A Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context: Recommendations by Association of Clinical Endocrinologists Consensus Group

Ravi Sankar Erukulapati, R.M. Manikandan, Leenatha Reddy Jakkidi, Santhosh Olety

Association of Bone Turnover Biomarkers and Subclinical Atherosclerosis in Subjects with Type 2 Diabetes: A Case-Control Study


Association between High-Sensitivity C-Reactive Protein and Metabolic Syndrome and Its Components in Older Adults: Findings from Neyshabur Longitudinal Study on Ageing (NelSA)

Amirhossein Sahebkar, Peyman Habibi, Faeze Sadat Talebian, Saeed Mohammadian Haftcheshmeh, Fatemeh Abdollahi, Nazanin Fekri, Tannaz Jamialahmadi, Željko Reiner, Seyed Reza Mirhafez

Efficacy of Insulin Degludec/Insulin Aspart (IDegAsp) vs. Insulin Glargine (IGlarU300) in Insulin-Naïve Patients with Type 2 Diabetes: A Retrospective Study

Dhruvi Hasnani, Santosh Jha, Banshi Saboo, Pusala Lakshmi Prasanna, Ami Sanghvi, Alpana Sowani, Vipul Chavda
Contents

EDITORIALS

‘Clinical Diabetology’: Highlights of 2023 and Future Direction
Viral N. Shah, Łukasz Stolarczyk

Dotting the I’s and Crossing the T’s of Insulin Therapy in India
Om J. Lakhani

GUIDELINES

A Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context: Recommendations by Association of Clinical Endocrinologists Consensus Group

ORIGINAL ARTICLES

Association of Bone Turnover Biomarkers and Subclinical Atherosclerosis in Subjects with Type 2 Diabetes: A Case-Control Study
Nagwa A. Lachine, Eman Y. Morsy, Abdelaziz Elnekiedy, Mohamed A. Sadaka, Gehan I. Khalil, Hesham G. Imam, Heba S. Kassab, Noha G. Amin

Association between High-Sensitivity C-Reactive Protein and Metabolic Syndrome and Its Components in Older Adults: Findings from Neyshabur Longitudinal Study on Ageing (NeLSA)
Amirhossein Sahebkar, Peyman Habibi, Faeze Sadat Talebian, Saeed Mohammadman Haftcheshmeh, Fatemeh Abdollahi, Nazanin Fekri, Tannaz Jamialahmadi, Željko Reiner, Seyed Reza Mirhafez

Type 2 Diabetes at a Military Health Centre in Brazil: Clinical and Pharmacotherapeutic Profile
André Henrique Freitas de Braga e Bessa, Julieta Ueta, Vinicius Diniz Mayrink, Rinaldo Eduardo Machado de Oliveira

Efficacy of Insulin Degludec/Insulin Aspart (IDegAsp) vs. Insulin Glargine (IGlarU300) in Insulin-Naïve Patients with Type 2 Diabetes: A Retrospective Study
Dhruvi Hasnani, Santosh Jha, Banshi Saboo, Pusala Lakshmi Prasanna, Ami Sanghvi, Alpana Sowani, Vipul Chavda

LETTER

The Intersection of Obesity and Skeletal Health: Insights from Post-COVID-19 Indian Population
Shuichi Okada, Kazuya Okada, Junichi Okada, Eijiro Yamada, Kumeo Ono
Greetings from the Editorial Board of ‘Clinical Diabetology’!

We have successfully completed the second year of ‘Clinical Diabetology’ (CD) after a significant change in the leadership and editorial boards at CD in January 2022 [1]. The Editor-in-Chief, Dr. Viral N. Shah, supported by new editorial team, has brought the Journal to a new height, and converted CD to the international platform. We are pleased to share some of our recent achievements and insights with readers of the Journal.

We continue to see increase in submissions to ‘Clinical Diabetology’ from around the world. Compared to 2022, the number of submissions to CD has grown further. However, we strive to maintain the quality of research publication and thus, the rejection rate has increased to over 40%.

In 2023, Editors were able to keep average ‘submission to early publication’ time of around 90 days, which was one of our first objectives (Fig. 1). Achieving this would have not been possible without contributions of expert reviewers helping us select the best research articles. We will continue to acknowledge our reviewers and provide them with a reviewer certificate as a token of our appreciation.

Readers of ‘Clinical Diabetology’ may have noticed that each issue has been standardized for structure with the goal of including an editorial, 5–6 original articles,
1–2 review articles, and 1–2 letters. We believe these numbers will escalate in months to come, however without compromise to quality.

After updating author instructions to facilitate manuscript formatting as well as enforcing some detailed policies as per COPE/ICMJE recommendations, we have recently modernized CD’s website to make the website informative and user-friendly. Hopefully, this will be appreciated by our readers.

We have observed growth of the numbers of both downloads and views of articles published in CD. Table 1 highlights the top three most downloaded research articles in the year 2023.

So, plenty is going on at ‘Clinical Diabetology’. Editors and the Publisher, however, are well aware of tasks still ahead of us. One of which is attracting more submissions from WHO Region of the Americas (AMRO), further technical optimization of review process, as well as reducing article production time. We invite you to join forces with us by submitting your research contributions, citing our most relevant papers and/or become a reviewer.

### Conflict of interest

Dr. Shah is a Editor-in-Chief for ‘Clinical Diabetology’. He reported receiving research grant from NovoNordisk, Alexion, Tandem Diabetes Care, and insulet and Honoraria from Sanofi, NovoNordisk, Embecta, Dexcom, Tandem Diabetes Care, Insulet, unrelated to this publication. Dr. Stolarczyk is a consultant advisor to Via Medica, publisher of scientific journals, including ‘Clinical Diabetology’.

### REFERENCES

Dotting the I’s and Crossing the T’s of Insulin Therapy in India

The discovery of insulin over a century ago stands as one of modern medicine’s most significant milestones, enduring through time. Yet, in India, we continue to confront fundamental challenges associated with insulin therapy.

Insulin is crucial for the survival of individuals with type 1 diabetes (T1D). It’s also the preferred treatment for managing hyperglycemia during pregnancy, in hospital settings, and for patients with multiple comorbidities, where its use is extensively prevalent in India. However, in the context of type 2 diabetes (T2D), the adoption of insulin therapy is frequently deferred, a notable concern in the Asian Indian healthcare landscape [1]. There are several reasons for this delay all of which have been explained in detail in the review by Wangnoo et al. [2].

Viewing the world through an economist’s lens often reveals hidden incentives driving actions. In India, the decision to initiate insulin therapy in patients with T2D is frequently influenced by such skewed incentives. From a physician’s standpoint, starting a patient on insulin is more time-consuming than prescribing an oral medication. Medical practice in India is predominantly volume-based, where physicians, due to lower payment per patient, see a higher number of patients daily to maintain their income. According to a study published in the British medical journal, primary physicians in India spend on an average 2 minutes per patient [3]. Therefore, time, alongside money, becomes a crucial factor. The additional time needed to explain to a patient the need to commence insulin therapy is often subconsciously balanced against the time it takes to prescribe a pill. For patients, adding insulin introduces an extra layer of complexity and expense in a population largely paying for healthcare out-of-pocket. This is compounded by prevalent myths and misconceptions about insulin use, adding to the hesitation in its adoption.

Physicians initiating insulin therapy in patients with T2D generally choose between basal insulin and premixed insulin. The IMPACT India survey by Mohan et al. [4] revealed that premixed insulin is often favored for initial insulin therapy in these patients. With the introduction of biosimilar basal insulin, an increase in the preference for basal insulin can be expected. The initiation and titration of insulin in T2D has been discussed in detail in the article titled “A Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context: Recommendations by Association of Clinical Endocrinologists Consensus Group” published in the current edition of the journal [5].

The article by Erukulapati et al. recommends initiating basal insulin in insulin naïve patients at a dose of 6–10 units per day, based on the initial HbA1c levels. However, from my perspective, the starting dose of basal insulin for Asian Indian patients should be higher than the recommendation in the aforementioned article. Our published retrospective study examined the optimal final dose of insulin glargine needed to achieve targeted fasting capillary glucose levels in hospitalized patients, as well as the variables influencing this final dose. Our findings indicated that the average final dose of basal insulin was 25 units (0.33 units/kg). The most significant variable affecting the final basal insulin dose was found to be the HbA1c value [6]. While utilizing this data, we proposed a formula to calculate the appropriate basal insulin dose: Basal insulin dose (in units/kg) = 0.064 + 0.030 × HbA1c [7]. A study conducted in a hospital setting might not directly translate to out-
Asian Indian patients frequently present with ‘glucotoxicity’ and signs of relative or absolute insulin deficiency at the onset of insulin therapy. A significant proportion of these patients exhibit clinical symptoms of diabetes in adulthood, akin to the condition historically termed ‘Flatbush’ diabetes [8]. This similarity often results in a considerably higher initial insulin requirement. Failure to meet this demand in both the initiation and titration phases can lead to persistent glucotoxicity and hinder achieving optimal glycemic control.

The technique of insulin administration remains a significant challenge for Asian Indian patients. In a study by Kalra et al. [9], substantial deficiencies were identified in the insulin injection practices among this group. A prevalent issue is the repeated use of insulin syringe or pen needle that leads to inadequate and improper insulin delivery. Additionally, the occurrence of lipohypertrophy is common among both T1D and T2D patients [10]. These problems are likely a result of the insufficient number of diabetes educators within the healthcare system. Moreover, physicians often lack the time to thoroughly instruct patients on proper insulin techniques. Patient compliance also poses a challenge, with many skipping their insulin doses for various reasons. The critical matter of correct insulin injection techniques is comprehensively addressed in the article by Erukulapati et al. [5].

The storage of insulin in India poses distinct challenges due to the country’s tropical climate, which subjects insulin to higher temperatures during storage and transportation. Furthermore, in India, insulin vials are more commonly used than insulin pens. The inconsistent 24-hour electricity supply in several regions makes refrigeration difficult. Notably, Pendsey et al.‘s study highlights an innovative solution: storing insulin in earthen clay pots, which effectively substitutes for refrigeration. This finding is particularly valuable for tropical environments like India, offering a practical approach to maintaining insulin efficacy [11]. Insulin management in patients receiving glucocorticoids presents a significant challenge. This became particularly evident during the recent COVID-19 pandemic, when glucocorticoid use was widespread, leading to frequent cases of hyperglycemia. We conducted a randomized, open-label trial comparing the standard basal-bolus insulin approach with a novel algorithm for managing glucocorticoid-induced hyperglycemia in hospitalized patients. This algorithm took into account various factors, including the type and dose of glucocorticoid and the patient’s baseline diabetes status prior to glucocorticoid administration. A key feature of the algorithm was the alignment of insulin action with the glucocorticoid profile. Our new approach demonstrated superior performance in terms of glycemic control and variability compared to the standard of care [12].

Following the publication of this algorithm, particularly during the COVID-19 pandemic, we recognized the significance of another variable: the patient’s baseline status of the hypothalamic-pituitary-adrenal (HPA) axis. Patients with long-term use of systemic or inhaled glucocorticoids often exhibit a suppressed HPA axis, which increases the risk of early morning hypoglycemia when using long-acting insulin [13]. We have since refined our algorithm to incorporate this variable and are currently conducting a study to further explore its implications.

Technology offers promising solutions for addressing the challenges associated with insulin initiation and proper usage in the Asian Indian context. Previously, we developed the “Centurion insulin app”, specifically designed to assist physicians in timely initiating insulin therapy for patients with T2D. We are committed to making this technology widely accessible; hence, we’ve made the app’s code open-source and published it on GitHub, inviting other developers to contribute and enhance its functionality [14]. Additionally, Singla et al. [15] are working on a machine learning algorithm tailored for insulin dosing in T1D patients, addressing a critical and complex issue. Furthermore, social media can be a powerful tool to debunk myths surrounding insulin use, while also promoting correct insulin techniques, usage, and storage practices.

In summary, administering insulin therapy within the Asian Indian healthcare framework presents distinct challenges. Therefore, the publication of specialized guidelines for adult insulin therapy in India by Erukulapati et al. [5], as featured in this journal, represents a significant advancement. Additionally, it is anticipated that this article will inspire young researchers to further explore and address the existing knowledge gaps in the application of insulin therapy.

**Conflict of interest**

The author declare no conflict of interest.

**REFERENCES**


Ravi Sankar Erulkapati1, R.M. Manikandan2, Leenatha Reddy Jakki3, Santhosh Olety Sathyanarayana4, Usha Ayyagar5, Srinath Ashwathiah6, Smitha Nalla7, Satish Kumar Sampath8, Sudeep Putta Manoha9, Sanjay Shah10, Chandan Kamath11, Bhanu Praveen12, Manish Kushe13, Radhika V. Kumar14, Ravi Kumar Bachuwar15, Murali Ganguri16

1Department of Endocrinology, Apollo Hospitals, Hyderabad, Telangana, India
2Department of Endocrinology, Apollo Speciality Hospitals, Madurai, Tamil Nadu, India
3Department of Pediatric Endocrinology, Rainbow Children’s Hospitals, Hyderabad, Telangana, India
4Department of Pediatric and Adolescent Endocrinology, Karnataka Institute of Endocrinology and Research, Bengaluru, Karnataka, India
5Department of Endocrinology, Apollo Hospitals, Chennai, Tamil Nadu, India
6Department of Endocrinology, BGS Gleneagles Global Hospital, Bengaluru, Karnataka, India
7Department of Endocrinology, KIMS Hospital, Secunderabad, Telangana, India
8Department of Endocrinology, Aster RV Hospital, Bengaluru, Karnataka, India
9Department of Endocrinology, Apollo Speciality Hospital, Bengaluru, Karnataka, India
10Department of Endocrinology, Narayana Super Speciality Hospital, Howrah, Kolkata, India
11Department of Endocrinology, Adhrit Endocrine and Diabetes Centre, Hubli, Karnataka, India
12Department of Endocrinology, Ashaya Super Speciality Proctology Hospital, Vijayawada, Andhra Pradesh, India
13Department of Endocrinology, DiabEndocare Super Speciality Clinic, Panaji, Goa, India
14Department of Endocrinology, Manipal Hospitals, Bengaluru, Karnataka, India
15Department of Endocrinology, Madhava Super Speciality Hospital, Nizamabad, Telangana, India
16Department of Endocrinology, LEAD Clinics, Vijayawada, Andhra Pradesh, India

A Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context: Recommendations by Association of Clinical Endocrinologists Consensus Group

The grading system used for recommendations:

The grading system uses A, B, C, or E to show the evidence level that supports each recommendation.

- A — Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
- B — Supportive evidence from well-conducted cohort studies
- C — Supportive evidence from poorly controlled or uncontrolled studies
- E — Expert consensus or clinical experience

ABSTRACT

Insulin therapy is critical for people with type 1 diabetes (T1D). Although oral antidiabetic drugs (OADs) remain the mainstay of treatment for people with type 2 diabetes (T2D) in the early stages, insulin therapy becomes essential as the disease progresses to sustain life. Whilst there are guidelines and consensus statements from reputed institutions and medical bodies pertaining to diabetes mellitus (DM), there is not a dedicated guideline or consensus statement that is based on an evidence-based grading system that deals exclusively with the “Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context”,...
guiding general physicians and general practitioners. Hence, this consensus statement uses the modified Delphi method.

The Association of Clinical Endocrinologists is a non-profit, non-commercial body registered in India, that serves as a platform for like-minded Endocrinologists who aspire to work for the cause of the science of Diabetes and Endocrinology, its utility and application for the betterment of the health of the people and the country. The authors request the readers to please do not confuse this Association of Clinical Endocrinologists with the American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) of the United States of America (USA).

Keywords: insulin therapy, diabetes mellitus, hyperglycemia, hypoglycemia, type 1 diabetes (T1D), type 2 diabetes (T2D)

Introduction
Diabetes mellitus (DM) is a chronic disease that affects 537 million people worldwide [1]. Globally, 150–200 million individuals depend on insulin, but this number is probably underestimated [2]. Insulin therapy is critical for people with type 1 diabetes (T1D). Although oral antidiabetic drugs (OADs) remain the mainstay of treatment for people with type 2 diabetes (T2D) in the early stages, insulin therapy becomes essential as the disease progresses to sustain life [3]. In India, it is estimated that approximately 4 out of every 10 people with T2D use insulin, either alone or in combination with OADs [4].

Rationale
The vast majority of the people with DM are managed by general practitioners and family physicians, most of them practicing in areas with less-than-ideal healthcare facilities in India. Whilst there are guidelines and consensus statements from reputed institutions and medical bodies pertaining to DM, there is not a dedicated guideline or consensus statement that deals exclusively with the “Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes in the Indian Context”, guiding general physicians and general practitioners. Hence, this consensus statement uses the modified Delphi method.

Methodology
The current analysis used a three-step modified Delphi method to establish the consensus. Delphi approaches are organized group communication methods where professionals assess complicated issues with inadequate and ambiguous knowledge through an iterative procedure. The distinguishing characteristic is that each new questionnaire includes the aggregated group responses from earlier ones, allowing the experts to be questioned to review and, if necessary, revise their conclusion statements [5]. In the last few decades, the Delphi techniques have played a crucial role in the development of best practice guidelines utilizing collective intelligence in situations when research is scarce, ethical, and logistically challenging, or the data is contradictory. However, much variation has been seen in attempts to evaluate the quality standard of Delphi investigations, and the details of the methodology are typically ambiguous [6]. Thorough use of scientific research methods, such as the Delphi Panel approach, enables high-quality, scientific expert surveying [7].

There are many forms of Delphi techniques such as the modified Delphi, policy Delphi, and the real-time Delphi [8].

Modified Delphi method
The modified Delphi technique involves gathering information initially using questionnaires and then conducting a formal in-person meeting, that maximizes the advantages [9].

The insights or expert opinions for the current analysis were sought using a 3-step modified Delphi method to enable members of the Association of Clinical Endocrinologists to pool their knowledge and develop recommendations that would facilitate a general physician or general practitioner to address various challenges and barriers and that may aid in proper utilization of insulin therapy in India.

This modified Delphi method comprised 2 email-based questionnaire rounds followed by a consensus physical meeting to allow direct interaction between the experts in the final round, which allowed panel members to clarify their points from the previous rounds and also present arguments to justify their points of view (Fig. 1).

The initial stage was the development of recommendation statements following a comprehensive literature review using PubMed and other online resources for clinical studies, existing guidelines, review articles, consensus statements, and national and international standards on insulin therapy in adults with diabetes. The relevant data was retrieved and reviewed, recommendation statements were developed and compiled into a Microsoft Excel sheet.

The process of developing the recommendations
Consensus statements by highly reputed medical bodies like the American Diabetes Association (ADA)
may not suit the Indian milieu due to a variety of reasons including practicality, affordability and the healthcare ecosystem being completely different in India compared to the Western world. While taking the ADA, National Institute for Health and Care Excellence (NICE), European Association for the Study of Diabetes (EASD), The International Society for Pediatric and Adolescent Diabetes (ISPAD), American Association of Clinical Endocrinologists (AACE) guidelines and other peer-reviewed evidence-based guidelines and consensus statements into consideration, the expert panel comprising 16 practicing Endocrinologists from the Association of Clinical Endocrinologists has drafted new recommendations with specific consideration for the Indian milieu keeping in mind the resources available to the general physician or a general practitioner.

Round 1
The recommendation statements were circulated to the panel members through email along with an explanation of the analysis, objectives, and instructions. The questionnaire was presented in a tabular format with columns beside the statements for addition of responses. The experts had to choose “Yes” for “Agree” or “No” for “Disagree” for each statement and were free to add comments and suggestions in the specified column if required. Anonymity of the answers and comments was maintained all through the process. Statements with at least 80% agreement were considered to have reached concordance and those that did not reach concordance were modified as per the panel’s inputs and recirculated in Round 2.

Round 2
The statements that did not reach concordance in Round 1 were circulated among the experts by email. The responses were collected and analyzed in the same manner as in Round 1. Statements not reaching 80% concordance were retained for discussion in Round 3. In the current analysis, 19 statements did not reach 80% concordance which were brought for further discussion to Round 3.

Round 3
Round 3 was a direct interaction round among the experts in person with one member acting as the facilitator in a physical meeting. The panelists were encouraged to discuss the statements until an agreement was reached to modify, eliminate, or retain the statement in the recommendations.

Statistical methods
The responses obtained for each statement were subjected to descriptive statistics, i.e., percentage of response to each consensus statement. 80% agreement for each consensus statement was considered as a standard to be included as a recommendation and statements that did not achieve 80% agreement were recirculated for further discussion and were accepted with iterations.
In the current analysis, of 214 recommendation statements circulated through email in Round 1, 80% concordance was achieved for 195 recommendation statements. Therefore, the remaining 19 recommendations were recirculated in Round 2 but, could not achieve 80% concordance. Hence, a Round 3, physical meeting was conducted with the experts to resolve and obtain consensus on these 19 recommendations, along with all other recommendations.

**Need for insulin**

Insulin therapy is crucial for people with T1D because the hallmark of the condition, the beta-cell function is nearly absent or diminished. Insulinopenia can cause hyperglycemia, tissue catabolism, hypertriglyceridemia, ketoacidosis, and other metabolic disturbances. For the first six or seven decades following the discovery of insulin, severe metabolic decompensation was avoided with once- or twice-daily injections. However, over the past three decades, evidence has shown that a more intensive insulin regimen, such as multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) via an insulin pump, offers the best compromise between effectiveness and safety for people with T1D [10]. The Diabetes Control and Complications Trial (DCCT) demonstrated that MDI of intensive therapy with short-acting (regular) and intermediate-acting human insulins or CSII decreased glycated hemoglobin (HbA1c) and were linked to better long-term outcomes [11].

People with T2D who fail to achieve or maintain HbA1c levels over time, even with multiple OADs, will eventually require insulin therapy [12]. However, it is equally crucial to make sure that insulin is started right away once the best combinations of OADs have failed to control blood glucose levels.

Healthcare providers (HCPs) should refrain from using insulin as a threat, a sign of failure, or a punishment, and instead should regularly and objectively explain to people the progressive nature of T2D. Educating to self-titrated insulin doses based on blood glucose monitoring (BGM) improves glycemic control in people with T2D who are initiated on insulin [13]. Structured comprehensive education on diet, hypoglycemia prevention and treatment, self-monitoring of blood glucose (SMBG), and other topics are crucial in any person using insulin [10].

Most guidelines advise people with high HbA1c levels at the time of presentation to begin short-term insulin therapy as soon as possible [10, 14, 15]. According to landmark trials from the previous decade, intensive glycemic control should be practiced in the early stages of diabetes, preferably within the first four years of diagnosis [16]. The traditional practice of delaying insulin therapy until a sustained inability of dietary changes and oral medications to achieve glycemic control has been changed in the past ten years to include insulin therapy much earlier, frequently in conjunction with OADs or glucagon-like peptide 1 receptor agonists (GLP-1RA). In people with T2D, the decision to use injectable therapy is influenced by clinical, pharmacological, and psychosocial factors [14].

In the Indian context, it is also important to consider factors like price, quality, cold chain maintenance, and ongoing availability of insulin preparations and delivery devices [14].

**Indications of insulin**

Some of the indications of insulin include people with T1D, newly diagnosed T2D with HbA1c > 10%, or catabolic/osmotic symptoms, when oral antidiabetic medications are contraindicated or failed to achieve goals, and need for flexible therapy, in persons with acute illness or surgery, pregnancy, glucose toxicity [3].

<table>
<thead>
<tr>
<th>Indications of insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. In people with T1D.</td>
</tr>
<tr>
<td>B. Individuals with newly diagnosed T2D with HbA1c &gt; 10% or catabolic/osmotic symptoms.</td>
</tr>
<tr>
<td>C. People with T2D who are unable to achieve glycemic targets with optimal OADs and GLP1-RAs, or cannot tolerate current OADs, or those who need more flexible therapy.</td>
</tr>
<tr>
<td>D. When adequate glycemic control is not achieved in people with myocardial infarction, stroke, or decompensated hepatic or renal insufficiency, or those who had major surgery.</td>
</tr>
<tr>
<td>E. In individuals with T2D and acute illness/infection or sepsis.</td>
</tr>
<tr>
<td>F. People with glucose toxicity.</td>
</tr>
<tr>
<td>G. In hospitalized people with diabetes, if clinically appropriate.</td>
</tr>
<tr>
<td>H. In people with stress/drug/steroid-induced hyperglycemia, post-transplant hyperglycemia, diabetes ketoacidosis (DKA)/hyperglycemic hyperosmolar state (HHS)/lactic acidosis.</td>
</tr>
<tr>
<td>I. Individuals with T2D who are planning pregnancy, during pregnancy, and lactation.</td>
</tr>
<tr>
<td>J. People with uncontrolled diabetes (persistent HbA1c level remains above the set target despite other antidiabetic drugs).</td>
</tr>
<tr>
<td>K. Individuals with secondary diabetes.</td>
</tr>
</tbody>
</table>

**Recommendations**
Classification of insulins

Based on their molecular structure, insulins are classified as human insulins and insulin analogs (Fig. 2) [3]. The insulin that is currently used is recombinant insulin, which is either directly derived from native human insulin or created by structurally altering the amino acid sequence of the insulin molecule (insulin analog). The main differences between human insulin and insulin analogs are in the pharmacokinetic parameters and propensity for adverse effects. When regular human insulin is injected subcutaneously (SC), it takes some time for it to break down into its monomer form and enter the bloodstream. Because of this, regular human insulin frequently fails to control postprandial glycemic excursions and tends to result in delayed hypoglycemia. The use of insulin analogs and their combinations significantly reduces these issues [17].

There are three characteristics of insulin that are relevant in clinical use [18]:

- **onset of action**: the length of time that insulin takes to reach the circulation and begin lowering blood glucose is referred to as the onset;
- **peak time of action**: peak time is when the insulin is at its maximum strength in lowering blood glucose;
- **duration of action**: duration is the amount of time that insulin keeps lowering blood glucose.

**Human insulins**

Human insulins are manufactured by using recombinant deoxyribonucleic acid (DNA) technology. Human insulins are classified as [3]:

A. Short-acting — human soluble insulin (regular)
B. Intermediate-acting — neutral protamine Hagedorn (NPH)
C. Premix-mixtures of regular and NPH insulin in 25/75, 30/70, and 50/50 proportions

The onset, peak, and duration of action of different kinds of human insulins are summarized in Table 1.

**Insulin analogs**

Insulin analogs were developed by modifying the amino acid sequence for better management of fasting plasma glucose (FPG) and postprandial plasma glucose.

---

**Table 1. Different Types of Human Insulins (Adapted from [19] and [20])**

<table>
<thead>
<tr>
<th>Human insulin types</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting (regular) [19]</td>
<td>30–60 minutes</td>
<td>2–4 hours</td>
<td>5–8 hours</td>
<td>Humulin® R Insuman® R Actrapid®</td>
</tr>
<tr>
<td>Intermediate-acting [19]</td>
<td>2–4 hours</td>
<td>4–12 hours</td>
<td>12–24 hours</td>
<td>NPH</td>
</tr>
<tr>
<td>Premix human insulins [20]</td>
<td>30 minutes</td>
<td>2–8 hours</td>
<td>Up to 24 hours</td>
<td>Mixtures of regular and NPH insulin in 25/75, 30/70, and 50/50 proportions</td>
</tr>
</tbody>
</table>

NPH — neutral protamine Hagedorn
(PPG) levels with minimal hypoglycemic risk. Based on their pharmacokinetic characteristics, insulin analogs are classified as rapid-acting insulin analogs (RAA), long-acting insulins (LAA) analogs, ultra-long-acting insulin analogs (ULAA), and pre-mix analog preparations [10].

The onset, peak, and duration of different kinds of analog insulin are summarized in Table 2.

### Table 2. Different Types of Analog Insulins Available in India (Adapted from [19], [20] and [21])

<table>
<thead>
<tr>
<th>Analog insulin type</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid-acting insulin (faster aspart) [19]</td>
<td>10–20 minutes</td>
<td>1–3 hours</td>
<td>3–5 hours</td>
</tr>
<tr>
<td>Ultra-rapid-acting insulin lispro [21]</td>
<td>15–18 minutes</td>
<td>1–2 hours</td>
<td>~ 4 hours</td>
</tr>
<tr>
<td>Rapid-acting analog (RAA) insulin (Insulin aspart, insulin glulisine, insulin lispro) [19]</td>
<td>15–35 minutes</td>
<td>1–3 hours</td>
<td>3–5 hours</td>
</tr>
<tr>
<td>Long-acting analogs (LAA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine [19]</td>
<td>2–4 hours</td>
<td>8–12 hours</td>
<td>22–24 hours</td>
</tr>
<tr>
<td>Detemir [19]</td>
<td>1–2 hours</td>
<td>4–7 hours</td>
<td>20–24 hours</td>
</tr>
<tr>
<td>Ultra-long-acting analogs (ULAA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine U300 [19]</td>
<td>2–6 hours</td>
<td>Minimal peak</td>
<td>30–36 hours</td>
</tr>
<tr>
<td>Degludec [19]</td>
<td>30–90 minutes</td>
<td>Minimal peak</td>
<td>&gt; 42 hours</td>
</tr>
<tr>
<td>Pre-mix analog preparations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic IAsp [21]</td>
<td>10–20 minutes</td>
<td>1–4 hours</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td>70% aspart protamine, 30% aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% aspart protamine, 50% aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic lispro [21]</td>
<td>15–30 minutes</td>
<td>1–3 hours</td>
<td>12–24 hours</td>
</tr>
<tr>
<td>75% lispro protamine, 25% lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% lispro protamine, 50% lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDegAsp co-formulation [21]</td>
<td>10–20 minutes</td>
<td>1–2 hours</td>
<td>&gt; 24 hours</td>
</tr>
<tr>
<td>70% degludec, 30% aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IDegAsp — insulin degludec + insulin aspart

Basal-bolus regimen (BBR) is the most preferable regimen in people with T1D [22]. Insulin regimens should be customized to the individual’s age, general health, lifestyle, treatment objectives, hypoglycemia awareness status, medication adherence, and ability to self-manage. Social and economic factors should also be considered [10].

Basal insulin dosage is estimated based on weight and is normally initiated at 0.1 to 0.2 units/kg body weight/day [10] and then up-titrated based on glycemic values, with typical doses ranging from 0.2 to 1.0 units/kg body weight/day. Short-acting insulins should be added for PPG control [13, 15]. Patient education programs such as dose adjustment for normal eating (DAFNE) which enable those with T1D to understand the principles of carbohydrate (CHO) counting and self-adjust insulin doses need to be encouraged [23]. Premix insulin regimens are sub-optimal but can be used where a person with T1D prefers these over BBR [10].

### Insulin regimens

#### Initiating and titrating insulins in people with T1D

It is of paramount importance to acknowledge that the choice of insulin regimen and the initiation, titration, and intensification doses of any insulin regimen instituted for any person with diabetes are based on multiple factors including the type of diabetes, Hba1c, current blood glucose readings, age, body weight, pregnancy and lactation, comorbidities, concurrent medication use, hypoglycemia risk, knowledge and skills of the HCP, the person’s lifestyle, awareness, affordability and choices of the person and the limitations of the healthcare system [10, 19]. The insulin regimens and doses suggested in this guideline for initiation, titration, and intensification are a rough guide only and due clinical discretion of the HCP is mandatory whilst individualizing insulin treatment.

Basal-bolus regimen (BBR) is the most preferable regimen in people with T1D [22]. Insulin regimens should be customized to the individual’s age, general health, lifestyle, treatment objectives, hypoglycemia awareness status, medication adherence, and ability to self-manage. Social and economic factors should also be considered [10].

Basal insulin dosage is estimated based on weight and is normally initiated at 0.1 to 0.2 units/kg body weight/day [10] and then up-titrated based on glycemic values, with typical doses ranging from 0.2 to 1.0 units/kg body weight/day. Short-acting insulins should be added for PPG control [13, 15]. Patient education programs such as dose adjustment for normal eating (DAFNE) which enable those with T1D to understand the principles of carbohydrate (CHO) counting and self-adjust insulin doses need to be encouraged [23]. Premix insulin regimens are sub-optimal but can be used where a person with T1D prefers these over BBR [10].

### Initiating and titrating insulins in people with T2D

The initial regimen of insulin therapy is based on the person’s age, clinical features, glucose profile, risk of hypoglycemia, cost, and person’s preference. Either basal insulin or premix insulin can be considered as an initial insulin regimen in people with T2D [12]. When FPG is high, consider initiating insulin therapy with
basal insulin. When both FPG and PPG are high, one may consider initiating insulin therapy with premix insulin [10]. BBR is the initial insulin regimen in acutely unwell and hospitalized people with T2D, women with T2D planning pregnancy when other regimens do not achieve optimal glycemic control, and in people with challenging lifestyles [15]. Analog insulins may be preferred over human insulins as they possibly reduce the risk of hypoglycemia and are flexible to use [10]. However, economic considerations must be taken into account.

Structured education and training should be provided for all insulin users regarding storage, administration, SMBG/continuous glucose monitoring (CGM), dose adjustment, hypoglycemia prevention, and treatment strategies. Concordance with insulin usage should be evaluated at regular intervals [10].

Insulin doses should be titrated regularly at least once a week, but more frequently if required [24]. FPG levels and PPG levels should be aimed at 80–130 mg/dL and 140–180 mg/dL respectively in the majority of people with T2D [24, 25]. These targets can be individualized, based upon the risk of hypoglycemia and the need for glycemic control. Initially, titration should be done to control FPG, followed by PPG for prandial insulin with the highest glycemic fluctuation, in a sequential order [25].

Insulin intensification should not be delayed for individuals not meeting treatment goals. Therapy intensification is recommended for those whose HbA1c is still uncontrolled following basal insulin introduction and titration [10]. The advantages and disadvantages of various insulin regimens are discussed below in Table 3 [26].

<table>
<thead>
<tr>
<th>Types of insulin regimen</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin</td>
<td>Effective and safe</td>
<td>Some individuals may not achieve glycemic targets</td>
</tr>
<tr>
<td></td>
<td>It is simple and easy for early facilitation of insulin</td>
<td>The regimen doesn’t offer optimum control of post-prandial hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Potentially less weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low risk of hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Useful for symptom relief if tight control is not a major issue</td>
<td></td>
</tr>
<tr>
<td>Premix/co-formulation</td>
<td>Better PPG control</td>
<td>Less flexibility (i.e., a person is unable to adjust the bolus or basal component of the insulin independently)</td>
</tr>
<tr>
<td></td>
<td>It is more effective in lowering HbA1c when compared to basal insulin alone</td>
<td>Fixed daily routine about lifestyle, CHO content, and meal timing is required</td>
</tr>
<tr>
<td></td>
<td>Simple for the person to understand than BBR</td>
<td>There is a time delay of injection with conventional mixture (need to inject 20–30 minutes before a meal)</td>
</tr>
<tr>
<td>Basal plus</td>
<td>Better flexibility</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>It is comparable to other conventional approaches in terms of glycemic control</td>
<td>Some may need progression to BBR</td>
</tr>
<tr>
<td></td>
<td>It offers the additional advantages of fewer hypoglycemic events</td>
<td>Careful patient evaluation and scheduling is necessary due to the complicated nature of this regimen</td>
</tr>
<tr>
<td></td>
<td>Personalization of therapy, and a simple self-management algorithm for titration</td>
<td></td>
</tr>
<tr>
<td>Basal-bolus</td>
<td>Potential for better metabolic control if used optimally</td>
<td>Requires multiple insulin injections</td>
</tr>
<tr>
<td></td>
<td>Closely mimics normal physiology</td>
<td>More complicated to support and teach</td>
</tr>
<tr>
<td></td>
<td>Potential for the better control of FPG and PPG</td>
<td>Needs CHO counting</td>
</tr>
<tr>
<td></td>
<td>Potential for a better lifestyle choice</td>
<td>Risk of hypoglycemia and weight gain</td>
</tr>
<tr>
<td></td>
<td>Offers optimum flexibility in terms of diet and activity</td>
<td>Needs better patient cooperation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires more frequent glucose monitoring</td>
</tr>
</tbody>
</table>

BBR — basal-bolus regimen; CHO — carbohydrate; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; PPG — postprandial plasma glucose
Recommendations

**Insulin therapy in people with T1D**

A. For individuals with T1D, BBR of basal and prandial insulin or CSII has proven to be an effective and safe therapy. A

B. BBR insulin therapy is considered as the standard regimen for the management of T1D. A

C. Basal insulin dosage is estimated based on weight and is normally initiated at 0.1 to 0.2 units/kg body weight/day and then up-titrated based on glycemic value, with typical doses ranging from 0.2 to 1.0 units/kg body weight/day. A

D. Short-acting insulins to be added for PPG control. A

E. Premix insulin regimens are sub-optimal but can be used where a person with T1D prefers these over BBR. C

F. Individuals with T1D should be instructed on how to adjust prandial insulin dosages to CHO intake, basal insulin as per FPG levels, and planned physical activity. B

G. Patient education programs such as DAFNE which enable people with T1D to understand the principles of CHO counting and self-adjust insulin doses need to be encouraged. B

**Insulin initiation in people with T2D**

A. HCPs should refrain from using insulin as a threat or as a sign of failure or punishment. B

B. Consider insulin therapy when a person fails to achieve or maintain HbA1c levels after administration of three OADs/GLP1-RA or if the person is intolerant to any individual agent or combination of agents. A

C. Despite the availability of several new oral medications, insulin should never be postponed if HbA1c levels remain high, since insulin has a far greater ability to decrease blood glucose than other medications. A

D. Involvement of a person with diabetes, and their carer is important in making a decision regarding the therapeutic choice of regimen, preparation, and delivery device. B

E. Metformin, GLP1-RA, sodium-glucose cotransporter-2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitors (DPP4i), and alpha-glucosidase inhibitors (AGIs) can be continued upon insulin initiation (unless contraindicated or not tolerated) for ongoing glycemic and metabolic advantages. Sulfonylureas are usually discontinued after insulin initiation with other insulin regimens, but they are usually used along with basal insulin regimen. B

F. Pioglitazone can be used with insulin therapy with extreme caution considering the weight gain and water retention side effects. C

G. The initial regimen of insulin therapy is based on the type of diabetes, the person’s age, clinical features, glucose profile, risk of hypoglycemia, cost, and personal preference. B

H. Either basal insulin or premix insulin can be considered as an initial insulin regimen in people with T2D. When FPG is high, consider initiating insulin therapy with basal insulin. When both FPG and PPG are high, one may consider initiating insulin therapy with premix insulin. B

I. BBR is the initial insulin regimen in acutely unwell and hospitalized people with T2D, women with T2D planning pregnancy when other regimens do not achieve optimal glycemic control, and in people with challenging lifestyles. B

J. Analog insulins may be preferred over human insulins as they possibly reduce the risk of hypoglycemia and are flexible to use. However, economic considerations must be taken into account. B

K. Individuals initiating insulin therapy and their caretakers should be educated about SMBG/CGM, as well as hypoglycemia prevention and treatment strategies. A

L. Structured education and training should be provided regarding dose adjustments, administration, storage, and other practical aspects of insulin. A

M. Insulin intensification should not be delayed for individuals not meeting treatment goals. A

N. Concordance of insulin usage should be evaluated at regular intervals. E

O. Review the ratio of basal and prandial insulin periodically to optimize blood glucose levels. C

**Insulin titration in people with T2D**

A. Insulin doses should be titrated regularly at least once a week. but more frequently if required. A

B. FPG levels and PPG levels should be aimed at 80–130 mg/dL and 140–180 mg/dL respectively. These targets can be individualized, based upon the risk of hypoglycemia and the critical need for glycemic control. A

C. Initially, titration should be done to control FPG, followed by PPG for prandial insulin with the highest glycemic fluctuation, in a sequential order. B
Simplifying insulin initiation in the context of Indian realities

Since T2D is a progressive condition, most people will eventually require treatment intensification. This generally entails gradually introducing a new glucose-lowering medication or moving to a more complex insulin regimen [27]. Complex treatment regimens may be more physiological and flexible but might result in an increased risk of hypoglycemia and a high treatment load, which can have a poor influence on both therapeutic adherence and overall quality of life (QoL). Treatment simplification strives to decrease individual treatment burdens while maintaining therapeutic efficacy and safety. Although there is evidence that simplifying insulin treatment can result in efficient glycemic control without jeopardizing therapeutic efficacy or safety, it is not commonly implemented in clinical practice [27].

The term “simplification” is seen to be the most appropriate to describe reducing the number of insulin injections (including termination) and modifying the treatment plan to each individual’s circumstances. Therefore, individuals with T2D who are on a complex insulin therapy regimen should be assessed frequently and insulin regimen simplification should be considered with the goal of improving clinical outcomes like risk of hypoglycemia and QoL [10, 27].

Barriers to insulin initiation

Even though the majority of practitioners consider the start of insulin therapy to be crucial to the management of T2D, many view it as the “last option” and report that their patients are hesitant to accept this treatment [28]. The unwillingness to initiate insulin therapy might be due to physician-related, patient-related, or system-related barriers [28].

Physician-related barriers may include their lack of knowledge of updated guidelines, experience of insulin therapy, beliefs and attitudes towards insulin and diabetes management, side effects of insulin therapy (e.g., hypoglycemia and weight gain), and perceptions of patients’ attitudes towards insulin therapy (patient’s adherence, and wish to prolong non-insulin therapy) [29].

Patient-related barriers include fear of needle and injection phobia, hypoglycemia and weight gain, negative effects of therapy on occupation and social life, the difficulty of administering injections, perceptions of personal failure in self-management, and the effectiveness of therapy [29].

System-related barriers include limited access to education, limited training of providers in injection techniques, overburdened workload among providers, and poor adherence [30].

Recommendations

A. A simplified and personalized insulin regimen that can be easily titrated and intensified improves patient compliance. B

B. Structured education is essential to address both clinician and patient barriers regarding the initiation and intensification of insulin therapy. E

C. Structured patient education is an ongoing process starting from initiation and continuing through titration and intensification of insulin treatment. B

Basal insulin regimen

Basal insulin includes human NPH insulin, LAA, ULAA, and also continuous RAA insulin delivery via an insulin pump [10]. Basal insulin regulates hepatic glucose production by maintaining a steady quantity of insulin in the background [24]. Presently, the Indian market offers NPH, glargine U100 and U300, detemir, and insulin degludec. Basal insulin analogs have a longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin [10]. LAA, such as glargine is currently the most widely used basal insulin after NPH. LAA is followed by the ULAA basal insulin analogs, such as insulin degludec and U300 glargine [10].

ULAA has documented a lower incidence of overall and nocturnal hypoglycemia, a longer duration of action, and a stable profile in comparison to LAA basal insulin analogs (glargine and detemir). Despite offering an equivalent level of glycemic control, LAA basal insulin analogs have been found to have a lower risk of hypoglycemia than NPH insulin [31]. Advantages of ULAA such as U300 glargine and degludec include a flat peakless profile, low variability, once-daily (OD) dosing, variable time of administration, and a reduced risk of nocturnal hypoglycemia [24].

Initiation of basal insulins

It is recommended to initiate basal insulin dosage at 6–8 units/day or 0.1 to 0.2 units/kg body weight/day if HbA1c is ≤ 8% and 8–10 units/day or 0.2 to 0.3 units/kg body weight/day if HbA1c is > 8% (Fig. 3) [32]. Lower and higher doses [33] than these may be needed based on individual clinical case scenarios.

Titration

The active titration period is defined as the time period when the physician adjusts the basal insulin
Ravi Sankar Erukulapati et al., A Practical Approach to the Initiation, Titration and Intensification of Insulin Therapy in Adults with Diabetes

**Figure 3. Steps for Initiation, Titration, and Intensification of Basal Insulin**

*If not on antidiabetic agents like GLP-1RA, SGLT-2i, DPP4i consider these agents; **See Figure 5 for titration of bolus insulin; ***Total basal + bolus dose if converted from basal plus regimen; #Premix/co-formulation

BG — blood glucose; BBR — basal-bolus regimen; DPP4i — dipeptidyl peptidase-4 inhibitors; GLP-1RA — glucagon-like peptide 1 receptor agonist; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; SGLT-2i — sodium glucose co-transporter 2 inhibitors; TDD — total daily dose

<table>
<thead>
<tr>
<th>Initiate basal insulin (with other antidiabetic agents as relevant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Choice of basal insulin should be based on person-specific considerations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HbA1c &lt; 8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–8 units/day or 0.1 to 0.2 units/kg body weight/day, preferably at bedtime</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HbA1c &gt; 8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–10 units/day or 0.2 to 0.3 units/kg body weight/day, preferably at bedtime</td>
</tr>
</tbody>
</table>

**Titration**

- Titrated at least once a week, but more frequently if required
- For hypoglycemia: determine and address the cause; if not clear,
  - BG 41–70 mg/dL: reduce TDD by 20%
  - BG ≤ 40 mg/dL: reduce TDD by 40%
  - FPG 80–130 mg/dL: no adjustments
  - FPG 131–160 mg/dL: increase by 2 units
  - FPG 161–200 mg/dL: increase by 4 units
  - FPG ≥ 201 mg/dL: increase by 6 units
- If glycemic goals not met, review other antidiabetic agents*

**Add a prandial insulin before the largest meal at 4 units or 0.1 units/kg body weight; whichever is less and titrate**

<table>
<thead>
<tr>
<th>FPG 80–130 mg/dL: no adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG 131–160 mg/dL: increase by 2 units</td>
</tr>
<tr>
<td>FPG 161–200 mg/dL: increase by 4 units</td>
</tr>
<tr>
<td>FPG ≥ 201 mg/dL: increase by 6 units</td>
</tr>
</tbody>
</table>

**Consider switching basal plus to premix regimen if glycemic goals not met and patient does not want to use BBR**

<table>
<thead>
<tr>
<th>If glycemic goals not met</th>
</tr>
</thead>
<tbody>
<tr>
<td>If glycemic goals not met</td>
</tr>
</tbody>
</table>

**Switch to basal bolus insulin regimen**

<table>
<thead>
<tr>
<th>If glycemic goals not met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change to premix insulin# twice daily (at breakfast and at dinner)</td>
</tr>
<tr>
<td>Divide the current daily basal dose*** into 60% breakfast and 40% dinner</td>
</tr>
</tbody>
</table>

See respective flow charts
dose. This period usually lasts up to 12 weeks after starting insulin therapy. Ideally, the maximum reduction in HbA1c and FPG should be achieved by week 12 after starting insulin therapy, and a minimal reduction should be seen after 12 weeks [34].

The recommended target for titration is FPG of 80–130 mg/dL usually. It is recommended to titrate the dose at least once a week, but more frequently based on FPG [24, 25]. The dose can be modified based on the lowest/mean value of the three most recent FPG values [24]. The dose may be reduced by at least 20% for individuals reporting hypoglycemia (< 70 mg/dL) [32] unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. Insulin therapy should be intensified, in case they fail to achieve glycemic goals even after optimal dose titration. In the Indian context, this regimen may be a simple and effective method for most people. Where possible, the insulin dose can also be titrated 2 units every 3 days [24, 32]. Consider reviewing other OADs and GLP-1RA, during the titration if these haven’t been optimized already.

If the glycemic goals are not met after optimizing OADs, either add 1 prandial insulin before the largest meal at 4 units or 0.1 units/kg body weight, whichever is less, i.e., change to the basal plus regimen, or opt for premix/co-formulation insulin twice daily (BID) (at breakfast and dinner) and divide the current basal dose into 60% at breakfast and 40% at dinner [24]. If the glycemic goals are not met by premix or co-formulation insulin BID, change to premix/co-formulation insulin thrice daily (TID) (breakfast, lunch, and dinner). If the glycemic goals are still not met, consider switching to BBR [10].

**Recommendations**

A. It is recommended to initiate basal insulin dosage at 6–8 units/day or 0.1 to 0.2 units/kg body weight/day if HbA1c is ≤ 8% and 8–10 units/day or 0.2 to 0.3 units/kg body weight/day if HbA1c is > 8%. B

B. The recommended target for titration is FPG of 80–130 mg/dL. A

C. It is recommended to titrate the dose at least once a week, but more frequently based on FPG. A

D. It is recommended to modify the dose based on the lowest/mean value of the three most recent FPG values. E

E. It is recommended to reduce the dose by at least 20% for individuals reporting hypoglycemia (< 70 mg/dL) unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. B

F. Insulin therapy should be intensified, in case person fail to achieve glycemic goals even after optimal dose titration. B

G. Prandial insulin can be added to basal insulin with the largest meal of the day, to make it basal plus. B

H. Insulin premix regimen can be considered as an option for intensification, in lieu of basal or basal plus insulin regimens if targets are not met. B

I. Intensification strategy can be based upon various factors such as type of diabetes, dietary pattern, lifestyle, weight gain, the person’s age, clinical features, glucose profile, risk of hypoglycemia, personal choice and cost. C

**Premix regimen**

**Once daily premix/co-formulation insulin regimen**

Premix insulin therapy is appropriate for people who are unable to calculate CHOs or have constant eating patterns and a predictable lifestyle. To attain the target HbA1c values, insulin therapy can be started with premix insulin OD and then intensified to BID or TID [35].

Premix insulins are indicated in people with T2D who did not attain glycemic targets with OADs or basal/basal plus insulin, and people with T1D (need to initiate with at least BID premix) [35].

A. Initiation

If HbA1c ≤ 8, OD premix insulin can be initiated at 6–8 units with the largest meal of the day.

B. Titration

The recommended target for titration is a pre-meal value of 80–130 mg/dL [24, 32]. The dose can be titrated at least once a week, but more frequently based on pre-dinner or pre-breakfast values [34]. It is recommended to modify the dose based on the lowest/mean value of the three most recent pre-breakfast/pre-dinner glucose values [34]. Premix analogs can be given immediately before or after the meal, while human premix insulins need to be given 30 minutes before the meal [20]. For individuals reporting hypoglycemia (< 70 mg/dL), it is recommended to reduce the dose by 20% unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia.
Premix analog insulins/co-formulations have a lower risk of hypoglycemia, and better safety, flexibility, and convenience compared to human premix or co-formulation [10].

Breakfast dose adjustments are titrated based on pre-dinner values. No dose adjustments are recommended if the pre-dinner values are \( \leq 140 \) mg/dL. If the pre-dinner values are between 141–180 mg/dL, can increase the dosage by 2 units. It is recommended to increase the dosage by 4 units and 6 units if the pre-dinner values are between 181–220 mg/dL and \( \geq 221 \) mg/dL respectively.

Dinner dose adjustments are titrated based on pre-breakfast values. No dose adjustments are recommended if the FPG values are between 80–130 mg/dL. If FPG values are between 131–160 mg/dL, it is recommended to increase the dosage by 2 units. It is recommended to increase the dosage by 4 units and 6 units if the FPG values are between 161–200 mg/dL and \( \geq 201 \) mg/dL respectively.

Recommendations

A. It is recommended to start premix insulin with 6–8 units OD with the largest meal of the day if HbA1c \( \leq 8\%\).  

B. The recommended target for titration is a pre-meal value of 80–130 mg/dL.  

C. It is recommended to titrate the dose at least once in a week but more frequently based on pre-dinner or pre-breakfast values.  

D. It is recommended to modify the dose based on the lowest/mean value of the three most recent pre-breakfast/pre-dinner glucose values.  

E. Premix analogs can be given immediately before or after the meal, while human premix insulins need to be given 15 minutes before the meal.  

F. It is recommended to reduce the dose by 20% for individuals reporting hypoglycemia (< 70 mg/dL) unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia.  

G. Premix insulin can be administered BID or TID as a part of intensification.  

H. Premix analog insulins/co-formulations have a lower risk of hypoglycemia, safety, flexibility, and convenience compared to human premix or co-formulation.  

Twice daily premix/co-formulation insulin regimen

A. Initiation

When BID premix/co-formulation is necessary and insulin is initiated in an insulin-naïve person, it is recommended to initiate BID premix/co-formulation at 12–16 units or higher doses and divide the total daily dose (TDD) as 60% at breakfast and 40% at dinner.

B. Titration

The recommended target for titration is a pre-meal value of 80–130 mg/dL. It is recommended to titrate the dose at least once a week, but more frequently based on pre-dinner and pre-breakfast values [24]. The dose can be modified based on the lowest/mean value of the three most recent pre-breakfast/pre-dinner glucose values. It is recommended to reduce the dose by 20% for individuals reporting hypoglycemia (< 70 mg/dL) unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia [10, 24].

Breakfast dose adjustments are made based on pre-dinner values. No dose adjustments are recommended if the pre-dinner values are \( \leq 140 \) mg/dL. If pre-dinner values are between 141–180 mg/dL, one may increase the breakfast dosage by 2 units. It is recommended to increase the dosage by 4 units and 6 units if the pre-dinner values are between 181–220 mg/dL and \( \geq 221 \) mg/dL respectively.

Dinner dose adjustments are titrated based on pre-breakfast values. No dose adjustments are recommended if the FPG values are between 80–130 mg/dL. If FPG values are between 131–160 mg/dL, it is recommended to increase the dosage by 2 units. It is recommended to increase the dosage by 4 units and 6 units if the FPG values are between 161–200 mg/dL and \( \geq 201 \) mg/dL respectively.

If the glycemic targets are not met and the target HbA1c is not reached even after 3 months, one may intensify premix/co-formulation from OD to BID and BID to TID. While intensifying from OD to BID, it is recommended to increase the TDD by 10% and split it into 60% at breakfast and 40% at dinner, and keep titrating till glucose values are achieved.

Recommendations

A. When BID pre-mix/co-formulation is necessary for an insulin-naïve person (HbA1c > 8%), it is recommended to start with 12–16 units or higher doses if appropriate and divide TDD as 60% at breakfast and 40% at dinner.
B. The recommended target for titration is a pre-breakfast value of 80–130 mg/dL and pre-dinner values ≤ 140 mg/dL. Breakfast insulin dosage is adjusted based on pre-dinner glucose values and dinner insulin dosage is adjusted based on pre-breakfast glucose values. A

C. It is recommended to reduce the dose by 20% for individuals suffering from hypoglycemia (≤ 70 mg/dL) unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. B

**Thrice daily premix/co-formulation insulin regimen**

A. **Initiation**

While intensifying from BID to TID, if pre-dinner values are above target, one may initiate 4–6 units at lunch and reduce the morning dose by 10% [35]. Whenever TID premix is considered, it is recommended to prefer 50/50 over 30/70 premix insulin (Fig. 4) [14].

B. **Titration**

The recommended target for titration is a pre-meal target of 80–130 mg/dL. For titrating TID premix/co-formulation, breakfast insulin dosage is adjusted based on pre-lunch glucose values, lunch insulin dosage is adjusted based on pre-dinner values, and dinner insulin dosage is adjusted on FPG values [24]. It is recommended to titrate the dose at least once a week, or more frequently based on fasting, pre-lunch, and pre-dinner values. The dose can be modified based on the lowest/mean value of the three most recent pre-breakfast/pre-lunch/pre-dinner values [24].

**Recommendations**

A. It is recommended to add 4–6 units at lunch when converting a premix BID regimen to a premix TID regimen and reduce the breakfast dose by 10%. Whenever TID premix is considered, it is recommended to prefer 50/50 over 30/70 premix insulin. B

B. Down-titration of the morning dose to 10% of TDD may be needed after adding the lunch dose. B

C. The recommended target for titration is a pre-meal target of 80–130 mg/dL. Breakfast insulin dosage increase is adjusted based on pre-lunch glucose values; lunch insulin dosage is adjusted based on pre-dinner values; and dinner insulin dosage increase is adjusted on FPG values. A

D. It is recommended to titrate the dose at least once a week, but more frequently if required, based on fasting, pre-lunch, and pre-dinner values. A

E. It is recommended to modify the dose based on the lowest/mean value of the three most recent pre-breakfast/pre-lunch/pre-dinner values. B

**Basal plus insulin regimen**

A “basal plus” method is the addition of a single prandial insulin injection to the already used basal regimen before the main meal or the meal commensurate with the highest PPG [36]. This regimen has proven to be an effective way to intensify insulin therapy before implementing a full BBR or in lieu of BBR [10, 14, 32]. Careful patient evaluation and scheduling are necessary due to the complicated nature of this regimen. This regimen is best suited for those with T1D and T2D who are younger, extremely motivated, energetic, and have diverse eating habits [37]. Basal plus regimen is a step-by-step approach to basal insulin intensification that can lead to BBR prescription if necessary.

A. **Initiation**

This can be initiated by starting a short-acting insulin at a dose of 4 units or 0.1 unit/kg body weight (whichever is lower), with the main meal of the day, while continuing the existing basal insulin [10].

B. **Titration**

The recommended target for basal dose titration is FPG of 80–130 mg/dL. The prandial insulin dose is recommended to be titrated once a week, but more frequently if required, based on the 2-hour PPG value [24]. For individuals reporting hypoglycemia (< 70 mg/dL), it is recommended to reduce the dose by at least 20% [10, 32].

**Recommendation on titration of basal insulin**

<table>
<thead>
<tr>
<th>FPG (mg/dL)</th>
<th>Dose adjustments (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80–130</td>
<td>0</td>
</tr>
<tr>
<td>131–160</td>
<td>+ 2</td>
</tr>
<tr>
<td>161–200</td>
<td>+ 4</td>
</tr>
<tr>
<td>≥ 201</td>
<td>+ 6</td>
</tr>
</tbody>
</table>

**Recommendation on titration of prandial insulin**

<table>
<thead>
<tr>
<th>PPG (mg/dL)</th>
<th>Dose adjustments (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 180 mg/dL</td>
<td>0</td>
</tr>
<tr>
<td>181–200</td>
<td>+ 1 to 2</td>
</tr>
<tr>
<td>201–220</td>
<td>+ 2 to 3</td>
</tr>
<tr>
<td>≥ 221</td>
<td>+ 3 to 4</td>
</tr>
</tbody>
</table>

**Recommendations**

A. When intensification with basal plus is necessary, start one injection at mealtime with the largest meal of the day. B
Figure 4. Steps for Initiation, Titration, and Intensification of Premix/Co-Formulation Insulin
When BID changed to TID consider changing 30/70 premix to 50/50 premix

**Breakfast insulin dosage is adjusted based on pre-lunch glucose values; lunch insulin dosage is adjusted based on pre-dinner values; and dinner insulin dosage is adjusted based on FPG values; #Premix/co-formulation

BG — blood glucose; BBR — basal-bolus regimen; BID — twice-daily; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; OD — once-daily; T2D — type 2 diabetes; TDD — total daily dose; TID — thrice-daily

---

**Figure 4: Steps for Initiation, Titration, and Intensification of Premix/Co-Formulation Insulin**

**Indications**
- Patients with T2D who did not attain glycemic targets with other antidiabetic agents
- Patients with T2D who did not attain glycemic targets with basal/basal plus insulin
- Patients with T2D who did not want BBR (need to initiate with at least BID premix)

**HbA1c ≤ 8%**
- Once-daily premix#
- Start with 6–8 units once daily with the largest meal of the day

**HbA1c > 8%**
- Twice-daily premix#
- Start with 12–16 units or higher doses. Divide TDD as 60% at breakfast and 40% at dinner

**Titration**
- Titrating at least once a week, but more frequently based on pre-meal values
- For hypoglycemia: determine and address the cause; if not clear,
  - BG 41–70 mg/dL: reduce TDD by 20%
  - BG ≤ 40 mg/dL: reduce TDD by 40%

**Breakfast dose adjustments** (based on pre-dinner values)
- ≤ 140 mg/dL: no dose adjustments
- 141–180 mg/dL: increase by 2 units
- 181–220 mg/dL: increase by 4 units
- ≥ 221 mg/dL: increase by 6 units

**Dinner dose adjustments** (based on pre-breakfast values)
- FPG 80–130 mg/dL: no adjustments
- FPG 131–160 mg/dL: increase by 2 units
- FPG 161–200 mg/dL: increase by 4 units
- FPG ≥ 201 mg/dL: increase by 6 units

**When HbA1c > 7% or BG values are above target values after 3 months**
- Intensify premix# OD to BID
  - Increase TDD by 10% and split into 60% at breakfast and 40% at dinner and keep titrating till glucose values are achieved

- Intensify premix# BID to TID
  - If pre-dinner values are above target, start 4–6 units at lunch and reduce morning dose by 10%**

---

**Breakfast insulin dosage is adjusted based on pre-lunch glucose values; lunch insulin dosage is adjusted based on pre-dinner values; and dinner insulin dosage is adjusted based on FPG values; #Premix/co-formulation

BG — blood glucose; BBR — basal-bolus regimen; BID — twice-daily; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; OD — once-daily; T2D — type 2 diabetes; TDD — total daily dose; TID — thrice-daily
B. Starting dose is 4 units or 0.1 unit/kg body weight, whichever is lower. The prandial insulin dose is recommended to be titrated at least once a week, but more frequently if required, based on the 2-hour PPG value. A

C. The recommended target for basal dose titration is FPG of 80–130 mg/dL. A

D. It is recommended to reduce the dose of basal/bolus by at least 20% for individuals suffering from hypoglycemia (< 70 mg/dL) depending on the time of hypoglycemia-FPG/PPG respectively, unless there is an identifiable and modifiable one-off cause for that episode of hypoglycemia. B

E. Basal plus regimen is a step-by-step approach to basal insulin intensification that can lead to BBR prescription if necessary. A

### Basal-bolus regimen

Basal-bolus regimen is used when basal insulin alone does not achieve target glycemic control. It almost replicates the natural production of insulin by the pancreas. A long-acting insulin is used as basal insulin to control fasting/pre-meal glucose and short-acting insulin as bolus is administered with each meal to control PPG excursions. To achieve the desired level of glycemic control with this regimen, frequent and active SMBG, understanding of the insulin-CHO ratio and correction factors, and titration of the insulin are required [37].

BBR is indicated in people who fail to achieve glycemic targets with basal/basal plus/premix/co-formulation insulin regimens with or without OADS, people with T1D, [10] secondary diabetes, and those with frequent hypoglycemia with premix/co-formulation insulins.

#### A. Initiation

To initiate this regimen in insulin naïve people, it is recommended to calculate the total insulin dose as 0.5 units/kg body weight for people with T1D [38] and 0.2–0.3 units/kg body weight for people with T2D [32]. It is recommended to divide TDD into 40% as basal insulin given usually at bedtime and 60% as prandial insulin divided into 3 doses at each meal.

To initiate this regimen in people switching from other insulin regimens (basal/basal plus/premix/co-formulation), an increase in TDD by 10% may be considered and then, divide TDD into 40% as basal insulin given usually at bedtime and 60% as prandial insulin divided into 3 doses at each meal.

#### B. Titration

The recommended target for titration of the prandial component is a 2-hour PPG value of ≤ 180 mg/dL. The recommended target for titration of basal components is a FPG value of 80–130 mg/dL. It is recommended to titrate the dose at least once a week, or more frequently based on FPG and PPG values for basal and bolus insulins respectively [24].

It is recommended to address the FPG first, this is typically best accomplished with a bedtime basal insulin dosage (‘Fix Fasting First’) [39].

It is recommended to modify the dose based on the lowest/mean value of the three most recent FPG values [24]. A lower starting dose, slower titration, and higher glucose targets may be recommended for those people at higher risk of hypoglycemia.

The TDD of basal and/or prandial insulin can be reduced by 20% if the blood glucose level is consistently < 70 mg/dL. FPG and PPG readings are considered for dose adjustments so that basal and prandial insulins are adjusted accordingly.

While titrating basal insulin, no dose adjustments are recommended if the FPG levels are between 80–130 mg/dL. If the FPG values are between 131–160 mg/dL, it is recommended to increase the dosage by 2 units, and if FPG values are between 161–200 mg/dL and ≥ 201 mg/dL, increase the dosage by 4 units and 6 units respectively.

While titrating prandial insulin, no dose adjustments are recommended if the 2h PPG levels are ≤ 180 mg/dL. If the PPG values are between 181–200 mg/dL, it is recommended to increase the dosage by 1–2 units. It is recommended to increase the dosage by 2–3 units and 3–4 units if the PPG values are between 201–220 mg/dL and ≥ 221 mg/dL respectively.

#### Recommendations

A. It is recommended to calculate the total insulin dose as 0.5 units/kg body weight for people with T1D and 0.2–0.3 units/kg body weight for people with T2D. B

B. 40% of the TDD to be given as basal insulin as a single dose usually at bedtime. B

C. 60% of the TDD to be given as prandial insulin divided as 3 doses at each meal. B

D. The recommended target for titration of basal component is a FPG value of 80–130 mg/dL. B

E. The recommended target for titration of the prandial component is a 2-hour PPG value of ≤ 180 mg/dL. B

F. It is recommended to titrate the dose at least once a week, or more frequently based on FPG and PPG values for basal and bolus insulins respectively. B

G. It is recommended to address the FPG first. This is typically best accomplished with a bedtime basal insulin dosage (‘Fix Fasting First’). B
It is recommended to modify the dose of the basal and prandial insulins (bolus doses) based on the lowest/mean value of the three most recent FPG and relevant PPG values respectively. **E**

A lower starting dose, slower titration, and higher targets may be recommended for those people at higher risk of hypoglycemia. **C**

**Insulin injection technique**

Insulin must be administered properly into the appropriate tissue. Although insulin therapy remains the cornerstone of diabetes management, the skill of injecting insulin is not properly understood by many users and even some HCPs. A proper insulin injection technique should consider appropriate injection sites in the body, injection technique, rotating injection sites,
caring of injection sites, and avoiding intramuscular (IM) insulin administration [40].

Insulin delivery devices
A. Insulin syringes
Insulin syringes were the most popular method for delivering SC insulin. The capacity and type of the syringe is chosen based on the dose and concentration of insulin [40]. Other things to consider when choosing an insulin syringe are needle gauge and needle length, as larger needles increase the risk of IM injections [40].

Insulin syringes may be utilized for insulin delivery considering individual and carer preferences, insulin type, dosage regimen, cost, and dexterity. It is advised not to draw insulin with syringes from insulin cartridges/penfills/pens. The best suggested needle length for an insulin syringe is 6 mm [40]. Needles longer than 6 mm for adults or teenagers are not advisable.

Glass syringes should be replaced with plastic fixed-needle syringes that have less dead space and are intended for single use [41]. Many people reuse insulin needles for a variety of reasons, including cost considerations [40]. The manufacturers do not advise this, as there is a link between lipohypertrophy (LH) and needle reuse. The reuse of needles triggers more pain at the injection site.

B. Insulin pens
Insulin pens are prefilled cartridges of insulin that are devised to make injections easier and more flexible. They eliminate the need to extract insulin from a vial; they may be especially beneficial for insulin delivery when away from home, at school, or on a holiday. While using a pen, it is recommended to count from 1 to 10 before removing the needle, to allow time for any air bubble in the cartridge to expand [19]. Wherever possible, usage of insulin pens is recommended over syringes due to convenience, accuracy of dosage, and safety reasons [42].

There are two main categories of insulin pens: disposable and durable. Disposable insulin pens are prefilled with insulin and are thrown away once they are empty [40]. Insulin pens are only permitted for single-person usage. Individuals should never share their insulin pen cartridges with others so as to avoid the risk of biological contamination in the pen cartridges even if a new needle is used [40].

Insulin pens may be considered as a better option than syringes for people with vision impairment or dexterity issues, children, and elderly people to ease the administration of accurate insulin doses. A 4 mm needle is recommended to be used with pens [40]. When compared to the traditional vial/syringe, the scale on insulin pens is simpler to read.

Disposal
Proper disposal of used insulin vials and syringes is mandatory [15, 19]. Ideally, they should be disposed off in sharps containers that have been carefully labeled and are available for sale in pharmacies and a few diabetes centers. Ideally, the needle may be taken out and rendered unusable using specialized needle clippers (like a safe clip) [19]. Syringes with removed needles can be disposed off in tins or opaque plastic containers [19]. People with diabetes and their family members who improperly dispose sharp objects are at risk of needle-stick injuries among themselves, domestic waste handlers, and the community [43]. HCPs ought to take responsibility for educating people about proper disposal and spreading awareness about it. In case of unavailability of sharp bins, needles should be gathered in a sturdy cardboard or glass container, or used soft drink tin, sealed and marked, and sent to the nearest healthcare facility.

According to a research study in New Delhi, 84.1% of people with diabetes put sharps right into their residential garbage containers [44]. The results of a recent worldwide injection technique questionnaire (ITQ) study, which included 7.6% of subjects from India, revealed that a significant amount of used sharps still end up in household garbage [45]. Improper disposal techniques resulted in sharps injuries in the community in 8.6% of the overall population [45].

Insulin concentrations
Insulins are available in the strengths of U40 and U100 concentrations in India. U100 means 100 units of insulin in 1 mL. U200 and U300 insulins are also available, but exclusively in the form of a pen. To minimize dosage problems, it is mandatory to use a U40 syringe for U40 insulin and a U100 syringe for U100 insulin vials [40].

Intravenous (IV) syringes should never be used for insulin delivery [40]. The date of opening the vial should be recorded with a black/marker pen, and it should be utilized usually within 28 days [46].

Most of the concentrated insulins, such as lispro U200, regular insulin U200, and regular insulin U500, were developed to overcome severe insulin resistance and satisfy the demands of a substantial supply of insulin. Concentrated U300 basal insulin glargine offers the advantages of low injection volume leading to less pain, low variability, and lesser risk of overall hypoglycemia, including nocturnal hypoglycemia, and can be prescribed as an alternative to U100 basal insulin [47].

Injection sites
The abdomen, thigh, and buttocks were suggested as the most common injection sites [10]. After the in-
Insulin has been injected, the person should count slowly till 10 and then withdraw the needle from the skin [3]. Insulin administration through SC tissue is most often employed in ambulatory persons. Additional methods include IV infusion which is only used in cases of DKA, HHS, when insulin administration is indicated in a nothing-by-mouth (NBM) scenario, in the emergency and intensive care unit (ICU) setting, to name a few [40]. IM insulin is almost never advised, due to erratic absorption, and risk of hypoglycemia and may be rarely considered in exceptional circumstances only [48].

**Injection site rotation**

Injections should be switched between sites systematically to maintain a healthy injection site so as to improve insulin absorption and lower the risk of LH [40]. LH occurs when there is an accumulation of SC fat at the injection site as a result of insulin’s adipogenic effects [40]. LH can cause irregular insulin absorption, increased glycemic variability, and unexplained hypoglycemia episodes. It manifests as soft or rubbery fatty swellings at the site of repeated insulin injections [40].

An alternative efficient strategy to rotate the injection site is to split the injection site into quadrants (abdomen) or halves (thighs, and buttocks). After using one quadrant or half for a week, switch to the next one in either a clockwise or an anticlockwise direction. Adolescents should use the abdominal area most often [40].

The distance between the new injection site and the previous injection site should be at least 1 cm [48]. Avoid injecting in areas with infections, edema, or LH. Injection sites should be examined by the HCPs at least once a year and preferably at every visit [48]. Education regarding correct injection site rotation and how to spot and stay away from areas of LH should be provided to individuals and/or their carers [48].

**Needle length**

Ideally, a 6 mm needle should be used with syringes and a 4 mm needle should be used with pens [40, 43]. In teenagers or adults who are slender to normal weight, a syringe needle injection should always be administered into a raised skinfold at 90° [40].

Ideally insulin needle should be used only once. If reusing the needle is intended, which is not ideal, it must be thoroughly recapped after each use. The needle should never be cleaned or washed and needles should be changed after a maximum of 3–4 uses, to avoid needle infection [3]. It is recommended to follow the correct site rotation policy.

**Storage and transport**

Insulin should preferably be stored in a cool (< 30°C) and dark environment, as per the manufacturer’s recommendations [40]. The ideal temperature for transporting insulin should be between 2 and 8°C [3]. Insulin vials can be kept in a pot with sand if refrigeration is not available [49].

Insulins’ potency and efficiency can be diminished when they are exposed to direct sunlight or high temperatures. Excessive agitation should be avoided to avoid potency loss, clumping, frosting, or precipitation. As a result, it is crucial to maintain the temperature while transporting [40, 49].

If refrigeration is not available, insulin should be kept cool for example, in an earthenware pot of water (inside a ziplock plastic bag), thermos flasks, or ice bags. Various unconventional methods of insulin storage include pot-in–pot refrigerators or the Zeer pot, mud pots, goat skin pots filled with water, vegetable gourds filled with water, and buckets filled with wet sand [50]. Regular insulin should not be used if it appears hazy. Cloudy insulin should not be used if it cannot be re-suspended [40, 49]. Regardless of where it is kept, opened insulin has a shelf life of 28 days and it needs to be discarded after that [46]. Before administering insulin, it should be taken out of the refrigerator and allowed to reach room temperature. ‘Never freeze insulins’ is the dictum [3, 40].

**Insulin stability**

Used vials can be stored in a clean plastic box and out of direct sunlight for six weeks at room temperature (20–25°C), or four weeks if the temperature rises to 30°C. Insulin can degrade or be converted to larger molecular weight components if it is stored at higher temperatures [43]. According to Pendsey et al., the insulin that has not been refrigerated may be thermostable for up to two months, and in some cases up to four months [51].

**The steps for using an insulin syringe and vial**

- Wash hands thoroughly.
- Check the expiry date and type of insulin.
- Bring insulin to room temperature.
- If the insulin is cloudy, roll the bottle between your hands until it is uniformly mixed.
- Extract air into the syringe equal to the dose of insulin to be taken.
- Pierce the rubber stopper of the insulin vial in the middle at a 90° angle and push the air in.
- Holding the bottle upside down, extract the dose into the syringe.
- Ready for injection. Place the syringe on the table carefully without letting the needle touch the surface.
- Select the site and it should be completely dry before injecting.
- To inject insulin, slowly push the needle through the skin fold.
- Count to 10 (more in case of large dose) before pulling the needle out. Release the skin fold.
- Clip the syringe needle with a safe clip. Dispose the needle safely.

### Recommendations

#### Insulin delivery devices

A. Wherever possible, use insulin pens over syringes due to convenience, accuracy of dosage, and safety reasons. **B**

B. Insulin pens are usually preferable for individuals using BBR insulin therapy. Insulin syringes may be utilized for insulin delivery considering individual and carer preferences, insulin type, dosage regimen, cost, and self-management capacities. **C**

C. Insulin pens should be considered for people with dexterity issues or vision impairment to facilitate accurate dosing and administration of insulin. **C**

D. Pen devices improve patient safety, convenience, and adherence. **B**

#### Insulin concentrations and strength

A. Concentrated U300 basal insulin offers the advantages of low injection volume leading to less pain, low variability, and lesser risk of hypoglycemia, including nocturnal hypoglycemia, and can be prescribed as an alternative to U100 insulin. **C**

B. In those people requiring very high dosage of insulin, pump therapy may be considered as an option, if affordable. **A**

C. High-concentration short-acting insulin can be administered in people who have severe insulin resistance and need higher doses of insulin in a single injection. **C**

D. Use U40 syringe only for U40 insulin and U100 syringe only for U100 insulin vials. **A**

E. Do not draw insulin with syringes from insulin cartridges/penfills/pens. **A**

#### Insulin transport and storage

A. The manufacturer's recommended storage guidelines included in the package inserts should be followed. **E**

B. Insulin can be transported from a healthcare institution to an individual's home without the use of an ice pack if no excessive temperature changes are anticipated. It is recommended to transport insulin on an ice pack if there is any doubt about whether it will be exposed to extreme temperatures (> 30°C). **A**

C. Insulin vials can be transported by keeping insulin in a pot with sand or in an earthenware pot of water (inside a ziplock plastic bag) if a refrigerator is unavailable. **B**

D. Insulin must not be exposed to heat or sunlight. Excessive agitation should be avoided to prevent clumping, frosting, precipitation, or loss of potency. **A**

E. While going on a holiday, insulin pens and vials may be carried appropriately using insulin storage boxes sold in some pharmacies or at least in a thermos flask with ice, or in a proper clean container if the outside temperature is > 30°C. Never leave insulin in a locked vehicle with the windows closed. **B**

F. If regular insulin seems cloudy, it shouldn’t be used. Insulin that is hazy and cannot be re-suspended should not be used. **A**

G. Vials that have been opened can be stored in a refrigerator (2–8°C) or at a controlled ambient temperature. Regardless of where it is kept, opened insulin has a shelf life of 28 days and it needs to be discarded after that. Before administering insulin, it should be taken out of the refrigerator and allowed to reach room temperature. Never freeze insulins. **A**

#### Injection sites

A. Abdomen, thigh, and buttocks are the recommended injection sites. **A**

B. IM insulin injections should not be given. **B**

C. After the insulin has been injected, the person should count slowly till 10 and then withdraw the needle from the skin. **B**

#### Injection site rotation

A. Systematic switching of injections from one site to another helps to keep injection sites healthy, optimize insulin absorption, and minimize the danger of LH. **A**

B. The distance between the new injection site and the previous injection site should be at least 1 cm. **A**

C. The injection site should be reviewed by HCPs at every possible opportunity. **A**
Hypoglycemia

Hypoglycemia is a major challenging event during the glycemic management of a person with diabetes. Level 1 hypoglycemia is termed when blood glucose is \( \geq 54 \text{ mg/dL} \) and \( < 70 \text{ mg/dL} \). Level 2 hypoglycemia is when the blood glucose is \( < 54 \text{ mg/dL} \) and level 3 hypoglycemia is when a severe incident is defined by changed mental or physical status needing help for treatment of hypoglycemia (Fig. 6) [52].

Hypoglycemia symptoms include shakiness, anger, disorientation, tachycardia, and hunger. For people with diabetes, hypoglycemia symptoms can be uncomfortable or scary. Hypoglycemia at level 3 might result in unconsciousness, seizures, coma, or even death. At each visit, doctors should assess the person’s risk of hypoglycemia, especially if they are on insulin [53].

It is worth considering insulin analogs for managing blood glucose in people with T1D or T2D who frequently experience severe hypoglycemia with human insulin [54]. People who experience frequent episodes of hypoglycemia require periodic SMBG (3 times or more per day) or CGM. Additional suggestions include checking the injection site often (irregular absorption can cause hypoglycemia), adjusting the insulin dose before and after activity, and making sure a CHO supplement and glucometer are readily available [25]. Compared to previously established basal analogs (detemir and glargine U100), ULAA basal analogs (degludex, and glargine U300), have more physiological basal profiles and fewer risks of nocturnal and overall hypoglycemia [10]. It is important to advise people to report to their doctor about episodes of hypoglycemia.

Management of hypoglycemia

The management of hypoglycemia is summarized in Figure 7. Most episodes of hypoglycemia can be self-treated by ingestion of glucose or CHO-containing juices, soft drinks, candy, other snacks, or a meal. A good amount of CHOs (15–20 g) can be given again in 15–20 minutes if necessary [55]. Since the glycemic response to oral glucose is transient, it is often advised to consume a larger snack or meal soon after the plasma glucose level is corrected to the normal range with oral glucose. When a hypoglycemic person is unable to consume CHOs orally, or in case of severe hypoglycemia, IV glucose or glucagon injection IM or SC is necessary [52].

Fast-acting CHOs should be given to people when their blood glucose falls below the normal range, which is \( < 70 \text{ mg/dL} \). Although pure glucose ingestion is preferred to correct hypoglycemia, any form of CHO that contains glucose is recommended to raise blood glucose levels rapidly [52].

When someone is unable or unwilling to take glucose or foods orally, hypoglycemia can be treated using glucagon injection IM or SC. Both the person and their caretakers (family members, roommates, school personnel, childcare providers, institution staff, or co-workers, etc.), should be primed about the usage of glucagon which includes glucagon storage and how to give it [52].
For treating hypoglycemia with IV glucose, the use of 5%, 10%, or 25% glucose solutions is preferable over the use of 50% glucose, because, the use of hyperosmolar solutions increases the risk of extravasation damage [56].

In order to reduce hypoglycemia, education on hypoglycemia avoidance, re-evaluation, and treatment regimen adjustments should be made [52]. Precipitating causes need to be investigated at the earliest opportunity and appropriately managed. Education about hypoglycemia prevention and treatment should be part and parcel of every visit of the person by the doctor [55].

Impaired awareness of hypoglycemia

Impaired awareness of hypoglycemia (IAH) is a common side effect of insulin treatment. Around 50% of insulin-treated people with T1D and T2D exhibit hypoglycemia unawareness, and 15–25% have a persistent IAH [57]. Identifying or recognizing a hypoglycemic event by the person is the first step in making HCPs aware of hypoglycemia [58].

Less stringent blood glucose targets, such as a three-month duration without hypoglycemia, as well as instruction on a CSII and CGM, are advised to lower the risk of developing severe hypoglycemia and to try to regain hypoglycemic consciousness [59].

Recommendations

A. Blood glucose < 70 mg/dL is hypoglycemia and any hypoglycemia requiring 3rd party assistance or blood glucose < 54 mg/dL is severe hypoglycemia. B

B. Risk or occurrence of hypoglycemia should be assessed at every visit. C

C. In a scenario of hypoglycemia or potential hypoglycemia, if there is no access to a glucometer or CGM to check blood glucose levels, the person should be treated based on symptoms and suspicion of hypoglycemia. B

D. Oral glucose (15–20 g) or equivalent is to be given for conscious person with blood glucose < 70 mg/dL. If there is continued hypoglycemia (blood glucose < 70 mg/dL) after 15 min, then repeat 15–20 g of oral glucose. Recheck blood glucose after 15–20 mins till the blood glucose is ≥ 70 mg/dL. Once blood glucose ≥ 70 mg/dL, give a snack or meal to prevent further hypoglycemia. B

E. Unconscious person with hypoglycemia should be administered IV bolus — 60 mL of 25% dextrose or 150 mL of 10% dextrose or 30 mL of 50% dextrose (only if a lesser concentration is not available due to the risk of extravasation injury) or 1 mg of glucagon IM as soon as possible. B

F. After treatment of hypoglycemia in an unconscious person as above with IV dextrose, recheck the blood glucose after 10 mins, and if still < 70 mg/dL, repeat treatment. Once blood glucose ≥ 70 mg/dL, and the person is awake and safe to swallow, allow oral intake of 15–20 g glucose (glucose powder/tablet/honey/sugar/sweet/chocolate). Once blood glucose ≥ 70 mg/dL, and if the person is not safe to swallow, start 5% dextrose IV 100 mL/hr. Repeat BGM every 30 mins and seek help from an expert. B

G. Be vigilant for hypoglycemia in people with impaired or declining cognition, advanced age, co-morbidities (renal or hepatic impairments), or decreased food intake due to any reason. B

H. Hypoglycemic unawareness is defined as having blood glucose < 70 mg/dL without symptoms. These people should be referred to an expert. E

I. Structured patient education about hypoglycemia avoidance, as well as re-evaluation and revision of the treatment plan to reduce hypoglycemia, should be initiated in people with hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia. B

J. Insulin-treated individuals with hypoglycemia unawareness, a level 3 hypoglycemic incident, or a pattern of unexplained level 2 hypoglycemia may be encouraged to raise their glycemic goals in order to partially reverse hypoglycemic unawareness and lower the risk of subsequent episodes. C

K. Consider insulin analogs over human insulin to manage blood glucose in adults with T1D or T2D who have frequent severe hypoglycemia. B

L. Newer ULAA analogs compared with existing basal analogs, have more physiological basal profiles and provide a lower risk of nocturnal hypoglycemia. B

M. Short-acting insulin analogs are superior to regular human insulin in reducing hypoglycemia. B

N. It is recommended to regularly check the injection sites (irregular absorption can cause hypoglycemia), take the necessary amount of food at mealtimes, adjust the insulin dose appropriately before and after physical activity, and make sure a glucometer and CHO supplements are easily accessible. A

O. Periodic SMBG (≥ 3 times a day), or CGM is necessary for people who have frequent episodes of hypoglycemia. B
**Blood glucose monitoring**

Individual glucose monitoring is a valuable tool for the self-management of diabetes, which allows people to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. It also provides guidance on dietary changes, physical activity, and medication modification, especially for insulin users. It can help people to improve glucose control, reduce hypoglycemia, and boost self-efficacy [42]. Monitoring blood glucose levels and identifying trends will enable prompt and appropriate modifications to insulin dose, dietary intake, and physical activity management which are the most crucial components of diabetes care. To identify these trends, tools like SMBG using glucometers and CGM can be used [60]. Where glucometers are not available for the individuals due to any reason, at least lab glucose checks are recommended in lieu of glucometer checks.

**Self-monitoring of blood glucose**

Self-monitoring of blood glucose is the simplest and may be the most useful technique for evaluating the efficacy and safety of glycemic management. SMBG refers to the monitoring and recording of blood glucose levels throughout the day by the person and/or caretaker at home or in a healthcare center [61]. The measured blood glucose levels assist individuals and clinicians in planning proper lifestyle (diet, exercise, and medication) changes.

To ensure that data is used effectively and quickly, both the person with diabetes and the HCPs must examine and analyze data that is recorded using a glucometer. People with diabetes should be educated on how to use BGM data to modify their dietary intake, physical activity levels, or drug therapy to achieve specific goals [61]. Proactive control of diabetes with SMBG can enhance therapeutic results and lower morbidity and mortality [62].

**Continuous glucose monitoring**

A CGM predicts blood glucose levels by monitoring the concentration of glucose in the interstitial fluid using a sensor implanted directly beneath the skin [63]. Time in range (TIR) is a useful metric of CGM for glycemic control and glucose patterns, and it correlates well with HbA1c [64]. However, people using CGM devices must have access to a glucometer at all times [42]. The guidance on CGM targets for the assessment of glycemic control among various groups is discussed in Table 4.

<table>
<thead>
<tr>
<th>Population groups</th>
<th>Time in range</th>
<th>Target range</th>
<th>Time below range</th>
<th>Below target level</th>
<th>Time above range</th>
<th>Above target level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of readings; time per day</td>
<td>Target range</td>
<td>% of readings; time per day</td>
<td>Below target level</td>
<td>% of readings; time per day</td>
<td>Above target level</td>
</tr>
<tr>
<td>T1D* and T2D</td>
<td>&gt; 70%;</td>
<td>70–180 mg/dL</td>
<td>&lt; 4%;</td>
<td>&lt; 70 mg/dL</td>
<td>&lt; 25%;</td>
<td>&gt; 180 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; 16 hours, 48 minutes</td>
<td></td>
<td>&lt; 1 hour</td>
<td>&lt; 6 mg/dL</td>
<td>&lt; 5%;</td>
<td>&gt; 250 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 1%</td>
<td>1 hour, 12 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 15 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy: T1D</td>
<td>&gt; 70%;</td>
<td>63–140 mg/dL</td>
<td>&lt; 4%;</td>
<td>&lt; 63 mg/dL</td>
<td>&lt; 25%;</td>
<td>&gt; 140 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; 16 hours, 48 minutes</td>
<td></td>
<td>&lt; 1 hour</td>
<td>&lt; 5%</td>
<td>6 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 15 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy: GDM and T2D</td>
<td>Not specified, but &gt; 90% achievable</td>
<td>63–140 mg/dL</td>
<td>Not specified, but &lt; 4% achievable</td>
<td>&lt; 63 mg/dL</td>
<td>Not specified, but &lt; 5% achievable</td>
<td>&gt; 140 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 1 hour</td>
<td>1 hour, 12 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not specified, but &lt; 1% achievable</td>
<td>&lt; 54 mg/dL</td>
<td>1 hour, 12 minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 15 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older/high risk</td>
<td>&gt; 50%;</td>
<td>70–180 mg/dL</td>
<td>&lt; 1%;</td>
<td>&lt; 70 mg/dL</td>
<td>&lt; 10%;</td>
<td>&gt; 250 mg/dL</td>
</tr>
<tr>
<td>T1D and T2D</td>
<td>&gt; 12 hours</td>
<td></td>
<td>&lt; 15 minutes</td>
<td>&lt; 2 hours, 24 minutes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For age < 25 years, if the HbA1c goal is 7.5%, set time in range target to approximately 60%
GDM — gestational diabetes mellitus; T1D — type 1 diabetes; T2D — type 2 diabetes
A. Standardized CGM metrics

The worldwide agreement on TIR offers recommendations for common CGM measurements (Fig. 8) and things to keep in mind when using them in clinical interpretation and treatment [65]. Time above range (TAR) and time below range (TBR) are additional helpful metrics for adjusting insulin doses and re-evaluating the treatment strategy. According to the most recent advanced technologies and treatments for diabetes (ATTD) international TIR consensus 2019, most people with T2D should aim to spend > 70% of their time per day (approx. > 17 h) in TIR (70–180 mg/dL), < 4% in TBR (< 70 mg/dL) and < 25% of the time per day in TAR (> 180 mg/dL) [66].

BGM and CGM can help manage medications, guide medical nutrition treatment, encourage physical activity, and prevent hypoglycemia [42]. The CGM measures TIR (including TAR and TBR) and gives insights for a more individualized diabetes treatment plan [64]. These indicators are now being incorporated into clinical practice.

In those who can afford, the use of CGM devices should be considered as soon as diabetes is diagnosed and insulin therapy is initiated [67]. This relieves the
strain of regular BGM and enables close monitoring of glucose levels with adjustments to insulin dose and lifestyle changes.

B. Types of CGM

CGMs are classified into two types based on data type: “real-time” and “flash.” Real-time CGMs (rtCGM) send glucose readings every 1–5 minutes over Bluetooth to a chosen receiver, mobile, or insulin pump. Flash CGMs, also known as intermittently scanned CGMs (isCGM) record glucose concentrations every 1–15 minutes, but downloads the data only to the designated reader when the user “flashes” the near field communication tag, at a point where the past 8 hours of data is retrieved [63].

Professional CGMs are CGM devices that are attached to a person with diabetes at the doctor’s clinic under remote control and worn for a specific amount of time (generally 7–14 days). The data is utilized to evaluate glycemic trends and patterns. Unlike rtCGM and isCGM devices, these are clinic-based and are not owned by the people [42].

**Recommendations**

<table>
<thead>
<tr>
<th>1</th>
<th>Number of days CGM device is worn (recommend 14 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Percentage of time CGM device is active (recommend 70% of data from 14 days)</td>
</tr>
<tr>
<td>3</td>
<td>Mean glucose</td>
</tr>
<tr>
<td>4</td>
<td>Glucose management indicator</td>
</tr>
<tr>
<td>5</td>
<td>Glycemic variability (% CV) target ≤ 36%*</td>
</tr>
<tr>
<td>6</td>
<td>TAR: % of readings and time &gt; 250 mg/dL Level 2 hyperglycemia</td>
</tr>
<tr>
<td>7</td>
<td>TAR: % of readings and time 181–250 mg/dL Level 1 hyperglycemia</td>
</tr>
<tr>
<td>8</td>
<td>TAR: % of readings and time 70–180 mg/dL In range</td>
</tr>
<tr>
<td>9</td>
<td>TBR: % of readings and time 54–69 mg/dL Level 1 hypoglycemia</td>
</tr>
<tr>
<td>10</td>
<td>TBR: % of readings and time &lt; 54 mg/dL Level 2 hypoglycemia</td>
</tr>
</tbody>
</table>

*B. Some studies suggest that lower %CV targets (< 33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas.

CGM — continuous glucose monitoring; CV — coefficient of variation; TAR — time above range; TBR — time below range; TIR — time in range

---

Figure 8. Standardized CGM Metrics (Adapted from [65])

| 1 | Number of days CGM device is worn (recommend 14 days) |
| 2 | Percentage of time CGM device is active (recommend 70% of data from 14 days) |
| 3 | Mean glucose |
| 4 | Glucose management indicator |
| 5 | Glycemic variability (% CV) target ≤ 36%* |
| 6 | TAR: % of readings and time > 250 mg/dL Level 2 hyperglycemia |
| 7 | TAR: % of readings and time 181–250 mg/dL Level 1 hyperglycemia |
| 8 | TAR: % of readings and time 70–180 mg/dL In range |
| 9 | TBR: % of readings and time 54–69 mg/dL Level 1 hypoglycemia |
| 10 | TBR: % of readings and time < 54 mg/dL Level 2 hypoglycemia |

C. Individuals who are on insulin using BGM should be encouraged to check blood glucose reading when appropriate as suggested by the physician and based on their insulin regimen. B

D. It is essential to individualize the type and selection of devices based on a person’s specific needs, desires, skill level, and device availability. A

E. When it comes to an individual whose diabetes is partially or totally managed by someone else (such as a person with cognitive disability), the talents and preferences of the carer are critical to the decision-making process. A

F. When recommending a device, ensure that those with diabetes and their carers receive initial and ongoing instructions and training, either in person or online, as well as regular evaluations of the technique, outcomes, and their capacity to use data, including uploading/sharing data (if applicable), to adjust therapy. B

G. Initiation of CGM, CSII, and/or automated delivery of insulin might be advantageous depending on a person’s/carer’s requirements and preferences and should be referred to an Endocrinologist or a physician with such skills. B

H. Glucometers are important tools to monitor capillary glucose in the comfort of one’s own home and are to be considered wherever appropriate. A
I. Regular SMBG is strongly recommended for people who are on BBR insulin therapy, on pre-gestational/gestational diabetes mellitus (GDM) using insulin, history of hypoglycemia unawareness, brittle diabetes, or with poor metabolic control on multiple OADs and/or insulin.  

J. Glucometer readings should not be used to diagnost T2D.  

K. Basal insulin is best monitored by FPG and should be monitored at least once a week. During initiation and intensification, more frequent monitoring is required.  

L. Prandial insulin is best monitored by paired pre-meal and post-meal glucose values.  

M. Premix insulin is monitored by fasting and pre-meal glucose values.  

N. CGM is a valuable tool in deriving information pertaining to glucose control, glucose variations, hypoglycemia, and the trends of the same.  

O. CGM targets for most adults with T2D and T1D aim to spend > 70% of their time per day (approx. > 17 h) in TIR (70–180 mg/dL), < 4% in TBR (< 70 mg/dL) and < 25% of the time per day in TAR (> 180 mg/dL).  

P. People using CGM devices must have access to glucometer at all times.  

### Insulin pump

CSII commonly known as insulin pumps are devices that deliver RAA throughout the day in order to regulate blood glucose levels. A CSII or insulin pump attempts to replicate pancreatic activity [68].  

Factors to take into account when starting pump therapy in people with diabetes include affordability, assessment of the person’s and their family’s readiness, selection of the pump type and initial pump settings, individual/family education on potential pump complications, transition from BBR, and introduction of advanced pump settings [42].  

Insulin pumps are safe and efficient in young people with T1D to achieve their desired glycemic results while lowering their risk of hypoglycemia and DKA, enhancing their QoL, and avoiding long-term consequences [42].  

CSII, an alternative to BBR, has been linked to better long-term results in intensive insulin treatment for T2D glycemic control [69]. Adults with severe hypoglycemia were less likely to experience severe episodes while receiving CSII through pump treatment.

### Recommendations

A. Insulin pump therapy may be recommended to people with T1D, people with GDM, those with T1D or T2D whilst pregnant, people with T2D who fail to achieve acceptable glycemic control with a basal/bolus regimen, those who have remarkably high insulin requirements, severe insulin resistance syndromes such as lipodystrophy, and people with insulin insufficiency (those who have undergone a pancreatectomy and/or those with cystic fibrosis).  

B. Structured education, CHO counting and training should be provided regarding insulin pump use, including aspects such as infusion set insertion technique and basic insulin dose adjustments at the initiation of the insulin pump therapy.  

### Intravenous insulin infusion

Intravenous insulin infusion is useful in people who are critically ill, in hyperglycemic emergencies, those with uncontrolled hyperglycemia on SC insulin regimens, and during the perioperative phase, people with NBM status or during labor [17]. There are no absolute contraindications to using IV insulin infusion, and the important precaution to take is to avoid hypoglycemia. Hypokalemia is a potential problem during usage of IV insulin; hence serum potassium levels need to be monitored and replaced appropriately. IV insulin has a rapid onset of action and a very short half-life, allowing its dose to be easily titrated in response to changing blood glucose levels [17].

In hospitalized people, insulin is the quickest and most effective medication for attaining glycemic control.

### Indications of IV insulin

- Uncontrolled hyperglycemia despite the use of multiple SC insulin injections
- DKA or HHS
- During childbirth and before an emergency surgery
- People who are extremely ill, such as those with sepsis and septic shock
- People with NBM status, or who have inconsistent meal patterns in terms of timing or nature
- Perioperative period
- Organ transplantation
- High-dose glucocorticoid treatment
- Dose-finding strategy prior to conversion to SC insulin
The majority of hospitalized people, with and without serious illnesses should maintain a blood glucose target of 140–180 mg/dL. In cases where a lower target of 110–140 mg/dL may be achieved without causing significant hypoglycemia, such tight glucose targets may be considered [70]. On the other hand, for terminally ill people, people with significant comorbidities, and people in situations where frequent BGM is not practical or if one is concerned about hypoglycemia, one may accept a target of < 250 mg/dL [70]. Less severe insulin regimens are more suitable in these people to reduce glucosuria, dehydration, and electrolyte abnormalities. The use of a sliding scale SC insulin regimen is strongly discouraged in the inpatient hospital setting [70]. Ideally, BBR is the treatment of choice in non-ICU hospital settings. For the majority of noncritically ill hospitalized people who receive appropriate nourishment, an insulin regimen including basal, prandial, and correction components is the optimal course of treatment. Usually, all OADs have to be stopped and insulin is initiated at a very low threshold in hospitalized people. Few selective DPP4i may be continued where appropriate considering other comorbidities [70].

**Transition from intravenous to subcutaneous insulin**

A transition procedure is advised when stopping IV insulin since it is linked to decreased morbidity [70]. It may be appropriate to consider administering a person with T1D or T2D, a dose of SC basal insulin 2 hours before transitioning from an IV infusion to an SC regimen due to the short half-life of IV insulin and the delayed onset of action of SC basal insulin. Initiating SC basal insulin before stopping an IV insulin may help reduce hyperglycemia [71]. The insulin dosage is best determined based on the insulin infusion rate during the last 6 hours when stable glycemic objectives were met [72]. Usually, the last 6 hours’ IV insulin administered is multiplied by 4 to get the total SC insulin that is required over 24 hours. Of the total calculated daily SC insulin requirement, 40% is given as basal SC injection, and the rest 60% is divided into three doses of bolus SC insulin injections over a span of 24 hours. Whilst calculating this, other factors such as the IV fluids that were being administered such as IV dextrose, any inotropes, or corticosteroids that were being administered, need to be taken into consideration. There needs to be an overlap of 30 minutes of IV insulin, after SC bolus insulin is given while transitioning from IV to SC insulins [17].

Hypoglycemia is a crucial consequence that has to be minimized during hospitalization due to dysregulated metabolism and/or diabetes treatment. Each hospital should thus establish and put into practice a hypoglycemia prevention and management plan. If a person’s blood glucose level is < 70 mg/dL, a standardized hospital-wide, hypoglycemia treatment strategy ought to be in place [73]. Additionally, every person should have their unique strategy created for both avoiding and managing hypoglycemia [74].

**Recommendations**

| A | Insulin is the suggested treatment modality in hospitalized people. Few OADs such as selective DPP4i can be used safely in certain scenarios. |
| B | HbA1c test should be done in all people with diabetes/or hyperglycemia (blood glucose > 140 mg/dL) admitted to the hospital if not done in the past 3 months. |
| C | Insulin administration should be based on validated protocols that allow for adjustments of insulin dosage based on glycemic fluctuations. |
| D | Target glucose range for the majority of critically ill and non-critically ill people is 140–180 mg/dL and a more stringent goal of 110–140 mg/dL can be targeted for selected individuals if this can be achieved without hypoglycemia. |
| E | Ideally, BBR is the treatment of choice in non-ICU hospital settings. |
| F | The preferred treatment for non-critically ill hospitalized people with poor nutritional intake is basal insulin or a basal plus bolus correction insulin regimen. |
| G | For the majority of non-critically sick hospitalized persons who get adequate nourishment, an insulin regimen including basal, prandial, and correction components is the optimal course of therapy. |
| H | Use of sliding scale SC insulin regimen is strongly discouraged in the inpatient hospital setting. |
| I | In a critical care environment, and ideally, in individuals who are NBM, continuous IV insulin infusion is the best way to meet glycemic goals. |
| J | It should be ensured that there is continuity between IV insulin infusion and the first dose of SC insulin. There needs to be an overlap of 30 minutes while transitioning from IV to SC bolus insulins. |
| K | Once competency is demonstrated and appropriate supervision is available, people with diabetes who are capable of utilizing diabetes equipment, such as insulin pumps and CGM systems safely should be encouraged to do so while receiving inpatient care or during outpatient treatments. |
| L | While transitioning from the hospital to the ambulatory setting, a detailed discharge plan should be tailored to the individual with diabetes. |
Insulin therapy in special populations

Pregnancy

A. Pregnancy planning and preconception

All women of reproductive age with diabetes should be advised about the necessity of reaching and maintaining euglycemia as safely as possible prior to conception and throughout pregnancy. Family planning should be discussed, and effective contraception advice should be provided until a woman’s treatment regimen and HbA1c are optimal for pregnancy. Preconception counselling should emphasize the significance of obtaining glucose levels as near normal levels as safely achievable, preferably HbA1c < 6.5%, to lower the risk of congenital abnormalities, preeclampsia, macrosomia, premature birth, and other problems [74].

Prior to pregnancy, all drugs that are risky in pregnancy should be discontinued, including OADs [74]. When corticosteroids are used in pregnancy for fetal lung maturation or any other indication, BGM and proactive optimization of glycemic control using insulin are mandatory [75]. Insulin is the drug of choice for treating hyperglycemia in pregnancy [3, 74]. Metformin can be used in certain circumstances where clinically appropriate [3].

While GDM is the primary cause of hyperglycemia found in pregnancy, preexisting T1D and T2D account for most of the remaining [25]. Glucose targets for pregnant women with diabetes are FPG < 95 mg/dL, 1-hour PPG < 140 mg/dL, and 2-hour PPG < 120 mg/dL, whilst avoiding hypoglycemia. HbA1c should be used as a supplementary indicator of glycemic control during pregnancy [74]. CGM when used in conjunction with pre and postprandial BGM, aids in the achievement of glycemic control in GDM [74].

B. Gestational diabetes mellitus

It is recommended to initiate insulin along with lifestyle changes if nutrition treatment or a meal plan fails to help women with GDM achieve their blood glucose goals, usually within two weeks of starting them [76]. As insulin does not cross the placenta significantly, it is the preferred medication for treating hyperglycemia in GDM. When compared to regular in-person treatment alone, telehealth consultations in addition, for pregnant women with GDM may enhance outcomes [74]. Both insulin aspart and insulin lispro have been demonstrated to be safe and effective for usage during pregnancy [77]. BBR or insulin pump technologies can be used for T1D-complicated pregnancy. BBR is the regimen of choice; however, a premix regimen can be considered in a resource-constrained setting. Information on available insulin analogs and associated pregnancy categories are summarized in Table 5.

C. Pre-existing T1D or T2D

Insulin is the drug of choice for people with preexisting T1D and T2D in pregnancy as it does not cross the placenta, in significant quantity. Structured education about the prevention, detection, and treatment of hypoglycemia is vital before, during, and after pregnancy, in people with diabetes and their family members [74]. In a meta-analysis of three available RAA (insulin lispro, aspart, and glulisine, respectively) in pregnant women with T1D or GDM, insulin lispro, and insulin aspart were found to be safe and effective for both mother and fetus, with glycemic control at least as good as with regular human insulin [78]. Women with diabetes planning pregnancy or who have become pregnant should be counselled on the risk of development and/or progression of diabetic retinopathy [74].

D. Blood glucose monitoring during pregnancy

Frequent SMBG is necessary to guide the treatment of GDM. To achieve ideal glycemic targets, ADA recommends performing SMBG four times daily, (one fasting and 3 tests post breakfast, post lunch, and post dinner) in both GDM and pre-existing T1D and T2D. However, individuals with pre-existing T1D or T2D should monitor their blood glucose levels pre-prandial also, i.e., seven tests each day, (one fasting, three before and three after each meal) [74].

CGM, when used in conjunction with pre and postmeal BGM, can aid in achieving the glucose targets in pregnant women with diabetes. rtCGM when used in addition to BGM, helps to lessen macrosomia and new-born hypoglycaemia in pregnancies complicated by T1D. It is not recommended to utilize standard estimates of HbA1c or glucose control indicator calculations during pregnancy [74].

E. Postpartum care

Insulin resistance decreases significantly, immediately after childbirth. Hence, insulin requirements must be monitored carefully and insulin doses should be reduced in those with pre-existing DM or even stopped in those with GDM [74].

F. Lactation

For mothers with prior GDM, breastfeeding lowers their chance of acquiring T2D [74]. A change in insulin dosage may be necessary since nursing might cause nocturnal hypoglycemia. Breastfeeding women should be encouraged to follow an individualized diet. It is important to ensure that women with diabetes previously treated with insulin, understand that they are more likely to have hypoglycemia in the postpartum period, particularly if they are breastfeeding, and encourage them to have a snack between meals.
Recommendations

A. Preconception counselling should be incorporated into routine diabetes care for all women with T2D in the reproductive age group. A

B. Effective reversible contraception is recommended until the treatment regimen and HbA1c are optimized for pregnancy. A

C. Preconception counselling should cover the significance of establishing glucose levels as close to normal as possible, preferably HbA1c < 6.5% to lower the risk of congenital abnormalities, pre eclampsia, macrosomia, premature birth, and other problems. A

D. Once a woman with diabetes decides to plan pregnancy in the near future, medications need to be optimized. A

E. All oral medications used for glucose control other than metformin need to be stopped while planning pregnancy. B

F. Insulin is safe in pregnancy and may be started if required for optimal glucose control. A

G. Statins, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) need to be stopped. B

H. Women with diabetes planning pregnancy or who have become pregnant should be counselled on...
the risk of development and/or progression of diabetic retinopathy. B

I. Glucose targets for pregnant women with diabetes are FPG < 95 mg/dL, 1-hour PPG < 140 mg/dL, and 2-hour PPG < 120 mg/dL, whilst avoiding hypoglycemia. B

J. HbA1c is slightly lower in pregnancy; the ideal target in pregnancy is < 6% if it can be achieved without significant hypoglycemia. The target may be relaxed to < 7% in certain cases to prevent hypoglycemia. B

K. HbA1c targets in diabetes and pregnancy can be facilitated by CGM. B

L. Insulin is the drug of choice for treating hyperglycemia in GDM. Metformin can be used in certain circumstances where clinically appropriate. A

M. All insulins can be used in pregnancy. However, class B insulins are preferred over class C, class D. C

N. Regular insulin or RAA may be used in women with preexisting diabetes to improve PPG. B

O. BBR is the regimen of choice. However, premix can be considered in resource-constrained settings. B

P. In a pregnancy complicated by T1D, either BBR or insulin pump technology can be recommended. A

Q. When corticosteroids are used in pregnancy for fetal lung maturation or any other indication, BGM and proactive optimization of glycemic control using insulin is mandatory. E

R. In women with diabetes poorly controlled on BBR, consider initiation of CSII, ideally at preconception. A

S. An ideal SMBG would be seven tests each day, one fasting, three before and three after each meal. If this is not possible, encourage one fasting test, and three tests, that are performed daily two hours after breakfast, lunch, and dinner. C

T. Insulin resistance lowers significantly immediately following delivery, and insulin requirements must be monitored and reduced or stopped as appropriate in the postpartum period. C

U. Educate women with insulin-treated pre-existing diabetes about their higher risk of hypoglycemia in the postpartum period, particularly while breastfeeding, and advise them to have a snack between meals. B

Elderly

Diabetes is a highly heterogeneous condition and a major health concern among the elderly. Regular evaluations of the medical, psychological, functional, and social domains are necessary for managing diabetes in older persons [80]. When evaluating older persons who have diabetes, it is crucial to correctly classify the type of diabetes, as well as other elements including its duration, the presence of complications, other comorbidities, and treatment-related concerns like hypoglycemia and anxiety. Screening for diabetes complications in older persons should be tailored to each individual and repeated regularly as the findings of screening tests may influence targets and treatment methods [80].

Episodes of hypoglycemia should be identified and treated during every visit. Older persons are more likely to have hypoglycemia for a variety of reasons, including insulin deficiency, which necessitates insulin treatment, and growing renal insufficiency. CGM is advised for older people with T1D and T2D to lessen hypoglycemia and to enhance glycemic outcomes and reduce glucose variability [80].

A. Glycemic targets in elderly people

Elderly adults with no coexisting chronic illnesses as well as unimpaired cognitive function and a good functional status may aim for stringent glycemic goals (HbA1c < 7.0–7.5%) if achievable without hypoglycemia. Older adults with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less stringent goals (HbA1c < 8.0%). Glycemic targets may be reduced for the elderly as part of individualized therapy [80].

It is important to avoid overtreating elderly persons with diabetes. It is advised that complex treatment regimens (particularly insulin) are simplified to lower the risk of hypoglycemia and for convenience. Polypharmacy needs to be avoided, wherever feasible, to reduce pill burden, drug interactions, and cost [80].

The usage of pens over syringes and analog insulins over human insulin needs to be considered for safety, flexibility, and convenience in the geriatric population. Telemmedicine consultations offer convenience and continuity of care for diabetes, especially for the elderly, similar to pregnancy. Costs of care need to be considered when designing treatment plans, to limit cost-related obstacles to adherence [80].

Recommendations

A. For older adults on insulin, CGM can be recommended where appropriate. A

B. Elderly adults with no coexisting chronic illnesses as well as unimpaired cognitive function and a good functional status may aim for stringent glycemic goals (HbA1c < 7.0–7.5%) if achievable without hypoglycemia. C
Insulin therapy during fasting

Many people with diabetes fast for religious reasons, increasing the risk of severe hypoglycemia. Insulin resistance/deficiency during fasting might result in excessive glycogen breakdown and increased gluconeogenesis [81]. When using insulin therapy during religious fasting, the person must be informed about the hazards associated with fasting, made familiar with SMBG, follow the recommended diet, engage in safe exercise, and modify their insulin doses accordingly [82]. People with T2D on intensive insulin therapy should be advised to refrain from fasting.

Individuals with a history of DKA, recurrent hypoglycemia, hypoglycemic unawareness, people on complex insulin regimes, people with end-organ damage, people with suboptimal glycemic control, pregnant and lactating women, people with T1D, and elderly individuals should be discouraged from fasting [82]. Individualized physician recommendations for changing the dose and timing of insulin injections during the fasting interval should be followed.

During fasting, frequent SMBG or CGM is indicated to reduce the risk of hypoglycemia and detect episodes of hyperglycemia. Planning meals with low glycemic index CHOs that include fruits, vegetables, and lean meats is necessary during fasting days. Sweets, sweetened beverages, and fried meals should be avoided [83]. CHO counting during meals assists in optimizing the dosage of insulin administration. During non-fasting hours, it is recommended to stay hydrated by sipping water and other non-sweetened beverages frequently. If hypoglycemia develops, the person should be advised to break the fast immediately, irrespective of the time [83]. Structured patient education about BGM, nutritional advice, exercise advice, medication dosage and timing, adjustments, symptoms of complications, and how to treat them is recommended [83].

Recommendations

A. People with T2D who are on intense insulin treatment should avoid fasting. B
B. More frequent BGM is recommended while fasting to reduce the risk of hypoglycemia and detect episodes of hyperglycemia. B
C. Individuals with a history of DKA, recurrent hypoglycemia, hypoglycemic unawareness, people on complex insulin regimes, people with end-organ damage, people with suboptimal glycemic control, pregnant and lactating women, people with T1D, and elderly individuals should be discouraged from fasting. A
D. Structured and individualized patient education about BGM, nutritional advice, exercise advice, medication dosage and timing, adjustments, symptoms of complications, and how to treat them is recommended. It should also include when to break a fast in order to minimize complications. E

Sick day management

Sickness is frequently associated with elevated blood glucose levels and an increased risk of ketoacidosis in those with T1D and others with DM who are insulin-dependent [49]. Insulin requirement increases significantly during acute sickness which eventually requires increased frequency of BGM. Depending on their glucose levels, people may require RAA, every 2 to 4 hours [25]. Additionally, ketone testing during sickness may aid in the management of individuals suffering from acute vomiting or hyperglycemia. It is critical to recognize the early signs and symptoms of DKA to prevent it [25]. Individuals and/or carers who suspect it should contact their doctor as soon as possible.

During an illness, the following are important to remember in those with T1D and others with DM who are insulin dependent. Check blood glucose levels periodically at least every four hours or more frequently if necessary. If blood glucose levels are consistently high (> 250 mg/dL) or if the person has vomiting, stomach discomfort, or rapid breathing, it is recommended to check for blood or urine ketones [49]. The person should be sent to the hospital right away if they have high ketones (> 17.43 mg/dL)/diarrhea more than three times in 24 hours or a temperature above 101°C for 24 hours [49].
In case of low blood glucose levels, a small dosage of glucagon or consuming CHO's and/or juices regularly is recommended. To maintain adequate calorie intake, drinking more calorie-free liquids, semi-solid meals, and beverages, such as thin soups, milk, buttermilk, or fresh lime juice, should be encouraged [49]. However, individuals should be encouraged to eat normally if they can tolerate it. Insulin doses may be lowered but should not be skipped entirely. Never stop insulin completely, especially basal insulin, as this is a typical error. If in doubt about managing during sick days, it is recommended to seek an expert opinion immediately [49].

**Recommendations**

A. In people with insulin-dependent diabetes, during sick days, it is recommended to continue taking insulin with dose adjustments. B

B. Individuals need to be advised to check their blood glucose and ketone levels at least every four hours and to keep track of the findings. B

C. Drinking more calorie-free liquid is recommended. However, persons should strive to eat normally if tolerated. C

D. Low blood glucose can be treated with a small dosage of glucagon or by consuming CHO's and/or juices on a regular basis. C

E. Although insulin dosages can be decreased, complete stoppage of insulin is dangerous, especially basal insulin. B

F. Maintaining an adequate calorie intake, semi-solid meals, and beverages, such as thin soups, milk, buttermilk, or fresh lime juice, should be encouraged. B

G. To control the elevated blood glucose levels, the insulin dosage may need to be raised, and extra doses of fast-acting insulin may be required. B

H. If blood glucose remains consistently high (> 250 mg/dL), it is important to check blood or urine ketones in all insulin-dependent patients with diabetes during sick day periods. B

I. The person should be sent to the hospital right away if they have high ketones (> 17.43 mg/dL)/diarrhea more than three times in 24 hours or a temperature above 101°C for 24 hours or clinically unwell. A

**Safety precautions for insulin users who drive**

**Disclaimer:** It is strongly advised that individuals with diabetes should strictly adhere to the law of the land and follow their clinician’s advice. These recommendations here are only a guide made based on the best available clinical evidence and consensus of the Association of Clinical Endocrinologists group.

The ability to drive safely in people with diabetes may be hampered by its symptoms or consequences, which can affect driving fitness in a variety of ways, including but not limited to hypoglycemia, hyperglycemia, vision impairment, peripheral neuropathy, and other diabetes problems. Furthermore, driving necessitates a high metabolic demand, which may lead to hypoglycemia episodes in individuals with diabetes which might result in driving errors and road traffic accidents [84]. Hence, precautions ought to be taken to protect themselves, co-passengers, and other road users.

People with diabetes should be advised to always have their glucometer, blood glucose strips, or CGM with them. It is recommended to check their blood glucose levels before the trip and for every two hours after they start driving. Frequent testing may be essential if there is a higher risk of hypoglycemia for any reason, such as after physical exercise or a change in meal schedule. If the blood glucose values are ≤ 90 mg/dL, it is recommended to advise them to have a snack. “Never drive if blood glucose is in the hypoglycemic range or if the person feels hypoglycemic” should be the dictum [85].

It is recommended to always maintain an emergency supply of fast-acting CHO's, such as glucose, or sweets, or chocolates, in the vehicle. The person needs to be advised to consume regular meals and snacks and take breaks during long journeys. It is recommended to always avoid alcohol while driving [85].

**Recommendations**

A. **Disclaimer:** It is strongly advised that individuals with diabetes should strictly adhere to the law of the land and follow their clinician’s advice. A

B. Hypoglycemia in individuals who are on insulin medication or other antidiabetic therapy is detrimental. Hence, precautions should be taken to protect themselves, co-passengers, and other road users. A

C. People with diabetes should be advised to always have their glucometer, blood glucose strips, or CGM with them. B

D. Individuals need to be advised to check their blood glucose before the trip and for every two hours after they start driving. B

E. There should be a maximum of 2 hours between the pre-driving glucose check and the first glucose check after driving has begun. B
F. If there is a higher risk of hypoglycemia for any reason, such as after physical exercise or a change in meal schedule, more frequent testing may be necessary. C

G. If the blood glucose values are \( \leq 90 \text{ mg/dL} \), it is recommended to advise them to have a snack. Never drive if blood glucose is in the hypoglycemic range or if the person feels hypoglycemic. B

H. It is recommended to always maintain an emergency supply of fast-acting CHOs, such as glucose or sweets, or chocolates in the vehicle. B

I. Individuals need to be advised to consume regular meals and snacks and take breaks on long journeys. Always avoid alcohol while driving. A

J. If a person suffers a hypoglycemic attack while driving, they should not start driving until 45 minutes after their glucose level has recovered to normal (at least 90 mg/dL) and also feeling absolutely normal. B

### Alcohol and insulins

People with diabetes who consume alcohol should be advised to avoid or limit alcohol intake [55]. Alcohol intake is associated with risks such as weight gain, hyperglycemia (for those who consume excessive quantities of CHO-rich drinks), and hypoglycemia (especially for those taking insulin or insulin secretagogue therapy) [86].

Individuals with diabetes should be educated about the indications, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially spirits, and if they are on insulin or insulin secretagogues [87]. It is also important to emphasize the need of glucose monitoring after consuming alcoholic drinks in order to limit the risk of hypoglycemia [86].

### Recommendations

**A. People with diabetes who drink alcohol should be advised to avoid or limit alcohol intake and those who smoke should be advised smoking cessation and not to use any tobacco products. C**

**B. It is recommended that all individuals with diabetes who are on insulin should have healthy snacks before consuming any alcohol drinks that are high in alcohol percentage, to avoid hypoglycemia. B**

**C. Certain alcohol beverages rich in CHOs, such as sweet cocktails may cause spike in blood glucose which warrants insulin dose adjustments with appropriate BGMs. C**

## Alcohol and insulins

People with diabetes who consume alcohol should be advised to avoid or limit alcohol intake [55]. Alcohol intake is associated with risks such as weight gain, hyperglycemia (for those who consume excessive quantities of CHO-rich drinks), and hypoglycemia (especially for those taking insulin or insulin secretagogue therapy) [86].

Individuals with diabetes should be educated about the indications, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially spirits, and if they are on insulin or insulin secretagogues [87]. It is also important to emphasize the need of glucose monitoring after consuming alcoholic drinks in order to limit the risk of hypoglycemia [86].

### Recommendations

**A. People with diabetes who drink alcohol should be advised to avoid or limit alcohol intake and those who smoke should be advised smoking cessation and not to use any tobacco products. C**

**B. It is recommended that all individuals with diabetes who are on insulin should have healthy snacks before consuming any alcohol drinks that are high in alcohol percentage, to avoid hypoglycemia. B**

**C. Certain alcohol beverages rich in CHOs, such as sweet cocktails may cause spike in blood glucose which warrants insulin dose adjustments with appropriate BGMs. C**
Overall, a lacune exists in the literature concerning recommendations for adjusting insulin therapy when initiating HD or PD, or when switching between the two.

C. Cardiovascular disease

The link between insulin and cardiovascular disease (CVD) is complicated. People with diabetes are more likely to develop CVD and its related clinical consequences. Premix insulins are more successful in lowering PPG than basal insulin analogs [15]. The insulin regimen selected should be individualized and based on the severity of hyperglycemia, the risk of hypoglycemia, and the possibility of interventional operations in the near future. If the glycemic objective is not met after adding basal insulin, a basal plus/premix regimen should be explored before moving on to a BBR [25].

People with T2D who are receiving combination treatment with premix insulin analogs and OADs should be closely evaluated for signs and symptoms of heart failure (HF), weight gain, and edema, and quick clinical intervention is advised if cardiac symptoms worsen [15]. Wherever appropriate, concomitant SGLT2i and/or GLP-1RA use along with insulins helps reduce the TDD of insulin, lessen weight gain and hypoglycemic episodes.

D. Post-transplantation diabetes mellitus (PTDM)

An acceptable step-by-step method for the management of late PTDM is lifestyle change followed by OADs and insulin. People with acute post-transplant hyperglycemia, however, should be managed in the opposite order from how it appears above [25]. Insulin is the drug of choice for the management of hyperglycemia, PTDM [10]. During the initial few months following transplantation, insulin treatment should be favored [25].

E. Post-immunotherapy new-onset diabetes (PINOD)

In general, less than 1% of individuals who receive immunotherapy develop new-onset DM [25]. Insulin is recommended as the preferred treatment for these individuals [25].

F. Glucocorticoid-induced hyperglycemia (GIH)

GIH and glucocorticoid-induced diabetes are linked to higher rates of mortality and morbidity and may have exacerbated long-term microvascular and macrovascular risks. The co-existence of inflammatory disorders and GIH further increases the risk of CVD. The coronavirus disease 2019 (COVID-19) pandemic has increased the clinical importance of glucocorticoid treatment by increasing the number of hospital admissions for acute viral infection. It has been demonstrated that COVID-19 increases the incidence of hyperglycemia and is linked to greater incidences of DKA, HHS, and new-onset diabetes. All patients undergoing high-dose glucocorticoid medication should have BGM for at least 48 hours after cessation of glucocorticoid treatment, and SC insulin therapy should be initiated as needed. The type of glucocorticoid and duration of action must be considered in determining insulin treatment regimens. For individuals who are on higher doses of glucocorticoids, an increase in the dosage of prandial and correctional insulin may be needed in addition to basal insulin [93]. The dose of correctional insulin is based on the dose of the administered glucocorticoid and the weight of the person [94].

Recommendations

A. Insulin analogs should be considered in people with T2D and hepatic impairment for enhanced glycemic control with minimal risk of hypoglycemia.

B. All insulins are considered safe across the spectrum of CKD. However, ultralong and ultrashort-acting insulins are preferred for safety, flexibility, and convenience.

C. It is recommended to consider lowering the basal insulin dosage by up to 25% on days of HD to avoid hypoglycemia.

D. Individuals undergoing HD are usually advised to avoid short-acting insulins during and immediately before HD.

E. In people undergoing PD, an increase of insulin dose up to 30% may be necessary to minimize the effects of dextrose absorption for the PD fluid. If possible, non-dextrose fluids to be used in lieu of dextrose-containing dialysis fluids.

F. In CKD people with GFR between 15–60 mL/min and < 15 mL/min, prompt adjustments with a reduction to 75% and 50% in insulin TDD respectively are often necessary. However, in individuals with GFR > 60 mL/min, no dose modifications may be required.

G. Insulin therapy is preferred during the first 1–2 months after transplantation along with appropriate OADs.

Future of insulins

The use of insulin therapy is crucial in the management of DM. SC injection is still the most common method for administering insulin. However, because of the short half-life of insulin, a person must endure many injections throughout the day to effectively regulate their blood glucose levels. This results in significant inconvenience and low compliance. Numerous initiatives have been attempted to enhance insulin administration, including the development of non-invasive routes, which mainly include buccal, oral, pulmonary, nasal, and trans-
We are expecting the launch of newer insulins in India soon which are already available in the USA and Europe but not yet available in India. On the other side, “biosimilar” refers to a protein molecule that is a perfect duplicate of already-existing insulin with the same amino acid sequence (except for small alterations in therapeutically relevant components) and no appreciable differences in efficacy and safety [15].

The advantage of biosimilar insulins is their low cost which makes them affordable for the majority. However, immunogenicity is a concern [96]. When switching from one kind of insulin to another insulin that are identical (biosimilar), it is recommended to carry out a dosage titration, always starting with a lower dose and up-titrating it to minimize hypoglycemia, with BGM [15].

**Article information**

**Data availability statement**

The initial stage was the development of recommendation statements following a comprehensive literature review using PubMed and other online resources for clinical studies, existing guidelines, review articles, consensus statements, and national and international standards on insulin therapy in adults with diabetes. The relevant data was retrieved and reviewed, recommendation statements were developed and compiled into a Microsoft Excel sheet.

While taking the American Diabetes Association (ADA), National Institute for Health and Care Excellence (NICE), European Association for the Study of Diabetes (EASD), The International Society for Pediatric and Adolescent Diabetes (ISPAD), American Association of Clinical Endocrinologists (AACE) guidelines and other peer-reviewed evidence-based guidelines and consensus statements into consideration, the expert panel comprising 16 practicing endocrinologists from the Association of Clinical Endocrinologists has drafted new recommendations with specific consideration for the Indian milieu keeping in mind the resources available to the general physician or a general practitioner.

**Conflict of interest**

The authors declare no conflict of interest.

**Funding**

Supported by an unrestricted educational grant from Cipla. Apart from the sponsorship, Cipla had no role in the development of this guideline and their drugs were not/will not be given any preferences.

**Authors contributions**

Ravi Sankar Erukulapati: prime author; lead of the Consensus Group, coordinated the entire process, drafted recommendation statements for rounds 1, 2, and 3.

Ravi Sankar Erukulapati and Murali Ganguri participated in the drafting of recommendation statements for rounds 1, 2, and 3.

All authors participated in rounds 1, 2, and 3 of modified Delphi process.

All authors participated in writing up the Consensus document.

Editorial assistance from Dr. Subhadra Polisetti, Dr. Satya Parvathi K, and Dr. Vamsi Krishna Kolukula from Medswan Global Healthtech Private Limited.

**Acknowledgments**

All the members of the Consensus Group are practicing clinicians who have had various professional engagements with numerous pharmaceutical companies across the world over the past several years. Editorial assistance was provided by Dr. Subhadra Polisetti, Dr. Satya Parvathi K, and Dr. Vamsi Krishna Kolukula from Medswan Global Healthtech Private Limited, along with Dr. Santhosh Oley Sathyarayananaya.

**REFERENCES**


Association of Bone Turnover Biomarkers and Subclinical Atherosclerosis in Subjects with Type 2 Diabetes: A Case-Control Study

**ABSTRACT**

Objective: The current study aims to assess the relationship between serum osteocalcin (OCN) and osteoprotegerin (OPG) levels and subclinical atherosclerosis.

Material and methods: This case-control study included 80 male subjects divided into 2 groups: 40 subjects with type 2 diabetes (T2D) without coronary artery disease and 40 control subjects without diabetes. To assess the association of OCN and OPG with subclinical atherosclerosis (defined as carotid intima-media thickness (cIMT) ≥ 0.9mm), multivariable linear regression models were applied.

Results: The mean age in the diabetes group was 54.1 ± 5.1 years while in the control group, it was 53.7 ± 6.6 years. The mean serum OCN level was significantly negatively correlated with hs-CRP, cIMT, HbA1c and FPG in the total sample (p = 0.001, < 0.001, < 0.001 and 0.006 respectively) while OPG level was significantly positively correlated with age and HbA1c (p = 0.047 and 0.009 respectively) in the total sample. Age and HbA1c were the only independent risk factors identifying subclinical atherosclerosis in multivariate analysis. A cut-off value of serum OCN level of ≤ 22 ng/mL was able to discriminate patients with subclinical atherosclerosis in the total sample (p = 0.003*) using receiver operator characteristic (ROC) curve analysis. Serum OCN level was significantly lower in the subclinical atherosclerosis group than in the control while OPG showed no significant difference between both groups.

Conclusions: OCN may be a better marker for subclinical atherosclerosis than OPG. This effect is attenuated in the presence of DM. (Clin Diabetol 2024; 13, 1: 43–51)

Keywords: atherosclerosis, osteocalcin, osteoprotegerin, carotid intima-media thickness, subclinical atherosclerosis

**Introduction**

Type 2 diabetes (T2D) is a multifactorial metabolic disease characterized by hyperglycemia that results predominantly from insulin resistance (IR) [1]. Patients with diabetes are at a higher risk of accelerated atherosclerosis, which is the major cause of cardiovascular morbidity and mortality [2].

Moreover, the accelerated atherosclerosis was attributed to several metabolic and vascular derangements. The presence of a pro-inflammatory state is highly responsible for driving the progression of accelerated atherosclerosis. Several vascular changes arise starting with endothelial dysfunction, in addition to platelet abnormalities and arterial smooth muscle changes along with the deposition of advanced glycated end-products (AGEs) resulting from long-standing hyperglycemia [3].

Address for correspondence:
Heba Sadek Kassab
Unit of Diabetes and Metabolism, Department of Internal Medicine, Faculty of Medicine, Alexandria University, 17 Champollion Street, El Messallah, Alexandria 21131, Egypt, Phone: +20 1005536874, e-mail: heba.kassab@alexmed.edu.eg

Clinical Diabetology 2024, 13; 1: 43–51
DOI: 10.5603/cd.98236
Received: 16.11.2023 Accepted: 13.12.2023
Early publication date: 12.01.2024

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.
Evidence is mounting for the relationship between atherosclerotic cardiovascular diseases (ASCVD) and bone metabolism [4, 5]. Among the early indicators of ASCVD is the detection of an increased carotid intima-media thickness (cIMT) [6]. It is suggested that atherogenic pathways modulate the arterial smooth cells into osteoblast-like cells. The transformed osteoblast-like cells produce several markers including osteoprotegerin (OPG), which in turn result in the advancement of vascular calcification [7]. OPG plays a role in bone mineralization by inhibiting RANKL and osteoclast recruitment [8]. In addition, bone remodeling is influenced by the adipose tissues through the leptin release and effects on osteoblasts. Thus, the bone system is suggested to be linked to energy metabolism, supporting the hypothesis of the endocrinal function of bones [9].

Osteocalcin (OCN) is another marker produced by osteoblastic cells and implicated in the development of bones [10]. OCN plays a vital role in glucose homeostasis and insulin sensitivity, explained by regulating the expression of an adipose-related gene [11, 12]. Several studies suggested the role of osteocalcin in the formation of atherosclerotic plaques, and the calcification of the coronary arteries [13, 14]. However, conflicting data exists regarding the direct role of OCN in endothelial and smooth muscle cell function [15].

Therefore, we aimed to shed light on the relationship between subclinical atherosclerosis and the serum levels of bone turnover biomarkers OCN and OPG and to investigate their values as early markers of ASCVD.

Materials and methods

Study design
This study is a case-control study.

Study participants
The present study included 80 male subjects. Subjects were recruited from those undergoing coronary angiography for a justified indication at the cardiology department, Alexandria University, and proved to be free of atherosclerotic coronary artery disease (ACAD).

The participating subjects were divided into two groups:
- group I: 40 subjects with T2D (diagnosis of diabetes according to the American Diabetes Association criteria) [1] aged 44–67 years;
- group II: 40 age-matched control subjects without diabetes aged 42–72 years.

Exclusion criteria
We excluded subjects with a history of an established ASCVD, including cerebrovascular strokes, a history of ACAD, and peripheral arterial diseases.

Patients with a history of an endocrinal disease other than T2D, any bone disorder, or metabolic diseases, and subjects with a recent history of infection within the last 2 months were also excluded from the study. Based on previous studies, female subjects were excluded from the study to avoid any bias in OCN level related to female hormonal changes and sex differences in atherosclerosis [16, 17].

Ethical approval
The study was approved by the ethics committee of Alexandria University following the criteria set by the Declaration of Helsinki. The participating subjects signed an informed consent at the beginning of the study.

Materials and methods

Clinical assessment
A detailed history taking was performed focusing on the history of diabetes. Anthropometric measures were taken including BMI calculation (weight in kg divided by the height in m²). The waist circumference (WC) and the hip circumference were measured, and the waist-to-hip ratio (W/H) was calculated as the ratio between the waist measurement and the hip measurement.

Assessment of ankle-brachial index (ABI)
Hand-held Doppler was applied to assess both the dorsalis pedis (DP) and posterior tibial (PT) arteries. The systolic pressure of the PT and DP arteries of each leg was measured using a Doppler probe of 5 MHz (Nicolet Elite 200 R, VIASYS Healthcare Inc., Madison, WI, USA). The lower value of the two calculated ABI ratios in both limbs was applied for statistical analysis [18].

Biochemical analysis
Blood samples were collected in the morning (8.00–10.00 a.m.) of the same day as the coronary angiography after an overnight fast of 10–12 hours. All subjects were advised not to smoke or exercise strenuously during the fasting period.

The collected venous samples were divided into 2 parts; one part in a plain vacutainer tube left to clot at 37°C. sera were separated by centrifugation and divided into 2 parts, one used for immediate assay of fasting plasma glucose (FPG), HbA1c, ALT, hs-CRP, insulin level, total cholesterol, triglycerides and HDL cholesterol. LDL cholesterol was calculated using the Friedewald formula. The other part was kept at −70°C for assay of OCN. Serum OCN was determined using sandwich-type
enzyme labeled immunoassay (Assay kit ab195214, USA) according to the manufacturer’s instructions. OCN measurements are reported in ng/mL. The serum OPG level was measured using an ELISA assay kit according to the manufacturer’s instructions. Homeostasis Model Assessment 2 (HOMA2) calculator was used to estimate insulin resistance (%S) (HOMA2-IR).

Measurement of the carotid intima-media thickness (cIMT)

All the study subjects were subjected to carotid duplex scanning of both carotid arteries. Using a high-resolution 7–12 MHz linear transducer in B mode (Philips ClearVue 350), the intima-media thickness (IMT) was measured on the common carotid artery. cIMT of the far wall was specified as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface. We assessed three sites on each side and the average was calculated for the cIMT: thickest point and at sites 1 cm upstream and downstream, free from plaques on the longitudinal views. A measure of cIMT ≥ 0.9 mm was identified as a marker of subclinical atherosclerosis [19].

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. The chi-square test was applied to investigate the association between the categorical variables. Alternatively, Fisher’s Exact or Monte Carlo correction test was applied when more than 20% of the cells had an expected count of less than 5. For continuous data, they were tested for normality by the Kolmogorov-Smirnov test. Quantitative data were expressed as mean and standard deviation (SD). Mann-Whitney test was used to compare two groups for not normally distributed quantitative variables. Student t-test was used to compare two groups for normally distributed quantitative variables, and Spearman coefficient was used to assess the correlation between two distributed abnormally quantitative variables.

Logistic regression analysis was used to detect the strongest risk factors discriminating atherosclerosis (cIMT ≥ 0.9 mm) in the total sample and diabetes group. The diagnostic performance of the markers was determined by the receiver operating characteristic curve (ROC), where an area greater than 50% defined acceptable performance, and an area of nearly 100% was considered the best performance for the test. The significance of the obtained results was judged at the 5% level.

Results

Baseline demographic and clinical characteristics of the study population

The mean age of the subjects in the T2D group was 54.1 ± 5.1 years while in the control group, it was 53.7 ± 6.6 years with no statistically significant difference. The mean diabetes duration in the T2D group was 11.1 ± 6.3 years. Subjects with T2D had significantly higher levels of OPG, hs-CRP and cIMT and significantly lower OCN and ABI than the control group. A comparison between the two studied groups is shown in Table 1.

Relationship of OCN & OPG serum levels with the studied parameters

The mean serum OCN level was significantly negatively correlated with hs-CRP, cIMT, HbA1c and FPG in the total sample (p = 0.001, < 0.001, < 0.001 and 0.006 respectively) and significantly negatively correlated with age and cIMT (p = 0.005 and 0.001, respectively) in the control group. However, there were no significant correlations between serum osteocalcin levels and the studied parameters in the diabetes group. On the other hand, the mean serum OPG level was significantly positively correlated with age and HbA1c (p = 0.047 and 0.009 respectively) in the total sample and significantly positively correlated with age (p = 0.003) in the diabetes group while in the control group, the mean serum OPG level was significantly positively correlated with total cholesterol, HDL-C and LDL-C (p = 0.010, 0.046 and 0.029 respectively).

On performing univariate logistic regression analysis to identify risk factors of subclinical atherosclerosis (cIMT ≥ 0.9 mm), age, smoking, OCN, HbA1c, FPG and UACR were the independent risk factors in the total sample. However, only age and HbA1c were the independent risk factors of subclinical atherosclerosis in multivariate analysis (Tab. 2). On the other hand, in the diabetes group, only HbA1c was the independent risk factor of subclinical atherosclerosis in univariate logistic regression analysis. (Data not depicted).

Sensitivity and specificity of OCN & OPG to identify subclinical atherosclerosis

Serum OCN level was able to discriminate patients with subclinical atherosclerosis in the total sample (p = 0.003*) with a cut-off value of ≤ 22 ng/mL with good sensitivity, specificity, and AUC (64.71, 63.04 and 0.696, respectively) (Fig. 1). Regarding the control group, a cut-off value of serum OCN level ≤ 25 ng/mL was set discriminating patients with subclinical atherosclerosis (p = 0.001*) with better sensitivity, specificity, and AUC (87.50, 68.75 and 0.873, respectively) while in diabetes group there was no significant discrimina-
tion between patients with subclinical atherosclerosis and those without (p=0.580). On the contrary, OPG failed to discriminate against patients with subclinical atherosclerosis in the 3 studied groups.

The total sample (n = 80) was re-classified according to cIMT into 2 groups: a group with subclinical atherosclerosis (cIMT ≥ 0.9 mm) and a control group. Serum OCN level was significantly lower in the subclinical atherosclerosis group than control while OPG showed no significant difference between groups. A comparison between the 2 groups is shown in Table 3.

Discussion

Previous data supported the endocrine capacity of bone and its role in glucose and lipid metabolism. OCN and OPG are well-known bone turnover biomarkers. Their relation to vascular calcification in patients with vascular diseases such as myocardial infarction and diabetes was previously thoroughly studied. However, its relation to subclinical atherosclerosis in males without ACAD (proved by coronary angiography) has not been studied yet.

The present study showed a significantly lower level of OCN and significantly higher OPG level in the diabetes group than in the control group. This supports that diabetes is a state of low bone turnover. In agreement with the results of the present study, Hygum et al.’s [20] results showed significantly higher OPG and significantly lower OCN levels in patients with diabetes. Another study by Starup-Linde et al. [21] showed significantly lower OCN levels in patients with diabetes. They also observed higher levels of plasma OPG level in patients with increasing plasma glucose levels.

The current study showed a significant negative correlation of serum OCN level with hs-CRP, cIMT, HbA1c and FPG in the total sample and a significant negative correlation of OCN with age and IMT in the control group suggesting its important association with atherosclerosis, inflammation and diabetes. In agreement with the results of the present study, a study by Seidu et al. [22] stated an inverse association between OCN and cIMT and the risk of atherosclerotic outcome and CVD. Moreover, the Changfeng study [23] which included male participants with normal glucose tolerance, disclosed the presence of an independent association between serum OCN and carotid atherosclerosis in this cohort. Furthermore, in euglycemic males, carotid plaque prevalence decreased significantly with

**Table 1. Comparison between the Two Studied Groups According to Different Parameters**

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>Group I (diabetes) (n = 40)</th>
<th>Group II (control) (n = 40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>54.1 ± 5.1</td>
<td>53.7 ± 6.6</td>
<td>0.763</td>
</tr>
<tr>
<td>Smoker [%]</td>
<td>29 (72.5%)</td>
<td>12 (30%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>DM duration [years]</td>
<td>11.1 ± 6.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPG [ng/mL]</td>
<td>506.4 ± 488.5</td>
<td>266.7 ± 272.7</td>
<td>0.029*</td>
</tr>
<tr>
<td>OCN [ng/mL]</td>
<td>20.3 ± 11.2</td>
<td>31 ± 13</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>hs-CRP [mg/L]</td>
<td>12.3 ± 11.2</td>
<td>5.3 ± 6.1</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>cIMT [mm]</td>
<td>0.95 ± 0.20</td>
<td>0.71 ± 0.18</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>FPG [mg/dL]</td>
<td>140.7 ± 76.1</td>
<td>92.5 ± 18.9</td>
<td>0.005*</td>
</tr>
<tr>
<td>HbA1c [%] (mmol/mol)</td>
<td>8.6 (70) ± 2</td>
<td>5.7 (39) ± 0.5</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>ABI</td>
<td>0.99 ± 0.08</td>
<td>1.05 ± 0.09</td>
<td>0.001*</td>
</tr>
<tr>
<td>Total cholesterol [mg/dL]</td>
<td>164.1 ± 44.8</td>
<td>167.8 ± 43.6</td>
<td>0.707</td>
</tr>
<tr>
<td>TG [mg/dL]</td>
<td>146.3 ± 52.4</td>
<td>131.4 ± 64.8</td>
<td>0.166</td>
</tr>
<tr>
<td>HDL-C [mg/dL]</td>
<td>36.5 ± 13.5</td>
<td>43.3 ± 16.4</td>
<td>0.048*</td>
</tr>
<tr>
<td>LDL-C [mg/dL]</td>
<td>98.3 ± 36.8</td>
<td>98.3 ± 32.3</td>
<td>0.994</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>28.4 ± 3.5</td>
<td>27.1 ± 3.6</td>
<td>0.104</td>
</tr>
<tr>
<td>WC [cm]</td>
<td>100.6 ± 4.6</td>
<td>97.5 ± 6.4</td>
<td>0.015*</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.97 ± 0.02</td>
<td>0.95 ± 0.03</td>
<td>0.005*</td>
</tr>
<tr>
<td>Albuminuria [%]</td>
<td>12 (30%)</td>
<td>0 (0%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>HOMA2IR</td>
<td>1.67 ± 1.68</td>
<td>1.54 ± 1.21</td>
<td>0.946</td>
</tr>
</tbody>
</table>

*Statistically significant at p ≤ 0.05

ABI — ankle-brachial index; BMI — body mass index; cIMT — carotid intima-media thickness; DM — diabetes mellitus; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; HDL-C — high-density lipoprotein cholesterol; HOMA2IR — Homeostasis Model Assessment 2 of insulin resistance; hs-CRP — high-sensitivity C-reactive protein; LDL-C — low-density lipoprotein cholesterol; OCN — osteocalcin; OPG — osteoprotegerin; SD — standard deviation; TG — triglycerides; WC — waist circumference
Increased OCN levels. Another study by Pennisi et al. [24], where half of their patients had DM, reported an association between lower serum levels of OCN and disorders in carotid arteries.

Moreover, Xu et al. [25] also found a significant negative correlation between OCN and cIMT in the total sample. Additionally, Zhang et al. [26] found a significant negative correlation between OCN, HbA1c and FPG. Bao et al. [17] similarly found that serum OCN levels had a significant negative correlation with HbA1c, FPG, BMI and HOMA-IR. These results go hand in hand with the results of the current study reflecting the important role played by OCN in the triad of diabetes, inflammation and atherosclerosis.

On the other hand, Reyes-Garcia et al. [27] found no significant correlation between OCN, BMI, HbA1c or FPG. However, they reported that serum OCN is an independent predictor of coronary heart disease in logistic regression analysis. On the contrary, Millar et al. [28] found no significant difference in OCN levels between patients with atherosclerosis and the control group. This discordance between their findings and our results may reflect the role of OCN in subclinical but not established atherosclerosis. Another study by Luo et al. [29] found no association between OCN and cIMT in the metabolically healthy Chinese population. This difference between their study and ours may arise from different study populations and methodologies.

### Table 2. Univariate and Multivariate Logistic Regression Analysis to Detect the Strongest Risk Factors Discriminating Subclinical Atherosclerosis (cIMT ≥ 0.9 mm) in the Total Sample (n = 80)

<table>
<thead>
<tr>
<th></th>
<th>OR (LL–UL 95% CI), p</th>
<th>OR (LL–UL 95% CI), p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [years]</strong></td>
<td>1.137 (1.040–1.242), p = 0.005*</td>
<td>1.159 (1.033–1.301), p = 0.012*</td>
</tr>
<tr>
<td><strong>Smoker [%]</strong></td>
<td>4.094 (1.583–10.587), p = 0.004*</td>
<td>2.625 (0.755–9.125), p = 0.129</td>
</tr>
<tr>
<td><strong>DM duration [years]</strong></td>
<td>1.103 (0.987–1.234), p = 0.084</td>
<td></td>
</tr>
<tr>
<td><strong>OPG [ng/mL]</strong></td>
<td>1.00 (0.999–1.001), p = 0.816</td>
<td></td>
</tr>
<tr>
<td><strong>OCN [ng/mL]</strong></td>
<td>0.942 (0.902–0.983), p = 0.006*</td>
<td>0.979 (0.925–1.035), p = 0.452</td>
</tr>
<tr>
<td><strong>hs-CRP [mg/L]</strong></td>
<td>1.023 (0.976–1.072), p = 0.345</td>
<td></td>
</tr>
<tr>
<td><strong>Hba1c <a href="mmol/mol">%</a></strong></td>
<td>2.052 (1.455–2.894), p = &lt; 0.001*</td>
<td>1.705 (1.077–2.698), p = 0.023*</td>
</tr>
<tr>
<td><strong>ABI</strong></td>
<td>0.051 (0.0–8.252), p = 0.252</td>
<td></td>
</tr>
<tr>
<td><strong>Total cholesterol [mg/dL]</strong></td>
<td>1.001 (0.991–1.011), p = 0.831</td>
<td></td>
</tr>
<tr>
<td><strong>TG [mg/dL]</strong></td>
<td>1.002 (0.995–1.010), p = 0.524</td>
<td></td>
</tr>
<tr>
<td><strong>HDL [mg/dL]</strong></td>
<td>-0.029 (0.941–1.002), p = 0.067</td>
<td></td>
</tr>
<tr>
<td><strong>LDL [mg/dL]</strong></td>
<td>1.006 (0.993–1.019), p = 0.376</td>
<td></td>
</tr>
<tr>
<td><strong>BMI [kg/m²]</strong></td>
<td>0.995 (0.878–1.127), p = 0.936</td>
<td></td>
</tr>
<tr>
<td><strong>WC [cm]</strong></td>
<td>1.042 (0.964–1.128), p = 0.301</td>
<td></td>
</tr>
<tr>
<td><strong>Waist-to-hip ratio</strong></td>
<td>2483189.856 (0.019–), p = 0.123</td>
<td></td>
</tr>
<tr>
<td><strong>FPG [mg/dL]</strong></td>
<td>1.014 (1.003–1.024), p = 0.008*</td>
<td>1.010 (0.998–1.022), p = 0.101</td>
</tr>
<tr>
<td><strong>UACR [mg/g]</strong></td>
<td>9.167 (1.855–45.293), p = 0.007*</td>
<td>2.178 (0.266–17.852), p = 0.468</td>
</tr>
<tr>
<td><strong>HOMA2IR</strong></td>
<td>1.346 (0.943–1.922), p = 0.102</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant at p ≤ 0.05; #All variables with p < 0.05 was included in the multivariate

ABI — ankle-brachial index; BMI — body mass index; CI — confidence interval; cIMT — carotid intima-media thickness; DM — diabetes mellitus; FPG — fasting plasma glucose; Hba1c — glycated hemoglobin; HDL — high-density lipoproteins; HOMA2IR — Homeostasis Model Assessment 2 of insulin resistance; hs-CRP — high-sensitivity C-reactive protein; LDL — low-density lipoproteins; LL — lower limit; OCN — osteocalcin; OPG — osteoprotegerin; SD — standard deviation; TG — triglycerides; UACR — urinary albumin/creatinine ratio; UL — upper limit; WC — waist circumference

**Figure 1.** ROC Curve for Osteoprotegrin and Osteocalcin to Discriminate Patients with Subclinical Atherosclerosis (cIMT ≥ 0.9 mm) (n = 34) in the Total Sample

cIMT — carotid intima-media thickness; OPG — osteopro-tegerin
from using different cohort (our cohort were only men) and the fact that in their study cardiovascular disease was excluded on the basis of medical history only while we excluded CAD by coronary angiography which is more specific. A study conducted by Kang [30] showed a significant negative correlation of OCN with serum glucose and HOMA-IR but not with coronary atherosclerosis reflecting its role in glucose metabolism and insulin resistance but not atherosclerosis.

The present study showed no significant correlations between serum OCN levels and other parameters in the diabetes group. Sheng et al.[31] in discordance with the results of the present study, found an association between low OCN levels and carotid atherosclerosis in people with T2DM. They found a significant negative correlation of OCN with FPG, fasting insulin, CRP and HOMA-IR. Kanazawa et al. [32] similarly found a negative correlation of OCN with cIMT, HbA1c and FPG in people with T2D. This difference may be due to the presence of other risk factors of atherosclerosis in the diabetes group and the present study cohort was free from CAD, which was confirmed by coronary angiography.

The present study showed a significant positive correlation of the mean serum OPG level with age and HbA1c in the total sample and a significant positive correlation with age in the diabetes group while in the control group, the mean serum OPG level was significantly positively correlated with total cholesterol, HDL-C and LDL-C. O’Sullivan et al. [33] reported similar results with higher levels of OPG, IL6 and hs-CRP in people with diabetes. However, in cases without vascular affection, OPG was the only significantly higher biomarker, suggesting a different pathophysiological process. They also found no significant correlation between OPG and all studied parameters in the diabetes group while in the control group, it correlated positively with age. Another study by Zwakenberg et al. [5] found no significant correlation between OCN, OPG and CVD in people with diabetes. The difference between their study and ours may result from using a different cohort including 82% females and the fact that their endpoint was established CVD.

The current study showed a significantly lower OCN level in patients with subclinical atherosclerosis while there was no significant relation between serum OPG level and subclinical atherosclerosis. In agreement with the results of the present study, Deng et al. [34] showed a significantly lower level of OCN in patients with carotid atherosclerosis than in the control group.

Table 3. Comparison between Patients with Subclinical Atherosclerosis (cIMT ≥ 0.9 mm) and Patients without Atherosclerosis Regarding Different Parameters in the Total Sample (n = 80)

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>Carotid intima-media thickness</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.9 mm (n = 46)</td>
<td>≥ 0.9 mm (n = 34)</td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>52.2 ± 4.9</td>
<td>56.1 ± 6.4</td>
</tr>
<tr>
<td>Smoker [%]</td>
<td>29 (72.5%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>DM duration [years]</td>
<td>8.9 ± 6.1</td>
<td>12.7 ± 6.3</td>
</tr>
<tr>
<td>OPG [ng/mL]</td>
<td>377.4 ± 418.3</td>
<td>398.9 ± 407.2</td>
</tr>
<tr>
<td>OCN [ng/mL]</td>
<td>29.4 ± 13.6</td>
<td>20.6 ± 10.9</td>
</tr>
<tr>
<td>hs-CRP [mg/L]</td>
<td>7.9 ± 9.1</td>
<td>10 ± 10.4</td>
</tr>
<tr>
<td>HbA1c <a href="mmol/mol">%</a></td>
<td>6.2 (44) ± 1.2</td>
<td>8.4 (68) ± 2.2</td>
</tr>
<tr>
<td>ABI</td>
<td>1.03 ± 0.09</td>
<td>1.01 ± 0.08</td>
</tr>
<tr>
<td>Total cholesterol [mg/dL]</td>
<td>165.1 ± 38.5</td>
<td>167.2 ± 51</td>
</tr>
<tr>
<td>TG [mg/dL]</td>
<td>135.2 ± 61.2</td>
<td>143.7 ± 56.5</td>
</tr>
<tr>
<td>HDL-C [mg/dL]</td>
<td>42.7 ± 16</td>
<td>36.2 ± 13.6</td>
</tr>
<tr>
<td>LDL-C [mg/dL]</td>
<td>95.4 ± 29.8</td>
<td>102.3 ± 40</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>27.7 ± 3.6</td>
<td>27.7 ± 3.6</td>
</tr>
<tr>
<td>WC [cm]</td>
<td>98.5 ± 6.1</td>
<td>99.8 ± 5.2</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.96 ± 0.03</td>
<td>0.97 ± 0.02</td>
</tr>
<tr>
<td>FPG [mg/dL]</td>
<td>99.3 ± 43.1</td>
<td>139.9 ± 71.8</td>
</tr>
<tr>
<td>Albuminuria [%]</td>
<td>2 (4.3%)</td>
<td>10 (29.4%)</td>
</tr>
<tr>
<td>HOMA2IR</td>
<td>1.36 ± 1.37</td>
<td>1.94 ± 1.53</td>
</tr>
</tbody>
</table>

*Statistically significant at p ≤ 0.05; p-value for comparing between < 0.9 mm and ≥ 0.9 mm

ABI — ankle-brachial index; BMI — body mass index; DM — diabetes mellitus; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; HDL-C — high-density lipoprotein cholesterol; HOMA2IR — Homeostasis Model Assessment 2 of insulin resistance; hs-CRP — high-sensitivity C-reactive protein; LDL-C — low-density lipoprotein cholesterol; OCN — osteocalcin; OPG — osteoprotegerin; SD — standard deviation; TG — triglycerides; WC — waist circumference
and a significant negative correlation between OCN and cIMT. Zhang et al. [26] found that serum OCN level was significantly lower in patients with coronary heart disease. Moreover, Xu et al. [25] reported similar results with significantly lower OCN levels in male patients with a moderate or high risk of ASCVD than those with low risk.

Maser et al. [35], in discordance with the results of the present study, suggested that OPG is better than OCN as a biomarker of arterial calcification in T2D. This difference may arise from the fact that most of their patients had established atherosclerosis, unlike our patients whose coronary angiography was free. These results may be complementary as OCN could be a better marker of subclinical atherosclerosis while OPG is better in advanced cases with established atherosclerosis. Davenport et al. [36] found significantly higher serum OPG levels in male patients with diabetes having CAD with multivessel disease. They concluded that serum OPG levels could help differentiate those high-risk patients.

Mogelvang et al. [37] studied serum OPG levels in patients with clinical and subclinical atherosclerosis and found that these patients had a significantly higher level of OPG. Their results showed a significant positive correlation between OPG and traditional risk factors of atherosclerosis including DM in both patients with and without clinical atherosclerosis. The difference between their results and ours may arise from the use of different cohorts and the fact that they (unlike our study) included both males and females and not all their patients had DM.

Our results showed that age, smoking, OCN, HbA1c, FPG and UACR were the independent risk factors of subclinical atherosclerosis (cIMT ≥ 0.9mm) in the total sample. However, in multivariate analysis, only age and HbA1c were the independent risk factors of subclinical atherosclerosis. In the diabetes group, only HbA1c was the independent risk factor of subclinical atherosclerosis in univariate logistic regression analysis. Zhang et al. [26] showed a linear relation between OCN and CHD risk in regression analysis. Xu et al. [25] found that BMI and HbA1c were the predictors of low OCN levels after performing multivariate regression analysis. On the contrary, Sheng et al. [31] found that age, gender, OCN systolic blood pressure, LDL-C and HDL-C were independently associated with cIMT in patients with T2D in multivariate regression analysis.

To the best of our knowledge, this is the first study to set a cut-off value of OCN discriminating patients with subclinical atherosclerosis from those without atherosclerosis in subjects approved to have no ACAD by cardiac angiography done during subjects’ recruitment.

However, the present study showed some limitations; including the small sample size, and that it included only the Egyptian population enrolled from a single center. Application of the study results to other races requires investigation. Study results could be generalized on males only because females were excluded due to the effect of gender on OCN level and different risk factors of atherosclerosis. Future follow-up research is required to confirm the independent association between OCN level and the development and progression of cardiovascular events and atherosclerotic diseases as the cross-sectional design of the study couldn’t confirm the causal relationship between bone turnover biomarkers and subclinical atherosclerosis.

**Conclusions**

The present study showed a significantly higher level of OCN and a significantly lower level of OPG in subjects with T2D than the control group. This reflects the state of low bone turnover in T2D. The OCN level showed better correlations and better regression results than OPG in detecting patients with subclinical atherosclerosis. This effect is attenuated in the presence of T2D and may be due to the presence of other factors affecting atherosclerosis in T2D. A cut-off value of ≤ 22 ng/mL for OCN could predict subclinical atherosclerosis in the total sample with good sensitivity, specificity and AUC. We could suggest that OCN is a better marker for subclinical atherosclerosis than OPG while both may have a role in established atherosclerosis and CAD.

**Article information**

**Data availability statement**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics statement**

The study design was approved by the ethics committee of Alexandria University.

**Author contributions**

Nagwa A. Lachine, Eman Y. Morsy and Noha G. Amin designed the study and defined the aim of work. They participated in the interpretation of data and writing the manuscript. Abdel Aziz Elnekiedy, Mohamed A. Sadaka, Gehan I. Khalil, Heba S. Kassab have participated to data collection and data analysis. Hesham G. Imam participated in data collection and analysis, in addition to writing the manuscript.
The authors declare no conflict of interest.

REFERENCES


Association between High-Sensitivity C-Reactive Protein and Metabolic Syndrome and Its Components in Older Adults: Findings from Neyshabur Longitudinal Study on Ageing (NeLSA)

ABSTRACT

Objective: To evaluate the association between high-sensitivity C-reactive protein (hsCRP) and metabolic syndrome (MetS), components of the MetS as well as diabetes, and cardiovascular complications.

Materials and methods: In this cross-sectional analysis, the data were collected from the registration phase of Neyshabur Longitudinal Study on Ageing (NeLSA) comprising a total of 6034 people aged 50 and older. Association between hsCRP and MetS and its components was conducted by univariate and multivariate analyses in the presence of covariates and confounding factors.

Results: Baseline data including age, body fat mass, body mass index, waist-to-hip ratio, fasting plasma glucose, triglyceride, creatinine, albumin, and hsCRP also systolic blood pressure, and diastolic blood pressure were higher in the MetS group compared to the control group (p < 0.001 for all variables other than hsCRP, which was not significant (p = 0.06)). Also the univariate and multi variate analysis illustrated one-unit increase in the serum level of hsCRP was associated with 18% higher risk for diabetes [OR: 1.18; 95% confidence interval (CI), 1.06–1.30] and increased high-density lipoprotein cholesterol (HDL-C) by 15% (OR:1.15; (95% CI, 1.01–1.29). In subjects with MetS, one-unit (log of 1 mg/L) increase in the serum level of hsCRP was associated with 34% higher risk for atherosclerotic cardiovascular disease (ASCVD) (OR: 1.34; 95% CI, 1.11–1.63).

Conclusions: There is an association between serum level of hsCRP and the presence of the components of MetS including HDL-C and diabetes, especially in women. (Clin Diabetol 2024; 13, 1: 52–59)

Keywords: high-sensitivity C-reactive protein, metabolic syndrome, atherosclerotic cardiovascular disease, diabetes
Introduction

Metabolic syndrome (MetS) is a cluster of conditions characterized by insulin resistance/glucose intolerance, abdominal obesity, elevated serum triglycerides (TGs) and low high-density lipoprotein cholesterol (HDL-C) levels [1–3]. According to this definition, the MetS is characterized by the number of symptoms including insulin resistance, hyperinsulinemia, impaired glucose tolerance (IGT), dyslipidemia [decreased HDL-C and increased TGs], hypertension (HTN), and central obesity [4]. The presence of MetS in young people may predict the risk of developing type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD) in the future [5]. The association between MetS and ASCVD is especially important in the context of present COVID-19 pandemic since MetS is a significant factor for more severe forms of the disease [6]. The prevalence of the MetS is increasing dramatically worldwide. In some countries, the incidence of MetS is considerably higher in women than in men. However, it is more prevalent among men in some other countries [7]. MetS is a low-grade inflammatory condition which is associated with excessive visceral fat tissue. C-reactive protein (CRP) is one of the main inflammatory markers in different conditions, including MetS. High-sensitivity CRP is a pattern-recognition molecule produced by the liver in several inflammatory conditions and it is widely used to indicate inflammatory responses in the body. Evidence suggests that hsCRP could be considered as an independent predictor of ASCVD, but it is also associated with components of MetS [8]. The role of hsCRP as an independent risk factor for coronary artery disease can be explained by several mechanisms [9]. Nevertheless, until now no clear correlation was found between the simultaneous effect of MetS and hsCRP on ASCVD. But as it could be expected, several studies showed that the risk of developing ASCVD increases with more expressed components of the MetS [10]. However, there are few exceptions to these findings that could not associate MetS with the increased risk of ASCVD. Elevated hsCRP is associated with an increased risk of myocardial infarction, sudden cardiac death, and peripheral arterial disease and has been independently associated with the prevalence of ASCVD in several prospective studies [11]. It is also used in screening and predicting short-term and long-term cardiovascular outcomes not only in patients with ASCVD but also in seemingly healthy individuals [12]. In this study, we tried to investigate the correlation between hsCRP levels, and MetS and its components as well as with diabetes.

Methods

Study design and subjects

This is a cross-sectional study which is a part of the Neyshabur Longitudinal Study on Ageing (NeLSA). NeLSA is a part of the Prospective Epidemiological Research Studies in Iran (PERSIAN), a national follow-up study which was launched in 2016 [13]. This study was performed in Neyshabur city located in the northeast of Iran with a population of about half a million people. NeLSA is the first comprehensive longitudinal study on ageing among people aged 50 years and older in Iran aiming to assess the different aspects of ageing, monitoring changes in health and wellbeing of older adults using a wide range of data including a detailed questionnaire on demographic, socioeconomic, lifestyle, physical and psychological aspects, clinical checkup, as well as mobility assessment, biological samples (blood, urine, nail and hair) and anthropometric measures [14]. Since the data for the current study is based on the registration phase of NeLSA at one point in time, the design and analysis of data were performed as a cross-sectional study. After the registration phase, NeLSA includes longitudinal follow-up phases that will track participants’ health and aging-related changes over time. It is important to note that while the current analysis is a cross-sectional study, it forms a part of the broader NeLSA study, which will allow for the examination of longitudinal trends and patterns in the future.

Written informed consent according to the Helsinki Declaration was obtained from all participants. The study was approved by the Research and Ethical Review Board of the Neyshabur University of Medical Sciences.

Data collection and measurements

Clinical study measurements were performed by a team of trained research staff. Height and weight were measured using a stadiometer and Seca scale, respectively. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²). For measuring waist circumference (WC), a non-elastic tape was placed horizontally around the participant’s waist (just above the hipbones) in a standing position. Anthropometric measurements were obtained by bio-electrical impedance analysis (BIA) using the InBody 770, Biospace Korea connected to a BSM 370.

MetS was assessed by using the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP) III criteria (2005 revision). Participants with three or more of the following criteria were defined as having MetS: 1) WC ≥ 90 cm in men or ≥ 80 cm in women; 2) HDL-C < 40 mg/dL in men or < 50 mg/dL in women.
Clinical Diabetology 2024, Vol. 13, No 1

3) triglycerides (TG) ≥ 150 mg/dL; 4) blood pressure (BP) ≥ 130/85 mmHg; 5) fasting plasma glucose ≥ 100 mg/dL, and/or drug treatment to control hyperglycemia, dyslipidemia and hypertension. We used NCEP-ATP III criteria definition for WC in this study because it has more suitable WC cut-off points for Middle Eastern men and women which are 94 and 80 cm, respectively.

Venous blood samples were analyzed after at least 8 hours of fasting. Whole blood samples were collected in blood tubes and fractionated by centrifugation at 3000 rpm for 15 min to obtain serum. The collected sera were aliquoted into 1.5 mL tubes, and following parameters [normal range (NR)] were analyzed by an analyzer (BT1500, Italy; Pars Azmun kits, Iran): fasting plasma glucose (FPG) (< 100 mg/dL), urea (19–44 mg/dL), creatinine (0.7–1.4 mg/dL), total bilirubin (0.3–1 mg/dL), triglycerides (TG) (< 200 mg/dL), total cholesterol (TC) (< 200 mg/dL), thyroid stimulating hormone (TSH) (0.3–4.78 mU/L), free thyroxine (FT4) (0.8–1.8 ng/mL), aspartate aminotransferase (AST) (8–33 U/L), alanine aminotransferase (ALT) (7–55 U/L), and alkaline phosphatase (ALP) (44–147 U/L). Whole blood samples in EDTA-K3 were also obtained for measuring blood cell count. The tubes were immediately inverted several times to mix the anticoagulant additive with blood. The blood was processed within 2 hours after using the automated hematology analyzer (Celltac Alpha MEK-6510 K, Nihon Kohden, Tokyo, Japan). The following parameters (NR) were determined: red blood cell count (RBC) (4–5.4 M/µL), white blood cell count (WBC) (4.5–11.5 K/µL), platelet count (150–450 K/µL), hemoglobin (12–15 g/dL), hematocrit (35–49%), mean corpuscular volume (MCV) (80–94 fl), mean corpuscular hemoglobin concentration (MCHC) (31–36g/dL), mean corpuscular hemoglobin (MCH) (27–33 pg), and mean platelet volume (MPV) (7–12fl).

Potential biases

To minimize sample selection bias in the Neyshabur Longitudinal Study on Ageing (NeLSA), a systematic approach was employed. Random sampling was used to select households from different regions of Neyshabur city, aiming for representative population coverage. However, it is important to recognize that despite random sampling, selection bias can still exist due to non-response rates and potential underrepresentation of certain demographic groups. To mitigate this, efforts were made to encourage participation through community engagement, informed consent, and assuring data confidentiality. Multiple attempts were made to contact selected participants, and non-response analysis was conducted to assess systematic differences between participants and non-respondents. If needed, statistical techniques like weighting adjustments were considered. Measurement bias was minimized by standardized procedures, rigorous training, validated measurement tools, and regular quality control checks. Confounding variables were addressed through careful study design, statistical adjustments, and controlling for potential confounders during analysis. While it may not be possible to eliminate all biases entirely, recognizing and addressing potential biases enhances the validity and reliability of the study findings.

Statistical analysis

The statistical methods employed in this study aimed to provide a comprehensive analysis by investigating the associations between hsCRP, MetS and its components, diabetes, and ASCVD. Through the utilization of appropriate statistical techniques and the consideration of confounding variables, the researchers sought to obtain reliable and meaningful results to support their research objectives.

Data management and analysis were performed using the SPSS 20 statistics software program (IBM Corporation, Armonk, NY). Data were presented as mean and 95% confidence interval (CI) for normally distributed continuous variables, as well as median and inter-quartile range for skewed continuous variables. Frequency and percentage were used for categorical variables. The associations between categorical variables were examined using the chi-square test and Wilcoxon test. Logistic regression analysis was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between serum hsCRP levels and MetS components, as well as diabetes ASCVD. In the logistic regression models, covariates such as age, sex, cigarette consumption, education level, physical activity, and body mass index (BMI) were included. These covariates accounted for their potential influence on the relationships of interest. The logistic regression analysis yielded estimates of odds ratios, which quantified the relative likelihood of an event (e.g., having MetS or ASCVD) occurring based on changes in the predictor variable (e.g., hsCRP levels).

To account for potential confounding effects, adjustments were made for confounding variables when analyzing the associations between hsCRP, MetS, diabetes, and ASCVD. The study also explored potential interactions and differences between subgroups. Subgroup analysis allowed for the investigation of variations in associations based on participant characteristics or other factors. In this study, subgroup analyses were performed based on gender and the presence or absence of MetS or diabetes to evaluate whether the associations between hsCRP and ASCVD differed within these groups.
Results
Baseline characteristics
Of 6034 participants, 47% were male and the mean age of participants was 58.9 years. The prevalence of MetS was 48%, 16% were males and 32% females, as shown in Table 1. According to this table, among those with MetS there were more women, less non-smokers, more non-smokers, non-addicted, older and more ASCVD. They had higher BMI, body fat mass (BFM), waist-to-hip ratio, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), TGs, FPG, albumin, and HDL-C (p < 0.05 for all these variables).

Association of metabolic syndrome and its components and diabetes with high sensitivity C-reactive protein
Table 2 shows the correlation between the serum hsCRP levels and the MetS components. Logistic regression models were performed to determine the effect of hsCRP serum levels on the odds of having MetS components. According to the results, serum hsCRP levels were only associated with HDL-C (OR: 1.15; 95% CI, 1.01–1.29) and diabetes (OR:1.18; 95% CI, 1.06–1.30) in the univariate model. Serum hsCRP levels were only associated with diabetes after adjusting for other variables including sex, cigarette consumption, education level, physical activity, and BMI. By increasing one mg/L of hsCRP, the odds of developing diabetes was increased by 14%. We also analyzed the effect of hsCRP on the MetS in both gender. No statically significant correlation was observed between serum level of hsCRP and the MetS in men. However, women showed a different result. There was an increasing trend in the odds of ASCVD, WC, and diabetes which was parallel with an increase in serum level of hsCRP. In addition, adjustment for other variables showed that with increasing serum level of hsCRP, the prevalence of diabetes also increased with an OR of 1.22 (95% CI, 1.05–1.41) for women. Therefore, increasing the serum hsCRP by one mg/L increased the odds of developing diabetes by 22%.

Table 1. Baseline Characteristics of Participants in Total and by Study Groups

<table>
<thead>
<tr>
<th>Categories</th>
<th>Total</th>
<th>Metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N = 2903)</td>
<td>No (N = 3131)</td>
</tr>
<tr>
<td>Gender, N (%)</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
<td>942 (16%)</td>
<td>1852 (31%)</td>
</tr>
<tr>
<td>Female</td>
<td>1961 (32%)</td>
<td>1279 (21%)</td>
</tr>
<tr>
<td>Smoking status, N (%)</td>
<td>Non-smoker</td>
<td>Daily/sometimes</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>2733 (45%)</td>
<td>2663 (44%)</td>
</tr>
<tr>
<td>Daily/sometimes</td>
<td>170 (3%)</td>
<td>468 (8%)</td>
</tr>
<tr>
<td>Addiction status, N (%)</td>
<td>No addiction</td>
<td>Occasional</td>
</tr>
<tr>
<td>No addiction</td>
<td>2500 (42%)</td>
<td>2408 (40%)</td>
</tr>
<tr>
<td>Occasional</td>
<td>140 (2%)</td>
<td>204 (3%)</td>
</tr>
<tr>
<td>Regular</td>
<td>263 (4%)</td>
<td>519 (9%)</td>
</tr>
<tr>
<td>ASCVD, N (%)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>2696 (44%)</td>
<td>3008 (50%)</td>
</tr>
<tr>
<td>Yes</td>
<td>207 (4%)</td>
<td>123 (2%)</td>
</tr>
<tr>
<td>Age [year]</td>
<td>58.92 (54.58, 64.83)</td>
<td>59.42 (55.08, 65.54)</td>
</tr>
<tr>
<td>BFM [kg]</td>
<td>26.30 (20.40, 32.80)</td>
<td>30.2 (25.8, 35.7)</td>
</tr>
<tr>
<td>BMI [kg/m2]</td>
<td>27.70 (24.80, 30.70)</td>
<td>29.5 (27.3, 32.3)</td>
</tr>
<tr>
<td>Physical activity, MET</td>
<td>64.57 (35.82, 146.14)</td>
<td>57.46 (35.25, 116.41)</td>
</tr>
<tr>
<td>hsCRP [mg/L]</td>
<td>0.2 (0.1, 0.4)</td>
<td>0.2 (0.1, 0.4)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.94 (0.90, 0.98)</td>
<td>0.97 (0.93, 1.00)</td>
</tr>
<tr>
<td>WC [cm]</td>
<td>94.20 (86.60, 101.80)</td>
<td>99.1 (93.6, 105.30)</td>
</tr>
<tr>
<td>SBP [mmHg]</td>
<td>116 (104, 128)</td>
<td>120 (108, 132)</td>
</tr>
<tr>
<td>DBP [mmHg]</td>
<td>70 (63, 79)</td>
<td>73 (65, 80)</td>
</tr>
<tr>
<td>HDL-C [mg/dL]</td>
<td>57.25 (50.00, 65.50)</td>
<td>55.6 (48.20, 63.75)</td>
</tr>
<tr>
<td>TG [mg/dL]</td>
<td>129.5 (96.5, 177.0)</td>
<td>160 (118, 210.15)</td>
</tr>
<tr>
<td>FPG [mg/dL]</td>
<td>105 (95.00, 120.8)</td>
<td>113 (102, 136)</td>
</tr>
<tr>
<td>Cr [mg/dL]</td>
<td>1.2 (1.1, 1.4)</td>
<td>1.2 (1.1, 1.39)</td>
</tr>
<tr>
<td>Albumin [g/dL]</td>
<td>5 (4.7, 5.2)</td>
<td>5 (4.8, 5.25)</td>
</tr>
</tbody>
</table>

*Wilcoxon and Chi-Square tests; Data was presented as number (%) and median (interquartile range) for categorical and continuous variables, respectively. ASCVD — atherosclerotic cardiovascular disease; BFM — body fat mass; BMI — body mass index; Cr — creatinine; DBP — diastolic blood pressure; FBG — fasting plasma glucose; HDL-C — high-density lipoprotein cholesterol; hsCRP — high sensitivity C-reactive protein; N — number; SBP — systolic blood pressure; TG — triglycerides; WC — waist circumference.
Association between atherosclerotic cardiovascular disease and high sensitivity C-reactive protein depending upon the presence or absence of the metabolic syndrome and diabetes

The effect of hsCRP on ASCVD in two groups — with and without MetS — is shown in Table 3. As it can be seen, the association between hsCRP and ASCVD is statically significant in the group with MetS. In this group the odds of having ASCVD increased by 36% when serum hsCRP increased by one mg/L (OR: 1.36; 95% CI, 1.13–1.64). This association was still significant despite adjusting for the effect of other confounding variables (OR: 1.34; 95% CI, 1.11–1.63). Furthermore, men with MetS were more likely to have ASCVD than women after increasing the serum hsCRP by one mg/L of (OR: 1.46 vs. OR: 1.28).

According to the information provided in table 3, the effect of serum hsCRP on ASCVD is significant only in the non-diabetic group in the univariate model (OR: 1.27; 95% CI, 1.05–1.51). With an increase in the serum hsCRP by one mg/L, the odds of having ASCVD increased by 27%. This figure decreased by 10 % and lost its statistical significance after adjusting for the confounding variables (OR:1.17; 95% CI, 0.96–1.36). Non-diabetic men were more likely to have ASCVD by hsCRP elevated for one 1 mg/L (OR:1.25; 95% CI, 1.00–1.52). However, statistically insignificant relationship was seen after adjusting for other variables in non-diabetic men concerning ASCVD after an increase in hsCRP by 1 mg/L serum (OR:1.46 vs. OR: 1.28).

Discussion

Based on the findings of this study, with increasing serum hsCRP, the chance of developing ASCVD, especially in men with MetS, increased dramatically. Elevated serum hsCRP levels were observed only in those with low HDL-C, which had an effect on the single-factor model. Serum hsCRP levels were associated with diabetes only after adjusting for other variables such as gender, smoking, level of education, physical activity and BMI. With an increase of 1 mg/L in hsCRP, the risk of developing diabetes increases by 14%.

Insulin resistance, a significant characteristic of both type T2D and MetS, may serve as a plausible underlying mechanism that establishes a connection between diabetes and elevated levels of high-sensitivity C-reactive protein (hsCRP) [15]. The impaired response of tissues to insulin observed in insulin resistance leads to the elevation of plasma glucose. It is postulated that inflammation, as discerned by heightened hsCRP levels, potentially disrupts the intricate pathways involved in insulin signaling, consequently fostering insulin
Consequently, it is hypothesized that heightened hsCRP levels may exert a direct inhibitory effect on insulin signaling, thereby aggravating glucose dysregulation and contributing to the development of diabetes [17]. Data analysis of the current study showed that there was no association between hsCRP and MetS in men. However, in women with elevated serum hsCRP the chances of having lower HDL-C, high WC and diabetes were increased. In addition, modulation of other variables showed that with increasing serum hsCRP, the prevalence of diabetes in women increased. This means that an increase of 1 mg/L in serum hsCRP increases the risk of diabetes by 22%. Those with increased hsCRP were more likely to be female, non-smoker, non-addicted, older, without ASCVD, with higher BMI, BFM, waist-to-hip ratio, waist circumference, SBP, DBP, TGs, FPG, albumin, and lower HDL-C.

Findings from other studies show that an increase in hsCRP is directly related to an increased risk of T2D in patients with MetS [18]. The study of Mirhafez et al. showed that among the MetS components, increased FBG, WC, TGs, and hypertension were associated with hsCRP levels. Recent studies on the relationship between some components of MetS and hsCRP suggest that hsCRP can be used to identify patients with MetS [19].

The findings of this study showed that with increasing serum hsCRP by 1 mg/L, the chance of developing ASCVD increased by 36% are very important. In previous studies, the association of circulating levels of hsCRP with ASCVD and MetS has been confirmed separately. Men with MetS were more likely to develop ASCVD if they had elevated serum hsCRP [20]. According to previous researches, MetS, diabetes, and ASCVD are associated with alterations in lipid metabolism [17]. HsCRP can modulate lipoprotein metabolism, promoting the production of pro-atherogenic lipoproteins, such as very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL). Elevated hsCRP levels may contribute to dyslipidemia, thereby increasing the risk of ASCVD [21].

However, there are studies that have shown different results [22]. The vast majority of studies have shown that patients with MetS either are at higher risk for ASCVD or already have ASCVD [11]. According to the Framingham database, the age-adjusted relative risk for ASCVD in men with MetS was 2.88, which was higher than in women (1.54) [23]. The risk of ASCVD is doubled in people with a history of MetS who already have T2D or obesity [24]. McNeill et al. found that older people (mean age 72 years) with MetS were 20 to 30 percent more likely to have an ASCVD event than those without it [25]. Finally, as expected, an increase in number and intensity of MetS components increases the risk
of ASCVD [26]. Nevertheless, a study on non-diabetic Native Americans found no association between MetS and the incidence of ASCVD [27]. In a study of people with pre-existing ASCHD, MetS was associated with an increased ASCVD-induced mortality in women, while it had no effect on the risk of ASCVD-induced mortality in men [28]. However, the main limitation for comparing the results of different studies are the different criteria used to define MetS. A meta-analysis showed a clear association between MetS and risk of ASCVD even after adjusting for traditional cardiovascular risk factors [29]. Nevertheless, there are several studies that showed that the risk of ASCVD in subjects with MetS is not greater than the sum of its components [30]. In the study by Mirhafiz et al. which used the definition of the International Diabetes Federation it was shown that most of the components of MetS were associated with an increase in serum hsCRP and the highest correlation was with serum hsCRP concentration and FBG [19]. Another study showed that changes of hsCRP in a multivariate model did not have a significant impact, while in a univariate model the level of hsCRP predicted the risk of T2D [31]. A number of epidemiological studies have indicated that high hsCRP is a significant risk factor for ASCVD in patients with hypertension and diabetes, and even in healthy individuals [32]. According to the results of a multivariate analysis by Velde M et al., including elevated hsCRP and the variables defining the MetS serum levels of hsCRP had added value to predicting new-onset ASCVD but not T2D [31]. There are a few exceptions to these findings. For example: a study on an Italian group of elderly people with T2D showed that MetS does not help predicting ASCVD further than the risks attributed to T2D. In this study, only in the non-diabetic subjects in univariate model, with increasing 1 mg/L hsCRP in serum, the risk of ASCVD increased for 27%. This study also showed that non-diabetic men were more likely to have ASCVD with an increase in hsCRP of 1 mg/L. However, after adjusting for other variables in non-diabetic men, no association could be found between an increase of 1 mg/L of serum hsCRP and ASCVD [33].

**Conclusions**

This study provides evidence of a positive correlation between serum hsCRP levels and the presence of MetS components including HDL-C and diabetes, particularly in women. These findings suggest that individuals with high hsCRP levels should be monitored closely for the development of MetS and its components. However, further research is needed to deepen our understanding of the underlying biological mechanisms driving these associations. Additionally, health-care professionals should consider incorporating hsCRP measurement into risk assessment and management strategies for MetS, diabetes and ASCVD. Continued investigation and prospective studies are warranted to determine the clinical utility of hsCRP as a predictive marker and to explore potential therapeutic interventions targeting inflammation in individuals at risk of MetS, diabetes, and ASCVD.

**Article information**

**Data availability statement**

Data will be made available on reasonable request.

**Ethics statement**

The study was approved by the Research and Ethical Review Board of the Neyshabur University of Medical Sciences.

**Author contributions**

Conceptualization: AS, SRM
Writing (original draft): AS, MAN
Writing (review) and editing: PH, SMH, NF, FST, ZR, SRM
Approval of the final version: all authors

**Funding**

This study was supported financially by a grant from Neyshabur University of Medical Sciences, Neyshabur.

**Conflict of interest**

The authors declare no conflict of interest.

**REFERENCES**

ABSTRACT
Objective: To analyze the clinical and pharmacotherapeutic profile of people with type 2 diabetes (T2D) at a military health center in Brazil.
Materials and methods: This is a cross-sectional study. The sample of 170 medical records was selected by means of probabilistic sampling. The data collected were sociodemographic, clinical and laboratory data related to diabetes, as well as prescribed medications.
Results: Most of the subjects were male (57.6%), elderly (64.7%) and inactive military (55.2%). Adequate glycemc control was observed in 75.9% of the subjects, which was positively associated with multimorbidity and mono-therapeutic treatment (p < 0.05). Negative associations were observed in those subjects attending medical appointments less frequently and using prescribed insulin (p < 0.05). Medications prescribed for treatment of T2D were the following: metformin (90.6%), sulfonylureas (22.9%), dipeptidyl peptidase inhibitors-4 (16.5%) and sodium-glucose 2 co-transporter inhibitors (10.0%), in which 50.6% were monotherapy. Multimorbidity was 97.6%, in which systemic arterial hypertension (71.8%), lipid disorders (65.9%) and cardiovascular diseases (26.5%) were the main clinical conditions.
Conclusions: The frequency of inadequate glycemic control among subjects using prescribed insulin shows the importance of monitoring this population by means of insulin dosage adjustment, stimuli for pharmacological measures, including education on diabetes. (Clin Diabetol 2024; 13, 1: 60–66)
Keywords: diabetes mellitus, military health, chronic disease, multimorbidity, drug utilization

Introduction
Diabetes mellitus (DM) constitutes a public health problem. It is estimated that the worldwide prevalence of DM is around 10.5%, with a trend towards an increase in the coming decade. Brazil is currently ranked sixth in the world regarding the number of people with diabetes aged 20–79 years old, with this population being estimated at 15.7 million people. The disease has an impact on direct health costs, which increased from 232 billion dollar in 2007 to 966 billion dollar in 2021 worldwide [1].
DM has obesity, physical inactivity and inadequate nutrition as the main risk factors leading to metabolic syndrome (MS), which has been observed even in more controlled occupational settings, such as the armed forces, where the prevalence of DM is around 17.6% among the military personnel [2, 3], what indicates...
the need for surveillance and attention concerning DM risk factors.

The health status of the Brazilian military personnel, particularly, lacks information. In this way, studies on this theme are necessary for supporting the health service planning in military corporations. In this context, the present study aims to analyze the clinical and pharmacotherapeutic profile of people with type 2 diabetes (T2D) at a military healthcare center in Brazil, to contribute to the enhance of knowledge on health military personnel in this health unit allowing, in the future, necessary interventions, in the health service to improve it.

Methods

This is a cross-sectional descriptive survey study using medical records from a military healthcare center located in the State of São Paulo, Brazil. The study included male and female individuals diagnosed with T2D, aged 30 years or older, using medications prescribed for diabetes and attending at least one medical appointment in 2019. Pregnant women were excluded.

The search for subjects was performed from a list of individuals who underwent glycated hemoglobin test (HbA1c) at the local clinical analysis laboratory in 2019 by randomly selecting those who met the eligibility criteria. The minimum sample size was calculated as 168 subjects, considering 80-percent rate of people with diabetes using medications [4], acceptable absolute error of 5% and confidence coefficient of 95%.

The following data were collected: age, color/race, schooling level, gender, and recipient’s status (social-economic); number of outpatient appointments and rate of emergency care in the year of 2019 (use of healthcare services); and glycated hemoglobin, fasting plasma glucose, systemic arterial hypertension, levels of non-HDL cholesterol, LDL cholesterol, triglycerides and serum creatinine, and identification of the most frequent conditions (clinical and laboratory diseases). It was considered specifically LDL cholesterol less than 50 mg/dL as a category, in accordance with the Brazilian Diabetes Society guidelines, aiming this target to the very high-risk patients with T2D. The parameters outpatient appointments and access to emergency care were stratified into the following groups: 1–4 times, 5–8 times and more than 9 times for which the prevalence found were 41.2%, 28.2% and 30.0%, respectively. On average, each subject was seen 2.8 times (SD = 3.4).

Multimorbidity was defined as the presence of two or more conditions in the same individual [5], with these conditions being classified into concordant (related to a similar pathophysiology with T2D) and discordant (not related to a similar pathophysiology with T2D) in relation to T2D [6, 7]. The prescribed medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system set by the World Health Organization. Polypharmacy was defined as being the concomitant use of five or more medications [8].

The result data were analyzed by means of descriptive statistics with distribution of absolute and relative frequencies. Odds ratio and 95% confidence interval (95% CI) were calculated by using conditional method [9]. In the present study, the use of regression adjustment is related to the Poisson model for binary response in the analysis of the effect of each independent variable on the presence of glycemic control. The adjusted analysis was initially used to investigate the effect of each independent variable in a regression, including all variables selected from the data set, before being performed in two steps: (i) regression adjustment with two independent variables (bivariate model) and (ii) greater model adjustment containing an independent variable and those identified as statistically significant (p < 0.05) in the bivariate modelling [10].

Ethical considerations

The present study was approved by the ethics research committee of the São Paulo Armed Force Hospital according to the protocol number 37488620.7.0000.8928.

Results

The resulting sample had 170 subjects whose characteristics are listed in Table 1. The majority were male, the average age was 63.3 years [standard deviation (SD) = 8.9], 27.1% had completed secondary school and 38.2% were dependent, that is, partners, parents and/or children of the military who are also users of the health system.

About the use of healthcare services, the rate of outpatient appointments was stratified into the following groups: 1–4 times, 5–8 times and more than 9 times, for which the prevalence found were 41.2%, 28.2% and 30.0%, respectively. On average, each subject had 6.5 appointments (SD = 4.5).

The access to emergency care was also stratified into the same groups of 1–4 times, 5–8 times and more than 9 times for which the prevalence found were 60.0%, 10.6% and 6.5%, respectively. The mean rate was 2.8 times (SD = 3.4). Emergency care was not used by 22.9% of the subjects.

Table 2 shows the results of the clinical and laboratory tests of the study subjects.

The presence of multimorbidity was observed in 97.6% of the subjects, with the majority (57.6%) having from 2 to 4 conditions. The conditions occurring
Clinical Diabetology 2024, Vol. 13, No 1

most simultaneously with T2D were systemic arterial hypertension (71.8%), lipid disorders (65.9%) and cardiovascular diseases (26.5%). As for the classification of the subjects in relation to concordant, discordant, and concordant/discordant conditions, the prevalence was 31.3%, 3.6% and 65.1%, respectively.

Among the subjects with adequate glycemic control, the highest rate (70.3%) was found in the category of subjects with both concordant and discordant conditions. This rate was followed by that of the categories of subjects with concordant diseases only (25.8%) and of those with discordant diseases only (3.9%).

As for the subjects who had inadequate glycemic control, it was found that 50.0% belonged to the concordant category, 47.4% to the concordant/discordant category and 2.6% to the discordant category.

As for prescribed medications, it was found that 5.7 drugs were prescribed per subject. In addition, 39.4% of the subjects were prescribed 1 to 4 drugs, whereas 60.6% were prescribed more than 5 drugs. The pharmacotherapy used for treatment of T2D is shown in Table 3.

Metformin was the main medication prescribed in the monotherapy treatment, corresponding to 90.5% of this group of drugs (metformin, insulin, or sulfonylureas). In addition, it was observed that in the category “metformin and other oral anti-diabetic drugs”, the most frequent association was that of metformin and sulfonylureas, with 9.4% in relation to the total of subjects.

Metformin was also used in dual therapy in combination with sodium-glucose 2 co-transporter inhibitors (SGLT2i) (dapagliflozin or empagliflozin), dipeptidyl peptidase inhibitors-4 (DPP-4) (sitagliptin, vildagliptin, alogliptin) or tiazolidinediones (pioglitazone), corresponding to 17.6% of the sample. In this category, it was also found that 10% of the subjects used triple and quadruple therapy using oral anti-diabetic drugs in several combinations with metformin, sulfonylureas, SGLT2i, DPP-4 inhibitors and tiazolidinedione.

In the category “insulin and oral anti-diabetic drugs”, the most frequent combination was that in which 7.6% of the sample used insulin and metformin, whereas other combinations involving insulin, metformin, and other oral anti-diabetic drugs such

Table 1. Social-Demographic Characteristics of the Study Sample (n = 170) (Air Force Health Centre, Pirassununga, SP, Brazil, 2019)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>98 (57.6%)</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>72 (42.4%)</td>
</tr>
<tr>
<td>Mean age ± standard deviation [years]</td>
<td>63.3 ± 8.9</td>
</tr>
<tr>
<td>Color/race</td>
<td></td>
</tr>
<tr>
<td>White (n, %)</td>
<td>131 (77.1%)</td>
</tr>
<tr>
<td>Non-white (n, %)</td>
<td>39 (22.9%)</td>
</tr>
<tr>
<td>Schooling level</td>
<td></td>
</tr>
<tr>
<td>Complete elementary school (n, %)</td>
<td>19 (11.2%)</td>
</tr>
<tr>
<td>Complete secondary school (n, %)</td>
<td>46 (27.1%)</td>
</tr>
<tr>
<td>Complete higher school (n, %)</td>
<td>26 (15.3%)</td>
</tr>
<tr>
<td>Not informed (n, %)</td>
<td>79 (46.5%)</td>
</tr>
<tr>
<td>Recipient’s status</td>
<td></td>
</tr>
<tr>
<td>Active (n, %)</td>
<td>6 (3.5%)</td>
</tr>
<tr>
<td>Reserve1 (n, %)</td>
<td>64 (37.6%)</td>
</tr>
<tr>
<td>Retired2 (n, %)</td>
<td>30 (17.6%)</td>
</tr>
<tr>
<td>Dependent3 (n, %)</td>
<td>65 (38.2%)</td>
</tr>
<tr>
<td>Pensioner4 (n, %)</td>
<td>5 (2.9%)</td>
</tr>
</tbody>
</table>

1 Reserve: inactive military, that no longer performs his/her functions, but can be recalled to the active service if necessary; 2 Retired: inactive military who is definitively out of service; 3 Dependent: partners, parents and/or children of the military who are also users of the health system; 4 Pensioner: widow/widower of the deceased military

Table 2. Clinical and Laboratory Results of the Study subjects (n = 170) (Air Force Health Centre, Pirassununga, SP, Brazil, 2019)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Mean ± standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycated hemoglobin [%]</td>
<td>170</td>
<td>6.5 ± 1.0</td>
</tr>
<tr>
<td>Fasting plasma glucose [mg/dL]1</td>
<td>166</td>
<td>129.6 ± 48.5</td>
</tr>
<tr>
<td>Systolic arterial hypertension [mmHg]2</td>
<td>107</td>
<td>126.0 ± 15.6</td>
</tr>
<tr>
<td>Diastolic arterial hypertension [mmHg]3</td>
<td>107</td>
<td>80.4 ± 9.2</td>
</tr>
<tr>
<td>Non-HDL cholesterol [mg/dL]4</td>
<td>158</td>
<td>182.4 ± 47.8</td>
</tr>
<tr>
<td>LDL cholesterol [mg/dL]5</td>
<td>154</td>
<td>101.3 ± 40.1</td>
</tr>
<tr>
<td>Triglycerides [mg/dL]6</td>
<td>158</td>
<td>175.7 ± 118.8</td>
</tr>
<tr>
<td>Men's serum creatinine [mg/dL]7</td>
<td>86</td>
<td>1.09 ± 0.7</td>
</tr>
<tr>
<td>Women's serum creatinine [mg/dL]8</td>
<td>66</td>
<td>0.9 ± 0.2</td>
</tr>
</tbody>
</table>

The missing data: 1 Fasting plasma glucose = 4; 2 Systolic arterial hypertension = 107; 3 Diastolic arterial hypertension = 63; 4 Non-HDL cholesterol = 12; 5 LDL cholesterol = 16; 6 Triglycerides = 158; 7 Men’s serum creatinine = 12; 8 Women’s serum creatinine = 6

HDL — high-density lipoproteins; LDL — low-density lipoproteins
as sulfonylureas (glibenclamide or gliclazide), DPP-4 inhibitors (vildagliptin) and SGLT2i (dapagliflozin or empagliflozin) corresponded to 5.3% of the subjects. In the category “other classes and combinations”, DPP-4 inhibitors (vildagliptin, linagliptin and sitagliptin) and SGLT2i (empagliflozin) were also prescribed. Among the classes of medications prescribed for other conditions rather than T2D, one can highlight the angiotensin receptor antagonists (44.8%), diuretics (44.1%), angiotensin-converting enzyme inhibitors (18.3%) and calcium channel blockers (15.3%).

Table 4 shows the results of association tests performed between dependent (glycemic control control) and independent variables (gender, age, color/race, recipient’s status, medical appointments, emergency care, multimorbidity, number of diseases, systemic arterial hypertension, dyslipidemia, overweight/obesity, hypothyroidism, psychiatric disorders, polypharmacy, medications for T2D and monotherapy for T2D).

### Discussion

Although the proportion of men in the population is 48.2% [11], in the present study it was observed that most of the subjects were male (57.6%), possibly due to the high rate of men serving in the Air Force (81.0%) [12]. The users of the healthcare center were military personnel who were active, inactive (retired/reserve), dependent and pensioners. However, it was found that the great majority of the subjects were inactive military personnel and their dependents, which can be partially explained by their older age compared to active ones [13]. It’s necessary to highlight that inactive military personnel have already completed their career in the military organization. Therefore, they are older compared to the active militaries who are still developing their career.

A systematic review study with meta-analysis of the prevalence of MS among personnel of the armed forces and military corporations of several countries found a proportion of 8.3% [14]. Another study of the Brazilian Navy personnel detected a prevalence of 8.3% [14].

---

**Table 3. Pharmacotherapy Used for Treatment of Type 2 Diabetes in the Study Sample (n = 170). (Air Force Health Centre, Pirassununga, SP, Brazil, 2019)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin (n,%)</td>
<td>86 (50.6%)</td>
</tr>
<tr>
<td>Metformin and other oral anti-diabetic drugs (n, %)</td>
<td>46 (27.1)</td>
</tr>
<tr>
<td>Insulin and oral anti-diabetic drugs (n, %)</td>
<td>22 (12.9%)</td>
</tr>
<tr>
<td>Insulin only (n, %)</td>
<td>5 (2.9%)</td>
</tr>
<tr>
<td>Sulfonylureas only (n, %)</td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td>Other classes and combinations (n, %)</td>
<td>7 (4.1%)</td>
</tr>
</tbody>
</table>

**Table 4. Glycemic Control (Glycated Hemoglobin Less than 7.0%) of the Subjects According to Social-Demographic and Clinical Variables (n = 170) (Air Force Health Centre, Pirassununga, SP, Brazil, 2019)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted analysis&lt;sup&gt;1&lt;/sup&gt;</th>
<th>PR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Male</td>
<td>0.95 (0.81–1.13)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Age group [years]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–49</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>50–59</td>
<td>0.85 (0.47–1.53)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>0.82 (0.46–1.44)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>0.93 (0.54–1.59)</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Color/race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-white</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>White</td>
<td>1.11 (0.89–1.39)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Recipient’s status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Active</td>
<td>1.13 (0.89–1.44)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Medical appointments (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>0.66 (0.48–0.91)</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>5–8</td>
<td>0.85 (0.61–1.18)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>≥ 9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Emergency care (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.79 (0.44–1.45)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>0.91 (0.63–1.32)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>5–8</td>
<td>0.96 (0.58–1.60)</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>≥ 9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Multimorbidity [5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>3.98 (0.63–24.90)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Number of diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4–5</td>
<td>1.18 (0.98–1.42)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>≥ 6</td>
<td>1.19 (1.05–1.34)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Systemic arterial hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>1.11 (0.89–1.39)</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>1.05 (0.86–1.27)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>1.12 (0.92–1.35)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>1.22 (1.06–1.41)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>1.18 (1.01–1.39)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Polypharmacy [8]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>0.94 (0.79–1.11)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Medications for T2D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral anti-diabetic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>0.23 (0.09–0.55)</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Oral anti-diabetic drugs and insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>0.31 (0.07–1.32)</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Monotherapy for T2D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>1.34 (1.09–1.65)</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Adjusted analysis by medical appointments, multimorbidity, number of diseases, use of oral anti-diabetic drugs and insulin, insulin only and monotherapy

CI — confidence interval; PR — prevalence ratio; T2D — type 2 diabetes
17.6% for MS [2], whereas a cross-sectional study of the Brazilian general population estimated a prevalence of 38.4% [15]. Therefore, military personnel are less likely to develop T2D compared to the general population since the former are required to practice physical activities regularly.

About the utilization of healthcare services, it was observed that there was a relationship between inadequate glycemic control and low rate of medical visits, thus indicating that individuals with chronic conditions (e.g., T2D) can benefit from the care provided by the health team as they need a minimum number of accesses to healthcare services. In fact, there is evidence that the care provided by a multiprofessional team for management of T2D favors the outcome of the patient. The inclusion of a pharmacist in the team should also be emphasized as such a professional can contribute to achieving the glycemic goals of these people with diabetes [16, 17]. In the present study, the reference value of HbA1c for an adequate glycemic control was below 7.0% [18, 19]. Therefore, 75.9% of the subjects in our sample had an adequate glycemic control, which is corroborated by another study reporting a rate of 62.0% among individuals living in the south-eastern region of the country [20].

About systemic arterial hypertension, it was observed that this condition was highly prevalent in the population studied, reaching 25.9% in the southeastern region [21]. This finding points to the opportunity of improving the treatment of the disease on a continuous basis.

As for the lipid profile, the parameters analyzed were found to be adequate only for approximately half of the sample, thus making this finding an important point of attention for patients with T2D. Regarding renal function markers in patients with T2D, it is known that the measurement of serum creatinine level is a very used parameter in the initial examination, although more parameters are required to obtain a precise diagnosis [22].

As for multimorbidity, other authors also reported a simultaneous prevalence of T2D and other conditions such as systemic arterial hypertension, lipid disorders and cardiovascular diseases [23, 24], which is in accordance with the present study.

It should be emphasized that the subjects of the present study had an average of 3.3 diseases, a figure close to that reported in the literature (i.e., 3.1 diseases per individual) [25]. This demonstrates the association between T2D and multimorbidity and reinforces the discussion on providing multi-professional care for these individuals on an integral basis through qualified healthcare providers [5]. As well as other studies [25, 26], a relationship between multimorbidity and adequate glycemic control was also found here. One can conclude that a higher number of medical appointments is related to a better provision of care for individuals so that they can control their T2D adequately.

Another important aspect in the analysis of multimorbidity was the stratification of subjects into those who had concordant, concordant-discordant, and discordant diseases. Our results were like those of another study using real-life data from primary health care [6], showing that many individuals with adequate glycemic control were those with concordant and discordant conditions. Nevertheless, another issue raised in the present study is that the hypertension rates as well as the lipid parameters, in general, were not adequate for most of the sample studied, differently from what occurs with HbA1c. Therefore, a strategic planning should be proposed to implement health actions aimed at the integrity of care.

Metformin was the mostly widely prescribed medication in the monotherapy for T2D. The prescription rate of metformin is coherent with the medical recommendations as the first line pharmacotherapeutic schemes for treatment of T2D due to its efficacy, good security profile, cardiovascular protection, reduced rate of hypoglycemia and weight gain neutrality, besides being easily available and free of charge from the Brazilian public health system [18, 27].

The current pharmacotherapeutic recommendations have been guiding the treatment with the aim to reduce the glycaemia as well as to prevent cardiovascular and renal damage, regardless of the levels of HbA1c, since individuals with T2D are more likely to develop cardiovascular diseases and renal harm compared to those not affected by this condition. This is why one of the principles for combining other oral anti-diabetic drugs lies in their cardiovascular and renal protective effects [18, 27]. The prescribed combination of insulin and oral anti-diabetic drugs is justifiably aimed at minimizing adverse events of the treatment with insulin, that is, hypoglycemia and weight gain. The concomitant use of insulin with metformin can lead to an adequate glycemic control and result in less hypoglycemic events and less weight gain compared to treatment with insulin only [28].

Polypharmacy is frequent in a scenario of multimorbidity, which can have negative consequences as it is associated with all causes of mortality, including acute myocardial infarction [29]. Therefore, it is important to review the prescribed medications periodically based on the best evident available in the literature.

About limitations, it was not possible to determine the causality between the variables analyzed because
this is a cross-sectional study. Furthermore, this is a single-center study performed in a military environment, thus the findings observed may be limited to other health units based in Brazil or in other countries. Another limitation is the quality of the information, as a high number of medical records lacked data on anthropometric measurements such as height, weight, and abdominal circumference. Moreover, failures in the recording of blood pressure as well as in the laboratory results were noted.

The present study has shown the clinical and pharmacotherapeutic profile of the people attending a military healthcare center, with most of the subjects having an adequate glycemic control and metformin being the most prescribed medication for control of T2D. However, the glycemic control was found to be inadequate for those subjects who used insulin. In addition, high rates of multimorbidity and polypharmacy were also observed.

**Article information**

**Data availability statement**

Data from this study can be requested from the corresponding author.

**Author contributions**

The authors approved the final version of the article and contributed to the conception and planning of the study, data analysis and interpretation, and writing of the manuscript.

**Funding**

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior — Brazil (CAPES) — Finance Code 001.

**Conflict of interest**

The authors declare no conflict of interest.

**REFERENCES**


Andre Henrique Freitas de Braga e Bessa et al., Type 2 Diabetes at a Military Health Centre


Efficacy of Insulin Degludec/Insulin Aspart (IDegAsp) vs. Insulin Glargine (IGlarU300) in Insulin-Naïve Patients with Type 2 Diabetes: A Retrospective Study

ABSTRACT
Objective: To investigate the efficacy of insulin degludec/insulin aspart (IDegAsp) co-formulation versus insulin glargine U300 (IGlarU300) in insulin-naïve individuals with type 2 diabetes (T2D) who had inadequate glycemic control with three oral antidiabetic drugs.

Materials and methods: In this multicenter, retrospective, observational study, insulin-naïve individuals with T2D were subjected to standard care. Healthcare practitioners across this multicentric study initiated treatment with either IDegAsp (group 1) or IGlarU300 (group 2) as the insulin of choice. The participants’ glycometabolic parameters, such as weight, body mass index (BMI), creatinine, hemoglobin A1c (HbA1c), fasting blood glucose (FBG), and postprandial blood glucose (PPBG) levels were analysed over 6 months. Changes in these parameters over 6 months were evaluated. Statistical significance was determined using the t-test.

Results: Both treatment groups showed equivalent improvements in glycometabolic parameters, such as HbA1c, creatinine, FBG, PPBG levels, and hypoglycemic episodes over 6 months when compared to the baseline levels. Additionally, at every follow-up, the weight and BMI of both groups were similar. No severe hypoglycemic events were observed in either treatment group.

Conclusions: Our findings support that IDegAsp is non-inferior to IGlarU300 and may be considered for treatment in insulin-naïve people with inadequately controlled T2D as an initiation insulin option.

Keywords: insulin naïve, type 2 diabetes, insulin degludec/aspart, insulin glargine

Introduction
Therapeutic inertia is a significant factor in optimal management of type 2 diabetes (T2D) [1, 2]. India has an estimated 77 million adults with T2D and an additional population of 25 million adults with prediabetes [3, 4]. Failure to initiate insulin early in people with uncontrolled hyperglycemia who are on up to four oral therapies may lead to multisystemic complications, such as cardiovascular, renal, and neurovascular complications [5–7]. According to the American Diabetes Association...
We aim to investigate whether IDegAsp demonstrates non-inferiority compared to IGLarU300 when used as the initial insulin regimen. To address this objective, we performed a multicenter, clinical observational study to retrospectively evaluate the efficacy of IDegAsp versus IGLarU300 in two groups of insulin-naive individuals with uncontrolled T2D levels subjected to either of the therapies from the day of treatment initiation to 6 months in a real-world setting. We assessed the 1) changes in weight, body mass index (BMI), HbA1c, creatinine, FBG, and PPBG levels over 6 months; 2) withdrawal of insulin in both treatment groups at subsequent visits and at the end of treatment; and 3) the rate of improvement in glycemic profiles and frequency of hypoglycemia in both treatment groups.

**Materials and methods**

**Study design**

This multicenter, retrospective, observational study was conducted at five centers, of which three were from Ahmedabad, Gujarat, India, and two were in Mumbai, Maharashtra, India. The study was conducted for six months (24 weeks), spanning from December 2022 to May 2023, in compliance with the EU Clinical Trial Directive 2001/20/EC, the International Conference on Harmonization guidelines for Good Clinical Practice, and the ethical principles of the Declaration of Helsinki. The study was approved by an independent ethics committee that complied with the local regulatory requirements.

**Study participants**

We included insulin-naive adults (age 8–65 years) with T2D and HbA1c levels > 9% who were unresponsive to triple OAD therapy. The data of individuals with type 1 diabetes, pregnant females, and critically ill patients were excluded. IDegAsp and IGLarU300 were prescribed according to the routine standard of care. The study cohort was divided into two study groups: individuals treated with IDegASP were assigned to one group (IDegAsp group) and those treated with IGLarU300 to the other group (IGLarU300). Propensity score matching was performed between groups, and an identical cohort was used for the study. Each group included 80 insulin-naïve patients with T2D (Suppl. Fig. 1). The baseline characteristics were recorded at the initial visit and upon completion of treatment for a comprehensive overview of the patients’ profiles over the study duration.

**Data collection**

The data were recorded from clinical observations and laboratory test reports of glycometabolic parameters, such as weight, BMI, creatinine, HbA1c, FBG, and PPBG, of participants at baseline and during follow-up. The height and weight were measured using a calibrated clinic stadiometer and digital weighing scale, respective-
Figure 1. Comparison of the Effects of IDegAsp and IGlarU300 on the Participants’ Glycometabolic Parameters. Changes in A. weight; B. BMI; C. HbA1c; and D. creatinine in response to 6 months of IDegAsp treatment; changes in E. weight; F. BMI; G. HbA1c; and H. creatinine in response to 6 months of IGlarU300 treatment; comparison of I. weight; J. BMI; K. HbA1c; and L. creatinine levels after 6 months of treatment with IDegAsp and IGlarU300

p < 0.05 is considered statistically significant

BMI — body mass index; HbA1c — glycated hemoglobin; IDegAsp — co-formulation insulin degludec/insulin aspart; IGlarU300 — insulin glargine 300 U/mL; n — number of individuals
ly. Owing to the retrospective nature of the study, the instruments could not be standardized across the centers. Data were recorded on a standardized Microsoft Excel sheet and distributed to the centers. The prescribing information was retrieved from the electronic health records of the participants. Additionally, the estimated glomerular filtration rate (eGFR) of the participants at baseline and each follow-up visit was recorded. FBG and PPBG levels were calculated using the glucose oxidase-peroxidase (GOD-POD) coupled method.

The GOD-POD method is linear up to 500 mg/dL, with good precision (coefficient of variation = 0.7% to 1.4%) and accuracy (average deviation = 0.97). Data were collected on documented or undocumented hypoglycemic events. Intake of supporting drugs, OADs, lipid-lowering agents, blood pressure-lowering agents, and multivitamins was recorded.

Evaluating outcome measures

At baseline (visit 1), the medical history of all participants, including any prior medical conditions and concurrent medication, was recorded in a case record form. Data were collected at baseline and follow-up visits for 6 months. The following parameters were studied to determine the insulin efficacy in both groups: (I) changes in glycometabolic parameters in response to medication in the IDegAsp group; (II) changes in glycometabolic parameters in the response to medication in the IGlarU300 group (III) differences in the glycometabolic parameters of both groups at the end of the study; (IV) changes in the FBG levels of both groups in response to medication at follow-up visits; (V) changes in the PPBG levels of both groups in response to medication at follow-up visits.

Assessment of changes in BMI, weight, HbA1c, and creatinine levels

The glycometabolic parameters recorded over 6 months were evaluated. The mean changes in BMI, weight, HbA1c, and creatinine values from baseline (visit 1/day 0) to the last visit (visit 5/day 180) were analyzed group-wise. Additionally, changes in the participants’ BMI, weight, HbA1c, and creatinine levels on taking IDeg-Asp and IGlarU300 were compared at 6 months (last visit/day 180).

Assessment of changes in FBG and PPBG levels

The changes in the FBG and PPBG levels of the participants in response to either IDegAsp or IGlarU300 were evaluated over 6 months. The FBG and PPBG levels of individuals treated with IDegAsp and IGlarU300 were compared at baseline (0 days), 2nd (30 days), 3rd (60 days), 4th (150 days), and 5th (180 days) visits were compared.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>IDegAsp N = 80</th>
<th>IGlarU300 N = 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>71.25</td>
<td>69.53</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>27.14</td>
<td>26.89</td>
</tr>
<tr>
<td>HbA1c [%]</td>
<td>11.24</td>
<td>10.63</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.01</td>
<td>1.022</td>
</tr>
</tbody>
</table>

After 6 months of treatment (24 weeks)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>IDegAsp N = 80</th>
<th>IGlarU300 N = 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight [kg]</td>
<td>71.16</td>
<td>69.92</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>27.05</td>
<td>26.76</td>
</tr>
<tr>
<td>HbA1c [%]</td>
<td>7.88</td>
<td>8.49</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.95</td>
<td>0.93</td>
</tr>
</tbody>
</table>

BMI — body mass index; HbA1c — glycated hemoglobin; IDegAsp — co-formulation insulin degludec/insulin aspart; IGlarU300 — insulin glargine 300 U/mL.

Statistical analyses

The total sample size was 160, evenly distributed with 80 individuals in each group. We utilized Cohen’s d formula to determine the effect size, revealing a small effect size.

The weight, BMI, Hb1Ac, creatinine, FBG, and PPBG levels of both groups were compared at baseline and follow-up. The data are represented as boxplots. Statistical analyses were performed using Microsoft Excel (Microsoft 365, Version 2305). The t-test was used to compare categorical variables. The two groups were compared using either a two-tailed equal variance or two-tailed unequal variance t-test, depending on whether the comparison was carried out within the same or different groups of participants, respectively. A confidence interval of 5% was used, and a p-value of less than 0.05 (p < 0.05) was considered to indicate statistically significant differences. At a significance level of alpha = 0.95, we attained a power > 95%, calculated using G*Power 3.1.9.7.

Results

Matched cohorts with similar baseline characteristics were included in the study and divided into two groups based on treatment with a once-daily dose of either IDegAsp or IGlarU300 for 6 months.

Baseline characteristics

The participants’ baseline characteristics and outcomes are summarized in Table 1. The IDegAsp group had a slightly higher mean baseline weight (71.25 kg).
and BMI (27.14 kg/m²) compared to the IGlarU300 group (69.53 kg and 26.89 kg/m², respectively). Additionally, the IDegAsp group started with a higher baseline HbA1c level (11.24%) compared to the IGlarU300 group (10.63%). Creatinine levels were similar at baseline, with IDegAsp at 1.01 and IGlarU300 at 1.022. Notably, both groups exhibited reductions in weight, BMI, and HbA1c after initiation, with minor variations in creatinine levels.

Changes in weight, BMI, HbA1c, and creatinine levels

Figure 1 summarizes the effect of IDegAsp and IGlarU300 alone on the participants’ weight, BMI, HbA1c, and creatinine levels. At 6 months of IDegAsp treatment, the participants’ HbA1c and creatinine levels had decreased significantly compared to those at baseline (p < 0.05); however, the changes in their weight and BMI were insignificant (Fig. 1A–D). At 6 months of IGlarU300 treatment, the participants’ HbA1c and creatinine levels decreased significantly from baseline (p < 0.05) but no significant changes in weight and BMI were observed (Fig. 1E–H).

The weight, BMI, HbA1c, and creatinine levels of both groups were compared at 6 months (visit 5) (Fig. 1I–L), and the HbA1c values of patients taking IDegAsp were found to be significantly lower than those taking IGlarU300 (p < 0.05).

Quantitative evaluation of IDegAsp and IGlarU300 efficacy

The cumulative percentages of participants with complete insulin withdrawal at the 2nd, 3rd, 4th, and 5th visits were as follows: IDegAsp group, 2.27%, 9.09%, 22.73%, and 31.82%, respectively; IGlarU300 group, 4.23%, 11.27%, 21.13%, and 29.58%, respectively. A steady increase was observed in the number of participants with complete insulin withdrawal after the 2nd visit. At 6 months, approximately 30% of the participants in both groups withdrew insulin completely.

Changes in FBG levels across treatment groups

The mean FBG value of both groups before treatment initiation was ~200 mg/dL (visit 1/day 0) (Fig. 2A). There was no significant difference in the mean FBG value across both groups at any visit, except at the 3rd visit (Fig. 2C). At the 4th visit, it decreased to ~100 mg/dL (90 days) and was maintained until the 5th visit (180 days) (Fig. 2D and 2E). No severe hypoglycemic events were observed in either treatment group.

Changes in PPBG levels across treatment groups

The mean PPBG value of both groups was ~350 mg/dL at baseline (visit 1/day 0) (Fig. 3A). It decreased to ~200 mg/dL at the 2nd visit (30 days) and remained stable after the 3rd visit (60 days) (Fig. 3B).
and 3C). At 4th and the 5th visits, the mean PPBG values of both groups decreased to ~180 mg/dL (Fig. 3D and 3E). However, there was no statistically significant difference in the mean PPBG levels of both groups at any of the visits. No severe hypoglycemic events were observed in either treatment group. The data pertaining to Self-Monitoring of Blood Glucose, (SMBG) and Continuous Glucose Monitoring (CGM), has been reserved for a future manuscript.

Discussion

This retrospective multicenter study compared the efficacy of IDegAsp and IGlarU300 in insulin-naïve individuals with uncontrolled T2D levels over 6 months. Both therapies led to similar improvements in glycometabolic parameters, such as HbA1c, creatinine, FBG, PPBG levels, and hypoglycemic episodes at 6 months compared to the baseline levels. The weight and BMI of both groups were similar across the study duration. The weight and BMI of both groups were similar across the study duration. Initiation of IDegAsp or IGlarU300 in insulin-naïve individuals with T2D resulted in a significant reduction in HbA1c, FBG, and PPBG levels. However, the participants’ weight and BMI remained similar at baseline and at the end of treatment. Glycemic control is critical in T2D management. Therefore, early initiation and intensification of insulin are necessary to ensure adequate insulin levels. However, there is clinical inertia regarding early insulinization in T2D [21, 22]. Second-generation insulin analogs are associated with a reduced risk of hypoglycemia, counseling time, fear, and anxiety. Moreover, early insulinization with novel insulin analogs can help preserve β-cell function and achieve faster improvement in target HbA1c levels [23]. However, no comparative study has reported the efficacy of the IDegAsp co-formulation and second-generation insulin analog, IGlarU300, in the Indian population with T2D. Therefore, the primary objective of this multicenter, retrospective study was to evaluate the effectiveness of IDegAsp versus IGlarU300 in insulin-naïve Indian patients with T2D inadequately controlled with OADs.

To accomplish this objective, the glycometabolic profile of individuals with T2D was treated with insulin analogs (IDegAsp or IGlarU300) over 6 months. The possibility of insulin-related weight gain in individuals with T2D poses a therapeutic challenge and frequently delays the initiation of insulin therapy. Therefore, managing insulin-related weight gain is critical to prevent metabolic and cardiovascular complications in T2D [24–26]. In the present study, there was no significant increase in the weight and BMI levels from baseline in both groups. According to the RSSDI clinical practice recommendations for the management of T2D 2022, IDegAsp causes the least weight gain compared to basal insulin and other premixed insulin preparations [24].

Figure 3. Comparison of PPBG Levels at Each Visit during 6 Months of Treatment with IDegAsp and IGlarU300

p < 0.05 is considered statistically significant

IDegAsp — co-formulation insulin degludec/insulin aspart; IGlarU300 — insulin glargine 300 U/mL; n — number of individuals; PPBG — postprandial blood glucose
However, Kisioglu et al. [20] retrospectively observed significant weight gain in patients treated with IDegAsp and IGlarU300. Additionally, we observed a significant decrease in the mean creatinine values of both treatment groups from baseline, suggestive of improvement in kidney function or stabilization of kidney disease progression due to improved glycemic control. However, improvement in kidney parameters could not be confirmed from the results of this study.

In the present study, there was an equivalent significant decrease in the mean HbA1c levels of both groups when compared to those at baseline. In the past, few studies have reported similar results. Kisioglu et al. [20] observed a significant decrease in the HbA1c and creatinine levels of patients treated with IDegAsp and IGlarU300. Similarly, Heise et al. [27] reported that insulin-naïve people with T2D subjected to once-daily IDegAsp versus once-daily IGlarU300 showed comparable significant improvement in glycemic control and low rates of hypoglycemia. In contrast, Tibadi et al. [28] performed a real-world comparative effectiveness study of IDeg vs. IGlarU300 in insulin-naïve adults with T2D, revealing that treatment with IDeg results in substantially greater reductions in HbA1c and a 30% lower risk of hypoglycemia than treatment with IGlarU30027.

In the study, several patients in both IDegAsp and IGlarU300 groups progressively stopped insulin treatment, indicating successful complete withdrawal at 6 months. Notable reductions in FBG and PPBG levels were observed in both treatment groups. However, no statistically significant difference in the mean FBG values of either group, in response to IDegAsp and IGlarU300, was observed at any visit, except visit 3. No statistically significant difference in the mean PPBG value was observed between the groups at any visit. These findings align with those of the BRIGHT trial, a randomized study comparing the efficacy of IGlarU300 and IDeg in insulin-naïve individuals with T2D. The BRIGHT trial showed that IGlarU300 was non-inferior to IDeg in reducing HbA1c and FBG levels [29]. Cindro et al.’s cross-over, open-label, randomized trial [30] revealed no significant difference in the mean FBG levels of insulin-naïve patients with T2D subjected to either IDegAsp or IGlarU300; however, they observed significant differences in low-density lipoprotein cholesterol levels. The present findings aligns with expert guidelines recommending IDegAsp initiation in insulin-naïve patients with inadequate glycemic control on OADs alone [19, 24, 31].

One strength of the present study was the inclusion of an insulin-naïve population. Comparing IDegAsp and IGlarU300 directly in an insulin-naïve population allowed for more accurate evaluation of the relative benefits and effectiveness of the two treatments and eliminated potential confounding factors associated with prior insulin use, such as variations in treatment regimens, previous insulin sensitivity, or resistance. This study demonstrates that the IDegAsp co-formulation is a viable and non-inferior option to IGlarU300 for initiating insulin therapy, which could alleviate concerns regarding the complexity and perceived risks of starting insulin injections in T2D management. However, the current study had some limitations. First, the sample size was small, and a larger sample might be more beneficial to compare the efficacy of both drugs. Second, in this trial, the daily glucose profile of everyone subjected to either drug was not evaluated, and neither participant was requested to self-monitor their FBG levels. Third, this was a retrospective study, and a pan-India prospective survey of the opinions of healthcare professionals could provide better insights into the impact of diet and habitat on IDegAsp and IGlarU300 efficacy in T2D management.

Conclusions

Our results indicate that IDegAsp was non-inferior to IGlarU300 and therefore has potential utility as an initiator molecule. Both drugs adequately improved glycemic parameters with a low risk of hypoglycemia in insulin-naïve patients with T2D. These findings support expert panel recommendations, suggesting IDegAsp as a preferred choice for initiating insulin therapy in individuals with uncontrolled T2D.

Article information

Supplementary material

The Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/98892

Data availability

Original contributions presented in the study are included in the article.

Ethics statement

The study was conducted between December 2022 and June 2023 in compliance with EU Clinical Trial Directive 2001/20/EC, the International Conference on Harmonization (ICH) guideline for Good Clinical Practice, and the ethical principles of the Declaration of Helsinki, and was approved by the Rudraksha Hospital Ethical Committee.

Author contribution

Conception and design of study: Dr. Dhruvi Hasnani.
Acquisition of data: Dr. Dhruvi Hasnani, Dr. Santosh Jha, Dr. Banshi Saboo, Dr. Ami Sanghvi, Dr. Alpana Sowani, and Dr. Vipul Chavda

Analysis or interpretation of data: Dr. Dhruvi Hasnani, Dr. Banshi Saboo, Pusala Lakshmi Prasanna, Dr. Ami Sanghvi, Dr. Alpana Sowani, and Dr. Vipul Chavda

Drafting and Revising the Manuscript: Dr. Dhruvi Hasnani, Dr. Santosh Jha, Dr. Vipul Chavda and Pusala Lakshmi Prasanna

Acknowledgments

The authors acknowledge Vibhuti Jain Rana, Hardik Jethaliya, Amol Chaudhari, and Snehal Jamalpure from Neovation Consultancy Services Pte. Ltd., Singapore, for their valuable assistance in statistical analysis and manuscript revision.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare no conflict of interest.

References


SGLT2 Inhibitor Significantly Improved Plasma Glucose Levels in a Patient with Latent Autoimmune Diabetes of Adults: A Case Report

Latent autoimmune diabetes of adults (LADA) is a type of diabetes mellitus (DM) with characteristics of both type 1 diabetes (T1D) and type 2 diabetes (T2D). LADA is a disease of adults and the Immunology for Diabetes Society (IDS) has specified three criteria for its diagnosis: 1) onset of DM after age 35, 2) positivity for either of the known anti-islet autoantibodies, 3) insulin treatment required for more than 6 months after the diagnosis of DM [1].

To date, the use of sodium-glucose cotransporter 2 inhibitors (SGLT2is) in LADA has not been well evaluated [2]. However, this single LADA case indicated that SGLT2i was significantly effective in maintaining satisfactory plasma glucose levels for over 9 years even after the complete depletion of insulin secretion.

In 2008, a 56-year-old male patient (body height: 163.0 cm, body weight: 50.3 kg, and body mass index: 18.9 kg/m²) was transferred to our clinic for the continuous treatment for DM. He had no significant previous medical history. Initially, he was diagnosed with T2D at the age of 45 years and was treated with oral hypoglycemic agents alone.

The patient’s routine peripheral blood laboratory test and urine examination findings in 2008 were within normal range. Chest X-ray examination and electrocardiogram were normal. He had light numbness in the bilateral lower limbs due to diabetic neuropathy and mild diabetic retinopathy. Because his anti-glutamic acid decarboxylase (GAD) antibody level was 27.9 U/mL (normal range, <5.0), according to the diagnosis criteria for LADA, we re-diagnosed his DM as LADA. The detailed treatment course is summarized in Figure 1.

SGLT2is contribute to achieve treatment goal in patients with T1D [1, 3]. By contrast, to date, the application of SGLT2is among patients with LADA have not been comprehensively assessed [1]. In our case, as shown in Figure 1, to date, mean HbA1c levels have been maintained at < 7.0 % for over 9 years without hospitalization and adverse effects including diabetes ketoacidosis (DKA) after ipragliflozin treatment was started.

In general, in patients with T1D, the risk of SGLT2i treatment must be weighed against that of DKA [4]. Therefore, the increase in absolute risk of DKA, even in closely supervised patients participating in clinical trials, raises a serious concern that DKA will be even more common if SGLTis are used in routine clinical practice by practitioners who do not have the expertise...
and resources of the clinical trialists to implement the complex recommendations necessary to mitigate risk for DKA [5]. It would be prudent to limit adjunctive use of SGLTis in T1D to specialists well versed in the risks associated with such therapy and who have the requisite resources to educate, train, and support carefully selected patients [5]. However, regarding ketosis, it has been reported that LADA is ketosis-resistant [2], which might be advantage to use SGLT2i in patients with LADA compared to other type of autoimmune diabetes.

This single case study indicated that SGLT2i had a significant contribution in producing and maintaining extremely good plasma glucose levels in patients with LADA.

Figure 1. Changes in HbA1c Levels with Time between 2008 and 2021
Initially, the patient’s glycated hemoglobin (HbA1c) level was maintained at < 7.0 % with oral hypoglycemic agents. However, he received NovoMix 30 (30% insulin aspart and 70% insulin aspart protamine) at a dose of 12 U/day at the age of 52 years (which was 7 years after the initial diabetes diagnosis). Thereafter, in addition to pioglitazone (30 mg/day), he continually used NovoMix 30, and the dosage was increased to 26 U/day. Upon transfer to our clinic, his C-peptide level based on the routine blood sample test was undetectable, and his glycated hemoglobin (HbA1c) level was 9.1 %. In addition to NovoMix 30 (31 U/day) and pioglitazone (30 mg/day), miglitol (100 mg/day), biguanide (500 mg/day), and vildagliptin (100 mg/day) were added in sequence. Nevertheless, his plasma glucose level was not controlled. In order to improve his plasma glucose control, after we obtained informed consent, we acquired patient’s consent besides approval of SGLT2i use for LADA from the Institutional Review Board of our hospital. Therefore, SGLT2i (ipragliflozin; 50 mg/day) was combined with NovoMix 30 (31 U/day), and vildagliptin (100 mg/day) in July 2014. The specific changes in HbA1c values as the one-year mean and standard deviation of HbA1c values in each year are summarized. Ipragliflozin was started in 2014.

Changes in HbA1c levels are presented between 2008 and 2023. HbA1c levels are expressed as mean ± standard deviation. The Y-axis indicates the HbA1c levels, and the X-axis represents the calendar year; HbA1c — glycated hemoglobin
to the analysis of data and writing of the case report. All authors read and approved the final manuscript.

**Funding**

No funding was received for this study.

**Conflict of interest**

The authors declare no conflict of interest.

**REFERENCES**