**Exenatide o.w. vs. Liraglutide o.d. (DURATION-6 trial)**\(^8\)

**Aim**

The DURATION-6 was a 26-week, randomised, open-label, multi-centre, head-to-head trial set up to evaluate whether exenatide o.w. was non-inferior to liraglutide o.d. in reducing HbA1c in patients with T2DM.

**Methods**

Metformin, SU, metformin plus SU or metformin plus pioglitazone-treated patients were randomised to 2 mg exenatide o.w. and 1.8 mg liraglutide once daily.

**Results**

The study failed to demonstrate the primary end-point of non-inferiority in HbA1c reduction for exenatide o.w. versus liraglutide o.d. There was a significantly greater reduction in HbA1c in liraglutide group vs. exenatide group (-1.5 vs. -1.3, p=0.002) (Figure 3).

Significantly greater percentage of patients treated with liraglutide achieved target HbA1c of 7% compared with exenatide o.w. (60.2% vs. 52.3%, p=0.008). Patients treated with liraglutide 1.8 mg also demonstrated significant weight loss than exenatide o.w. (-3.58 kg vs. -2.68 kg, p<0.001). No episodes of major hypoglycaemia were reported in both arms and minor hypoglycaemia was reported in 10.8% and 8.9% patients with exenatide and liraglutide, respectively.

**Conclusion**

The primary endpoint of non-inferiority in HbA1c reduction for exenatide o.w. vs. liraglutide was not met. Once daily liraglutide demonstrated a greater efficacy than exenatide in
terms of glycaemic control and was accompanied with weight loss. Significantly more liraglutide-treated patients achieved target HbA1c of 7%, although GI side effects and withdrawals due to adverse events (AEs) were higher with liraglutide.

**Albiglutide o.w. vs. Liraglutide o.d. (Harmony-7 trial)**

**Aim and methods**

This 32-week head-to-head, open-label, multi-centre trial was designed to compare the efficacy of albiglutide o.w. vs. liraglutide o.d. in reducing HbA1c in patients with T2DM. In addition to patient’s baseline medication of oral anti-diabetic drugs, including metformin, SUs, thiazolidinediones, they were randomised to two groups: 404 patients received 30 mg albiglutide, titrated to 50 mg at week 6; and 408 patients received 0.6 mg liraglutide, titrated to 1.2 mg at week 2 and 1.8 mg at week 3.

**Results**

The mean HbA1c decreased significantly in patients receiving liraglutide once daily than exenatide o.w. (-0.99% vs. -0.78%, p<0.001) (Figure 4). The decrease in HbA1c with albiglutide did not meet the pre-specified end-point of non-inferiority to liraglutide. Greater weight loss has occurred in patients receiving liraglutide o.d. than albiglutide o.w. (-2.2 vs. -0.64 kg, respectively). The GI AEs were the most common in both treatment groups (35.9% in albiglutide and 49.0% in liraglutide group). Compared to patients in albiglutide group, greater proportion of patients in liraglutide group experienced nausea (liraglutide vs. albiglutide) (29.2 vs. 9.9%), vomiting (9.3 vs. 5.0%), and pre-rescue hypoglycaemic episodes (21 vs. 16%).

**Conclusion**

Liraglutide once daily was associated with greater reduction in HbA1c than o.w. albiglutide.

**Lixisenatide o.d. vs. Liraglutide o.d.**

**Aim and methods**

This 28-day randomised, open-label, parallel group, multicentre study was set up to assess the pharmacodynamics of lixisenatide o.d. vs. liraglutide o.d. in patients with T2DM insufficiently controlled on metformin. Primary endpoint was change in plasma glucose concentration-time curve from baseline to day 28 in 4-hour period after start of standardised breakfast test meal (AUC0:30–4:30 hour). Patients were randomised to receive 10 µg lixisenatide (for Weeks 1-2 and 20 µg thereafter) or 0.6 mg liraglutide (on Week 1, 1.2 mg on Week 2 and 1.8 mg thereafter) approximately 30 minutes before breakfast.

**Results**

The 24-hour profile showed a significant decrease in FBG level in patients receiving liraglutide vs. lixisenatide (-1.30 vs. -0.3 mmol/l, p<0.001) (Figure 5). The mean HbA1c decreased significantly from baseline in patients receiving liraglutide compared with lixisenatide (-0.51% vs. -0.32%, p<0.01) at Day 28. The body weight change from baseline at Day 28 was significantly greater with liraglutide than exenatide (-2.4 kg vs. -1.6 kg, p<0.01). No episodes of hypoglycaemia were reported in both the groups.

**Conclusion**

Compared to lixisenatide, liraglutide provided better control on FBG and PPBG in the 24-hour profile and was associated with a greater reduction in HbA1c and body weight.

**Semaglutide o.w. vs. Liraglutide o.d.**

**Aim**

The aim was to investigate dose response of semaglutide o.w. on change in HbA1c in subjects with T2DM. The safety, tolerability and pharmacodynamics of different doses of semaglutide vs. placebo and an open-label liraglutide o.d. were also investigated.

**Methods**

In this 12-week, randomised, double-blind, placebo-controlled trial, around 411 patients with T2DM (mean HbA1c 8.1%; body weight (87.5) on metformin only/diet & exercise alone 80/20% and diabetes duration of 2.6 ± 3.1 years had participated. Patients were randomised to: one of the five s.c. 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Semaglutide doses o.w. (0.1-1.6 mg), open label s.c. Liraglutide o.d. (1.2 mg, 1.8 mg) or placebo o.w. Two semaglutide doses were titrated (T) in weekly increments of 0.4 mg.

**Results**

A dose dependent reduction in HbA1c was observed with semaglutide (0.1 mg to 1.6 mg) and liraglutide (1.2 mg and 1.8 mg). Compared to liraglutide 1.8 mg, greater number of patients had reached the HbA1c target with semaglutide ≥0.8 mg (semaglutide 0.8 mg T: 69% vs. liraglutide 1.8 mg: 57%) (Figure 6). Reduction in body weight up to 4.8 kg was observed from baseline (87.5 kg) in a dose dependent manner (p<0.01 for doses ≥0.8 mg) in semaglutide treated group vs. placebo (1.2 kg). Few subjects reported minor episodes of hypoglycaemia (semaglutide: 5, liraglutide: 3); no episodes of major hypoglycaemia.

**Conclusion**

Semaglutide dose-dependently reduced HbA1c and body weight for 12 weeks in patients with T2DM. Higher doses semaglutide were more effective than liraglutide. No safety concerns were identified in semaglutide group.

**Summary**

Incretin-based therapies address majority of the treatment gaps in T2DM. Compared with DPP-4 inhibitors, liraglutide demonstrated superior glycaemic control with additional advantages of weight loss and minimal incidences of GI events. Also, when compared with exenatide and albiglutide, liraglutide showed marked reduction in HbA1c, similar weight loss and lower incidence of GI events compared to exenatide b.i.d. and greater weight loss and increased incidences of GI events compared to once weekly exenatide and once weekly albiglutide. Taken together, the data suggests that at the moment, liraglutide is the only therapeutic class with beneficial effects on multiple pathologies inherent to T2DM. However, much remains to be answered, on how better liraglutide performs in competition with newer alternatives in coming years.

**References**

Introduction

Management of T2DM remains challenging and continues to evolve with time. Data accumulated over time have shown that incretin system has pleiotropic action not only on the control of blood glucose but also on various organs including heart, gut, and brain as well as the fat reserves of the body. In this context, harnessing the incretin system, in particular GLP-1 receptor agonists may represent a therapeutic solution.

GLP-1 and gastrointestinal tract

GLP-1, a peptide hormone found in the small intestine and colon, is released in response to luminal nutrients and has now been shown to exert a number of important functions on the GI tract. In the GI tract, GLP-1 inhibits gastric emptying, and the signal is carried by the vagal afferent nerves of portal system to influence central circuits in the hypothalamus, which in turn stimulates satiety and hence reduced food intake and increased energy expenditure. Gastric emptying as measured by paracetamol area under curve [0-60 minutes] was delayed with liraglutide (Figure 1).

This delayed gastric emptying is important in glycaemic control as it promotes satiety and causes slower rise in blood glucose, fats and ultimately affects glucose and lipid control1-5. Meta-analysis of LEAD 1-6 trials also demonstrated significant (p<0.0001) reduction in total cholesterol, low-density lipoprotein cholesterol and triglycerides in patients treated with liraglutide6. GLP-1 infusion influences appetite sensation with significant increase in the absolute mean of VAS scores for satiety (p<0.02), fullness (p<0.03) and decreased scores for hunger (p<0.02) and prospective food consumption (p<0.02) compared with saline infusion7.

GLP-1 and heart

GLP-1 has acute effects on the cardiovascular system. It has been postulated that GLP-1 increases glucose uptake by non-insulin dependent mechanisms (GLUT-1 translocation) and activates anti-apoptotic kinases in the heart; increases diuresis and sodium excretion in response to sodium overload and volume expansion in kidney; promotes nitric oxide-dependent vasorelaxation in peripheral tissues and reduces tumour necrosis factor α-mediated...
secretion of plasminogen activator inhibitor-1 in cultured endothelial cells\textsuperscript{14}. As seen across the LEAD studies, treatment with two highest doses of liraglutide led to consistent reduction in systolic blood pressure\textsuperscript{11} (Figure 2). Essentially GLP-1 acts on several organ systems like pancreas, gut, hepatic portal vein, kidney, vascular system and heart that send signals to brain and influences reduced food intake and increased energy expenditure\textsuperscript{18}.

**GLP-1 and brain**

GLP-1 action in brain is linked to regulation of appetite and satiety. Studies in animal models have shown that GLP-1 possess neurotropic properties and protects neurons against glutamate-induced apoptosis\textsuperscript{17}. Amyloid beta is neurotoxic and is believed to be involved in the pathogenesis of Alzheimer’s disease. In a study, GLP-1 has been reported to reduce amyloid beta peptide levels in the brain in a dose dependent manner (6.6 ng) similar to that of nerve growth factor (20 µg)\textsuperscript{19} (Figure 3). Taken together, these results suggest that GLP-1 can modify amyloid precursor protein processing and protect against oxidative injury. Treatment with GLP-1 analogues beneficially affects neurological degeneration and promotes neurogenesis. In a mouse model, treatment with liraglutide has shown significant reduction in amyloid plaque load, dense-core plaques formation, and inflammatory response (all p<0.001) compared with saline controls. Furthermore liraglutide significantly promoted neurogenesis in the dentate gyrus region (p<0.001)\textsuperscript{19}. A recent study analysing the effect of liraglutide on the impairment of learning and memory formation induced by amyloid-beta protein in a rat model have shown that liraglutide significantly improved spatial learning and memory in a dose-dependent manner\textsuperscript{20}. However, clinical relevance of this data on animal models is yet to be proved.

**GLP-1 and fat**

Several published studies pertaining to the acute effect of intravenous administration of GLP-1 on ad libitum energy intake has shown that GLP-1 infusion significantly reduced energy intake compared with control\textsuperscript{16}. In another study, continuous subcutaneous infusion of GLP-1 for 6 weeks in patients with T2DM showed significant weight reductions compared with control\textsuperscript{27}. Further, liraglutide induced dose-dependent weight reduction in patients with T2DM with 3 kg versus baseline and 1.2 kg versus placebo\textsuperscript{27}. Weight reduction with liraglutide was also seen in all the LEAD studies and liraglutide-DPP-4 inhibitor comparator trials. A significant weight reduction of 3.7 kg was seen in the metformin plus liraglutide combination group (Figure 4)\textsuperscript{28-30}.

Moreover, across all the LEAD 1-6 trials, occurrence of liraglutide induced weight reduction was found in patients...
with or without GI side effects. Further, liraglutide induced weight reduction was observed in all patients irrespective of their BMI value. Greater weight loss was seen in patients with higher initial BMI. Patients with T2DM and obesity randomised to liraglutide 3.0 mg for first year (maintained on 2.4/3.0 mg for the second year) demonstrated a sustained mean weight loss of 10.3±7.1 kg from baseline over 2 years. Data from randomised controlled studies suggest that in short-term adding exercise to dietary therapy does not significantly increase weight loss compared with dietary therapy alone. On the other hand, in long-term physical activity was found to be necessary for weight loss maintenance. A dose-response relationship between amount of exercise per week and change in body weight has shown that at 18 months, weight loss in participants who spent ≥200 minutes per week in physical activity was greater than those exercising for ≥150 minutes per week and those exercising <150 minutes per week.

There is now evidence that obese patients with visceral fat who lose a moderate amount of body weight show a selective mobilisation of visceral fat. A computed tomography abdominal scan of a patient who lost only 5 kg of body weight, through lifestyle modification (diet and/or exercise) illustrated a substantial loss of visceral adipose tissue by ~30%. Such preferential mobilization of visceral fat could explain the substantial metabolic benefits of weight loss by lifestyle modification over bariatric surgery in viscerally obese patients with atherogenic dyslipidaemia or impaired glucose tolerance. Thus, the importance of waist rather than weight management is emphasized. Similar to this, a significant reduction in absolute and percentage visceral body fat was seen with liraglutide 1.8 mg plus metformin combination than glimepiride plus metformin combination (Figure 5).

**Figure 4: Weight reduction**

**Figure 5: Visceral body fat reduction**
Summary

Incretin-based therapies have established a foothold in the diabetes armamentarium and present a new approach to the management of T2DM. Clearly, a better understanding of the incretin system has provided a novel approach to glycaemic control, with benefits beyond glucose lowering. In addition to improving glycaemic control, GLP-1 agonists produce clinically relevant reductions in gastric emptying, systolic blood pressure, body weight, visceral body fat and may thereby help to achieve other goals of treatment. Furthermore, they can induce benefits in terms of neuroprotection and neurogenesis. Thus early use of incretin-based therapies is a reasonable choice for patients, when first-line therapy does not achieve glycaemic control.

References

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References