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Glucagon-like peptide-1 receptor agonists favorably address all components of metabolic syndrome

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Abstract

Cardiovascular death is the leading cause of mortality for patients with type 2 diabetes mellitus. The etiology of cardiovascular disease in diabetes may be divided into hyperglycemia *per se* and factors operating through components of metabolic syndrome (MetS). Hyperglycemia causes direct injury to vascular endothelium and possibly on cardiac myocytes. MetS is a cluster of risk factors like obesity, hyperglycemia, hypertension and dyslipidemia. The incidence of this syndrome is rising globally. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are a group of drugs, which address all components of this syndrome favorably. Experimental evidence suggests that they have favorable actions on myocardium as well. Several compounds belonging to GLP-1RA class are in market now and a large number awaiting their entry. Although, originally this class of drugs emerged as a treatment for type 2 diabetes mellitus, more recent data generated revealed beneficial effects on multiple metabolic parameters. We have studied literature published between 2000 and 2016 to look into effects of GLP-1RA on components of MetS. Results from recently concluded clinical trials suggest that some of the molecules in this class may have favorable effects on cardiovascular outcome.

Key words: Metabolic syndrome; Diabetes; Glucagon-like peptide-1 receptor agonists; Lipids; Body weight; Microalbuminuria

Core tip: The incidence of metabolic syndrome (MetS) is on the rise globally. This will have a negative impact on cardiovascular outcome. Whereas most of the anti-hyperglycemic agents have neutral or negative effects on components of MetS, glucagon-like peptide-1 receptor agonists drugs favorably address all components of MetS. By doing so, they may have a cardio protective role. We have reviewed recent literature to give an updated account on the topic. Results from recently concluded clinical trials suggest that some of the molecules in this class may have favorable effects on cardiovascular

outcome.

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INTRODUCTION

In 1977, Haller[1] used the term "metabolic syndrome (MetS)" for association of obesity, diabetes mellitus, lipid disorder, hyperuricemia, and hepatic steatosis which increase the risk of atherosclerosis.

In 1988, Reaven[2] observed clustering of risk factors for coronary heart disease and stroke - like central obesity, hypertension, hyperglycemia and dyslipidemia, which may have a direct relationship with insulin resistance and termed the cluster, MetS X. This is also known as insulin resistance syndrome or simply, MetS.

The prevalence of diabetes and obesity is on the rise globally. In 2002, the prevalence of MetS in the United States was 34% in the adult population[3]. This will have an impact on cardiovascular mortality and morbidity.

Some authorities have suggested other components like non-alcoholic fatty liver disease (NAFLD), Microalbuminuria, high levels of C-reactive protein (CRP) and polycystic ovary syndrome (PCOS), as parts of MetS[4].

Recent figures in the United States estimate that there has been a reduction in the prevalence of hypertension and dyslipidemia, but an increase is noted in central obesity and hyperglycemia in the year 2010, when compared with figures of the year 1999-2000[5].

As defined by the 2009 Joint Scientific statement, the qualifying criteria for MetS demands the presence of any three or more of the following biological thresholds: (1) waist circumference $\geqslant$ 102 cm (male adults) and $\geqslant$ 88 cm (female adults); (2) fasting plasma glucose $\geqslant$ 5.55 mmol/L (100 mg/dL); (3) blood pressure of 130/85 mmHg; (4) triglycerides 1.69 mmol/L ($\geqslant$ 150 mg/dL); and (5) high-density lipoprotein-cholesterol (HDL-C) 1.03 mmol/L (< 40 mg/dL) (male adults) and 1.29 mmol/L (< 50 mg/dL) (female adults). Prescription drug use was estimated for lipid-modifying agents, anti-hypertensive, and anti-hyperglycemic medications[5,6].

The National Health and Nutrition Examination Survey (NHANES) in 1999 and 2010 (in 2-year survey waves) estimated the prevalence of MetS in adult population ($\geqslant$ 20 years of age). As per the results from 1999-2000 and 2009-2010: There was a reduction in the age-adjusted prevalence of MetS (based on biologic thresholds) by 2.6% (from 25.5% to 22.9%). Further perusal of the different components of MetS during this period revealed the prevalence of hypertriglyceridemia to be decreased by 9.2% (33.5% to 24.3%), as did the hypertension by 8.3% (32.3% to 24.0%). Nevertheless the prevalence of hyperglycemia increased by 7% (12.9% to 19.9%), as did elevated waist circumference by 10.7% (45.4% to 56.1%). These trends varied considerably by sex and race/ethnicity. Changes in the prevalence of hypertension, suboptimal triglycerides, and high-density lipoprotein-cholesterol have corresponded with increases in anti-hypertensives and drugs for dyslipidemia, respectively[6].

As regards to obesity, the prevalence is on the rise. Results from the 2011-2012 NHANES indicate that among United States adults aged 20 and over, 33.9% are overweight (BMI 25.0-29.9), 35.1% are obese (BMI 30.0-34.9), and 6.4% are extremely obese (BMI $\geqslant$ 35.0), The survey indicated wide variation of obesity in terms of age, sex and ethnicity[7].

Native glucagon-like peptide-1 (GLP-1) is a gut hormone, produced by L-cells of distal ileum and colon in response to entry of nutrients, and has a very short half-life of about 2 min. GLP-1 is rapidly destroyed by the circulating enzyme dipeptidyl peptidase-Ⅳ (DPP-Ⅳ). GLP-1 receptors have been found in various tissues like pancreatic islet cells, the gastrointestinal tract, nervous system, cardiovascular system, kidneys and lungs.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are structurally similar to native GLP-1, but resist degradation by the enzyme DPP-Ⅳ. GLP-1RA is a new class of injectable drugs, emerged for treatment of type 2 diabetes, but has also shown beneficial effects on weight, blood pressure and lipid parameters.

Traditionally GLP-1RAs were developed as an injectable formulation, as they were rapidly degraded by the gastrointestinal enzymes when administered orally[8]. However this scenario is expected to change in the near future, with oral semaglutide preparing to hit the market. It was strongly debated, how a complex protein structure could escape the onslaught from GI juices. In the oral preparation of semagutide, a new carrier termed Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate (SNAC) is co-packaged to facilitate its absorption from the gut. SNAC helps in increasing the solubility of semaglutide, as well as increases its permeability across cell membrane by increasing the local (gastric mucosa) pH[9].

We have searched PubMed, Cochrane Library, EMBASE and Google for articles on GLP-1RA, published between 2000 and 2016, and we have found uniformly beneficial effects of GLP-1RA on cardiovascular system, obesity, hyperglycemia, hypertension and lipids. These effects of GLP-1RA have been discussed in the following paragraphs. So, this class of drug may have a favorable effect on cardiovascular mortality and morbidity.

Several GLP-1RA are already in the market and some are in the process of development. Below is a list of GLP-1RA: (1) Exenatide (Byetta) FDA approval in 2006; (2) Liraglutide (Victoza) FDA approval in 2010; (3) Exenatide Long Acting (Bydureon) FDA approval in 2012; (4) Lixisenatide (Lyxumia) EU approval in 2013; (5) Albiglutide (Tanzeum - United States; Eperzan - EU) FDA approval in 2014; (6) Dulaglutide (Trulicity) FDA approval in 2014; (7) Taspoglutide - development has been halted due to injection site skin reaction and gastrointestinal

side effects; and (8) Semaglutide - injectable and oral - undergoing clinical trials.

Fixed ratio combination of GLP-1RA and basal insulin are also available treatment option for patients with inadequate glycemic control: (1) Insulin Degludec/Liraglutide (Xultophy) EU approval in 2014; and (2) Insulin Glargine/Lixisenatide (Lixilan) Regulatory submission to USFDA in 2015.

Insulin Glargine/Lixisenatide combination has been studied in two pivotal Phase Ⅲ trials; LixiLan-L and LixiLan-O, which included 1906 patients with type 2 diabetes. The results of these trials show that LixiLan significantly lowers HbA1c compared to both insulin glargine and lixisenatide. LixiLan-L included 736 patients, whose type 2 diabetes was not adequately controlled on basal insulin alone or combined to 1-2 oral antidiabetic agents. At the end of 30 wk, mean HbA1c declined from 8.1% to 6.3% with LixiLan and from 8.0% to 6.5% with glargine. With LixiLan, 84.4% achieved an HbA1c of < 7.0% compared to 78.3% with glargine. There was also 1.2 kg of weight loss with LixiLan compared to a gain of 0.4 kg with glargine. In addition, there was no difference in rates of hypoglycemia with LixiLan compared to glargine[10,11].

GLP-1RA - ANTIHYPERGLYCEMIC EFFECT

The antihyperglycemic effect of GLP-1RA is substantial. The action is mediated by: (1) glucose dependent insulin secretion by the pancreatic beta cells; (2) suppression of glucagon by the alpha cells; and (3) slowing of gastric emptying[12].

In several clinical trials, with or without metformin, the GLP-RA(s) achieved HbA1c reduction between 0.9%-1.6%. There have been significant reductions of, both fasting and post-prandial plasma glucose levels (vide infra).

Treatment with exenatide 10 mg, twice daily over 30 wk to patients with type 2 diabetes, produced mean reductions in HbA1c of 0.9%-1.0%, compared to placebo, when added to metformin, a sulfonylurea or combination of both[13].

In another 26 wk controlled trial, extended-release exenatide injection once weekly, produced a mean HbA1c reduction of 1.6%, as opposed to reduction of 0.9% by exenatide twice daily ($P < 0.0001$)[14].

In a trial comparing exenatide twice daily *vs* liraglutide once daily, greater post-breakfast plasma glucose lowering was seen with the former while greater fasting plasma glucose was seen with the latter. There was equivalent impact on post-lunch plasma glucose excursion[15].

In another study, adding liraglutide to failing metformin and sulfonylurea therapy, resulted in superior reduction in HbA1c (-1.33%) *vs* basal insulin glargine (-1.09%), and this difference was statistically significant ($P = 0.0015$)[16].

In a head-to-head trial comparing glycemic efficacy of albiglutide once weekly *vs* liraglutide once daily, the latter was found to be more powerful. Patients with type 2 diabetes, inadequately controlled with oral antihyperglycemic agents, were randomized to receive either albiglutide 30 mg once-weekly ($n = 422$) or liraglutide uptitrated from 0.6 mg daily to 1.8 mg once daily ($n = 419$). At the end of 32 wk, there was HbA1c reduction of 0.78% in the albiglutide group and 0.99% in the liraglutide group; treatment difference was 0.21%. However, gastrointestinal side effects were less in the albiglutide group and injection-site reaction was less in liraglutide group[17].

Another head-to-head trial (AWARD-1) compared the efficacy and safety of dulaglutide against exenatide. Patients with type 2 diabetes, receiving metformin (1.5 to 3.0 g) and pioglitazone (30-45 mg) were randomized to four groups of treatment: Dulaglutide 1.5 mg weekly, dulaglutide 0.75 mg weekly, exenatide 10 μg daily, or placebo (placebo-controlled period: 26 wk). Mean baseline HbA1c was 8.1%. Change of HbA1c from baseline to the end of study was -1.51% ± 0.06% for dulaglutide 1.5 mg, -1.30% ± 0.06% for dulaglutide 0.75 mg, -0.99% ± 0.06% for exenatide, and -0.46% ± 0.08% for placebo. Dulaglutide, at both doses, was superior to placebo at 26 wk ($P < 0.001$) and exenatide at 26 and 52 wk ($P < 0.001$). More number of patients reached HbA1c targets with dulaglutide 1.5 mg and 0.75 mg than with placebo and exenatide (all $P < 0.001$). Incidence of hypoglycemia, at 26 and 52 wk, was lower in patients receiving dulaglutide 1.5 mg than in the exenatide group; no dulaglutide-treated patients reported severe hypoglycemia. The common gastrointestinal adverse events for dulaglutide were transient, mild to moderate nausea, vomiting, and diarrhea[18].

The first phase 3a trial results of semaglutide, a once-weekly administered GLP-1RA were announced recently in July, 2015. In this placebo controlled trial, semaglutide was administered in once-weekly doses of 0.5 mg and 1.0 mg, as monotherapy for 30 wk in 388 type 2 diabetes patients, previously on exercise and diet. The trial results showed that from a mean baseline HbA1c of 8.1%, with doses of 0.5 and 1.0 mg of semaglutide, achieved reduction in HbA1c of 1.5% and 1.6%, respectively, compared to no change in the placebo group. Seventy four percent and 73% of the people treated with 0.5 mg and 1.0 mg semaglutide, respectively, achieved the HbA1c target below 7%, compared with 25% of the people treated with placebo[19].

The large amount of data accumulated with the use of different GLP-1RA shows a significant reduction in blood glucose values, with a greater drop seen with higher baseline values of HbA1c, in a dose-dependent manner[12].

GLP-1RA: EFFECTS ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

In short term clinical trials (approximately 26 wk), on

patients with type 2 diabetes and hypertension, GLP-1RA(s) have produced a reduction of 1-7 mmHg of systolic blood pressure (SBP), whereas reduction in diastolic blood pressure (DBP) was variable.

A meta-analysis of 16 randomized controlled trials, with 3443 subjects in the GLP-1RA therapeutic arm and 2417 subjects in the control arm, studied effects on blood pressure. The GLP-1RA exenatide, reduced SBP significantly in comparison to both placebo and insulin glargine, with mean differences of -5.24 and -3.46 mmHg, respectively ($P < 0.00001$ for both). In the exenatide-treated group, mean DBP reduction was 5.91 mmHg, compared with the placebo group, -0.99 mmHg ($P < 0.00001$). The meta-analysis studied changes in systolic blood pressure. Results showed a mean reduction of 5.60 mmHg and 2.38 mmHg in the 1.2 and 1.8 mg treatment arms with liraglutide respectively, as compared to placebo and glimepiride arms ($P < 0.00001$; $P = 0.05$ respectively).

In the 1.8-mg-treated group, liraglutide significantly reduced SBP, compared to placebo and glimepiride treatment, with mean differences of -4.49 and -2.62 mmHg, respectively ($P < 0.00001$, and $P < 0.00001$, respectively)[20].

In a study duration of 26 wk, the SBP reduction achieved with exenatide, 10 μg twice daily and liraglutide, 1.8 mg daily were found to be similar (-2.0 mmHg *vs* -2.5 mmHg, respectively; $P = 0.6409$). An additional 14 wk follow-up of the subjects in a partial cross-over design revealed no significant difference in the SBP reduction (ΔSBP of 3.8 mmHg, when patients were switched from exenatide to liraglutide and (ΔSBP of 2.2 mmHg for patients, who continued on liraglutide).

It is interesting to note that blood pressure changes took place before loss of weight was observed-so the effect on blood pressure was independent of weight loss[15].

GLP-1RA: EFFECTS ON LIPIDS

GLP-1RAs have variable effects on different components of lipid profile, the highest being on the triglycerides. Nevertheless, beneficial effects in the LDL cholesterol and HDL cholesterol may also be noted.

Both exenatide and liraglutide resulted in a significantly greater reduction in triglycerides. After 26 wk, there was a significantly greater reduction of triglyceride with liraglutide, 1.8 mg daily as compared to exenatide (-0.22 to -0.40 mmol/L; $P = 0.0485$) [15].

In a study from Greece, 20 obese type 2 diabetes patients were randomized to receive, either liraglutide or exenatide treatment and underwent a standardized meal tolerance test, early in the morning, after 10 h fast at baseline and after a two-week treatment period. Both exenatide and liraglutide, were equally effective in lowering postprandial lipemia, after the first administration and after 2 wk of treatment[21].

In a recent prospective study, the impact of GLP-1 analogs on carotid intima media thickness (CIMT) was assessed using lipid sub-fractions as surrogates. As MetS predisposes an individual to high cardiovascular risk, a reference to this study, may be relevant, to the topic under discussion. Adding liraglutide to type 2 diabetes patients, already on metformin and low CV risk, resulted in statistically significant ($P < 0.001$) improvement in total cholesterol and triglyceride (10% drop from baseline), LDL-cholesterol (19% reduction from baseline) and increase in HDL-C (18% increment from baseline). There was a significant decrease in CIMT from baseline, however, this effect was found to be independent of changes in plasma glucose or lipids[22].

What remains to be determined from long-term prospective trials is, whether these modest improvements in lipids will translate into cardiovascular benefit or not.

GLP-1RA: EFFECTS ON MICROALBUMINURIA

In a study of 16 wk duration on patients with type 2 diabetes, comparing GLP-1RA exenatide with glimepiride, improvement of glucose control was similar, but a 24-h urinary albumin was reduced by 40% in exenatide group, compared to 5% reduction in glimepiride group. Apart from that, urinary transforming growth factor-beta and type Ⅳ collagen in the exenatide group were also significantly reduced, compared to, no change in glimepiride-treated group[23].

Both exendin-4 (exenatide) and liraglutide ameliorated albuminuria, decreased oxidative stress and inflammatory cytokines, in a rat model of diabetic nephropathy. In the exendin-4 study, glomerular macrophage infiltration was prevented by suppression of ICAM-1 production on glomerular endothelial cells and by inhibition of pro-inflammatory cytokine release from macrophages[24].

Clinical experiences with liraglutide from real-life scenario demonstrated significant improvements in urinary albumin excretion rates, as well as decline in eGFR. In an Indian data on type 2 diabetic patients, with mean duration of diabetes of approximately 12 years and baseline clinical albuminuria, there was statistically significant reduction in urinary albumin excretion rate ($P < 0.05$), after 12 wk of treatment with liraglutide[25].

GLP-1RA: EFFECT ON BODY WEIGHT

The mechanisms linking appetite to weight gain has both peripheral sensory inputs and central response. GLP-1RA(s) have consistently demonstrated weight loss in all the clinical trials. Nausea and gastrointestinal slowing were initially postulated as the major mechanisms. However, weight loss was documented independent of gastrointestinal effects. In addition, weight loss was seen with liraglutide despite tachyphylaxis at gastric level. Hence, GLP-1RA(s) are responsible for weight loss by mechanisms, interfering both at central and peripheral sites. Recent studies using structural and functional

Table 1 Body weight parameters: Baseline[24]

	BMI (kg/m^2)	Body weight (kg)	WC (cm)
Metformin	36.6 ± 3.5	103.2 ± 6.3	122.3 ± 7.0
Liraglutide	39.3 ± 4.2	108.9 ± 15.1	124.9 ± 9.9
COMBI	37.6 ± 5.1	105.5 ± 20.6	121.9 ± 17.7

COMBI: Combination of liraglutide and metformin; WC: Waist circumference; BMI: Body mass index.

Table 2 Post-treatment (3-mo) body weight parameters[24]

	BMI (kg/m^2)	Body weight (kg)	WC (cm)
Metformin	36.1 ± 3.8	102 ± 6.8	120.7 ± 7.8
Liraglutide	37.6 ± 5.1	105.1 ± 13.8	121.7 ± 9.6
COMBI	35.5 ± 5.5	99.0 ± 21.2	116.4 ± 18.4

COMBI: Combination of liraglutide and metformin; WC: Waist circumference; BMI: Body mass index.

imaging techniques have demonstrated, reduced activity in the limbic system of the brain, as well as improved hypothalamic connectivity, leading to early satiety and modification of feeding behavior[26-28].

A recent study, comparing the effects of metformin monotherapy *vs* liraglutide monotherapy *vs* combination (COMBI) of both, in patients with polycystic ovary syndrome, documented impressive results as far as weight loss and reduction in waist circumference were concerned. Mean weight loss with COMBI was greatest, 6.5 ± 2.8 kg followed by liraglutide 3.8 ± 3.7 kg and only about 1.2 ± 1.4 kg with metformin. It is interesting to note that there was a significant reduction in waist circumference in the liraglutide arm (3.2 ± 2.9 cm) and in the COBMI arm (5.5 ± 3.8 cm) (Tables 1 and 2). Seventeen patients with PCOS recruited in this study had MetS (6 in metformin group, 4 in COMBI and 7 in liraglutide group). MetS persisted in all the 6 women in metformin arm at the end of the trial whereas it resolved in 3 women in both liraglutide and COMBI groups[29].

Two different doses of liraglutide, 1.8 mg or 3 mg daily, were tried in the SCALE Diabetes trial in patients with type 2 diabetes and obesity or overweight. A total of 846 patients were randomized to receive liraglutide 3 mg daily or liraglutide 1.8 mg daily or placebo in addition to lifestyle intervention. Mean baseline weight was 105.7 kg with liraglutide (3.0-mg dose arm), 105.8 kg with liraglutide (1.8-mg dose arm), and 106.5 kg with placebo. Mean weight loss was 6.4 kg with liraglutide (3.0-mg dose), 5.0 kg with liraglutide (1.8-mg dose), and 2.2 kg with placebo[30].

The results of SUSTAIN 1 trail are highly encouraging in terms of body weight reduction. The absolute weight reduction with 0.5 mg and 1.0 mg semaglutide are 3.8 kg and 4.6 kg as compared to 1 kg weight loss in the placebo arm respectively[19].

GLP-1RA AND HEPATIC AND MUSCLE INSULIN RESISTANCE

In a study, the effect of exenatide on muscle glucose uptake and hepatic glucose production (HGP) was studied in non-diabetic (control) and streptozotocin plus high fat diet induced diabetic rats. With hyperinsulinemic-euglycemic clamp, glucose uptake into gastrocnemius muscles was measured. In the diabetic rats, exenatide reduced the basal production of glucose (94.70 ± 13.46 μmol/kg per minute *vs* 121.07 ± 16.55 μmol/kg per minute, $P < 0.01$). This was effect of exenatide on HGP. Also, there was increased glucose uptake into muscle (0.24 ± 0.02 μmol/g per minute *vs* 0.17 ± 0.02 μmol/g per minute, $P < 0.01$) - an effect on increased muscle insulin sensitivity. These effects of exenatide were absent in the non-diabetic rats[31].

GLP-1RA AND NON-ALCOHOLIC FATTY LIVER DISEASE

As mentioned earlier in the Introduction, some authorities have suggested NAFLD to be a component of MetS. In an interesting review article from Italy, the authors have shown strong correlation of hepatic fat deposition and MetS. They have also commented that, NAFLD is the hepatic component of MetS[32].

In another review article, recently published, the authors concluded NAFLD as a risk factor for type 2 diabetes (28 longitudinal studies) and also for MetS (19 longitudinal studies). As regards to being a part of MetS, the issue has been complicated by documentation of high grade steatosis not associated with insulin resistance. On the contrary, a low-grade fatty liver was found to be genetic angle to this story and a direct cause and effect relationship, is not yet evident. The authors concluded that, NAFLD could be considered as a precursor to MetS, instead of a component of the same[32,33].

Liraglutide was found to be effective in improving NAFLD and non-alcoholic steato-hepatitis (NASH). In a study conducted in Japan, the effect of liraglutide on NAFLD was compared to sitagliptin and pioglitazone. Treatment with liraglutide, significantly reduced liver enzymes, HbA1c and body weight[34].

The effect of liraglutide on NASH, was studied in the recently published LEAN (Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis) trial. Patients were assessed with histology prior to, and at end of study (48 wk). More patients in the 1.8 mg liraglutide arm achieved histological resolution, compared to the placebo arm. However, this was a study in a very small group of patients (26 patients in each arm). Hence a study on a larger population of patients with longer duration needs to be done to come to a definitive conclusion[35].

GLP-1RA AND CORONARY HEART DISEASE

We have seen that, GLP-1RA have favorable actions on components of MetS. Some studies have looked into

their direct effects on coronary artery disease and left ventricular function.

In a study from South Korea, 58 patients with ST-segment elevation myocardial infarction and thrombolysis were put on either exenatide twice daily or placebo. After six months, there was significant reduction of infarct size in the exenatide group, compared to the placebo group. There was also improvement of left ventricular function in the exenatide group, in comparison to placebo[36].

In a recently published meta-analysis of 37 clinical trials with different GLP-1RA, of duration from 24 wk to 208 wk, compared with placebo, or pioglitazone or dipeptidyl peptidase-4 inhibitors, a favorable effect on major adverse cardiovascular event (MACE) was observed with GLP-1RA(s). In placebo-controlled trials, Mantel-Haenzel odds ratio for MACE for exenatide, liraglutide and taspoglutide was 0.45 (0.20-1.02), 0.60 (0.22-1.62) and 0.50 (0.03-8.06), respectively; number of trials 6, 5 and 1 respectively; $P = 0.055$, 0.31 and 0.62 respectively for the three GLP-1RA(s)[37].

The result of "Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)" study was slightly disappointing. The study recruited patients with type 2 diabetes who had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 d, to receive either lixisenatide or placebo (1:1 randomization), in addition to locally determined standards of care. The primary composite end points were cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. A total number of 6068 patients were randomized and were followed for a median of 25 mo. A primary end-point event occurred in 406 patients (13.4%) in the lixisenatide group and in 399 (13.2%) in the placebo group [hazard ratio (HR) for lixisenatide, 1.02; 95%CI: 0.89-1.17], which showed the non-inferiority of lixisenatide to placebo ($P < 0.001$) but did not show superiority. There was no significant between-group difference in the rate of hospitalization for heart failure (HR in the lixisenatide group, 0.96; 95%CI: 0.75-1.23) or the rate of death (HR = 0.94; 95%CI: 0.78-1.13). Lixisenatide treatment was not associated with a higher rate of severe hypoglycemia, pancreatitis, pancreatic neoplasms, or allergic reactions, compared to placebo. The ELIXA study also showed that addition of a GLP-1RA, lixisenatide, did not increase risk of myocardial infarction or hospitalization due to heart failure, in such high-risk patients with type 2 diabetes[38].

Another trial "Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER)" was started in September, 2010. The trial enrolled 9340 type 2 diabetes subjects with high risk of cardiovascular disease till April 2012. LEADER is a multicenter, international, randomized, double-blind, placebo-controlled clinical trial. The primary end point is the composite outcome of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The result of LEADER trial will throw light regarding the cardiovascular safety of liraglutide relative to the current standard of usual care[39].

On March 04, 2016, in a press release, Novo Nordisk, manufacturer of liraglutide, informed the top-line result of LEADER trial. Treatment with liraglutide has demonstrated, significant reduction of cardiovascular risk in all three components of primary endpoint. The details of the trial results will be presented in the 76th Scientific Session of the American Diabetes Association in June 2016[40].

Once weekly injectable GLP-1RA semaglutide, that has recently completed its Phase 3a clinical trials, has also shown significant reduction in the risk of major adverse cardiovascular events, in its long-term cardiovascular safety SUSTAIN-6 trial. This was announced very recently by its manufacturer on 28 April 2016. SUSTAIN 6 is a 2-year trial to evaluate cardiovascular and other long-term outcomes with semaglutide in approximately 3300 people with type 2 diabetes[41].

A recently published meta-analysis looked into the cardiometabolic efficacy and adverse effects of once-weekly GLP-1RAs, in adults with type 2 diabetes. The authors studied results of clinical trials with albiglutide, dulaglutide, once-weekly exenatide, and taspoglutide and looked into cardiometabolic (primary outcome, fasting plasma glucose and HbA1c) or safety outcome. Results of a total number of 34 trials were studied. All once-weekly GLP-1RAs reduced HbA1c and fasting plasma glucose. Taspoglutide 20 mg, once-weekly exenatide, and dulaglutide 1.5 mg, have also shown a reduction in body weight. The greatest difference in HbA1c reduction was found between dulaglutide 1.5 mg, and taspoglutide 10 mg (-0.4%); for fasting plasma glucose, once-weekly exenatide and albiglutide (-12.6 mg/dL), and for weight reduction, taspoglutide 20 mg, and dulaglutide 0.75 mg (-1.5 kg). Once-weekly exenatide increased heart rate compared with albiglutide and dulaglutide (1.4 to 3.2 beats/min). The risk for hypoglycemia was similar for all; use of taspoglutide 20 mg weekly was associated with the highest risk for nausea (odds ratio, 1.9 to 5.9)[42].

POSSIBLE MECHANISMS OF ACTION: GLP-1 RECEPTOR DEPENDENT OR INDEPENDENT

Endogenous GLP-1 can act through the GLP-1 receptors present on the endothelium, endocardium, cardiomyocytes and vascular smooth muscle cells. Once degraded by DPP-4 the intact GLP-1 (7-36) gets degraded to metabolites some of which like GLP-1 (9-36) can act independent of the GLP-1 receptor and induce vasodilation *via* the cGMP pathway[43].

However exogenous GLP-1RA being resistant to the action of DPP-4 enzyme acts exclusively through the GLP-1 receptor and induce the metabolic and vascular effects. Amongst the various injectable GLP-1RAs, liraglutide is the only one, which is partially resistant to the degrading effect of DPP-4, due to the fatty acid side chain of the molecule, which attaches to plasma albumin

and protects the cleavage site[44]. As a result we can expect both GLP-1R dependent and independent effects on cardio-metabolic parameters from this molecule. GLP-1 (9-36) has been documented to have GLP-1R independent effects in reducing blood pressure as well as improving cardiac function post ischemia[45]. It is worth speculating whether, this additional mechanistic property was responsible for the differential CV results between ELIXA and LEADER trials.

CONCLUSION

MetS has a strong connection with cardiovascular morbidity and mortality. Most of the conventional antihyperglycemic agents address plasma glucose excursions without having any additional impact on the other components of MetS. Some, like insulin, sulphonylureas and thiazolidinediones actually worsen certain components of MetS. The introduction of GLP-1 receptor analogs changed the picture. In addition to reducing plasma glucose, we came across, a group of drugs, which could also reduce body weight, blood pressure, lipids and improve urinary albumin excretion. The drugs have shown a trend toward favorable effects on coronary artery disease and left ventricular function. The entire composite included under the umbrella of MetS can now be tackled more effectively with one single antihyperglycemic agent. Results from recently concluded clinical trials indicate that some the drugs in this class may reduce cardiovascular risk in patients with type 2 diabetes.

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