Endocrine and metabolic effects of Glucagon like peptide 1 receptor agonists (GLP1RA)
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Abstract
This brief review describes the potential non-glycaemic effects and benefits of glucagon like peptide 1 receptor agonists (GLP1RA). It lists various indications in which this class of drugs has been used, and explains the rationale behind this use. The potential uses of GLP1RA extend across the entire spectrum of endocrinology and metabolism, from hypothalamic obesity to non-alcoholic steatohepatitis (NASH) to polycystic ovary syndrome (PCOS). The article also discusses and addresses endocrine-related concerns related to the GLP1RAs.

Keywords: Incretin therapy, Exenatide, Liraglutide, Exenatide QW.

Introduction
Glucagon like peptide 1 receptor agonists (GLP1RA) are a class of glucose-lowering drugs which act through the GLP1 receptors. Through approved for use in type 2 diabetes, the ubiquitous distribution of GLP1 receptors suggests that these molecules can be utilized to benefit persons with other conditions, including endocrine and metabolic dysfunction. This brief review describes the rationale and evidence related to use of GLP1RA in various disease states apart from diabetes.

Hypothalamic Obesity
The rationale for use of GLP1RA in hypothalamic obesity is based upon the presence of GLP1R in the hypothalamus. Apart from peripheral actions, GLP1RA, both short-acting and long acting, act on centrally located receptors to suppress appetite and increase energy expenditure. Some of these effects are mediated by the AMPK pathway, which is inhibited by stimulation of GLP1R located in the nucleus of tractus solitarius, parabrachial nucleus, area postrema, hypothalamic paraventricular nucleus, and dorsal medical hypothalamus.1,2

GLP1RA have been studied in both euglycaemic and diabetic patients with moderate to severe hypothalamic obesity. Over a period of up to 51 months, 8 out of 9 patients experienced substantial weight loss ranging from 9 to 22 kg (mean-13.1 ± 5.1 kg), with improved insulin sensitivity and glycaemic control. Five patients reported increased satiation, two complained of gastro intestinal side effects, and one did not continue with therapy because of intractable nausea and vomiting.3 In another report, liraglutide was found to be effective in two obese patients with hypothalamic hyperphagia and MRI-detectable hypothalamic lesions. These diabetic patients experienced suppression of appetite, normalization of glycaemic control and weight loss (3kg and 11 kg), with liraglutide 0.3mg/day (the dose approved in Japan).4

The Thyroid
GLP1 receptors are present in the thyroid gland. While studies in rodent models reveal a high density of GLP1 receptors in C-cells, primates such as monkeys have a much lower GLP1 receptor concentration, and humans, an even lesser number.5 Animal studies, however, have raised concerns about the possible impact of GLP1RA therapy on thyroid cell proliferation.

In view of this, GLP1RA are to be used with caution in persons with a history or a family history of medullary thyroid carcinoma (MTC).6 Calcitonin measurement is not indicated in persons on long term GLP1RA therapy. Post-marketing surveillance does not reveal an increase in the incidence of MTC in GLP1RA treated patients.7

The Bone
Liraglutide and exenatide do not have any known effect on the parathyroid gland. However, GLP1RA have been found to have anabolic effects on bone. Studies in diabetic murine models have demonstrated that GLP1 and liraglutide improve trabecular architecture and promote bone formation.8

A recent meta-analysis of randomized controlled trials demonstrated a significant reduction in risk of incident bone fractures with liraglutide (Mantel-Haenszel odds ratio) [MH-OR] 0.38; 95% confidence interval [CI] 0.17-0.87). However, exenatide treatment was associated with an increased risk of incident bone fractures (MH-OR 2.09; CI 1.03-4.21).9 Bone mineral density did not change.
significantly over 2 years of liraglutide therapy in the LEAD- (Liraglutide Effect and Action in Diabetes)-3 trial.10

The Pancreas
The effect of GLP1RA on the exocrine pancreas has been the subject of much controversy and debate. This issue has been reviewed in detail by various authors. Multiple meta-analyses and retrospective studies have demonstrated conclusively, however, that there is no increase in the risk of pancreatitis or pancreatic cancer, with incretin-based therapy.11-13

The Adrenal
Liraglutide may offer benefits to adrenal health when prescribed for the management of type 2 diabetes. Borderline significant increase in dehydroepiandrosterone-sulfate (DHEAS) have been documented in 12 male patients of type 2 diabetes, aged 48.6±10.4 years, who received 6 months of liraglutide. These patients experienced improvement in glycaemic control, weight as well as waist circumference.14 Liraglutide has also been demonstrated to reduce salivary cortisol, a marker of stress, in persons with binge eating disorder.15

The Liver
Pilot studies have reported beneficial effects of liraglutide in non-alcoholic steatohepatitis (NASH), a hepatic manifestation of metabolic syndrome. In the LEAN trial, 1.8 mg of liraglutide, administered daily for 48 weeks, helped resolve NASH, with no worsening of fibrosis, in 39% subjects, and reduced hepatic fat content in 82.6% subjects. Significant weight and fasting glucose reduction was noted with liraglutide.16 Liraglutide, in a dose of 0.9 mg/day, improved liver enzymes, glucose levels, body mass index and visceral fat accumulation, at 24-44 weeks, in 19 Japanese subjects, and decreased histological inflammation (on liver biopsy) at 96 weeks, in 6 out of 10 subjects.17

The Ovaries
Liraglutide has been shown to cause significant weight loss in women with polycystic ovary syndrome (PCOS), when prescribed as monotherapy18 or in combination with metformin. In an observational study of overweight/obese women treated with liraglutide for a minimum of 4 weeks, In another study, obese women treated with a combination of liraglutide and metformin lost more weight (6.5±2.8kg) as compared to those randomized to liraglutide (3.8±3.7kg) or metformin (1.2±1.4kg) (p<0.001).19

Another trial is studying the effect of liraglutide on menstrual cyclicity20 (LIPOS; Liraglutide in PCOS).

The Male Gonads
GLP1RA do not have a direct effect on testosterone in males. However, it is expected that it will reduce SHBG (sex hormone binding globulin) and aromatase activity, by reducing fat,21 and enhance endogenous testosterone concentration and activity. There is however, a single published case report which describes adverse effects of liraglutide on male fertility.22

The Central Nervous System
GLP-1 receptors are distributed throughout the brain. Activation of the GLP-1 receptor is associated with a number of cellular survival phenomena viz. enhanced learning, protection against apoptosis (programmed cell death) and cell death secondary to oxidative insult.23 This may have beneficial effects in Parkinson’s disease and Alzheimer’s disease.

A proof of concept, single-blind trial evaluated the progress of 45 patients with moderate Parkinson’s disease (PD), randomly assigned to receive subcutaneous exenatide injection for 12 months or to act as controls. There was a clinically relevant improvement in PD across motor and cognitive measures compared with the control group. Exenatide-treated patients had a mean improvement at 12 months on the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) of 2.7 points, vs a mean decline of 2.2 points in the control group (P = 0.037).24

Trials in Alzheimer’s disease are ongoing, evaluating neurodegeneration, blood flow and cognition,25,26

Psoriasis
GLP-1 receptors are expressed on invariant natural killer T (iNKT) cells. Animal studies with GLP1 RAs have shown a dose-dependent inhibition of iNKT cell cytokine secretion, increased number of iNKT cells in circulation and reduction in the number of psoriatic plaques.27

A study evaluated the effect of liraglutide the psoriasis area and severity index (PASI) and the dermatology life quality index (DLQI) in people with both psoriasis and diabetes. The immunomodulatory properties were also evaluated by measuring circulating lymphocyte subset numbers and monocyte cytokine production. Liraglutide therapy decreased the median PASI from 4.8 to 3.0 (P = 0.03) and the median DLQI from 6.0 to 2.0 (P = 0.03). Circulating iNKT cells increased from 0.13% of T lymphocytes to 0.40% (P = 0.03). A non-significant 54% decrease in the proportion of circulating monocytes that produced tumour necrosis factor alpha (P= 0.07) was also seen. GLP-1 analogue therapy has beneficial effects on psoriasis severity, and also increases circulating iNKT cell number and modulates monocyte cytokine secretion. These effects may result from improvements in weight and glycaemic control as well as from direct immune effects of GLP-1 receptor activation.28
Two isolated case reports, one on exenatide and on liraglutide, have reported similar findings. 29-30

Summary
The multiple pleiotropic effects of GLP1RA allow their potential usage in a wide spectrum of endocrine and metabolic diseases. Most of the advantages listed above are mediated by, or linked to the effect of GLP1RA on insulin resistance or weight. It must be noted, however, that all these uses, except for obesity, are not approved, and are off-label at present

References