



REVIEW ARTICLE

## ROLE OF LIRAGLUTIDE IN A MAJOR COMPLICATION OF DIABETES: A CRITICAL REVIEW OF CLINICAL STUDIES

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**Diabetes is a most common, serious and chronic illness resultant from the error of insulin secretions or action. Liraglutide is a synthetic glucagon-like peptide-1 receptor agonist (GLP-1 RA) that shares 97% of homology with the glucagon-like peptide-1 (GLP-1) human structure. It acquires a much-extended circulating half-life. Including of numerous in-vitro and in vivo studies explaining the liraglutide efficiency on diabetes, however, various preclinical and clinical studies representing the potential benefit of liraglutide in other complicated diseases induced by diabetes. The therapeutic conclusion of liraglutide in association with other difficulties generated in diabetic patients is complex and includes numerous positive roles. So, there is a necessity of clinical studies to clarify the roles of liraglutide in other complications caused by diabetes. In the coming time, liraglutide uses lonely or in combination may be the predictable approach in the successful management of other diabetes tempted complications. The aim of this review is to collect evidence on the real-world clinical efficiency of liraglutide on main diseases created by diabetes. In present study, results from electronically searchable data are included from randomized clinical studies, cohort studies, clinical trials in addition to other related articles.**

**Key words:** Diabetes, Retinopathy, Nephropathy, Neuropathy, Liraglutide, Clinical studies.

### INTRODUCTION

Diabetes is a most common disease represented by the elevated level of blood glucose caused by insufficient insulin secretion and/or insulin

action in the pancreatic  $\beta$  cells (Sharma *et al* 2017). According to the report of International Diabetes Federation (IDF) in 2013, 382 million individuals were affected by diabetes in all

around the world and this number will raise up to more than 592 million by the year 2025 (Chellappan *et al* 2017). The main consequence of diabetes is the weakening of the body's ability to use food as either the insulin not properly producing by the pancreas or the body cannot accurately use insulin (American Diabetes, 2009).

The lower level of blood glucose (Hypoglycemia) is most frequently observed in patients with diabetes when the body gets too much insulin, very less food, a late meal, or more than the normal amount of exercise. Whereas when the body gets less amount of insulin, a higher quantity of food, or very little exercise, it outcomes in elevated levels of blood glucose (hyperglycemia) (Kazmi *et al* 2012).

Hyperglycemia may also have contributed to stress. Diabetes is primarily classified into three categories: type-1 diabetes mellitus (T1DM), type-2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM). T1DM, also called as insulin-dependent diabetes mellitus (IDDM), or "juvenile diabetes" reveals the autoimmune disorder and destruction of the pancreatic  $\beta$ -cells which further leads to the suppression or termination of insulin production (Khadra *et al* 2011). T2DM, also termed as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes which is triggered by either lower level or absence of insulin resistance to insulin (King, 2012). T2DM is the more widespread form and responsible for 90% of all diabetes cases globally (Brunton, 2008).

Insulin resistance-related with obesity because of free fatty acids (FFA) and inflammatory cytokines released from the expanded adipose tissue (Guilherme *et al* 2008). GDM arises in around 7% cases of pregnancies and there is a bigger risk of morbidity and death to mother, fetus as well as a successive neonate. Special care and therapy are essential for GDM (Buchanan *et al* 2012). Women with the history of GDM have a suggestively higher risk of T2DM and of cardiovascular disease (CVD) during the following years after delivery (Kim, 2014; Herath *et al* 2017).

### Glucagon-like peptide-1 (GLP-1)

Literature reports indicates that natural and synthetic peptides are associated with a wide spectrum of pharmacological properties (Greenwood *et al* 2011; Dahiya, 2007; 2008; Dahiya and Kumar, 2008; Dahiya and Gautam, 2011; Dahiya and Singh, 2017; Dahiya *et al*

2017). GLP-1RA are a novel class of anti-diabetic medicines that imitate the incretin hormones effects (Gupta *et al* 2017). Incretin hormone synthesizes in response to intake of food, GLP-1 can trigger insulin secretion by  $\beta$ -cells of the pancreas in a glucose-dependent way in addition to repress release of glucagon from  $\alpha$ 2-cells (Kim and Egan, 2008). GLP-1 receptors are mediating the action of GLP-1 in the maintenance of glucose homeostasis. Even though there is a number of potentially beneficial effects of GLP-1, however, it is inappropriate as a therapy in T2DM because of its short half-life (Nadkarni *et al* 2014).

### Liraglutide

Liraglutide is a synthetic GLP-1RA which shares 97% homology with the GLP-1 structure of human and retains an extended circulating half-life (Figure 1).

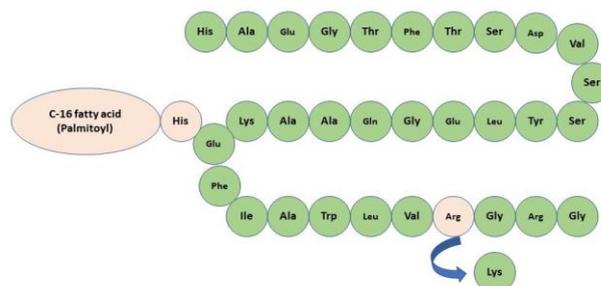


Fig. 1. Structural formula of liraglutide

It has prolonged pharmacokinetics as a consequence of accumulation at its site of injection, albumin binds in the circulation results in decreased susceptibility to degradation of enzyme, thus making it a new anti-diabetic therapy appropriate for once a daily injection subcutaneously (Tiwari *et al* 2017). Liraglutide has a potential of glucose-lowering effects across 24 h, with perfections in fasting as well as postprandial glucose levels (Christensen *et al* 2011).

In clinical studies, liraglutide as a monotherapy has attained HbA1c reductions up to 1.6% in drug-naive subjects. The occurrence of hypoglycemia with the treatment of liraglutide is comparatively little, possibly reflecting a glucose addiction of its insulintropic action (Peters, 2013). Clinically liraglutide also has effects on body weight, along with mean decreases of 2-4 kg occurring in a big number of clinical trials (Schwartz and Kohl, 2010).

Moreover, facts are signifying positive effects on cardiovascular risk factors such as systolic blood

pressure is decreased by 2-6 mmHg with therapy of liraglutide, whereas Phase II clinical studies have proved molecular markers improvements of cardiovascular risk (Tiwari *et al* 2017). Liraglutide therapy also seems to have positive effects on pancreatic  $\beta$ -cell function, with clinical data viewing  $\beta$ -cell function improvements as well as capacity of insulin secretion (Garber, 2011).

### Literature search methodology

The main aim of the present study is to review

the literature on liraglutide and its clinical studies in diabetic patients in the last 10 years (2007 to 2017). Various databases such as science direct, pubmed, google scholar, and clinicaltrials.gov were used to explore for original articles and clinical trials available in the english language with the following keywords in combination "liraglutide", "retinopathy", "nephropathy", "neuropathy", "cardiovascular problems" and "diabetes". To date, the published clinical trials have studied the liraglutide effects on diabetes caused complications (**Table 1**).

**Table 1.** Clinical trials to investigate the effect of liraglutide alone or in combination in various conditions in diabetes

Identifier no.	Dose of liraglutide	Observing effect	Duration	Number of patients	Phase	Year started	Country
NCT01208012	0.6, 1.2 and 1.8 mg	Endothelial function and microvascular blood flow	12 weeks	44	4	2010	Germany
NCT01499108	0.6, 1.2, and 1.8 mg	Blood pressure lowering effect	49 days	32	4	2011	Denmark
NCT01593137	1.8 mg	Clinical, endothelial and image markers of cardiovascular risk	12 months	–	4	2012	Spain
NCT00620282	1.8 mg	Endothelial function	12 weeks	–	3	2008	United States
NCT01511692	1.8 mg	Appetite	4 weeks	43	1	2012	Germany
NCT01753362	1.8 mg	Overweight	26 weeks	84	3	2012	United States
NCT01620489	1.8 mg	Moderate renal impairment	26 weeks	279	3	2012	United States
NCT02109315	6.0 mg	Hypoglycemia-induced oxidative stress, inflammation and endothelial dysfunction	8 weeks	20	1	2014	Spain
NCT02201550	1.8 mg	Immune cells in obese	12 weeks	9	1	2014	Denmark
NCT01179048	1.8 mg	Cardiovascular outcome	90 days	9340	3	2010	United States
NCT02686177	1.2 mg	Angiogenesis	4 weeks	40	4	2016	France
NCT01784965	0.6, 1.2, and 1.8 mg	Calorie restricted diet augments weight loss	14 weeks	69	3	2009	United States
NCT01595789	0.6, 1.2, and 1.8 mg	Coronary artery disease	26 weeks	41	4	2012	Denmark

NCT00993304	0.6, 1.2, and 1.8 mg	Blood triglyceride (fat) levels	12 weeks	20	1	2009	Denmark
NCT02655770	1.8 mg	Diastolic dysfunction on cardiac mri	18 weeks	40	4	2016	Denmark
NCT01399645	0.6, 1.2, and 1.8 mg	Liver fat fraction	12 weeks	35	2	2011	Canada
NCT01785043	0.6, 1.2, and 1.8 mg	Endothelial function	3 months	13	4	2013	Spain
NCT01425580	1.8 mg	Heart failure	18 weeks	62	2	2012	Sweden
NCT02721888	1.2 mg	Fatty liver content and lipoprotein metabolism	6 months	120	4	2012	France
NCT02138045	0.6, 1.2, and 1.8 mg	Diabetic neuropathy	26 weeks	40	1	2014	Denmark
NCT01394341	1.8 mg	Severe renal insufficiency	12 weeks	40	4	2011	Denmark
NCT01761318	0.6, 1.2, and 1.8 mg	Cardiovascular endpoints	26 weeks	50	4	2013	Netherlands
NCT01740921	1.8 mg	Microvascular function	4 months	39	-	2011	United Kingdom
NCT01664676	1.2 mg	Kidney function	15 hours	11	4	2012	Denmark
NCT03260881	0.6, 1.2, and 1.8 mg	Epicardial fat inflammatory genes	12 weeks	40	4	2017	United States
NCT01931982	1.8 mg	Microvascular myocardial function	10 weeks	20	4	2013	Denmark
NCT01755572	0.6, 1.2, and 1.8 mg	Blood pressure outcomes	21 days	22	4	2013	Canada
NCT01472640	1.8 mg	Left ventricular function in chronic heart failure	24 weeks	240	-	2011	Denmark
NCT02963922	3.0 mg	Overweight or obesity	56 weeks	400	3	2017	United States
NCT01272232	1.8 mg and 3.0 mg	Overweight or obese	56 weeks	846	3	2011	United States
NCT01847313	0.6 mg	Diabetic kidney disease	26 weeks	20	3	2013	Ireland
NCT02147925	0.6, 1.2, and 1.8 mg	Liver fat	26 weeks	150	4	2014	China

Website: ClinicalTrials.gov

### **Complications of diabetes and liraglutide**

Diabetes is associated with many complications. Acute metabolic problems are related with mortality such as diabetic ketoacidosis from the extremely high level of blood glucose concentrations (hyperglycemia) and coma as the

consequence of the low level of blood glucose (hypoglycemia) (Kitabchi *et al* 2009). The subsequent complications are grouped under "microvascular disease" (due to injury to small blood vessels) and "macrovascular disease" (due to injury to the arteries) (Martín-Timón *et al*

2014). Microvascular difficulties include neural damage (neuropathy), eye disease (retinopathy) and kidney disease (nephropathy) which are deliberated in detail later inside this review (Cade, 2008).

The most important macrovascular problems include accelerated CVD resultant in myocardial infarction and cerebrovascular disease revealing as strokes (Long and Dagogo-Jack, 2011). Even though the underlying etiology remnants controversial, there is also myocardial dysfunction related to diabetes which looks at least in part to be independent of atherosclerosis. Other chronic complications of diabetes include dementia, depression and sexual dysfunction (Laakso, 2010).

### **Diabetic retinopathy**

Diabetic retinopathy is the common reason of sightlessness in adults (Liew *et al* 2014). After 20 years diagnosis, approximately all T1DM patients and at least 60% of T2DM patients will show indication of retinopathy (Lee *et al* 2015). This visual loss has a reflective negative impact on the patient's lives (Coyne *et al* 2004). According to the previously reported studies, slight or insignificant visual weakening is also linked with poor quality of life (Murchison *et al* 2017). The primary stages of retinopathy are considered by improved vascular permeability which develops to ischemia and retinal microvasculature neovascularization (Zhang *et al* 2011). Randomized controlled trials have revealed that carefully maintenance of near-regular glycemia and strict blood pressure control may contribute significantly towards reducing the diabetic retinopathy progression (Frank, 2004). Numbers of preclinical and clinical studies suggested a potential protective role for GLP-1RA in diabetic retinopathy (Salcedo *et al* 2012).

Based on earlier preclinical studies reports, it was elucidated that GLP-1 and longer-lasting protease-resistant analogs cross the blood-brain barrier (BBB) and show a neuroprotective effect in the various mouse models of numerous neurodegenerative diseases, such as Alzheimer disease, Parkinson disease etc. Based on the preclinical literature, it has been planned to observe the expression of liraglutide in human and db/db mice retinas. They have systemic and topically administer (eye drops) GLP-1R agonists in db/db mice and human then found the abundant expression of GLP-1R in the retinas from db/db mice and human retina.

Furthermore, they have confirmed that systemic administration of a GLP-1R agonist (liraglutide) inhibits retinal neurodegeneration (glial activation, neural apoptosis, and electroretinographically abnormalities). These results could be associated with the substantial decrease in extracellular glutamate along with an increase of prosurvival signaling pathways (Hernandez *et al* 2016). A recent outcome of a clinical trial using a liraglutide (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results-A Long-Term Evaluation [LEADER]) in subjects with T2DM have presented that liraglutide reduced the diabetic retinopathy events than the placebo (Marso *et al* 2016). Though limited human studies propose a probable adverse effect of GLP-1 based treatments on retinopathy progression (Prasad-Reddy and Isaacs, 2015).

### **Diabetic nephropathy**

Diabetic nephropathy is a main causing factor of chronic kidney disease, and presently the common reason of end-stage renal failure (Yuan *et al* 2017). Managing of diabetic patients with chronic kidney disease is more complex and economically more expensive than managing of patients with diabetes alone (Inzucchi *et al* 2012). Hyperperfusion and hyperfiltration of Glomerular are heralded the nephropathy onset, followed by leakage of albumin in urine (Albuminuria), and afterward development of renal failure (Dabla, 2010). Albuminuria is indicating a renal pathology and also its an independent marker of risk related to CVD (de Zeeuw, 2004). There is a further progression of cardiovascular risk of diabetic patients that reflects a reduction in the glomerular filtration rate (GFR) (Schneider *et al* 2016). Around every 3rd of diabetic patient develop substantial nephropathy, and the related pathophysiologic modifications in the renal system of these patients are heterogeneous and complex (Tan *et al* 2017). Poorly diabetic control, higher blood pressure, and genetic predisposition are related to progressive kidney disease because of diabetic nephropathy (Van Buren and Toto, 2011).

Many preclinical kinds of literature reported that that GLP-1RA bind to GLP-1 receptors in the kidney and have direct nephron protection through anti-apoptotic, antioxidant, and anti-inflammatory, effects (Thomas, 2017; Li *et al* 2016). A retrospective study has included 84 Japanese T2DM patients diagnosed with overt

nephropathy (stage 3 or 4), and from past 12 months had on liraglutide treatment. Body mass index, glycol albumin, estimated glomerular filtration rate, HbA1c, and urine albumin-to-creatinine ratio was measured during a 6 and 12 months of liraglutide administration. They found a significant reduction in a level of HbA1c and glycol albumin and improvement in estimated glomerular filtration rate after administration of liraglutide compare to baseline. Based on results, they have concluded that liraglutide has a nephron protective activity from an early stage of nephropathy to the conservative stage of renal failure by improvement of weight loss or blood glucose (Tamasawa *et al* 2017). Another study was carried out to examine the effects on body mass index, glucose metabolism and kidney function of 18 diabetic nephropathy patients after 6 months administration of liraglutide. After 6 months of liraglutide administration, the blood glucose levels and average HbA1c were significantly reduced, though, no significant changes in kidney function. The outcomes suggested the improvement in glucose metabolism and body mass index reduction without observable changes in kidney function after administration of liraglutide to diabetic nephropathic patients (Ryuge *et al* 2012). In support of this study, it has been planned to study the effect of liraglutide on proteinuria and the progression of diabetic nephropathy in T2DM patients. They have included 23 T2DM patients with diabetic nephropathy, who had already been treated with renin-angiotensin system blockade under the restriction of dietary sodium. They were given a liraglutide to these selected patients for 48 weeks. After 48 weeks of administration of liraglutide, they have seen a significant reduction in a body mass index, HbA1c, and proteinuria as well as also a significant reduction in a rate of decline in estimated glomerular filtration rate whereas not observed any changes in systolic blood pressure. Based on results suggested that liraglutide treatment can be not only used for reducing the level of body mass index and HbA1c, but also for reducing the progression of nephropathy in T2DM patients (Imamura *et al* 2013).

One more clinical study performed in Japan decided to observe the hemodialysis effect on the blood glucose profile and level of liraglutide after administering liraglutide injection (0.6 mg or 0.9 mg) in 10 Japanese T2DM patients with end-stage renal disease (ESRD). On day 1 and 3, hemodialysis was conducted which had not

shown any significant changes in maximum plasma concentration, the area under the concentration-time curve, tmax of liraglutide in T2DM patients with ESRD.

Likewise, hemodialysis did not alter the duration of hyperglycemia and hypoglycemia, mean or minimum glucose levels following administration of liraglutide. Whereas, substantial rises in mean amplitude of glycemic excursions (MAGE) as well as standard deviation (SD) as markers of fluctuation in glucose value, and the maximum glucose level were detected during hemodialysis.

During hemodialysis, no side effects including a lower level of glucose were seen after the injection of liraglutide and it was well tolerated in T2DM patients with ESRD undergoing hemodialysis.

Based on results, researchers have recommended that hemodialysis did not disturb the pharmacokinetic profile of liraglutide, except for MAGE, SD, along with the maximum glucose level. Hence, it might be possible to use liraglutide therapy during hemodialysis in T2DM patients with ESRD. Without adjusting a dose (Osonoi *et al* 2014).

### **Diabetic neuropathy**

DM is a common globally rising metabolic disease which is related with long-term complications of central nervous system (CNS) and peripheral nervous system (PNS) that results in nerves damage because of high level of blood sugar for a long period of time (Gogia and Rao, 2017). Peripheral, autonomic, proximal, and focal are the 4 types diabetic neuropathy, shows the symptoms of nerve damage such as tingling, numbness, pain in the toes, hands, legs, arms and fingers, indigestion, nausea or vomiting, dizziness and faintness due to drop in blood pressure as well as urination problem, dry vaginal in women and erectile dysfunction in men (American Diabetes Association, 2009).

Many kinds of literature reported a neuroprotective effect of GLP-1 analog, liraglutide in various neurodegenerative disorders in non-diabetic patients. Qi *et al.*, group has induced an Alzheimer in a mice model through an amyloid  $\beta$  protein ( $A\beta$ ) and observed an effect of liraglutide by administered with 25 nmol/day, liraglutide for 56 days. They found the significant effect of liraglutide by seen an alleviated cognitive impairment in AD through a reduction in phosphorylation of tau (Qi *et al* 2016). In addition to this, a study was conducted

on a rat model of middle cerebral artery occlusion (MCAO) and given a liraglutide. They have discovered a significant decrease stress-related hyperglycemia without causing hypoglycemia, reduced infarct volume, and improved neurologic deficits. On the basis of their observation, they concluded that liraglutide has therapeutic potential for patients with ischaemic stroke, particularly those with T2DM (Zhu *et al* 2016).

A number of studies have performed on the experimental animal which proved the neuroprotective activity of liraglutide such as anticonvulsant (Gupta *et al* 2017), anti-parkinsonian (Athauda and Foltynie, 2017; Hansen *et al* 2016) in non-diabetic conditions. Only a clinical trial is going on to observe the effect of liraglutide on diabetic neuropathy. This trial was started in May 2014 and last updated on 22 April 2015 as per the US government website the clinicaltrial.gov. Purpose of this trial is to explore whether liraglutide has a long-term effect on clinical symptoms and biomarkers in patients with diabetic neuropathy (NIH).

### **Cardiovascular diseases (CVD) associated with diabetes**

CVD is the major cause of illness and death in DM patients (Leon and Maddox, 2015). DM patients have a 3 to 5 times more risk of CVD and up to 3 times increase in death compared to nondiabetic persons (Fox, 2010). Diabetes, smoking, high body mass index, high cholesterol level (hypercholesterolemia), family history and age are the major risk factors for CVD such as atherosclerosis and coronary heart disease (CHD) (Daniels *et al* 2011). A high pulse pressure causes hardening of arteries which is an independent risk factor for CVD (Warren *et al* 2010). Few studies confirmed that the burden of risk factor tended to be more among women, with a larger incidence of obesity and trends toward more rates of diabetes mellitus, high blood pressure and home stress (Masic *et al* 2011). Apart from the major cardiac complications, other CVDs are also linked with DM patients such as disturbed conductivity of the left ventricle (LV) (Serhiyenko and Serhiyenko, 2015; Lauruschkat *et al* 2008), atrial fibrillation (AF) due to increased oxidant stress (OS) (Berry *et al* 2007). There is also evidence that high blood pressure might induce diabetic angiopathy through the OS generation or through the advanced glycation end products (AGEs) accumulation, leading to nitrous oxide

systems (NOS) (Tabit *et al* 2010; Bertoluci *et al* 2015).

Based on the number of the reported literature of preclinical studies related to liraglutide effect on CVD in diabetes-induced experimental animals, has exhibited a significant protective effect. Inoue *et al.*, group have observed an effect of liraglutide (0.3 mg/kg; s.c./12 h) in streptozotocin (STZ) induced a type 1 diabetes in rat's model. They were evaluated the lipid metabolism, apoptosis, genes that affect apoptosis, myocardial triglyceride, expression of protein kinase C (PKC). In the results, they found that protective effect of liraglutide *via* activation of the AMPK-Sirt1 pathway (Inoue *et al* 2015). In another study, liraglutide effect was seen on kidney fibrosis and atherosclerosis in a moderate uremia mouse model. They found a beneficial effect of liraglutide by reducing atherosclerosis and attenuating kidney inflammation (Bisgaard *et al* 2016).

Further, a clinical trial explored liraglutide effects on numerous cardio-metabolic risk markers of the metabolic syndrome in subjects with T2DM. They conducted an 18-month prospective and real-world study. All subjects had T2DM and the metabolic syndrome based on the American Heart Association and the National Heart Lung and Blood Institute (AHA/NHLBI) criteria. They included the 121 subjects with T2DM and the metabolic syndrome, naïve to incretin-based therapies and treated with metformin only. For the study, liraglutide (1.2 mg/day) was added to metformin (1500-3000 mg/day).

For metabolic parameters, fasting plasma samples were collected and thickness of carotid-intima media was evaluated. They found a significant decrease in body mass index, waist circumference, HbA1c, fasting glycemia, triglycerides, total- and LDL-cholesterol, and carotid-intima media thickness throughout the 18-month follow-up. Correlation investigation presented a significant association among changes in triglycerides and carotid-intima media thickness. Hence, they proved that liraglutide improves cardio-metabolic risk factors in subjects with the carotid-intima media thickness in a real-world study (Rizzo *et al* 2016). In another eight months of prospective study, 29 subjects with T2DM and non-alcoholic fatty liver disease (NAFLD) were included. Liraglutide (0.6 mg/day; 14 days) followed by 1.2 mg/day, was administered along with metformin. They have observed a significant

reduction in a level of glycated hemoglobin in both groups. There were no observable changes in a lipid level, body weight, and waist circumference. Significant reduction in carotid-intima media thickness in T2DM patients with NAFLD, but not in T2DM patients without NAFLD (Rizvi *et al* 2015).

In addition to this, the outcome of 48 weeks liraglutide therapy was assessed on major risk factors of CVD in 115 T2DM outpatients (55 women and 60 men), on therapy of anti-hypertensive, stable hypoglycemic, and lipid-lowering drugs.

They observed a substantial decrease from baseline of fasting blood glucose levels, HbA1c, waist, total cholesterol, triglycerides, body weight circumference, non-HDL-C and LDL-cholesterol, and significant increase in the level of HDL-cholesterol as well as a significant decrease in both systolic and diastolic blood. They finally concluded that 48 weeks of liraglutide therapy with continuing hypoglycemic therapy significantly improves all major risk factors related to CVD and decreases cardiometabolic risk (Russo *et al* 2015).

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## CONCLUSION AND PERSPECTIVES

Results from the reported literature clearly show that liraglutide applies pleiotropic effects on humans in addition to potential hypoglycemic activity. The therapeutic effect of liraglutide in a major complication induced by diabetes is complex and involves in various beneficial effects. Our review supports consideration of a modification to prescribing guidelines for liraglutide's usage to allow in diabetic patients associated with complications like retinopathy, nephropathy, neuropathy and cardiovascular diseases. Literature indicates that less number of the clinical study was conducted on the effect of liraglutide on neuropathic diseases. Although a number of animal studies have performed for observing the liraglutide effect on diabetic neuropathy and showed positive effects, however clinical studies are required to perform so that actual human data can be analyzed. Any novel extension of liraglutide use in diabetic patients will need to be accompanied by a suitable reduction in dosage amount and careful follow-up valuations of different main organ functions.

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