

A Practical Guide to Diabetes Mellitus

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Foreword

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Contents

1. Physiology	1
<i>Solomon Sathishkumar, Elizabeth Vinod</i>	
• Pancreas	1
• Diabetes Mellitus	10
2. Introduction and Overview of Glycemic Disorders	15
<i>Nihal Thomas, Senthil Vasan K</i>	
Part A: Epidemiology and Pathogenesis of Glycemic Disorders	15
• Epidemiology and Evolution	15
• Pathogenesis	20
Part B: Classification and Approach to Glycemic Disorders	27
• Classification	27
• History Taking in Diabetes	30
• Diagnosis of Diabetes Mellitus	32
• Concept of Prediabetes	32
• Diagnosis of Impaired Fasting Glycemia and Impaired Glucose Tolerance	33
• Cluster Classification of Type 2 Diabetes Mellitus	34
• Concept of “The Metabolic Syndrome”	35
• Screening for Diabetes	38
• Summary of Recommendations for Adults with Diabetes	39
• Glycated Hemoglobin	40
3. Practical Medical Nutritional Therapy	44
<i>Mini Joseph, Leepica Kapoor, G Sai Mala</i>	
• Goals of Nutrition Therapy	44
• Maintenance of Body Weight	45
• Macronutrients	46
• Carbohydrates	46
• Protein	49
• Fat	50
• Micronutrients	52
• Non-nutritive Sweeteners	53
• Alcohol and Diabetes	53
• Fenugreek	54
• Food Exchanges	54

- Nutrition Labeling 54
 - Meal Planning 54
 - Carbohydrate Counting 62
 - Insight from the Nutritional Studies in Vellore 65
- 4. Exercise 69**
Jubbin Jagan Jacob
- Physiological Changes Occurring during Exercise 69
 - Clinical Implications of the Effects of Exercise in Diabetes 70
 - Benefits of Exercise in Patients with Diabetes 70
 - Potential Adverse Effect of Exercise in Patients with Diabetes 71
 - Exercise Prescription 72
 - Types of Physical Activity 78
 - Practical Considerations 83
- 5. Counseling and Psychiatric Aspects of Diabetes 87**
Dheeraj Kattula, Stephen Amarjeet Jiwanmall, Ruchita Mehra
- Part A: Counseling 87**
- Steps in Counseling 87
 - Case Studies 99
- Part B: Psychiatric Aspects of Diabetes 104**
- Diabetes and Psychiatric Disorders—Clinical Patterns 104
 - Implications of Psychiatric Comorbidity in Diabetes 105
 - Diagnostic Tools for Screening and Confirming Psychiatric Disorders 105
 - Delirium 106
 - Substance Use: Nicotine 106
 - Substance Use: Alcohol 107
 - Mood Disorders 108
 - Anxiety Disorders 109
 - Schizophrenia and Other Psychotic Disorders 110
 - Eating Disorders 111
- 6. Oral Antidiabetic Agents 116**
Nitin Kapoor, Senthil Vasan K, Nihal Thomas
- Role of Oral Antidiabetic Agent Therapy in Type 2 Diabetes Mellitus 116
 - Biguanides 118
 - Sulfonylureas 119
 - Meglitinides 122
 - Alpha-glucosidase Inhibitors 123
 - Thiazolidinediones 124
 - Incretin Effect 126
 - Emaglutide 130

- Sodium-glucose Cotransporter-2 Inhibitors 132
 - Hydroxychloroquine in Diabetes 134
 - Bromocriptine 134
 - Guidelines for Initiating Oral Antidiabetic Agents 135
- 7. Parenteral Therapeutic Agents 144**
Johns T Johnson, Sahana Shetty, Nitin Kapoor, Nihal Thomas
- Insulin Therapy 144
 - History 145
 - Classification of Insulin 146
 - Once Weekly Insulin 154
 - Glucagon-like Peptide-1 Analogs 159
 - Amylin Analog 167
 - Case Studies 168
- 8. Insulin Therapy: Practical Aspects 173**
Mercy Inbakumari, Flory Christina
- Insulin Syringes 174
 - Factors that Affect Rate of Absorption of Insulin 178
 - Complications of Insulin Therapy 179
 - Barriers to Insulin Therapy 183
 - Sick Day Management 184
 - Alternative Methods of Insulin Delivery 185
 - Dose Adjustment for Normal Eating 194
 - Recent Advances in Insulin Therapy 195
 - International Color Codes for Insulin Preparations 198
- 9. Gadgets and Glucose Monitoring 202**
Felix Jebasingh K, Vijayalakshmi A
- Self-monitoring of Blood Glucose 202
 - Continuous Glucose Monitoring System 209
 - Flash Glucose Monitoring System 211
 - i-Port Insulin Delivery Device 214
 - Other Gadgets Used in Diabetes 217
 - Newer Upcoming Products for Diabetes-related Problems 218
- 10. Peripheral Neuropathy 220**
Johns T Johnson, Kripa Elizabeth Cherian, Mahesh DM, Nihal Thomas
- Definition 220
 - Risk Factors 221
 - Classification 221
 - Pathogenesis 222

• Clinical Presentation	224	
• Differential Diagnoses	230	
• Management	234	
11. Feet, Foot Care, Vascular Disease and Neuroarthropathy		246
<i>Felix Jebasingh K, Flory Christina, Bharathi S, Hari Krishna Nair, Nihal Thomas</i>		
Part A: Footcare and Neuroarthropathy	246	
• Ulceration	246	
• Neuroarthropathy	257	
• Peripheral Artery Occlusive Disease	265	
Part B: Wound Care in Patients with Diabetes	273	
• Wound Assessment	273	
• Wound Cleansing	274	
• Debridement	275	
12. Therapeutic Footwear		280
<i>Felix Jebasingh K, Judy Ann John, Bobeena Rachel Chandy, Anand John Samuel</i>		
• Foot Injury Mechanism due to Sensory Neuropathy	281	
• Foot Injury Mechanism due to Motor and Sensory Neuropathy	281	
• Foot Examination for Selecting Appropriate Foot Orthotics	282	
• Selection of Footwear	287	
13. Hypertension and Diabetes		306
<i>Sudeep K, Jubbin Jagan Jacob</i>		
• Hypertension in India	306	
• Blood Pressure Definition and Classification	307	
• Pathophysiology of Hypertension in T2DM and T1DM	307	
• Secondary Hypertension	310	
• Screening and Evaluation of Hypertensive Subjects	310	
• Target Blood Pressure	313	
• Management of Hypertension in Diabetes	314	
• Resistant Hypertension	322	
• Out-of-office Blood Pressure Monitoring	322	
• Interventions in the Treatment of Resistant Hypertension	323	
14. Diabetic Kidney Disease		327
<i>Santosh Varughese, Suceena Alexander</i>		
• Definition	328	
• Normoalbuminuric Chronic Kidney Disease in Diabetes	328	
• Risk Factors	329	
• Classification	329	
• Survival in Patients with Diabetic Kidney Disease	331	
• Pathogenesis of Diabetic Kidney Disease	331	

- Pathology 333
 - Differentiating from Other Causes of Kidney Diseases 335
 - Management 335
 - What Should be done When the Glomerular Filtration Rate has Begun to Decline? 340
 - Avoidance of Further Injury 341
 - Supportive Treatment for the Chronic Kidney Disease Patient 342
 - Investigations 345
 - Renal Replacement Therapy 345
- 15. Macrovascular Complications of Diabetes Mellitus 349**
- Part A: Cardiovascular Complications and Dyslipidemia 349**
Johns T Johnson, Saravanan Eswaramurthy, Viji Samuel Thomson
- Epidemiology 349
 - Management of Coronary Artery Disease 353
 - Diabetic Medications and Cardiovascular Outcomes 362
- Part B: Stroke and Diabetes 364**
Sanjith Aaron
- Risk for Stroke in a Patient with Diabetes 365
 - Primary and Secondary Stroke Prevention Strategies in Diabetic Patients 365
 - Diabetes in the Setting of Acute Ischemic Stroke 366
 - Other Special Considerations in a Diabetic Patient with a Stroke 367
- 16. Ocular Disease and Retinopathy 370**
Smitha Jasper, Saban Horo, Padma Paul
- Vision and Refraction Changes in Diabetes 370
 - Diabetes and Changes in the Orbit and Extraocular Muscles 371
 - Ocular Surface Changes in Diabetes 372
 - Diabetes and the Lens 372
 - Diabetes and Glaucoma 373
 - Diabetes and the Pupil 374
 - Diabetes and the Optic Nerve 374
 - Acute and Chronic Causes of Vision Loss in Diabetes 375
 - Diabetic Retinopathy 376
 - Ophthalmoscopy 385
 - Recording of Fundus Findings 388
 - Optical Coherence Tomography 389
- 17. Diabetes and Metabolic (Dysfunction)-associated Fatty Liver Disease 394**
Nitin Kapoor, Nihal Thomas
- Problem Statement 394
 - Natural History of the Disease and Pathophysiology 395

• Evaluation of Nonalcoholic Fatty Liver Disease	396	
• Management of Nonalcoholic Fatty Liver Disease and Diabetes	398	
18. Autonomic Neuropathy		402
<i>Johns T Johnson, Kanakamani Jeyaraman</i>		
• Epidemiology of Diabetic Autonomic Neuropathy	402	
• Pathogenesis	403	
• Clinical Manifestations of Diabetic Autonomic Neuropathy	404	
• Current Guidelines for the Diagnosis of Diabetic Autonomic Neuropathy	421	
• Management Implications of Diabetic Autonomic Neuropathy	422	
• Differential Diagnosis for Autonomic Neuropathy	422	
19. Infections in Diabetes		425
<i>George M Varghese, Abi Manesh S, Abraham OC</i>		
• Predisposing Factors	425	
• Infections Prevalent in Patients with Diabetes	426	
• Infections Unique to Patients with Diabetes	427	
• Specific Infections	427	
• Immunizations Recommended in Diabetes	437	
20. Hyperglycemic Emergencies		444
<i>Jubbin Jagan Jacob, Johns T Johnson</i>		
• Precipitating Factors	444	
• Pathophysiology of Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State	445	
• Clinical Recognition, Establishing a Diagnosis, and Assessment of Comorbidities	447	
• Diagnostic Evaluation and Laboratory Studies	448	
• Clinical Management of Diabetic Ketoacidosis and Recognition of Complications	449	
• Complications	455	
• Special Situations	456	
• Use of Inpatient Standard Management Protocols in Diabetic Ketoacidosis	460	
• Clinical Management of Hyperosmolar Hyperglycemic State	460	
• Prognosis	461	
21. Hypoglycemia		464
<i>Jubbin Jagan Jacob, Johns T Johnson, Nihal Thomas</i>		
• Levels of Hypoglycemia	464	
• Clinical Classification of Hypoglycemia	465	
• Pathophysiology of Counter-regulation	465	
• Causes	465	

- Clinical Recognition of Hypoglycemia 466
 - Prevention Strategies 467
 - Clinical Management of Hypoglycemia 469
 - Long-term Management 471
 - Hypoglycemia-associated Autonomic Failure 471
 - Recurrent Hypoglycemia 471
 - Consequences 471
 - Hypoglycemia In Pregnancy 472
- 22. Pregnancy and Diabetes 476**
Mahesh DM, Philip Finny, Kanakamani Jeyaraman, Johns T Johnson
- Terminology 476
 - Pregestational Diabetes 485
 - Management 488
 - Future Risks in Mother 494
- 23. Diabetes in Childhood, Adolescence, and Youth 500**
Remya Rajan R, HS Asha, Riddhi Dasgupta, Aaron Chapla, Nihal Thomas
- Epidemiology 500
 - Diagnosis 500
 - Classification 501
 - Management 507
 - Chronic Complications 515
 - Acute Complications 517
 - Type 2 Diabetes Mellitus in Youth 519
 - Neonatal Diabetes 523
- 24. Diabetes in the Elderly 533**
Rahul Baxi, Nihal Thomas
- Diabetes in the Older Adult: How does it Differ? 533
 - Management of Diabetes in the Elderly 534
- 25. Secondary Diabetes and Other Specific Types 544**
Kishore Kumar Behera, Dukhabandhu Naik, Nitin Kapoor, Aaron Chapla, Nihal Thomas
- Classification of Secondary Diabetes 544
 - Chronic Complications in Secondary Diabetes 558
 - Other Specific Types of Diabetes 559
- 26. Perioperative Care 565**
Sam Jenkins Stephenson Vetharaj, Georgene Singh
- Metabolism at Rest 566
 - Metabolic Challenge of Surgery and Surgical Stress Response 566

- Stress Hyperglycemia 566
 - Preoperative Management of Diabetic Patients 568
 - Approach to a Diabetic Patient Undergoing Surgery 568
 - Classification and the Type of Surgery 574
 - Anesthetic Consent 574
 - Premedication 575
 - Fasting Guidelines 576
 - Prehabilitation 576
 - Intraoperative Anesthetic Management of Diabetic Patients: Choice of Anesthesia 578
 - General Principles of Management 579
 - Intraoperative Glycemic Management 580
 - Intraoperative Glycemic Management for Minor Surgery 582
 - Major Surgery 583
 - Major Surgery Regimen in Resource Poor Settings 584
 - Christian Medical College Regimen 584
 - Management of Complications 586
 - Emergency Surgery in the Diabetic Patient 588
 - Postoperative Management of Diabetic Patients 590
 - Control of Infections 593
 - Surgical Wound Management 593
 - Special Clinical Scenarios 593
 - Preconceptional Care 594
 - Antenatal Care 595
 - Management of Labor and Delivery 595
 - Postpartum Care 597
 - For the Neonate 598
 - Child with Diabetes 598
- 27. Diabetes with Obesity 605**
Nitin Kapoor, Inian Samarasam, Nihal Thomas
- Definition of Obesity 605
 - Epidemiology of Obesity and Its Impact on Diabetes 606
 - Etiopathogenesis of Obesity 607
 - Evaluation of Obesity 608
 - Management 611
- 28. Musculoskeletal Manifestations of Diabetes Mellitus 623**
Ashish Jacob Mathew
- Adhesive Capsulitis of Shoulder or Frozen Shoulder 624
 - Tendinopathies Associated with Diabetes Mellitus 625
 - Dupuytren's Contracture/Disease 626

- Diabetic Neuropathic Osteoarthropathy—Charcot Joints 627
 - Diabetic Muscle Infarction 628
 - Septic Arthritis 628
 - Diffuse Idiopathic Skeletal Hyperostosis 629
 - Scleredema Adultorum of Buschke 629
 - Osteoporosis 630
 - Osteoarthritis 630
 - Gouty Arthritis 632
 - Chronic Regional Pain Syndrome 632
- 29. Cutaneous Manifestations of Diabetes Mellitus 635**
- Anju George, Renu George*
- Microangiopathies 636
 - Neurovasculopathies 639
 - Obesity- and Hyperlipidemia-related Skin Disorders 640
 - Infections 642
 - Scleroderma-like Skin Changes 647
 - Skin Diseases Associated with Diabetes Mellitus 648
 - Cutaneous Complications of Insulin and Oral Antidiabetic Agents 654
- 30. Laboratory and Analytical Methods 657**
- Pamela Christudoss, Geethanjali Arulappan*
- Laboratory Errors 657
 - Preanalytical, Analytical, and Postanalytical Errors 658
 - Role of Laboratory in Diabetes Management 661
 - Available Assays 663
 - Other Tests of Relevance 668
- 31. Recent Advances in Diabetes Mellitus 673**
- Kalyani Sridharan, Sahana Shetty, Nihal Thomas*
- Advances in Basic Science 673
 - Advances in Disease Biomarkers 674
 - Advances in Genetics 675
 - Advances in Glucose Monitoring 675
 - Advances in Therapy 675
 - Artificial Intelligence and Diabetes Mellitus 682
- 32. Inhospital Management of Diabetes 684**
- Rahul Baxi, Nihal Thomas*
- Effects of Hyperglycemia in Hospitalized Patients and Benefits of Glycemic Control 684
 - Which Patient Should We Admit? 685
 - Aims and Targets 686

• Inpatient Diabetes Team	687
• Paradox: Barriers to Glycemic Control in Hospital	687
• Common Errors in Management	687
• Glucose Control	689
• Diabetes Management in the Critically Ill Patients	692
33. Integrating Systems	696
<i>Flory Christina, Nihal Thomas, Balu Krishna S</i>	
Part A: Team Approach to the Management of Diabetes	696
<i>Flory Christina, Nihal Thomas</i>	
• Disease Prevention	696
• Prevention and Its Importance	697
• Integrated Diabetes Clinics	698
• Functionaries of an Integrated Diabetes Clinic and Their Role	699
• Improving Foot Care for People with Diabetes Mellitus: An Integrated Care Approach	703
• Diabetes Support Groups	704
Part B: Telehealth—Bridging Distances	711
<i>Balu Krishna S</i>	
• Telehealth for Education and Training	711
• Impact of Telehealth on Education and Training	711
• Telehealth for Direct Care of Patients	712
• Administrative Challenges and Issues	713
Answers to All MCQ's	715
Appendices	719
1. Dietary Recommendations	721
2. A Quick Guide for Choosing Footwear, MCR Add-ons and Braces	727
3. Evidence in Medicine	728
4. Diabetes Case Record	729
5. Patient Handouts and Educational Material	732
Final Assessment	738
Index	763

7

CHAPTER

Parenteral Therapeutic Agents

Johns T Johnson, Sahana Shetty, Nitin Kapoor, Nihal Thomas

*“Fifty-one aminoacids certainly works,
modify B-29, the shorter it lurks,
Exenatide it's not from a wizard,
But from the saliva of a desert lizard.”*

■ INTRODUCTION

Insulin therapy is the cornerstone of treatment in patients with type 1 diabetes mellitus (T1DM) and later in the course of type 2 diabetes mellitus (T2DM). Over the years, insulin treatment has advanced from bovine and porcine insulin to recombinant human insulin. Various insulin delivery systems from conventional subcutaneous insulin injection using the insulin syringe to pen device, subcutaneous insulin infusion pumps, and inhaled insulin to artificial pancreas are now available. Proper insulin injecting techniques and patient education on self-monitoring of blood glucose (SMBG) and insulin dose titration are of utmost importance for effective insulin therapy. Parental therapies targeting the incretin system with an additional advantage of weight loss and lesser hypoglycemic events have further expanded the therapeutic armamentarium of diabetes mellitus (DM).

■ INSULIN THERAPY

The discovery of insulin for the treatment of DM was a major milestone in the field of medicine in the 20th century. The physiological insulin replacement is the mainstay of management of T1DM and advanced T2DM. The pathophysiology of T1DM involves absent insulin secretion secondary to autoimmune β -cell destruction, whereas in T2DM there is an absent first phase insulin response and the second phase insulin release is delayed and insufficient. With advancement of T2DM, β -cells are exhausted with resulting decrease in insulin secretion. β -cells exposed to higher glucose concentrations over a prolonged period of time, as in diabetes leads to the blunting of the β -cell response. This is referred to as glucotoxicity. Insulin therapy provides higher glucose reductions when compared to other therapies (**Fig. 1**) and can be

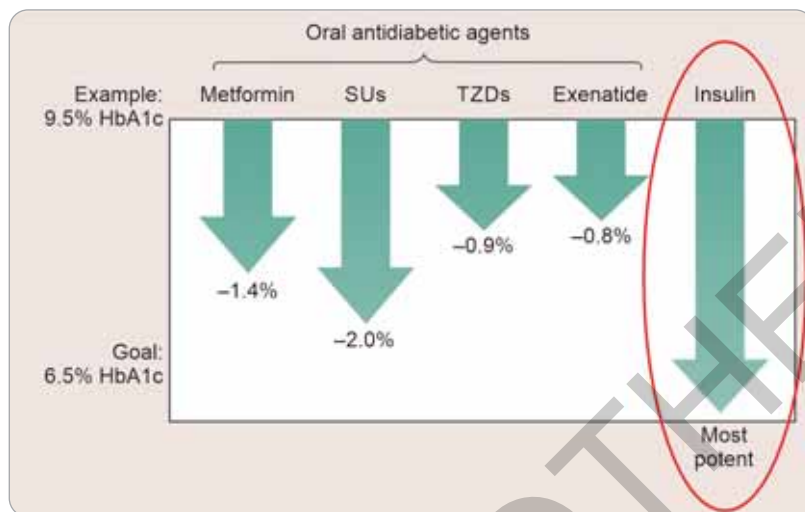


FIG. 1: Insulin delivers superior glucose reductions versus other agents.

(HbA1c: glycated hemoglobin; SUs: sulfonylureas; TZDs: thiazolidinediones)

Source: Adapted from the American Association of Clinical Endocrinologists (AACE) medical guidelines for the management of diabetes mellitus. *Endocr Pract.* 2000;6(1):43-84.

delivered in regimens mimicking physiologic insulin secretion. The aim of insulin therapy is to approximate the physiologic insulin profile via insulin replacement; however, this is limited by peripheral hyperinsulinemia and portal hypoinsulinemia in peripherally administered insulin, when compared to physiological endogenous insulin being secreted directly into the portal circulation, variable subcutaneous insulin absorption and the risk of hypoglycemia.

■ HISTORY

The history of insulin begins with a description of endocrine pancreas pathophysiology and its link to the development of diabetes, followed by isolation of pancreatic islet extracts. In 1921, Frederick G Banting hypothesized that the ligation of pancreatic ducts before extraction of the pancreas destroys the enzyme-secreting parts, whereas the islets of Langerhans, which were believed to produce an internal secretion regulating glucose metabolism, remained intact. Banting along with Charles H Best in John JR MacLeod's laboratory at the University of Toronto produced an extract of pancreas that reduced the hyperglycemia and glycosuria in dogs made diabetic by the removal of their pancreas. Biochemist James B Collip later developed a novel protocol to purify what they later named "insulin" (Latin: insula, island), from pancreatic islets of whole bovine pancreata without the need for pancreatic duct ligation experiments. Following this, many milestones were set in the path of insulin discovery (**Fig. 2**). Beef insulin was the first commercially available preparation followed by porcine. A recombinant DNA technique was later employed in the preparation of human insulin. In the mid-1950s the molecular structure of insulin was determined by Frederick Sanger.

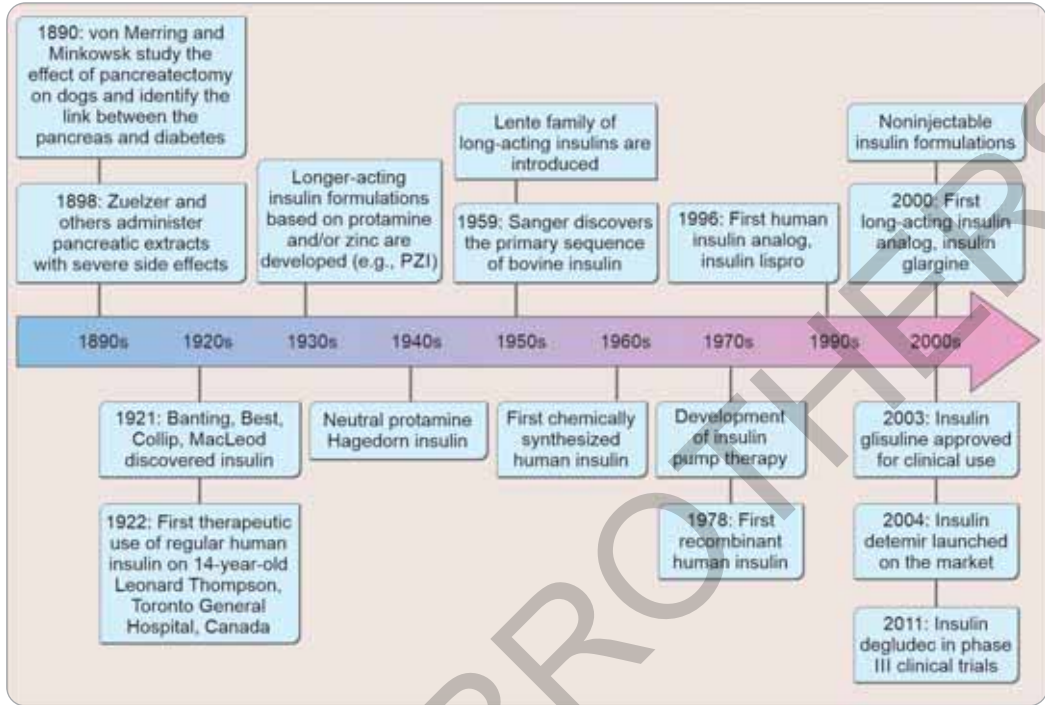


FIG. 2: Milestones in the development of insulin replacement therapy.

(PZI: protamine zinc insulin)

Source: Adapted from Borgoño CA, Zinman B. Insulins: Past, present, and future. *Endocrinol Metab Clin North Am.* 2012;41(1):1-24.

■ CLASSIFICATION OF INSULIN

Insulin formulations are classified as rapid-, short-, intermediate-, or long-acting insulins based on their pharmacokinetic (PK) properties, including onset, peak, and duration of action, summarized in **Table 1**. The unique PK parameters of individual insulin products depend primarily on the rate and extent of absorption into the systemic circulation following subcutaneous injections.

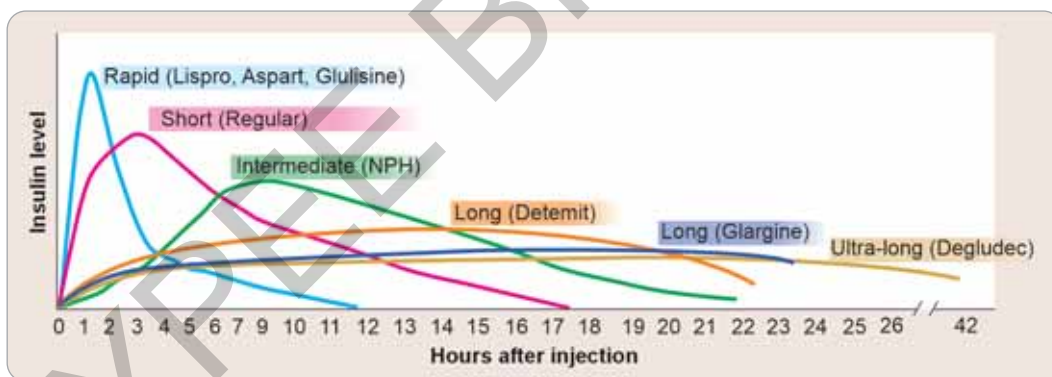
Short-acting Regular Insulins

Regular human insulin was the first insulin product generated utilizing recombinant DNA technology. The peptide sequence and tertiary structure of regular recombinant human insulin is identical to that of its endogenous counterpart. However, the PK profile of recombinant regular insulin characterized by delayed onset of action (30–60 minutes), relatively late peak effect (2–4 hours) and a longer duration of action (6–8 hours) compared with the sharper peak secretion of endogenous insulin is secondary to the self-aggregation into quaternary structures of dimers and hexamers in solutions of higher concentration containing zinc ions (**Fig. 3**). This propensity to self-associate delays the absorption of regular human insulin, which must first dissociate into dimers and monomers in the subcutaneous

TABLE 1: Classification of insulin.

Insulin	Onset	Peak (hours)	Effective duration (hours)	Maximum duration (hours)
<i>Bolus or mealtime insulin</i>				
• Aspart	• 5–10 minutes	• 1–3	• 3–5	• 4–6
• Lispro	• <15 minutes	• 0.5–1.5	• 2–4	• 4–6
• Glulisine	• <15 minutes	• 0.5–1.5	• 2–4	• 4–6
• Regular	• 30–60 minutes	• 2–3	• 3–6	• 6–10
<i>Basal insulin</i>				
• NPH	• 2–4	• 4–10	• 10–16	• 14–18
• Glargine	• 1	• No peak	• 24	• 24
• Detemir	• 2–3	• No peak	• 24	• 24
• Degludec	• 30–90 minutes	• No peak	• >24	• 42
<i>Combinations</i>				
• 50% NPH/50% regular	• 30–60 minutes	• Dual	• 10–16	• 14–18
• 70% NPH/30% regular	• 30–60 minutes	• Dual	• 10–16	• 14–18
• 75% NPH/25% lispro	• <15 minutes	• Dual	• 10–16	• 14–18
• 70% APS/30% aspart	• 10–20 minutes	• Dual	• 24	• 24
• 70% IDeg/30% IAsp	• 10–20 minutes	• Dual	• >24	• 42

(APS: aspart protamine suspension; IDeg: insulin degludec; NPH: neutral protamine Hagedorn)

**FIG. 3:** Pharmacokinetic profiles of human insulin and insulin analogs.

Source: Adapted from Meah F, Juneja R. Insulin tactics in type 2 diabetes. *Med Clin North Am.* 2015;99(1):157-86.

space to effectively diffuse into general circulation and exert its glucodynamic action. Given its delayed onset of action, regular insulin should be administered 20 minutes before meals.

Intermediate-acting Human Insulin: Isophane Neutral Protamine Hagedorn

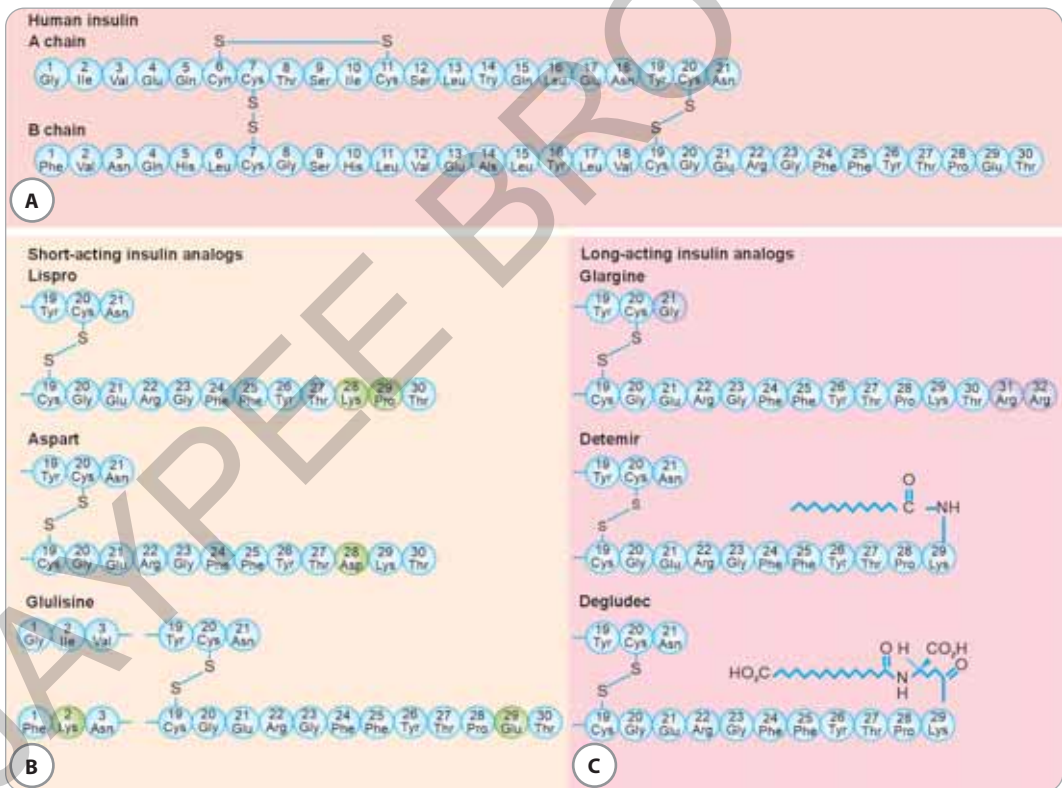
Neutral protamine Hagedorn (NPH) is composed of recombinant insulin suspended in a neutral pH solution of protamine and zinc. This unique suspension allows for a significant delay in the absorption of insulin from the subcutaneous tissue, resulting in an onset of action

1.5–4 hours after injection, a pronounced peak 4–10 hours after administration, and duration of up to 12–20 hours.

Neutral protamine Hagedorn does not constitute an appropriate surrogate for endogenous basal insulin production in view of its pronounced peak action profile and intermediate duration of action. However, NPH has retained clinical utility as basal insulin when administered twice daily and in a premixed insulin preparation combined with regular human insulin, especially in view of its low cost as compared to long-acting insulin analogs.

Insulin Analogs

Insulin analogs are produced through targeted structural manipulation of the human insulin molecule like amino acid substitutions, inversions, or additions (**Fig. 3**) using recombinant technology and protein bioengineering techniques leading to alteration in pharmacodynamic and PK profiles (**Figs. 4A to C**). In general, rapid-acting, and long-acting insulin analogs have been modified to possess a weaker or stronger ability to self-associate and hence, a faster or slower diffusion rate following subcutaneous tissue injection, respectively.

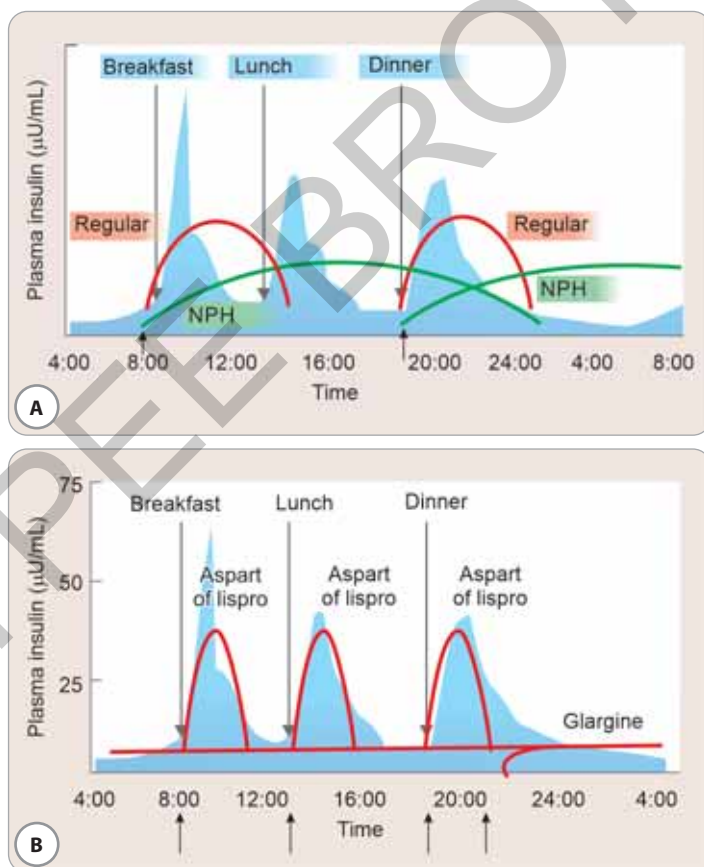


FIGS. 4A TO C: The primary structure of human insulin and insulin analogs. (A) Native human insulin; (B) Rapid-acting insulin analogs (lispro, aspart, and glulisine); (C) Long-acting insulin analogs (glargine, detemir, and degludec). Modifications of each insulin analog are highlighted in the figure.

Source: Adapted from Borgoño CA, Zinman B. Insulins: Past, present, and future. *Endocrinol Metab Clin North Am.* 2012; 41(1):1-24.

Rapid-acting Insulin Analogs (*Lispro, Aspart, and Glulisine*)

Insulin lispro is produced by transposition of amino acids proline and lysine at positions B28 and B29 leading to a conformational change that augments steric hindrance between interfaces implicated in dimerization. The substitution of proline at B28 by a negatively charged aspartic acid residue in the case of insulin aspart results in repulsion of monomers. In insulin glulisine, replacement of lysine at B29 for glutamine and aspartic acid at B3 for lysine simultaneously provides stability and a reduced ability to self-associate. The resulting PKs is compatible with physiologic time-activity profiles of meal-stimulated insulin release. The rapid onset of action of insulin lispro, aspart, and glulisine allows for greater flexibility and convenience in the timing of administration, that is, either at mealtime or even immediately postprandially with improved normalization of postprandial glucose excursions, however, carries the risk of early postprandial hypoglycemia and preprandial hyperglycemia compared with regular insulin (**Figs. 5A and B**).



FIGS. 5A AND B: (A) Basal-bolus therapy using split-mixed regimen and bedtime intermediate insulin. (B) Basal-bolus therapy using glargine and aspart of lispro.

Source: Adapted from Hirsch IB. Insulin analogs. *N Engl J Med.* 2005;352(2):174-83.

Ultrafast Acting Insulins: Faster Aspart

Faster aspart marks the era of ultrafast acting insulins which are next-generation mealtime insulins developed to more closely mimic the normal insulin physiology. Fast-acting insulin aspart (faster aspart) (FIAsp) is insulin aspart (IAsp) with two added excipients: Niacinamide (absorption modifier) and L-arginine (added for stability). Niacinamide increases the absorption of insulin aspart by facilitating monomer formation and permeation of monomer into the bloodstream from the subcutaneous tissue. This rapid monomer formation and increased permeation makes faster aspart to have ultrafast onset of action.

Faster aspart provides an overall left-shift of the pharmacokinetic/pharmacodynamics profiles resulting in earlier onset, twice as large initial exposure, and up to 2.5-fold greater initial glucose-lowering effect within the first 30 minutes, as well as earlier offset of exposure and effect compared with insulin aspart. This was reflected by superior 1-hour postprandial glucose control as compared to conventional prandial insulin analogs in the ONSET-1 and ONSET-2 phase III clinical trials. FIAsp had a greater reduction in glycated hemoglobin (HbA1c) concentrations from baseline in patients with T1DM when compared with insulin aspart, whereas had similar outcome in patients with T2DM. FIAsp can be considered a viable option for those patients with T1DM and T2DM who desire to inject immediately prior to a meal or within 20 minutes following a meal and need better postprandial glycemic control or in elderly patients wherein frequent hypoglycemia occurs postprandially.

Ultra Rapid-acting Lispro Insulin

Ultra rapid lispro (URLi) insulin is formulated with treprostinil and citrate to facilitate the absorption of insulin lispro. Peak effect is seen in 2.0–2.9 hours and the noninferiority of URLi compared to insulin lispro was demonstrated in PRONTO-T1D and PRONTO-T2D trials.

Long-acting Insulin Analogs

Long-acting insulin analogs in view of their longer duration of action without a pronounced peak can be used as basal component of basal-bolus insulin regimen in insulin replacement therapy or as an augmentation therapy in addition to oral glucose-lowering agents (OGLAs) in patients who failed to achieve optimum glycemic control with maximum recommended OGLAs.

Insulin Glargine and Insulin Detemir

Insulin glargine is produced by replacement of asparagine with glycine at position A21 and the addition of two arginine residues at position B30, respectively resulting in a molecule that is less soluble at neutral, physiologic pH yet stable in the acidic pH of its storage solution. Thus, when injected into the neutral milieu of the subcutaneous tissue, glargine forms an amorphous precipitate from which insulin molecules are slowly released into the circulation.

In insulin detemir, deletion of amino acid threonine at position B30 and acylation of a 14-carbon aliphatic fatty acid (myristolytic acid) to the ϵ -amino group of lysine at position B29, enhances its affinity for albumin and forms multimeric complexes within the subcutaneous tissues leading to sustained release postinjection.

Insulin glargine and detemir have comparable PK profile with an onset of action within 1–3 hours of administration and a relatively peakless, dose-dependent, mean duration of action

of approximately 24 hours representing better surrogates for basal insulin replacement. The principal advantage of insulin glargine and detemir over NPH insulin is a lower frequency of hypoglycemic reactions, longer duration of action and reduction in glycemic excursion due to *dawn phenomenon*. Lesser incidence of hypoglycemia and most importantly reduction in nocturnal hypoglycemic events and reduced incurring weight gain as compared to NPH have been seen in various studies. Riddle et al. showed a 25% reduction in the incidence of nocturnal hypoglycemia and 21–48% reductions in other categories of symptomatic hypoglycemia with insulin glargine when compared with NPH. Hermansen et al. showed a 21% reduction in overall risk of hypoglycemia ($p = 0.036$) and a 55% reduction in nocturnal hypoglycemia ($p < 0.001$) with detemir as compared to NPH in a study of around 600 patients with T1DM. Reduced intraindividual variability of glargine and detemir over NPH was also demonstrated in T1DM patients by Heise et al. by euglycemic clamp conditions.

The glucose-lowering effect of these basal insulin analogs tends to wax and wane considerably over 24 hours with once-daily dosing resulting in hyperglycemia late in the expected action profile (*Dusk phenomenon*), which might necessitate a twice daily administration.

It was previously postulated that long-acting insulin analogs are associated with increased risk of cancer in view of higher affinity to insulin-like growth factor 1 (IGF-1) receptors; however, recent meta-analysis and long-term follow-up studies have not shown increased risk of malignancy with glargine and detemir. Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, which looked into cardiovascular (CV) outcomes over a 6-year period in 12,612 persons [predominantly persons with early T2DM and some (12%) with impaired glucose tolerance], in addition to demonstrating CV safety, showed no increased cancer risk with glargine.

Insulin Degludec

Insulin degludec (IDeg) is an ultra-long-acting basal insulin analog produced by the conjugation of hexadecanedioic acid via γ -L-glutamyl spacer at the amino acid lysine positioned at B29 leading to the formation of multihexamers in subcutaneous tissues. Slow-sustained release from subcutaneous tissue leads to the longer duration of action of around 42 hours making it once daily basal insulin with advantages of flexibility in dosing time and reduced hypoglycemic episodes. It has a half-life of 25 hours, which is almost twice as long as glargine, with a lower degree of variability in its glucose-lowering effect over 24 hours at a steady state.

Noninferiority of degludec over glargine in terms of efficacy with a reduced risk of nocturnal hypoglycemia have been demonstrated by studies in T1DM (BEGIN basal-bolus type 1 study) and T2DM (BEGIN basal-bolus type 2 study) patients. The CV safety was established by a CV outcome trial, the DEVOTE study. Once-daily dosing of IDeg has shown a low peak: Trough ratio, low intra-individual variability and the plasma concentrations less critically dependent upon the time of injections. This leads to an advantage of greater flexibility in dose timing and reduced nocturnal hypoglycemia as compared to other long-acting basal insulins. The PK property of degludec raises the concern of “*insulin stacking*” which is an excessive accumulation of insulin in the circulation on daily administration of a basal insulin whose duration of action exceeds 24 hours, thereby leading to an increased risk in the frequency, duration, or severity of hypoglycemia. However, this can be prevented if ultra-long-acting insulins are dosed in appropriate amounts and adjusted at appropriate time intervals based on glucose profile.

In view of the lower incidence of hypoglycemia especially nocturnal hypoglycemia and lower day-to-day variability in its glucose lowering effect, IDeg is recommended in patients with recurrent hypoglycemic events and significant glycemic variability with other long-acting insulin; however, the limiting factors are the higher cost, and the stacking effect.

Glargine U300

Glargine U300 is a newer higher strength formulation of insulin glargine. It is produced at 300 IU/mL unlike the usual glargine at 100 IU/mL, which alters its PK and pharmacodynamic properties resulting in the formation of a more compact subcutaneous depot with its surface area reduced by half and its volume by two-thirds. Retarded and prolonged dissolution from the subcutaneous tissue leads to longer duration of action with reduced hypoglycemic events. Noninferiority to insulin glargine U100 with 25% reduction in nocturnal hypoglycemic episodes were seen over 6 months in phase 3 randomized parallel-group studies (EDITION), predominantly in persons with T2DM. It may be specifically useful in those with recurrent hypoglycemia especially nocturnal hypoglycemia and those on higher insulin doses.

The determinants of absorption and duration of action of human and analogue insulins are summarized in **Figure 6**.

Premixed Insulin Preparations

Premixes of conventional insulin products and fixed-ratio mixes of insulin analogs are available in different ratios as shown in **Table 1**. Premixed insulin represents a convenient alternative to basal-bolus insulin therapy, with a decreased number of daily injections, in patients requiring insulin therapy other than T1DM. The fixed ratio of short-acting and intermediate-acting insulins in premixed insulin limits adjustment of doses of each component based on glucose readings and also predisposes to hypoglycemia if proper timing of meals according to the PKs of each insulin component is not followed.

Insulin Degludec/Insulin Aspart (IDegAsp; 70% IDeg, and 30% IAsp)

IDegAsp is a soluble combination of two individual insulin analogs IDeg and insulin as part in one product, designed to provide mealtime glycemic control due to the IAsp component and basal glucose-lowering effect from the IDeg component. IDeg exists as highly stable dihexamers in a neutral solution in the presence of phenol and zinc. Upon injection, phenol diffuses and IDeg undergoes a conformational change, leading to formation of soluble multihexamers at the injection site. With the gradual diffusion of zinc, the IDegmultihexamers continuously disassemble and release monomers for absorption into the circulation. IDegAsp provides rapid onset and peak glucose-lowering effect due to the bolus IAsp component, as well as a flat and long-lasting glucose lowering effect from the basal IDeg component, during both once-and twice-daily dosing across several different patient populations studied. IDegAsp has shown favorable clinical benefits compared with biphasic insulin in phase 3 studies and may be used as an alternative to basal-bolus and basal-only therapy. However, fixed ratio of basal and bolus components as in other premixed insulin may limit finer adjustments to control fasting and postmeal hyperglycemia.

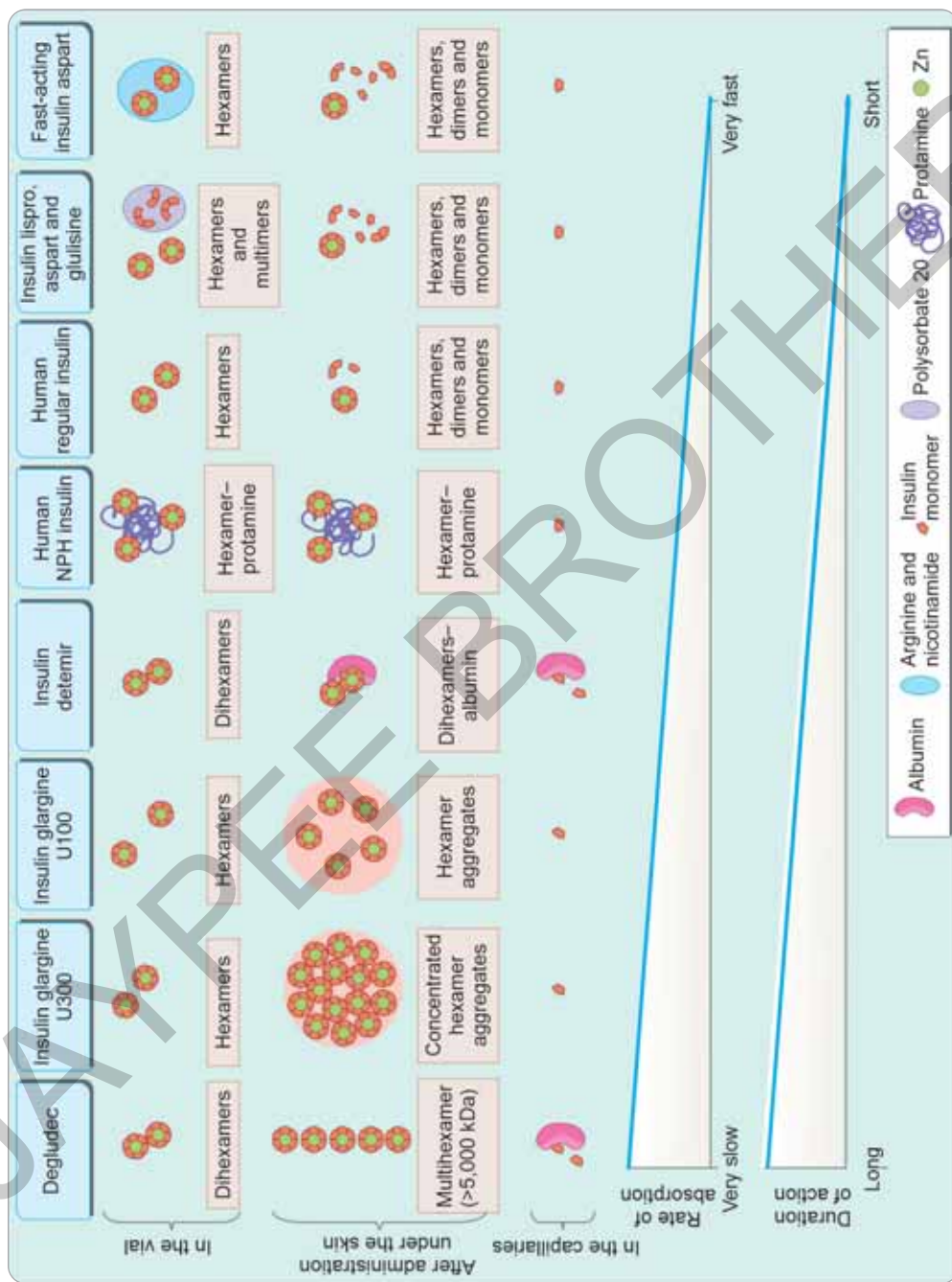


FIG. 6: Determinants of absorption and duration of action of human and analog insulins. Source: Adapted from Mathieu C, Gillard P, Benhalima K. Insulin analogues in type 1 diabetes mellitus: getting better all the time. Nat Rev Endocrinol. 2017;13:385-99.

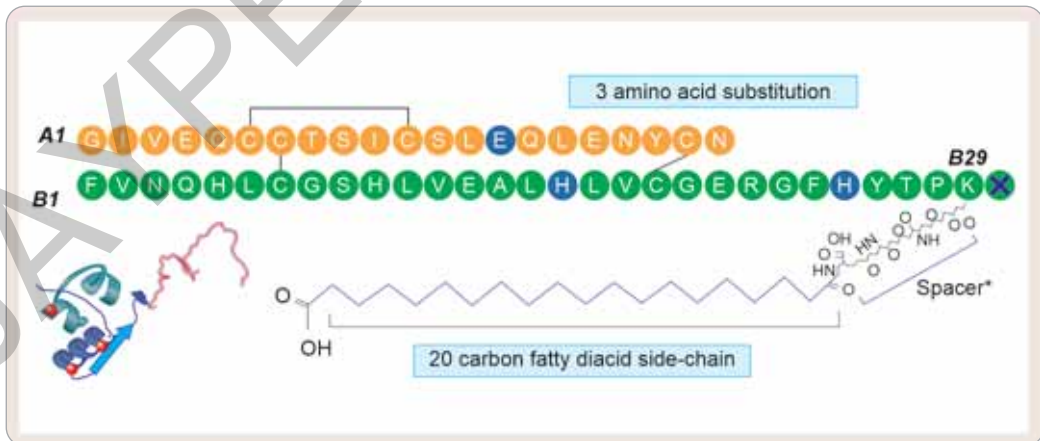
■ ONCE WEEKLY INSULIN

The guidelines for standards of care from the American Diabetes Association and the European Association for the Study of Diabetes recommend treatment escalation when individualized glycemic targets are not reached in patients with T2DM. Despite these recommendations, clinical inertia is highly prevalent in the management of T2DM, with the longest delays reported for insulin initiation. People generally prefer fewer injections and greater flexibility than is typical of the current once-daily treatment options. Reducing the number of injections could potentially increase acceptance of and adherence to insulin treatment among patients with T2DM, thereby potentially improving glycemic control.

Insulin icodec is a novel, long-acting basal insulin analog, with a time to maximum concentration of 16 hours and a half-life of approximately 1 week. These pharmacokinetic and pharmacodynamic profiles make Icodec insulin suitable for once-weekly injection. The long half-life of insulin icodec was achieved by introducing modifications to the insulin molecule aiming to obtain a safe, albumin-bound circulating depot of insulin icodec, providing protracted insulin action and clearance. The addition of a C20 fatty diacid-containing side chain imparts strong, reversible albumin binding, while three amino acid substitutions (A14E, B16H, and B25H) provide molecular stability and contribute to attenuating insulin receptor (IR) binding and clearance, further prolonging the half-life (Fig. 7). Studies have shown that, in people with T2DM, once-weekly treatment with insulin icodec had glucose-lowering efficacy and a safety profile similar to those of once-daily insulin glargine U100.

Indications for Insulin Therapy

- Type 1 diabetes mellitus
- Type 2 diabetes mellitus patients who have failed to achieve glycemic goals with the maximal dose of OGLAs.
- Gestational diabetes



*gGlu-2xOEG (gammaGlutamate Oligoethylene glycol).

FIG. 7: Structure of once weekly icodec insulin.

- Individuals with T2DM, during periods of physiological stress such as surgery, infection, or acute illness
- Progressive complications threatening organ functions—nephropathy, proliferative retinopathy, maculopathy, etc.
- Diabetes ketoacidosis/hyperosmolar hyperglycemic nonketotic coma
- Secondary diabetes (pancreatitis and corticosteroids)
- Chronic renal failure
- Use of parenteral nutrition or high calorie supplements

Algorithm for Starting/Shifting to Insulin During the Course of Treatment of Diabetes Mellitus (Box 1)

BOX 1: Algorithm for starting/shifting to insulin during the course of treatment of diabetes mellitus.

At diagnosis:

- Ketosis (in absence of starvation)/ketoacidosis/dehydration
- Marked hyperglycemia (without carbohydrate/calorie abuse)
- Acute medical event with actual/potential decompensation
- Marked hyperglycemia with uncertain near-future environment (foreign travel)

Early after diagnosis (within 2 years):

- Latent autoimmune diabetes in adults (LADA) phenotype or secondary pancreatic phenotype
- Presence of glutamic acid decarboxylase (GAD) antibodies/low body mass index (BMI)/waist circumference/no dyslipidemia
- Deterioration in glucose control in 6–24 months' despite uptitration of multiple oral agent therapy
- Concomitant disease: Pancreatitis, hepatic cirrhosis, chronic steroid therapy, relapsing inflammatory disease, antirejection therapy, etc.

Later in the course of continuing care:

- Taking one to four other glucose-lowering therapies and glycated hemoglobin (HbA1c) not in the target
- Progression of hyperglycemia despite oral agent uptitration
- Previous patient education given and personal lifestyle input unlikely to improve
- Patient preference for injectable natural hormone to drug
- Development of end-organ damage like chronic kidney disease when other oral glucose-lowering therapies cannot be offered

Source: Adapted from Diabetes Care. 2014;37:1499-508.

Insulin Therapy Initiation, Titration, and Follow-up (Table 2)

Insulin therapy may be used either as augmentation therapy or as replacement therapy.

Augmentation therapy is provided by adding basal insulin to oral glucose-lowering agents in patients with partial β -cell failure. The goal of basal insulin is to suppress hepatic glucose production and improve fasting hyperglycemia.

Replacement therapy in the form of basal-bolus insulin regimen, premixed insulin or insulin pump is recommended for those where endogenous insulin production is minimal or

■ CASE STUDIES

Case 1

A 58-year-old gentleman working as a lawyer, known to have T2DM for 10 years, systemic hypertension and dyslipidemia, is on tablet metformin 1 g twice daily, tablet glimiperide 4 mg twice daily and sitagliptin 50 mg once daily, tablet telmisartan 40 mg once daily and tablet atorvastatin 10 mg bedtime. His biochemical evaluation shows fasting plasma glucose of 210 mg/dL, PPG of 280 mg/dL, HbA1c is 8.5%. What would you advise?

Assessment: Patient has uncontrolled T2DM despite being on maximum dose of OGLAs. Augmentation therapy with basal insulin analog like glargine or detemir can be advised at bedtime with an initial dose of 10 units or 0.2 U/kg in addition to current OGLAs. He should also be educated on SMBG and titration of insulin dose to target the fasting glucose of 80–120 mg/dL and postprandial glucose of 120–140 mg/dL. If on subsequent follow-up, the postprandial sugars show rising trend or if HbA1c is >7%, patient can be started with premixed insulin at initiation dose of 0.3 U/kg/day with total dose split into two-thirds before breakfast and one-third before dinner and subsequently titrated based on SMBG.

Case 2

A 16-year-old boy working as a mason presents with history of polyuria, polydipsia, and weight loss of 6 kg over 3 months. His biochemical evaluation shows fasting plasma glucose is 280 mg/dL, postprandial plasma glucose is 380 mg/dL, HbA1c is 10.5%, and GAD antibody is positive. How would you manage?

Assessment: Patient has T1DM and thus requires replacement insulin therapy in the form of basal-bolus regimen using short-acting human insulin or insulin analogs as bolus insulin for prandial coverage and long-acting insulin analogs or NPH for basal coverage. Based on the economic status of this patient, he can be advised regular insulin with each meal and bedtime long-acting insulin like glargine or detemir. He can be started on 0.5 U/kg/day of total insulin dose which can be split into 40% dose as basal insulin bedtime and 60% regular insulin for prandial coverage (20% before breakfast, lunch, and dinner). The patient must be educated on dietary plan, physical activity, SMBG, and hypoglycemic symptoms. The insulin has to be titrated based on SMBG reading every 2–3 days.

Case 3

A 34-year-old lady presents at 28 weeks gestation with 75 g oral glucose tolerance test (OGTT) of fasting 118 mg/dL, 1-hour glucose is 328 mg/dL, 2-hours glucose is 242 mg/dL. Urine ketones is negative. Clinically, she is obese with signs of insulin resistance in the form of acanthosis nigricans. What would be the management plan?

Assessment: Patient has overt diabetes in pregnancy and needs strict glycemic control to prevent maternal and fetal complications. She would be advised tablet metformin 500 mg twice daily which can be increased to maximum of 1 g twice daily and insulin therapy. Insulin therapy in the form of basal bolus would be advisable. She can be started with regular insulin 2–4 units

SELF-ASSESSMENT

- 1. A 55-year-old Mr R who is a known patient with type 2 diabetes mellitus (T2DM) for 15 years presented with a history of inability to sleep at night due to persistent pricking sensation of both his feet. On examination his feet were normal, monofilament recorded 10 grams in both feet and biothesi-ometer read 40 volts bilaterally. Both fundi showed severe nonproliferative diabetic retinopathy (NPDR). Systemic examination was normal. He has been on glibenclamide, metformin 1 g TID. His HbA1c was >12%. All of the following are true, *except*:**
 - (a) Peripheral neuropathy is an indication to start him on insulin.
 - (b) Best option is to add another oral hypoglycemic agent for better control of sugars.
 - (c) MCR footwear should be ideally prescribed for his neuropathy.
 - (d) He would require long-term insulin therapy.
 - (e) Severe NPDR is an indication for insulin therapy.
- 2. The usual starting dose of insulin in augmentation therapy is:**
 - (a) 0.15 units/kg/dose
 - (b) 0.35 units/kg/dose
 - (c) 0.50 units/kg/dose
 - (d) 0.05 units/kg/dose
- 3. All of the following are indications to initiate insulin therapy early, *except*:**
 - (a) MODY
 - (b) LADA
 - (c) Gestational diabetes
 - (d) Fibrocalcific pancreatitis
 - (e) Secondary OAD failure
- 4. All of the following are true about insulin analogs, *except*:**
 - (a) There is no pronounced insulin peak with insulin glargine.
 - (b) They are superior to human insulin in preventing complications of diabetes.
 - (c) Insulin lispro is safe in pregnancy.
 - (d) Insulin detemir may be administered as twice daily injections in type 1 diabetes mellitus.
 - (e) Rapidly acting analogs are superior to regular insulin in lowering postprandial sugars.
- 5. Which of the following is not a short-acting insulin?**
 - (a) Lispro
 - (b) Detemir
 - (c) Aspart
 - (d) Glulysine
 - (e) Actrapid
- 6. Which of the following is associated with weight gain?**
 - (a) Exenatide
 - (b) Regular insulin
 - (c) Detemir
 - (d) Liraglutide
- 7. Which of the following OAD should be ideally stopped while starting a patient on insulin?**
 - (a) Metformin
 - (b) Glimepiride
 - (c) Pioglitazone
 - (d) Acarbose
- 8. Which of these drugs can be used in a patient with diabetic nephropathy in renal failure (Creatinine: 4.3 mg/dL)?**
 - (a) Glibenclamide
 - (b) Metformin
 - (c) Insulin
 - (d) Aminoglycoside
 - (e) Detemir

A Practical Guide to Diabetes Mellitus

The 9th edition of the manual has undergone significant progressive evolution since its first edition in 2004. It combines the diversity of essential information, the aspects of practical clinical skill, and the brevity of what knowledge is truly required and is supported by illustrations, tables, and flowcharts which ensure tranquil reading, with poetic prologues for each chapter. The present edition has several piouettes which counterpoise Avant-Gard, which range from revised chapters, to updated evidence about medications for diabetes and obesity, and to information on novel gadgets and therapeutic inroads in the field. A chapter on musculoskeletal manifestations of diabetes mellitus has been incorporated, along with a variety of added clinical pictures and diagrammatic illustrations to entice mental cooperation and provoke the indulgence and enthusiasm of the bibliophile.

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