Original Article

OPEN ACCESS

# Comparative Efficacy of Metformin and Liraglutide in Pediatric Type 2 Diabetes

**Aamir Naseem[1], Malik Sikandar Mehmood[2], Roshaan Bashir[3], Maria Ilyas[4], Muhammad Tariq[5], Abdul Azeem[6]**

[1]The Children's Hospital and University of Child Health Sciences Lahore, Pakistan, Paediatric Endocrinology and Diabetes
[2]Assistant Professor pharmacology Department of Pharmacology, MH hospital Rawalpindi,
[3]Senior registrar Departments of pediatrics alnafees medical college and hospital Islamabad,
[4]Senior lecturer Department of pharmacology Wateem medical and dental college,
[5]Consultant peadiatrician Children Hospital Pakistan institute of Medical Sciences Islamabad,
[6]Assistant Professor Department of Pharmacology Watim Medical& Dental., College, Rawat, Rawalpindi

Author`s Contribution

*[1,2]Substantial contributions to the conception or design of the work; or the acquisition, [4,6]Active participation in active methodology, [2,3]analysis, or interpretation of data for the work, [5]Drafting the work or revising it critically for important intellectual content*

*Funding Source: None*
*Conflict of Interest: None*

*Received: Mar 05, 2024*
*Accepted: May 30, 2024*

***Address of Correspondent***
*Malik Sikandar Mehmood*
*Assistant Professor pharmacology*
*Department of Pharmacology, MH hospital Rawalpindi*
*maliksikandar92@gmail.com*

**ABSTRACT**

**Objective:** To assess the safety and efficacy of liraglutide versus metformin in patients with type 2 diabetes in the pediatric age group.

**Methodology:** This was an open-label, 24-week randomized controlled experiment study conducted in Nov 2023 to Feb 2024 IRB no 685623-2023 in the children hospital and university of child health sciences Lahore. Three to sixteen-year-old Children with type 2 diabetes were randomized to receive either metformin or liraglutide. The main outcome was the variation in HbA1c at week 24. The research was completed by 150 subjects in all, and analysis was done on this cohort.

**Results:** At week 24, the metformin group had a decrease in HbA1c (p value = 0.001), going from 8.0 ± 0.7% to 7.2 ± 0.8% (53 ± 2 mmol/mol), and in the liraglutide group (p = 0.001), going from 7.7 ± 0.7% to 7.1 ± 0.6% (52 ± 2 mmol/mol). However, the group comprised liraglutide grasped maximum decline more quickly as compared to metformin group. The incidence of hypoglycemia and other parameters studied did not differ significantly across the groups.

**Conclusion:** During a 24-week period, individuals with T2DM treated with liraglutide and metformin alone had comparable reductions in HbA1c, with no discernible differences in other metrics.

*Cite this article as: Naseem A, Mehmood MS, Bashir R, Ilyas M, Tariq M, Azeem A. Comparative Efficacy of Metformin and Liraglutide in Pediatric Type 2 Diabetes. Ann Pak Inst Med Sci. 2024; 20(SUPPL-1):584-588. doi. 10.48036/apims.v20iSUPPL-1.1228*

## Introduction

Recently, type 2 diabetes has grown to be a serious problem among kids and teenagers.[1] The lifestyle choices made by an individual can impact the onset of type 2 diabetes, including nutrition, activity, and weight control, as well as genetics and family history. Between 2007 and 2017, there was a notable 4.8% annual increase in frequency of type 2 diabetes in children and adolescents.[2,3] According to epidemiological research, in the US, the frequency of type 2 diabetes has significantly increased amongst children and adolescents.[4] Asian nations have an even greater frequency of T2DM amongst young patients than T1DM.[5] Investigations have shown that approximately 85% children diagnosed with T2DM are fat or overweight at the time of diagnosis.[6,7] The risk of comorbidities such as the levels of dyslipidemia, hypertension, and hyperglycemia rose over time over time among individuals with T2DM who were first diagnosed in infancy.[8,9]

Pharmacological intervention and healthy lifestyle change are commonly used in the control of childhood and teenage T2DM. Four drugs— exenatide, liraglutide, metformin, and insulin—have been licensed to date for the management of type 2 diabetes in adolescents and children by the US Food and Drug Administration (FDA). Nevertheless, all of these drugs have the potential to cause negative side effects. Especially for patients who are overweight, metformin is the first-line medication for

lowering elevated levels of blood sugar in adolescents and children with type 2 diabetes.[10] Metformin is used to lower the concentration of glucose absorbed from the intestines, raise insulin sensitivity, and decrease the amount of glucose generated in the liver. The main issue with its safety is gastrointestinal intolerance, which includes nausea, diarrhea, and pain in the abdomen.[11]

Liraglutide is analogues of GLP-1 (glucagon-like peptide). The FDA authorized ligarglutide in 2019; it effectively lowers blood sugar levels without causing hypoglycemia or weight gain.[12] Adolescent glucose control can be successfully improved by adding liraglutide to metformin, as proven by studies.[13,14]

Similarly, diarrhea, vomiting and nausea were the most often reported GLP-1 analogue's side effects. Therefore, in order to improve glucose regulation, lower the risk of adverse responses, and avoid long-term and potentially fatal problems, it is imperative to create pharmacological treatment alternatives for children with type 2 diabetes.

# Methodology

For the purpose of comparing metformin vs. liraglutide, only those patients included who had undergone modifications in lifestyle, a-glucosidase inhibitor, and metformin in low dosage (750 mg/day or less) over a period of three months. Study was conducted in Nov 2023 to March 2024 IRB no 685623-2023 in the children hospital and university of child health sciences Lahore. Those taking insulin secretagogues, such as glinides, thiazolidinedione, sulfonylureas or insulin, were excluded from the study. The children's hospital and the University of Child Health Sciences in Lahore served as recruitment sites for the study's participants. The exclusion criteria included having type 1 diabetes, not being able to take metformin or liraglutide due to contraindication, and having severe diabetic retinopathy (either preproliferative or proliferative). The study Liraglutide vs metformin for the treatment of type 2 diabetes received approval from the Children's Hospital and University of Child Health Sciences Lahore's ethics council.

For every research participant, the guardian of the patient provided written informed permission. Liaglutide and metformin were applied for both the groups, A and B (1:1). 150 participants in the pediatric age range (up to 16 years) were examined; each group had 75 individuals.

Protocol of the study: The research was a 24-week, randomized controlled, open-label trial. Randomization was used to assign subjects to either liraglutide or metformin group. At week 0, oral hypoglycemic medications that were used before to randomization were stopped. Throughout the trial, the participants were urged to maintain their lifestyle modifications. First, 500–750 mg of metformin was taken daily. After that, the dosage was increased every week until 1500 mg. If tolerated, the attending doctors were permitted to raise the dose to 2250 mg per day after week 10. Liraglutide was initially administered subcutaneously at a dose of 0.3 mg once day. Over time, the dosage was increased to 0.9 mg daily, which is the safest amount that has been authorized in a number of nations. For 24 weeks, the patients were monitored once a month. The main outcome was the variation in HbA1c at week 24.

We calculated the HbA1c decrease in the metformin and liraglutide groups.[13,14] Samples of blood and urine were obtained at each visit after an overnight fast. The following laboratory variables were measured using standard automated procedures: insulin, creatinine, plasma glucose, triglycerides, high-density lipoprotein cholesterol, LDL cholesterol, aspartate aminotransferase, alanine aminotransferase and so forth.[15,16] To determine HbA1c, high-performance liquid chromatography (HPLC) was employed.

Statistical analysis: P values and the median were computed for non-normal data after analyzing the data employing SPSS version 22. Regularly distributed data were shown as means and standard deviations.

# Results

Baseline features of enrolled patients: The metformin patients group (n = 75) and liraglutide patients group (n = 75) were matched for age (11 ± 3 vs. 10 ± 4 years, p = 0.34), sex (male/female) (50/25 vs. 45/30, p = 0.57), duration of diabetes (3.7 ± 3.5 vs. 4.6 ± 3.9 years, p = 0.45) and HbA1c (8.1 ± 0.6% vs. 7.9 ± 08% (63 ± 7 vs. 60 ± 7 mmol/mol), p = 0.19) (Table 1). The mean daily dose of metformin at week 24 was 1705 ± 342 mg, and liraglutide was up-titrated to 0.9 mg/day in all patients during the study.

**Table I: Baseline characteristics of patients. (N=75)**

| | Metformin | Liraglutide | p value |
|---|---|---|---|
| Age in years | 11 ± 3 | 10 ± 4 | 0.34 |
| Gender (male/female) | 50/25 | 45/30 | 0.57 |
| Duration of diabetes in years | 3.7 ± 3.5 | 4.6 ± 3.9 | 0.45 |
| Fasting plasma glucose (mg/dL) | 160 ± 35 | 161 ± 35 | 0.91 |
| HbA1c (%) | 8.1 ± 0.6 | 7.9 ± 0.8 | 0.25 |

| | | | |
|---|---|---|---|
| HbA1c (mmol/mol) | 63 ± 7 | 60± 7 | 0.19 |
| LDL-cholesterol (mg/dL) | 115 ± 25 | 117 ± 25 | 1.01 |
| HDL-cholesterol (mg/dL) | 50 ± 11 | 48 ± 11 | 0.59 |
| Triglyceride (mg/dL) | 200 ± 60 | 159 ± 60 | 0.42 |
| Simple retinopathy (%) | 4.1 | 4.3 | 0.89 |
| Microalbuminuria (%) | 9.1 | 8.9 | 0.89 |

At week 24, HbA1c significantly dropped in the metformin group (p value = 0.001), going from 8.0 ± 0.7% to 7.2 ± 0.8% (53 ± 2 mmol/mol), and in the liraglutide group (p = 0.001), going from 7.7 ± 0.7% to 7.1 ± 0.9% (52 ± 2 mmol/mol). (Figure 1)

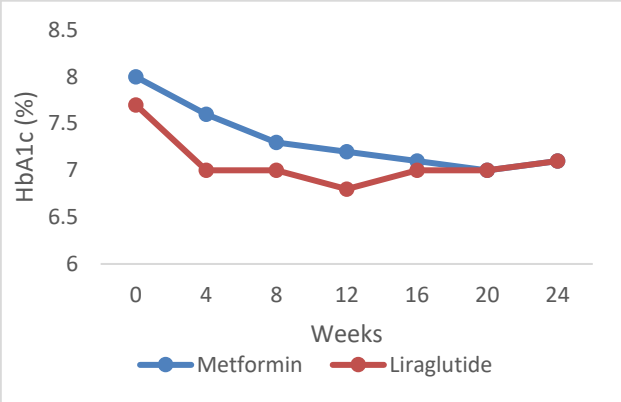


**Figure 1. change in HbA1c from 0 to 24 week.**

HbA1c decreased for the course of the trial in the metformin group, but increased quickly in the liraglutide group during the first four weeks of the research. Consequently, the liraglutide group saw a substantially higher change in HbA1c at week 4 compared to the metformin group. At week 24, there was no discernible difference in the groups' HbA1c changes. (Figure 2)

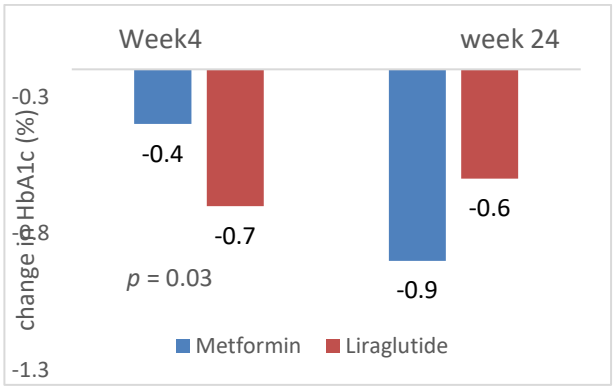


**Figure 2. Variation in HbA1c at weeks 4 and 24.**

Between the groups, the rate of achieving HbA1c of less than 7% at week 24 was similar (61% vs. 59% in metformin vs. liraglutide, p = 0.81). AST, ALT, creatinine, low-density LDL cholesterol, HDL cholesterol, insulin, plasma glucose and triglyceride did not significantly change in either group during this investigation. (Figure 3)

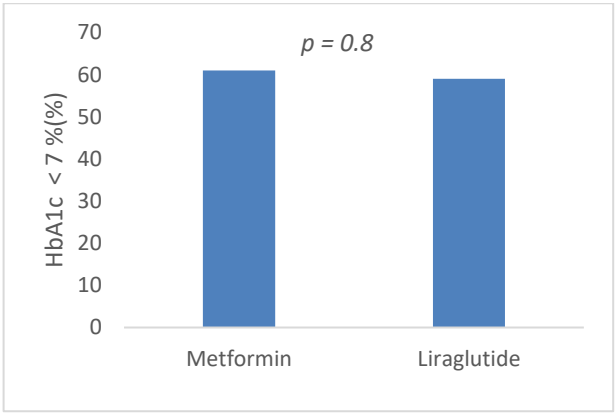


**Figure 1. Rate of achievement of HbA1c < 7% (%)**

# Discussion

In this trial, individuals with T2DM who received treatment with metformin or liraglutide monotherapy saw comparable 6-month reductions in HbA1c of 0.7–1%. The majority of clinical trials have compared the efficacy of GLP-1RA with other anti-diabetic medications because metformin is typically recommended as the first line treatment.[18,21,22] Relatively few studies have directly compared the efficacy of GLP-1RA with that of metformin. In individuals with type 2 diabetes who have not used metformin before, the effectiveness of exenatide extended release (once weekly) has been documented.[21,23]

Our results are in line with the study's observation that both groups saw a comparable drop in HbA1c. Notably, our study's liraglutide dosage of 0.9 mg per day is lower than the typical dosage in other nations (i.e., 1.2-1.8 mg per day). This is in line with a prior meta-analysis that shown Asians have greater GLP1RA effectiveness than other ethnic groups.[13] Dulaglutide, a once-weekly GLP-1RA, has been shown in more recent research to exhibit greater HbA1c reduction when compared to metformin.[24] These findings imply that GLP-1RAs have a comparable, if not greater, glucose-lowering impact than metformin.

In the liraglutide group, the reduction in HbA1c reached a near-maximum level at week 12, but in the metformin group, the reduction in HbA1c was detected gradually until 24 weeks. The results of earlier trials with other GLP-1RAs were in line with the variation in the timecourse of the glucose-lowering action between liraglutide and metformin.[23,24] This discrepancy might be

caused by variations in the two medications' pharmacokinetic properties, modes of action, and titration times. Liraglutide primarily operates by increasing insulin secretion, whereas metformin mostly reduces hepatic glucose synthesis.[25,26] Continuous glucose monitoring has further corroborated the rapid improvement of glycemic control within a month after starting liraglutide medication.[27] According to reports, blood pressure and lipid profile—two cardiovascular risk factors—might somewhat improve with GLP-1RA administration.[20,28,29] Both groups' lipid profiles and blood pressure were unchanged during this investigation. However, exenatide extended release and metformin have been shown to improve cardiovascular risk factors and body weight in a comparable manner.[19,23] This suggests that weight loss is the primary mechanism through which GLP-1RA and metformin improve cardiovascular risk factors. In a recent study, Rizzo et al. found that in 20 T2DM patients, liraglutide (1.2 mg/day) added to metformin for two months decreased oxidative stress indicators.[30] In line with other research, there was a minimal incidence of hypoglycemia throughout the trial and it was comparable among the groups.[23, 24]

# Conclusion

Individuals with type 2 diabetes who received metformin, liraglutide, and monotherapy had a comparable decrease in HbA1c during a 24-week period, with no variation in the occurrence of hypoglycemia. These results will be helpful in the selection of anti-diabetic medications for T2DM patients in the pediatric age range. They also support metformin as a first-line therapy when cost is taken into account.

# References


1. Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S, et al. Type 2 diabetes in adolescents and young adults. Lancet Diabetes Endocrinol.2018; 6(1):69–80. doi: 10.1016/S2213-8587(17)30186-9
2. Dabelea D. Diabetes in youth-looking backwards to inform the future: Kelly West award lecture 2017. Diabetes Care (2018) 41(2):233–40. doi: 10.2337/dci17-0031
3. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, et al.. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA.2014; 311(17):1778–86. doi: 10.1001/jama.2014.3201
4. Lawrence JM, Divers J, Isom S, Saydah S, Imperatore G, Pihoker C, et al.. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001-2017. JAMA.2021; 326(8):717–27. doi: 10.1001/jama.2021.11165
5. Kapellen TM. Pharmacotherapy of children and adolescents with type 2 diabetes mellitus. In: Kiess W, Schwab M, van den Anker J, editors. Pediatric pharmacotherapy. handbook of experimental pharmacology, vol. vol 261. Cham: Springer.2019; 119–129.
6. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. Nat Rev Endocrinol.2011;8(4):228–36. doi: 10.1038/nrendo.2011.183
7. Shah AS, Nadeau KJ, Dabelea D, Redondo MJ. Spectrum of phenotypes and causes of type 2 diabetes in children. Annu Rev Med (2022) 73:501–15. doi: 10.1146/annurev-med-042120-012033
8. International Diabetes Federation. IDF diabetes atlas. 10th edn. Brussels, Belgium: (2021).
9. TODAY Study Group. Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, et al. Long-term complications in youth-onset type 2 diabetes. N Engl J Med.2021; 385(5):416–26. doi: 10.1056/NEJMoa2100165
10. Tan J, Wang Y, Liu S, Shi Q, Zhou X, Zhou Y, et al. Long-acting metformin vs. metformin immediate release in patients with type 2 diabetes: A systematic review. Front Pharmacol.2021; 12:669814. doi: 10.3389/fphar.2021.669814
11. Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. Curr Med Res Opin.2004; 20(4):565–72. doi: 10.1185/030079904125003278
12. Shyangdan D, Cummins E, Royle P, Waugh N. Liraglutide for the treatment of type 2 diabetes. Health Technol Assess.2011; 15 Suppl 1:77–86. doi: 10.3310/hta15suppl1/09
13. Tamborlane WV, Barrientos-Pérez M, Fainberg U, Frimer-Larsen H, Hafez M, Hale PM, et al.. Ellipse trial investigator. liraglutide in children and adolescents with type 2 diabetes. N Engl J Med (2019) 381(7):637–46. doi: 10.1056/NEJMoa1903822
14. Trujillo J. Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes. J Clin Pharm Ther.2020 Suppl 1(Suppl 1):43–60. doi: 10.1111/jcpt.13225
15. Saisho Y, Kou K, Tanaka K, Abe T, Kurosawa H, et al. (2011) Postprandial serum C-peptide to plasma glucose ratio as a predictor of subsequent insulin treatment in patients with type 2 diabetes. Endocr J 58: 315-322.
16. Kodani N, Saisho Y, Tanaka K, Kawai T, Itoh H. Effects of mitiglinide, a short-acting insulin secretagogue, on daily glycemic variability and oxidative stress markers in Japanese patients with type 2 diabetes mellitus. Clin Drug Invest.2013; 33: 563-570.
17. Committee on the Standardization of Diabetes MellitusRelated Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. Diabetol Int. 2012; 3: 8-10
18. Esposito K, Ciotola M, Carleo D, Schisano B, Sardelli L, et

al. Post-meal glucose peaks at home associate with carotid intima-media thickness in type 2 diabetes. J Clin Endocrinol Metab.2008; 93: 1345-1350.

19. Ashwell SG, Bradley C, Stephens JW, Witthaus E, Home PD (2008) Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. Diabetes Care 31: 1112-1117.
20. Ishii H, Iwase M, Seino H, Shuto Y, Atsumi Y. Assessment of quality of life in patients with type 2 diabetes mellitus before and after starting biphasic insulin aspart 30 (BIAsp 30) therapy: IMPROVE study in Japan. Curr Med Res Opin.2011; 27: 643-650.
21. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, et al. AACE comprehensive diabetes management algorithm. 2013. Endocr Pract 19: 327-336.
22. International Diabetes Federation Guideline Development Group. Global Guideline for Type 2 Diabetes. Diabetes Res Clin Pract.2014; 104: 1-52.
23. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzalez JG, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week dou-ble-blind study. Diabetes Care.2021; 35: 252-258.
24. Umpierrez G, Tofé Povedano S, Pérez Manghi F, Shurzinske L, Pechtner V (2014) Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care 37: 2168-2176.
25. DeFronzo RA, Barzilai N, Simonson DC (1991) Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. J Clin Endocrinol Metab 73: 1294-1301.
26. Meier JJ (2012) GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 8: 728-742.
27. Mori Y, Taniguchi Y, Sezaki K, Yokoyama J, Utsunomiya K (2011) Liraglutide narrows the range of circadian glycemic variations in Japanese type 2 diabetes patients and nearly flattens these variations in drug-naive type 2 diabetes patients: a continuous glucose monitoring– based study. Diabetes Technol Ther 13: 1139-1144.
28. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, et al. (2008) Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin 24: 275-286.
29. Inoue K, Maeda N, Fujishima Y, Fukuda S, Nagao H, et al. (2014) Long-term impact of liraglutide, a glucagonlike peptide-1 (GLP-1) analogue, on body weight and glycemic control in Japanese type 2 diabetes: an observational study. Diabetol Metab Syndr 6: 95.
30. Rizzo M, Abate N, Chandalia M, Rizvi AA, Giglio RV, et al. Liraglutide reduces oxidative stress and restores heme oxygenase-1 and ghrelin levels in patients with type 2 diabetes: a prospective pilot study. J Clin Endocrinol . 2014; 100: 603-606