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ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Jun-Ling Shi, PhD, Professor, School of Life Sciences, Northwestern Polytechnical University, Xi'an 710072, Shaanxi Province, China. sjlshi2004@nwpu.edu.cn

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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LETTER TO THE EDITOR

Chiglitazar and Thiazolidinedione in patients with type 2 diabetes: Which is better?

Kotha Sugunakar Reddy, Archana Gaur, Sakthivadivel Varatharajan, Arvind Kumar Morya

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Kotha Sugunakar Reddy, Department of General Medicine, All India Institute of Medical Sciences, Hyderabad 508126, Telangana, India

Archana Gaur, Department of Physiology, All India Institute of Medical Sciences, Hyderabad 508126, Telangana, India

Sakthivadivel Varatharajan, Department of Medicine, All India Institute of Medical Sciences, Hyderabad 508126, Telangana, India

Arvind Kumar Morya, Department of Ophthalmology, All India Institute of Medical Sciences, Hyderabad 508126, Telangana, India

Corresponding author: Arvind Kumar Morya, MBBS, MNAMS, MS, Additional Professor, Department of Ophthalmology, All India Institute of Medical Sciences, Bibi Nagar, Hyderabad 508126, Telangana, India. bulbul.morya@gmail.com

Abstract

This published Meta-Analysis by Lin *et al* is an indirect comparison between two drugs Chiglitazar and Thiazolidinedione which are commonly used for glycemic control in type-II diabetes mellitus. In terms of safety and efficacy, this Meta-Analysis is inconclusive.

Key Words: Type-II diabetes mellitus; Glucose intolerance; Hyperglycemia; Research methodology

Core Tip: The authors had done an indirect comparison between the new anti-diabetic drug Chiglitazar with Thiazolidinediones. It is premature to compare a single, relatively smaller study to 142 studies on Thiazolidinediones which are spanning over 28 years. Also, the efficacy of different thiazolidinediones has not been comprehensively compared and emphasized in the analysis and discussion.

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TO THE EDITOR

We have read with great interest the article entitled "Indirect Comparison of Efficacy and Safety of Chiglitazar and Thiazolidinedione in Patients with Type 2 Diabetes: A Meta-Analysis" authored by Lin C *et al*, published in the *World Journal of Diabetes* [2023; 14 (10): 1573-1584][1]. I would like to extend my sincere congratulations to the authors for conducting this comparative meta-analysis and contributing to the growing body of knowledge on oral hypoglycemic drugs.

With a diabetes pandemic in visibility, there is an urgent need of newer molecules and modality of treatments for type 2 diabetes mellitus, Chiglitazar represents a new wave of non- thiazolidinedione medications that can regulate gene expression by binding in a configuration-restricted manner and inhibiting the phosphorylation of hPPARγ, Chiglitazar operates as a pan-agonist, offering a detailed mechanism that elucidates its ability to fully activate PPARγ and partially activate PPARα and PPARβ[2].

The article under discussion offers a unique perspective by comparing the efficacy and safety of the newer molecule, Chiglitazar with the much older thiazolidinediones through an indirect meta-analysis. While this approach is commendable, it is important to acknowledge that adjusted indirect comparisons are not without their limitations, and they are subject to potential heterogeneity among the studies being compared[3]. Moreover, this method relies on a bridge comparator, which in this case, is the placebo used in the included studies.

It is worth noting that the article does not explicitly mention the specific method and type of indirect comparison used. However, it can be inferred that an adjusted indirect comparison with the Bucher Method was employed to estimate the relative effects of the two treatments[4]. One of the drawbacks of this method is that it assumes a similarity between the studies, which may not always hold true, especially given the potential heterogeneity among study populations, such as differences in races.

The comparison made in this article involves 142 studies on different thiazolidinediones, conducted over a 28-year span, compared to a single study conducted on 166 patients with Chiglitazar. This discrepancy in the quantity and timing of the studies is a critical factor to consider when drawing conclusions about the efficacy and safety of Chiglitazar in comparison to thiazolidinediones. The substantial time gap between the studies could result in variations in treatment guidelines, diagnostic criteria, and patient populations, which can influence the comparability of the results.

The present article on indirect meta-analysis discusses both the standard (32 mg) and augmented (48 mg) doses of Chiglitazar. However, it is notable that the article predominantly emphasizes the results related to the augmented dose's effects and safety without providing a comprehensive analysis of the standard dose results. Additionally, the rationale for using an augmented dose and the motivation for testing Chiglitazar with this dose are not sufficiently addressed. A randomized double-blind trial, conducted over 24 wk in a small group in China, explored the efficacy and changes in insulin resistance and retinol binding protein levels revealed no significant reductions in HbA1c levels from the baseline in the full analysis population for Chiglitazar at doses of 32 mg, 48 mg, and sitagliptin at 100 mg but Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) values in the Chiglitazar at 48 mg group were notably lower, HOMA-β levels for both Chiglitazar doses (32 mg and 48 mg) decreased significantly compared to the sitagliptin 100 mg group. Chiglitazar, at both doses, notably elevated total cholesterol and high-density lipoprotein cholesterol (HDL-C) compared to sitagliptin 100 mg[5].

When scrutinizing the statistical analysis and discussion, it becomes apparent that the study results for different thiazolidinediones and comparisons between them, such as Pioglitazone, Rosiglitazone, Troglitazone, and Englitazone's efficacy, are not adequately addressed. The forest plot displaying pooled efficacy from different thiazolidinedione study groups reveals considerable heterogeneity in efficacy endpoints, including HbA1c, low-density lipoprotein cholesterol, TG-C, HDL-C, FBS, HOMA-IR, and HOMA-Beta, with percentages ranging from 98% to 100%. Such high levels of heterogeneity can be considered problematic, and comparing pooled efficacy can be misleading. It would be more appropriate to explore alternative methods, such as matched adjusted indirect comparison, while including individual patient data to improve the accuracy of the analysis.

The collective indirect comparisons pertaining to safety endpoints, which encompass hypoglycemia, edema, bone fractures, upper respiratory tract infections, and urinary tract infections, do not exhibit statistically significant results. The confidence intervals for these comparisons are notably wide, indicating a lack of statistical significance.

In light of these limitations, it would be premature to draw confident conclusions regarding the preferability of Chiglitazar over thiazolidinediones, particularly when comparing a single, relatively smaller study to 142 studies spanning over 28 years. The efficacy of different thiazolidinediones has not been comprehensively compared and emphasized in the analysis and discussion. Therefore, the need for a more robust and nuanced evaluation remains.

In conclusion, I/we wish to express our gratitude to the authors for sharing their knowledge and research work, which involves comparing a newer molecule with older ones concerning efficacy and safety. This article serves as a source of motivation for healthcare professionals to delve deeper into the study of newer molecules like Chiglitazar, ultimately enriching the arsenal of oral hypoglycemic drugs and instilling growing confidence in our practice.

FOOTNOTES

Author contributions: Morya AK designed and formulated the research; Reddy KS, Gaur A and Varatharajan S performed the research; Reddy KS, Gaur A and Varatharajan S analyzed data and wrote the letter; and Morya AK revised the letter; all the authors have read and approved the final manuscript.

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ORCID number: Sakthivadivel Varatharajan 0000-0002-5691-670X; Arvind Kumar Morya 0000-0003-0462-119X.

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