Testosterone Society® Diabetes Diagnosis and Management Guidelines

Authored by: Colette Nelson, FNP-C, RD, RN, CDCES, MSCP, AAFE; Jason Bennett, APRN, PMHNP-BC; Omar Hajmousa, PharmD

Reviewed by: Thomas O'Connor, MD; Akira Kobayashi, MD; Nikki Icard, DNP-C, Manny Singh, DNP, FNP-C; April Snell, DNP, APRN, PMHNP-BC, FNP-BC,LMFT, LPC-MHSP; Alexia Wallace, FNP-BC; Florencia Baldassarre, APRN, FNP-C; Sean Dakshaw, DO; John Flauding, FNP-C; Elias Pastene, MD

Audience: This protocol is intended for clinicians with a foundational understanding of physiology and pharmacology who evaluate and manage patients receiving testosterone or other androgen therapies. It is designed to strengthen clinical decision-making around HbA1C interpretation, glycemic monitoring, and diabetes-related risk assessment in this population.

Scope: This document provides a clinician-focused framework for evaluating and managing HbA1C and related glycemic abnormalities in patients receiving testosterone or androgen therapy. It addresses prediabetes, type 1 diabetes, type 2 diabetes, latent autoimmune diabetes in adults, and other relevant causes of hyperglycemia or insulin resistance. Guidance is based on the 2026 ADA Standards of Care in Diabetes and AACE recommendations, with emphasis on application to patients treated with testosterone or other androgens.

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Table of Contents

Demographics of Diabetes[1]: 3

Complications of Diabetes[2]: 3

Common patient Profile: 3

Latent Autoimmune Diabetes in Adults (LADA) – "Type 1.5 Diabetes" 3

Recommended Diagnostic Workup 4

Management Implications: 4

MOSH: Male Obesity-Associated Secondary Hypogonadism[3,4]: 4

Polycystic Ovary Syndrome (PCOS) 4

Hypercortisolism (Cushing's Syndrome): 5

Screen patients with any of the following: 5

Physical Findings Disproportionate to Lifestyle: 5

TRT Red Flags to watch out for when testosterone is optimized but the patient is experiencing: 6

Initial Screening Protocol: 6

Treatment Overview (Non-Surgical Candidates) 6

Key Testosteronology Society™ Takeaways: 7

- Do not escalate TRT blindly in refractory metabolic patients. 7
- Severe insulin resistance out of proportion to BMI think cortisol. 7
- Poor GLP-1 response + muscle wasting = screen. 7
- Elevated AM cortisol twice = run DST. 7
- U-500 insulin + no fat loss = cortisol until proven otherwise. 7

Clinical Pearl 7

Typical Lab Values for Diagnosis of Diabetes[5] 7

Screening: 8

Therapeutic targets Goals: 8

Supporting labs 8

Common medications relevant to TRT patients that can cause hyperglycemia[7]: 12

Treatment 14

Non-Pharmacologic Therapy[5,6]: 15

Pharmacologic Therapy – Monitoring, adjustment, … etc.: 16

Expected A1C lowering effects of medications for T2DM[9] 16

Preferred: 17

GLP-1 receptor agonists: 17

SGLT2 inhibitors: 20

SGLT2/SGLT1 21

Insulin 21

Metformin: 24

Avoid: 25

Hyperlipidemia and diabetes[19]: 25

Figures: 26

References: 26

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Demographics of Diabetes[1]:

- 38.4 million Americans have diabetes (11.6%):
  - 29.7 million are diagnosed
  - 8.7 million remain undiagnosed
- 97.6 million U.S. adults (38 %) have prediabetes.
- Deaths / Mortality: 7th leading cause of death:
  - 95,190 deaths in 2023 (3.1 % of all deaths) and 22.4 per 100,000 population
- Type 1 cases: ~ 2 million Americans, including ~ 304,000 under age 20

Complications of Diabetes[2]:

- Increased stroke risk
- Diabetic retinopathy
- Periodontal disease
- Heart disease
- Chronic Kidney Disease
- Peripheral vascular disease
- Diabetic foot infections, osteomyelitis, and amputation
- Nerve damage

Common patient Profile:

Latent Autoimmune Diabetes in Adults (LADA) – "Type 1.5 Diabetes"

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- Latent Autoimmune Diabetes in Adults (LADA) represents a slowly progressive form of autoimmune diabetes that phenotypically overlaps with type 2 diabetes mellitus (T2DM) but immunologically resembles type 1 diabetes (T1DM). It is frequently misclassified at diagnosis.
- In adults presenting with new-onset hyperglycemia — including those identified during testosterone replacement therapy (TRT) evaluation — the majority are diagnosed with prediabetes or T2DM.
- However, approximately 10–30% of adults initially labeled as T2DM demonstrate autoimmune markers consistent with LADA.
- Clinical Clues Suggestive of LADA
- Consider LADA in adults who:
- Are lean or normal BMI
- Are physically active
- Do not exhibit classic metabolic syndrome features
- Have a disproportionately poor response to oral hypoglycemic agents
- Show rapid glycemic deterioration despite lifestyle optimization
- Have personal or family history of autoimmune disease
  - These patients often demonstrate a transient response to oral hypoglycemic agents (OHAs) due to residual beta-cell function, followed by progressive insulin deficiency. Early recognition is critical, as delayed insulin initiation may accelerate beta-cell exhaustion.

Recommended Diagnostic Workup

Comprehensive autoimmune diabetes panel

- GAD65 antibodies (most sensitive marker)
- IA-2 antibodies
- ZnT8 antibodies
- Insulin autoantibodies (IAA) (particularly if no prior insulin exposure)
- Fasting C-peptide
- Fasting insulin level
- Concurrent glucose level for proper C-peptide interpretation

Management Implications:

- Early basal insulin consideration to reduce glucotoxicity and preserve remaining beta-cell mass; with a Continuous Glucose Monitor
- Avoid prolonged reliance on sulfonylureas, which may accelerate beta-cell decline;
- GLP-1 receptor agonists and DPP-4 inhibitors may have adjunctive benefit in early stages, but insulin remains the definitive therapy as C-peptide declines
- GLP1 show promise in beta cell proliferation; still being investigated but looks promising in the SURPASS-1 (40 weeks): Tirzepatide (5–15 mg) significantly increased biomarkers of β-cell function (e.g., HOMA2-β, lower proinsulin ratios) compared with placebo, suggesting reduced β-cell stress and improved endogenous insulin secretion.

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MOSH: Male Obesity-Associated Secondary Hypogonadism[3,4]:

- Definition: A functional, reversible form of hypogonadotropic hypogonadism seen in men with obesity, insulin resistance, and metabolic syndrome. The androgen deficiency is secondary to metabolic dysfunction, not primary testicular failure.
- Pathophysiology: Excess adiposity leads to increased aromatization of testosterone to estradiol which leads to decreased GnRH & LH secretion resulting in reduced testicular testosterone production.
- Presentation:
  - S/Sx of hypogonadism
  - Low total and free T
  - Low/normal FSH/LH
  - Visceral obesity
  - Insulin resistance/T2DM
  - Dyslipidemia and low HDL
  - Inflammation (increased IL-6 and TNF- α)
- Treatment: MOSH can be reversed with weight loss, TRT, metabolic optimization, and using GLP-1RAs and dual agonists.

Polyendocrine Metabolic Ovarian Syndrome (PMOS)[5,6]

- Formerly known as Polycystic Ovary Syndrome (PCOS)
- GLP1s have robust data to support their use in this condition. They directly target the most treatment-limiting driver of PCOS morbidity in many patients—obesity with insulin resistance—thereby improving downstream hyperandrogenism and ovulatory

dysfunction. In an RCT network meta-analysis including 47 RCTs/2626 participants, GLP-1 RAs (especially with metformin) were among the most favorable options for improving hyperandrogenemia and menstrual recovery vs control/other insulin sensitizers (overall confidence often low/very low, but directionally consistent across trials)

- Standard therapy includes Metformin 500 mg with largest meal and titrate to 1000 mg BID), Spironolactone (for persistent hirsutism/acne 50-100 mg) daily
- Combined oral contraceptive (COC) brand names for these progestins are: Preferred for PCOS
    - Drospirenone + ethinyl estradiol (COC): Yaz, Yasmin, Beyaz (and common generics: Ocella, Syeda, Zarah, Gianvi, Nikki, Loryna)
    - Drospirenone-only pill (POP, not a COC): Slynd
    - Dienogest + estradiol valerate (COC): Natazia – contains bioidentical estradiol
    - Drospirenone + estetrol (E4) – contains bioidentical fetal estrogen
    - Desogestrel + ethinyl estradiol (COC): Desogen, Apri, Reclipsen, Enskyce, Isibloom, Emoquette, Cyred, Caziant

- First and second generation such as norethindrone and levonorgestrel have androgenic activity, which can worsen acne and hair growth
- Third-generation progestins are the first line in PCOS patients with acne, hair growth, androgenic symptoms, fluid retention, and PMDD tendencies due to the following:
    - Blocks androgen receptor activity
    - Lowers free testosterone
    - Reduces acne + hirsutism
    - Counteracts estrogen-related water retention
    - May reduce bloating and fluid weight
    - Anti-androgenic
    - Anti-mineralocorticoid (spironolactone-like effect)
    - May reduce water retention
    - Can mildly lower blood pressure

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Hypercortisolism (Cushing's Syndrome)[7,8]:

- Hypercortisolism is an under-recognized cause of severe insulin resistance, failure of GLP-1/GIP therapy even at 15 mg Mounjaro/ 2.4 mg Wegovy, poor TRT response, muscle wasting despite adequate testosterone, central fat gain with thin extremities
- Cortisol excess should be ruled out before escalating TRT, peptides, insulin, or GLP-1 therapy.

Screen patients with any of the following:

- Refractory Metabolic Disease
- T2DM requiring more than 60 to 150 units of basal insulin
- Patients using U-500 insulin
- Minimal glycemic or weight response to high doses of GLPs/GIPs and retatrutide (once approved)

Physical Findings Disproportionate to Lifestyle:

- Facial rounding ("moon facies")
- Facial plethora

- Dorsocervical fat pad (“buffalo hump”)
- Supraclavicular fullness
- Wide violaceous striae
- Easy bruising
- Thin/fragile skin
- Proximal muscle weakness
- Central adiposity with thin extremities

TRT Red Flags to watch out for when testosterone is optimized but the patient is experiencing:

- Persistent muscle loss; high cortisol is catabolic
- Severe fatigue
- Sleep disruption
- Visceral fat not improving
- High insulin resistance despite adequate androgen levels
- Rising blood pressure on TRT without explanation

Initial Screening Protocol:

- Fasting AM cortisol elevated on ≥ 2 labs proceed to screening.
- First-Line Test: Low-Dose Dexamethasone Suppression Test (DST) is the most sensitive screening test.
- Protocol:
  - 1 mg dexamethasone at 11 PM
  - Serum cortisol drawn 8–9 AM
  - Interpretation:
  - ≤1.8 µg/dL → Normal suppression
  - 1.8 µg/dL → Abnormal (non-suppressed)
  - Any abnormal DST requires confirmatory testing
- Confirmatory Testing
  - Late-Night Salivary Cortisol (LNSC) detects loss of circadian rhythm and is excellent for mild disease.
  - 24-Hour Urinary Free Cortisol (UFC) confirms overt hypercortisolism but may miss mild cases.
- Differentiating source after confirmed hypercortisolism
  - Step 1: Adrenocorticotropic hormone (ACTH) level and DHEA level:
    - ACTH low + DHEA low = Adrenal source/ exogenous steroids
    - ACTH /DHEA Normal/High = ACTH-dependent (pituitary)
    - ACTH very high + DHEA high – Ectopic ACTH (small cell lung CA)

Treatment Overview (Non-Surgical Candidates)

- Glucocorticoid Receptor Blockade: Korlym (Mifepristone)
  - Mechanism: Blocks cortisol receptor but does NOT reduce cortisol level; there is still circulating cortisol hence the potential drop In potassium.
  - Monitoring: baseline potassium recheck at 2 weeks and at dose escalation.
  - Common effects: Fatigue, nausea, progesterone receptor blockade, endometrial thickening, spotting/bleeding, not malignant but requires monitoring

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    - Adjunct therapy includes spironolactone for potassium control
- Cortisol Synthesis Inhibition: Isturisa (Osilodrostat); rarely used
    - Mechanism: Inhibits 11β-hydroxylase
    - Risk: adrenal insufficiency
    - May increase ACTH raise testosterone in women and decrease in men. Chronic ACTH excess can be associated with low testosterone in men, but the usual mechanism is cortisol excess (ACTH-driven hypercortisolism) suppressing the hypothalamic–pituitary–gonadal axis and/or directly inhibiting Leydig-cell steroidogenesis,
- Recorlev (levoketokonazole)
    - Mechanism: Blocks adrenal steroidogenesis
    - Risk: adrenal insufficiency, QT prolongation (baseline EKG required)
    - Monitor LFTs

Korlym (mifepristone) vs. Recorlev (levoketoconazole): Sex-Based Prescribing Considerations

- Korlym (mifepristone) is a glucocorticoid receptor antagonist with concurrent progesterone receptor antagonism. This antiprogestational activity promotes unopposed endometrial proliferation, which may result in endometrial thickening, cystic dilatation of endometrial glands, and vaginal bleeding.
- Korlym is contraindicated in women with unexplained vaginal bleeding, endometrial hyperplasia with atypia, or endometrial carcinoma.
- Due to these endometrial risks — particularly in women with unknown endometrial status, Korlym is preferentially considered in male patients.
- Recorlev (levoketoconazole) is a steroidogenesis inhibitor that reduces cortisol production without progesterone receptor antagonism. Because it does not carry the same endometrial risks, Recorlev may be the preferred agent in female patients when endometrial status is unknown or when antiprogestational effects are a concern.

Key Testosteronology Society® Takeaways:

- Do not escalate TRT blindly in refractory metabolic patients.
- Severe insulin resistance out of proportion to BMI think cortisol.
- Poor GLP-1 response + muscle wasting = screen.
- Elevated AM cortisol twice = run DST.
- U-500 insulin + no fat loss = cortisol until proven otherwise.

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- Cortisol excess: blocks muscle growth, increases visceral fat, worsens insulin resistance, blunts testosterone benefits. You cannot out-testosterone high cortisol.

Typical Lab Values for Diagnosis of Diabetes[9]

	Normal	Prediabetes	Diabetes
Fasting BG (mg/dL)	< 100	100-125	≥126

HbA1C	< 5.7%	5.7%-6.4%	≥ 6.5%
Oral Glucose Tolerance Test after 2 hours (mg/dL)	< 140	140-199	≥ 200
Random BG (mg/dL)	X	X	≥ 200

These lab values are what the 2026 ADA Guidelines use for a diagnosis of diabetes. There was consensus among the group for early intervention before reaching those values.

Screening:

- HbA1C is recommended in the population taking TRT every 3 years if normal.
- Use clinical judgement in overweight patients
- H/o gestational diabetes: every 3 years for life
- Childhood obesity: every 3 years at age of 10
- Patients with diabetes: every 3 months when changing therapy until HbA1C is stabilized at therapeutic levels.

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Therapeutic targets Goals:

Dimension	ADA[9]	AACE[10]
Glycemic target (A1C) for non-pregnant adults	Targets generally < 7% for many non-pregnant adults, with individualization	More aggressive: often aims for ≤ 6.5%, where safe and feasible
Fasting/pre-prandial & post-prandial glucose goals	E.g., ADA: pre-prandial ~80-130 mg/dL, post-prandial < 180 mg/dL for many.	More stringent: e.g., pre-prandial < 110 mg/dL, post-prandial < 140 mg/dL (for patients without major comorbidities/hypoglycemia risk) per AACE

Supporting labs

Lab Test	Typical Reference Range (Adult Male)	Key Findings & Interpretation
Total Testosterone	300 - 1000 ng/dL3 (Figure 1-4)	A testosterone level <300 ng/dL is generally considered the diagnostic threshold per AUA and <264 per the Endocrine Society. For

	You can use this tool to convert units.	insurance coverage, two separate test results below this level are typically required. Low T can cause metabolic dysfunction leading to insulin resistance.
Free Testosterone	5 - 21 ng/dL (varies by lab) Or 50 - 210 pg/mL	Low free T can be clinically significant even with low-normal total T.
Complete Blood Count (CBC)	Hgb: 13-17 g/dL Hct: 42-52% RBC: 4.5-6.1 million cells/mcL WBC: 4-10 K cells/mcL Plt: 150-400 K/mcL	Baseline to monitor for erythrocytosis (Hct >50% is a relative contraindication).
Comprehensive Metabolic Panel (CMP)	Varies	Assess baseline liver and kidney function and current FBG.
Lipid Profile (including ApoB and Lp(a))	Total Cholesterol <200 mg/dL LDL <100 mg/dL HDL >60 mg/dL TG <150 mg/dL ApoB < 90 mg/dL Lp(a) < 75 nmol/L or < 30 mg/dL	Establishes baseline cardiovascular risk; AHA guidelines recommend cholesterol control in patients age 40-75 with diabetes. Note: A patient achieving optimal parameters is rare, but this is the goal.
TSH & Free T4, T3	TSH: 0.4-4.0 mIU/L	Screens for hypothyroidism, a key differential diagnosis with overlapping symptoms. Low thyroid is correlated with lower SHBG, T and E and metabolic dysfunction.
Autoimmune Diabetes (LADA) 30 % of T2DM is misdiagnosed. Don't miss these characteristics.	GAD65 Normal: Negative. Abnormal: Positive (typically >5-20 U/mL depending on assay)	Autoantibodies (GADA) The most common and sensitive marker in adult-onset T1DM. Positive in approximately 70-80% of newly diagnosed T1DM patients. Often persists longer than other antibodies.
	IA-2 Autoantibodies (IA-2A) Normal: Negative Abnormal: Positive (assay-specific thresholds).	Present in 40-70% of newly diagnosed T1DM, particularly in younger patients. Associated with a more rapid progression to diabetes
	Insulin Autoantibodies (IAA) Normal: Negative. Abnormal: Positive	Often the first autoantibody to appear in young children (<3 years), positive in 40-60% of T1DM patients. Less predictive as a single antibody in adults

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	Zinc Transporter 8 Autoantibodies (ZnT8A) Present in 50-70% of newly diagnosed T1DM. Particularly useful in adults and can identify cases missed by other antibodies	Present in 50-70% of newly diagnosed T1DM. Particularly useful in adults and can identify cases missed by other antibodies
	C-Peptide (Insulin Secretion Marker Normal: >0.6 ng/mL (>0.2 nmol/L) Preserved β-cell function: ≥0.23-0.6 ng/mL (≥0.08-0.2 nmol/L) Islet failure: ≤0.6 ng/mL (≤0.2 nmol/L) Severe insulin deficiency: <0.24 ng/mL (<0.08 nmol/L)	Diagnostic Interpretation: Multiple autoantibodies (≥2 positive): Approximately 90% will progress to T1DM within 15 years. Indicates stage 1 or 2 T1DM depending on glucose levels Single autoantibody: Lower risk (10-15% 10-year progression). May represent early autoimmunity or false positive Low/absent C-peptide + positive autoantibodies + hyperglycemia: Confirms established T1DM (stage 3) with insulin deficiency Additional markers: HLA-DR3-DQ2 and HLA-DR4-DQ8 genotypes increase T1DM risk but are not diagnostic alone
Adult onset (often operationally ≥30–35 years) and not insulin-requiring at diagnosis (≥6 months in many definitions), but with higher likelihood of needing insulin earlier than typical type 2. On average, leaner/less insulin resistant than antibody-negative type 2, but not necessarily lean; metabolic syndrome can still be present in many Don't miss this diagnosis as many of these men have low testosterone as a result of elevated BG and non-efficacious use of oral hypoglycemic agents when these patients need insulin. Don't miss the opportunity to diagnose an increasing number of autoimmune diabetes cases in the past 5 years s/p covid.		
HOMA – IR HOMA-IR = Fasting Glucose (mg/dl) x Fasting Insulin / 405 *Minimal consensus on using HOMA-IR to identify insulin resistance	< 1.0 Insulin sensitive 1.0–1.9 Early insulin resistance 2.0–2.9 Moderate insulin resistance ≥ 3.0 Significant insulin resistance Many endocrinologists consider: • >2.0 abnormal • >2.5 clearly pathologic	Pattern 1: Low insulin + low C-peptide Think Type 1 / LADA Run autoimmune panel (GAD, IA-2, ZnT8) Pattern 2: High insulin + high C-peptide + normal glucose Early insulin resistance Glucose is still normal, but beta cells are compensating This is your classic "A1c 5.3 but metabolically inflamed" patient. Pattern 3: High glucose + high insulin + high C-peptide T2DM with preserved beta function Pattern 4: High glucose + low C-peptide

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		Beta-cell failure Late T2DM or autoimmune diabetes
Insulin Level	High consensus reference ranges < 6 µIU/mL- optimal 7-10 – mild insulin resistance > 10 insulin resistance Greater than 15 Quest reference range; anything less than 18.4 normal	High Insulin • Insulin resistance • PCOS • Metabolic syndrome • Prediabetes • Cushing's • Early T2DM Insulin rises years before glucose does.
C-peptide	~0.5 – 2.0 ng/mL (lab dependent) Quest Reference range; < 0.8 - 3.85 ng/mL Who to test: Diabetes diagnosed <30 years Not obese Negative autoantibodies C-peptide preserved Strong autosomal dominant family history Unusual response to therapy (e.g., extreme sulfonylurea sensitivity)	Low C-Peptide • Type 1 diabetes • LADA • Advanced beta-cell burnout in T2DM • Pancreatic failure • Exogenous insulin use (if insulin high but C-peptide low) High C-Peptide • Insulin resistance • Early T2DM • Obesity/metabolic syndrome • Insulinoma • Reactive hypoglycemia
Maturity Onset Diabetes in the Youth (MODY)[11,12]	Fasting C-peptide >0.6 ng/mL Targeted MODY panel (most common genes): GCK HNF1A HNF4A HNF1B Testing modalities: Next-generation sequencing panels	MODY is a monogenic, autosomal dominant form of diabetes caused by mutations affecting pancreatic β-cell function, not insulin resistance or autoimmune destruction. • Onset: typically, <25–35 years • Impaired insulin secretion with preserved insulin sensitivity • Lean patient with "type 2" phenotype • Strong vertical inheritance (parent to child) • Stable mild hyperglycemia without progression • Negative antibodies with preserved C-peptide

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Common medications relevant to TRT patients that can cause hyperglycemia[14]:

Clinicians should use a risk-benefit approach to decide whether to treat through therapy with these medications or seek alternative therapy.

Drug	Mechanism
Glucocorticoids	• Upregulation of hepatic gluconeogenesis • Inhibition of GLUT-4 in skeletal muscle • Appetite Stimulation
Psychiatric Medications *See three tables below for a comprehensive list	• Inhibition of GLUT-4 translocation in skeletal muscles • Increased appetite through actions on serotonin (5-HT2C), histamine (H1) and muscarinic (M3), and dopaminergic (D2) receptors • Pancreatic Beta Cell apoptosis and impaired Beta Cell response
Beta Blockers *Carvedilol and nebivolol have neutral of favorable effects on BG	• Weight gain • Inhibition of Beta-2 adrenergic-mediated insulin release • Decreased insulin sensitivity • Decreased first-phase insulin secretion • Changes in peripheral blood flow
Thiazides *Less effect with indapamide	• Reduction of insulin secretion due to hypokalemia • Increases in free fatty acid levels which can reduce insulin secretion, reduce insulin sensitivity, increase hepatic gluconeogenesis
Statins	• Decreased insulin secretion • Disruption of beta cell function due to inhibition of HMG-CoA • Insulin resistance via inflammation in obesity and dysregulated metabolic function • Increased food and fat intake in patients taking statins due to having the “security blanket” of protection from statins
Antivirals (ART Therapy) *PIs and NRTIs	• PIs can inhibit GLUT-4 and insulin secretion • PIs can inhibit TG clearance resulting in central fat deposition and insulin resistance
Antineoplastics *Most of these patients will be managed by an oncologist but it is important for a Testosteronologist® to understand these mechanisms	mTOR such as sirolimus and everolimus: • Decreased glycogen synthesis and glucose uptake in skeletal muscles • Beta cell Apoptosis in in-vitro studies TKIs such as nilotinib and imatinib: • Decreased peripheral insulin sensitivity with nilotinib therapy • TKIs can cause regression of pancreatic islets, decreased glucose uptake and changes in IGF-1 signaling PI3K and AKT inhibitors such as alpelisib and idelalisib: • Disrupt intracellular response to insulin • Immune Checkpoint Inhibitor therapy such as Anti PD-1,

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	CTLA-4, PD-L1, and LAG-3: • Immune mediated damage to beta cells, incidence is 1-2% • These therapies are often coupled with glucocorticoids • Mechanism of onset is similar to T1DM
Androgen Deprivation Therapy	• Lower testosterone levels increase insulin resistance
Calcineurin Inhibitors	• Beta cell apoptosis and decreased insulin secretion
Interferon Alpha	• Beta cell destruction • Increased insulin resistance
Growth Hormone[15]	• Increased gluconeogenesis in the liver and decreases glucose uptake in adipose tissue • Increased insulin Resistance
Growth Hormone Secretagogues*: **Mild:** Sermorelin Ipamorelin **Moderate:** CJC-1295 w/ DAC Tesamorelin GHRP **High:** MK677 (ibutamoren)	• Increase hepatic gluconeogenesis • Decrease peripheral glucose uptake • Increased lipolysis and increased FFA lead to insulin resistance • Decrease insulin sensitivity in muscle/adipose tissue Sermorelin/Ipamorelin/CJC-1295/ Tesamorelin/GHRH > 300-500 mcg can raise fasting BG MK 677 - > 25 mg can raise fasting BG *Anecdotal, not supported by evidence

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Selective Serotonin Reuptake Inhibitors (SSRIs)						
Drug/Class	**Weight Effect**	**Diabetes Risk**	**Lipids**	**Appetite**	**Mechanism**	**Clinical Notes**
Sertraline (Zoloft)	Mild to moderate gain (5-15 lb possible long term)	Mild increase with chronic use	Minimal	Appetite often increases after depression improves	Serotonin modulation, appetite normalization, reduced energy expenditure in some patients	Early nausea may cause temporary weight loss; long-term gain common
Fluoxetine (Prozac)	Often weight loss initially; long-term neutral to mild gain	Minimal	Minimal	Appetite suppression early	Most activating SSRI	Best SSRI for overweight patients but weight neutrality often disappears

						after 6-12 months
Escitalopram (Lexapro)	Moderate gain	Mild increase	Minimal	Increased carbohydrate cravings reported	Reduced satiety in susceptible patients	One of the more common SSRIs associated with gradual weight gain
Paroxetine (Paxil)	Highest weight gain among SSRIs	Increased insulin resistance reported	Can worsen triglycerides	Significant appetite increase	Anticholinergic properties plus serotonin effects	Generally least favorable SSRI metabolically
Citalopram (Celexa)	Mild-moderate gain	Mild	Minimal	Variable	Similar to escitalopram	Intermediate metabolic profile

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Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)			
Drug	**Weight**	**Metabolic Effects**	**Comments**
Venlafaxine (Effexor)	Usually neutral	Minimal glucose effects	Mild appetite suppression early
Duloxetine (Cymbalta)	Neutral	Little effect on insulin sensitivity	Often preferred in diabetes because of neuropathy benefit
Desvenlafaxine (Pristiq)	Neutral	Minimal	Weight stable in most studies

Second Generation Antipsychotics (SGAs)				
Medication	Weight Gain	Diabetes Risk	Dyslipidemia	Metabolic Comments
Olanzapine (Zyprexa)	Very High (20-50+ lb common)	Very High	Very High	Gold standard for causing metabolic syndrome
Clozapine	Very High	Very High	Very High	Similar to olanzapine; highest diabetes risk
Quetiapine (Seroquel)	Moderate-High	Moderate	Moderate	Dose dependent
Risperidone	Moderate	Moderate	Mild-Moderate	Less than olanzapine but clinically significant
Paliperidone	Moderate	Moderate	Moderate	Similar to risperidone

Aripiprazole (Abilify)	Low	Low	Minimal	Weight neutral in many patients; transient gain possible
Lurasidone (Latuda)	Very Low	Very Low	Minimal	One of the best metabolic profiles
Cariprazine (Vraylar)	Neutral	Low	May improve metabolic markers indirectly	Clinical trials show minimal weight gain
Ziprasidone (Geodon)	Neutral	Low	Minimal	Often chosen in obese patients
Brexpiprazole (Rexulti)	Mild	Mild	Mild	More weight gain than aripiprazole

Treatment

Non-Pharmacologic Therapy[9,10]:

AACE and ADA Guidelines Recommend a combined approach of nutrition, physical activity, sleep, behavioral support, and smoking cessation.

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Parameter	ADA	AACE
Nutrition	Achieve and maintain at least 7% of initial body weight: • Caloric deficit of 500-1000 kcals/day to lose 1-2 lbs/week. • Mediterranean, plant-based, DASH	Maintain optimal weight, calorie restriction, plant-based diet
Physical Activity	150 mins/week of moderate intensity physical activity • Max 75 min/week of strength training can be applied to the 150 min/week goal	• 150 min/week Moderate Exertion • Strength training
Sleep	Consistent uninterrupted sleep even on weekends	• 6-8 hours/night • Basic sleep hygiene
Behavioral Support	Diabetes Prevention Program	• Community Engagement • Alcohol Moderation
Smokin Cessation	Both guidelines encourage smoking cessation and eliminating tobacco	

Pharmacologic Therapy – Monitoring, adjustment, … etc.:

Expected A1C lowering effects of medications for T2DM[16]

Intervention	Mechanism of action	Expected HbA1c change (%)	Glucose	Weight	BP[a]	Lipid profile	Advantages	Associated Risks
Step 1: Initial therapy **Lifestyle modification**	– Reduce weight – Increase activity –Quit smoking/alcohol	1.0–2.0	↓↓	↓	↓	↓	– Natural – No known side–effect	– Inability to sustain glycaemic control in many after one year
Metformin	– Decreases hepatic glucose output – Increases insulin sensitivity and lowers fasting glycaemia[44, 80]	1.0–2.0	↓↓	↔	↔	↓LDL ↔HDL ↓Trigly[b]	– Weight stability or moderate weight loss – No hypos – ↓Cardiac events	– GI side effects – Contraindicated in renal problems – Lactic acidosis (in the presence of renal failure and hypovolaemia). – CKD, Hypoxia
Second line **Sulfonylureas** • Chlorpropamide • Glibenclamide • Gliclazide • Glimepiride • Glipizide • Glyburide	– Enhance insulin secretion	1.0–2.0	↓↓	↑↑↑	↔	↓LDL ↔LDL ↓Trigly	– Rapidly effective – ↓Microvascular risk	– Weight gain – Hypoglycaemia – Blunting of myocardial ischaemic preconditioning – Low durability
Thiazolidinediones • Pioglitazone • Rosiglitazone	– Reduces peripheral insulin resistance – ↑Insulin sensitivity	0.5–1.4	↓↓	↑↑↑	↑	↑LDL ↑HDL Trigly ↑(Rosi) ↓(Pio)	– Improves insulin sensitivity – Improves lipid profile – No hypos – ↑Durability – ?↓CVD events	– Fluid retention, CHF – Weight gain, bone fractures – Risk of bladder cancer – ?↑risk of MI
GLP–1RA[c] agonists • Exenatide • Liraglutide • Lixisenatide • Dulaglutide • Albiglutide • Semaglutide	– Bind and activate glucagon–like peptide (GLP–1 RA) receptors to • Suppress glucagon secretion, • Increase insulin secretion and • Slow gastric emptying • Reduce appetite	0.5–1.0	↓↓	↓↓	↓	↓LDL ↔HDL ↓Trigly	– Prevent weight gain or promote loss – No hypos – Reduce cardiovascular events with selected GLP1RA – Reduce postprandial glucose excursions	– GI side effects – High cost – ?Acute pancreatitis – Subcutaneous injection
SGLT2[d] inhibitors • Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin • Ipragliflozin	– Reversibly inhibit SGLT2 in the proximal convoluted tubules of the nephrons causing… • Decrease in glucose absorption • Increase in urinary glucose excretion[80]	0.7–1.3	↓	↓	↓	↑LDL ↑HDL ↔Trigly	– Reduce body weight – Lowers Systolic blood pressure – No hypos – Effective at all stages of T2DM – Reduce cardiovascular events – Improve heart failure and renal outcomes	– Genitourinary infections – Polyuria – Volume depletion, hypotension and dizziness – Transient ↑ in creatinine – Diabetic ketoacidosis

Preferred:

GLP-1 receptor agonists:

- First line - Ideal for patients with obesity, and/or associated comorbidities such as CVD, CKD, or OSA. Also has evidence supporting fatty liver disease improvement, kidney disease improvement, and cardiovascular benefits.
- While these benefits are considered class effects, this table covers medications indicated for the benefits[9]:

Medication	Semaglutide	Tirzepatide	Orforglipron
Glycemic Control	High to very High	High to very High	High (approaching injectable GLP-1 efficacy in trials)
Weight Loss	High (Wegovy)	Very High (Zepbound)	High (dose-dependent; not yet at tirzepatide magnitude)
CVD (MACE)	Yes (Ozempic & Wegovy)	Under evaluation	Under evaluation (no completed CVOT yet)
CKD	Yes (Ozempic only)	No	Under evaluation (no renal outcomes data yet)
OSA	No	Yes (Zepbound)	No data
MASH	Yes (Wegovy)	Under evaluation	Under evaluation (early signals, not definitive)

*Other GLPs that are used less frequently include dulaglutide, liraglutide, exenatide with many others in the pipeline.

Dosing:

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- Semaglutide (Ozempic)[17]: Start at 0.25 mg/week x 4 weeks then increase to 0.5 mg/week based on glycemic control. Can increase to 1 mg/week after 4 weeks on 0.5 mg/week. Can increase to a max of 2 mg/week after 4 weeks on 1 mg/week.

- Semaglutide (Wegovy)[18]:Start at 0.25 mg/week x 4 weeks then 0.5 mg/week x 4 weeks then 1 mg/week x 4 weeks then 1.7 mg/week (maintenance) based on treatment response. Can increase to a maximum of 2.4 mg/week after 4 weeks on 1.7 mg/week dose.

- Tirzepatide (Mounjaro and Zepbound)[19,20]: Start at 2.5 mg/week x 4 weeks then increase to 5 mg/week based on treatment response. Can increase in 2.5 mg/week increments every 4 weeks for a maximum dose of 15 mg/week. The recommended treatment dose of Zepbound for OSA is 10 or 15 mg/week.

- Orforglipron (Foundayo)[21]
  Week 0–4: 3 mg daily, Week 4–8: 6 mg daily, Week 8–12: 12 mg daily, Week 12+: 24 mg or 36 mg daily (based on response and tolerability) . Higher doses (36 mg) associated with greatest weight loss and A1c reduction. Similar titration philosophy to injectable GLP-1s but with daily oral increments

- Oral Semaglutide (Oral Wegovy)[18]
  Day 0-30 1.5 mg daily, Day 31-60 4 mg daily, Day 61-90 9 mg daily, Then 25 mg daily as a maintenance dose. Can switch to Wegovy 1.7 mg SubQ Weekly if patients can't tolerate the 25 mg/day dose.

Adverse Effects:

Adverse Reactions at Highest Doses (%)[% Placebo] Top 5 Most Occurring					
Ozempic[17]	Nausea (20%) [6%]	Vomiting (9%) [2%]	Diarrhea (2%) [2%]	Abdominal Pain (6%) [5%]	Constipation (3%) [1.5%]
Wegovy[18]	Nausea (44%) [16%]	Diarrhea (30%) [16%]	Vomiting (24%) [6%]	Constipation (24%) [11%]	Abdominal Pain (20%) [10%]
Mounjaro[19]	Nausea (18%) [4%]	Diarrhea (17%) [9%]	Decreased Appetite (11%) [1%]	Vomiting (9%) [2%]	Constipation (7%) [1%]
Zepbound[20]	Nausea (28%) [8%]	Diarrhea (23%) [8%]	Vomiting (13%) [2%]	Constipation (11%) [5%]	Abdominal Pain (10%) [5%]
Foundayo[21]	Nausea 13–36%	Diarrhea 19–27%	Vomiting 5–23%	Constipation 8–29%	Abdominal Pain ~9–20%

Contraindications[17-20]

- Hypersensitivity to any of the active or inactive ingredients.
- Personal or FH of Medullary Thyroid Carcinoma (MTC) or Multiple Endocrine Neoplasia Type 2 (MEN 2)

Warnings/precautions[17-20]

- Risk of thyroid C-Cell Tumors
- Acute Pancreatitis
- Diabetic Retinopathy
- Sharing Pens Between Patients
- Hypoglycemia
- AKI
- Severe GI Adverse Events - Avoid in severe gastroparesis.
- Hypersensitivity Reactions
- Acute Gallbladder Disease
- Pulmonary Aspiration During General Anesthesia - Due to delayed gastric Emptying
- Increased Resting Heart Rate (Wegovy only)
- Suicidal Ideation and Behavior (Wegovy and Zepbound)

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Microdosing GLP-1 RAs:

- No evidence-based protocol for microdosing semaglutide or tirzepatide. No data in clinical benefit or safety of microdosing upon conducting a literature review.
- There might be benefits to microdosing in patients that cannot tolerate adverse effects especially when titrating the dose.
- Need a high level of health literacy as dose errors can be common when microdosing.
- Evidence suggests:
    - Lower doses still have metabolic effects
    - Full clinical efficacy usually occurs at standard titrated doses
    - Formal trials on microdosing are very limited

Dietary Recommendations and Considerations when starting therapy: From Colette's clinical practice:

***The following is anecdotal clinical practice and not fully supported by evidence**

- Muscle wasting: 1 gm of protein per lb of IDBW; weight training minimum of 3x/wk

- Fatigue: Drink ½ your bodyweight in ounces; Include an electrolyte beverage (IV hydration, LMNT, Vitamin water zero, Propel Zero) as they help with blunted thirst mechanism from the GLP
- Constipation: Benefiber (soluble), Konsyl/Metamucil (insoluble); docusate (stool softener); rather than prescribing a laxative consider lactulose via prescription. Stool softeners like Docusate. Prescription meds: Linaclotide(Linzess), Plecanatide (Trulance) Lubiprostone (Amitiza)
- GERD: Tums or H2 blockers vs PPI due to long term risk of osteoporosis, B12 def, and renal implications. Smaller meals, lower fat, and more bland foods
- Hair loss: minimum 100 gm/day of protein, most likely due to reduced food intake and drastic weight loss (telogen effluvium). Test of nutrient deficiencies: iron panel, ferritin, zinc, vit D, CBC, vit B12, folate, TSH. Consider a compounded topical blend:
  Minoxidil 6–8%
  Finasteride 0.1–0.3%
  Dutasteride 0.02–0.1%
  Tretinoin (retinoic acid) 0.01–0.025%
  Latanoprost 0.0025–0.005%
  Topical corticosteroid (choose one):
  Hydrocortisone 1% (mild, safest long-term) OR Fluocinolone 0.01% (better penetration, still scalp-safe)
- Nausea/vomiting: ginger, turmeric, peppermint tea, actual ginger. avoid high fat, fried, heavy meals, nuts/seeds, sauces, and large meals. Prescriptive anti-emetics (Zofran/Reglan) or Pyridoxine 25 mg TID
- Digestive enzymes – consider Creon pancrelipase, a mixture of: lipase (fat digestion), protease (protein digestion), amylase (carbohydrate digestion) is often covered by insurance

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Switching Between GLPs[23]:

- Dose equivalency chart:

Drug	Route	Approximate Equivalent dose (mg)						
Semaglutide	SubQ	[redacted]	0.25	0.5	1	2 1.7-2.4	[redacted]	
	PO	3	7	14	[redacted]			
Tirzepatide	SubQ	[redacted]		2.5	5		7.5	10-15

- Start with the equivalent dose or one dose lower than the previous GLP.
- Start the new GLP when the next dose is due.
- If patient is experience GI side effects, start at the lowest dose after symptoms are resolved.

GLPs for T1DM

Current AACE and ADA guidelines do not list GLPs as a therapy option for T1DM. However, they are being assessed in multiple trials currently[21].

Results: Tirzepatide improved HbA1c (mean difference -0.4% [95% CI -0.7 to 0.0%] vs. placebo; P = 0.05) and reduced total daily insulin dose (-24.2 units/day tirzepatide and -0.3 units/day placebo; difference from baseline vs. placebo -35.1% [95% CI -46.5 to -21.3%; P = 0.0002]). There were no significant adverse events in either group.

SGLT2 inhibitors:

- Offer cardiovascular and renal protection. SGLT2 is one of the four pillars of treating HF and are indicated in CKD. SGLT2 have been shown to cause minor increases in erythrocytosis[7-10]. Extra H/H monitoring can be considered especially in patients with known or uncontrolled AIE.
- High efficacy for glycemic control, intermediate effect for weight loss, and canagliflozin and empagliflozin have shown benefits in MACE[5].

Dosing for glycemic control in T2DM:

- Empagliflozin (Jardiance)[26]: 10 mg QAM then can be increased to 25 mg QDAY for additional glycemic control if tolerated. Not recommended for glycemic control in patients with eGFR < 30 mL/min/1.73 m^2 for efficacy.
- Dapagliflozin (Farxiga)[27]:5 mg QDAY then can be increased to 10 mg QDAY for additional glycemic control if tolerated. Not recommended for glycemic control in patients with eGFR < 45 mL/min/1.73 m^2 for efficacy.
- Canagliflozin (Invokana)[28]:100 mg QDAY before the first meal of the day then can be increased to 300 mg QDAY for additional glycemic control if tolerated. eGFR 30 to ≤ 60; max 100 mg/day. Not recommended for initiation under eGFR 30.

Adverse Effects[26-28]

AE occurring in > 3% of subjects at the highest dose from pkg insert [AE%][placebo%]					
Jardiance	UTI [7.6] [7.6]	Female Genital Mycotic Infection [1.6] [6.4]	URTI [3.8] [4]	Increased Urination [1] [3.2]	
Farxiga	Female Genital Mycotic Infection [1.5] [6.9]	Nasopharyngitis [6.2] [6.3]	UTI [3.7] [4.3]	Back Pain [3.2] 4.3]	Increased Urination [1.7] [3.8]
Invokana	UTI [3.8] [4.4]	Increased Urination [0.7] [4.6]	Female Genital Mycotic Infection [2.8] [11.6]	Male Genital Mycotic Infection [0.7] [3.8]	Vulvovaginal pruritus [0] [3.2]

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Contraindications[26-28]:

Hypersensitivity reactions to the active ingredient or any inactive ingredients

Warnings/Precautions:

- DKA in T1DM and Other Ketoacidosis[26-28]
- Volume Depletion[26-28]
- Lower Limb Amputation[26-28]
- Genitourinary infections[26-28]
- Hypoglycemia[26-28]
- Hypersensitivity Reactions[26,28]
- Bone Fracture[27]

SGLT2/SGLT1

- These medications produce a more robust weight loss effect.

Sotagliflozin (dual SGLT1/2; FDA-approved for heart failure; also studied in diabetes). ADA 2026 Standards cite SCORED trial outcomes with SGLT1/2 inhibitor)
Licogliflozin (dual SGLT1/2; investigational; evaluated in metabolic/liver-fat trials

Insulin

Consider adding insulin when HbA1C is > 8% per the AACE guidelines rather than 10% or more in the ADA guidelines or if not meeting glycemic goals despite maximally tolerated first line options. Consider closer monitoring of BG when using insulin and testosterone together.

Dosing for T2DM

Start long-acting insulin (insulin degludec preferred) at 0.2-0.3 units/kg QDAY and self-titrating every 3 days to a fasting BG of 80-130 mg/dL initially. Then consider short-acting following the formulation/ dosing table below:

Insulin for T1DM

Continue current therapy while adjusting Basal based on fasting sugar and bolus insulin based on post-prandial blood sugar, carb counting and correction factors. Such adjustments are influenced by CGM numbers, A1C, and hypoglycemia.

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Monitoring

ALL PATIENTS on insulin (basal/bolus)/CSII device are eligible for a continuous glucose monitor (CGM) – consider Dexcom G7 (15 days) approved Jan 2026, Freestyle Libre 3 plus or their OTC equivalents, STELO or LINGO. Less popular CGMS, Medtronic Guardian or the Eversense Sensionics implantable 365-day sensor. Many insulin pumps are automated and require a CGM device to help self-adjust insulin using sophisticated AI technology.

Billable codes:

Insertion 99249, interpretation 95251; this can be billed every 30 days as part of Remote Monitoring code:

CGM Remote Monitoring

- 99453 (setup)
- 99454 (device data)
- 99457 (+ 99458 if needed additional 20 min)

Insulin Formulations and dosing for T1DM:

Basal insulin	Prandial Insulin
Suppresses glucose production between meals and overnight Maintains a nearly constant level of glucose throughout the day between meals and overnight	Secreted in response to food intake Makes it possible to compensate for postprandial elevations in blood glucose[2]

Examples of Basal Insulins • Levimir (detemir) – 12-16 hr • Toujeo (glargine) u/300 – 36 hours • Tresiba (Degludec) u/100 & u/200 – 42 hours • Lantus (glargine) – 16-18 hours • Basaglar/Semglee/ Rezvoglar (Biosimilar to Glargine) - 16-18 hours • **Insulin Icodec (Awiqli™) once weekly** basal insulin analog – 7-8 days Approved for T2DM March 26, 2026 *T1DM indication in EU	**Examples of Prandial Insulins** • Apidra – onset <10 min; peak 60-90 min • Novolog/Kirsty Aspart–onset 15-25 min; peak 60-90 • Fiasp (aspart)– onset 2 min; peak 60-90 min - Niacinamide (vitamin B3 to accelerate absorption) + Arginine) • Humalog (lispro)– onset 10-15 min; peak 60-90 min • Admelog (lispro biosimilar) – onset 10-15 min , peak 60-90 min • Lyumjev™ (lispro) – onset < 2 min ; peak 60 – 75 min (Treprostinil (vasodilator) + Citrate) • Afrezza (Inhaled) – onset < 1 min, measurable effect in 12 min; peak effect 35- 45 min
DOSING GUIDE – Daily Basal Insulin	**DOSING GUIDE – Bolus Insulin**
0.2-0.6 units/kg/day at diagnosis, with lower doses (0.2 units/kg/day) sufficient during the honeymoon period or when presenting outside of ketoacidosis [1] Approximately **30-50% as basal insulin**, remainder as prandial [1] Typical starting dose: **0.5 units/kg/day** in metabolically stable adults (~50% basal, 50% prandial) [1] For HbA1C <8%: **0.1-0.2 units/kg/day** For HbA1C >8%: **0.2-0.3 units/kg/day** [6] **Preferred formulations**: Long-acting analogs (glargine, degludec) over NPH due to reduced hypoglycemia risk HONEYMOON phase; giving insulin actually rests the beta cell and often gives the false hope that a patients diabetes is in Remission. I recommend staying on a low dose of basal insulin even it is only 3-5 units to protect the beta cell and growth factors some Type 1s are shorter due to the elimination of insulin during this time. Type 2 DM: start 0.5 u/kg if you exceed 0.7 u/kg consider starting on a basal/bolus regime If you start a GLP/GIP reduce basal insulin by 20-40%. Some patients with significant weight loss can get off insulin entirely	If on BASAL/BOLUS use TDD If on BASAL consider 50% basal and 50% bolus TDD Determine Carb Ratio using the 500 RULE Determine the Sensitivity using the 1500 Rule Example: TDD 45 units Carb ratio: 500 / 45 = 11.1 (1u:10 gm carbs) Sensitivity: 1500 / 45 = 33; 1 units lowers blood sugar 33 units Goal post-prandial blood glucose < 140 mg/dl If using Afrezza 2:1 ratio, if determined dose of RAA for the meal was 6 units ; inhale a 12 unit Afrezza
DOSING GUIDE: Once Weekly Basal Insulin (Off-label for T1DM)[28]	**DOSING AFREZZA[29]**

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Initiation (Insulin-Naïve Patients) Start 70 units once weekly; 10 units x 7 days - No loading dose required Titrate based on fasting glucose response -Titrate 20-unit increments with FPG target 80-130 -Conversation: Awiqli dose: day after last daily basal dose. Week 1: 1.5 × Total daily basal dose × 7, rounded to • nearest 10 units. Week 2: prior total daily basal dose × 7, rounded to nearest 10 units. Week 3 • onward: titrate from prior dosage based on metabolic needs, glucose monitoring, and glycemic goal. If required dose >700 units, split into 2 injections	Afrezza comes in 4u/8u/12u fixed dosing. Afrezza dosing equivalents at 2:1 to injected rapid-acting insulin. Example: 6 units of Humalog = 12 units of Afrezza. This insulin has a fast onset < 1 mlnute and fast offset < 120 min. You can do a follow-up dose if BG is > 140 mg/dl at 90 min post meal, resulting in less risk of hypoglycemia, less reactive eating, making it the only weight-neutral rapid-acting insulin in clinical trials. ○ NDC 4 u (90) each ○ NDC 8 u (90) each ○ NDC 12 u (90) each ○ NDC 4 (90) / 8 (90) – inhale 4 to 24 units three times a day disp 360 each ○ NDC 4 (60) / 8(60) / 12 (60) – inhale 4 to 24 units three times a day disp 360 each ○ NDC 8 (90) / 12 (90) – inhale 4 to 36 units three times a day disp 360 each ○ Most patients need 2 boxes ○ Cash pay $100 a box; only commercial paying patients ○ Use savings card www.afrezzasavingscard.com ○ Send to ASPN pharmacy

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These medications are used for the emergency treatment of severe hypoglycemia < 55 mg/dl when a person cannot safely consume carbohydrates by mouth. They quickly raise blood sugar and help restore consciousness while awaiting medical care.

Afrezza (inhaled insulin)[29-31]

Can be considered due to its unique delivery mechanism and pharmacokinetics, especially in patients with fear of needles. Contraindicated during episodes of hypoglycemia, chronic lung disease such as asthma or COPD, and in hypersensitivity to insulin or any excipients in Afrezza. Consult the package insert for dosing/administration.

Feature	Type 1 Diabetes	Type 2 Diabetes
Initial insulin dose	0.2-0.6 units/kg/day (lower in honeymoon)	0.1-0.3 units/kg/day based on HbA1C
Basal:prandial ratio	30-50% basal, 50-70% prandial	Start basal only; add prandial if needed
Preferred initial regimen	AID > CSII > MDI (basal-bolus from start)	Basal insulin alone, intensify as needed
Role of GLP-1 RA	Not applicable	Preferred before prandial insulin
Typical total daily dose	0.4-1 unit/kg/day	~1 unit/kg/day (higher insulin resistance)
CGM recommendation	Standard of care from diagnosis	Consider when on basal insulin

Practical Pearls from 2026 ADA Guideline Updates

- **Avoid overbasalization**: Watch for bedtime-to-morning glucose differential ≥50 mg/dL, postprandial hyperglycemia, or basal dose >0.5 units/kg/day in type 2 diabetes [1][6]
- **Patient education on self-titration** improves glycemic management in type 2 diabetes [1]
- **Weekly insulins** (icodec, efsitora) recently FDA-approved in the US,reducing injection burden [6]
- **Insulin is not a failure**: Emphasize the progressive nature of type 2 diabetes and utility of insulin to achieve goals

Glucagon:

Should be prescribed for all patients on insulin

Gvoke HypoPen:

a ready-to-use injectable glucagon given under the skin with an auto-injector.

Baqsimi:

a nasal powder glucagon that is sprayed into the nose and absorbed through the nasal lining.

Metformin:

A valid first-line option for diabetes due to cost of GLPs and SGLT2is. Start 500 mg daily, titrate weekly by 500 mg/day to a target of 1000 mg BID. ER formulation can mitigate GI side effects. Metformin is renally adjusted. **Do not initiate and decrease dose by 50% in eGFR 30-45 mL/min. Discontinue if eGFR < 30 mL/min. Contraindicated.** Assess Vitamin B-12 deficiency when monitoring a patient on metformin.

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Metformin has a remarkably broad range of **off-label applications** beyond its FDA-approved indication for type 2 diabetes, spanning oncology, metabolic health, anti-aging, neuroprotection, and cardiovascular protection. Below is a comprehensive summary organized by domain.

Off-Label Use	Level of Evidence	Key Findings	References
PCOS	RCTs, guidelines	Improves insulin resistance, menstrual regularity, androgen levels; recommended by international guidelines for metabolic features	[36-38]
Prediabetes/Obesity	RCTs (DPP)	~3% weight loss; 6.2% at 15-year follow-up in DPP; reduces diabetes incidence	[35]
Cancer risk reduction	Meta-analyses, observational	HR 0.90 (95% CI 0.86–0.94) for cancer incidence; strongest for colorectal, breast, endometrial	[40,41]
Anti-aging/Longevity	Preclinical, observational, trials planned	Attenuates hallmarks of aging; TAME trial designed to test multimorbidity prevention	[42-44]
Neuroprotection	Preclinical, limited clinical	Crosses BBB; modulates neurotransmitters; potential in Alzheimer's, Parkinson's, stroke	[45,46]
Cardiovascular protection	Observational, secondary analyses	Reduced all-cause mortality, HF hospitalizations, LVH regression in non-diabetics	[32-34,42]

Antipsychotic weight gain	RCTs	Mitigates weight gain from atypical antipsychotics	[33]

Avoid:

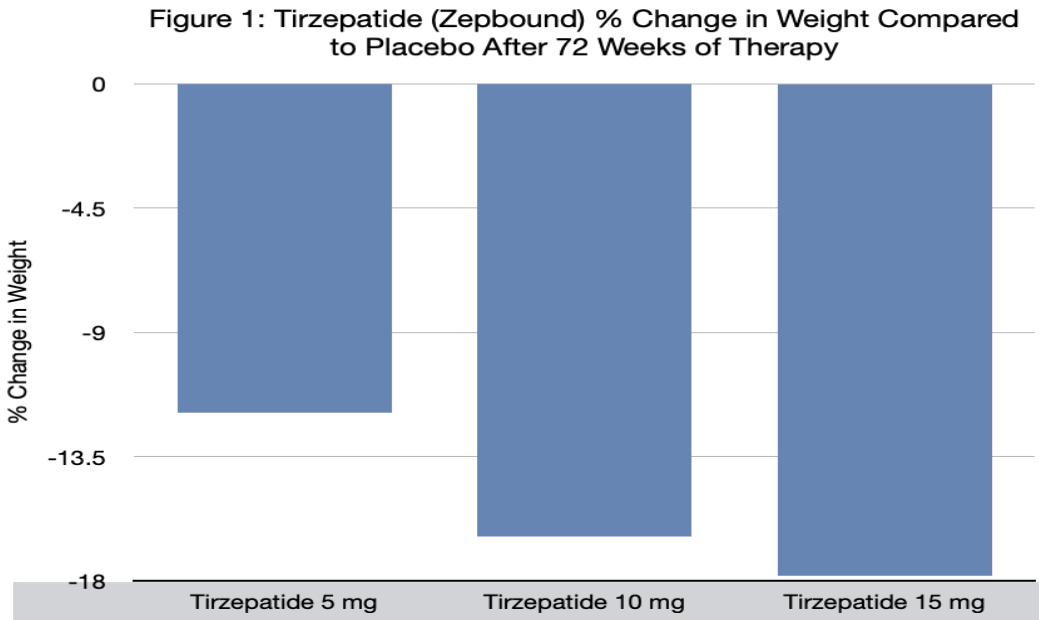
- **TZDs:** Can exacerbate water retention, a potential side effect of TRT. Contraindicated in HF.
- **Sulfonylureas:** TRT can improve insulin sensitivity, increasing the risk of hypoglycemia with these classes of medication. Although evidence is lacking, counsel patients on signs and symptoms of hypoglycemia.
- **DPP-4is:** Can be considered in patients that can't afford GLP-1s, SGLT2i, or insulin. However, they are not as effective as the options above and do not provide the protections that the other medications do. Do not use with GLP-1s. Social media has made the practice of using DDP4s with a GLP1 which is contraindicated in evidence based medicine stating that it will make the GLP1 more effective and last longer. No clinical data and Endogenous GLP-1 contributes very little compared to injected GLP-1 RAs. The receptor is already strongly stimulated. You hit a ceiling effect, GI side effects are more likely and kidney clearance, recommend discouraging patients from this practice.
- **α-Glucosidase inhibitors (Acarbose)** used clinically for diabetes are with modest HbA1c lowering and prominent dose-limiting GI adverse effects. Common adverse effects include flatulence, diarrhea, abdominal pain, and elevated transaminases.

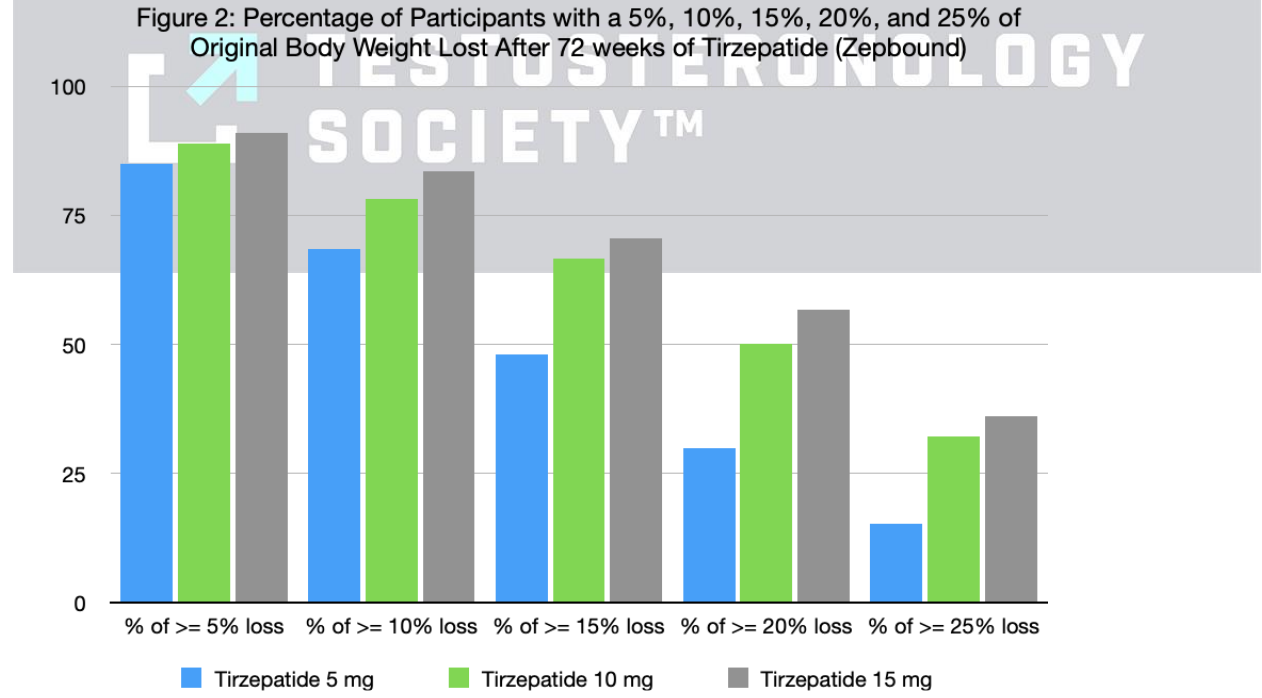
Hyperlipidemia and diabetes[47]:

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- AHA guidelines recommend lipid lowering therapy in patients ages 40-75 with diabetes. While statins can cause increases in HbA1C, risk versus benefit evaluation is crucial.
- Goal: Lower is better for LDL, tailored to the patient's individual cardiovascular risk.
- Lifestyle: A healthy diet and exercise are recommended to control cholesterol.
- Medication Considerations: Preferred: A moderate intensity statin (e.g., Rosuvastatin) is preferred due to potent LDL lowering and pleiotropic anti-inflammatory effects. Combination therapy with Ezetimibe and/or PCSK9 inhibitors may be necessary. Alternatives: Bempedoic acid and/or Inclisiran can be considered for statin-intolerant patients or as add-on therapy.

Figures:





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