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Benefits of timely basal insulin control in patients with type 2 diabetes☆

Dragana Lovre, Vivian Fonseca *

Tulane University Health Sciences Center, New Orleans, LA

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SUMMARY

Worldwide, both underdiagnosis and undertreatment leave many patients exposed to long periods of hyperglycemia and contribute to irreversible diabetes complications. Early glucose control reduces the risk of both macrovascular and microvascular complications, while tight control late in diabetes has little or no macrovascular benefit. Insulin therapy offers the most potent antihyperglycemic effect of all diabetes agents, and has a unique ability to induce diabetes remission when used to normalize glycemia in newly diagnosed patients. When used as a second-line therapy, basal insulin is more likely to safely and durably maintain A1C levels ≤7% than when insulin treatment is delayed. The use of basal insulin analogs is associated with a reduced risk of hypoglycemia and weight gain compared to NPH insulin and pre-mixed insulin. Patient self-titration algorithms can improve glucose control while decreasing the burden on office staff. Finally, recent data suggest that addition of incretin agents to basal insulin may improve glycemic control with very little, if any increased risk of hypoglycemia or weight gain.

1. Growing burden of diabetes

Preventing diabetic complications in the growing population of people with diabetes depends first on improving the rate of diagnosis. Most diabetes agencies in the world recommend similar diagnostic criteria based on the fasting plasma glucose (FPG; ≤126 mg/dL) and 2-hour oral glucose tolerance test (OGTT; ≤200 mg/dL), but so far only the American Diabetes Association (ADA) recommends using the A1C test for diagnosis (Association AD, 2013; Force IDFcGT, 2012). Despite some challenges and controversies (lack of availability and/or standardization of the A1C assay in some areas and reliability of A1C results in patients with hemoglobinopathies and other conditions), the A1C test can be a convenient and useful tool for screening because patients' glucose levels can be tested in a nonfasting state (Association AD, 2013). Regardless of the diagnostic method used (and clinicians should make this choice according to their own preferences), at-risk populations should be screened on a regular basis, because prompt diagnosis and initiation of treatment are essential for preventing diabetic complications.

1.1. Undertreatment

Unfortunately, among the diagnosed, undertreatment prevails throughout the world, where as many as one-half to two-thirds of patients do not have an A1C <7% (Ali et al., 2013). According to data from the 2010 National Health and Nutrition Examination Survey (NHANES), only 52% of patients in the U.S. have A1C levels <7%, while 13% have A1C levels >9% (Ali et al., 2013). A 2009 study by the International Diabetes Management Practice Study (IDMPS) found that in Eastern Europe, Latin America, and Asia, only 36% of patients with type 2 diabetes (and even fewer with type 1) had ever had their A1C measured. Of those, only 36% had an A1C <7% (Chan, Gagliardino, Baik, et al., 2009).

Nevertheless, various studies across the globe suggest that there has been a reduction in the rate of diabetes-related amputations (Association AD, 2013). In the U.S., the incidence of microalbuminuria has declined, and end-stage renal disease has leveled off in recent years, while the number of patients at severe risk of coronary heart disease has declined. These figures emphasize the importance of intensive glucose control for reducing the risk of microvascular complications, which can have a dramatic impact on morbidity and mortality (Lopez Stewart et al., 2007).

In order to achieve glycemic targets it is more practical and perhaps more effective to first reduce the fasting glucose. Control of fasting glucose is necessary to achieve A1C levels close to 7%, because of the relative contributions of fasting and postprandial glucose to overall glycemia (Riddle, Umpierrez, DiGenio, Zhou, & Rosenstock, 2011; Woerle, Neumann, Zschau, et al., 2007). At levels much greater than 7%, fasting glucose is the important determinant of A1C, whereas postprandial glucose may become more important around 7%—a level of

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* Corresponding author at: Tulane University Health Sciences Center, 1430 Tulane Avenue, SL 53, New Orleans, LA 70112. Tel.: +1 504 988 4026; fax: +1 504 988 6271.
E-mail address: vfonseca@tulane.edu (V. Fonseca).

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glycemia that may be sufficient for many patients. In addition, fasting as well as postprandial glucose contributes to macrovascular disease. Above approximately 100 mg/dL, rising fasting glucose is associated with an increase in vascular death and coronary heart disease; this relationship is almost linear once fasting glucose passes into the diabetic range (Sarwar, Gao, Seshasai, et al., 2010; Seshasai, Kaptoge, Thompson, et al., 2011). Targeting fasting glucose and lowering it to see whether we can eliminate or reduce this risk of cardiovascular disease are rational strategies.

Failure to start basal insulin is caused by multiple factors including apprehension by patients and physicians, and fear of weight gain. In insulin-naive patients with type 2 diabetes, psychological insulin resistance (PIR) is not uncommon and contributes to unnecessarily long delays for initiating insulin and consequently extending periods of hyperglycemia (Polonsky & Jackson, 2004).

Clinicians as well may inadvertently influence patients' beliefs about insulin through the use of such unfortunate terms as "oral agent failure" (Polonsky & Jackson, 2004).

Another barrier to start insulin is the expectation of weight gain. In a recent >2000 patients retrospective analysis of patient-level data with insulin glargine it was reported that most patients had limited weight change (+/− 2.5 kg) after 24 weeks of insulin glargine (Shaefer et al., 2014). The same analysis showed that younger patients were the ones that gained more weight where as the elderly gained less weight and had lower risk of hypoglycemia (Shaefer et al., 2014).

In 2010 a pooled analysis of randomized controlled trials of patients with T2DM looked at weight and HbA1C changes comparing insulin glargine and detemir which showed similar weight gain of 2.5 kg vs 1.7 kg respectively (Dailey, Admane, Mercier, & Owens, 2010). Using findings such as this one can help guide the physicians on informing patients of realistic expectations about weight when starting basal insulin and redirect the emphasis to basal insulin impact on improvement of glycemic control rather than weight changes.

1.2. The legacy effect: early vs late glycemic control and complications risk

Glycemic goals should be determined by individual patients' duration of disease, comorbidities, and other risk factors (Inzucchi, Bergenstal, Buse, et al., 2012; Ismail-Beigi et al., 2011). Aggressive A1C lowering in individuals with advanced type 2 diabetes only modestly reduces macrovascular complications and poses added risk for these patients (Inzucchi et al., 2012; Skyler, Bergenstal, Bonow, et al., 2009). However, data suggest that there may be benefit without such risk for intensive glucose lowering in patients with early type 2 diabetes. In these patients, reducing glucose to near-normal levels is essential for long-term control of macrovascular risk, as shown by long-term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS). Early control of glucose in the UKPDS had a sustained benefit on macrovascular risk, even when glycemic control deteriorated later. UKPDS participants had few or no complications at study entry, and their FPG and A1C levels were kept low for the intervention phase of the study, which lasted approximately 10 years. After that point, glucose levels rose during the post-trial monitoring phase, but a clear macrovascular benefit remained (Chan et al., 2009).

The concept of the legacy effect emerged from these results and was supported by data from the opposite end of the diabetes spectrum, which showed that uncontrolled glycemia from the beginning of diabetes onset leads to complications that are irreversible (Del Prato, 2009; Gerstein, Miller, Byington, et al., 2008; Holman, Paul, Bethel, Matthews, & Neil, 2008). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) studies, participants had a long duration of type 2 diabetes (8–12 years) and as well as existing cardiovascular complications and baseline A1C levels between 8.0% and 9.4% (Duckworth, Abraira, Moritz, et al., 2009; Gerstein et al., 2008; Patel, MacMahon, Chalmers, et al., 2008). All of these studies clearly demonstrated that late intervention does little to prevent macrovascular disease or stop its progression, probably because once complications set in, they are irreversible and frequently continue to develop through activation of their own biochemical processes and pathways, which may not be reversed by instituting improved glycemic control at a late stage (Brownlee, 2001; Rolo & Palmeira, 2006; Nishikawa, Edelstein, & Brownlee, 2000). Thus, the "bad legacy" of the ACCORD, VADT, and ADVANCE patients' long-standing hyperglycemia undermined the benefits of later strict glucose control, and it is unrealistic to expect that suddenly reducing blood glucose to normal after 10 or 15 years of diabetes would reverse macrovascular complications.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study also did not show a macrovascular benefit in a population somewhat different from that in previous studies. This study compared the use of insulin glargine to maintain an FPG ≤95 mg/dL vs standard care in patients with either prediabetes or newly diagnosed diabetes as well as established cardiovascular disease or multiple risk factors for CVD, and reported a neutral effect on cardiovascular outcomes. However, these results do not refute the legacy effect concept. First, the benefits of early glucose control may take much longer to become apparent—the median follow-up of the UKPDS post-trial monitoring was 17 years, compared with a median of 6 years in ORIGIN (Gerstein, Bosch, Dagenais, et al., 2012; Holman et al., 2008). Second, ORIGIN participants' cardiovascular risks were severe—eligible patients had to have had a prior cardiovascular event or evidence of kidney or vascular disease. Of more than 12,000 study participants, 59% had a prior cardiovascular event, and thus this study might be considered a secondary rather than a primary prevention trial (Association AD, 2013). Given the extent of cardiovascular comorbidities and the trial's relatively short follow-up period, ORIGIN cannot provide any firm conclusions on the macrovascular benefits of intensive therapy in patients with early diabetes.

2. The rationale for earlier insulin initiation

The availability of increasing numbers of noninsulin antidiabetic agents has fostered a reluctance to use insulin among physicians and patients both, and surveys of clinicians have shown a persistent misconception that insulin therapy can be delayed indefinitely if patients adhere to noninsulin regimens (Hayes, Fitzgerald, & Jacober, 2008; Peyrot, Rubin, Lauritzen, et al., 2005). This failure to promptly advance therapy exposes patients to excess glycemic burden (Brown, Nichols, & Perry, 2004). A retrospective analysis of data from primary care practices in Europe showed that between 2005 and 2010, the time from type 2 diabetes diagnosis to insulin initiation increased by approximately 2 years. During the same period, the percentage of patients with at least 1 macrovascular complication increased (Kostev & Mergenthaler, 2011). As discussed, once such macrovascular complications set in, they cannot be reversed with tight glycemic control, regardless of treatment (Duckworth et al., 2009; Gerstein et al., 2008; Patel et al., 2008).

In contrast, achieving good glycemic control sooner than later significantly reduces the risk of diabetic complications, and this may include the use of insulin to achieve good control. As described earlier, patients treated with insulin in the UKPDS experienced not only a reduced risk of microvascular complications in the short term but also of macrovascular disease during long-term follow-up (Anonymous, 1998a; Holman et al., 2008). In addition, the UKPDS showed that early addition of insulin to oral therapy reduced the risk of complications (Wright, Burden, Paisey, Cull, & Holman, 2002).

Another concern with insulin is the incidence of hypoglycemic episodes; the UKPDS showed that the risk of major hypoglycemic episodes was not increased with the early addition of insulin to sulfonylurea therapy (Wright et al., 2002).

Insulin therapy may also slow or even halt diabetes progression. In patients with newly diagnosed type 2 diabetes, several small-scale studies have demonstrated that short term intensive insulin

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