COLLEGE OF PHARMACY
UNIVERSITY OF UTAH
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The association between insulin adherence based on prescription fill rate measures and glycemic control: a systematic review and meta-analysis

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Danielle Nguyen[1], Xi Liang[1], Sajesh Veettil[1], Chia Jie Tan[1], Chanthawat Patikorn[1], Stefanie Nguyen[2] , Diana Brixner[1], Nathorn Chaiyakunapruk[1]

[1]College of Pharmacy, University of Utah, Salt Lake City, UT; [2]Northwestern Medicine, Chicago, IL

Background

- Insulin adherence is vital to achieving glycemic control. [1-7] Several interventions, have been implemented to improve adherence; part of the Inflation Reduction Act aims to improve adherence through ameliorating cost barriers. [1-7]
- There is no widely accepted insulin adherence (based on prescription fill measures) endorsed by the Pharmacy Quality Alliance, only persistence.[8-11]
  - Prescription fill measures of adherence include medication possession ratio (MPR), proportion of days covered (PDC), and others.[8-11]
    - MPR is the "total day supply in a defined period" divided by the "number of days in the defined period." PDC is similar but cannot exceed 100%.
  - Insulin adherence is difficult to measure given that it is a liquid and titratable.
- There remains unclear evidence whether improving insulin adherence (based on prescription claims) is associated with better glycemic control.

Objective

To determine the association between glycemic control and insulin adherence (based on prescription fill measures).

Methods

Study design: systematic review and meta-analysis

Inclusion criteria

- Randomized controlled trials (RCTs) or cohort studies
- Included adults with type 2 diabetes mellitus (T2DM)
- Reported a measure of glycemic control, such as hemoglobin A1C (HbA1c)
- Described a measure of insulin adherence based on prescription fill measures

Search strategy: PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Trials were searched from inception to 10/12/22.

Analysis

- Two different analyses were run: one with adherence as a categorical variable and one with adherence as a continuous variable.
  - Data were pooled using a random-effects model by applying the DerSimonian Laird Method.[13] Results are presented as mean differences (MD) and their 95% confidence interval (CI).
  - Study heterogeneity was evaluated using the I^2 statistic.
- Sensitivity analyses were performed by removing studies with low study quality (utilizing the Newcastle Ottawa Scale (NOS)),[14] a small sample size (< 25 % variance),[15] an unclear adherence definition, poor quality of the prescription fill history, or duplicated populations.
- A subgroup analysis was performed based on the adherence definitions and insulin type.

Results

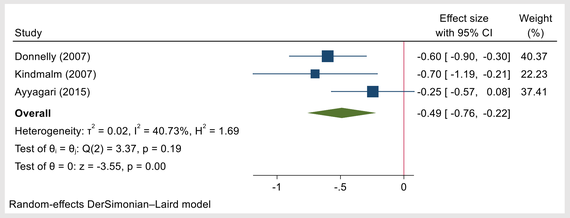
Study Characteristics

- A total of 11 studies were found for inclusion.[12,16-25] Only 10 could be used for quantitative synthesis.[12,16-19, 21-25]
  - 10 studies were retrospective cohort studies; [12,16-24] 1 was an RCT.[25]
- 10 of 11 studies pulled data from a claims-based database.[12, 16, 18-25]One study used paper records.[17]
- Five studies were low risk of bias.[17,19-21,25] Five were at a moderate risk of bias.[12,21-23,25] One study had a high risk of bias.[17]

Baseline Characteristics

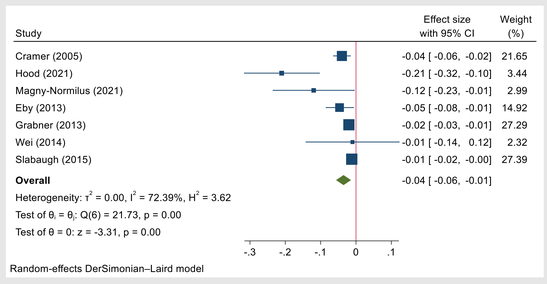
- The average age of the patients ranged from 47 to 66 years old. [12,16-25]
- Most patients were male; the percentage in the studies ranged from 29% to 97.6%. [12,16-25]

Figure 1. Adherence as a Categorical Variable[16-17, 22]



Compared to non-adherent patients, adherent patients had a HbA1c MD of -0.49 (95% CI -0.76, -0.22, I^2 = 40.73%).

Figure 2. Adherence as a Continuous Variable[12, 18-19, 23-25]



An increase in adherence of 1% was associated with an HbA1c MD of -0.04 (95% CI -0.06, -0.01, I^2 = 72.39).

- Findings remained robust even with the sensitivity analyses.

Table 1. Adherence Definition Subgroup Analysis

Subgroup analyses	No. studies	n	Effect size (95% CI)	I^2 %
Adherence as a Continuous Variable				
1. By adherence definitions				
MPR	5[12,18-19, 21,25]	12,714	-0.02 (-0.04 to -0.01)	50%
PDC/adjusted MPR	1[24]	951	-0.21 (-0.32 to -0.10)	N/A
2. By insulin type				
Long-acting	3[19,21,23]	5,610	-0.02 (-0.02 to -0.01)	0%
Short-acting	1[18]	760	-0.05 (-0.08 to -0.01)	N/A
All insulins/not noted	3[12,24-25]	7,295	-0.11 (-0.22 to -0.00)	82%
MPR = medication possession ratio; N/A = not applicable; PDC = proportion of days covered				

For adherence as a continuous variable, I^2 was reduced from 72.39% to 33.73%. Adjusted MPR was grouped under PDC if it was adjusted to cap at 1.

Discussion

- Insulin adherence (measured by prescription fill measures) were found to be statistically and clinically significantly associated with glycemic control.
  - Addition of an oral hypoglycemic agent resulted in a 0.5 decrease in HbA1C; becoming adherent to insulin had the same effect.[26]
- Significant heterogeneity was found in part due to the wide variation of how insulin adherence was measured, as noted by the subgroup analysis.
- Limitations included:
  - There was limited generalizability as most patients were older and male.
  - Observational studies were subject to confounding, such as titration of insulin during the study period or addition of other hypoglycemic agents.

Conclusion

- Given that claims databases are widely available in the United States, as well as some other countries, prescription fill measures may be a viable way to measure insulin adherence on a broad scale.[27-30]
- Evidence exists to support using insulin claims data to measure adherence.
  - The HbA1c association can be used in diabetes modeling studies to determine long-term outcomes or to evaluate policy outcomes.

References

Please scan this QR code to see references.

For more information or a reprint of this poster, please contact Nathorn Chaiyakunapruk at u0811173@umail.utah.edu