CARDIOVASCULAR ACADEMY SOCIETY

e-Bulletin

Liraglutide and its role on decreasing cardiac complications in type 2 diabetic patients

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Introduction

Type 2 dıabetes is a pandemic disease affecting an increased number of people in the world every year. According to the International Diabetes Federation (IDF) statistics in 2013, the world population affected by diabetes exceeded 457 million people and is expected affect more than 590 million people in 2035 [1].

Pathophysiologically, type 2 dıabetes starts with insulin resıstance, although clinically diabetes appears when there occurs a decrease in insulin secretion [2]. When a patient is diagnosed with diabetes, about 50 percent of beta cells are not functioning, and as type 2 diabetes is a progressive disease, the reduction trend of beta cells will continue. [3]

If diabetes is not diagnosed and treated in a timely manner, this can lead to long-term complications, which are divided ınto two general categories, microvascular and macrovascular [2]:
The microvascular complications are:

- Diabetic retinopathy
- Diabetic nephropathy
- Diabetic neuropathy

And macrovascular complications are:

- Cardiac complications
- Peripheral vascular diseases
- Cerebrovascular diseases

Vascular diseases are the most common cause of morbidity and mortality in type 2 diabetes patients; and macrovascular complications, especially cardiac complications and cerebrovascular disease, are lethal in 50 percent of patients [4].

The UKPDS study showed that the blood sugar control can help limit the complications named above, in a way that one percent reduction in HbA1c levels will lead to 43 percent reduction in peripheral vascular diseases and amputations, 37 percent reduction in renal complications, and 19 percent reduction in eye complications, and also in renal

deficiency (16 percent), myocardial infarction (14 percent), and cerebrovascular accidents (12 percent) [5].

Treatment

The drugs used in the treatment of type 2 diabetes are divided into two categories [6]:

• Oral antı-dıabetıc drugs and non-insulin injectionables: including biguanides (e.g. metformin), insulin secretogogues including sulfonylureas (e.g. glibenclamide and gliclazide) and meglitinides (e.g. repaglinide), thiazolidinediones (e.g. pioglitazone and roziglitazon), alpha-glucosidase inhibitors (e.g. acarbose and miglitol), sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin), Dipeptidyl peptidase 4 (DPP4) inhibitors (e.g. sitagliptin and vildagliptin), and Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP1-RA) (e.g. liraglutide)

• Insulin including basal, prandial and premixed insulin

Comparison of various treatments with regard to efficacy

A study conducted by Nathan et al. in 2009, showed that the alpha-glucosidase inhibitors had the smallest efficacy among the anti-diabetic drugs, leading to reduction in HbA1c by about 0.5 percent; and among non-insulin drugs, sulfonylureas, metformin and GLP-1RA had the highest efficacy, leading to reduction in HbA1c by 1.5 percent. Insulins are known as agents with no limitation in lowering HbA1c and have been shown by various studies to lower HbA1c by 2.5 to 3 percent (Table 1) [7, 8].

Monotherapy	Route of Administration	A1c (%) Reduction
Sulfonylurea	PO	1.5-2.0
Metformin	PO	1.5
Glitazones	PO	1.0-1.5
Meglitinides	PO	0.5-2.0
α-glucosidase inhibitors	PO	0.5-1.0
DPP-4	PO	0.5-0.7
GLP-1 agonists	Injectable	0.8-1.5
Amylin analogs	Injectable	0.6
Insulin	Injectable	Open to target

Table 1

Comparison of various treatments with regard to hypoglycemia

In the studies conducted by Riddle et al. (2003) and Kahn et al. (2006), it ıs shown that of thiazolidinediones, metformin and sulfonylureas, the least occurrence of hypoglycemia was caused by thiazolidinediones and the most occurrence was caused by sulfonylureas [9, 10].

Among the various insulin types, basal insulin caused less occurrences of hypoglycemia than rapid-acting insulin and premıxed insulin, and insulin analogues caused less hypoglycemia than human insulin.

Comparison of various treatments with regard to weight gain

The UKPDS showed that of metformin, sulfonylureas and insulins, the least weight gain was caused by metformin and the most weight gain was caused by insulin [11].
In a double-blind study, using metformin led to weight loss and a reduction in waist circumference. The extent of weight loss in the mentıoned study was directly proportional to the continuation of the treatment on the patient's side, during the two-year period of the study, the extent of the resulting weight loss was significantly more in the group treated with metformin than the group which was given placebo [4]..

Treatment strategies

The patient's treatment is usually started with oral glucose lowering agents, and insulin will then be used if glycemic control cannot be achieved [6]. The UKPDS showed that all the treatment regimens of diabetes first led to a relative control of the glycemic indices in the patients, although the improvement is temporary and the patient's blood glucose level will rise again [11].

On the other hand, all the combined regimens used to treat diabetes are accompanied with some degrees of increased risk of hypoglycemic episodes [9, 10].
Weight gain ıs also another complication which can be attributed to the management of diabetes, and will lead to the increased development of insulin resistance and therefore to the disease aggravation [9, 10].
Among other complications which accompany diabetes are obesity and cardiovascular complications such as arterial hypertension. The studies have shown that the increased arterial hypertension is directly proportional to the mortality of diabetic patients. [12, 13]
Therefore, a number of issues may influence the treatment of diabetic patients, which in brief include the following:

- A progressive trend of beta cells reductıon, leading to the patient's blood sugar status becoming out of control
- Complications caused by treatment, including hypoglycemia and weight gain
- Increased occurrence of cardiovascular complications in diabetic patients and its effect on the mortality rate of patients.

Incretins and incretin effect

Incretins [Glucagon-lıke peptıde 1 (GLP-1) and gastrıc inhıbitory polypeptide (GIP)] are a group of hormones which are secreted by the L-cells in the end of the intestine and stimulate increased secretion of insulin in response to increased level of blood glucose by the pancreatic beta cells. Incretins are normally degraded by a group of enzymes named dipeptidyl peptidase 4 (DPP4) and are eliminated from the blood circulation in five minutes.
Certain studies show that an increase in the blood sugar level in response to the oral intake of glucose will lead to a more insulin secretıon than when the same amount of increase is generated by the intravenous infusion of glucose. This is called "incretin effect". [14]
Studies have also shown that in type 2 diabetes, the insulin secretion will not increase in response to the physiological levels of GLP-1 [15], although it will return to normal levels with the pharmacologic levels of GLP-1. [16]

On the other hand, it has been shown that in type 2 diabetes, an increase is also seen in glucagon secretion level, while the pharmacologic levels of GLP-1 will lead to reduced blood glucose level by limiting the endogenous glucagon secretion [17].

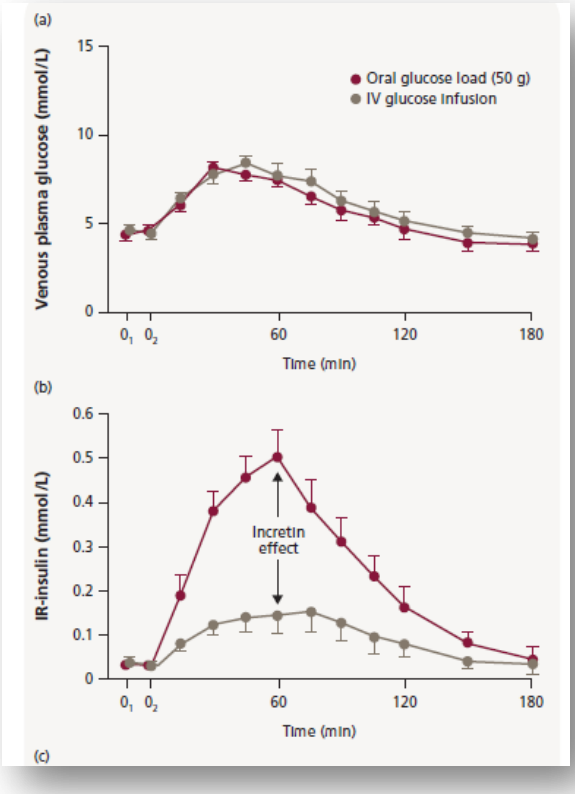

Figure 1

Incretin-based therapies (Table 2)

With the suitable effects of incretins in treating diabetes, a variety of drugs with the same physiologic structure were introduced for treating diabetes. Such drugs may be divided into two groups:

- DPP4 inhibitors, which prolongs the action of endogenous GLP-1 by inhibiting the mentioned enzyme;
- GLP-1 receptor agonists, which provide a resistant form of the GLP-1 to DPP4 enzyme.

Table 2

Class/Generic Name	Daily Dosage (mg)	Duration of Action (h)
GLP-1 agonist		
Exenatide	0.01–0.02	4–6
Liraglutide	0.6–1.8	12–24
Dipeptidyl Peptidase-4 Inhibitors		
Saxagliptin	2.5–5	12–16
Sitagliptin	100	12–16
Vildagliptin	50–100	12–24

Liraglutide

Liraglutide is an GLP-1 analogue which is comparable to the normal molecule of GLP-1 by 97 percent. The only difference is the addition of a 16-carbon fatty acid (palmitoyl) to the amino acid number 26 and the replacement of lysine with arginine in position 34 (Figure 2).

These changes will prolong its action due to the following reasons:

• Formation of heptamer in the subcutaneous tissue, and the time needed for breakdown of heptamer into GLP-1 monomers . [18]

• The resulting molecule binds to albumin in the blood stream; this prolongs the action because of the time needed for separation from albumin and also because of resistance to the endogenous DPP4.

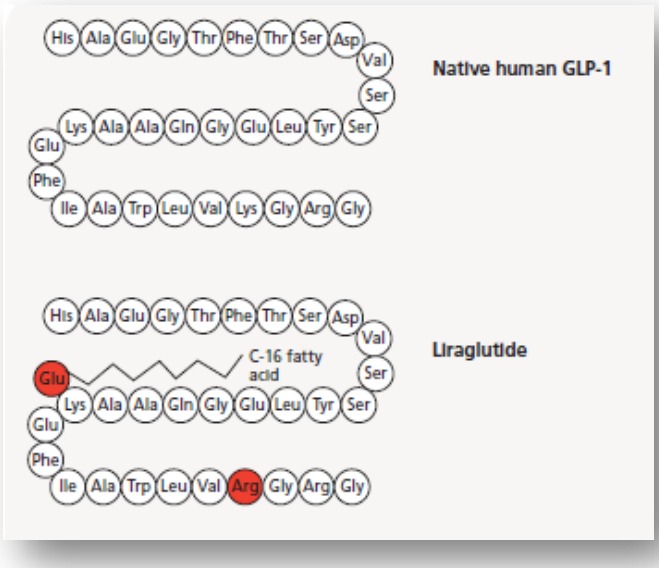

Figure 2

With regard to pharmacokinetics and pharmacodynamics, these changes will prolong the plasma half-life by 13 hours. It is to be noted that the natural half-life of endogenous GLP-1 is about 1.5 to 2.1 minutes.

The effects of liraglutide in blood glucose control [19, 20,21,22]

• By influencing the pancreas, liraglutide induces insulin secretion, which secretion is dependent upon the blood glucose level. On the other hand, as liraglutide influences the pancreas, the insulin production is increased and the secretion of glucagon is suppressed. The increased secretion of insulin on consumption of liraglutide is dependent upon the blood glucose level; hence, consumption of liraglutide will not increase the risk of hypoglycemia. On the other hand, liraglutide will not affect the anti-insulin hormones response to hypoglycemia in type 2 diabetic patients.

• Liraglutide generates a feeling of satiety by influencing the hypothalamus and decreases the amount of postprandial blood sugar by lowering the energy intake.

• Liraglutide influences the liver, thereby glucose production in the liver, which is specially effective in lowering the fasting plasma glucose level in the patients.

• Liraglutide influences the gastro-intestinal (GI) system and decreases the movements of the GI system, leading to a feeling of satiety and improved postprandial blood glucose level.
• The overall effects of liraglutide on the hypothalamus and GI system decreases the patient's energy intake, leading to weight loss. The weight loss is accompanied by reduction in the visceral fat; in addition, the patients weight loss increases with increased BMI.
• Liraglutide influences the muscular and fat tissues to increase the amount of glucose uptake by these tissues.
• Liraglutide improves the function of the pancreatic beta cells in type 2 diabetic patients by 30 percent, which has been confirmed by HOMA-B studies.

Cardiac effects of liraglutide [23, 4]

A major part of the positive effects of liraglutide in decreasing the cardiovascular complications of diabetes is because of its effect in the patients glycemic control. However, it has also been observed that GLP-1 analogues can:
• Protect the myocardium against ischemic conditions in animal studies;
• Improve the myocardium function;
• Improve the endothelium function
• Induce diuresis and natriuresis, leading to decreased arterial blood pressure.

It has also been shown that liraglutide has positive effects on the cardiovascular system and causes prolonged survival, decreased occurrence of heart rupture and enhanced cardiac function in the animal models of myocardial infarction.
Treatment with liraglutide for seven days prolonged the survival of mice in which myocardial infarction had been experimentally induced.

In the mice treated with liraglutide, myocardial hypertrophy was decreased and the cardiac function was improved. In addition, the size of the infarcted area in the mentioned animals was decreased significantly.

Weight loss

Multiple studies have shown that an intensive treatment of type 2 diabetes has played a significant role in decreasing the cardiovascular complications, although the intensive treatment, as compared to the conventional treatment, leads to more weight gain, which may in turn aggravate hyperglycemia by inducing insulin resistance in the patient. According to the studies, liraglutide has caused weight loss in patients, and hence, it can play a better role in decreasing the cardiac complications [4].

Lipid profile

Increased level of triglyceride and LDL and decreased level of HDL have been recognized as the risks factors of cardiovascular diseases. The studies conducted on liraglutide administered in type 2 diabetic patients have shown that liraglutide will significantly lower the total cholesterol level and LDL level, free fatty acids, and triglyceride [4].

Heart rate

Despite the fact that the general profile of liraglutide decreases the cardiovascular complications of diabetes, it has been found that using liraglutide is accompanied by increased heart rate, which can potentially lead to an increase in cardiovascular

complications of diabetes. In a meta-analysis of 22 studies, a significant increase was observed in the number of heart rates in patients treated with liraglutide that is 2.71 per minute (from 1.45 to 3.97). The mechanism of the increase in the number of heart rates and the clinical effects of these changes in the heart rate due to using liraglutide still remains unknown [24, 4].

Arterial blood pressure

In the UKPDS study, it was confirmed that an intensive treatment of arterial hypertension would lead to a significant decrease in mortality rates, cerebrovascular accidents, and microvascular complications. In a meta-analysis of 31 studies it was found that liraglutide decreased the mean arterial blood pressure by 1.79 mmHg (from 0.64 to 2.94 mmHg); however, the decrease in the diastolic blood pressure was not statistically significant [24, 4].

Hypoglycemia

Hypoglycemia, as one of the complications caused by diabetes treatment, plays a conspicuous role in the occurrence of cardiovascular complications. Hypoglycemia can increase the risk of cardiovascular diseases in diabetic patients by inducing inflammation, impaired coagulation, sympatho-adrenal response, and endothelial dysfunction. As liraglutide will not lead to hypoglycemia in patients, it may play an important role in decreasing the cardiovascular complications [4].

The position of liraglutide in the management of type 2 diabetes guideline recommended by American Diabetes Association (ADA) in 2015 (Figure 3) [6].

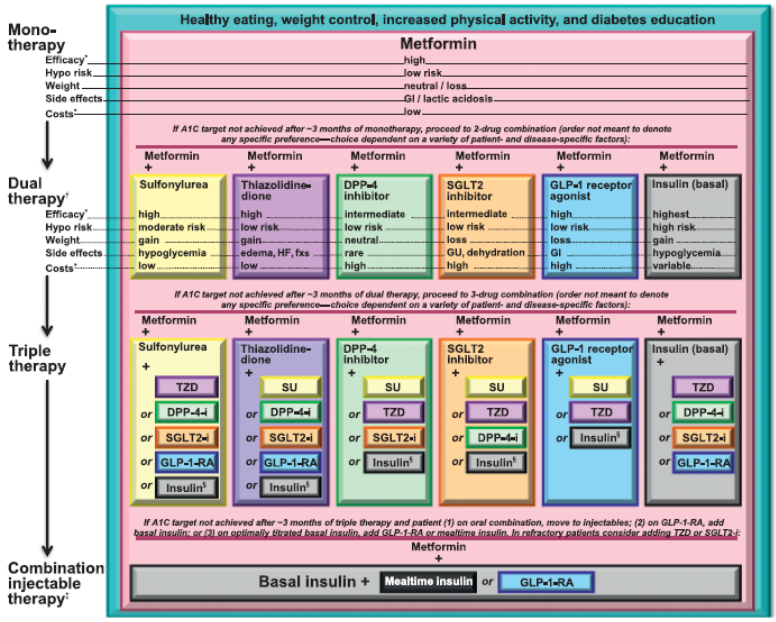

Figure 3

Due to the positive effects of GLP-1 in controlling the blood glucose in people with diabetes, and its positive cardiac effects, ADA recommends using this agent in, treating diabetes in two places: ,

1. After metformin, as a second-line drug
2. As a drug that can be added to the basal insulin after starting basal insulin in cases who does not achieve the glycemic targets.

Conclusion

Liraglutide is an GLP-1RA with a 24 hours duration of action, which is designed to be injected once a day, and may be a suitable drug in treating type 2 diabetic patients on account of its positive effect in controlling the blood glucose levels in diabetic patients without an increased risk of hypoglycemia, in addition to its positive effects with respect to the body weight and decreased occurrence rate of cardiovascular complications of diabetes.

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