Type 1 Diabetes

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Disclosures

- None

Learning objectives

- Classification of diabetes
- T1DM pathophysiology - GAD65 antibody and C-peptide.
- Pharmacologic treatment of T1DM
- TDD for MDI and insulin pump
- CGM report
- DKA transition to MDI
- T1DM clinical trials

Classification of Diabetes

CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

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Recommendations on GDM

- **Test for undiagnosed diabetes at the first prenatal visit in those with risk factors.**
- **Test for GDM at 24-28 weeks.**
- **Test women with GDM for prediabetes or DM at 4-12 wks postpartum, using 75-g OGTT.**
- **Women with GDM should have lifelong screening for DM at least every 3 yrs.**
- **Women with GDM found to have prediabetes should receive lifestyle intervention or metformin.**

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Recommendations on CFRD and post-transplantation DM

- Annual screening for CFRD with OGTT should begin by age 10 yrs.
- A1c is not recommended to diagnose diabetes.
- CFRD treatment is insulin regimen.
- Beginning 5 yrs after the diagnosis of CFRD, annual monitoring of complications of diabetes.
- OGTT is the preferred test to make the diagnosis of post-transplantation DM.

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Monogenic diabetes

Table 2.7—Most common causes of monogenic diabetes (119)

	Gene	Inheritance	Clinical features
MODY			
	GCK	AD	GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
	HNF1A	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes			
	KCNJ11	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1, HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes; autoimmune thyroid disease; exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction.

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T1DM and Immune checkpoint inhibitor

Table 4 Summary of results.

Characteristic	All cases (n = 91)
Age, years	
Median (range)	61 (22–84)
Gender	
Female/male	36 vs 55
Ethnicity	
Asian	14/91 (15%)
Tumor types	
Melanoma	48/91 (53%)
NSCLC	14/91 (15%)
Past medical history*	20/91 (22%)
Prior immunotherapy	22/91 (24%)
IL-2	2/91
Interferon	7/91
Ipilimumab	16/91
Nivolumab	3/91
Immune checkpoint inhibitor	
Anti-CTLA-4	3/91 (3%)
Anti-PD-1	65/91 (71%)
Anti-PD-L1	7/91 (8%)
Anti-CTLA-4 + anti-PD-1	14/91 (15%)
Anti-PD-L1 + 4-1BB blockade	1/91
CTLA-4 or PD-1 blockade	1/91
Time-to-diagnosis in cycles (range)	4.5 (1–17)
Combination therapy	2.7 (1–5)
With/without DKA	4 vs 5.9
GADA pos./GADA neg.	3.1 vs 5.9
Diabetic ketoacidosis	64/91 (71%)
Glycemia, median (range)	565 mg/dL (209–1211)
Glycated hemoglobin, median (range)	7.6% (5.4–11.4)
Low-C-peptide at diagnosis	58/69 (84%)
Elevated lipase	13/25 (52%)
Positive pancreas autoantibodies	
At least one	47/88 (53%)
Two or more	13/88 (15%)
Type of pancreas autoantibodies	
GADA	51%
IA-2	18%
ICA	13%
Anti-insulin	26%
ZnT8	4%
HLA analysis	51/91 (56%)
Susceptible	31/51 (61%)
Susceptible and protective	2/51 (4%)
Neutral	10/51 (20%)
Protective	8/51 (16%)
Thyroid dysfunction with ICI	21/91 (24%)
Prior history of thyroid dysfunction	2/21

*Diabetes mellitus, thyroid disease or risk thereof.
4-1BB, CD137; CTLA-4, cytotoxic T lymphocyte antigen 4; DKA, diabetes ketoacidosis; GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IA-2, insulinoma-associated antigen-2; ICA, islet-cell antibodies; ICI, immune checkpoint inhibitor; IL-2, Interleukin-2; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ZnT8, zinc transporter 8.

de Filette JMK, et al. Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. Eur J Endocrinol. 2019 Jul.

Criteria for the diagnosis of Diabetes

Table 2.2—Criteria for the diagnosis of diabetes
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

- **Plasma glucose not a1c should be used to diagnose the acute onset of T1DM.**
- **Screening for T1DM risk with a panel of autoantibodies is recommended in a research trail or in first-degree family members of T1DM.**
- **Persistence of two or more autoantibodies predicts clinical diabetes and may be used in a clinical trial.**
- **Autoimmune markers: islet cell autoantibodies, GAD65-ab, insulin, the tyrosine phosphatases IA-2 and IA-2B and ZnT8.**

GAD65 antibodies and C-peptide

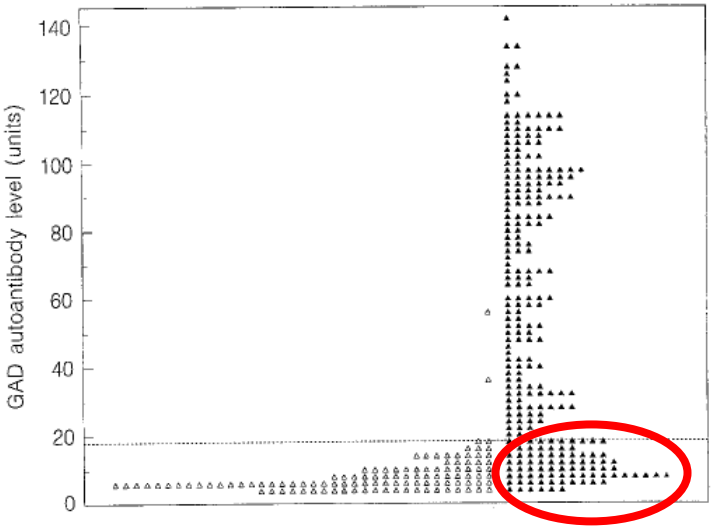

Fig. 1. The levels of antibodies to glutamate decarboxylase (anti-GAD) in 109 non-diabetic children (△) and 261 newly-diagnosed diabetic children (▲). The dashed line represents the 98th percentile for anti-GAD among the non-diabetic children (18 units)

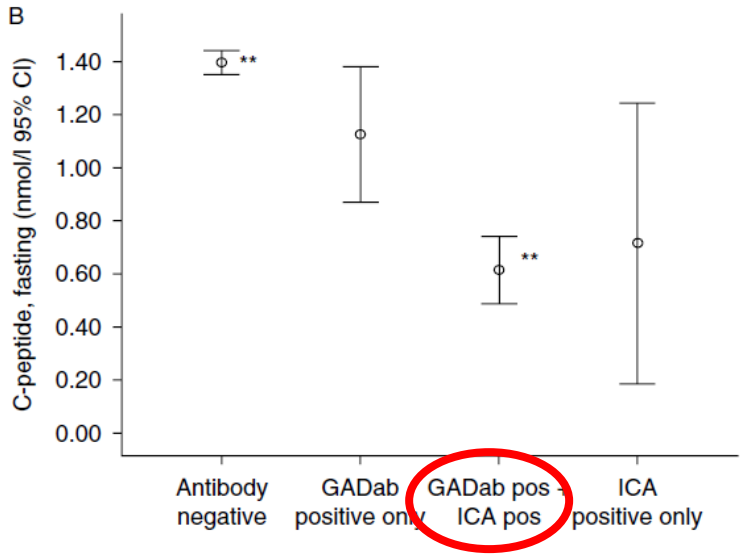

Figure 1 (A) Mean fasting C-peptide (nmol/l), per age and BMI group in non-autoimmune diabetes. (B) Mean fasting C-peptide, including 95% confidence intervals, per antibody positivity; all in adults with newly diagnosed diabetes. $^{**}P<0.001$.

Verge CF, et al. Anti-glutamate decarboxylase and other antibodies at the onset of childhood IDDM: a population-based study. *Diabetologia* 1994 37 1113–1120.

Thunander M, et al. Levels of C-peptide, body mass index and age, and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden. Eur J Endocrinol. 2012 Jun;166(6):1021-9.

Case 1

- **Mr. G, 21 yo, diagnosed with T1DM age 11. On insulin pump for 8 yr. Weight 99kg. Currently on Medtronic 670G pump with below settings:**
-

Basal rate: (47.5 units per day)
MN 2.05
0430 2.00
0700 1.85
1400 2.00
2000 2.10

ICR
MN 1: 8
0500 1: 4
1000 1: 6
1200 1: 5
1600 1:3.2

ISF
MN 1:28
0530 1:23
1000 1:21
1400 1:22

Blood glucose target:
MN 90-110
0700 80-100
2200 90-110

Date	Result Name	Value	Ind	Ref Range
11/08/2019 9:02	Glucose Level	185 mg/dL	(H)	(65 - 99)
11/08/2019 9:02	Hemoglobin A1c	7.8 %	(H)	(- <=5.6)
11/08/2019 9:02	Estimated Average Glucose (eAG)	177		(Not Established -)
11/08/2019 9:02	BUN	13 mg/dL		(8 - 25)
11/08/2019 9:02	Creatinine	0.92 mg/dL		(0.60 - 1.50)
11/08/2019 9:02	Cholesterol	130 mg/dL		(- <=199)
11/08/2019 9:02	HDL	46 mg/dL		(>=40 -)
11/08/2019 9:02	Cholesterol/HDL Ratio	2.9		(- <=4.9)
11/08/2019 9:02	LDL, Calculation	73 mg/dL		(- <=99)
11/08/2019 9:02	Non HDL Cholesterol	84 mg/dL		(- <=159)
11/08/2019 9:02	Triglycerides	55 mg/dL		(- <=149)
11/08/2019 9:02	VLDL	11 mg/dL		(- <=29)
11/08/2019 9:02	T4 Free	1.3 ng/dL		(0.8 - 1.7)
11/08/2019 9:02	TSH	1.60 mU/L		(0.45 - 4.50)
11/08/2019 9:02	Vitamin D, 25 Hydroxy	16.8 ng/mL	(L)	(>=20.0 -)
11/08/2019 9:02	C Peptide	<0.1 ng/mL	(L)	(1.1 - 4.4)

Case 2

- **Ms. N, 39 yo, diagnosed with T1DM in childhood and on MDI since then. Weight 100kg.**
- **Current diabetic regimen:**

Levemir 40 units BID
Humalog 20 units TIDAC
Humalog ISF 1:25 over 100 mg/dl

Glucose	**433**	**High**	mg/dL	65 - 99	01
BUN	20		mg/dL	6 - 20	01
Creatinine	0.82		mg/dL	0.57 - 1.00	01
eGFR If NonAfricn Am	90		mL/min/1.73	>59	
eGFR If Africn Am	104		mL/min/1.73	>59	
BUN/Creatinine Ratio	**24**	**High**		9 - 23	
Sodium	139		mmol/L	134 - 144	01
Potassium	4.6		mmol/L	3.5 - 5.2	01
Chloride	101		mmol/L	96 - 106	01
Carbon Dioxide, Total	24		mmol/L	20 - 29	01
Calcium	9.3		mg/dL	8.7 - 10.2	01
Protein, Total	6.4		g/dL	6.0 - 8.5	01
Albumin	3.8		g/dL	3.5 - 5.5	01
Globulin, Total	2.6		g/dL	1.5 - 4.5	
A/G Ratio	1.5			1.2 - 2.2	
Bilirubin, Total	<0.2		mg/dL	0.0 - 1.2	01
Alkaline Phosphatase	70		IU/L	39 - 117	01
AST (SGOT)	9		IU/L	0 - 40	01
ALT (SGPT)	15		IU/L	0 - 32	01
Hemoglobin A1c					
Hemoglobin A1c	**10.4**	**High**	%	4.8 - 5.6	01
Please Note:					01
Prediabetes: 5.7 - 6.4 Diabetes: >6.4 Glycemic control for adults with diabetes: <7.0					
C-Peptide, Serum	2.5		ng/mL	1.1 - 4.4	01

Pharmacologic therapy T1DM

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

9.1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. A

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. A

9.3 Consider educating individuals with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity. E

9.4 Individuals with type 1 diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access to this therapy after they turn 65 years of age. E

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Insulin Development

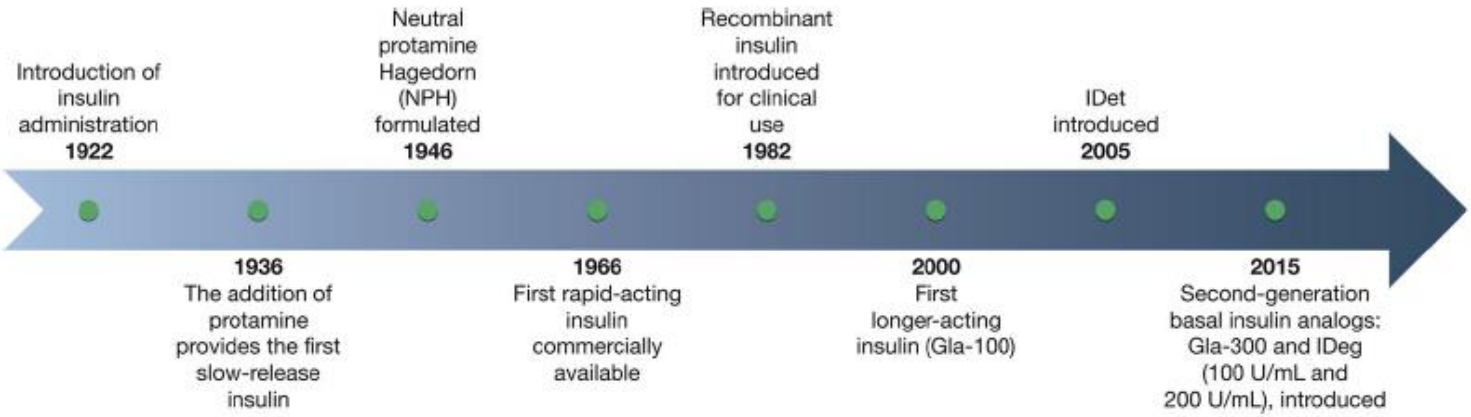

Fig. 1 Advances in insulin development. *Gla-100* insulin glargine 100 units/mL, *Gla-300* insulin glargine 300 units/mL, *IDeg* insulin degludec, *IDet* insulin detemir

Cheng AYY, et al. Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different Adv Ther. 2019 May;36(5):1018-1030.

Long acting insulin

Table 1 Pharmacokinetic properties of available basal insulins

	Degludec [13, 14] (0.4–0.8 U/kg)	IDet [70, 71] (0.4–0.8 U/kg)	Glargine U100 [13, 72–75] (0.3–0.8 U/kg)	Glargine U300 [72, 76] (0.4 U/kg)	NPH insulin [75, 77] (0.3–0.4 U/kg)
Peak action, h	Minimal peak	2–3[a]	8–12[b]	Minimal peak	5
Mean half-life, h	24–27	5.0–7[c]	12–14	19	4.0
Duration of action, h	> 42	20–23[a]	20–26[d]	30–36	13[a]
Recommended dosing interval	Once per day	Once or twice per day	Once per day	Once per day	Once or twice per day

Degludec insulin degludec, *IDet* insulin detemir, *glargine U100* insulin glargine 100 units/mL, *glargine U300* insulin glargine 300 units/mL, *NPH* neutral protamine Hagedorn

[a] Duration may be shorter

[b] Peaks were compared across several studies from 0.3 to 0.8 U/kg

[c] Depending on dose

[d] Reported range at 0.3 U/kg

Thalange N, et al. Clinical Use of Degludec in Children and Adolescents with T1D: A Narrative Review with Fictionalized Case Reports2019. Diabetes Ther. Aug;10(4):1219-1237.

Long-acting insulin analogs

Table 1 Mechanisms of protraction of human regular insulin, NPH insulin, and first- and second-generation long-acting insulin analogs. Based on Heise and Mathieu [2]; Pandyarajan and Weiss [3]

Insulin	Modification	Mechanism of protraction
Gla-100	Arg^{B31}–Arg^{B32} tag $Asp^{A21} \rightarrow Gly$	Soluble in acidic pH pre-injection. Forms microprecipitates while equilibrating with physiologic pH at the injection site; free glargine then dissociates from the injection depot and is absorbed into the circulation
IDet	Modification of Lys^{B29} by a tethered fatty acid	Self-association at the injection depot as dihexamers and reversible binding, via fatty acid linker, to albumin at the injection depot and in the circulation
Gla-300	Arg^{B31}–Arg^{B32} tag $Asp^{A21} \rightarrow Gly$	Soluble in acidic pH pre-injection. Precipitates at physiologic pH, but with more compact microprecipitates compared with Gla-100, resulting in a reduced surface area from which more protracted absorption can occur
IDeg	Modification of Lys^{B29} by a dicarboxylic acid Addition of a fatty acid side chain	Multihexamer chain formation at the injection depot, with dissociation of zinc allowing hexamer breakdown as well as binding to serum albumin via attached fatty acid linker

Gla-100 insulin glargine 100 units/mL, *Gla-300* insulin glargine 300 units/mL, *IDeg* insulin degludec, *IDet* insulin detemir, *NPH* neutral protamine Hagedorn

Cheng AYY, et al. Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different. . Adv Ther. 2019 May;36(5):1018-1030.

Short-acting insulin analogs

Table 1 Mechanisms of protraction of human regular insulin, NPH insulin, and first- and second-generation long-acting insulin analogs. Based on Heise and Mathieu [2]; Pandyarajan and Weiss [3]

Insulin	Modification	Mechanism of protraction
Short-acting regular insulin	Nil (animal and recombinant human forms)	Nil
Intermediate-acting NPH insulin	Nil (animal and recombinant human forms)	Preformed precipitate of protamine–insulin conglomerates the crystals of which are retained in 'heaps' at injection depot
Lispro	$Pro^{B28} \rightarrow Lys$ $Lys^{B29} \rightarrow Pro$	More rapid circulation/action than regular human insulin
Aspart	$Pro^{B28} \rightarrow Asp$	More rapid circulation/action than regular human insulin
Glulisine	$Asn^{B3} \rightarrow Lys$ $Lys^{B29} \rightarrow Glu$	More rapid circulation/action than regular human insulin

Cheng AYY, et al. Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different. . Adv Ther. 2019 May;36(5):1018-1030.

Glucose-lowering effect of different insulin

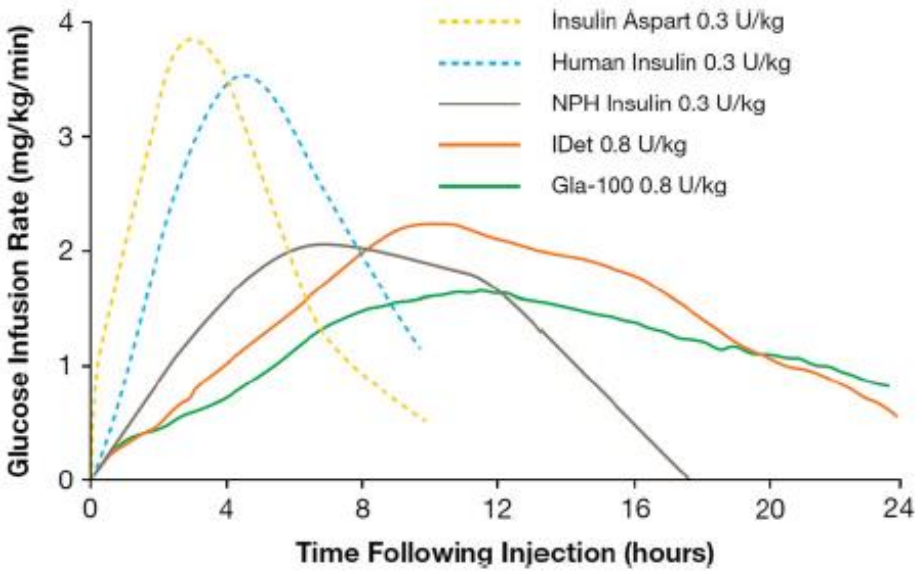

Fig. 4 Glucose-lowering effect of different insulin preparations based on data from published PD studies of patients with T2D. *Gla-100* insulin glargine 100 units/mL, *IDet* insulin detemir, *NPH* neutral protamine Hagedorn, *PD* pharmacodynamic, *T2D* type 2 diabetes. Adapted from Evans, 2011 [7] © 2011, Blackwell Publishing Ltd.

Cheng AYY, et al. Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different. . Adv Ther. 2019 May;36(5):1018-1030.

Concentrated Insulin

Table 1 – Concentrated insulins currently available.

	Regular U-500[a,b]	Regular U-500[a,b]	Glargine U-300[a,c]	Glargine U-300[c]	Degludec U-200[a,d,e]	Lispro U-200[a,e,f]
Device	Vial	Pen	Pen	Pen	Pen	Pen
PK/PD characteristics	Prandial and basal	Prandial and basal	Basal	Basal	Basal	Prandial
Bioequivalent	No	No	No	No	Yes	Yes
Unit increments	5	5	1	2	2	1
Maximum dose (Units)	250 [g]	300	80	160	160	60
Units/device	10,000	1500	450	900	600	600
Storage and handling in use (days)	40	28	42	42	56	28
Minimum daily units[h]	250[i]	54[i]	11	20	11	21

Regular U-500, regular U-500 insulin (Humulin®); Glargine U-300, insulin glargine U-300 (Toujeo®); Degludec U-200, insulin degludec U-200 (Tresiba®); Lispro U-200, insulin lispro U-200 (Humalog 200®); PD, pharmacodynamics; PK, pharmacokinetics.

[a] Hood. *Diabetes Technol Ther* 2017; 19(4): 203–5.
[b] HUMULIN® Prescribing Information, 2016.
[c] TOUJEO® Prescribing Information, 2018.
[d] TRESIBA® Prescribing Information, 2018.
[e] Ovalle et al. *Curr Med Res Op* 2018; 34(6): 1029–1043.
[f] HUMALOG®, Prescribing Information, 2017.
[g] Using dedicated U-500 syringe.
[h] Minimum needed to empty the device before contents expire.
[i] Indicated for people with diabetes requiring > 200 units of daily insulin.

Schloot NC, et al. Concentrated insulins in current clinical practice. Diabetes Res Clin Pract. 2019 Feb;148:93-101.

Median cost of insulin products

Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (44) and NADAC (45) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting analogs	• Lispro biosimilar	U-100 vial	$280	$226
		U-100 prefilled pen	$361	$289
	• Glulisine	U-100 vial	$324	$260
		U-100 prefilled pen	$417	$334
	• Lispro	U-100 vial	$330	$264
		U-100 3 mL cartridges	$408	$326
		U-100 prefilled pen; U-200 prefilled pen	$424	$340
	• Aspart	U-100 vial	$347	$278
		U-100 3 mL cartridges	$430	$343
		U-100 prefilled pen	$447	$358
	• Inhaled insulin	Inhalation cartridges	$993	$606
Short-acting	• Human Regular	U-100 vial	$165 ($165, $178)	$135 ($135, $146)
Intermediate-acting	• Human NPH	U-100 vial	$165 ($165, $178)	$135 ($135, $144)
		U-100 prefilled pen	$377	$304
Concentrated Human Regular insulin	• U-500 Human Regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Basal analogs	• Glargine biosimilar	U-100 prefilled pen	$261	$209
	• Glargine	U-100 vial; U-100 prefilled pen	$323	$259
		U-300 prefilled pen	$331	$266
	• Detemir	U-100 vial; U-100 prefilled pen	$353	$281
	• Degludec	U-100 prefilled pen; U-200 prefilled pen	$388	$310
Premixed insulin products	• NPH/Regular 70/30	U-100 vial	$165 ($165, $178)	$135 ($135, $144)
		U-100 prefilled pen	$377	$306
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$340
	• Lispro 75/25	U-100 vial	$342	$273
		U-100 prefilled pen	$424	$340
	• Aspart 70/30	U-100 vial	$360	$288
		U-100 prefilled pen	$447	$358
Premixed insulin/GLP-1 receptor agonist products	• Degludec/Liraglutide	100/3.6 prefilled pen	$793	$638
	• Glargine/Lixisenatide	100/33 prefilled pen	$537	$431

AWP, average wholesale price; GLP-1, glucagon-like peptide 1; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.2**; median listed alone when only one product and/or price.

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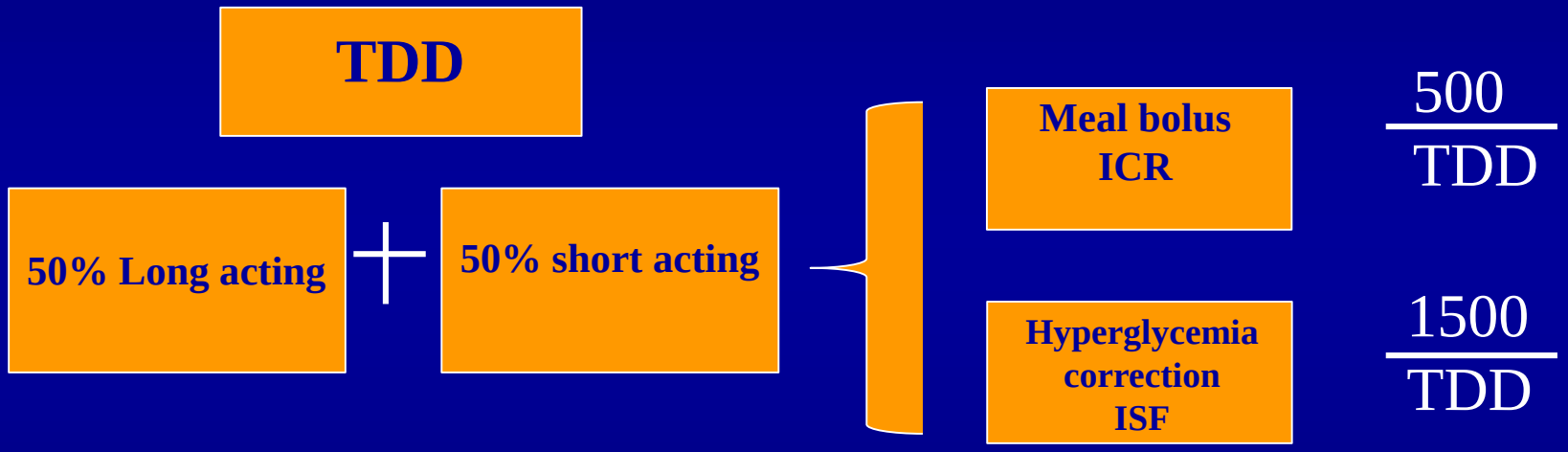
Initial TDD (total daily insulin dose)

- **TDD = wt (kg) x 0.3 - 0.5 – T1DM or pt with CKD**
- **TDD = wt (kg) x 0.7-1.0 – for obese / insulin resistant pts**



TDD = 30 units/day. ICR 1:16. ISF 1:50 over BG target
TDD = 50 units/day. ICR 1:10. ISF 1:30 over BG target
TDD = 100 units/day. ICR 1:5. ISF 1:15 over BG target

Insulin pump use in T1DM

- **Basal rate: (u/hr, 47.5 units per day)**
  MN 2.05
  0430 2.00
  0700 1.85
  1400 2.00
  2000 2.10

  ICR
  MN 1: 8
  0500 1: 4
  1000 1: 6
  1200 1: 5
  1600 1:3.2

  ISF
  MN 1:28
  0530 1:23
  1000 1:21
  1400 1:22

  Blood glucose target:
  MN 90-110
  0700 80-100
  2200 90-110
- **AIT: 3 hrs**

- **Pump insulin delivery is more efficient. ~ 80% of MDI basal as a starting point.**
- **Different ICR and ISF**
- **Different BG target**
- **Temporal Basal use when changing from Long acting to pump.**

Insulin pumps

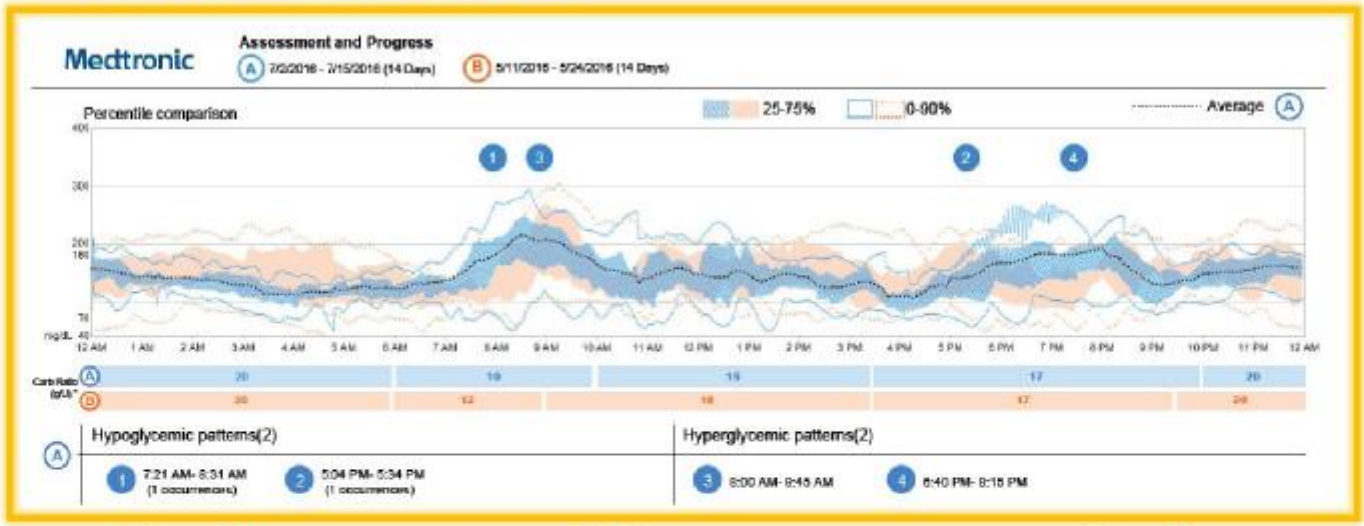
Medtronic 670G

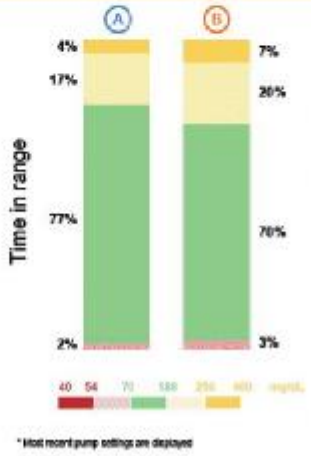
Tandem T slim pump

Omnipod

Insulin pump report

ASSESSMENT & PROGRESS REPORT

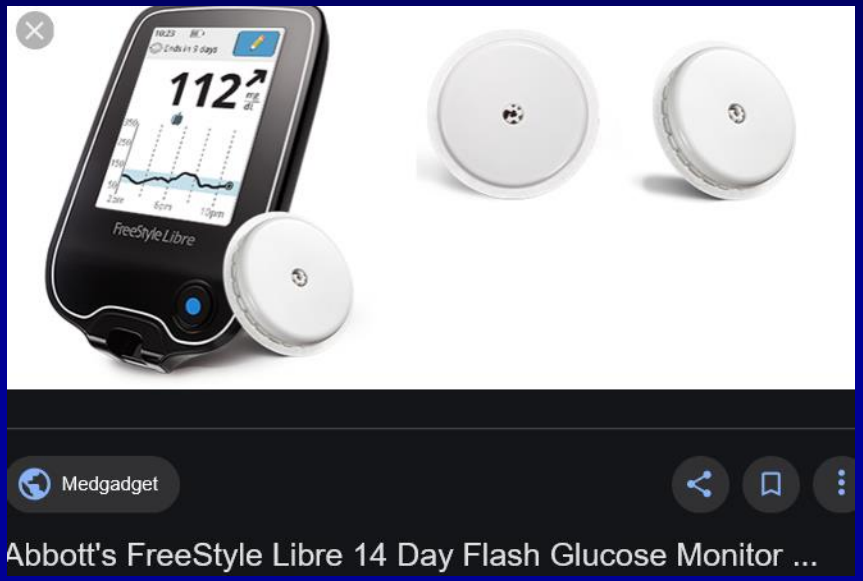




Auto Mode Exits	A	B
No Calibration	3	0
High SG Auto Mode Exit	0	0
Auto Mode max delivery	0	0
Auto Mode min delivery	0	0
BG required for Auto Mode	1	0
Sensor Algorithm Underread	0	0
Sensor Updating	0	0
No SG values	3	0
Sensor Expired	0	0
Auto Mode disabled by user	1	0
Alarms	2	0
Pump Suspend by user	0	0
Auto Mode Warm Up	0	0
Unidentified	2	2

Statistics	A	B
Auto Mode (per week)	96% (6d 18hrs)	0% (0hrs)
Manual Mode (per week)	4% (6hrs)	100% (7d 00hrs)
Sensor Wear (per week)	96% (6d 16hrs)	96% (6d 16hrs)
Average SG ± SD	149 ± 51 mg/dL	149 ± 55 mg/dL
Average BG	176 ± 74 mg/dL	147 ± 62 mg/dL
BG / Calibration (per day)	7.8 / 4.1	10.2 / 3.8
Total daily dose (per day)	23 units	18 units
Bolus amount (per day)	14U (61%)	9U (49%)
Auto Basal / Basal amount (per day)	9U (39%)	9U (51%)
Set Change	Every 4.6 days	Every 4.6 days
Reservoir Change	Every 4.6 days	Every 4.6 days
Meal (per day)	7.0	5.5
Carbs entered (per day)	166 ± 42g	148 ± 28g
Active Insulin time	3:00 hrs	3:00 hrs

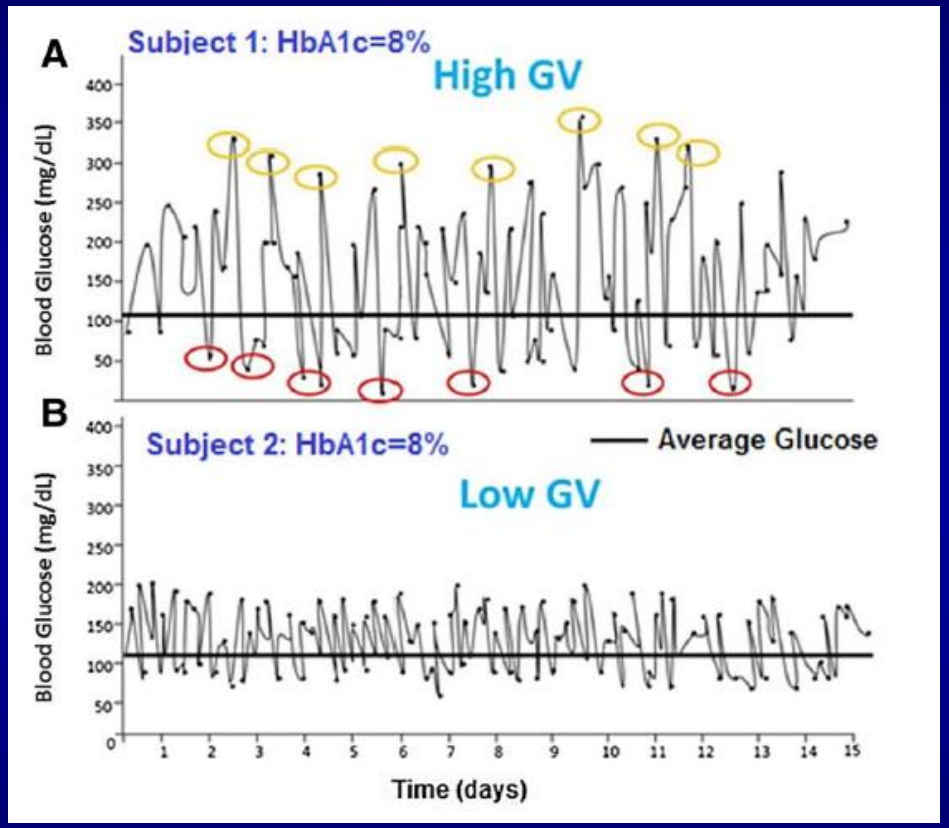
Continuous Glucose Monitor



Continuous Glucose Monitoring (CGM)

Table 1 New definitions of hypoglycemia, hyperglycemia, and time in glycemic range

Outcome	Definition
Hypoglycemia	Level 1: glucose < 70 mg/dL (3.9 mmol/L) and glucose ≥ 54 mg/dl (3.0 mmol/L)
	Level 2: glucose < 54 mg/dL (3.0 mmol/L)
	Level 3: a severe event characterized by altered mental and/or physical status requiring assistance
Hyperglycemia	Level 1 (elevated glucose): glucose > 180 mg/dL (10 mmol/L) and glucose ≤ 250 mg/dlL(13.9 mmol/L)
	Level 2 (very elevated glucose): glucose > 250 mg/dL (13.9 mmol/L)
Time in range	Percentage of readings in the range of 70–180 mg/dL (3.9–10.0 mmol/L) per unit of time



Chehregosha H, et al. A View Beyond HbA1c: Role of Continuous Glucose Monitoring . Diabetes Ther, 2019 Jun;10(3):853-863.

CGM report

Statistical Summary :

Avg Glucose mg/dL	Glycemic Estimate	Very Low Below 60 mg/dL	Low Alert Below 70 mg/dL	In target Range 70-180 mg/dL	High Alert Above 180 mg/dL	Very High Above 250 mg/dL	Coeloficient of Valiation	SD mg/dL	% Time CGM Active
169 88-116	7.5% < 5	12.9% 0*	15.7% < 4*	41.0% > 90*	41.0% 6*	19.5% 0*	46.3% 19.25	90 10 – 26	70.6% Data Sufficiency

GLUCOSE EXPOSURE CLOSE-UP

	Wake 6 AM to 12 AM	Sleep 12 AM to 6 AM	24 Hours
AUC-Hourly	177 89-121	104 85-109	159 89-113

VARIBILITY CLOSE-UP

Coelificient of Variation	Avg △ Median Curve mg/dL/hr
53.3% 19-25	16.4 2 - 5

HYPOGLYCEMIA AND HYPERGLYCEMIA EPISODES CLOSE-UP

	<50	<60	<70	<180	>250	>400
Avg Hours Per Day	2.2	3.0	3.7	10.1	4.6	0.2
Mean Episodes/Day	1.4	1.9	2.2	3.3	1.9	0.3
Mean Duration (Hours)	1.5	1.6	1.7	3.1	2.3	0.9

*Indicates references ranges, which are derived from normal reference population means ± standard deviations. The five curves below represent frequency distributions of glucose data piloted according to time without regard to data

CGM Data Point | 50% - Median | 25/75% - IQR | 10/90% | Target Range

Visual Display:

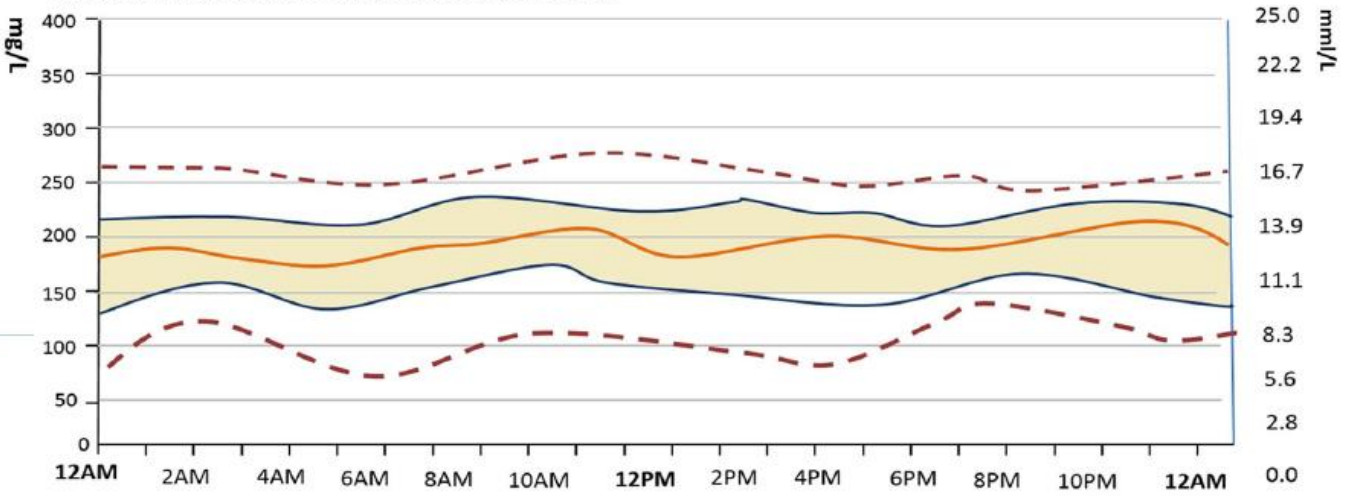


Fig. 2 The electronic CGM profile

Chehregosha H, et al. A View Beyond HbA1c: Role of Continuous Glucose Monitoring . Diabetes Ther, 2019 Jun;10(3):853-863.

Individualized Glycemic targets

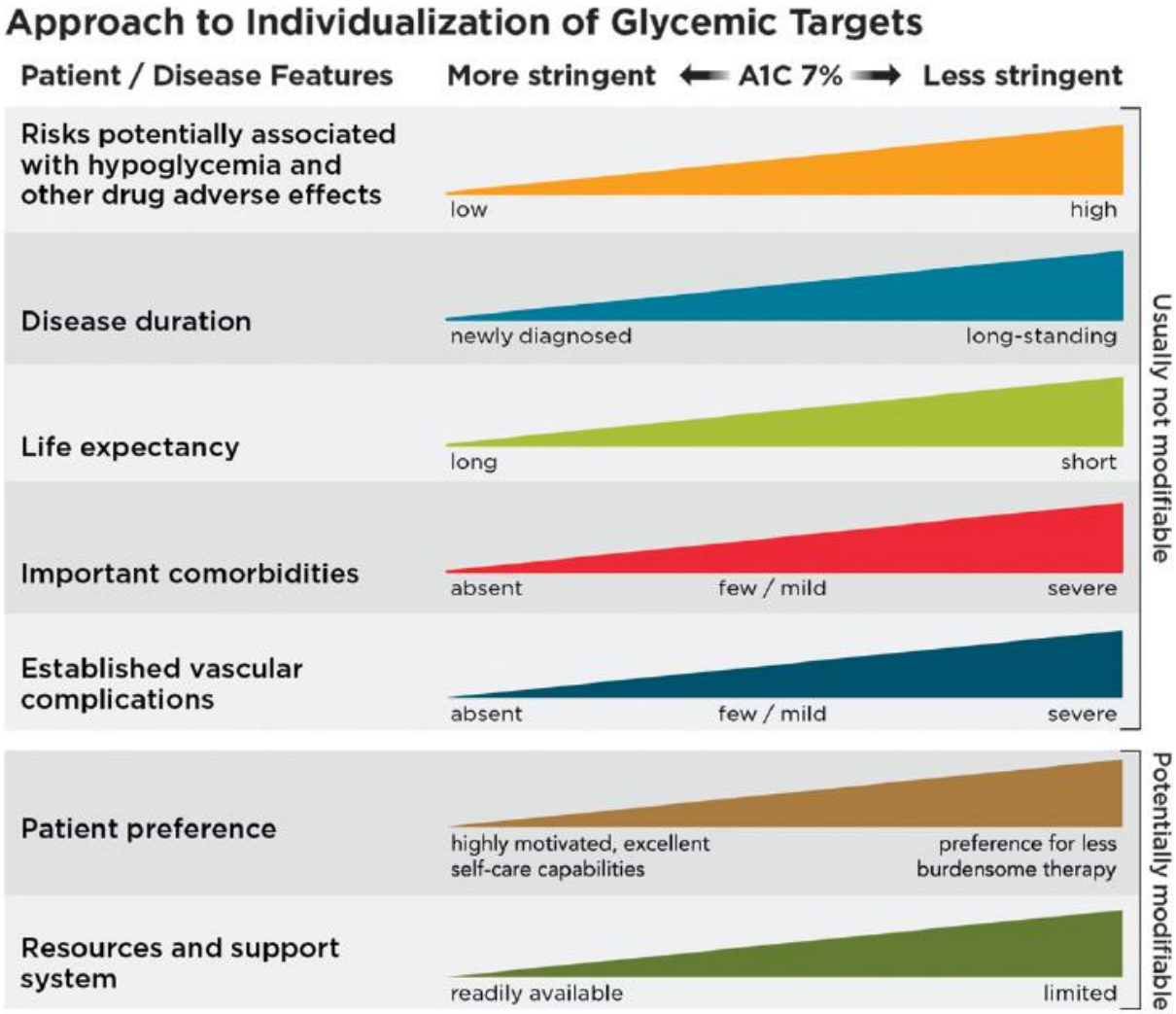


Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (40).

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Assessment of hypoglycemia risk

Table 4.3—Assessment of hypoglycemia risk

Factors that increase risk of treatment-associated hypoglycemia

- Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)
- Impaired kidney or hepatic function
- Longer duration of diabetes
- Frailty and older age
- Cognitive impairment
- Impaired counterregulatory response, hypoglycemia unawareness
- Physical or intellectual disability that may impair behavioral response to hypoglycemia
- Alcohol use
- Polypharmacy (especially ACE inhibitors, angiotensin receptor blockers, nonselective β-blockers)

See references 114–118.

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Hypoglycemia recommendations

- Symptomatic and asymptomatic hypoglycemia – CGM
- Glucose 15-20 g is the preferred treatment with BG < 70 mg/dl. Recheck BG in 15 min.
- Glucagon should be prescribed for level 2 hypoglycemia (< 54 mg/dl)
- Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia trigger evaluation of treatment plan.
- Hypoglycemia unawareness or level 2 hypoglycemia should raise glycemic targets for a few weeks in order to partially reverse hypoglycemia unawareness.

Table 6.3—Classification of hypoglycemia (44)

Level	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance

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Glucagon and Baqsimi

Management of hyperglycemic Crises

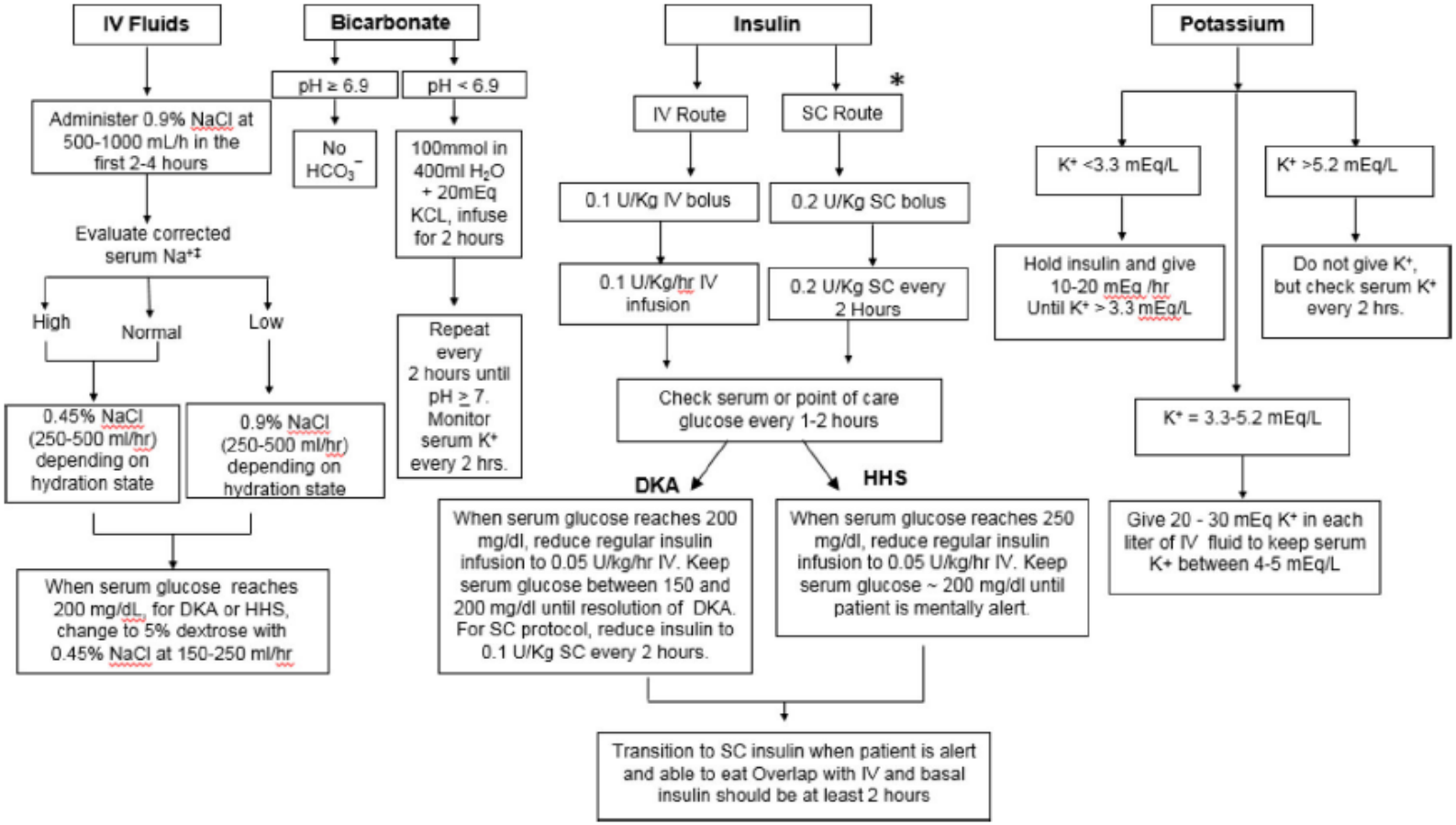


Figure 2.

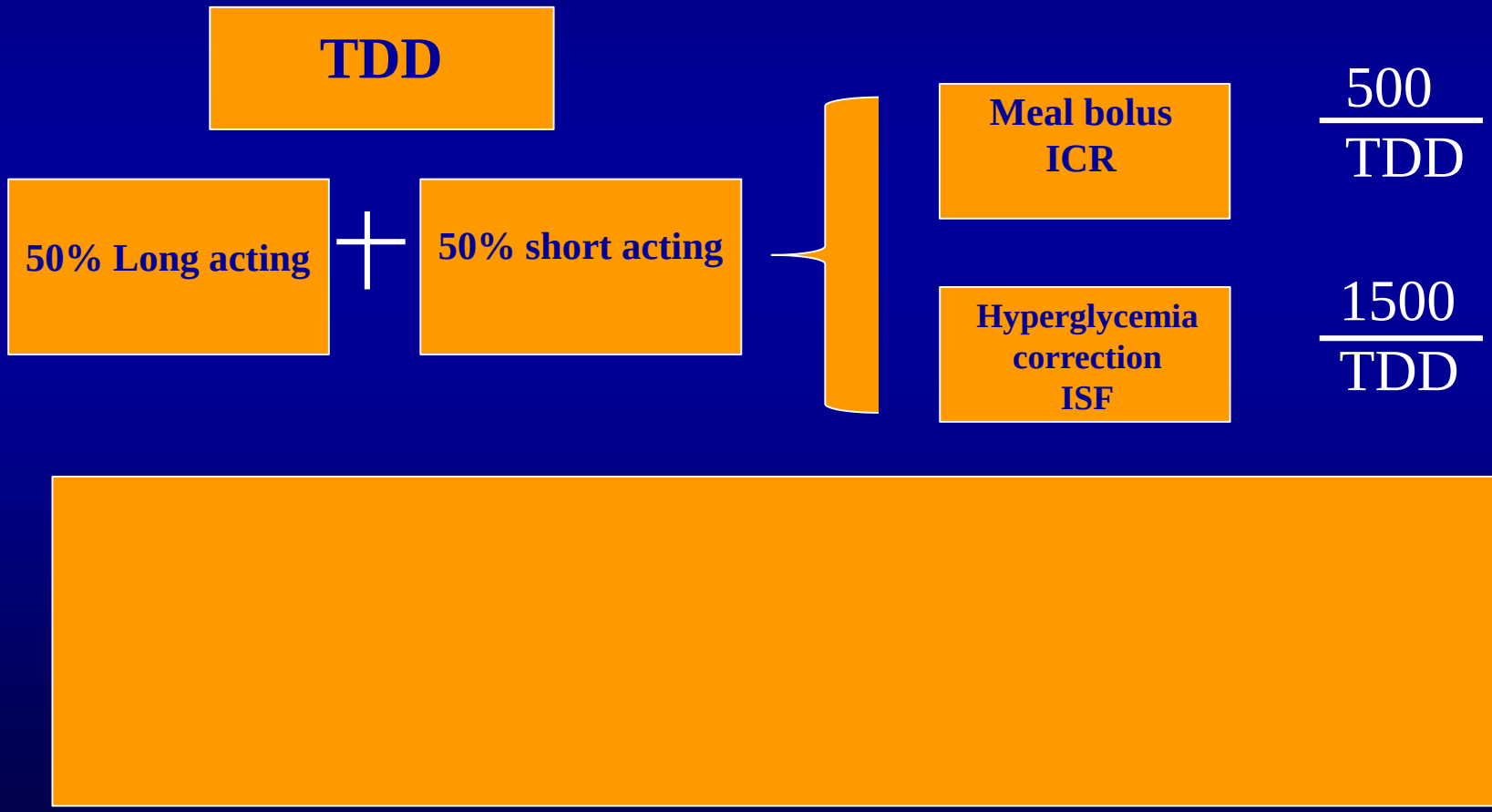
Management of Hyperglycemic Emergencies

*Subcutaneous Insulin Protocol has not been validated for HHS

Fayfman M, et al. Management of Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. Med Clin North Am. 2017 May;101(3):587-606.

Initial TDD (total daily insulin dose)

- **TDD = wt (kg) x 0.3 - 0.5 – T1DM or pt with CKD**
- **TDD = wt (kg) x 0.7-1.0 – for obese / insulin resistant pts**



Glycemic targets in hospitalized patients

- **Insulin therapy should be initiated for BG > 180 mg/dl. Target BG range of 140-180 mg/dl in critically ill pts and non critically ill pts.**
- **More stringent goal 110-140 mg/dl for selected pts without significant lows.**

Perioperative care:

- **Target glucose 80-180 mg/dl.**
- **Withhold metformin the day of surgery.**
- **Withhold any other oral hypoglycemic agents the morning of surgery or procedure and give half of NPH or 60-80% of long-acting analog or pump basal.**
- **Monitor BG every 4-6 hrs and dose with rapid-acting insulin as needed.**

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T1DM clinical trials

Table 2. List of prominent clinical trials utilising different interventions.

INTERVENTION	TRIAL	PROMINENT FINDINGS/ONGOING TRIAL
Insulin	Open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape) (NCT00965549)	Patients, who received a combination of once daily fast-acting and basal insulin, demonstrated a similar HbA1c level and significantly better treatment satisfaction as compared with basal insulin alone
Insulin pump	Randomised controlled trial to determine the REPOSE in adult patients with T1DM (ISRCTN61215213)	Long-lasting reduction in HbA1c and improved psychosocial responses observed in patients using insulin pump
Artificial pancreas	Randomised trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy in T1DM patients (NCT02241889)	Adjusting insulin and glucagon delivery using dual-hormone artificial pancreas at exercise onset significantly reduced hypoglycaemia
	Outpatient overnight glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or conventional insulin pump therapy in children and adolescents with type 1 diabetes (NCT02189694)	Delivering insulin and glucagon using dual-hormone artificial pancreas demonstrated better nocturnal glycaemic control
Immune modulation/ incretins	Clinical proof-of-concept trial to evaluate therapeutic applicability of IL-21 antibody – NNC01144-0006 (NCT02443155) and liraglutide on β cell function in recently diagnosed T1DM patients	Ongoing
Immune modulation	Trial to determine the role of B-lymphocyte depletion using rituximab in T1DM patients	Four-dose course of rituximab partially preserved beta cell function over a period of 1 year
	Randomised controlled CD3-antibody trial in recent-onset T1DM patients (NCT00627146)	Treatment with ChAglyCD3 for 6 days suppressed the rise in insulin requirements over 48 months.
	Trial of regulatory T cells in renal transplantation for immunosuppression minimisation (The ONE study UK Treg Trial–NCT02129881)	Ongoing

Pathak V, et al . Therapies for Type 1 Diabetes: Current Scenario and Future Perspectives. Clin Med Insights Endocrinol Diabetes.. 2019 May 3;12

T1DM clinical trials

SGLT2 inhibition	Efficacy and safety study of DEPICT-1 (NCT02268214)	Reduction in HbA1c levels (0.4%-0.5%) and daily insulin requirements coupled with weight loss was observed
	Tandem3 trial to evaluate therapeutic applicability of Sotagliflozin in combination with insulin (NCT02531035)	Significant reduction in HbA1c levels with no severe hypoglycaemia or diabetic ketoacidosis was observed in T1DM patients
Stem cell mobilisation	A randomised open-labelled trial to evaluate Plerixafor for treating T1DM (NCT03182426)	Ongoing
β cell encapsulation	Safety, tolerability, and efficacy trial of VC-01 in T1D patients	Ongoing
	Open label trial to assess the safety and efficacy of transplanted macroencapsulated human islets within bio-artificial βAir device in T1DM patients (NCT02064309)	Insignificant increase in C-peptide levels, no impact on glycaemic control, and glucose stimulated insulin secretory response
Microencapsulation	Open label investigation of safety and effectiveness of DIABECELL in T1D patients	Marginal reduction in HbA1c and less frequent hypoglycaemia
Stem cells	Safety, tolerability, and efficacy study of VC-01 combination product in T1DM patients (NCT02239354)	The PEC-Encap product candidate was safe and tolerable. Also, when delivered at a subtherapeutic dose, the device also protected the implanted cells from alloimmune and autoimmune rejection and the patient from sensitisation
Incretins	Randomised, double-blind, placebo-controlled trial to evaluate the efficacy of liraglutide as an add-on therapy to insulin for overweight T1DM patients	Liraglutide treatment was associated with reductions in hypoglycaemic events, bolus and total insulin dose, body weight, and increased heart rate.

Abbreviations: DEPICT-1, Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes; HbA1c, haemoglobin A1C; IL, interleukin; REPOSE, Relative Effectiveness of Pumps Over MDI and Structured Education; SGLT2, sodium–glucose co-transporter 2; T1DM, type 1 diabetes mellitus; Tregs, regulatory T cells.

Pathak V, et al . Therapies for Type 1 Diabetes: Current Scenario and Future Perspectives. Clin Med Insights Endocrinol Diabetes.. 2019 May 3;12

Summary

- Classification of diabetes
- T1DM pathophysiology - GAD65 antibody and C-peptide.
- Pharmacologic treatment of T1DM
- TDD for MDI and insulin pump
- CGM report
- DKA transition to MDI
- T1DM clinical trials