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# Comparative effects of liraglutide doses with and without exercise on glycemic control and lipid profiles: A Randomized Controlled Trial.

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## Abstract

**Background:** Liraglutide, a GLP-1 receptor agonist, is widely used to manage type 2 diabetes and obesity, showing potential benefits in improving glycemic control and lipid profiles, yet its effects across different doses and combined with exercise remain underexplored. This study seeks to determine the effects of three different doses of liraglutide, both with and without exercise, on blood glucose levels and lipid profiles in individuals with varying degrees of diabetes and metabolic risk.

**Methodology:** This three-arm randomized controlled trial at Isra University Hospital, Hyderabad, assessed the effects of varying doses of Liraglutide (Saxenda) on Glycated Hemoglobin (HbA1c) levels and lipid profiles over six months. Sixty participants aged 20-60 were randomly assigned to receive different doses of Liraglutide, with or without an exercise regimen.

**Results:** In Group A, Subgroup (i) exhibited a non-significant reduction in HbA1c from 4.85±1.35 to 4.77±1.2 after six months ($p>0.05$). However, Subgroup (ii) showed a significant reduction ($p<0.05$) in HbA1c levels after six months. Similarly, Groups B and C also demonstrated significant reductions in HbA1c after three months of intervention, with continued improvements over six months.

**Conclusion:** Liraglutide demonstrates significant potential as a therapeutic option for improving both glycemic control and lipid profiles. The study suggests that liraglutide has cardiovascular protective effects that extend beyond the reduction of LDL-C, highlighting its broader clinical benefits.

## Keywords

Lipid Profile, Blood Glucose Level, Glycated Hemoglobin, Liraglutide, Low Density Lipoprotein Cholesterol.

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## Introduction

Pancreatic cell function is critically compromised by inadequate insulin secretion, a condition that intricately disrupts glucose and lipid metabolism. Key molecular players in the development of chronic diseases such as type 2 diabetes include nuclear factor-kappa B (NF-kB) and monocyte chemoattractant protein-1 (MCP-1)[1]. Diabetic individuals commonly exhibit elevated triglyceride (TG) levels and reduced high-density lipoprotein (HDL) cholesterol levels, collectively referred to as diabetic dyslipidemia. This dyslipidemia is prevalent among those with insulin resistance and often precedes the clinical manifestation of diabetes. In individuals with normal insulin sensitivity, insulin inhibits the formation of very low-density lipoprotein (VLDL), but chronic insulin resistance impairs this effect, leading to increased VLDL secretion from the liver. Additionally, insulin resistance diminishes the activity of lipoprotein lipases, exacerbating dyslipidemia[2,3]. The condition is further aggravated by increased lipolysis in adipocytes and elevated levels of circulating free fatty acids, which contribute to excessive triglyceride-rich lipoprotein production in the liver and intestines. Excess carbohydrate intake compounds these effects, as carbohydrates are stored as glycogen in the liver and as triglycerides in adipose tissue[4,5].

Elevated VLDL levels, through the action of cholesteryl ester transfer protein (CETP), promote the transfer of triglycerides to HDL, resulting in cholesterol-enriched VLDL and triglyceride-depleted HDL particles[6]. CETP also facilitates the exchange of triglycerides for LDL cholesteryl esters, producing smaller, denser, and lipid-depleted LDL particles. These lipid profile abnormalities—characterized by high VLDL, triglycerides, and LDL, coupled with low HDL levels—contribute to an increased risk of atherosclerosis in diabetic individuals[7,8]. To mitigate these risks, effective treatment strategies must address both glycemic and lipid management.

Glucagon-like peptide-1 (GLP-1), discovered in the early 1980s as a product of glucagon enzymatic cleavage in intestinal L cells[9], plays a crucial role in glucose metabolism. This incretin hormone, which is secreted in response to glucose intake, enhances glucose-stimulated insulin secretion while minimizing the risk of hypoglycemia by acting only in the presence of hyperglycemia[10,11]. GLP-1 also suppresses glucagon release through somatostatin release from pancreatic islet cells[12-14], and has additional benefits such as promoting satiety, reducing appetite, lowering blood pressure, and decreasing postprandial triglyceride and free fatty acid levels. Liraglutide, a GLP-1 receptor agonist, is commonly used to manage type 2 diabetes at a standard dose of 1.2 mg daily, with escalation to 1.8 mg daily if necessary[15].

While liraglutide's effects on blood glucose are well-documented, there is limited evidence comparing the impact of different doses of liraglutide, with and without exercise, on both blood glucose levels and lipid profiles. This study aims to investigate the effects of three different doses of liraglutide in combination with exercise on blood glucose levels and lipid profiles.

## Methodology

### Trial Design

This study was a three-arm randomized controlled trial conducted at Isra University Hospital, Hyderabad. The trial was designed to assess the effects of different doses of Liraglutide (Saxenda) on HbA1c levels and lipid profiles over six months. Participants were randomly assigned to one of three treatment groups, each receiving a different dose of Liraglutide, with or without an exercise regimen.

### Participants

A total of 60 participants were recruited for the study, with equal distribution across the three groups. Eligible participants were aged between 20 and 60 years and were required to meet specific inclusion criteria. Participants with known cardiovascular disease (CVD), stroke, cancer, recent surgical procedures (such as angiography, angioplasty, or coronary artery bypass grafting), or diagnosed mental and psychological illnesses were excluded.

- **Inclusion Criteria:**

The study included participants from both genders, aged between 20 and 60 years, who met the specified inclusion criteria. This age range was chosen to capture a broad adult population that could benefit from the intervention. The selection process ensured that both male and female participants were equally represented in the study.

- **Exclusion Criteria:**

Exclusion criteria were implemented to eliminate potential confounding factors that could impact the study's outcomes. Participants with known diseases such as cardiovascular disease (CVD), stroke, or cancer were excluded to avoid any complications related to these conditions. Additionally, individuals with a recent history of surgical procedures, including angiography, angioplasty, or coronary artery bypass grafting (CABG), were not considered for participation. Those with diagnosed mental and psychological illnesses were also excluded to ensure that the study focused on participants without underlying conditions that could affect the results.

**Interventions**

Participants were divided into three groups, each receiving a different dose of Liraglutide, administered subcutaneously once daily for six months. The groups were structured as follows:

**Group A: Liraglutide 0.6 mg**

- Subgroup (i): Non-diabetic participants received Liraglutide at a dose of 0.6mg daily for six months.
- Subgroup (ii): Borderline diabetic participants received Liraglutide 0.6mg daily for six months, combined with daily exercise.

**Group B: Liraglutide 1.2 mg**

- Subgroup (i): Borderline diabetic participants received Liraglutide at a dose of 1.2mg daily for six months. Participants started with 0.6mg daily for the first week, followed by 1.2mg from week 2 onwards.
- Subgroup (ii): Diabetic participants received Liraglutide 1.2mg daily for six months, combined with daily exercise. The dosing regimen was the same as Subgroup (i).

**Group C: Liraglutide 1.8 mg**

- Subgroup (i): Diabetic participants received Liraglutide at a dose of 1.8mg daily for six months. Participants started with 0.6mg daily for the first week, increased to 1.2mg daily in week 2, and 1.8mg daily from week 3 onwards.
- Subgroup (ii): Diabetic participants received Liraglutide 1.8mg daily for six months, combined with daily exercise. The dosing regimen was the same as Subgroup (i).

All participants in Subgroup (ii) of each group were advised to engage in 30 minutes of simple walking exercises before breakfast.

**Outcomes**

- Primary outcome: The primary outcome measure was the change in HbA1c levels. HbA1c was measured at baseline, three months, and six months to assess the effects of Liraglutide on glucose control.
- Secondary outcome: The secondary outcome measure was the lipid profile, including triglyceride, LDL, and HDL levels, which were also assessed at baseline, three months, and six months.

**Sample Size**

A total of 60 participants were included in the study, with 20 participants allocated to each group. The sample size was determined based on the estimated effect size of Liraglutide on HbA1c levels, considering a power of 80% and a significance level of 0.05.

**Randomization**

Participants were randomized into the three groups using a computer-generated randomization sequence. Randomization was performed to ensure equal distribution across the treatment arms, minimizing selection bias.

**Blinding**

This study was not blinded, as both the participants and the researchers were aware of the treatment

allocations. However, outcome assessors were blinded to the group assignments to minimize detection bias.

**Ethics**

The study adhered to the ethical principles outlined in the Belmont Report for Human Subjects. All participants provided informed consent before enrollment and were assured of their autonomy and confidentiality throughout the study. The research protocol was reviewed and approved by the Institutional Review Board of Skin Laser Ethics Committee (IRB # SLH-IRB-065/05/2022).

**Statistical Methods**

Data were analyzed using SPSS version 24. Descriptive statistics, including frequency and percentage, were used to summarize demographic data.

Continuous variables were analyzed using one-way analysis of variance (ANOVA) to compare the effects of different doses of Liraglutide on HbA1c and lipid profiles. A 95% confidence level was used for all statistical tests, and the significance level was set at 0.05.

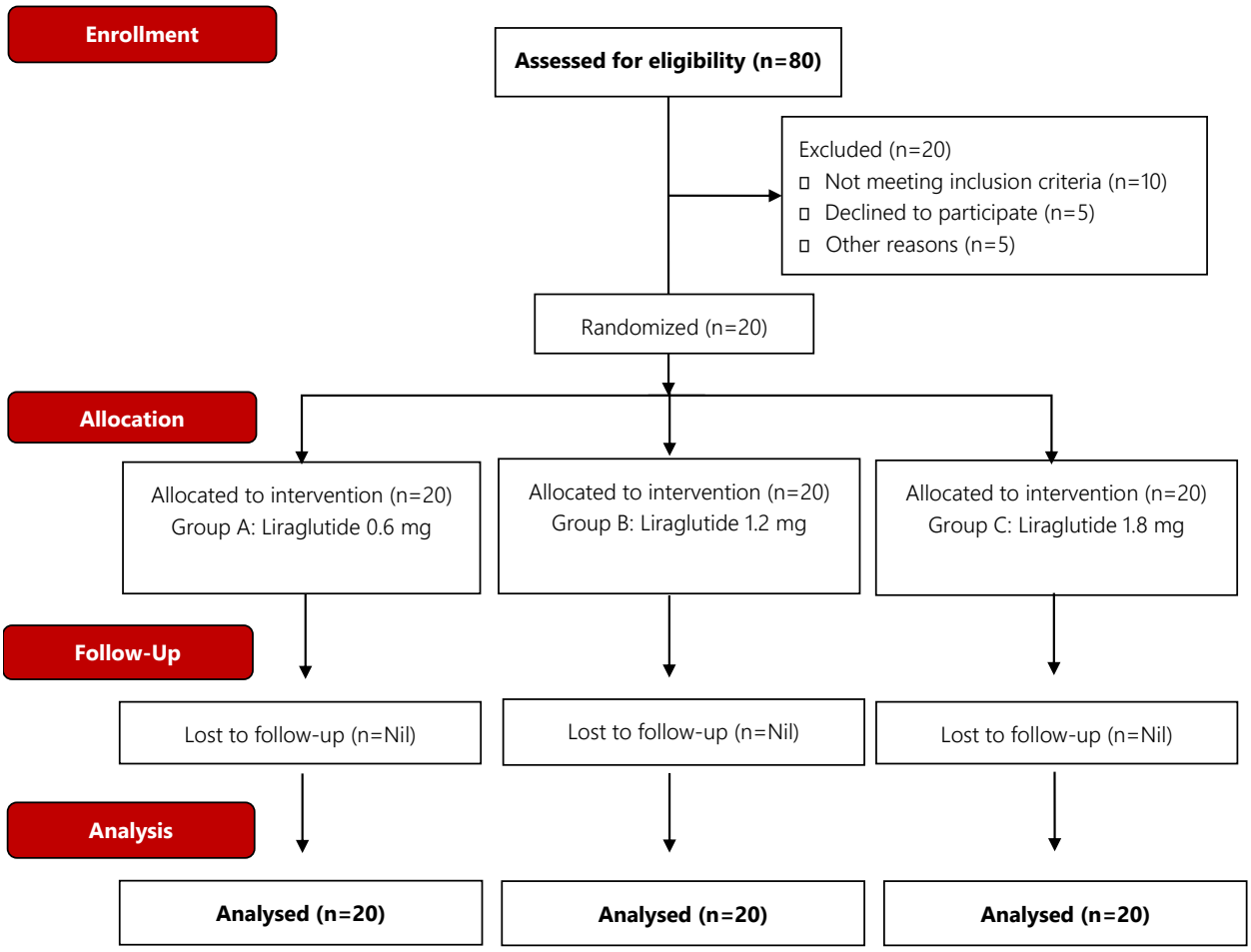


**Figure 1: CONSORT Flow Diagram**

## Results

### Recruitment

A total of 60 participants were recruited for the study, with 22 (36.66%) being male and 38 (63.33%) being female. The mean age of the participants was 56.6 ± 2.3 years. Out of these, 8 males (36.36%) and 2 females (5.2%) were identified as smokers. Detailed demographic information is provided in Table 1.

### Baseline Data

At baseline, HbA1c levels were assessed for all participants, and baseline levels of triglycerides, LDL, and HDL were recorded. The data revealed varying baseline values across the three groups, reflecting the diversity of participants in terms of their initial metabolic status.

### Outcomes and Estimation

- **Within-Group Comparisons**

**1. Glycated Hemoglobin (HbA1c) Levels:**

**Group A:** In Subgroup (i), HbA1c levels slightly decreased from 4.85 ± 1.35 at baseline to 4.77 ± 1.2 after six months, with a non-significant difference ($p = 0.08$). In Subgroup (ii), a significant reduction was observed, with baseline levels of 5.67 ± 1.18 decreasing to 5.12 ± 1.08 ($p < 0.005$).

**Group B:** Both subgroups showed significant reductions in HbA1c levels. In Subgroup (i), levels decreased from 5.62 ± 1.28 at baseline to 5.12 ± 1.35 after six months. Subgroup (ii) demonstrated a decrease from 6.34 ± 2.37 to 5.15 ± 1.22.

**Group C:** Significant reductions were noted in both subgroups. Subgroup (i) showed a decrease from 6.84 ± 2.22 to 5.9 ± 1.5, while Subgroup (ii) decreased from 6.79 ± 1.98 to 5.5 ± 2.5.

**2. Lipid Profile Levels:**

**Triglycerides:** Significant reductions were observed in all groups. Group A (Subgroup ii) had the most notable decrease, from 209.56 ± 2.5 at baseline to 202.54 ± 1.56 after six months ($p < 0.05$). Group B and C also showed significant reductions.

**LDL:** Group A (Subgroup ii) showed a reduction from 166.56 ± 1.54 to 143.25 ± 2.45 ($p < 0.001$). Groups B and C demonstrated similar significant reductions in LDL levels.

**HDL:** Significant increases were observed in HDL levels across all groups. Group A (Subgroup ii) increased from 45.89 ± 1.77 to 55.69 ± 3.56 ($p < 0.01$), with similar improvements seen in Groups B and C.

**Table 1: Demographic details of the participants.**

| Variables | | N(%) |
|---|---|---|
| **Gender** | Male | 22(58.88) |
| | Female | 38(41.11) |
| **Age (years) Mean±SD** | | 56.60±2.30 |
| **Smoker** | Yes | 10(16.66) |
| | No | 50(83.33) |
| | Male Smokers | 8(36.36) |
| | Female Smokers | 2(5.20) |

**Table 2: Within-group analyses of glycated hemoglobin and lipid profile levels at different intervals.**

| Groups | Subgroup | Baseline | Follow-Up | | p-value |
|---|---|---|---|---|---|
| | | | After 3 Months | After 6 Months | |
| **Glycated Hemoglobin levels** | | | | | |
| **Group A** | **i** | 4.85±1.35 | 4.84±2.25 | 4.77±1.2 | 0.080 |
| | **ii** | 5.67±1.18 | 5.38±1.48 | 5.12±1.08 | |
| **Group B** | **i** | 5.62±1.28 | 5.3±1.85 | 5.12±1.35 | <0.005* |
| | **ii** | 6.34±2.37 | 5.51±2.5 | 5.15±1.22 | |
| **Group C** | **i** | 6.84±2.22 | 6.3±1.7 | 5.9±1.5 | <0.05* |
| | **ii** | 6.79±1.98 | 6.1±1.8 | 5.5±2.5 | |
| **Lipid Profile levels (Triglyceride)** | | | | | |
| **Group A** | **i** | 210.42±1.56 | 208.25±1.5 | 206.58±2.22 | <0.05* |
| | **ii** | 209.56±2.5 | 205.14±1.65 | 202.54±1.56 | |
| **Group B** | **i** | 209.33±1.6 | 205.12±2.09 | 200.56±1.58 | <0.05* |
| | **ii** | 210.45±2.1 | 206.14±2.31 | 198.42±3.1 | |
| **Group C** | **i** | 213.23±2.12 | 204.23±1.28 | 198.56±2.3 | <0.05* |
| | **ii** | 215.56±2.3 | 205.12±2.33 | 195.62±2.85 | |
| **Lipid Profile levels (LDL)** | | | | | |
| **Group A** | **i** | 163.25±1.26 | 159.56±1.25 | 150.62±1.65 | <0.001* |
| | **ii** | 166.56±1.54 | 152.65±3.21 | 143.25±2.45 | |
| **Group B** | **i** | 169.65±1.65 | 152.22±2.66 | 143.26±2.01 | <0.001* |
| | **ii** | 168.52±3.22 | 149.65±1.98 | 140.78±2.36 | |
| **Group C** | **i** | 170.65±2.75 | 150.11±3.21 | 140.12±3.12 | <0.001* |
| | **ii** | 165.32±2.88 | 145.23±2.98 | 135.11±1.98 | |
| **Lipid Profile levels (HDL)** | | | | | |
| **Group A** | **i** | 43.25±1.85 | 49.89±2.56 | 50.14±2.41 | <0.01* |
| | **ii** | 45.89±1.77 | 53.25±2.10 | 55.69±3.56 | |
| **Group B** | **i** | 40.25±1.98 | 50.18±2.33 | 58.14±2.14 | <0.01* |
| | **ii** | 42.19±1.35 | 55.88±2.41 | 59.93±3.21 | |
| **Group C** | **i** | 40.07±1.65 | 58.24±1.98 | 65.4±3.01 | <0.01* |
| | **ii** | 39.95±1.45 | 60.5±3.58 | 63.85±2.2 | |

*p<0.05 is considered statistically significant.

- **Between-Group Comparisons**

Between-group analyses indicated that high-dose Liraglutide combined with exercise was significantly more effective ($p < 0.05$) in reducing HbA1c, triglycerides, and LDL levels compared to lower doses of Liraglutide, whether used alone or with exercise. Additionally, high-dose Liraglutide with exercise was as effective as high-dose Liraglutide alone in improving HDL levels.

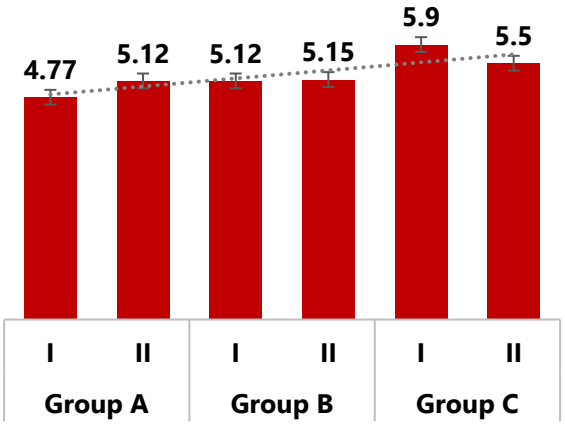


**Figure 1a: Dose response effect of Liraglutide on HbA1C**

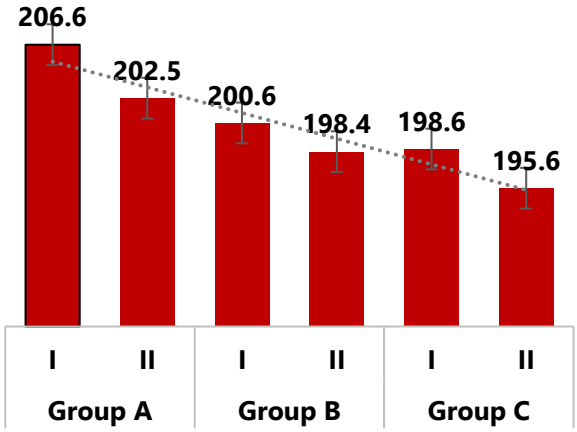


**Figure 1b: Dose response effect of Liraglutide on Triglycerides**

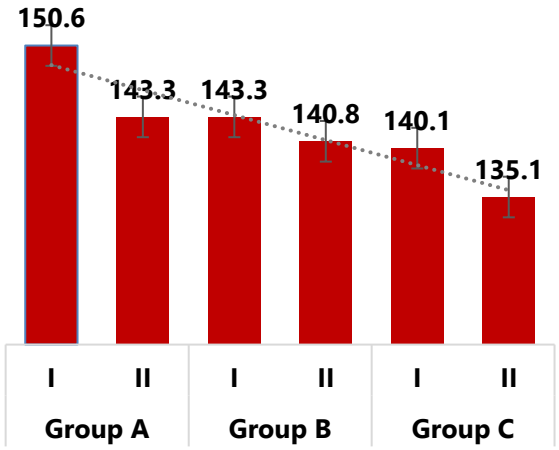


**Figure 1c: Dose response effect of Liraglutide on LDL**

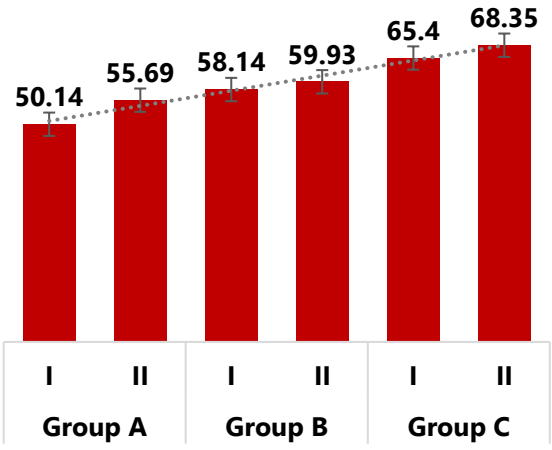


**Figure 1d: Dose response effect of Liraglutide on HDL**

**Adverse Effects**

No significant adverse effects were reported throughout the study. All participants tolerated the treatment and exercise regimen well, with no severe adverse events documented. Regular monitoring ensured that any potential side effects were promptly addressed.

## Discussion

This study evaluated the impact of different therapies on HbA1c levels and lipid profiles in participants divided into three groups, A, B, and C, each with two subgroups (i and ii). The results demonstrated notable changes in HbA1c levels across the groups. In Group A, HbA1c levels decreased from 4.85 ± 1.35 to 4.77 ± 1.2 in Subgroup (i) and from 5.67 ± 1.18 to 5.12 ± 1.08 in Subgroup (ii) over six months. In Groups B and C, initial HbA1c values were high but showed significant reductions ($p < 0.05$) after three months, with continued improvements by six months. Additionally, triglyceride and LDL levels decreased significantly ($p < 0.005$), while HDL levels improved. Between-group analyses indicated that high-dose liraglutide combined with exercise and diet management was significantly more effective ($p < 0.05$) than low-dose liraglutide, both with and

without exercise, in lowering HbA1c, triglycerides, and LDL levels. Moreover, high-dose liraglutide in conjunction with exercise and diet management was also significantly more effective in increasing HDL levels compared to low-dose liraglutide alone.

These findings align with previous research, although there are some discrepancies. For instance, another study noted that liraglutide significantly improved glycemic management and reduced HbA1c levels compared to a placebo, accompanied by weight reduction and decreased insulin dosage, although the risk of hypoglycemia initially was higher with liraglutide but normalized over time[16-17]. This suggests that liraglutide could be a viable treatment option for type 2 diabetes patients needing high insulin dosages, although further research is required to confirm these benefits and assess long-term risks and benefits[17].

In a different study, liraglutide was shown to significantly reduce blood glucose, total cholesterol, triglycerides, and LDL cholesterol levels in db/db mice and to enhance cholesterol efflux in HepG2 cells[15,18]. This study also revealed that liraglutide activated the ERK1/2 pathway, promoting cholesterol transport and reducing hepatic lipid buildup. Similarly, post hoc analyses from the LEADER trial demonstrated that liraglutide reduced major adverse cardiovascular events (MACEs) and cardiovascular mortality across various baseline LDL-C levels and statin use, suggesting additional cardiovascular protective benefits beyond LDL-C reduction[15-18].

The strength of this study lies in its demonstration of liraglutide's efficacy in managing lipid profiles, reducing HbA1c levels, and improving glycemic control in type 2 diabetes mellitus patients. The data suggest that liraglutide is particularly effective when combined with diet and exercise management, lowering HbA1c, triglycerides, and LDL levels while boosting HDL levels. Furthermore, liraglutide's capacity to reduce cardiovascular events regardless of baseline LDL-C levels underscores its potential cardiovascular benefits.

## Limitations

Long-term and larger-scale trials are needed to evaluate the extended safety and effectiveness of liraglutide across diverse populations. The current study primarily focuses on short-term outcomes, which may not fully capture the long-term cardiovascular benefits and risks associated with liraglutide. Future research should also address additional significant clinical outcomes, such as cardiovascular mortality and morbidity, to provide a more comprehensive understanding of liraglutide's overall impact on health.

## Conclusion

Liraglutide demonstrates significant promise as an effective therapeutic option for improving both lipid profiles and glycemic control, as evidenced by the trial results. The findings suggest that liraglutide not only enhances glycemic management and lipid levels but also provides cardiovascular protective benefits across various LDL-C levels, indicating potential advantages beyond mere LDL-C reduction.

## Conflicts of Interest

None.

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