Expert-Group Practical Advice on Insulin Initiation and Titration for Patients with Type 2 Diabetes in the Gulf Region

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Abstract
The type 2 diabetes mellitus (T2DM) management represents a major challenge in the Gulf region. Hyperglycemia is a major risk factor for microvascular and macrovascular complications and increased mortality. Early dietary and lifestyle changes alongside a step-wise targeted pharmacological approach to achieve a glycated hemoglobin (HbA\textsubscript{1c}) level of <7\% are recommended to limit these complications. However, achievement of this HbA\textsubscript{1c} target remains a major challenge, especially in the Gulf region. Both physician and patient-led barriers limit timely initiation and titration of insulin. An expert-group advisory committee reviewed the current guideline recommendations, strategized best practice, and curated clinical practical advices to enable primary-care physicians to optimally initiate and titrate insulin in patients with T2DM.

Introduction

Type 2 Diabetes Mellitus: A Progressive Disease
Type 2 diabetes mellitus (T2DM) is characterized by a progressive decline in \(\beta\)-cell function and worsening peripheral insulin resistance in the liver, skeletal muscle, or adipose tissue [1, 2] which leads to an increase in fasting and postprandial blood glucose (BG) levels and glycated hemoglobin (HbA\textsubscript{1c}) [3, 4]. Elevated fasting, postprandial, and increased excursion of glucose are independent risk factors for diabetes-associated microvascular and macrovascular complications (Fig. 1) [4].

Increasing Prevalence of T2DM in the Gulf Region: An Alarming Situation
Recent data indicate that the Arabian Gulf region accounts for a pooled T2DM prevalence of \(\sim\)24\%, compared to a global prevalence of \(\sim\)8.8\% [5]. Some of the highest prevalence rates in the world are in Bahrain (33.6\%), Saudi Arabia (29.1\%), the United Arab Emirates (25.8\%), and Kuwait (25.4\%) [6].
The American Diabetes Association (ADA) [7] and the American Association of Clinical Endocrinologists (AACE) [8] have set HbA1c goals (<6.5%–7.0%) to limit the development of complications [9]. Glycemic control is poor (HbA1c >7%) throughout the Gulf region, as evidenced in Saudi Arabia (59%–70.7%), the United Arab Emirates (68%–69%), Bahrain (86.5%–88.8%), and Oman (54%–65%) [5]. In primary care in the Gulf region, only 9.6% and 35% of patients achieved optimal FPG and HbA1c levels, respectively [10]. In two separate studies from Oman, among T2DM patients treated in primary care, only 30% and 23% achieved an HbA1c level of <7% [11, 12]. The DiabCare survey in 1,290 patients with T2DM in the Gulf Cooperation Council (GCC) demonstrated poor glycemic control with a mean HbA1c of 8.3%, FPG of 155.9 mg/dL, and a postprandial glucose of 218.2 mg/dL [13].

Role of Insulin in the Management of T2DM
Insulin therapy is the most effective treatment for improving glycemic control [14] and is the key to achieving HbA1c levels <7%, within 9 years of diabetes diagnosis [15, 16].

Cardiovascular Benefits of Optimal Glycemic Control
There is debate regarding the benefit of improved glycemic control on cardiovascular (CV) outcomes [17]. However, recent analysis of trials with GLP-1 agonists and SGLT2i show a clear benefit in terms of CV outcomes [18] with ~20% reduction in MACE events per 0.5% reduction in HbA1c [19]. The Kumamoto study, the UK Prospective Diabetes Study, and three landmark trials (Action to Control Cardiovascular Risk in Diabetes, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation, and Veterans Affairs Diabetes Trial) have confirmed that optimal glycemic control reduces the onset and progression of microvascular complications in patients with T2DM [20].

Non-CV Benefits of Early Insulin Therapy
Other trials, including Outcome Reduction with an Initial Glargine Intervention, EASIE, EARLY, and GLORY, have demonstrated additional clinical benefits of early initiation of insulin therapy in patients with T2DM, including preservation of β-cell function and improvements in fasting and postprandial plasma glucose. These early clinical benefits may preserve glucose homoeostasis, reducing the need for complex treatment regimens and lowering the risk of long-term complications even if control deteriorates, possibly through metabolic memory [14]. Furthermore, a meta-analysis showed no difference in the risk of all-cause mortality and adverse CV events between insulin and noninsulin glucose-lowering therapies [21].

Clinical Benefits of Insulin Analogs
The primary benefits of insulin analogs like glucose control, adverse effects, cost, adherence, and quality of life should be considered when choosing the type of insulin. Insulin analogs are associated with less postprandial hyperglycemia and delayed hypoglycemia. A recent meta-analysis showed better glycemic control with insulin analogs compared to human insulin with a reduced incidence of nocturnal hypoglycemia [22]. A systematic review showed that insulin glargine (IGlar) was superior to neutral protamine Hagedorn insulin and premixed insulin preparations and noninferior to insulin detemir in T2DM patients [23]. Additionally, while glycemic control is comparable between second- and first-generation basal insulin, second-generation insulin has a lower risk of hypoglycemia and weight gain [24].

Second-Generation Basal Analogs: Real-World Evidence
Real-world factors affecting the adherence to insulin therapy are hypoglycemia, weight gain, and the complexity of insulin regimens. Second-generation basal insulin analogs, e.g., IGlar 300 U/mL (Gla-300) and insulin degludec, have demonstrated improved pharmacokinetic and pharmacodynamic profiles compared to first-generation insulin. Both randomized controlled and real-world
studies have shown a lower within-day fluctuation in plasma insulin levels with second-generation insulin analogs. A greater flexibility in insulin dosing makes it more suitable for once-daily treatment and allows a sustained glucose-lowering effect and decreased risk of hypoglycemia, especially in the titration period [25]. A trial-level meta-analysis revealed that Gla-300 showed a similar HbA1c reduction to Gla-100, with a lower risk of day time and nocturnal hypoglycemia [26].

Gla-300 has demonstrated safety and efficacy in the EDITION clinical trials and has proven to be clinically beneficial in real-world studies. DELIVER-D demonstrated that switching from Gla-100 to Gla-300 or IDeg provides similar glucose-lowering efficacy and reduction in hypoglycemia. LIGHTNING reported a comparable HbA1c reduction and equally lower incidence of severe hypoglycemia for Gla-300 and IDeg compared to first-generation basal insulin analogs. In the BRIGHT study, Gla-300 was noninferior to IDeg [25]. Insulin use is increasing to achieve optimal glycemic targets adopted by clinical practice guideline recommendations and the demonstration of real-world clinical benefits to prevent T2DM progression and CV complications [27].

**Role of Primary Care in the Management of T2DM**

There is a huge burden of uncontrolled diabetes and associated comorbidities [11]. Only 20% of patients with T2DM visit an endocrinologist [10]. Within the Gulf region, 59% and 89% of patients have failed to achieve the desired HbA1c and FBS target [10].

**T2DM Management Challenges in Primary Healthcare in the Gulf Region**

A fear of hypoglycemia and weight gain with inadequate time for discussing insulin initiation and titration are major underlying reasons for not achieving glycemic targets.
targets (Fig. 2) [28]. Insulin initiation and titration inertia can be attributed to issues related to healthcare professionals (50%), patients (30%), and system barriers (20%) [29, 30]. Although 50% of primary-care physicians (PCPs) from the Gulf region had a positive attitude toward insulin initiation, reported physician-led barriers were lack of knowledge regarding insulin therapy (83%), with 51% of all physicians lacking the clinical experience to prescribe insulin. Patient-led barriers included refusal to initiate insulin in 57%, attributing to a fear of injections in 84.1%, and a fear of insulin therapy-associated complications in 23% [31].

**Practical Advice for Insulin Initiation and Titration in the Gulf Region: A Novel Initiative for Primary-Care Physicians in the Gulf Region**

The Practical Advice for Insulin Initiation and Titration in the Gulf Region project is a novel initiative to empower PCPs in the Gulf region. In 2020, an expert advisory panel was established to review current guidelines and develop clinical practical advices for the Gulf region. The Expert Group Advisory Committee Meeting was held virtually and had the following objectives:

1. To gather insights on initiation and titration of insulin by PCPs
2. To identify and meet the challenges of PCPs and patients
3. To create awareness on the best available guidelines for PCPs in the Gulf region
4. To improve the standard of care for people with T2DM

**Insulin Initiation and Intensification Strategies**

Insulin initiation and titration can be challenging for many primary-care providers who are involved in the treatment of patients with T2DM. Multiple insulin algorithms have been developed to help PCPs initiate and titrate insulin. Best practice approaches are required as diabetes management is no more a “one-size-fits-all approach” [32]. A practical insulin initiation and intensification approach may facilitate the optimization of glycemic control. Early initiation of insulin may prevent and delay the development and progression of diabetes-related morbidity and mortality.

**Guideline Recommendations**

**Insulin Initiation or Intensification Strategy: AACE Guidelines [33]**

The AACE recommends initiating long-acting basal insulin at a total daily dose (TDD) of 0.1–0.2 units/kg for patients with an HbA1c level of <8% or 0.2–0.3 units/kg for patients with an HbA1c level of >8%, with insulin titration every 2–3 days to reach the glycemic target. For those on fixed regimens, the TDD may be increased by 2 units, whereas for those on adjustable regimens, the dose should be adjusted by 1 unit or 10%–20% of the TDD according to FPG values, as indicated in Table 1.

| If glycemic control is not achieved, add prandial insulin | TDD 0.3–0.5 U/kg |
|----------------------------------------------------------|------------------|
| Basal bolus                                               | Start: 50% of TDD in three doses before meals |
| Begin prandial insulin before each meal                    | Insulin titration every 2–3 days to reach the glycemic goal: |
| 50% basal/50% prandial                                    | Increase the prandial dose by 10% or 1–2 units if 2-h postprandial or next premeal glucose consistently >140 mg/dL |
| TDD 0.3–0.5 U/kg                                          | If hypoglycemia, reduce TDD basal and/or prandial insulin by: |
| Start: 10% of the basal dose or 5 units                   | BG consistently <70 mg/dL: 10%–20% |
|                                                           | Severe hypoglycemia (requiring assistance from another person) or BG <40 mg/dL: 20%–40% |

**Glycemic goal**

- <7% for most patients with T2DM; fasting and premeal
- BG <110 mg/dL; absence of hypoglycemia
- HbA1c, and FBG targets may be adjusted based on patient’s age, duration of diabetes, the presence of comorbidities, diabetic complications, and hypoglycemia risk

- TDD, total daily dose; NPH, neutral protamine Hagedorn; FBG, fasting blood glucose; BG, blood glucose; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin.

The recommendations established by the ADA for the treatment with insulin mixtures should be followed in most people with T2DM [34].

“Initially, the usual dose of basal insulin should be divided, and 2/3rd of the dose should be administered before the morning meal and 1/3rd of the dose before the evening meal.”
### Table 1. AACE-recommended approach to initiating and titrating insulin in T2DM

| Steps                                      | Glucose value/HbA1c values | Total daily insulin dose |
|--------------------------------------------|----------------------------|--------------------------|
| 1. Start basal insulin (long-acting insulin) | HbA1c < 8% HbA1c > 8%     | 0.1–0.2 U/kg 0.2–0.3 U/kg |

Insulin titration every 2–3 days to reach glycemic goal: fixed regimen: increase TDD by 2 U

| Adjustable regimen                        | FBG >180 mg/dL FBG 140–180 mg/dL FBG 110–139 mg/dL | Add 20% of TDD Add 10% of TDD Add 1 unit |
|-------------------------------------------|-----------------------------------------------------|------------------------------------------|
| In case of hypoglycemia, reduce TDD by   | BG <70 mg/dL: 10–20% BG <40 mg/dL: 20–40%            |                                          |

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH).

FBG, fasting blood glucose; NPH, neutral protamine Hagedorn; BG, blood glucose; HbA1c, glycated hemoglobin; TDD, total daily dose.

**Fig. 3.** Treatment algorithm to initiate or intensify injectable therapy. BMI, body mass index; GLP-1 Ras, glucagon-like peptide 1 receptor agonists; HbA1c, glycated hemoglobin. Adapted from Alawadi [2020] [35].
• “The insulin dose should be adjusted by adding 1 to 2 U or 10% to 15% once or twice a week until the target values in the glucose self-monitoring are obtained. In the case of 4 blood glucose measurements per day, the insulin dose before breakfast should be adjusted to control the blood glucose concentration after lunch and before supper, and the dose administered before dinner should be changed to control the blood glucose levels measured before bedtime and before breakfast.”

• “If hypoglycemia occurs, the appropriate insulin dose should be reduced by 2 to 4 U or 10% to 20%.”

Recommendations on Insulin Therapy for Special Populations

"Patient characteristics and associated comorbidities play an important role in achieving HbA1c goals in patients with T2DM. An appropriate insulin regimen should be considered for special population, including elderly patients, children, adolescents, pregnancy and lactation, and those with cardiac and renal impairment” [35, 36].

Heart Failure

Patients with T2DM on a combination therapy of premixed insulin analogs and oral antidiabetic drugs should be carefully monitored for signs and symptoms of heart failure. Weight gain and edema should prompt clinical action and referral. Insulin selection criteria may vary according to the severity of hyperglycemia and risk of hypoglycemia [36].

Renal Impairment

“Patients with chronic kidney disease (CKD) are at increased risk of hypoglycemia due to decreased clearance of insulin and some medications used to treat diabetes as well as an impairment of renal gluconeogenesis from a lower kidney mass. The kidney is responsible for 30% to 80% of insulin removal; reduced is associated with a prolonged insulin half-life and a decrease in insulin requirements. The insulin dose must be tailored to each patient to achieve glycemic goals, whilst limiting hypoglycemia. The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on Diabetes Management in CKD recommended the following HbA1c goals and insulin dose” [36, 37].

Treatment Algorithm for Injectable Therapy

“The Emirates Diabetes Society Consensus Guidelines (EDSC) recommend risk-based pharmacotherapy for patients with diabetes. Treatment algorithms (adapted from the EDSC standards of care) are shown in Figure 3. If BMI
**Table 2. Insulin dose titration**

| Fasting blood sugar, mg/dL average over 3 days | Adjustment of basal insulin dose, units of insulin |
|-----------------------------------------------|--------------------------------------------------|
| ≥180                                         | Add 8 units                                     |
| 160–179                                      | Add 6 units                                     |
| 140–159                                      | Add 4 units                                     |
| 120–139                                      | Add 2 units                                     |
| 100–119                                      | Add 1 unit                                      |
| 80–99                                        | No change                                       |
| 60–79                                        | Subtract 2 units                                |
| <60                                          | Subtract 4 or more units                        |

| Premeal blood sugar, mg/dL average over 3 days | |
|-----------------------------------------------|--------------------------------------------------|
| If prelunch average is not in the desired range, adjust prebreakfast dose | Add 3 units                                     |
| If predinner average is not in the desired range, adjust prelunch dose | Add 2 units                                     |
| If pre-bedtime snack average is not in the desired range, adjust predinner dose | Add 2 units                                     |

| Titration schedule for long-acting insulin | |
|-------------------------------------------|--------------------------------------------------|
| ≥180                                      | Add 3 units                                     |
| 160–179                                   | Add 2 units                                     |
| 140–159                                   | Add 2 units                                     |
| 120–139                                   | Add 1 unit                                      |
| 100–119                                   | Maintain dose (desired range)                    |
| 80–99                                     | Subtract 1 unit                                 |
| 60–79                                     | Subtract 2 units                                |
| <60                                       | Subtract 4 or more units                        |

Fasting blood sugar (after 8 h of no calorie consumption): 70–100 mg/dL*

Preprandial (before meal): 80–130 mg/dL. Peak post-meal blood sugar (within 1–2 h after the start of a meal): <180 mg/dL. * The ADA does not give specific goals for fasting blood sugars, but 70–100 mg/dL is typically considered a normal range.

<25 or and HbA1c<2% upper limit of normal, initiate basal insulin alone or in combination with GLP-1RA. If HbA1c is above target, intensify with insulin. If BMI ≥25 or and HbA1c >2% upper limit of normal, initiate basal insulin in combination with GLP-1RA; if BMI <25, initiate basal insulin or mixed insulin. If HbA1c is still above target, intensify insulin” [35].

**Key Expert Recommendations on Insulin Initiation and Intensification Strategies**

After careful consideration of all the existing guidelines and their clinical judgment and experience, the EGAC made the following recommendations on insulin initiation dose, follow-up visits after first initiation, insulin dose titration, and patient support systems represented in Figure 4.

**Insulin Dose Titration**

A proactive approach to altering the insulin regimen is the key factor in achieving optimal glycemic control. Several simple and practical algorithms are available to guide patients and physicians through the step-by-step process of initiating and optimizing insulin therapy, while limiting hypoglycemia and weight gain.

**ADA Recommendations for Insulin Dose Titration**

The ADA recommends that an insulin regimen be adjusted every 3–4 days until self-monitoring of BG (SMBG) targets are reached (Table 2) [34].

Understanding the Gap between the Titration Period in Randomized Control Trials and Real-World Practice

The experts recommended a short titration period, although most of the clinical trial algorithms were achieved over a 12-week titration phase, followed by a maintenance phase. In real-world practice, the titration period...
varies depending on how soon the patient visits the clinic and may take 2 weeks to 3 months. The point of a continuous titration period based on the BG levels was also highlighted based on the unpredictable lifestyle and eating habits of patients. A proactive approach following the patient with an algorithm should allow titration within 12 weeks. For insulin-naive patients, a shorter titration period is usually recommended to assess their coping strategies.

**Effective Titration of Insulin Dose to Optimize BG Control**

The optimum dose can be reached within 1–2 months and may be faster for some patients with healthcare support systems. Continuous BG monitoring is the key to attaining the glycemic target. Besides, face-to-face communication, online consultation, and communication via telephone or text messaging may facilitate the optimization of insulin therapy. Based on an EGAC panel vote, 6/10 members recommended that physicians should review “every 3 days.”

**Key Expert-Group Recommendations on When and How to Titrate Insulin**

- The advisory panel recommended the ADA/Canadian guidelines for insulin titration.
- Compare the insulin types and choose the most effective and suitable regimen for patients depending on their baseline HbA1c, the use of glucose-lowering therapies and prior insulin secretagogue usage, socioeconomic status, duration of disease, tolerability, etc.
- Noncommercial or commercial unbiased platforms can be used for insulin titration.
- In RCTs, the titration phase period is ~ 12 weeks; in real practice, a shorter period is advised but may range from 2 weeks to 3 months.
- In some cases, continuous titration may be suggested to chase the target.
- As per the real-world evidences, a change by 1 insulin unit is recommended “every 3 days” [38, 39].

**Importance of SMBG in the Optimization of Insulin Titration**

SMBG plays a key role in the clinical decision-making process and self-management of diabetes, recommended by the American Association of Diabetes Educators (AADE). In clinical practice, SMBG demonstrated positive clinical outcomes, prevents hypoglycemia, and improves glycemic control and quality of life [40].

“As per the Canadian Guidelines, basic SMBG requirements must be met. Individuals with diabetes (or a family member/caregiver) must have the knowledge and skills to use a home blood glucose monitor and record the results to enable a review to change the insulin dose and improve HbA1c while limiting hypoglycemia” [41].

**Recommended SMBG Patterns for People Using Insulin (Fig. 5)**

**Expert-Group Recommendations on Relationship between the Patient’s Profile and Frequency of SMBG**

SMBG is important to make insulin dose adjustments and essential for mitigating hypoglycemia. The goals and needs should dictate SMBG frequency and timing, and all patients on insulin or other therapies that may result in hypoglycemia should be encouraged to perform and monitor
the test at least 3–5 times per week (Table 3). In patients who are at high risk of hypoglycemia with poor glycemic control or have fluctuations in blood sugar, BG should be monitored at least 3 times/day. The BG target should be set to 100 mg/dL with appropriate dose adjustment.

Once a patient reaches the HbA\textsubscript{1c} target of ≤7%, daily FPG test is not recommended. SMBG testing after three meals and at bedtime before the patients’ visit to the clinic is advisable. Basal insulin is best monitored by FPG 1–2 times a week.

Prandial insulin is best monitored by paired premeal and post-meal glucose values. If patients are using multiple-dose injection and premixed insulin, their prebreakfast and predinner and 1-h postprandial glucose values should be monitored to allow dose adjustment. The EGAC highlighted the importance of carbohydrate counting and suggested providing educational support using clinical case scenarios and training to patients and PCPs.

Expert-Group Recommendations on SMBG Monitoring Schedule

Experts shared their concerns regarding the implementation of current guidelines, especially in real-world practice as there are no current guidelines providing recommendations on SMBG monitoring schedule. A simple and flexible approach is suggested with a SMBG monitoring frequency of two or three times a week following the initiation of insulin therapy which can be tailored according to the patient’s insulin regimen. After the achievement of the agreed HbA\textsubscript{1c} target, SMBG should be performed at least once a week.
Summary of Expert-Group Recommendations on Diabetes Self-Management

• Guidance should be related to the type of treatment.
• Self-management should be encouraged in all diabetic patients.
• SMBG is recommended 3–5 times/week after insulin initiation to optimize titration.
• SMBG should be performed 2–3 times a week during maintenance.
• Basal insulin dose should be adjusted according to FPG 1–2 times a week.
• Fasting and postprandial plasma glucose values are required for optimal titration of basal insulin.
• Prandial insulin is best monitored by paired premeal and post-meal glucose values.
• After achievement of the HbA₁c target, SMBG is recommended at least once a week.
• Awareness of carbohydrate counting with educational support should be provided to clinicians and patients.

Conclusion and Summary of Key Clinical Practice Points

The explosion of diabetes in the Gulf region demands clinical practice recommendations. Glycemic control is poor in the Gulf region and associated with increasing complications. PCPs and patients do not adhere to cumbersome insulin initiation and titration algorithms. The expert EACG has developed practical recommendations on insulin initiation and titration for patients with T2DM in the Gulf region. The expert’s recommendations and reflections include the real-world approach to PCPs, supported by ADA/EASD/IDF/NICE guidelines for insulin initiation, optimization, and maintenance in T2DM. Second-generation insulin analogs (IGlar 300/Degludec) offer significant clinical benefits compared to first-generation analogs in randomized clinical trials, meta-analyses, and real-world studies. Studies have demonstrated less hypoglycemia with second-generation BI analogs compared to first-generation BI analogs in older adults and those with renal impairment, obesity, and CV disease.

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Author Contributions

All the authors have contributed in developing this manuscript; the first author and last author have the major contribution in amending and enhancing the content of the manuscript. All the authors have approved the final manuscript for submission and are accountable for the accuracy and integrity of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Insulin Initiation and Titration for Type 2 Diabetes Patients in the Gulf Region

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