

Clinical Outcomes and Complications of Basal, Bolus, and Combination Insulin Regimens in Type 2 Diabetes Mellitus: Evidence from Published Case Reports

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Abstract: Insulin therapy remains a cornerstone in the management of type 2 diabetes mellitus (T2DM), especially in patients experiencing progressive loss of pancreatic beta-cell function or those with inadequate glycemic control despite oral antidiabetic therapy. This review synthesized clinical outcomes from 44 peer-reviewed case reports published between 2019 and 2024, identified through systematic searches in PubMed and Scopus. The included cases involved 15 males and 29 females, with patient ages ranging from 11 to 91 years (mean 53 ± 20.85 years). Subcutaneous insulin was the most frequently used route of administration, while intravenous insulin was reserved for managing acute complications. The most commonly reported complication was diabetic ketoacidosis (DKA), especially in patients with delayed insulin initiation or in those receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, a class of oral glucose-lowering agents, one of whose side effects is known to elevate the risk of euglycemic DKA. Other triggers included COVID-19 infection and severe insulin resistance. Most patients received basal insulin regimens, whereas basal-bolus combinations were preferred in more complex or unstable cases. Insulin was frequently combined with oral agents, such as metformin, dipeptidyl peptidase IV (DPP-IV) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, or sodium-glucose cotransporter 2 (SGLT2) inhibitors, reflecting a trend toward individualized treatment strategies. Biomarkers such as glycated hemoglobin (HbA1c) and C-reactive protein (CRP) were routinely used to monitor glycemic control and systemic inflammation. These findings underscore the clinical importance of early insulin initiation, continuous monitoring, and personalized regimens to improve outcomes in advanced or complicated T2DM. Emerging therapies, such as once-weekly basal insulin formulations, show promise for enhancing adherence and glucose stability, although further research is needed to evaluate their long-term effectiveness and cost-efficiency.

Keywords: diabetic ketoacidosis, glycated hemoglobin, HbA1c, glycemic control, insulin therapy, type 2 diabetes mellitus

Introduction

Diabetes Mellitus (DM) remains one of the most pressing global health challenges, with its prevalence steadily rising over the past decades. In 2019, it was estimated that over 454 million people worldwide were living with DM, a number projected to reach 548 million by 2045.¹ Beyond its sheer prevalence, DM ranks among the top ten global causes of death, with approximately 4 million deaths in 2021 attributed to the disease.^{2,3} These alarming statistics highlight the urgent need for optimized management strategies to curb complications and mortality.⁴

DM encompasses two primary types: type 1 (T1DM) and type 2 (T2DM).⁵ T1DM, often diagnosed in childhood or adolescence, is initiated by the interaction of genetic predisposition and environmental influences, and characterized by

autoimmune destruction of pancreatic beta-cells, leading to absolute insulin deficiency, necessitating lifelong insulin replacement.⁶ It is also frequently associated with other autoimmune conditions such as autoimmune thyroiditis, celiac disease, and vitiligo.⁷ Conversely, T2DM, which accounts for more than 90% of all diabetes cases globally,⁸ is characterized by insulin resistance (IR) and progressive beta-cell dysfunction.^{6,7,9} Unlike T1DM, insulin therapy in T2DM is often delayed and typically introduced after oral antidiabetic agents fail to maintain glycemic control.¹⁰

The pathophysiology of T2DM involves impaired insulin signaling in skeletal muscle, adipose tissue, and the liver, reducing glucose uptake and enhancing hepatic glucose output.^{6,11,12} These metabolic disruptions lead to hyperglycemia, including secondary hyperglycemia. Secondary hyperglycemia often results from non-primary diabetes causes such as infections or corticosteroid use, hyperinsulinemia, and inflammation,¹³ and lipid accumulation, triggering further insulin resistance (IR) and oxidative stress. On a molecular level, dysregulation of signaling pathways such as IRS-1/2 and Akt/PKB impairs glucose homeostasis.^{14–16} A study using ³¹P-magnetic resonance spectroscopy demonstrated reduced oxidative phosphorylation and mitochondrial capacity in insulin-resistant individuals, especially among older adults or those with a family history of T2DM.^{17,18}

T2DM is multifactorial in origin, with modifiable risk factors including obesity, physical inactivity, and unhealthy diets, in addition to non-modifiable risks such as age and genetic predisposition.^{18–20} Lifestyle modifications—such as adoption of Mediterranean or DASH diets, improved sleep, and reduction of sedentary behaviors—have been shown to prevent or delay disease onset.^{20–22}

Despite early treatment with agents like metformin or SGLT2 inhibitors to address IR, many patients with T2DM eventually require insulin therapy due to progressive beta-cell decline.²³ Insulin initiation is typically warranted in patients with a glycated hemoglobin (HbA1c) value > 9%, symptomatic hyperglycemia, weight loss, or ketosis.²⁴ Delayed insulin initiation or inappropriate use of SGLT2 inhibitors can precipitate diabetic ketoacidosis (DKA) even in type 2 patients.²⁵ Moreover, early insulin use has been shown to restore beta-cell function and induce glycemic remission in a subset of patients,^{26,27} though concerns such as hypoglycemia, weight gain, and cardiovascular risks necessitate careful regimen selection.²⁸

Thus, individualized insulin strategies are essential, considering patient comorbidities, disease duration, and treatment goals.^{29,30} The optimal choice of basal vs bolus insulin and timing of administration remains a key consideration. A recent meta-analysis identified glargine U-300 and degludec U-100 as effective basal options, with morning glargine U-100 preferable in patients with tight glycemic targets (HbA1c <7.0%).³¹ In addition to efficacy, patient-centered factors such as treatment satisfaction, adverse effects, and cost also influence the selection of injectable therapies, particularly among GLP-1 receptor agonists such as semaglutide and liraglutide.³² In addition to cardiovascular and metabolic complications, poor glycemic control in diabetes mellitus (DM) has been identified as an important risk factor for infections, including tuberculosis (TB). Chronic hyperglycemia impairs cellular immunity, particularly macrophage and T-cell function, thereby increasing susceptibility to TB by approximately two- to threefold. Hemoglobin A1c (HbA1c), the primary marker of long-term glycemic control, reflects the degree of metabolic dysfunction in DM and is strongly associated with adverse clinical outcomes. Elevated HbA1c levels not only predict microvascular and macrovascular complications but are also linked to impaired immune responses, delayed TB treatment success, and higher infection-related morbidity. These findings underscore the importance of timely and effective insulin therapy to optimize glycemic control and reduce infection risk in patients with DM.³³

Given the rapid evolution of diabetes treatment guidelines, this review aims to synthesize clinical insights from published case reports over the last five years, with particular focus on insulin therapy in T2DM. By analyzing clinical outcomes, biomarkers such as HbA1c and C-reactive protein (CRP), and treatment regimens, this review offers practical guidance for personalized insulin use, with the goal of optimizing outcomes and reducing complication rates in T2DM.

Materials and Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparent and standardized reporting.³⁴ The research question was formulated using the PICO framework as follows:

- Population (P): Individuals diagnosed with type 2 diabetes mellitus (T2DM) as documented in peer-reviewed case reports;

- Intervention (I): Administration of insulin therapy, including various regimens (eg, basal, bolus, premixed, or combination);
- Comparison (C): Not consistently applicable due to the descriptive nature of case reports;
- Outcome (O): Reported clinical outcomes following insulin therapy, such as glycemic control, adverse effects, and laboratory parameters.

Thus, the primary research question was: “What are the clinical outcomes associated with insulin therapy in patients with T2DM as reported in case reports published in the last five years?”

To ensure efficient and structured literature screening, the Rayyan AI-powered systematic review platform was utilized for initial deduplication and article screening (<https://www.rayyan.ai/>).

Literature Search Strategy

An electronic search was conducted using two databases: PubMed and Scopus, covering the publication period from January 2019 to April 2024. The PubMed search strategy utilized the following MeSH terms: (“Diabetes Mellitus, Type 2” [MeSH]) AND “Insulin” [MeSH] AND “Case Reports” [Publication Type]. This strategy was designed to increase precision and capture all relevant reports. In Scopus, the following free-text keywords were used: “Case AND report AND diabetes AND mellitus AND type 2 AND insulin AND therapy”. Search filters were applied to limit results to English-language, full-text, peer-reviewed case reports. A PRISMA-based flowchart illustrating the article selection process is presented in Figure 1.

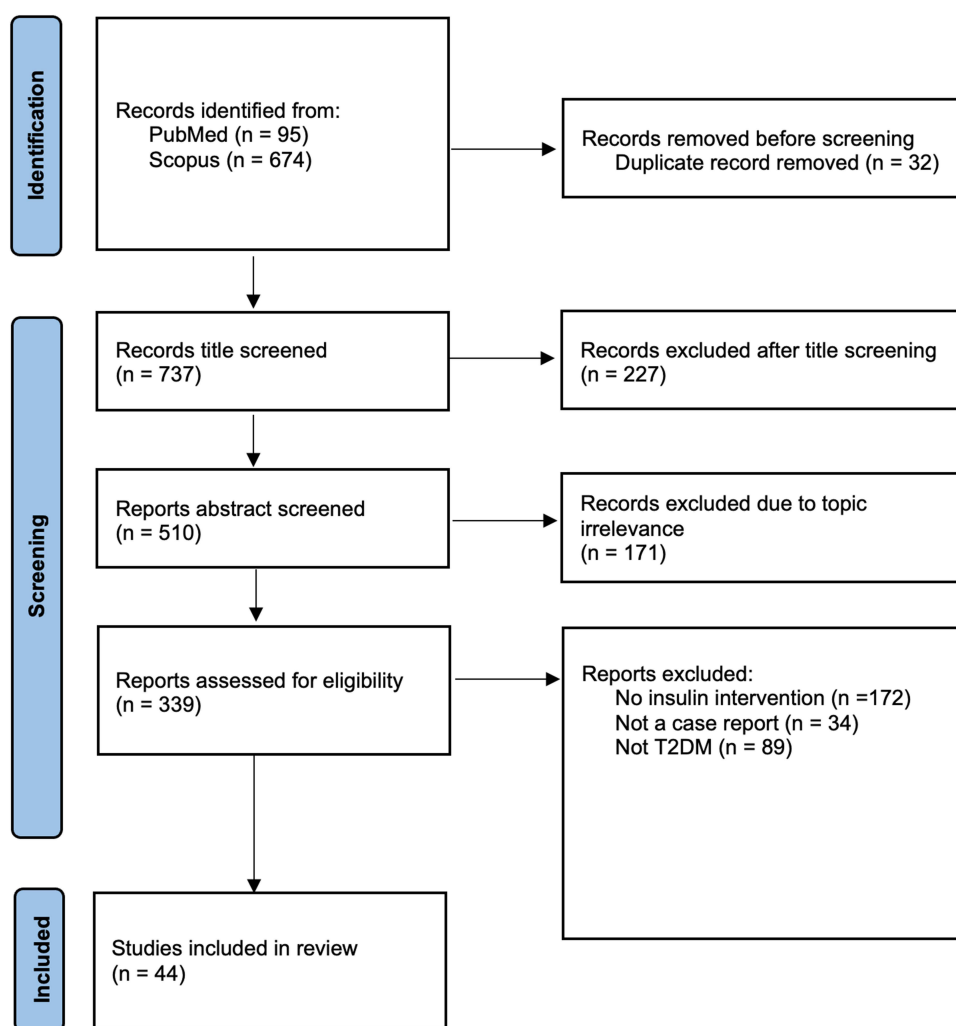


Figure 1 Search strategy flowchart based on PRISMA (identification of studies via PubMed and Scopus databases).

Inclusion and Exclusion Criteria

Inclusion criteria: Case reports published between 2019 and 2024; focused on T2DM patients receiving insulin therapy; contained quantitative or qualitative clinical outcomes (eg, HbA1c levels, glycemic control, adverse effects); written in English and published in peer-reviewed, open-access journals.

Exclusion criteria: Reports without specific insulin interventions; studies on T2DM history only (no current insulin use); non-case-report formats (eg, systematic reviews, editorials, abstracts, book chapters, letters).

Screening and Selection Process

All search results were exported into EndNote 20 (Clarivate Analytics) for initial reference management and duplicate removal. Following this, titles and abstracts were manually screened using Microsoft Excel 365 by a primary reviewer, based on pre-specified eligibility criteria. Studies with ambiguous eligibility were flagged and independently discussed among the authors until consensus was achieved. Full-text articles were then retrieved and evaluated for final inclusion.

Data Extraction and Analysis

Data extraction was performed using a structured form to capture variables related to:

- Patient demographics (age, sex, BMI, duration of diabetes);
- Insulin regimen (type, dosage, administration timing, modifications);
- Clinical outcomes (HbA1c, fasting glucose, C-reactive protein [CRP], blood pressure, hypoglycemia episodes, weight changes, comorbidities);
- Publication characteristics (authors, year, country, setting).

Descriptive statistics were used to summarize clinical and demographic characteristics. Continuous variables (eg, age, diabetes duration) were reported as means $\pm$ standard deviations, while categorical variables (eg, sex, insulin types used) were presented as frequencies and percentages. All statistical analyses were performed using Microsoft Excel 365 (Microsoft Corporation, Redmond, WA, USA).

Results

Table 1 provides the qualitative synthesis of results. The studies covered, published between the years 2019 and 2024, involve a total of 44 patients,^{12,35–76} thereby considerably adding to the dataset compared to the previous analyses. Of the patients, 15 were males^{35,41,44,46,49,54,58,60,63,66–69,71} and 29 were females,^{12,35–40,42,43,45,47,48,50–53,55,57,59,61–63,65,70,72–76} showing a larger percentage of female cases and corroborating previous reports of greater prevalence in women. The age of the patient ranged from 11 to 91 years, with a mean of 53 ± 20.85 years. Multiple cases were described in four studies. The duration of type 2 diabetes mellitus (T2DM) in the cases ranged from newly diagnosed to 30 years, showing the heterogeneity of disease duration. Most were on regular treatment for either T2DM or its complications before the described health event. Among the pharmacologic treatments, the most commonly prescribed drug was metformin. Moreover, basal insulin therapy was depicted in seven cases,^{12,35–40} bolus in 12 cases,^{41–52} and a combination of both therapies in 23 cases.^{53–76} In one article, the insulin therapy was initially prescribed and adjusted after C-peptide, while in the last article, the insulin therapy was only considered briefly.

Case Reports Highlights

Several illustrative cases underscore the diverse clinical indications and responses to insulin:

Basal insulin therapy was depicted in seven cases, all of which can be resolved either by insulin regimen adjustment or patient adherence.^{12,35–40} In the first case reported by Elmahal and Ramadan (2021) involving a 35-year-old female with poorly controlled comorbid T2DM, hypertension, and morbid obesity, with an HbA1c of 12.3%, and thus, a basal insulin glargine 50 units at bedtime was initiated. Her medication regimen two weeks before hospitalization consisted of metformin, gliclazide modified-release once daily before breakfast, sitagliptin, valsartan, rosuvastatin, and ranitidine. She

Table 1 Patient Demographics of Included Studies

Study ID	Reference	Insulin Regimen										Conditions in Admission		Clinical Outcomes
		Age (Years)	Sex	T2DM (Years)	Insulin Details (Basal or Bolus or Combination)	Type of Insulin Therapy or Regimen	Dosage	Location of Administration	Insulin Purpose (Glycemic Control or Correction, or DKA)	Oral Therapy & Purpose (Glycemic Control, Lipid, Blood Pressure)	Therapy Duration	Conditions	Laboratory Parameter	
1	[35]	35	F	8	Basal	Insulin glargine	50 units/day	SC	Glycemic control	Metformin 1000 mg, gliclazide 120mg, sitagliptin 50mg, valsartan 160 mg, rosuvastatin 10 mg, ranitidine 300 mg	2 weeks	Obesity, subclinical hypothyroidism, and gastric banding failure	BMI 54.8, HbA1c 12.3, CRP 13, BP 146/85	Weight reduction with edema resolution.
2	[36]	11	F	New onset	Basal	Degludec + metformin post-crisis		IV → SC	Combined HHS/DKA correction	Metformin (post-crisis)	60 hours of infusion, then SC; relapse 2 years later	Severe obesity, HTN, insulin resistance	BMI 41.9 to 36.8 to 39.8, HbA1c 11.6, glucose 402–647 mg/dL, BP 200/114 to 140/70 mmHg	Stabilized both episodes
3	[37]	77	F	18 (since 2005)	Basal	Insulin glargine U-300	26 units/day	IV + SC	DKA correction	Empagliflozin (SGLT2i), Metformin (glycemic), discontinued in ICU	22 days of hospitalization	STEMI, AF, pneumonia, obesity, hyperlipidemia	BMI 35, HbA1c 7.8, glucose 140–247 mg/dL (eu-DKA), CRP 91.1, BP 140/90 mmHg	Recovered, discharged on insulin
4	[12]	45	M	42	Basal	Basal		SC	DKA, initial control	Metformin, Gliclazide, Atorvastatin	NA	KPD, obesity, HTN	BMI 28.4, HbA1c 15.1, glucose 1221	Mostly oral control
5	[38]	59	F	Unknown (new diagnosis at admission)	Basal	Insulin glargine	32 units/day	IV	HHS & DKA correction	Metformin + Gliclazide (glycemic)	18 days in hospital; 15 months follow-up	Deep vein thrombosis (past), HHS, ketoacidosis, lactic acidosis	BMI 36.5, HbA1c 13.6, glucose 1897 mg/dL, BP 95/84 mmHg	Normalized consciousness and insulin secretion restored
6	[39]	28	F	–	Basal	IV insulin	An insulin drip at 0.1 U/kg/hour	IV insulin infusion	Triglyceride reduction in HTG-AP	Niacin, statin, fenofibrate (lipid); insulin at discharge	4 days inpatient	HTG-AP, obesity, recurrent AP, dyslipidemia	HbA1c 10.7, glucose 331 mg/dL	TG ↓ from 11602 → <1000 mg/dL; discharged stable

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Table I (Continued).

Study ID	Reference	Insulin Regimen										Conditions in Admission		Clinical Outcomes
		Age (Years)	Sex	T2DM (Years)	Insulin Details (Basal or Bolus or Combination)	Type of Insulin Therapy or Regimen	Dosage	Location of Administration	Insulin Purpose (Glycemic Control or Correction, or DKA)	Oral Therapy & Purpose (Glycemic Control, Lipid, Blood Pressure)	Therapy Duration	Conditions	Laboratory Parameter	
7	[40]	58	F	21	Basal	Insulin glargine	16 units/day	SC	Glycemic control	NA	2 months	PDR, nephropathy	HbA1c 11 to 7.3	Stable glucose, vision worsened
8	[41]	26	M	7	Bolus	IV bolus + infusion		IV	DKA correction	Canagliflozin (SGLT2i), others	16 days of hospitalization	Severe eDKA, adenovirus infection	BMI 41.5, HbA1c 13.3, glucose 13.6 mmol/L, CRP 64, BP 110/50 mmHg	Recovered, extubated, DKA resolved
9	[42]	79	F	Not specified	Bolus	Faster-acting insulin aspart		SC (pump)	Glycemic control in terminal care	Metformin + Linagliptin (pre-admission)	Closed-loop use ~3 days	Terminal illness, bowel cancer, hydrocephalus, pneumonia	Glucose mean levels 11.3 mmol/L (sensor)	Safe glucose control, died during palliation
10	[43]	65	F	18	Bolus	IV insulin		IV continuous	Glycemic control	Fenofibrate (lipid), antihypertensives	–		BMI 31.3, HbA1c 7.7	–
11	[44]	67	M	NA	Bolus	Human insulin		SC	Glycemic control, ulcer healing	Metformin (implied)	6 months	β-thalassemia, trophic ulcer, neuropathy	BMI 32.7, HbA1c 6.5, Glucose 15 to 13 mmol/L	Ulcer healed, glycemia improved
12	[45]	40	F	11	Bolus	Lispro + Heparin, then URLi		CSII (Lispro + Heparin), switched to URLi	Overcome subcutaneous resistance	–	11 years Lispro + Heparin, then switched to URLi	SIR syndrome, menorrhagia, and obesity	BMI 36.5, HbA1c 8.9	Maintained glycemic control, and bleeding improved
13	[46]	21	M	0	Bolus	Human insulin		IV then SC	Ketosis correction	None reported	Several intermittent episodes over 8 years	Recurrent ketosis, no antibodies	BMI varied 31.1–30.6, HbA1c 10.9, glucose 872 mg/dL	Eventually needed long-term insulin therapy
14	[47]	54	F	5	Bolus	Regular insulin	0.03 UI/kg/h	IV	eDKA correction	Empagliflozin, Linagliptin (pre-hospital)	14 days of hospitalization	COVID-19, rheumatoid arthritis	BMI 27.5, HbA1c 10.29, glucose 159 mg/dL, BP 145/90 mmHg	Recovered, discharged on MDI insulin (glargine + lispro)

15	[48]	56	F	9	Bolus	Human insulin	> 300 units/day		DKA treatment	Metformin + α -glucosidase inhibitor (glycemic); steroids (antibody-related)	A few days (acute)	Anti-insulin antibody, insulin allergy, and spinal disc herniation	HbA1c 11.8, glucose 275 mg/dL	DKA resolved with high-dose insulin, continued on oral agents
16	[49]	55	M	Since 1995 (29 years)	Bolus	Human insulin			Glycemic control (before lifestyle program)	None post-remission	1-year lifestyle program	Liver transplant (2016), NAFLD, cirrhosis	HbA1c 6.3 (post-remission), glucose normal (OGTT cleared)	T2DM remission
17	[50]	40s	F	Not specified	Bolus	Regular insulin		IV	eDKA correction	Empagliflozin (stopped pre-op)	~48 hrs post-op before diagnosis	Moyamoya disease, cerebral infarct, surgery	Glucose 133–167 mg/dL, BP stable post-op	DKA resolved, the patient later died from a stroke
18	[51]	77	F	Long-standing	Bolus	Lispro + human insulin	36 units/day	SC → IV → SC	Glycemic control	Acarbose, Sitagliptin, Metformin (glycemic)	10+ days	Heart failure edema	BMI Normal range, HbA1c 10.1, glucose 16.3–30 mmol/L	Edema resolved, better control
19	[52]	50	F	12	Bolus	Human insulin		IV insulin	DKA correction	Dulaglutide (stopped)	~3 days	LADA, hyperuricemia, lipid disorder	BMI 24.26, HbA1c 10.6, glucose 27.85 to 7.23 mmol/L	DKA corrected
20	[53]	53	F	0	Combination	Insulin glargine + insulin glulisine	Insulin glargine 26 units/day + insulin glulisine 12 units 3 times before meals	SC + IV	DKA correction	Metformin (glycemic control)	~1 week	ITP, steroid-induced DKA	BMI 27, HbA1c 14.7, 570 mg/dL	Resolved DKA, discharged on insulin + metformin
21	[54]	85	M	20	Combination	Insulin glargine + insulin Aspart	Insulin glargine 40 units/day + insulin Aspart six hourly	SC	Glycemic control	Multivitamin, Gabapentin (neurologic)	5 days of hospitalization	Urinary auto-brewery syndrome, epilepsy, dementia	HbA1c 7.25, FPG 190 to 98, PPG 295 to 132, BP stable	Resolved ethanol intoxication, returned to baseline

(Continued)

Table 1 (Continued).

Study ID	Reference	Insulin Regimen										Conditions in Admission		Clinical Outcomes
		Age (Years)	Sex	T2DM (Years)	Insulin Details (Basal or Bolus or Combination)	Type of Insulin Therapy or Regimen	Dosage	Location of Administration	Insulin Purpose (Glycemic Control or Correction, or DKA)	Oral Therapy & Purpose (Glycemic Control, Lipid, Blood Pressure)	Therapy Duration	Conditions	Laboratory Parameter	
22	[55]	36 (Case 1), 32 (Case 2)	F	T1DM x 18y (Case 1), x 24y (Case 2)	Combination	Levemir + Humalog	Levemir 15 units in the morning and 12 units in the afternoon + Humalog 6 units with breakfast, 7 units with lunch, and 20 units with dinner	SC	Glycemic control in pregnancy	None during pregnancy	Pregnancy + up to 9 months postpartum	Pregnancy, nephropathy, ESRD	BMI case 1: 35–38, case 2: around 39, HbA1c case 1: 10.1, case 2: 9.9, glucose 300–400 mg/dL, hypertensive, poorly controlled	Both progressed to ESRD and dialysis
23	[56]	55	M	NA	Combination	Insulin Aspart + Detemir		SC	DKA	Glipizide (glycemic)	Short-term (2–15 days)	COVID-19, DKA, pneumonia	BMI 31.1, HbA1c 9.5, Glucose level 948 mg/dL, CRP >19.0, BP 161/77	Recovered, ICU, discharge
24	[57]	55	F	13	Combination	Human insulin		IV infusion, basal-bolus	Glycemic control, HHS	Metformin, linagliptin (replaced), dulaglutide; statin, aspirin, anti-HTN	3 weeks	HIV, HHS, sepsis, ASCVD, renal artery stenosis	BMI 20.2, HbA1c 15.5 to 10.5, glucose 54.5 to 6.44 mmol/L, CRP 312.1 to 37.1 mg/L, BP 155/90 mmHg	Glycemic control improved; insulin discontinued
25	[58]	57	M	20	Combination	NPH (Jusline N) + Prior trials: aspart, glargine, glulisine	10 units of NPH insulin (Insulatard, strength: 100 IU/mL, Novo Nordisk, Bagsvaerd, Denmark)	SC	Glycemic control	Metformin + Glimpiride (glycemic); Captopril (BP)	Desensitization 8 days, follow-up 8 months	Penicillin allergy, insulin allergy	BMI 23, HbA1c 11.6–14, FPG 118 mg/dl, PPG < 186 mg/dl	Successful desensitization, good glycemic control

26	[59]	48	F	T1DM x 4 years	Combination	Insulin aspart + Insulin glargine	Aspart 18 units/day + Insulin glargine 16 units/day	IV	DKA correction	None reported	3 weeks in ICU	Influenza A, pneumonia, ARDS, cytokine storm	BMI 25.2, HbA1c 13.3, glucose 801 mg/dl, CRP 4.16, BP 96/42 mmHg	Recovered from DKA & ARDS
27	[60]	77	M	10	Combination	Not specified		SC	Glycemic control	Sitagliptin + Glimepiride (glycemic)	4 months	Autoimmune pancreatitis	BMI 20.4, HbA1c 10.1, glucose 421 mg/dl, CRP 0.04, BP 96/56 mmHg	Remission with diet only
28	[61]	81	F	New-onset (secondary to AIP)	Combination	Insulin glulisine + Insulin glargine	22 units/day and 8 units/day for glulisine and glargine	IV then SC	Glycemic control, HHS	None during acute care	~5 months	Type 2 autoimmune pancreatitis, HHS	BMI 51.1 kg/146.4 cm, HbA1c 10.1, glucose 814 mg/dl, CRP 0.47, BP 143/85 mmHg	Recovered, insulin stopped
29	[62]	91	F	8	Combination	Insulin aspart + Insulin degludec	18 units/day of insulin aspart and 6 units/day of insulin degludec	SC	Glycemic control	Multiple cardiovascular drugs	38 days of hospitalization	Acute submandibular sialadenitis, multiple cardiovascular diseases	BMI 40.3 kg/150 cm, HbA1c 8.6, glucose 335 mg/dl, CRP 1.61 to 20.1 mg/dL, BP 122/50 mmHg	Improved; infection resolved
30	[63]	57	M	3	Combination	Insulin aspart + NPH	Insulin aspart 50 units/day and NPH insulin 60 units/day	IV → SC → NPH	Severe hyperglycemia	Metformin (glycemic)	9 days of intensive	Asthma, OSA	BMI 33.5, HbA1c 6.1, glucose 270 mg/dL, CRP 58	ICU, extubated, transferred
31	[64]	59	F	20	Combination	Unspecified	Mixed insulin 36 units 2 times/day, then switched to oral	SC (discontinued)	Initial glycemic control	Vildagliptin/metformin, glimepiride, statin, antihypertensive	1-year follow-up	HIV, hypertension, dyslipidemia, CKD (GFR 50)	BMI 33.7, HbA1c 12.1 to 6.5, glucose 14.6 mmol/L to 6.6, BP 141/99 mmHg	Good glycemic and metabolic control on oral agents
32	[65]	43	F	17	Combination	Insulin glargine + Lispro		IV → SC	EDKA	Metformin, Dulaglutide (glycemic)	3 days inpatient, then outpatient	Ketogenic diet, recent SGLT2i	BMI 31.3, 169 mg/dL (euglycemic DKA, CRP normal, BP 115/80	Stabilized and discharged

(Continued)

Table I (Continued).

Study ID	Reference	Insulin Regimen										Conditions in Admission		Clinical Outcomes
		Age (Years)	Sex	T2DM (Years)	Insulin Details (Basal or Bolus or Combination)	Type of Insulin Therapy or Regimen	Dosage	Location of Administration	Insulin Purpose (Glycemic Control or Correction, or DKA)	Oral Therapy & Purpose (Glycemic Control, Lipid, Blood Pressure)	Therapy Duration	Conditions	Laboratory Parameter	
33	[66]	22	M	Diagnosed at 8 (Type A IR)	Combination	Insulin glargine + Lispro	Up to 2.23 IU/kg/day	High dose SC (discontinued)	Glycemic control	Metformin, sitagliptin, dapagliflozin, semaglutide (glycemic)	2-year follow-up	Type A insulin resistance syndrome	BMI 20.3 to 24.8 to 22.9, HbA1c 10 to 6.4	Stopped insulin; HbA1c 6.4%
34	[67]	58	M	16	Combination	Regular human insulin + insulin glargine		IV	DKA correction	Sitagliptin + Metformin (glycemic)	~3 weeks	Insulin allergy	BMI 19.6, HbA1c 11.2, glucose 20.79 mmol/L, BP 150/90 mmHg	Resolved DKA, switched to SC insulin
35	[68]	79	M	10	Combination	Humulin R + Insulin glargine		SC	Glycemic control	Acarbose, Sitagliptin (glycemic)	1 year	Diabetic nephropathy, gout	BMI 26.6, HbA1c 10.2, glucose 11–22 mmol/L	Glucose normalized
36	[69]	51	M	Long-standing	Combination	Detemir + Insulin aspart	Detemir 20 units twice daily	SC	Glycemic control	Metformin + sitagliptin + rosuvastatin (glycemic and lipid)	~5 days after dapagliflozin	Acute pancreatitis post dapagliflozin	HbA1c 8.5, glucose 190 mg/dl fasting; 295 mg/dL post-prandial, BP 155/96 mmHg	Pancreatitis resolved after stopping dapagliflozin
37	[70]	22	F	T1DM since age 10 (case 1)	Combination	Regular + Insulin glargine	300-330 units/day to 90 units/day	IM	Glycemic control in SIRS	Dapagliflozin 10 mg (reduces insulin need)	Several years ago, dapagliflozin was added at age 20	SIRS	BMI 20.9, HbA1c 10–11% to 7–8%, glucose 300–500 mg/dL to 100–140 mg/dL	DKA-free, HbA1c stable, insulin dose reduced by 70%
38	[71]	21	F	T1DM since age 18 (case 2)	Combination	Regular + Insulin glargine	300-330 units/day to 90 units/day	IM	Glycemic control in SIRS	Dapagliflozin 10 mg	Over a year	SIRS	HbA1c 12% to 7–8%	DKA-free, stable glycemic control, 66% insulin dose reduction
39	[71]	59	M	4	Combination	Insulin aspart + Degludec	16 units/day and later increased to 32 units/day	SC	Glycemic control	Metformin + Linagliptin (glycemic)	32 days	Penile/scrotal edema, MRSA infection	BMI 20.4, HbA1c 11.7, glucose 295 mg/dL, CRP 2.58	Edema resolved after dose reduction and catheter removal

40	[72]	62	F	10	Combination	Insulin glargine + Insulin aspart		IV → SC → Pump	DKA correction, long-term control	Metformin (IR)	2–3 years	Insulin allergy (detemir), antibody- mediated IR, pruritic rashes	BMI 27.5, HbA1c 8.5, glucose 24.7 mmol/L, BP stable	Improved control; allergic reactions persisted
41	[73]	60	F	15	Combination	Insulin aspart + Detemir	Insulin aspart 3 times/day + Detemir nightly (adjusted)	SC	Perioperative glucose control	Metformin, acarbose, pioglitazone (glycemic); telmisartan, bisoprolol (BP)	23 days pre/ post-op	Hypertension, obesity, HBsAg +, femur fracture	BMI 42.6, HbA1c 8.2, glucose varied (eg, FBG 127, 65, 141 mg/ dL), BP 150/80 to 140/80 mmHg	Stable perioperative course; ORIF successful
42	[74]	NA	F	Long-standing	Combination	Detemir + Lispro	Insulin detemir 50 units every 12 hours	SC, dose adjusted	Steroid- induced hyperglycemia	Metformin, Repaglinide, Pioglitazone (glycemic)	10+ months	Cancer, on chemotherapy	HbA1c 7.3–8.7, CRP normal	Glycemia is managed with adjusted insulin
43	[75]	57	F	Misdiagnosed for several years	Initially prescribed, adjusted after C-peptide	Not specified		Yes	Correction, later reclassified	Gliflozin avoided; therapy adjusted based on insulin reserve	Not specified	LADA	BMI 41, HbA1c 9.5, FPG not specified	Accurate diagnosis and therapy adjustment
44	[76]	70	F	> 20 years	Brief consideration only	N/A		None long-term	Not applicable (preventive role)	Metformin, DPP4i, lifestyle	20+ years follow-up	Hypertension, fracture- triggered calorie drops	BMI 40.9 (case 1), 23.3 (case 2), HbA1c 6.6% to 6.3%, OGTT profile improved, BP case 1: 170/ 100 mmHg	Stable insulin secretion, HbA1c maintained

Abbreviations: AF, Atrial Fibrillation; ARDS, Acute Respiratory Distress Syndrome; ASCVD, Atherosclerotic Screening Cardiovascular Disease; BMI, Body Mass Index; BP, Blood Pressure; CKD, chronic kidney disease; CRP, C-Reactive Protein; DKA, Diabetic Ketoacidosis; eu-DKA, Euglycemic Diabetic Ketoacidosis; ESRD, End-Stage Renal Disease; FPG, Fasting plasma glucose; GADA, Glutamic acid decarboxylase autoantibodies; HbA1c, Glycated Hemoglobin; HTG-AP, Hypertriglyceridemia-Induced Acute Pancreatitis; HHS, Hyperosmolar Hyperglycemic Syndrome; HTN, Hypertension; IA, Insulin autoantibodies; ITP, Immune Thrombocytopenic Purpura; IV, Intravenous; KPD, Diabetic Ketoacidosis; LADA, Latent Autoimmune Diabetes in Adults; MRSA, Methicillin-Resistant *Staphylococcus aureus*; NAFLD, Nonalcoholic fatty liver disease; OGTT, Oral glucose tolerance test; ORIF, Open Reduction and Internal Fixation; OSA, Obstructive Sleep Apnea; PDR, Proliferative Diabetic Retinopathy; PPG, Postprandial glucose; SC, Subcutaneous; SIR, Severe Insulin Resistance; SIRS, Subcutaneous Insulin Resistance Syndrome (SIRS); STEMI, ST-Elevation Myocardial Infarction; TG, Triglycerides; URLLi, Ultra Rapid Lispro.

developed progressive edema on both the trunk and extremities two weeks after the basal insulin therapy. Edema resolved with insulin regimen adjustments.³⁵ The second case reported by Mohn et al (2021) described an 11-year-old girl with a family history of obesity and T2DM. She presented with marked hypertension, acanthosis nigricans, and insulin resistance (IR). She was initially diagnosed with essential hypertension and commenced on amlodipine and bisoprolol, but her condition deteriorated to develop severe hyperglycemia, metabolic acidosis, and ketonemia, consistent with a mixed hyperosmolar hyperglycemic state (HHS) and diabetic ketoacidosis (DKA). She was managed with fluid resuscitation and intravenous basal insulin, later converted to subcutaneous therapy. T2DM was established against a background of increased HbA1c, high C-peptide levels, and negative pancreatic islet autoantibodies. She responded after 17 days and was discharged on metformin and basal insulin therapy, but she presented with the same episode two years later due to non-compliance. She again responded to insulin, fluid, and glucose infusion and became metabolically stable.³⁶ The third case, reported by Oriot et al (2023), was a 77-year-old female with a history of hyperlipidemia, hypertension, obesity, and T2DM. She was on long-term metformin and empagliflozin. She was noted to have mild tachycardia, normal oxygen saturation, and hyperglycemia on evaluation. She developed atrial fibrillation and was commenced on antithrombotic therapy following successful stenting, and acute respiratory distress syndrome and pneumonia with elevated C-reactive protein on the seventh day of hospitalization. During her stay in the intensive care unit, she was diagnosed with euglycemic DKA (eu-DKA) likely precipitated by empagliflozin, and thus was treated with intravenous fluid and basal insulin. She was discharged on day 22 with ongoing heart failure and diabetes management with basal insulin glargine U-300 and metformin. On the six-month follow-up visit, she had lost 10 kg and was still ongoing with her heart failure and diabetes management with preserved sinus rhythm.³⁷ Furthermore, Ramaldes et al (2021) presented four cases of ketosis-prone T2DM (KPD) from Southeast Brazil, which included three males and one female, all obese or overweight, aged 30–50 years, with a family history of T2DM. They presented with a blood glucose level of 809.5 ± 344.2 mg/dL, metabolic acidosis, ketonuria, and negativity for glutamic acid decarboxylase antibodies (GAD-65). Beta-cell reserve was intact, as indicated by C-peptide levels of 1.19 ± 0.53 ng/mL at diagnosis. T2DM duration was two to six years, and diabetic retinopathy was present in one patient. The patients have been given basal insulin therapy for four to twelve months. After the achievement of glycemic control, there was a dramatic restoration of beta-cell function, with over 75% of the patients becoming insulin-independent and subsequently maintained on oral hypoglycemic medications.¹² The fifth case, which was reported by Sato et al (2020), was a 59-year-old female with a history of deep vein thrombosis and no prior diagnosis of diabetes, who was admitted to the emergency room in a vegetative state. Before admission, she had experienced physical stress due to relocation and excessive consumption of sugar-sweetened beverages, followed by three days of profound thirst, nausea, and anorexia. She was found unresponsive at home with hypotension, hypothermia, irregular deep breathing, and extremely elevated hyperglycemia. Laboratory findings revealed high plasma glucose, hypernatremia, hypokalemia, elevated plasma osmolality, and extremely high β -hydroxybutyrate. She responded to supportive treatment, and on the 18th day, restoration of insulin secretion became evident in the form of elevated postprandial C-peptide. She was being given 32 units of basal insulin glargine and 40 mg of gliclazide. One year and three months later, with stable BMI and HbA1c at 6.9%, she was having good glycemic control on 750 mg metformin, 10 mg gliclazide, and 18 units of basal insulin glargine.³⁸ In the sixth case presented by Sawalha et al (2020), a 28-year-old white female who had a history of poorly controlled T2DM, dyslipidemia, obesity, and recurrent pancreatitis, who presented with epigastric pain, nausea, and vomiting, had no history of alcohol use, gallstone disease, smoking, or recent drug adjustment. Laboratory analysis revealed severe hypertriglyceridemia, elevated pancreatic enzymes, hyperglycemia, metabolic acidosis, and hypocalcemia—values characteristic of acute pancreatitis caused by hypertriglyceridemia (HTG-AP). Radiologic findings were typical of acute pancreatitis without necrosis or pseudocyst formation. Intravenous infusion of insulin was initiated at 0.1 U/kg/h, with a dramatic reduction in triglycerides within 24 hours and normalization (<1000 mg/dL) on day four. She was discharged on a regimen including basal insulin, niacin, and her current lipid-lowering therapy, with advice to initiate insulin pump therapy for better glycemia and lipid control.³⁹ In the seventh case from Wang et al (2021), a 58-year-old Chinese lady with a 21-year history of poorly controlled T2DM developed progressive right eye visual impairment over one year. Clinical evaluation showed bilateral proliferative diabetic retinopathy (PDR): the right eye had tractional retinal detachment (TRD) with widespread fibrovascular growth, and the left eye had high-risk PDR with neovascularisation

and retinal nonperfusion. Management in the right eye comprised pars plana vitrectomy (PPV), panretinal photocoagulation (PRP), and tamponade using silicone oil, and resulted in modest visual improvement. Despite medical advice, the patient refused PRP in the left eye initially and was subsequently lost to follow-up. She re-presented two months later with a sudden loss of vision in the left eye, which had developed extremely rapidly to macula-involving TRD, despite improved glycemic control following the initiation of a new insulin regimen consisting of pre-prandial asparaginsulin (6 units) and nocturnal glargine (16 units). She was treated with intravitreal conbercept, PPV, PRP, and injection of silicone oil in the left eye. Her postoperative vision was 20/160 in both eyes and remained unchanged on follow-up for two months.⁴⁰

Bolus insulin therapy was depicted in twelve cases, most of which involved complications such as DKA or severe IR and were effectively managed through individualized insulin adjustments.^{5,41–52} Almazrouei et al (2022) discussed a case of a 26-year-old male patient with a history of poorly managed T2DM who presented with agitation, dyspnea, abdominal pain, fever, and sore throat. He was diagnosed with DKA and metabolic acidosis with hyperglycemic features, severe acidemia, and excessive ketones. Despite standard management including fluid resuscitation, insulin, and sodium bicarbonate, his clinical course deteriorated and necessitated mechanical ventilation and renal replacement therapy (RRT). At 38 hours, intensive ketone monitoring and insulin titration were performed in addition to three intermittent hemodialysis sessions and continuous venovenous hemodiafiltration, which restored the metabolic acidosis. Resolution of acidosis was achieved by hour 62, and by day four, the patient was extubated and on basal-bolus insulin. Remarkably, ketonemia lasted until day 12. Organics on urine organic acid analysis showed extended ketosis. Additional testing revealed adenovirus through a respiratory viral panel, and while in the hospital, the patient developed deep vein thrombosis at the femoral line and pulmonary embolism. He was discharged after a 16-day inpatient admission.⁴¹ Boughton et al (2019) reported a 79-year-old woman with a history of resected colon cancer, hypothyroidism, deep vein thrombosis on tinzaparin therapy, and T2DM on metformin and linagliptin therapy, who presented acutely unwell with vomiting, inappropriately increased stoma output, and dizziness. She has a background of independence in the activities of daily living. Early CT scanning revealed multiple large posterior fossa hemorrhages, resulting in reversal of tinzaparin and control of blood pressure. Due to dehydration, metformin was withheld, and corrective doses of insulin aspart were administered. Her neurological status worsened, with a follow-up CT scan demonstrating mass effect and hydrocephalus, for which she was sent to neurosurgery. Despite continued intravenous insulin (2–4 U/h), relentless hyperglycemia required frequent intervention. Enteral nutrition via nasogastric tube was initiated due to fluctuating consciousness. The infusion rate was gradually increased, and a carbohydrate load was given.⁴² Davis (2020) described a case of a 65-year-old woman with insulin-treated T2DM who started fenofibrate therapy for the deteriorating diabetic retinopathy. Blood glucose responses improved and insulin needs reduced after three months of fenofibrate treatment, most likely secondary to reduced appetite. However, concomitant impairment of renal function was also noted. Two weeks' withdrawal of fenofibrate resulted in normalization of renal function.⁴³ From the eleventh cases described by Gluvic et al (2020), a 67-year-old man was admitted with refractory distal neuropathic pain, a trophic ulcer in the right toe, and electromyographically confirmed distal sensorimotor polyneuropathy. His clinical history included non-transfusion-dependent thalassemia, and his daughter was diagnosed with carrying the β -thalassemia trait. Though his HbA1c was normal, his five-point glycemic profile revealed mild postprandial hyperglycemia with concern regarding inconsistency in long-term glycemic control. Physical examination was performed and revealed obesity, normal blood pressure, and a small trophic ulcer on the right toe, with distal pulses being present and no other abnormality. Imaging examinations revealed no sign of chronic microvascular or macrovascular diabetic complications.⁴⁴ The twelfth case, presented by Ishii et al (2022), was that of a 40-year-old Japanese female patient who had a long-standing diagnosis of T1DM at the age of 16, subsequently reclassified as T2DM with severe IR. She presented with persistent hyperglycemia despite treatment with high-dose insulin, both continuous subcutaneous and intravenous insulin infusions. Initially admitted at age 29 with refractory hyperglycemia and severe IR, her HbA1c was 11.5% despite having been given 210 units/day of insulin glargine, 50 units regular insulin pre-prandial, and 270 units/day regular insulin via continuous subcutaneous infusion—a total daily dose (TDD) of 630 units/day. The TDD of 100–120 units/day was achieved with the aid of continuous infusion of lispro-heparin successfully for 11 years under stable glycemic control. On re-admission, comparative assessment of lispro-heparin versus ultra-rapid lispro (URLi) proved to be of similar glycemic efficacy, with URLi inducing slightly

higher serum insulin levels. The patient was changed to continuous subcutaneous insulin infusion (CSII) using URLi (43 units/day), and glycemic control was optimized with diet and exercise compliance.⁴⁵ In the thirteenth case reported by Satomura et al (2020), a 21-year-old man with a dramatic weight loss for over a month, preceded by hyperglycemic manifestations and DKA. Laboratory diagnosis included a blood glucose of 872 mg/dL, HbA1c of 10.9%, and total ketone bodies of more than 5000 μ mol/L. In the absence of any clear autoimmune markers, his postprandial C-peptide was directly altered by an aggressive insulin therapy, permitting post-discharge discontinuation of insulin. He experienced four episodes of ketosis during the following eight years, each typically preceded by unexplained weight loss. Although insulin therapy may be interrupted after each event, it ultimately became inevitable due to rising beta-cell failure. His HbA1c was < 7.2%. The rate of his weight loss and beta-cell destruction was beyond usual processes observed for T2DM, pointing to an atypically fast progression of insulin depletion.⁴⁶ The fourth case from Secinaro et al (2022) was a 54-year-old female with T2DM, rheumatoid arthritis who presented with fever, cough, and dyspnea for two days. She was compliant with a severely carbohydrate-limited diet secondary to her poor health condition. Her DM was treated with metformin, later changed to empagliflozin and linagliptin because of intolerance. She had an HbA1c of 8.9%. Nasopharyngeal swab for SARS-CoV-2 was positive, and chest CT scan revealed subpleural ground-glass opacities. On presentation, she showed mild dehydration, increased anion gap, metabolic acidosis, and a slight increase in blood glucose. Euglycemic DKA was suspected. Intravenous insulin at 0.03 U/kg/h and isotonic saline were given, and she clinically improved. She required non-invasive ventilation for the first three days and thromboprophylaxis. The patient was discharged stable at 14 days, with continued diabetes management.⁴⁷ Takahashi et al (2022) reported a case of a 56-year-old Japanese woman with a 9-year history of T2DM who was admitted in a coma and diagnosed with DKA. She recently switched from glargine to degludec/aspart because of localized injection site reactions. Two weeks after restarting insulin, she presented with generalized tiredness and DKA, which was accompanied by hyperglycemia, metabolic acidosis, and increased ketones. Metabolic acidosis recurred after dose reduction, indicating severe IR. Endocrine evaluation was normal; however, there were elevated anti-insulin antibodies, hyperinsulinemia, and elevated specific IgE to human insulin, confirming insulin allergy. Insulin therapy was withheld following remission from DKA, and glucose levels were established using metformin and voglibose without any event.⁴⁸ Tripathi et al (2024) reported a 55-year-old Indian male patient with a 17-year duration of T2DM, who was on insulin therapy in the past, and underwent liver transplant for end-stage cirrhosis. He was on Huminsulin at discharge with HbA1c 8.1%, and started a diabetes care program with a vegan diet, exercise, and psychological counseling. Three months later, hypoglycemia appeared, and insulin was withdrawn, resulting in an HbA1c of 6.6%, then 6.3%. He achieved remission of diabetes for over one year, with a body weight loss of 11 kg.⁴⁹ Wang and Isom (2020) reported a case of a female in her forties with T2DM who received cerebral revascularization for moyamoya disease. She developed slurred speech postoperatively, and MRI verified an acute infarction in the territory of the left anterior cerebral artery. Despite an initial good recovery, she subsequently developed acute metabolic acidosis. Although DKA was not originally suspected, elevated ketones and β -hydroxybutyrate led to a diagnosis of euDKA, likely precipitated by preceding SGLT2 inhibitor therapy. Intravenous dextrose and insulin therapy alleviated the acidosis; however, due to extensive brain injury, her course was one of deterioration, and she passed away following the onset of comfort care measures.⁵⁰ Ying Hu et al (2021) reported the case of a diabetic woman aged 77 whose diabetes was not well managed with seven units of insulin taken three times daily, together with acarbose and sitagliptin. She was hospitalized with acute hyperglycemia (HbA1c 10.1%). Continuous subcutaneous insulin infusion (lispro, initially 36 U/day) was raised to 98 units/day since glycemic control remained inadequate, resulting in better glycemic control, consistent with impaired subcutaneous insulin absorption. Long-term control was established on 56 units/day of insulin and oral antidiabetic agents.⁵¹ In the nineteenth case published by Zhang et al (2024), a 50-year-old diabetic woman with a BMI of 24.46 kg/m² was initially treated with oral hypoglycemic drugs but showed poor glycemic control. After multiple episodes of DKA in two years, impaired beta-cell function, and GAD and insulin autoantibodies, she was given insulin therapy. Her glycemia remained labile, along with dyslipidemia and hyperuricemia. Six days before presentation, she discontinued insulin and initiated dulaglutide, with consequent severe nausea, vomiting, and fatigue. Although she experienced transient improvement with emergency management, she developed progressive vomiting and dyspnea. She was again admitted with severe metabolic acidosis, hyperglycemia, and positive ketones, establishing the diagnosis of DKA. The treatment included fluid resuscitation and

low-dose insulin infusion. Acid–base balance was normalized on day three, and glycemic control was re-established, making transfer to intensive insulin therapy possible⁵²

The combination of both insulin therapies was predominantly reported in 23 cases, with one article describing C-peptide–guided insulin adjustments, while in the last article, insulin therapy was only briefly considered.^{53–76} In the twentieth case from Alakkas et al (2020), a female patient aged 53 with a known history of immune thrombocytopenia (ITP) presented with five days of mild gum bleeding and epistaxis, and polyuria, nocturia, polydipsia, and recent weight gain. She had discontinued her prednisolone taper due to oral candidiasis and had missed follow-up appointments. On examination, she was hydrated, BMI of 35 kg/m², with severe thrombocytopenia. Investigation findings were positive for newly diagnosed T2DM (HbA1c 14.7%, RBS 551 mg/dL, glucosuria, and mild ketonuria). She was hospitalized to manage a flare of ITP and received methylprednisolone, IVIG, and platelet transfusions. Within days of initiation of steroids, she developed DKA, which required an ICU stay. On day three, her condition improved with remission of DKA and adequate platelet counts. She was discharged on the combination insulin therapy and a stepped regimen of metformin to 1.5 g/day. In six months, she showed significant clinical improvement with an HbA1c of 6.9%, weight loss, better medication adherence, and no rebleeding or rehospitalization; thus, insulin was discontinued, and she continued with metformin.⁵³ In the twenty-first case reported by Alduraywish (2021), an 85-year-old man with a 20-year history of T2DM—initially managed with oral hypoglycemic agents before being changed to insulin—presented with an alteration of mental status after a week of medication non-adherence. He had suffered from nephrolithiasis, epilepsy, chronic constipation, and daily intake of multivitamins and cod liver oil. Upon admission, he was confused, dehydrated, and disoriented without recent weight loss. Laboratory investigations revealed HbA1c $\leq$ 7.6% and elevated blood and urine ethanol concentrations, cloudy urine with glucose, ketones, lactate, and dense pyuria. Microscopy was positive for *Candida albicans*. He was treated with a subcutaneous combination insulin regimen (glargine 40 IU/day and aspart every 6 h) and intravenous saline. Amphotericin B intravenously 40 mg/day for five days to eradicate the fungi.⁵⁴ In the twenty-second case, described by Bin Attique et al (2021), a 36-year-old Hispanic woman with T1DM and hypertension presented at 12 weeks' gestation with nephrotic-range proteinuria in the context of normal creatinine clearance. Glycemic control was suboptimal in pregnancy, and hypertension was resistant to multiple changes. At 36 weeks, she also developed superimposed preeclampsia with severe features and was admitted with high blood pressure, going on to deliver a low-birth-weight infant by caesarean section. Postpartum, her renal function worsened, and a renal biopsy revealed progressive diabetic nephropathy. Eight months postpartum, she developed end-stage renal disease (ESRD) and commenced hemodialysis. Similarly, a 32-year-old Hispanic woman with poorly controlled T1DM and hypertension before pregnancy presented early in pregnancy with hyperglycemia. Despite optimized insulin therapy, renal function worsened during pregnancy, with rising creatinine and persistent proteinuria. She presented with preterm labor at 24 weeks and delivered a non-viable fetus by Caesarean section. She persisted with deteriorating renal function, and nine months postpartum, she developed ESRD and was initiated on peritoneal dialysis.⁵⁵ The twenty-third case series reported by Croft et al (2020) described patients with T2DM and no prior history of diabetic ketoacidosis (DKA) who developed new-onset DKA concomitant with COVID-19 infection. The authors implied that COVID-19 is a precipitating cause of DKA in patients with T2DM, and strict compliance with antidiabetic therapy was strongly advised.⁵⁶ Another case report was of a 55-year-old woman with HHS in the setting of sepsis. HIV and insulin-dependent diabetes were comorbid conditions. She was found to be dehydrated, febrile, and tachycardic on physical examination, with altered mental status and a genital infection. Laboratory results revealed hyperglycemia, HbA1c 15.5 mmol/mol, serum osmolality 389.4 mOsm/kg, and bicarbonate 24.6 mmol/L, with negative serum ketones. Intravenous fluid, insulin, and antibiotics were administered. Basal-bolus insulin therapy significantly improved glycemic control and reduced insulin requirements, allowing low-dose metformin and linagliptin therapy to be subsequently initiated. As atherosclerotic disease developed, dulaglutide was introduced and linagliptin was discontinued, with consequent sustained glycemic control, better adherence, and improved quality of life.⁵⁷ The twenty-fifth case, described by Elfekih et al (2019), was a 57-year-old man with poorly controlled T2DM and a known penicillin allergy, who presented with immediate hypersensitivity minutes after taking subcutaneously 10 units of neutral protamine Hagedorn (NPH) insulin in addition to metformin and glimepiride, resulting in insulin discontinuation. He had a BMI of 23 kg/m² and newly developed hypertension, with negative diabetic autoantibodies and elevated total IgE. Various insulins were attempted, and alternative causes such as syringe or excipient sensitivity were excluded. He was ultimately successfully managed with a desensitization regimen of graduated doses of NPH insulin along with antihistamines and corticosteroids.⁵⁸ Horiya et al (2022) reported the case of a 48-

year-old Japanese woman with T1DM who presented with altered consciousness following a diagnosis of influenza A and oseltamivir treatment. Investigations demonstrated raised inflammatory markers, renal impairment, profound hyperglycemia, severe ketonemia, and severe acidosis on blood gas. Imaging confirmed pneumonia, making the diagnosis influenza A-associated pneumonia with DKA. Intensive treatment involved fluid resuscitation, insulin therapy (18 units/day insulin aspart and 16 units/day insulin glargine), and treatment for hypoxia and shock. Two days after admission, respiratory function worsened, necessitating intubation. Chest CT revealed worsening bilateral lung consolidation, and she was diagnosed with acute respiratory distress syndrome (ARDS). Over the subsequent three weeks, she had persistent hypoxemia, pneumonia, rhabdomyolysis, and electrolyte abnormalities. Her condition later improved, and she was discharged to a general ward. Cytokine analysis revealed that cytokine storm with elevated interleukin-6 was implicated in the pathogenesis of ARDS after DKA.⁵⁹ In a case reported by Irie et al (2019), a 77-year-old man with a 10-year history of T2DM that was initially managed with diet and later with sitagliptin and gliclazide presented with persistently elevated levels of HbA1c. His history was positive for pharyngeal carcinoma and prostatitis with no relevant family history. Clinical and neurological exams were unremarkable. Laboratory investigations revealed impaired glycemic control (HbA1c 10.1%), mildly suppressed insulin and C-peptide, and elevated serum IgG4. Imaging demonstrated a hypoechoic pancreatic body lesion with obstruction of the main pancreatic duct. Prednisolone therapy led to improvement in both pancreatic and IgG4 parameters, although glycemic control initially worsened, necessitating insulin. Insulin therapy was discontinued after four months, with continued dietary therapy maintaining HbA1c < 7% and endogenous insulin secretion for at least six months.⁶⁰ Case presentation by Iwamoto et al (2022) discusses an 81-year-old Japanese woman, not diagnosed with diabetes previously, with striking hyperglycemia and HbA1c of 9.7%, accompanied by hyperketonemia and metabolic acidosis. Imaging revealed enlargement of the pancreas without dilatation of the ducts or neoplastic masses, as in AIP, but biopsy was not performed due to procedural risks. Intensive insulin therapy was initiated with a peak daily dose of 22 units of glulisine and 8 units of glargine, resulting in improved glycemic control and partial return of endogenous insulin secretion. After several months, insulin treatment was discontinued, and blood glucose and HbA1c values were within normal range without any further need for insulin or oral hypoglycemic medications.⁶¹ A case reported by Iwamoto et al (2023) described a 91-year-old woman with a history of recurrent myocardial infarcts, heart failure, T2DM, atrial fibrillation, and pacemaker implantation, who developed fever, neck swelling, and elevated inflammatory markers after 20 days of parenteral nutrition via nasogastric tube. Glycemic control was poor with fasting plasma glucose levels of 200 to 400 mg/dL despite insulin treatment (18 units/day insulin aspart and 6 units/day insulin degludec). Her medication included azosemide, acetazolamide, spironolactone, bisoprolol, enalapril, edoxaban, and isosorbide. Bilateral swelling of the submandibular glands was seen on imaging, and the patient was diagnosed with acute submandibular glanditis most likely due to long-term nasogastric tube feeding. Treatment involved antibiotic therapy, submandibular massage, and intense glycemic control.⁶² According to Jornayvaz et al (2020), a 57-year-old man with a three-year history of T2DM, asthma, and obstructive sleep apnea tested positive for COVID-19. He had been on metformin earlier with an HbA1c of 6.1% and progressed to have acute respiratory failure requiring admission to the ICU, mechanical ventilation, and vasopressor support. The course of the disease clinically was marked by profound IR, necessitating high-dose intravenous insulin aspart (maximum 50 units/hour) for hyperglycemia control. On the ninth day, the insulin requirement fell dramatically without any occurrence of hypoglycemia. Extubation was on day 13, and transition to subcutaneous NPH insulin at 60 units/day on stabilization.⁶³ Kabakambira and Kong (2023) documented a 59-year-old woman with 20 years of T2DM, hypertension, and HIV, who presented with uncontrolled blood glucose despite treatment with insulin. She received 36 units/day of premixed insulin, telmisartan-hydrochlorothiazide, aspirin, and antiretroviral drugs (dolutegravir, abacavir, and lamivudine). Glucose readings were high, and her HbA1c was 12.1%. She was obese, having hypertension, dyslipidemia, and retained C-peptide, reflecting intact beta-cell function, and renal function testing revealed moderately impaired function without microalbuminuria.⁶⁴ A case reported by Latif et al (2020) involving a female patient of 43 years old with T2DM diagnosed, being controlled on metformin for the past three years, and recently started on empagliflozin. She presented with generalized weakness, nausea, vomiting, cough, and dyspnea after two weeks of strict diet control on a ketogenic diet. On admission, she was tachycardic, tachypneic, normotensive, and had mild dehydration with no focal abdominal or neurological deficits. She was treated for DKA with intravenous fluid, cefepime, insulin infusion, and 5% dextrose in the ICU. The blood glucose increased rapidly on treatment. She was discharged on day three in stable condition on metformin 1000 mg twice daily and dulaglutide 0.75 mg weekly, and empagliflozin was discontinued.⁶⁵ The 33rd case, presented by Martínez-Montoro et al

(2022), involved a 22-year-old Spanish man diagnosed with diabetes at the age of 8, who initially presented with hyperglycemia, polyuria, polydipsia, and negative autoantibodies. He was lost to follow-up for five years after initial insulin treatment. At his return, he had elevated HbA1c and insulin, a normal BMI, and developed acanthosis nigricans. Genetic testing revealed a new heterozygous INSR mutation (Asp1177Glu) shared with his mother and grandfather, defining type A IR syndrome. Metformin therapy in the initial phase offered temporary glycemic control, which later deteriorated, leading to intensified therapy. Combination therapy with semaglutide and dapagliflozin led to significant weight loss, insulin withdrawal, and long-term glycemic control (HbA1c 6.4%).⁶⁶ Nguyen et al (2019) reported a 58-year-old male patient with 16 years of T2DM, who also had severe DKA and epigastric pain in the background. Prior therapy was with oral hypoglycemics and biphasic insulin analogues, but was followed by allergic reactions at the injection sites. The worsening response to withdrawal of insulin resulted in precipitous DKA with high anion gap metabolic acidosis, necessitating fluid resuscitation, bicarbonate, and CVVHDF. He later developed respiratory failure requiring mechanical ventilation and hypotension following IV insulin infusion. Despite initial apprehension regarding insulin allergy, the patient stabilized on supportive measures and sustained IV insulin. Metabolic parameters returned to normal for days, allowing for CVVHDF cessation and extubation. He was switched to regular human insulin, insulin glargine, metformin, and sitagliptin. Three months later, glycemic control improved, though subtle local allergic reactions continued.⁶⁷ In a case reported by Shen et al (2019), a 79-year-old man with a decade-long history of T2DM, diabetic nephropathy, and chronic gout experienced worsening glycemic variability over the preceding year. Initially well-controlled with metformin, the treatment was modified due to renal impairment, switching to a subcutaneous insulin pump (lispro), and subsequently to Humulin R and glargine. He complained of recurrent nocturnal hypoglycemia with severe daytime hyperglycemia; he was thus given acarbose. An oral glucose tolerance test showed severely elevated insulin and C-peptide, an increased HbA1c to 10.2%, and positive anti-insulin antibodies. Glycemic variability persisted despite treatment until a combination of high-dose acarbose and sitagliptin achieved normoglycemia. On follow-up after one year, his HbA1c level had decreased to 7.0%, and insulin and C-peptide levels normalized.⁶⁸ A Hispanic man aged 51 with T2DM, dyslipidemia, and a history of cholecystectomy presented in the case by Sujanani et al (2020). He had no prior history of alcohol use, autoimmune disease, or pancreatitis, but admitted to being a smoker. Raised serum lipase was seen on laboratory findings, and imaging was in favor of acute pancreatitis. He had been initiated on dapagliflozin five days before this presentation, and it also included insulin detemir 20 units BID, sitagliptin–metformin (50–1000 mg BID), and rosuvastatin 20 mg daily. Conservative management with NPO status, IV fluids, and insulin was initiated, and both dapagliflozin and sitagliptin were discontinued. Glimepiride was initiated at discharge due to worsening hyperglycemia, and dapagliflozin (an SGLT2 inhibitor) was restarted, but it caused pancreatitis relapse. Following permanent discontinuation of dapagliflozin, no events recurred.⁶⁹ In a case series by Sweis et al (2022), a 22-year-old female with T1DM, at first presented with stable glycemic control on insulin therapy following a single initial early DKA admission. For 7 years, she has experienced recurring DKA, with rising insulin requirements, up to 400 units/day, with compromised glycemic control. Autoimmune and lipodystrophy etiologies were excluded, and she was diagnosed with severe insulin resistance syndrome (SIRS). Conversion to intramuscular insulin (regular and glargine) benefited clinically. Supplementing with dapagliflozin markedly reduced her insulin needs to 90 units/day, controlled glycemia, and prevented repeated DKA.⁷⁰ The 39th case presented by Takeda et al (2021) was that of a 59-year-old Japanese male patient with diabetes diagnosed four years prior who came in for admission with treatment for chronic lower limb ulcers. Physical examination was positive for lower extremity ulcers and erosions, and on the left hallux, as well as diminished Achilles tendon reflexes. He was first treated with debridement and antibiotics (vancomycin and cefmetazole) and insulin treatment (aspart and degludec), initially 16 units/day, and followed by escalation to 32 units. He had an acute onset of weight gain by day 14, bilateral leg edema, painless scrotal and penile swelling, fever, and acute urinary retention.⁷¹ Teo et al (2022) reported the case of a 62-year-old Chinese female with a 10-year history of T2DM who presented with polyuria, polydipsia, and DKA. She had been well-controlled in diabetes on metformin and glipizide for the first seven years, but glycemic control declined over the past three years (HbA1c 10%). Insulin detemir was started three weeks before admission, but discontinued after two weeks due to allergic symptoms. Her comorbidities were obesity, hyperlipidemia, and hypertension. Hypersensitivity testing showed reactivity to insulin glulisine but not glargine or aspart. She was discharged on aspart and glargine multiple daily injections, but still had progressively worsened glycemic control. In the face of a negative C-peptide, metformin was continued to oppose IR.⁷² Viryani and Soelistijo (2022) reported a 60-year-old Indonesian woman with hypertension and T2DM of 15 years' duration who presented with bilateral wounds of the toes,

paresthesia, fever, and an open left femoral fracture due to a fall. Her previous medical history was of insulin treatment (aspart 3×38 U, detemir 38 U daily) and obesity, on amlodipine. Physical examination revealed digital ulcers, preserved ankle-brachial index, sensory loss, high BP, and obesity. Laboratory results were HbA1c 8.2%, and imaging confirmed a subtrochanteric fracture. Treatment involved insulin adjustment, oral antidiabetic drugs, antihypertensive medication, and pain control. Although surgical delay due to hyponatremia and hyperglycemia, stabilization of her condition followed. She underwent successful ORIF on day 23 with later postoperative glycemic control and ongoing medication with regular follow-up.⁷³ Zhang and Karam (2021) reported a case in a 70-year-old female patient who had a history of T2DM for 19 years and came with complications such as retinopathy, peripheral neuropathy, coronary artery disease, and metastatic pancreatic adenocarcinoma. She was otherwise well, with diabetes that was relatively well controlled (HbA1c 7.4%) on metformin, repaglinide, pioglitazone, and insulin detemir. At cancer diagnosis, she had anorexia, weight loss, and hypoglycemia in excess, requiring insulin adjustment and withdrawal of some oral agents. She was commenced on chemotherapy (gemcitabine, paclitaxel, dexamethasone), and CGM was employed for refinement of insulin dosing. Later, the change to high-dose fluorouracil and dexamethasone caused post-chemotherapy hyperglycemia despite elevated insulin. CGM demonstrated fairly stable glucose apart from steroid intake, but poor control of treatment. Her HbA1c was elevated to 8.7%, but weight, hemoglobin, and organ function were preserved.⁷⁴ Lisco et al (2023) presented the case of a 57-year-old female patient with established T2DM since the age of 42, class III obesity, and several cardiovascular risk factors. Glycemic control was inadequate despite management with metformin and a basal-bolus insulin regimen. She progressed to developed a few complications, including non-proliferative diabetic retinopathy, non-alcoholic fatty liver disease, and lumbar radiculopathy. Low fasting C-peptide and elevated positivity for islet autoantibodies (GADA, IA2) on assessment made a re-diagnosis of latent autoimmune diabetes in adults (LADA). Her treatment was modified to include semaglutide and reduce insulin, but avoid SGLT2 inhibitors due to the risk of DKA. This was followed by improved glycemia control, weight reduction, and reduced requirement for insulin. But with progressive β -cell failure, subsequently full insulin therapy had to be re-instituted.⁷⁵ In a recent report by Oota (2024), a Japanese woman in her late 70s with a 21-year history of diabetes and a two-decade history of treated hypertension was found to have diabetes incidentally, without classic symptoms. Her initial regimen included metformin and manidipine hydrochloride. Her blood pressure was 170/100 mmHg and BMI 40.9 kg/m² at presentation, with fasting glucose of 128 mg/dL and HbA1c of 6.6%. Long-term antihypertensive and statin (atorvastatin) therapy stabilized cardiovascular status. Of interest, 75 g OGTTs performed previously were normal with preserved insulin secretion, even though β -cell function progressively deteriorated. Longitudinal data demonstrated a stable body weight-HbA1c correlation over two decades.⁷⁶

Discussion

The cases collectively demonstrate insulin therapy's pivotal role in managing T2DM complications such as DKA,^{36,41,46,48,52,53,56,59,65,67,70,72} euDKA,^{37,47,50} HHS,³⁶ diabetic nephropathy,^{40,43,55} and other severe metabolic dysregulations. The wide range of regimens and therapeutic adjustments reflects the need for individualized approaches based on clinical context, comorbidities, and patient response.

Insulin therapy remains a cornerstone in the management of T2DM, reflecting the progressive decline in beta-cell function that necessitates escalating treatment over time. Beyond glycemic control, insulin plays a pivotal role in preventing acute metabolic decompensation, particularly in patients with advanced disease or comorbid conditions.²⁹ However, its timely initiation is often hindered by psychological insulin resistance, concerns about hypoglycemia, and potential for weight gain.⁷⁷ This highlights the importance of individualized therapeutic strategies that consider patient-specific factors, including comorbidities, disease duration, and prior treatment response.

Combination therapy is frequently employed to enhance glycemic outcomes. Among the most common regimens are those integrating insulin with metformin or DPP-4 inhibitors such as sitagliptin.⁷⁸ Subcutaneous insulin remains the predominant route due to its practicality, while intravenous insulin is reserved for acute emergencies, such as diabetic ketoacidosis (DKA).

Although traditionally considered a hallmark of type 1 diabetes, DKA is increasingly reported in T2DM, particularly in the context of precipitating factors such as infections, inappropriate insulin withdrawal, and use of sodium-glucose cotransporter-2 (SGLT2) inhibitors.⁷⁹ Notably, in this review, 12 patients developed DKA in the setting of COVID-19,

consistent with evidence of viral-mediated beta-cell dysfunction and heightened insulin resistance.⁸⁰ Some patients also experienced insulin allergy, severe insulin resistance, or secondary complications like diabetic neuropathy, necessitating intensified insulin therapy. These findings underscore the importance of prompt metabolic stabilization, especially in patients with overlapping comorbidities such as cardiovascular disease or hypertension.⁸¹

Glycemic and inflammatory control are commonly monitored using glycated hemoglobin (HbA1c) and C-reactive protein (CRP). HbA1c remains the gold standard for long-term glycemic monitoring, while CRP provides insight into systemic inflammation, both of which are relevant for therapeutic guidance.^{82,83} Most patients in this review were managed effectively with basal insulin regimens, although those with poor glycemic control or severe metabolic derangement benefited from a basal-bolus approach. While the latter provides superior glycemic reduction, it requires careful titration and carries a higher risk of hypoglycemia.⁸⁴

Recent innovations, such as once-weekly insulin icodec, offer a promising alternative to daily injections. Clinical trials have demonstrated that icodec achieves non-inferior glycemic control compared to insulin glargine with reduced injection burden and potentially better adherence.⁸⁵ Nevertheless, comprehensive care in T2DM extends beyond glycemic control. Many patients may also require antihypertensive agents, statins, and occasionally corticosteroids to address comorbid conditions and systemic inflammation.⁸⁶

Despite the variability in clinical responses, the majority of cases demonstrated improved glycemic control and reductions in inflammatory markers post-intervention. These outcomes emphasize the value of early, individualized insulin initiation and continuous treatment adjustment. Further studies are warranted to explore long-term outcomes, adherence challenges, and the cost-effectiveness of emerging insulin analogs.

Conclusion

This comprehensive review reinforces the critical role of insulin therapy in the management of type 2 diabetes mellitus (T2DM), particularly in patients with poorly controlled glycemia, complex comorbidities, or in acute metabolic crises. Subcutaneous insulin remains the preferred route for long-term management, while intravenous insulin is typically reserved for emergencies such as diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), or sepsis-related hyperglycemia.

Findings from 44 case reports demonstrate wide heterogeneity in clinical presentation, comorbid burden, and treatment response. Most cases required combination therapy, particularly with metformin, GLP-1 receptor agonists, or SGLT2 inhibitors, reinforcing the necessity of individualized regimens tailored to patient profile, disease progression, and treatment goals. Notably, treatment outcomes were often influenced by factors such as delayed insulin initiation, psychological resistance to injection, poor adherence, and complex pharmacological interactions in polypharmacy settings.

The emergence of once-weekly basal insulins represents a promising innovation that may improve adherence, reduce hypoglycemia risk, and simplify treatment protocols, especially in older adults or those with cognitive impairment. However, robust data on long-term safety, patient-reported outcomes, and cost-effectiveness are still limited.

In conclusion, optimal insulin therapy in T2DM should be guided by clinical context, supported by timely monitoring, and adapted to individual patient needs. Future research should emphasize early initiation strategies, smart delivery technologies, and personalized titration algorithms. By integrating patient-centered care, biomarker-based decision-making, and therapeutic flexibility, insulin therapy can more effectively prevent complications and improve quality of life for people living with T2DM.

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