FEATURE ARTICLE

Therapeutic Inertia and Delays in Insulin Intensification in Type 2 Diabetes: A Literature Review

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BACKGROUND | Therapeutic inertia leading to delays in insulin initiation or intensification is a major contributor to lack of optimal diabetes care. This report reviews the literature summarizing data on therapeutic inertia and delays in insulin intensification in the management of type 2 diabetes.

METHODS | A literature search was conducted of the Allied & Complementary Medicine, BIOSIS Previews, Embase, EMCare, International Pharmaceutical Abstracts, MEDLINE, and ToxFile databases for clinical studies, observational research, and meta-analyses from 2012 to 2022 using search terms for type 2 diabetes and delay in initiating/intensifying insulin. Twenty-two studies met inclusion criteria.

RESULTS | Time until insulin initiation among patients on two to three antihyperglycemic agents was at least 5 years, and mean A1C ranged from 8.7 to 9.8%. Early insulin intensification was linked with reduced A1C by 1.4%, reduction of severe hypoglycemic events from 4 to <1 per 100 person-years, and diminution in risk of heart failure (HF) by 18%, myocardial infarction (MI) by 23%, and stroke by 28%. In contrast, delayed insulin intensification was associated with increased risk of HF (64%), MI (67%), and stroke (51%) and a higher incidence of diabetic retinopathy. In the views of both patients and providers, hypoglycemia was identified as a primary driver of therapeutic inertia; 75.5% of physicians reported that they would treat more aggressively if not for concerns about hypoglycemia.

CONCLUSION | Long delays before insulin initiation and intensification in clinically eligible patients are largely driven by concerns over hypoglycemia. New diabetes technology that provides continuous glucose monitoring may reduce occurrences of hypoglycemia and help overcome therapeutic inertia associated with insulin initiation and intensification.

New diabetes medications (e.g., sodium–glucose cotransporter 2 [SGLT2] inhibitors and glucagon-like peptide 1 [GLP-1] receptor agonists) and new technology for monitoring glucose levels (e.g., continuous glucose monitoring [CGM] systems) have proven to be effective in the management of diabetes (1). Despite their availability, the proportion of the U.S. population with diabetes achieving healthy A1C levels has failed to improve (2,3). A comparison of data collected from the National Health and Nutrition Examination Survey (NHANES) on adults with diabetes between the periods 2003–2010 and 2011–2014 revealed that a lower proportion of individuals in the latter time period achieved the recommended A1C target of <7% (52.2 vs. 50.9%, respectively) (2). The same study showed only small changes in the achievement of individualized targets (69.8 vs. 63.8%, respectively). Conversely, the percentage of patients with diabetes who had an A1C >9% actually increased by ~3% from 2003–2010 to 2011–2014 (2). A similar study comparing NHANES data between the periods of 2007–2010 and 2015–2018 revealed a decline of 4% in individuals who achieved an A1C target of <8%, from 79.4% in 2007–2010 to 75.4% in 2015–2018 (3).

Many factors contribute to these disappointing findings. One important factor is therapeutic inertia, defined by the American Diabetes Association as "a lack of timely adjustment to therapy when a patient's treatment goals are not met" (4). In the context of diabetes care, therapeutic inertia refers to being slow to add or change a patient's care plan, which includes medications, health checks, diabetes education, nutrition therapy, exercise, and emotional support, when the patient's A1C is above goal (4). A recent review by Andreozzi et al. (5) described the roles of health care professionals, patients, and the national health care system in therapeutic inertia in diabetes. It highlighted clinician-based factors contributing to therapeutic inertia specific to insulin initiation or intensification, including concerns about the risks of hypoglycemia and weight gain, as well as a perceived lack of patient ability to adhere to insulin-based therapies, among others.

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Disparities in diabetes care contributing to higher rates of diabetes complications and mortality among racial/ethnic minorities and low-income adults in the United States have been well documented, prompting greater scrutiny of social determinants of health (SDOH) and implicit bias in diabetes care in these populations (6,7). Recent reviews focused on SDOH in diabetes (6,7) have described several key factors contributing to these disparities. Although these factors are numerous and varied, racial bias and discrimination, coupled with poor access to quality care, are likely the ones most closely related to therapeutic inertia. Additionally, underserved populations are significantly less likely to have access to, or to use, newer medications and diabetes-related technology (8–12).

To better understand therapeutic inertia and delays in insulin intensification in patients with type 2 diabetes, we performed a literature search to clarify attitudes toward therapeutic inertia and insulin intensification, time until insulin intensification, consequences of delay in insulin intensification, clinical benefits of insulin intensification, and the relationship between insulin intensification and health care resources.

Research Design and Methods

For this review, we conducted a comprehensive search of recent human-related literature on type 2 diabetes and delay in initiating or intensifying insulin published from January 2012 to March 2022 using the Allied & Complementary Medicine, BIOSIS Previews, Embase, EMCare, International Pharmaceutical Abstracts, MEDLINE, and ToxFile databases. Keywords in titles and abstracts were combined using "OR"/"AND" operators and included search terms for type 2 diabetes and delay in initiating or intensifying insulin. Additionally, references cited in key articles were also searched manually.

After the initial search was performed, studies were screened for eligibility. Studies were eligible for inclusion if they were clinical studies, meta-analyses, or observational research pertaining to humans. Exclusion criteria included articles that were *1*) not relevant to the subject; *2*) published >10 years before the search date range; *3*) pertaining to pregnancy; *4*) not clinical studies, meta-analyses, or observational research; and *5*) nonhuman studies.

Results

A total of 116 publications were initially identified. Ninety-nine publications were excluded based on the exclusion criteria. The final inclusion set consisted of 22 publications (13–34), of which 17 were based on the search criteria and an additional five were detected through a review of references included in key studies. Results are presented by categorical organization of findings.

Attitudes Toward Therapeutic Inertia and Insulin Intensification

Therapeutic inertia in diabetes care is multifactorial, with clinician, provider, and health system contributions (13–16). Major drivers of therapeutic inertia include fear of hypoglycemia, concerns about weight gain, and the perceived complexity of insulin regimens (13–16). For example, the results of a physician survey–based study conducted by Peyrot et al. (13) found that 87.6% of physicians agreed that insulin-treated patients do not have adequate glucose control and that 75.5% would treat more aggressively if not for concerns over hypoglycemia. Results from a more recent physician survey–based study conducted by Leto et al. (17) revealed that the five most inappropriate actions contributing to therapeutic inertia in clinical practice were *1*) nonuse of sulfonylureas/glinides, *2*) failure to appreciate the risk of lack of hypoglycemia awareness, *3*) reluctance to initiate intensification of diabetes therapy, *4*) failure to initiate treatment changes for patients who are not at glycemic target, and *5*) failure to train patients for hypoglycemia treatment.

Time Until Insulin Intensification

In a review of published literature on the subject, Giugliano et al. (18) concluded that the greatest contributing factors to therapeutic inertia were failure to initiate or intensify insulin treatment. In support of this assertion, several studies have documented long delays in the time until insulin intensification. Escalada et al. (19) found that, in patients with poorly controlled diabetes, 31–46% of general practitioners, internists, and endocrinologists waited 3–6 months before initiating insulin, and 58–71% confirmed elevated A1C levels twice before initiating insulin. Other studies have found that, for patients with type 2 diabetes on two or three antihyperglycemic agents, the median time to insulin initiation was from 5 years to >7.1 years (20–22). Furthermore, the mean A1C for patients with type 2 diabetes on two to three antihyperglycemic agents who were initiating insulin was observed to be 8.7–9.8% (20,21,23–25), indicating a significant delay in insulin initiation. Khunti et al. (26) documented a median time until 3.7 years for insulin intensification from basal insulin, despite having an A1C >7.5%. Other studies have detected low rates of insulin intensification (5.1–30.9%) among clinically eligible (A1C ≥7.5%) patients with type 2 diabetes (16,20,26,27). A study following type 2 diabetes patients who were newly initiated on basal insulin therapy found that, after 6 months, 81% remained in poor glycemic control, and after 12 months,

only 34% of the patients with uncontrolled glycemia underwent the addition of another antihyperglycemic agent (28).

Consequences of Delayed Insulin Intensification

A study by Paul et al. (27) identified significantly increased risks of myocardial infarction (MI) (67%), stroke (51%), heart failure (64%), and composite macrovascular events (62%) after a 1-year delay in treatment intensification. Hosomura et al. (29) found that clinically eligible patients who initiated insulin for the first time as recommended by physicians had a median time to an A1C of 7.0% of 18 months compared with 30 months for those who did not initiate insulin the first time. A meta-analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes), UKPDS (UK Prospective Diabetes Study), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial) cardiovascular trials showed reductions of 15% in MI and 9% in cardiovascular events in the tight glycemic control group (30). It has also been shown that therapeutic inertia in patients with type 2 diabetes was associated with a shorter median time of 46 months to progression of diabetic retinopathy (DR) compared with the median not being reached during a 4-year study in the noninertia group, in addition to the finding of a higher incidence of DR (10 vs. 2.2 cases per 1,000 person-months, in the inertia vs. noninertia groups, respectively) (31).

Clinical Benefits of Insulin Intensification

A retrospective study conducted by Hersi et al. (32) compared groups with early insulin intensification (<1 year), delayed insulin intensification (>1 year), and no insulin intensification. Findings indicated that early treatment intensification was linked to 18, 23, and 28% reductions in the risk of heart failure, MI, and stroke, respectively. The results from one study in patients with type 2 diabetes initiating basal insulin found a decrease in A1C of 1.4% and a decrease of severe hypoglycemic events from 4 to <1 per 100 person-years (33).

Relationship Between Insulin Intensification and Health Care Resources

Using Medicare Benefits Schedule codes (general practitioner [GP], specialist, allied health, nurse, procedures, imaging, and pathology), Johnson et al. (34) detected an increase in health service usage (HSU) events from a median of 18–23 6 months after insulin initiation. The investigators reported that this increase was largely attributable to an increase in GP consultations from six to eight. HSU and GP consultations subsequently returned to baseline at 12 months (34).

Discussion

This literature review revealed a time to insulin intensification of at least 5 years in patients with type 2 diabetes with an average A1C before intensification >8%. These findings are strongly suggestive of significant delays in insulin initiation and intensification for clinically eligible patients with type 2 diabetes.

The main reason for this delay appears to be fear of hypoglycemia; however, there was even a decrease in hypoglycemia as insulin was intensified. This counterintuitive finding is corroborated by the ACCORD study; the highest rates of severe hypoglycemia were observed in those with the highest baseline A1C and the smallest A1C reductions (35,36).

Additional findings suggest that such delays pose a variety of serious health risks, including the risk of DR progression and potentially fatal cardio- and cerebrovascular events. Several of the reviewed studies have shown that these risks can be dramatically reduced when insulin intensification is initiated promptly, indirectly highlighting the dangers of therapeutic inertia. In addition to decreasing health risks, insulin intensification was not found to be associated with long-term increases in HSU, which should stimulate a greater interest in reducing therapeutic inertia at the payer level.

Recognizing the lack of improvement of outcomes in type 2 diabetes, the American Diabetes Association in 2020 launched its Overcoming Therapeutic Inertia initiative (37). Part of addressing therapeutic inertia is understanding and addressing the patient and physician attitudes contributing to less timely treatment modification. Survey-based publications on patient and provider attitudes pertaining to insulin initiation and intensification identified in this literature search indicated that fear of hypoglycemia and a history of severe hypoglycemic events contribute importantly to therapeutic inertia (15,19).

However, patient-related factors must also be considered. For example, many patients are resistant to initiating and/or intensifying insulin because of their beliefs and perceptions about this mode of therapy, a condition first referred to by Polonsky et al. (38) as "psychological insulin resistance." In addition to fear of hypoglycemia, some patients are resistant because they believe insulin therapy will be harmful (e.g., will cause blindness), or they may believe that starting insulin means their diabetes is worsening (38). Other reasons can include the desire to avoid the pain of injections, low confidence in their ability to safely use insulin, and the worry that insulin therapy will be too restrictive (38). Lack of social support

(39) and psychological conditions such as depression, distress, and anxiety can also affect patient acceptance and adherence to insulin therapy (40).

Treatment with newer medications such as GLP-1 receptor agonists and SGLT2 inhibitors provide an alternative to insulin in managing hyperglycemia with a very low risk of hypoglycemia. However, these medications may not be acceptable for some patients because of intolerance of side effects and/or cost.

It is noteworthy that the advent of new diabetes-related technology specifically focused on assessing glucose levels in a continuous manner to avoid hypoglycemic events (41) and improve quality of life and psychological conditions (42,43) may alleviate these concerns and contribute to decreased therapeutic inertia. Numerous studies conducted over the past decade have shown that use of CGM is associated with significant reductions in A1C and severe hypoglycemic events in patients with diabetes receiving insulin via a variety of delivery methods (41–44). Gavin and Bailey (43) recently noted that, in addition to improvements in clinical outcomes for patients with type 1 or type 2 diabetes using CGM, the results of several studies have also indicated significant improvements in patient psychosocial measures, including reduced fear of hypoglycemia.

Additionally, associations between CGM use and significant reductions in hospitalizations for severe hypoglycemia and diabetic ketoacidosis (DKA) have been detected in large observational registry and database studies (45), strongly suggesting a level of cost-effectiveness that may be valuable for consideration by payers interested in reducing the huge financial burden associated with diabetes.

Given that new diabetes technology has been found to improve diabetes management, better understanding of how racial/ethnic group identity and socioeconomic status affect access to these new tools may be useful to help mitigate therapeutic inertia. The 2021 U.S. Census found that Hispanics and Blacks have lower median incomes than non-Hispanic Whites ($51,560, $41,361, and $70,642, respectively) (46). Lower socioeconomic status and minority race/ethnicity have been associated with higher A1C levels (12,47,48) and greater risks for negative health outcomes (e.g., DKA, DR, lower limb amputation, major cardiovascular disease, stroke, and end-stage renal disease) in patients with diabetes (6,49–52), and these populations are also the most likely to experience therapeutic inertia (53,54). Non-Hispanic Blacks and people with the lowest annual incomes also have the highest rates of severe hypoglycemia (55–58). A study conducted by Miller et al. (47) showed that, regardless of income level and type of insurance (i.e., none, state/federal, or private), individuals using CGM had lower A1C levels than nonusers of CGM. In addition, initiating CGM has been found to reduce severe hypoglycemia (41,59). Recent evidence suggests that patients with diabetes from minority racial/ethnic groups are less likely than their non-Hispanic White counterparts to use CGM (8–12), and likewise that those with lower socioeconomic status are less likely to use diabetes technology (47,48).

Collectively, the results of this comprehensive literature review on the causes and consequences of delay in initiating and intensifying insulin for patients with type 2 diabetes support an urgent need for overcoming the therapeutic inertia that places this patient population at high risk for negative health outcomes. New diabetes technology, including CGM, may contribute to a dramatic decline in the therapeutic inertia driven by concerns about increased hypoglycemia with insulin initiation or intensification, which can now be readily assessed and more comprehensively addressed.

Conclusion

Therapeutic inertia remains a barrier to the optimal care of patients with uncontrolled type 2 diabetes. Patients, providers, and payers are uncomfortable with insulin initiation and intensification largely because of concerns about provoking hypoglycemia, which can lead to hospitalizations and an ever-increasing cost burden. Based on recent developments in diabetes technology, including the widespread use of CGM, hypoglycemia may become less of a persistent consequence of intensified insulin treatment, and this in turn may reduce therapeutic inertia via improved confidence among all stakeholders. Barriers to CGM access will need to be addressed to decrease therapeutic inertia and provide effective treatment for all patients regardless of their racial/ethnic identity or socioeconomic status.

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DUALITY OF INTEREST

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AUTHOR CONTRIBUTIONS

J.R.G. contributed to the concept and design of the study, provided data regarding health disparities, participated in writing the initial

draft, and provided critical revision of the manuscript. R.M.A. contributed to the acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. N.S.V. participated in the acquisition of the data, analysis and interpretation of data, and drafting of the manuscript and provided administrative, technical, or logistic support and supervision. All authors reviewed the manuscript and approved its submission. J.R.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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