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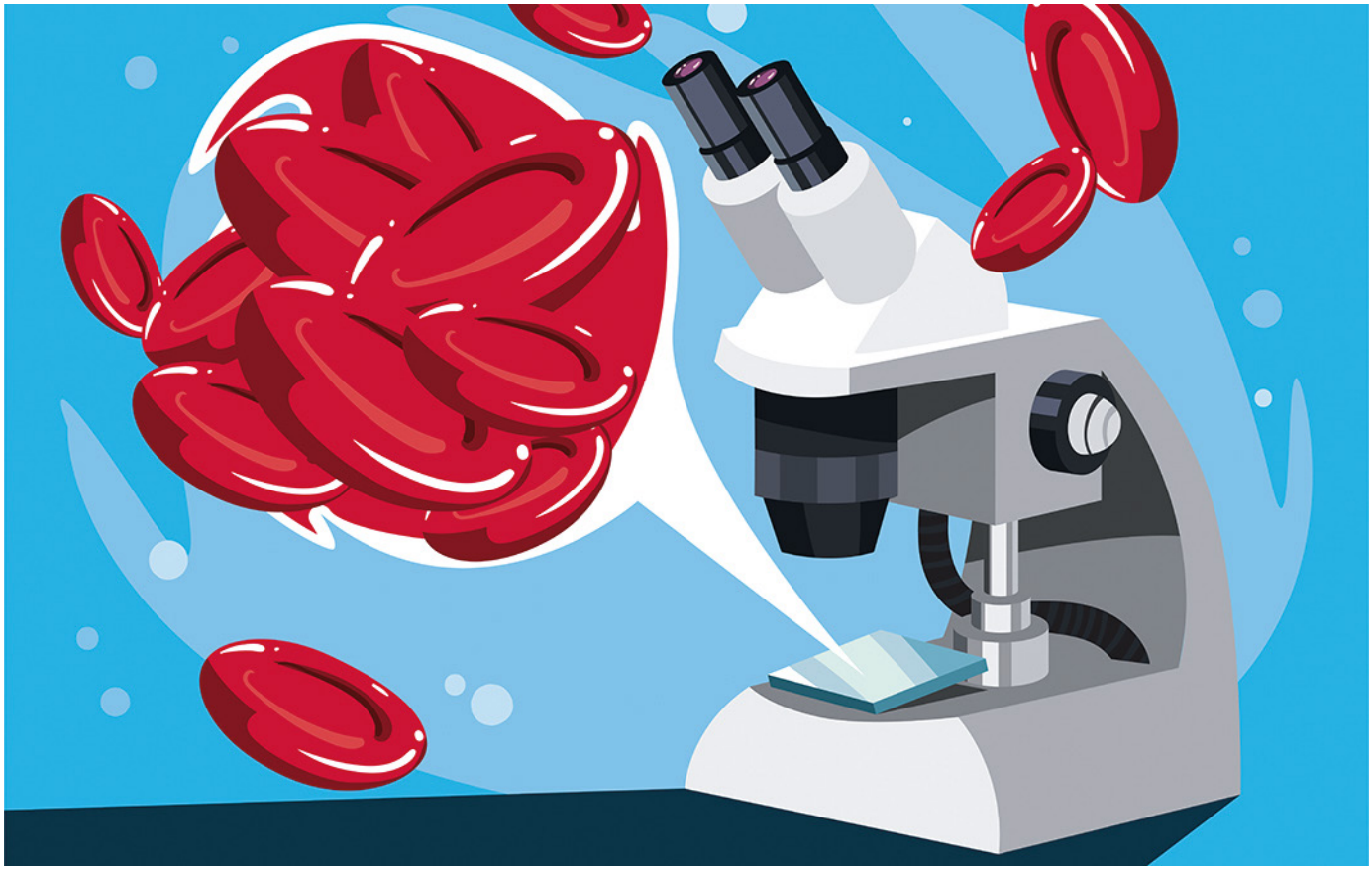


Metabolic phenotyping and personalized therapy in type 2 diabetes:

an approach beyond HbA1c

For decades, the management of type 2 diabetes mellitus (T2DM) has focused almost exclusively on a single parameter: glycated hemoglobin, or HbA1c. This marker, which reflects average blood glucose levels over the preceding 2 to 3 months, has been the cornerstone of diagnosis, follow-up, and therapeutic targets. However, clinical practice and the growing body of scientific evidence increasingly show that T2DM is not a uniform disease but rather a complex and heterogeneous metabolic syndrome with multiple phenotypes.

Two people with diabetes may have the same HbA1c and yet have completely different pathophysiological mechanisms, risks of complications, and treatment requirements. This has driven the development of the concept of **metabolic phenotyping:** the identification of clinical subtypes within T2DM that allow both diagnosis and treatment to be personalized.

In this article, we explore why HbA1c, although necessary, is not sufficient, and which additional factors should be incorporated into the follow-up of people with diabetes: obesity and dysfunctional visceral adiposity, metabolic fatty liver disease, pancreatic steatosis, and renal function assessed through albuminuria and glomerular filtration rate.

THE HETEROGENEITY OF T2DM: NOT ALL DIABETES IS THE SAME

The traditional classification of diabetes into type 1 and type 2 is overly simplistic. In 2020, researcher Emma Ahlqvist and her team at the Diabetes Center of Lund University (Sweden) published a study that changed the way this disease is understood. Using simple clinical data—such as age at onset, body mass index (BMI), HbA1c, pancreatic secretory function, and insulin resistance—they identified **5 distinct subtypes of adult-onset diabetes** with markedly different prognoses and risks of complications (1).

Although the exact proportion of each subtype varies according to the population studied, analyses of European and Asian cohorts provide an approximate distribution that is clinically informative ***(Table 1)***. The most common subtype is mild age-related diabetes (MARD), which includes people with later disease onset and a relatively preserved metabolic profile and accounts for approximately 35%-40% of cases. This is followed by mild obesity-related diabetes (MOD), which includes younger people with substantial overweight and moderate insulin resistance and has an approximate prevalence of 20%-25%. Severe insulin-resistant diabetes (SIRD) accounts for approximately 15%-20% of cases and is associated with the highest risk of kidney disease and fatty liver disease. Severe insulin-deficient diabetes (SIDD, ~6%-10%) and severe autoimmune diabetes (SAID, ~5%-8%) account for smaller proportions but have specific therapeutic implications.

The relevance of this model lies not only in the classification per se but also in its practical implications. People with the subtype characterized by the greatest insulin resistance (SIRD) have the highest risk of developing diabetic kidney disease and fatty liver disease, whereas those with the most severe insulin deficiency (SIDD) are at greater risk of retinopathy and neuropathy. Identifying each person's subtype may help guide treatment from the outset, anticipate complications, and individualize management (2).

OBESITY AND VISCERAL ADIPOSITY: WHEN FAT BECOMES A PROBLEM

Not all body fat is the same or has the same impact on health. Fat stored in subcutaneous tissue—beneath the skin—has a relatively benign behavior. **Visceral fat**, which accumulates around the internal abdominal organs, is of greater concern. When abdominal fat accumulates excessively, it begins to behave abnormally, **releasing free fatty acids and harmful proinflammatory factors**—such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and resistin—that interfere with insulin signaling in the liver, muscle, and pancreas, triggering insulin resistance and chronic low-grade inflammation (3).

This process, known as **lipotoxicity**, consists of lipid accumulation in tissues not designed to store them—including the liver, pancreas, muscle, heart, and kidneys—progressively impairing their function. This is precisely where visceral obesity takes on its most concerning cardiovascular dimension: dysfunctional visceral fat not only disrupts glucose metabolism but also independently increases the risk of myocardial infarction, stroke, heart failure, and cardiovascular »

SUBTYPE	MAIN FEATURE	APPROXIMATE %*	MAIN COMPLICATION	THERAPEUTIC APPROACH
SIDD	Very low insulin secretion, high HbA1c	~6-10%	Retinopathy, neuropathy	Early insulin intensification
Severe insulin deficiency	High insulin resistance, visceral obesity, fatty liver disease	~15-20%	Nephropathy, MASLD	SGLT2 inhibitors, GLP-1 RA/dual agonist, weight loss
MOD. Mild obesity-related diabetes	Obesity, moderate insulin resistance, early onset	~20-25%	Cardiovascular complications	Lifestyle modification, GLP-1 RA/dual agonist
MARD. Mild age-related diabetes	Late onset, relatively preserved metabolism	~35-40%	Variable, depending on comorbidities	Individualized, conservative approach
SAID. Severe autoimmune diabetes	GAD-positive, mild phenotype	~5-8%	Retinopathy	Close monitoring, insulin if progression occurs

TABLE 1. Adult-onset diabetes subtypes according to the Ahlqvist et al. model (adapted).
*Approximate percentages based on European and Asian cohorts; values may vary according to the population.

» death. It does so through multiple mechanisms: promoting atherogenic dyslipidemia (increased triglycerides and reduced HDL cholesterol), promoting hypertension, activating the renin-angiotensin system, and generating sustained vascular inflammation that damages the arterial wall (3).

In clinical practice, waist circumference is a simple, accessible, and highly informative measurement: a waist circumference > 88 cm in women and > 102 cm in men indicates increased abdominal adiposity and greater cardiometabolic risk. Management of T2DM cannot be based solely on glycemic control; it must comprehensively address reduction of visceral fat and the associated metabolic inflammation.

INCRETIN-BASED DRUGS: GLP-1 RECEPTOR AGONISTS AND DUAL GLP-1/GIP AGONISTS IN OBESITY-ASSOCIATED T2DM

The combination of T2DM and obesity has found a particularly relevant therapeutic option in incretin-based drugs, specifically glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GLP-1/GIP agonists. These drugs mimic the action of intestinal hormones released after food intake, stimulating glucose-dependent insulin secretion, reducing appetite, and promoting clinically significant weight loss. Unlike other glucose-lowering drugs, they act simultaneously on glycemic control and body weight.

Clinical trials from the SUSTAIN program (once-weekly semaglutide, a GLP-1 RA) demonstrated consistent HbA1c reductions of 1.5-1.8 percentage points, weight loss of 3-5 kg, and—most importantly—a significant reduction in major cardiovascular events (myocardial infarction, stroke, and cardiovascular death) »

» in people with high-risk T2DM. In the SUSTAIN-6 trial, semaglutide reduced the risk of major cardiovascular events by 26% compared with the control group (HR, 0.74) (8).

Trials from the SURPASS program (once-weekly tirzepatide, a dual GLP-1/GIP agonist) went a step further: tirzepatide demonstrated superior glycemic and weight-lowering efficacy compared directly with semaglutide in SURPASS-2, with HbA1c reductions of up to 2.3 percentage points and weight loss of up to 9.5 kg (9, 10). The proportion of participants achieving HbA1c levels < 5.7%—considered within the nondiabetic range—reached 52% with the highest dose in the SURPASS-1 study (9).

These results reinforce the importance of metabolic phenotyping: subtypes with a greater component of visceral obesity and insulin resistance (MOD and SIRD) are the most likely to benefit from these treatments. Early identification of these individuals and selection of treatments with dual glycemic and weight-lowering effects is already supported by robust scientific evidence and can be implemented in primary care.

THE LIVER AS A METABOLIC BAROMETER: HEPATIC STEATOSIS AND T2DM

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the accumulation of fat in the liver in the absence of significant alcohol consumption. It is estimated to affect almost 38% of the global adult population, with an even higher prevalence among people with T2DM, exceeding 60%-70% in some studies. This association is not coincidental: insulin resistance generated by visceral adiposity activates de novo lipogenesis in the liver, creating a vicious cycle that simultaneously worsens diabetes and hepatic steatosis (4).

MASLD is not an isolated liver disease; it is the hepatic sign of a systemic metabolic disorder that significantly increases the risk of cardiovascular disease, chronic kidney disease, and certain cancers. From a clinical standpoint, screening for fatty liver in people with T2DM should be part of routine assessment. Abdominal ultrasonography is a simple, noninvasive, and widely available diagnostic tool that enables early detection (4).

PANCREATIC STEATOSIS: THE PANCREAS ALSO ACCUMULATES FAT

A less widely recognized but increasingly relevant factor in the pathophysiology of T2DM is pancreatic steatosis, ie, fat accumulation within the pancreas. As in the liver, excess lipids in pancreatic tissue exert a direct lipotoxic effect on beta cells, which are responsible for insulin production, progressively impairing their secretory function (3).

Studies in people with overweight or obesity who develop T2DM have shown that reducing pancreatic fat through sustained lifestyle changes may be associated with partial recovery of insulin secretory capacity and may even lead to diabetes remission in some cases. This reinforces the concept that T2DM is not always irreversible and that identifying a phenotype characterized by pancreatic fat accumulation may have specific therapeutic implications.

RENAL FUNCTION: AN ESSENTIAL BAROMETER DURING FOLLOW-UP

Diabetes is the leading cause of chronic kidney disease worldwide. Kidney involvement affects more than one-third of people with T2DM and is one of the complications with the greatest impact on quality of life and mortality (5). Two key parameters are available for detecting kidney damage at its earliest stages:

- **Albuminuria:** the presence of albumin in the urine, indicating early glomerular damage. Detection of even small amounts (microalbuminuria) can predict renal deterioration years before it becomes apparent on other tests.
- **Estimated glomerular filtration rate (eGFR):** reflects the kidneys' overall filtration capacity and is calculated from serum creatinine, age, and sex. A progressive decrease indicates loss of renal function.

These parameters directly guide therapeutic decisions: sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) and GLP-1 »

A PERSON MAY HAVE AN APPARENTLY NORMAL WEIGHT AND YET ACCUMULATE SUFFICIENT VISCERAL FAT TO DEVELOP INSULIN RESISTANCE, CHRONIC INFLAMMATION, AND T2DM

NEW INCRETIN-BASED DRUGS (GLP-1 RECEPTOR AGONISTS AND DUAL GLP-1/GIP AGONISTS) REPRESENT A MAJOR THERAPEUTIC ADVANCE IN PEOPLE WITH OBESITY-ASSOCIATED T2DM, WITH DEMONSTRATED BENEFITS ON GLYCEMIA, BODY WEIGHT, AND CARDIOVASCULAR RISK

» RAs have demonstrated renoprotective effects independent of their glucose-lowering action, and their appropriate use depends in part on eGFR.[5] Albuminuria and eGFR provide complementary windows into the actual status of the kidneys and the progression of systemic metabolic disease.

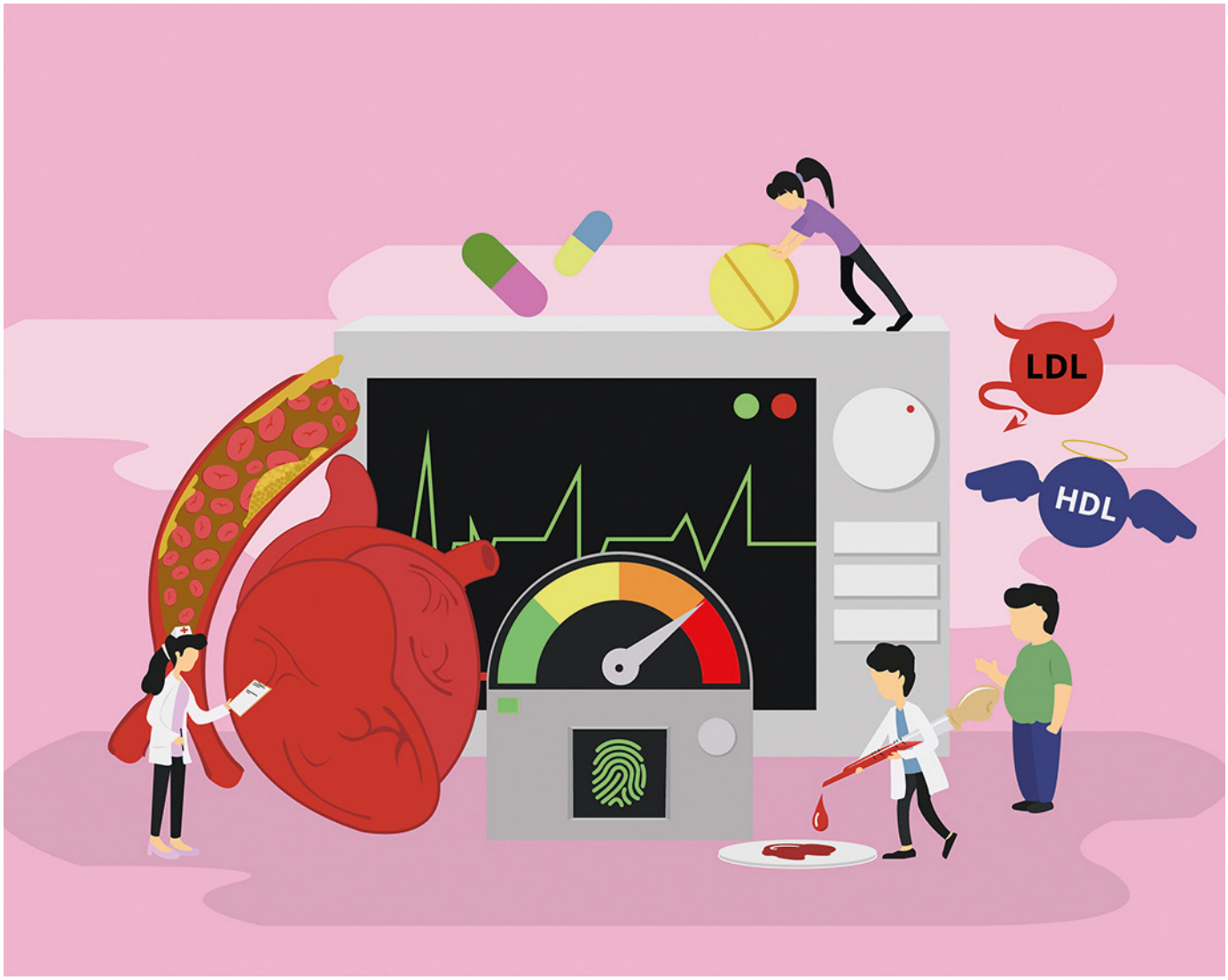
TOWARD A COMPREHENSIVE ASSESSMENT MODEL: BEYOND HBA1C

Integrating metabolic phenotyping into routine clinical practice does not require complex technologies or extraordinary resources. Rather, it involves broadening the clinical perspective and systematically collecting information that is already readily available to many health care professionals. A comprehensive assessment of people with T2DM should include, alongside HbA1c, waist circumference as an indicator of visceral adiposity; annual measurement of albuminuria and eGFR to monitor renal function; detection of fatty liver by ultrasonography in the presence of overweight or marked insulin resistance; and assessment of the individual clinical phenotype to guide selection of the most appropriate pharmacological treatment, including newer incretin-based drugs when justified by the obesity and insulin-resistance profile.

Personalized therapy is not a future aspiration; it is a current necessity supported by scientific evidence and one that primary care professionals are in a position to implement for the benefit of people with diabetes. **D**

CONCLUSIONS

- T2DM is a heterogeneous disease; metabolic phenotyping makes it possible to identify clinical subtypes with different risks of complications and responses to treatment, enabling truly personalized care.
- Obesity and visceral adiposity behave abnormally by releasing harmful proinflammatory factors that promote insulin resistance and increase cardiovascular risk. Measurement of waist circumference is an essential clinical indicator.
- Hepatic steatosis and pancreatic steatosis are manifestations of systemic lipotoxicity closely associated with T2DM; their detection and treatment may favorably modify disease progression and may even facilitate remission.
- GLP-1 RAs and dual GLP-1/GIP agonists, supported by the SUSTAIN and SURPASS clinical programs, provide particularly relevant glycemic, weight-related, and cardiovascular benefits in people with T2DM associated with obesity and insulin resistance.
- Periodic measurement of albuminuria and eGFR is essential for detecting early kidney damage, guiding therapeutic decisions, and monitoring the overall progression of metabolic disease.



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