JAMD
THE JOURNAL OF AMD

INTERNATIONAL SYMPOSIUM
FACING THE CHALLENGE OF CLINICAL INERTIA IN 2021

Overcoming therapeutic inertia: ADA perspective

Kamlesh Khunti[1]
[1]Leicester Diabetes Centre, University of Leicester, UK.

Corresponding author: **kk22@leicester.ac.uk**

OPEN ACCESS
PEER-REVIEWED

Citation Khunti K. Overcoming therapeutic inertia: ADA perspective. JAMD 25:31-33, 2022.
DOI 10.36171/jamd22.25.1.5
Editor Luca Monge, Associazione Medici Diabetologi, Italy
Received February, 2022
Accepted April, 2022
Published May, 2022

Data Availability Statement All relevant data are within the paper and its supporting Information files.
Funding The Author received no specific funding for this work.
Competing interest The Author declares no competing interests.

Evidence for early, tight glycemic control

Good outcomes are obtained with early glycemic control, as shown by the UK Prospective Diabetes Study (UKPDS), but the legacy benefits continue ten years after the study ending, and are also present for lipid and blood pressure management. The ADA and EASD consensus report now has, for the first time, evidence-based recommendations: among them, on a blue circle on the top of the flowchart, it is recommended to "avoid clinical inertia", and "to reassess and modify clinical treatment regularly, every 3-6 months"[1].

Therapeutic inertia

When we look at mean glycated hemoglobin (data from the UK database, 2010-2017), after first-line therapy, second-line therapy, up to the fourth-line therapy, we do not see much of the change in terms of improvements in HbA1c outcomes, despite progress is being made in a number of therapeutic areas with some fantastic therapies to improve outcomes[2]. This is really therapeutic inertia: the failure to advance therapy or de-intensify therapy when appropriate to do so[3].
Therapeutic inertia is very different from clinical inertia. Therapeutic inertia mainly refers to a treatment regimen, while clinical inertia could be much wider: preventing and delaying negative outcomes, including referral to self-education programs, lack of screening, lack of assessments, the lack of preventive measures or referrals, for example.
We used to think that clinical inertia was mainly present when we came to initiate insulin or indeed intensify insulin, but now we have all warning evidence showing that therapeutic inertia is present throughout every step of the process, even initiating a first-line therapy.
A database of a study with more than 80,000 people in the UK shows that people with HbA1c >/= 7.5% present a medium of three years to intensify therapy when taking one oral antidiabetic drug (OAD), 7 years when on two OADs, and more than 6 years to intensify therapy with insulin when taking three OADs[4].

Even with insulin, patients remain poorly controlled on OAD treatment for prolonged periods of time in clinical practice, with high differences among countries in the assessment of initiating QD insulin detemir in patients with T2DM treated with >/= 1 OADs, with a mean pre-insulin HbA1c ranging from 8.3% in China to nearly 10% in Turkey and in the UK(5). We are not late only in initiation, but also in titration: with an initiation dose at range of 0.1 to 0.3 U/kg, but at 24 weeks some countries were still only at about 0.15 U/kg, some had titrated more aggressively, and this is despite studies showing that with insulin detemir, for example, at 52 weeks we can get to 0.7 U/kg without getting any hypoglycemia. Despite that, this was not occurring in titration[5].

We see inertia even in patients treated with basal insulin. As shown in another study that included patients with HbA1c >/= 7.5% treated with basal insulin, about 30% had intensified therapy while about 32% stopped basal insulin, and it took a median of 3.7 years to intensify therapy.[6]

Summarizing, we can say that therapeutic inertia is a global problem and all of these studies show that we wait too much to switch from an oral therapy to insulin therapy, as we usually wait an average of 2 to 7 years.

However, therapeutic inertia is not only the failure to advance therapy, but also the failure to de-intensify therapy when it is appropriate to do so. This is what is called "quaternary prevention", that is interventions that protect a group at risk of over-medication, for example with patients who become older, frail, who are not very well, and stop therapy as well, since this also is therapeutic inertia.

Consequences of inertia

The study of Osataphan showed the impact of therapeutic inertia on microvascular complications, such as retinopathy. People who had timely intensification had a lower risk of progression, and the incidence of diabetic retinopathy in those who had inertia was about 4.9 higher than in people who did not[7].

Consequences of inertia can be seen also in cardiovascular complications, with a significant increase of myocardial infarction, stroke, heart failure, and composite cardiovascular events in the case of therapeutic inertia. Among patients with newly diagnosed type 2 diabetes from a UK retrospective cohort study, 26% didn't receive treatment intensification within the first 12 months[8]. Another US study reported that therapeutic inertia is also associated with mortality: for example, a 3-year delay in intensification would be associated with a 37% increased mortality, and a 6-year delay would be associated with a 54% risk of mortality[9]. Therefore in summary, therapeutic inertia is associated with both microvascular and macrovascular outcomes, as well as mortality.

Potential solutions

In terms of barriers, which is a very complex area, there are patient-level barriers, physician-level barriers, and system-level barriers. The latter refers to resources that are unable to access or do not have access to certain medications.

In term of physician- and patient-level barriers, some of them are very similar: fear of hypoglycemia, impaired quality of life, lack of patient adherence to treatment, financial restrictions, complex regimes so that people do not intensify their therapy properly[10].

In terms of number of interventions to overcome inertia, not many interventions are been tried truly, and this is an area that we need to look at in the future. Nevertheless, some of the areas that are been used to overcome therapeutic inertia include education programs, motivating and supporting patients on self-management, trying to improve adherence to medications and to guidelines, developing quality measures, and using effective information systems.

A systematic review of 36 studies and over 22,000 participants, published in 2021 as part of an ADA initiative, showed that the interventions having the best effect to mitigate therapeutic inertia were those that empower nonphysician providers such as pharmacists, nurses and diabetes educators to initiate and intensify treatment independently, whereas physician-based interventions probably have the least efficacy, with a 0.3% reduction[11]. So now we have overwhelming evidence that we can do something to contrast therapeutic inertia.

Overcoming Therapeutic Inertia initiative

Three years ago, an ADA initiative was started to overcome therapeutic inertia by empowering patients and healthcare professionals, trying to opti-

mize care and treatment programs, and adopting algorithms that could be put in the computer systems to create and use a patient registry, and integrate programs to support healthcare professionals to improve outcomes. The three main pillars that can help us overcoming therapeutic inertia are research, education and awareness, and collaborative barrier busting. Quite a lot of work has already been done, and a key point was the collaboration between a number of groups[12].

In summary, type 2 diabetes is a progressing disease and tight glycemic control is associated with long terms benefits, but there are huge amounts of barriers in translating evidence in clinical practice for improving outcomes. So, we need to work together to overcome clinical inertia and to arrive to a solution, individualizing interventions.

References

1. Davies MJ, D'Alessio DA, Fradkin J et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 61: 2461–98. https://doi.org/10.1007/s00125-018-4729-5, 2018.

2. Dennis JM, Henley WE, McGovern AP, Farmer AJ, Sattar N, Holman RR, Pearson ER, Hattersley AT, Shields BM, Jones AG. MASTERMIND consortium. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: A retrospective analysis of primary care data, 2010-2017. Diabetes Obes Metab 21:1576-1584. doi: 10.1111/dom.13687, 2019.

3. Khunti K, Millar-Jones D. Clinical inertia to insulin initiation and intensification in the UK: A focused literature review. Prim Care Diabetes 11:3-12. doi: 10.1016/j.pcd.2016.09.003, 2017.

4. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 36:3411-7. doi: 10.2337/dc13-0331, 2013.

5. Khunti K, Caputo S, Damci T, Dzida GJ, Ji Q, Kaiser M, Karnieli E, Liebl A, Ligthelm RJ, Nazeri A, Orozco-Beltran D, Pan C, Ross SA, Svendsen AL, Vora J, Yale JF, Meneghini LF; SOLVE Study Group. The safety and efficacy of adding once-daily insulin detemir to oral hypoglycaemic agents in patients with type 2 diabetes in a clinical practice setting in 10 countries. Diabetes Obes Metab 14:1129-36. doi: 10.1111/j.1463-1326.2012.01665.x, 2012.

6. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes Obes Metab 18:401-409. doi: 10.1111/dom.12626, 2016.

7. Osataphan S, Chalermchai T, Ngaosuwan K. Clinical inertia causing new or progression of diabetic retinopathy in type 2 diabetes: A retrospective cohort study. J Diabetes 9:267-274, 2017.

8. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 14:100. doi: 10.1186/s12933-015-0260-x, 2015.

9. Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, Karter AJ. The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study). Diabetes Care 42:416-426. doi: 10.2337/dc17-1144, 2019.

10. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, Landgraf R, Kleinebreil L. International DAWN Advisory Panel. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 28:2673-79. doi: 10.2337/diacare.28.11.2673, 2005.

11. Powell RE, Zaccardi F, Beebe C, Chen XM, Crawford A, Cuddeback J, Gabbay RA, Kissela L, Litchman ML, Mehta R, Meneghini L, Pantalone KM, Rajpathak S, Scribner P, Skelley JW, Khunti K. Strategies for overcoming therapeutic inertia in type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 23:2137-2154. doi: 10.1111/dom.14455, 2021.

12. https://www.therapeuticinertia.diabetes.org/