

# Reframing Type 2 Diabetes as Cardiometabolic Disease: A Five-phenotype Model Beyond Glycated Hemoglobin

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Received: April 07, 2026

Accepted: April 27, 2026

Published: May 01, 2026

**Citation:** Goulden PA. 2026. Reframing Type 2 Diabetes as Cardiometabolic Disease: A Five-phenotype Model Beyond Glycated Hemoglobin. *J Obes Chronic Dis* 10(1): 4-11.

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## Abstract

Type 2 diabetes has traditionally been framed as a disorder of hyperglycemia caused by insulin resistance (IR) and progressive beta-cell failure. That model remains biologically useful, but it is clinically incomplete. Contemporary outcome trials show that therapies with modest glycemic effects, particularly glucagon-like peptide-1 (GLP-1) receptor agonists, dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and metabolic surgery-substantially reduce cardiovascular events, heart failure (HF), chronic kidney disease (CKD) progression, and weight-related morbidity. This mismatch suggests that type 2 diabetes is better understood as a cardiometabolic systems disease in which hyperglycemia is an important downstream manifestation, but not the sole driver of clinical risk. In this narrative review and perspective, cardiometabolic load is defined as the cumulative burden of visceral adiposity, ectopic liver and pancreatic fat, adipocyte dysfunction, endothelial injury, cardiorenal stress, inflammation, and reduced muscle reserve. A pragmatic five-phenotype model for clinical use is proposed: visceral adiposity dominant, sarcopenic IR, cardiorenal dominant, metabolic dysfunction-associated steatotic liver disease (MASLD)/lipotoxicity dominant, and beta-cell fragile. The framework is placed alongside existing data-driven diabetes clustering systems, and approaches for validation are outlined through prospective testing of risk prediction and treatment response. The model is also linked to prior work on fetal programming and Marshallese cardiometabolic risk, where early-life adversity, nutritional transition, and social determinants can create severe metabolic disease at modest body mass index (BMI). A phenotype-based approach may better align therapy with dominant biology while preserving the established importance of glycemic control.

## Keywords

Type 2 diabetes, Cardiometabolic disease, Phenotypes, Visceral adiposity, Metabolic dysfunction-associated steatotic liver disease, Developmental origins of health and disease, Glucagon-like peptide-1 receptor agonists, Sodium-glucose cotransporter 2 inhibitors

## Introduction

We have become better at lowering glycated hemoglobin (HbA1c) than at altering the biology that shortens the lives of our patients. National data suggest that many adults with newly diagnosed type 2 diabetes now reach glycemic targets, yet far fewer achieve comprehensive risk factor control across blood pressure, lipids, smoking, and weight [1]. That disconnect matters, because myocardial

infarction, HF, CKD, cirrhosis, frailty, and disability do not arise from glucose alone.

The canonical teaching model of type 2 diabetes, from the triumvirate to the ominous octet, remains elegant and useful [2]. It explains glucose flux, but it does not fully explain why one patient with a BMI of 29 kg/m<sup>2</sup> and heavy visceral fat is metabolically sicker than another with the same BMI and much lower organ fat burden. It does not explain why contemporary agents can move cardiovascular and renal event curves long before major glycemic divergence. Even recent overviews that correctly describe type 2 diabetes as a multi-organ disease still tend to place hyperglycemia at the center [3, 4]. Clinically, this perspective is reversed. By the time HbA1c rises, a great deal of the meaningful disease is already established.

This is not an argument that glycemia does not matter. HbA1c remains an important measure of glucose exposure and microvascular risk. However, the relationship between HbA1c and hard cardiovascular outcomes is far looser than our older algorithms implied. In a trial evaluating cardiovascular outcomes with sitagliptin, the association between time-varying HbA1c and cardiovascular outcomes was U-shaped, with lowest risk near 7% [5]. Action to Control Cardiovascular Risk in Diabetes, Action in Diabetes and Vascular Disease, and Veterans' Affairs Diabetes Trial each tempered the notion that more aggressive glucose lowering necessarily improves survival or major cardiovascular outcomes [6-8]. The field has already evolved, driven not by theory but by outcomes. Our biology and our treatment algorithms need to catch up.

Here, type 2 diabetes is framed as a cardiometabolic systems disease defined by organ burden. The term cardiometabolic load is used to describe the cumulative burden of visceral adiposity, ectopic liver and pancreatic fat, adipocyte dysfunction, endothelial injury, cardiorenal stress, chronic inflammation, and reduced muscle reserve. On this basis, a pragmatic five-phenotype heuristic for clinical use is proposed:

visceral adiposity dominant, sarcopenic IR, cardiorenal dominant, MASLD/lipotoxicity dominant, and beta-cell fragile. The goal is practical: to identify, at the point of care, the biology driving risk in the individual patient (Table 1).

## Literature Approach

This manuscript is a narrative synthesis and perspective rather than a systematic review or meta-analysis. Sources included PubMed/MEDLINE indexed reviews and original studies, landmark cardiovascular and renal outcome trials, major mechanistic studies of ectopic fat and organ injury, consensus statements on MASLD nomenclature, and prior published work in developmental programming and Marshallese diabetes research. Studies were selected because they were clinically influential, mechanistically relevant, or representative of a broader evidence stream that informs phenotype-driven diabetes care.

The cited trials and mechanistic studies are therefore illustrative rather than exhaustive. The purpose is not to estimate pooled treatment effects, but to build a clinically usable framework that can be tested prospectively. This limitation matters. A glucocentric model can be overstated by selective trial reading, but so can a cardiometabolic model. The argument here is positioned as hypothesis-generating and translational, not as a replacement for guideline-based risk management.

### Cardiometabolic load, not HbA1c alone

Recent reviews of adult type 2 diabetes increasingly emphasize that the disease involves multiple organs and interacting metabolic pathways [9]. The argument can be extended further while maintaining this distinction. Hyperglycemia is not the entire disease process. It is one visible output of a deeper systems failure in energy storage, substrate partitioning, vascular biology, and tissue reserve. Glycemia remains central to microvascular risk and must still be treated. The problem is that HbA1c alone is an incomplete

**Table 1:** Proposed five-phenotype model of type 2 diabetes.

Phenotype	Clinical signature	Useful markers	Therapeutic priorities
1. Visceral adiposity dominant	Central adiposity, high visceral-to-subcutaneous fat ratio, hypertriglyceridemia, and steatotic liver at modest BMI	Waist or waist-to-height ratio (WHtR), TG, ALT, and liver imaging if already available	GLP-1 or GIP/GLP-1 therapy early, add SGLT2 inhibitor for organ protection, consider surgery when severe
2. Sarcopenic IR	Low muscle mass or myosteatosis, frailty, poor glucose disposal, glycemic volatility despite normal or modest BMI	Grip strength, gait speed, body composition imaging when available	Resistance training, adequate protein within renal limits, cautious weight-centric pharmacotherapy
3. Cardiorenal dominant	Albuminuria, falling eGFR, congestion, limited cardiac reserve, risk driven by HF or CKD	Urine albumin-to-creatinine ratio (ACR), eGFR trend, blood pressure, HF history	SGLT2 inhibitor as foundation, optimize renin-angiotensin-aldosterone system (RAAS) blockade and/or mineralocorticoid receptor antagonism (MRA) therapy when indicated, add GLP-1 therapy for atherosclerotic cardiovascular disease (ASCVD) risk when appropriate
4. MASLD or lipotoxicity dominant	Hepatic fat overload, high TG, elevated alanine aminotransferase (ALT), liver burden out of proportion to BMI, possible pancreatic fat	ALT, aspartate aminotransferase (AST), platelets, FIB-4, FibroScan or liver imaging when available	GLP-1 based therapy, selected pioglitazone use, SGLT2 inhibition, surgery when appropriate
5. Beta-cell fragile	Rapid glycemic decline, low insulin reserve, lean or mildly overweight phenotype, early oral therapy failure	C-peptide, diabetes autoantibodies when phenotype is atypical	Early insulin or combination therapy, then layer organ-protective agents as indicated

proxy for the organ burden that drives cardiovascular, renal, hepatic, functional, and survival outcomes.

Operationally, cardiometabolic load can be considered qualitatively across five domains: visceral adiposity, liver-centered lipotoxicity, cardiorenal stress, muscle reserve, and beta-cell reserve. In routine practice, high load is suggested by combinations of central adiposity, elevated triglycerides (TG), rising aminotransferases or fibrosis-4 index (FIB-4), albuminuria, falling estimated glomerular filtration rate (eGFR), HF, low grip strength or slow gait speed, and low or falling C-peptide. These are imperfect surrogates, but they give the clinician a more honest view of the disease than HbA1c alone (Table 2).

Ectopic fat is central to that burden. Magnetic resonance studies show that liver and pancreatic fat correlate strongly with hepatic IR and impaired beta-cell function, even among individuals with similar BMI [10]. The implication is straightforward and clinically important. Two patients may share the same weight yet carry very different metabolic risks depending on where excess energy is stored. Visceral and ectopic depots are not passive. They are biologically active and clinically consequential.

Adipose tissue biology sits at the center of this story. Santoro and Kahn [11] made the case clearly: adipose tissue is not merely a warehouse for calories; it is a regulator of systemic insulin sensitivity [11]. Once adipocytes lose the capacity to store lipids safely, free fatty acid spillover into liver, muscle, and pancreas drives lipotoxicity and broad metabolic dysfunction. The patient with worsening TG, central adiposity, and rising aminotransferases is often not just gaining weight. That patient is losing buffering capacity.

Skeletal muscle is the other neglected organ in everyday diabetes care. Chronic energy surplus contributes to mitochondrial stress, oxidative injury, and reduced metabolic flexibility [12]. Muscle that cannot efficiently oxidize substrate becomes insulin resistant. Muscles that are small, fat-infiltrated, or functionally weak also lose their role as the major sink for postprandial glucose disposal. This matters most in older adults and in patients with deceptively normal weight, for whom sarcopenia and myosteatosis may be more important than total fat mass.

The vasculature and the kidneys are not bystanders. Endothelial dysfunction, vascular inflammation, altered shear stress, and renal hyperfiltration may predate overt diabetes by years [13]. Low-grade inflammation links visceral fat to

atherosclerosis, HF, CKD, and steatotic liver disease (SLD) [14]. Visceral adipose tissue (VAT) is not metabolically equivalent to subcutaneous fat, and BMI alone misses that distinction [15]. In this framework, HbA1c is a late marker of an injury process that often begins long before hyperglycemia is obvious.

### Developmental programming and population vulnerability

If type 2 diabetes is a systems disease, its roots often extend far upstream of the first abnormal HbA1c. The developmental origins of health and disease literature has long shown that the intrauterine and early postnatal environment can shape later body composition, insulin sensitivity, stress responses, and vascular risk [16]. That work mattered because it shifted the focus from adult behavior alone to biologic programming across the life course.

Prior work has contributed to that literature in two linked ways. In the Hertfordshire cohort, lower birth weight and lower infant weight were associated with higher adult glucose intolerance and diabetes risk, and with altered patterns of insulin secretion and resistance in later life [17]. In the Southampton stress-axis cohort, boys who had been smaller at birth demonstrated an exaggerated cortisol response to psychosocial stress, independent of gestational age and several important confounders [18]. These data do not prove a single mechanistic pathway, but they support a plausible model in which altered fetal growth helps set later stress biology, adiposity distribution, blood pressure, and metabolic vulnerability.

That life-course perspective became especially relevant in our work with Marshallese communities in Arkansas. There, historic displacement, environmental exposures, disruption of traditional food systems, rapid nutritional transition, and structural barriers to care converge in ways that intensify cardiometabolic risk [19, 20]. Using a community-based participatory framework, a family-based model of diabetes self-management education was adapted for Marshallese households, first in a pilot intervention and later in a randomized controlled trial [19, 20]. The family model improved engagement and glycemic outcomes compared with standard education, which reinforced a broader lesson: diabetes care is more effective when biology and social context are treated together rather than in parallel.

The Marshallese experience also illustrates a point that clinicians recognize across several populations. Severe metabolic diseases can be present at modest BMI when central

**Table 2:** Practical surrogates of cardiometabolic load for phenotype-driven care.

Domain of burden	Clinic-level measures	Clinical meaning
Visceral adiposity	Waist circumference, WHtR, existing CT or MRI if available	A rough estimate of central fat burden and likely inflammatory load
Liver-centered lipotoxicity	ALT, AST, platelets, FIB-4, FibroScan or liver imaging	SLD activity and fibrosis risk
Cardiorenal stress	Urine ACR, eGFR trajectory, blood pressure, HF history	Endothelial injury, nephron stress, pressure and flow burden
Muscle reserve	Grip strength, gait speed, body composition imaging, clinical frailty	Lean mass, myosteatosis, and functional reserve
Glycemic reserve	HbA1c, fasting glucose, postprandial profile, C-peptide when needed	Glucose exposure and beta-cell reserve, not whole-disease burden

fat storage, ectopic fat deposition, early-life programming, and social adversity align. That pattern is one reason BMI is such a blunt instrument. It measures size. It does not measure where energy is being stored, what organs are under strain, or how much physiologic reserve remains.

The Marshallese example should not be read as unique. It is a clear illustration of a broader principle: population history, early-life biology, body composition, and access to care can change the way type 2 diabetes presents. South Asian populations, for example, develop diabetes at lower BMI than many European ancestry populations and often show central adiposity, lower lean mass, ectopic fat deposition, and beta-cell vulnerability [21-23]. Data-driven subgroup work in Asian Indian cohorts also supports the idea that clinically important phenotypes may differ across populations [24]. The framework proposed here is therefore not ethnicity-specific. It asks the same organ-based questions in every patient: where is the fat, how much muscle reserve remains, are the heart and kidney under strain, is the liver overloaded, and how fragile does beta-cell function?

### Why modern therapies change outcomes

Outcome trials support a broader disease model. If HbA1c were the primary driver of long-term events, therapies with the largest glycemic effects would deliver the largest cardiovascular and renal benefits. Instead, GLP-1 receptor agonists, dual incretin agonists, SGLT2 inhibitors, and metabolic surgery often reduce cardiovascular events, kidney disease progression, and weight-related morbidity out of proportion to their effect on HbA1c [25-31].

The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity Trial is illustrative. In adults with overweight or obesity and established cardiovascular disease, but without diabetes, semaglutide reduced major adverse cardiovascular events by 20% [25]. Because participants did not have diabetes, these benefits cannot be attributed to lowering glucose. More plausible mechanisms include weight loss with preferential visceral fat reduction, improved endothelial function, reduced inflammation, and altered substrate handling [25, 26].

The SGLT2 evidence base makes the same point. Empagliflozin, Cardiovascular Outcomes, and Event Trial in Type 2 Diabetes Mellitus Patients, Dapagliflozin and Prevention of Adverse Outcomes in HF, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, and Dapagliflozin and Prevention of Adverse Outcomes in CKD showed early and sustained reductions in cardiovascular death, HF hospitalization, and progression of kidney disease [27-30]. The timing and consistency of these effects argue against HbA1c as the main explanation. The benefits align better with cardiorenal unloading, intraglomerular pressure reduction, natriuresis, shifts in myocardial energetics, and lower interstitial congestion [26-30]. In practice, these agents function as cardiorenal therapies that also lower glucose.

Metabolic surgery completes the picture. Glycemic improvement after Roux-en-Y gastric bypass and related procedures often precedes major weight loss, implying early

neuroendocrine and hepatic effect rather than a slow calorie deficit alone [31]. Changes in GLP-1, peptide YY, bile acids, gut-brain signaling, appetite tone, and hepatic insulin sensitivity help explain why surgery can reset metabolic physiology so powerfully. Different interventions enter the system through different doors, but the final common pathway is similar. They reduce cardiometabolic load. They unload the liver, the heart, the kidney, the vascular tree, and in some patients the pancreas as well.

### Relationship with existing phenotype systems and validation

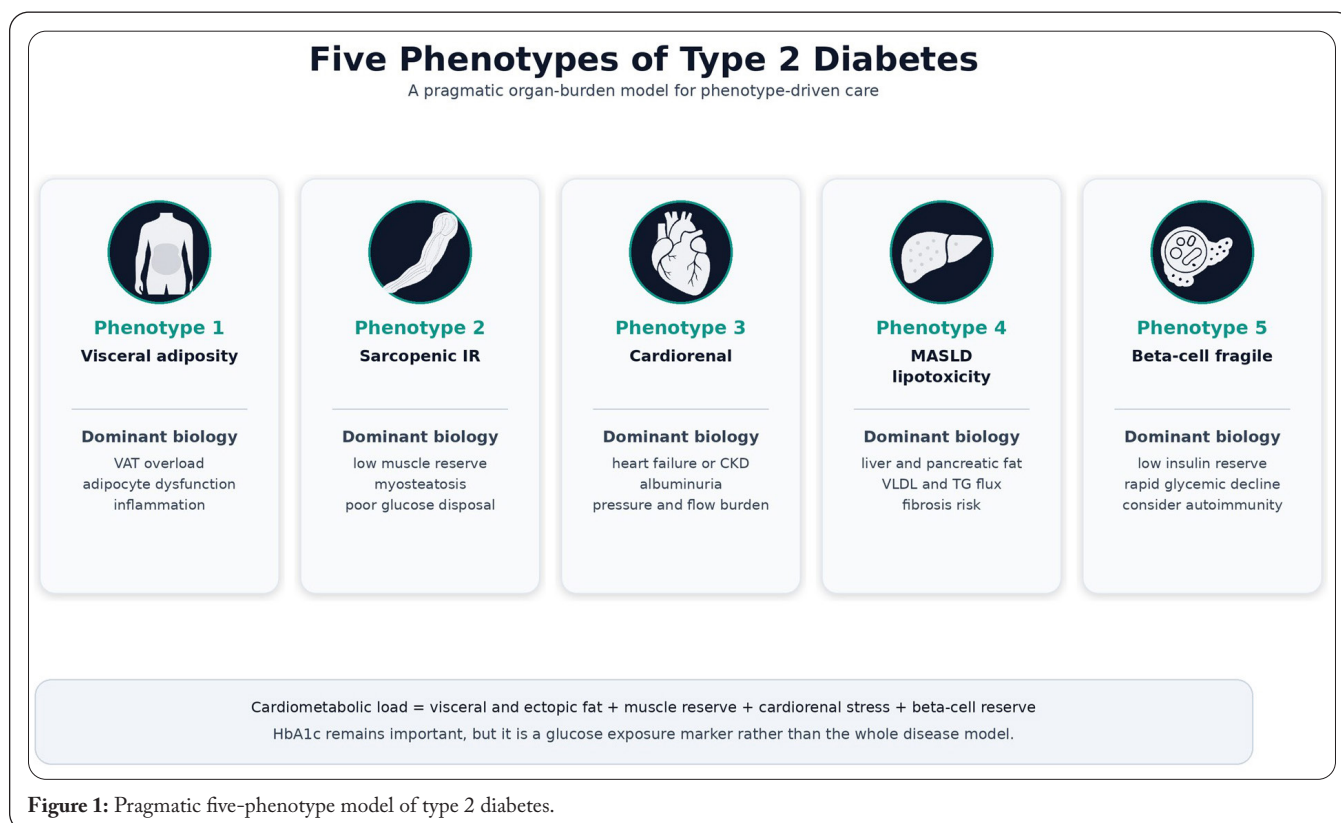
Several data-driven systems already recognize that adult-onset diabetes is heterogeneous. Ahlqvist et al. [32] used six variables, including age at diagnosis, BMI, HbA1c, glutamate decarboxylase antibodies, and homeostasis model assessment 2 estimates of beta-cell function and IR, to describe five subgroups: severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes, and mild age-related diabetes [32]. Subsequent cohorts, including the German Diabetes Study, found differences in complication trajectories across these subgroups [33]. At the same time, Dennis et al. [34] showed that simple continuous clinical features can perform as well as clusters for some predictions of progression and treatment response [34]. That caution is important.

The five-phenotype framework proposed here is not meant to replace data-driven clustering systems. It is a bedside organ-burden heuristic. Its categories overlap with the clustering literature, but they are organized around treatable biology rather than statistical separation alone. Severe insulin-resistant diabetes overlaps conceptually with visceral adiposity and MASLD/lipotoxicity dominant disease; severe insulin-deficient diabetes overlaps with beta-cell fragile disease; mild obesity-related diabetes overlaps with visceral adiposity dominant disease; and cardiorenal or sarcopenic disease may cut across several statistical clusters.

The model should be validated before being treated as a formal taxonomy. A practical validation framework would address three questions. First, can clinicians or an electronic health record algorithm assign dominant and secondary phenotypes reproducibly using routine markers such as WHtR, TG, FIB-4, urine ACR, eGFR, HF history, grip strength, gait speed, C-peptide, and autoantibodies? Second, does phenotype assignment improve prediction of major adverse cardiovascular events, HF hospitalization, kidney decline, fibrosis risk, frailty, and insulin requirement beyond age, BMI, HbA1c, diabetes duration, and baseline eGFR? Third, does phenotype assignment predict differential response to GLP-1 based therapy, SGLT2 inhibition, pioglitazone, metabolic surgery, resistance training, or early insulin? The ideal study would use continuous phenotype scores as well as categorical labels, because real patients commonly overlap categories (Figure 1).

### A phenotype-based model for type 2 diabetes

If organ burden drives risk, treatment should track dominant biology rather than HbA1c alone. The five-



**Figure 1:** Pragmatic five-phenotype model of type 2 diabetes.

phenotype model is intended as a clinical organizing framework, not a rigid taxonomy. It is designed for the patient in front of the clinician, where the dominant driver may be visceral fat, muscle deficit, heart or kidney strain, liver-centered lipotoxicity, or beta-cell fragility. Many patients span more than one category, so the goal is to identify the dominant and secondary drivers rather than to force a single label.

### Phenotype 1: Visceral adiposity dominant

This is the classic central adiposity phenotype, although it often appears in patients who do not look dramatically obese on first inspection. The hallmarks are disproportionate abdominal adiposity, a high visceral to subcutaneous fat ratio, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and frequent SLD. These patients often have marked metabolic risk at a modest BMI because the problem is not simply fat mass, but the depot in which that fat is stored [10, 15].

Therapy should target appetite, visceral fat, inflammation, and organ protection early. GLP-1 receptor agonists or dual GIP/GLP-1 receptor agonists are usually the most rational starting point when access allows, with SGLT2 inhibition layered in when cardiovascular, HF, or kidney risk is present. Metabolic surgery should be considered sooner rather than later in severe or refractory disease. In this phenotype, delaying disease-modifying therapy until after repeated A1c-driven escalations is a missed opportunity.

### Phenotype 2: Sarcopenic IR

This is the under-recognized muscle phenotype. Patients may be older, frail, chronically inflamed, or simply metabolically vulnerable despite normal or only modestly elevated BMI. Imaging studies showed long ago that lower

muscle attenuation on computed tomography reflects greater lipid infiltration of skeletal muscle, a state associated with impaired insulin action [35]. Clinically, these patients often have low grip strength, poor gait speed, volatile glycemia, and limited metabolic reserve.

Mechanistically, sarcopenic IR combines reduced muscle quantity, impaired muscle quality, intramyocellular lipid accumulation, mitochondrial stress, anabolic resistance, and low-grade inflammation. Because skeletal muscle is the major site of insulin-stimulated glucose disposal, loss of muscle reserve reduces the body's capacity to buffer postprandial glucose. A patient can therefore have a normal BMI and still have severe metabolic vulnerability if the apparent leanness reflects low muscle rather than metabolic health. This is the phenotype in which indiscriminate weight loss can be a trap: lowering weight while losing more lean mass may improve HbA1c in the short term while worsening frailty, function, and long-term reserve.

The therapeutic priorities are different here. Resistance training and adequate protein intake, within renal limits, are foundational because the target organ is muscle rather than adipose tissue alone. Weight loss that strips lean mass can worsen rather than improve long-term metabolic health. GLP-1 based therapy may still be appropriate, but monotherapy aimed purely at weight reduction should be used thoughtfully. Cardiorenal indications for SGLT2 inhibition still stand. Secondary causes of muscle loss, including hypogonadism, systemic illness, disordered eating, and medication effects, should be actively sought.

### Phenotype 3: Cardiorenal dominant

In this phenotype, the heart and the kidney are the failing organs and HbA1c is often a poor index of true danger.

Albuminuria, falling eGFR, congestion, sodium retention, and limited cardiac reserve dominate the risk profile. Some patients also carry substantial visceral adiposity, but the main threat is pressure, flow, fibrosis, and decompensation rather than hyperglycemia itself.

SGLT2 inhibitors are foundational because they directly address cardiorenal physiology and improve outcomes across diabetes status [27-30]. RAAS blockade, MRA therapy, and other kidney-protective strategies should be used aggressively when indicated. GLP-1 based therapy is often helpful for atherosclerotic risk reduction. The common clinical error in this phenotype is over-basalizing insulin while under-treating albuminuria, congestion, and progressive nephropathy.

**Phenotype 4: MASLD/lipotoxicity dominant**

The liver-centered phenotype is common and frequently underdiagnosed. Hepatic fat overload drives increased hepatic glucose output, overproduction of very low-density lipoprotein particles, hypertriglyceridemia, and inflammatory spillovers. Pancreatic fat may further impair first-phase insulin secretion. Many of these patients have elevated alanine aminotransferase (ALT), but not all do, and some have striking liver burden despite relatively normal body size [36, 37].

At the systems level, MASLD is a disorder of lipid flux, not merely a liver ultrasound finding. VAT drains into the portal circulation, increasing hepatic free fatty acid delivery. When hepatic oxidation and export cannot safely handle that flux, liver fat, very low-density lipoprotein secretion, TG, remnant particle burden, and hepatic IR rise together [14, 36]. Pancreatic fat can then impair first-phase insulin secretion. This phenotype links the liver, adipose tissue, pancreas, and vascular tree into one lipotoxic circuit.

The newer MASLD and metabolic dysfunction-associated steatohepatitis (MASH) nomenclature is clinically useful because it defines liver disease positively by metabolic dysfunction rather than by exclusion [37]. In this phenotype, GLP-1 based therapy is highly attractive because it reduces body weight, appetite, and liver fat. Pioglitazone still has a place in carefully selected patients, particularly when cost is decisive and HF risk is low. SGLT2 inhibitors and metabolic surgery also reduce hepatic burden. A pragmatic clinic-level approach includes serial attention to TG, aminotransferases, fibrosis risk by FIB-4, and waist measures rather than waiting for advanced liver disease to declare itself.

**Phenotype 5: Beta-cell fragile**

Some patients present with rapid decline in glycemic control out of proportion to visible IR. They may be lean or only mildly overweight, have low or low-normal C-peptide at diagnosis, and fail oral therapy early. In these patients, intrinsic beta-cell vulnerability, genetic clustering, latent autoimmune diabetes, or another cause of impaired insulin secretion should be considered. The dominant biology is not excess glucose exposure but inadequate insulin reserve.

Early insulin, combination therapy, or both may be appropriate to relieve glucotoxic stress, while SGLT2 inhibitors and GLP-1 based agents can still be layered in when there is sufficient reserve or when cardiovascular and renal protection are priorities. Autoantibody testing and longitudinal C-peptide measurement are often more informative here than another round of A1c-driven escalation.

**Clinical workflow for overlapping phenotypes**

Most patients will not sit cleanly in one box. The practical question is therefore not only which phenotype is present, but which phenotype is currently driving risk. A useful clinic workflow is shown in table 3. The first step is to confirm diabetes type and immediate glycemic safety, including symptoms, ketosis risk, weight loss, and the need for insulin. The second step is to identify organ threats that change outcomes now: established ASCVD, HF, CKD, albuminuria, advanced MASLD or MASH risk, severe hypertriglyceridemia, and frailty. The third step is to assign a dominant phenotype and, when present, one or two secondary phenotypes.

Treatment priority should then follow organ threat. Cardiorenal dominant disease usually deserves SGLT2 inhibition and kidney or HF optimization even when HbA1c is close to target. Beta-cell fragile disease, especially with catabolism or low C-peptide, requires early insulin or combination therapy before pursuing weight-centric strategies. Visceral adiposity and MASLD/lipotoxicity dominant disease justify early GLP-1 or GIP/GLP-1 based therapy, SGLT2 inhibition when organ risk is present, selected pioglitazone use when appropriate, and metabolic surgery when disease is severe. Sarcopenic IR requires resistance training, protein adequacy within renal limits, and caution against treatment plans that worsen lean mass. Reassessment every 3 to 6 months should include HbA1c, but also waist, TG, aminotransferases or FIB-4, albuminuria, eGFR trajectory, and a simple functional

**Table 3:** Pragmatic workflow for phenotype-driven care when phenotypes overlap.

Step	Clinical action	Purpose
1	Confirm diabetes type and glycemic safety: symptoms, catabolism, ketosis risk, current therapy, hypoglycemia risk, need for insulin	Do not miss beta-cell failure, autoimmune diabetes, or immediate need for insulin
2	Map organ burden: waist or WHtR, TG/HDL, ALT/AST/platelets and FIB-4, urine ACR, eGFR trend, ASCVD or HF history, grip strength or gait speed, C-peptide when indicated	Identify the organ system currently driving risk
3	Assign dominant and secondary phenotypes rather than forcing one label	Reflect real-world overlaps such as visceral adiposity plus MASLD or cardiorenal plus sarcopenic disease
4	Prioritize therapy by organ threat: cardiorenal and beta-cell fragile disease first when present; visceral and MASLD load next; protect muscle reserve throughout	Treating biology is most likely to change outcomes
5	Reassess every 3 to 6 months with HbA1c plus load markers: waist, TG, ALT or FIB-4, ACR/eGFR, and functional status	Track trajectory, not only glucose exposure

measure when feasible.

### Illustrative clinical vignette

A de-identified clinical vignette shows why phenotype matters. Consider a middle-aged Marshallese man with no insurance, marked food insecurity, and shift work, presenting with an HbA1c of 11.2%, TG of 348 mg/dL, ALT of 78 U/L, and a BMI of 29 kg/m<sup>2</sup> with clear central adiposity. In the old model, he is simply a patient with poorly controlled type 2 diabetes who needs more medication. In the model proposed here, he is better understood as having overlapping phenotype 1 and phenotype 4 disease, with visceral adiposity, steatotic liver burden, early beta-cell strain, and major social determinants of health.

That reinterpretation changes treatment priorities. The immediate goal is not only to lower HbA1c, although that matters. The goal is to unload visceral and hepatic fat, protect the heart and kidney, simplify the regimen, and build realistic access. Metformin may remain in place, but it is rarely sufficient. If possible, GLP-1 based therapy should be secured through patient assistance. SGLT2 inhibition should be added when feasible for cardiorenal protection. Pioglitazone becomes a reasonable, inexpensive alternative in selected patients if access to incretin therapy fails and edema risk is acceptable. Family-based diabetes education, culturally tailored nutritional change, walking after meals, and community support are not extras in such a case. They are part of the treatment.

Most importantly, the measures of success also change. Waist circumference, TG, aminotransferases, urine ACR, and day-to-day treatment friction become as relevant as HbA1c. When biology is treated honestly, glucose often follows.

### Rethinking targets and staging

None of this requires abandoning HbA1c. It requires putting HbA1c back in its proper place. HbA1c measures glycemic exposure. It does not directly measure visceral adiposity, liver fat, endothelial injury, cardiorenal stress, beta-cell reserve, or muscle quality. Those missing dimensions are exactly where modern therapies exert much of their value.

A phenotype-driven clinic therefore needs additional practical surrogates of cardiometabolic load. Waist circumference or WHtR is cheap and often more informative than BMI. TG and triglyceride to HDL cholesterol ratio can serve as rough markers of remnant burden and ectopic fat. ALT is crude but still useful, while FIB-4 offers a pragmatic first-pass estimate of fibrosis risk in SLD and is included in contemporary diabetes comorbidity assessment recommendations [38]. Urine ACR and eGFR trajectory help expose vascular and renal injury early. Grip strength, gait speed, or existing body composition imaging can uncover a sarcopenic phenotype that weight alone hides.

The staging logic may ultimately resemble the Edmonton Obesity Staging System adapted for diabetes [39]. In such a model, HbA1c would be one line in the assessment, not the headline. Stage would be driven by organ damage, body composition, functional reserve, and social complexity. That is closer to how experienced clinicians already think when they are not forced back into a narrow algorithm.

Endocrinology is well placed to lead this reframing because our discipline sits at the intersection of adipose biology, gut-brain signaling, beta-cell function, obesity medicine, liver disease, and cardiorenal therapeutics. The task now is to translate that understanding into practical pathways that prioritize phenotype and organ burden early rather than after years of serial A1c escalation.

## Conclusion

Type 2 diabetes is not merely a glucose disease that happens to have complications. It is a cardiometabolic systems disease in which hyperglycemia is one visible output of a deeper disorder in energy storage, tissue stress, vascular biology, and reserve. That reframing better aligns with biology, the outcome trial literature, and the patient in clinical practice whose A1c never fully explains the seriousness of the disease.

The five-phenotype model proposed here is a clinical organizing framework rather than a finished taxonomy. It is intended to anchor treatment decisions in dominant biology: visceral adiposity, muscle loss, cardiorenal strain, liver-centered lipotoxicity, or beta-cell fragility. It should now be tested against hard outcomes, treatment response, and implementation feasibility. The practical message is straightforward: to change outcomes, treat cardiometabolic load while preserving the proven importance of glycemic control. HbA1c remains important, but it is not sufficient.

The Monday-morning question for clinicians should therefore change. Not simply, what is the HbA1c?, but rather, which phenotype is dominant and which organ is carrying the heaviest burden? Once that question is asked honestly, treatment choices become clearer.

## Acknowledgements

None.

## Conflict of Interest

None.

## References

1. Fang M, Selvin E. 2021. Thirty-year trends in complications in U.S. adults with newly diagnosed type 2 diabetes. *Diabetes Care* 44(3): 699-706. <https://doi.org/10.2337/dc20-2304>
2. DeFronzo RA. 2009. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 58(4): 773-795. <https://doi.org/10.2337/db09-9028>
3. Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. 2022. Type 2 diabetes. *Lancet* 400(10365): 1803-1820. [https://doi.org/10.1016/s0140-6736\(22\)01655-5](https://doi.org/10.1016/s0140-6736(22)01655-5)
4. Jacob S, Krentz AJ, Deanfield J, Rydén L. 2021. Evolution of type 2 diabetes management from a glucocentric approach to cardio-renal risk reduction: the new paradigm of care. *Drugs* 81(12): 1373-1379. <https://doi.org/10.1007/s40265-021-01554-6>
5. McAlister FA, Zheng Y, Westerhout CM, Buse JB, Standl E, et al. 2020. Association between glycated haemoglobin levels and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the TECOS randomized clinical trial. *Eur J Heart Fail* 22(11): 2026-2034. <https://doi.org/10.1002/ejhf.1958>

6. Group ACCRDS, Gerstein HC, Miller ME, Byington RP, Goff DC, et al. 2008. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358(24): 2545-2559. <https://doi.org/10.1056/nejmoa0802743>
7. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, et al. 2008. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358(24): 2560-2572. <https://doi.org/10.1056/nejmoa0802987>
8. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, et al. 2009. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 360(2): 129-139. <https://doi.org/10.1056/nejmoa0808431>
9. Kalyani RR, Neumiller JJ, Maruthur NM, Wexler DJ. 2025. Diagnosis and treatment of type 2 diabetes in adults: a review. *JAMA* 334(11): 984-1002. <https://doi.org/10.1001/jama.2025.5956>
10. Cao MJ, Wu WJ, Chen JW, Fang XM, Ren Y, et al. 2023. Quantification of ectopic fat storage in the liver and pancreas using six-point Dixon MRI and its association with insulin sensitivity and  $\beta$ -cell function in patients with central obesity. *Eur Radiol* 33(12): 9213-9222. <https://doi.org/10.1007/s00330-023-09856-x>
11. Santoro A, Kahn BB. 2023. Adipocyte regulation of insulin sensitivity and the risk of type 2 diabetes. *N Engl J Med* 388(22): 2071-2085. <https://doi.org/10.1056/nejmra2216691>
12. Choi W, Woo GH, Kwon TH, Jeon JH. 2025. Obesity-driven metabolic disorders: the interplay of inflammation and mitochondrial dysfunction. *Int J Mol Sci* 26(19): 9715. <https://doi.org/10.3390/ijms26199715>
13. Beckman JA, Creager MA, Libby P. 2002. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 287(19): 2570-2581. <https://doi.org/10.1001/jama.287.19.2570>
14. Shulman GI. 2014. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med* 371(12): 1131-1141. <https://doi.org/10.1056/nejmra1011035>
15. Cypess AM. 2022. Reassessing human adipose tissue. *N Engl J Med* 386(8): 768-779. <https://doi.org/10.1056/nejmra2032804>
16. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. 2008. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 359(1): 61-73. <https://doi.org/10.1056/NEJMra0708473>
17. Phillips DIW, Goulden P, Syddall HE, Sayer AA, Dennison EM, et al. 2005. Fetal and infant growth and glucose tolerance in the Hertfordshire cohort study: a study of men and women born between 1931 and 1939. *Diabetes* 54(Suppl 2): S145-S150. [https://doi.org/10.2337/diabetes.54.suppl\\_2.s145](https://doi.org/10.2337/diabetes.54.suppl_2.s145)
18. Jones A, Godfrey KM, Wood P, Osmond C, Goulden P, et al. 2006. Fetal growth and the adrenocortical response to psychological stress. *J Clin Endocrinol Metab* 91(5): 1868-1871. <https://doi.org/10.1210/jc.2005-2077>
19. McElfish PA, Bridges MD, Hudson JS, Purvis RS, Bursac Z, et al. 2015. Family model of diabetes education with a Pacific Islander community. *Diabetes Educ* 41(6): 706-715. <https://doi.org/10.1177/0145721715606806>
20. McElfish PA, Long CR, Kohler PO, Yearly KHK, Bursac Z, et al. 2019. Comparative effectiveness and maintenance of diabetes self-management education interventions for Marshallese patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 42(5): 849-858. <https://doi.org/10.2337/dc18-1985>
21. McKeigue PM, Shah B, Marmot MG. 1991. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 337(8738): 382-386. [https://doi.org/10.1016/0140-6736\(91\)91164-p](https://doi.org/10.1016/0140-6736(91)91164-p)
22. Yajnik CS, Fall CHD, Coyaji KJ, Hirve SS, Rao S, et al. 2003. Neonatal anthropometry: the thin-fat Indian baby. the Pune maternal nutrition study. *Int J Obes Relat Metab Disord* 27(2): 173-180. <https://doi.org/10.1038/sj.ijo.802219>
23. Siddiqui MK, Anjana RM, Dawed AY, Martoeau C, Srinivasan S, et al. 2022. Young-onset diabetes in Asian Indians is associated with lower measured and genetically determined beta cell function. *Diabetologia* 65(6): 973-983. <https://doi.org/10.1007/s00125-022-05671-z>
24. Anjana RM, Baskar V, Nair ATN, Jebarani S, Siddiqui MK, et al. 2020. Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study. *BMJ Open Diabetes Res Care* 8(1): 1-8. <https://doi.org/10.1136/bmjdr-2020-001506>
25. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, et al. 2023. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 389(24): 2221-2232. <https://doi.org/10.1056/nejmoa2307563>
26. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. 2021. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. *Lancet* 398(10296): 262-276. [https://doi.org/10.1016/s0140-6736\(21\)00536-5](https://doi.org/10.1016/s0140-6736(21)00536-5)
27. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, et al. 2015. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 373(22): 2117-2128. <https://doi.org/10.1056/nejmoa1504720>
28. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, et al. 2019. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 381(21): 1995-2008. <https://doi.org/10.1056/NEJMoa1911303>
29. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, et al. 2019. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 380(24): 2295-2306. <https://doi.org/10.1056/nejmoa1811744>
30. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, et al. 2020. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 383(15): 1436-1446. <https://doi.org/10.1056/NEJMoa2024816>
31. Rhee NA, Vilsbøll T, Knop FK. 2012. Current evidence for a role of GLP-1 in Roux-en-Y gastric bypass-induced remission of type 2 diabetes. *Diabetes Obes Metab* 14(4): 291-298. <https://doi.org/10.1111/j.1463-1326.2011.01505.x>
32. Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, et al. 2018. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 6(5): 361-369. [https://doi.org/10.1016/s2213-8587\(18\)30051-2](https://doi.org/10.1016/s2213-8587(18)30051-2)
33. Zaharia OP, Strassburger K, Strom A, Bönhof GJ, Karusheva Y, et al. 2019. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol* 7(9): 684-694. [https://doi.org/10.1016/s2213-8587\(19\)30187-1](https://doi.org/10.1016/s2213-8587(19)30187-1)
34. Dennis JM, Shields BM, Henley WE, Jones AG, Hattersley AT. 2019. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol* 7(6): 442-451. [https://doi.org/10.1016/s2213-8587\(19\)30087-7](https://doi.org/10.1016/s2213-8587(19)30087-7)
35. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. 2000. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *J Appl Physiol* 89(1): 104-110. <https://doi.org/10.1152/jappl.2000.89.1.104>
36. Kotronen A, Yki-Järvinen H. 2008. Fatty liver: a novel component of the metabolic syndrome. *Arterioscler Thromb Vasc Biol* 28(1): 27-38. <https://doi.org/10.1161/atvbaha.107.147538>
37. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, et al. 2023. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 79(6): 1542-1556. <https://doi.org/10.1016/j.jhep.2023.06.003>
38. American Diabetes Association Professional Practice Committee for Diabetes. 2026. 4. comprehensive medical evaluation and assessment of comorbidities: standards of care in diabetes-2026. *Diabetes Care* 49(Suppl 1): S61-S88. <https://doi.org/10.2337/dc26-s004>
39. Sharma AM, Kushner RF. 2009. A proposed clinical staging system for obesity. *Int J Obes (Lond)* 33(3): 289-295. <https://doi.org/10.1038/ijo.2009.2>