2. Executive Summary

Analysis of 24 SNPs across seven glycation-related functional categories reveals three independent mechanisms that converge to explain the observed HbA1c–glucose discordance:

- **Extended red blood cell lifespan** — Heterozygous variants in both ANK1 (ankyrin-1) and SPTA1 (spectrin alpha), the two key RBC membrane structural proteins, combined with homozygous TMPRSS6 variants affecting iron/erythropoiesis dynamics. Longer-lived RBCs accumulate more glycation at any given glucose concentration.
- **Increased reactive glycating agents** — Homozygous GLO1 variant (rs1049346) with additional heterozygous hit (rs4746) reduces methylglyoxal detoxification. Homozygous AKR1B1 variant increases polyol pathway flux, generating fructose (7–10x more reactive than glucose as a glycating agent).
- **NADPH/glutathione competition (amplifying loop)** — AKR1B1 consumes NADPH, reducing glutathione regeneration. GLO1 requires glutathione as a cofactor, creating a vicious cycle where the polyol pathway impairs methylglyoxal clearance.

Genetically intact pathways:

- Deglycation enzymes (FN3K/FN3KRP) — repair system intact
- AGE receptor (RAGE) — normal binding and expression, limiting downstream inflammatory damage
- G6PD — RBC oxidative defense intact
- Erythropoietin, BMP2, SLC30A8 — broader erythropoiesis and iron pathways clear

Clinical Implication: The patient's HbA1c likely overestimates true glycemic exposure. CGM data is a more accurate reflection of actual glucose control than HbA1c suggests. This should be considered when making treatment decisions based on HbA1c targets.

3. Detailed SNP Results by Functional Category

Genotype Color Key:

Homozygous Risk (2 alleles)	Heterozygous (1 allele)	No Risk Alleles (0)

3.1 Direct HbA1c / Glycation Rate Modifiers

Gene	SNP	Genotype	Risk Alleles	Functional Interpretation
TMPRSS6	rs855791	**G/G (1/1)**	**2**	Homozygous. Regulates hepcidin (master iron regulator). Lower serum iron, altered erythropoiesis dynamics. Associated with higher HbA1c relative to glucose.
TMPRSS6	rs4820268	**A/A (1/1)**	**2**	Homozygous. Second variant at same locus. Reinforces hepcidin dysregulation and altered RBC production dynamics.
HFE	rs1799945	**C/G (0/1)**	**1**	H63D heterozygous. Mild increase in iron absorption. Partially counterbalances TMPRSS6 effect on iron availability.

Not found (likely homozygous reference / no risk): *rs1050828 (G6PD) — RBC oxidative defense intact. rs1800562 (HFE C282Y) — no major hemochromatosis variant.*

3.2 Hemoglobin Variants & RBC Biology

Gene	SNP	Genotype	Risk Alleles	Functional Interpretation
ANK1	rs4737009	**G/A (0/1)**	**1**	Ankyrin-1: RBC membrane anchor protein. Variant affects membrane stability and RBC lifespan. GWAS-associated with HbA1c independent of glucose.
SPTA1	rs11085824	**A/G (0/1)**	**1**	Spectrin alpha: RBC membrane structural lattice. Works with ankyrin to determine cell flexibility and durability. GWAS-associated with HbA1c.

Not found (likely homozygous reference / no risk): *rs7776054 (ANK1), rs2748427 (HK1 — RBC glycolysis intact), rs16926246 & rs9399137 (HBS1L-MYB — erythropoietic regulation standard), rs1800746 (GHR)*

3.3 Fructosamine / Deglycation Enzymes

Gene	SNP	Genotype	Risk Alleles	Functional Interpretation
FN3KRP	rs6474359	**Not found**	**0**	Likely homozygous reference. Deglycation enzyme intact.
FN3K	rs1046896	**Not found**	**0**	Likely homozygous reference. Primary hemoglobin deglycation enzyme intact.

Both deglycation enzymes genetically standard. The glycation gap is not driven by impaired glycation removal.

3.4 Iron Metabolism & Erythropoiesis (Broader Panel)

No variants found at any of the four loci tested: rs235756 (BMP2), rs11558471 (SLC30A8), rs1800888 (ADRB2), rs17476364 (EPO). Broader iron metabolism and erythropoiesis pathways are genetically standard. Iron-related contribution to glycation gap is concentrated specifically in TMPRSS6 and HFE.

3.5 Advanced Glycation End Products Receptor (RAGE)

No variants found at any of the three AGER loci tested: rs2070600 (Gly82Ser), rs1800624 (promoter), rs184003. RAGE binding affinity and expression levels are genetically standard. Downstream inflammatory response to AGEs is not genetically amplified.

3.6 Glyoxalase System (Methylglyoxal Detoxification)

Gene	SNP	Genotype	Risk Alleles	Functional Interpretation
GLO1	rs1049346	**A/A (1/1)**	**2**	Homozygous. Glyoxalase 1: primary enzyme for methylglyoxal detoxification. Methylglyoxal is 20,000x more reactive than glucose for protein glycation. Reduced GLO1 activity increases reactive carbonyl burden.
GLO1	rs4746	**T/G (0/1)**	**1**	Heterozygous. Second GLO1 variant. Two hits in glyoxalase system represent meaningful impairment of methylglyoxal clearance.

GLO1 uses glutathione as a cofactor. Glutathione availability is further compromised by the AKR1B1 finding below, creating an amplifying loop.

3.7 Aldose Reductase / Polyol Pathway

Gene	SNP	Genotype	Risk Alleles	Functional Interpretation
AKR1B1	rs759853	**A/A (1/1)**	**2**	Homozygous. Aldose reductase: rate-limiting enzyme of the polyol pathway. Higher activity diverts more glucose to sorbitol/fructose (fructose is 7–10x more reactive as a glycating agent). Also consumes NADPH, depleting the glutathione pool that GLO1 requires.

4. Integrated Glycation Risk Profile

Pathway	Risk Level	Key Variants
Polyol Pathway (aldose reductase)	**HIGH (homozygous)**	rs759853 (AKR1B1)
Methylglyoxal Detoxification	**HIGH (homo + het)**	rs1049346 (homo), rs4746 (het) — GLO1
Iron / Hepcidin Regulation	**HIGH (homozygous x2)**	rs855791, rs4820268 (TMPRSS6)
RBC Membrane — Ankyrin	**MODERATE (heterozygous)**	rs4737009 (ANK1)
RBC Membrane — Spectrin	**MODERATE (heterozygous)**	rs11085824 (SPTA1)
Iron Absorption (HFE)	**MILD (heterozygous)**	rs1799945 (H63D) — partial counterbalance
Deglycation Enzymes (FN3K)	**LOW (no risk)**	Not found — repair system intact
AGE Receptor (RAGE)	**LOW (no risk)**	Not found — inflammatory response standard
G6PD (RBC oxidative defense)	**LOW (no risk)**	Not found — intact
Erythropoiesis (EPO, BMP2)	**LOW (no risk)**	Not found — production rate standard

5. Current Management & Glycation Pathway Alignment

5.1 Current Medications

Medication	Dose	Effect on Glucose Metabolism
Imeglimin	1000 mg BID	Improves mitochondrial efficiency, reducing overflow of glycolytic intermediates (including methylglyoxal precursors). Indirectly supports compromised GLO1 pathway.
Empagliflozin	25 mg	FAVORABLE: Lowers circulating glucose, reducing substrate for both glycation and polyol pathway. Less glucose entering cells means less AKR1B1 flux, less NADPH consumption, and more glutathione available for GLO1.
Acarbose	100 mg w/carbs	FAVORABLE: Flattens postprandial glucose spikes. AKR1B1 becomes more active at higher glucose concentrations (high Km), so spike reduction disproportionately reduces polyol pathway flux.
Tirzepatide	2.6 mg	Favorable through glucose lowering. Lower average glucose reduces

	2x/wk	substrate for both glycation and polyol pathway.
Rapamycin	12 mg q2wk	MIXED: Autophagy promotion may help clear glycated proteins. However, negative effect on glucose control could transiently increase polyol pathway flux post-dose.
Telmisartan	80 mg	FAVORABLE: ARBs reduce AGE accumulation and RAGE expression. PPAR-gamma agonism may reduce methylglyoxal production.
Rosuvastatin	10 mg	Modest evidence for reducing AGE formation independent of lipid effects, possibly through anti-inflammatory mechanisms.

5.2 Current Supplements — Glycation-Relevant Effects

Only supplements with meaningful glycation pathway interactions are listed below.

Glutathione Support (Critical for GLO1 Cofactor)

Supplement	Dose	Relevance to Glycation Profile
NACET	100 mg	Most directly glycation-relevant supplement. Supports glutathione production — the essential cofactor for GLO1. With AKR1B1 consuming NADPH (depleting glutathione) and GLO1 genetically compromised, maintaining glutathione pool is critical. Current dose is modest; may benefit from increase.
Glycine	3 g	Glutathione precursor (glutathione = glutamate + cysteine + glycine). Supports the same pool GLO1 depends on.
Taurine	6 g total	Evidence for reducing methylglyoxal-derived AGEs, protecting against polyol pathway damage, and preserving glutathione levels. Substantial dose well-suited to glycation profile.

Methylglyoxal Scavenging & AGE Inhibition

Supplement	Dose	Relevance to Glycation Profile
CacaoVia (cocoa flavanols)	750 mg	Studied as a GLO1 inducer — may upregulate glyoxalase expression, partially compensating for genetic variants. One of the most targeted interactions for GLO1 findings.
Ergothioneine	20 mg total	Evidence as a direct methylglyoxal scavenger in addition to its antioxidant role. Directly relevant to GLO1 impairment.
Olive Leaf Extract	1000 mg total	Oleuropein has evidence for inhibiting AGE formation and modest aldose reductase inhibitory activity (relevant to AKR1B1).
Melatonin	5 mg	Evidence as a direct scavenger of reactive carbonyl species including methylglyoxal. Underappreciated glycation-relevant effect.

Mitochondrial Support (Reducing Glycolytic Overflow)

Supplement	Dose	Relevance to Glycation Profile
Ubiquinol (CoQ10)	100 mg EOD	Supports mitochondrial electron transport efficiency, reducing overflow of glycolytic intermediates into methylglyoxal production.
PQQ	20 mg	Mitochondrial biogenesis. More efficient mitochondria means less glycolytic overflow and less methylglyoxal generation.

6. Additional Supplements to Consider

The following supplements are not currently in the regimen but could address specific glycation-related genetic findings. All additions should be discussed with the treating physician, particularly those with drug interaction potential.

Supplement	Suggested Dose	Genetic Target	Rationale & Notes
Benfotiamine	150–300 mg	AKR1B1 / GLO1	Lipid-soluble vitamin B1. Activates transketolase, diverting glycolytic intermediates away from methylglyoxal and polyol pathways. Directly addresses both GLO1 and AKR1B1 vulnerabilities. Extensive evidence for reducing AGE formation. No significant drug interactions. Priority: HIGH.
Pyridoxamine	50–200 mg	GLO1 (bypass)	Active vitamin B6 form that directly traps methylglyoxal and other reactive carbonyls, preventing AGE formation. Compensates for reduced GLO1 enzymatic clearance. Standard pyridoxine does not have same effect. Check multivitamin B6 form. Priority: HIGH.
Alpha-lipoic acid	300–600 mg	GLO1 (cofactor)	Regenerates glutathione (supporting GLO1 cofactor), recycles vitamin C. Evidence for reducing AGE formation. Dual benefit: also supports glucose metabolism (GLUT4). CAUTION: Can lower blood glucose; introduce carefully. Priority: HIGH.
Carnosine	500 mg–1 g	GLO1 (bypass)	Dipeptide that acts as a direct methylglyoxal and reactive carbonyl scavenger. Forms sacrificial adducts, protecting hemoglobin and other proteins. Also inhibits AGE crosslink formation. Priority: MODERATE–HIGH.
Increased NACET/NAC	200–300 mg NACET or 600 mg NAC	GLO1 (cofactor)	Current 100 mg NACET is modest given the convergence of GLO1 impairment and AKR1B1 NADPH depletion. More glutathione substrate to support GLO1 function. Priority: MODERATE–HIGH.
Sulforaphane	10–30 mg (broccoli seed extract)	GLO1 (inducer)	Activates Nrf2 pathway, upregulating GLO1 expression and glutathione synthesis enzymes. One of few interventions that can increase GLO1 protein levels to compensate for genetic variants. Priority: MODERATE.
Trans-resveratrol	150–300 mg	AKR1B1 / GLO1	Evidence for reducing AGE formation and inhibiting aldose reductase activity (AKR1B1). Activates SIRT1 which can upregulate GLO1. Potential interaction with rapamycin. Priority: MODERATE.
Rutin or Quercetin	500 mg	AKR1B1	Flavonoids with demonstrated aldose reductase inhibitory activity. Partially counteracts increased polyol pathway flux. Quercetin also has GLO1-inducing properties. Priority: MODERATE.

7. Suggested Monitoring Panel

Test	Rationale
CGM (continuous glucose monitor)	Primary glycemic assessment tool. More accurate reflection of true glucose exposure than HbA1c given the genetic glycation gap.
HbA1c	Continue monitoring but interpret with awareness that it likely overestimates glycemic exposure. Track trend rather than absolute value.
Fructosamine / Glycated albumin	Alternative glycation marker reflecting 2–3 week glucose average. Not affected by RBC lifespan. Would confirm whether glycation gap is RBC-specific or systemic.
Iron panel (serum iron, ferritin, transferrin sat., TIBC)	Confirm whether TMPRSS6 homozygous genotype is manifesting as altered iron stores. Supports RBC lifespan hypothesis.
Reticulocyte count	Low reticulocyte count would suggest slower RBC turnover (longer lifespan), supporting the ANK1/SPTA1 mechanism.
Glutathione (RBC or whole blood)	Assess glutathione pool status given convergence of GLO1 cofactor demand and AKR1B1 NADPH depletion.
Methylglyoxal or MG-H1 (if available)	Direct measure of the reactive carbonyl that GLO1 detoxifies. Elevated levels would confirm GLO1 functional impairment.
Advanced glycation end products (AGEs, skin AF)	Skin autofluorescence or serum AGE levels would assess cumulative glycation burden across all proteins, not just hemoglobin.

Note: This analysis covers common GWAS-identified variants only. Each common variant has a small individual odds ratio; clinical significance arises from the cumulative pattern and its interaction with environmental factors. Variants not found in the VCF are interpreted as likely homozygous reference (no risk alleles), as the 60x sequencing depth provides high confidence in variant detection. The glycation gap analysis should be interpreted alongside the companion Glucose Dysregulation Genetic Report for a complete picture of the patient's metabolic genetic profile.