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INVITED REVIEW

# Insulin resistance in the 21st century: new takes on an old problem—2025 *Diabetes*, *Diabetes Care*, and *Diabetologia* Expert Forum

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## Abstract

Insulin resistance is a hallmark of type 2 diabetes and several other metabolic diseases. However, efforts to improve insulin resistance are hindered by the biological complexity inherent to insulin action, as well as conceptual and methodological limitations to date. In September 2025, the editors of *Diabetes*, *Diabetes Care* and *Diabetologia* convened an Expert Forum in advance of the 61st Annual Meeting of the European Association for the Study of Diabetes (EASD). Participants reviewed the latest research, clarified key concepts and recommended future research priorities. Their insights were presented at a symposium during the EASD meeting and are offered in more detail here. The authors challenge the historical view of insulin resistance as a single, uniform pathophysiological condition, describing it instead as a diverse and highly plastic set of adaptive, maladaptive, acute and chronic responses that manifest differently throughout the body, in numerous biological processes, within and among individuals, and under various physiological and environmental conditions. They describe existing methods of measuring whole-body and tissue-specific insulin resistance and offer a primer on the two main insulin signalling networks. Next, they review current therapeutic options, which offer mostly indirect effects on insulin resistance, and highlight promising strategies to inform the eventual development of true insulin-sensitising agents. The authors call for continued investigation of the complex factors accounting for variability in insulin resistance, as well as pathway-specific defects, with the ultimate goal of developing targeted and more effective therapies for type 2 diabetes and the broader spectrum of cardiometabolic complications and related comorbidities.

**Keywords** Carbohydrate metabolism · Glucose transport · Hormone receptors · Insulin action · Insulin sensitivity and resistance · Lipid metabolism · Protein metabolism · Review · Transcription factors

## Abbreviations

| | |
|---|---|
| Adipo-IR | Adipose insulin resistance index |
| CKD | Chronic kidney disease |
| CRF | Cardiorespiratory fitness |
| DAG | Diacylglycerol |
| EGP | Endogenous glucose production |
| eNOS | Endothelial NO synthase |
| GDR | Glucose disposal rate |
| GIP | glucose-dependent insulinotropic polypeptide |
| GLP-1 | Glucagon-like peptide 1 |
| GRADE | Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness trial |
| GWAS | Genome-wide association study |
| HEC | Hyperinsulinaemic–euglycaemic clamp |
| HIRI | Hepatic insulin resistance index |
| IGT | Impaired glucose tolerance |
| ISI | Insulin sensitivity index |
| Lipo-IR | Lipid-induced insulin resistance |
| KITT | Rate constant for plasma glucose disappearance during ITT |
| *M* value | Rate of whole-body glucose metabolism |
| MASLD | Metabolic dysfunction-associated steatotic liver disease |
| M/I ratio | Metabolised glucose divided by mean plasma insulin concentration |
| MRS | Magnetic resonance spectroscopy |

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Extended author information available on the last page of the article

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| | |
|---|---|
| OGIS | Oral glucose insulin sensitivity |
| PET | Positron emission tomography |
| PMOS | Polyendocrine metabolic ovarian syndrome |
| PPAR | Peroxisome proliferator-activated receptor |
| QUICKI | Quantitative insulin-sensitivity check index |
| SGLT2 | Sodium–glucose cotransporter 2 |
| SIRD | Severe insulin-resistant diabetes |
| Site-1 | Primary, high-affinity insulin receptor binding site |
| Site-2 | Secondary, lower-affinity insulin receptor binding site |
| V2F | Variant-to-function |

## Introduction

Insulin resistance can be a physiological adaptive phenomenon or a pathological characteristic of numerous chronic diseases, including type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD) and obesity. However, despite extensive investigation and its well-established clinical relevance, understanding insulin resistance remains challenging because of the biological complexity inherent to insulin action, as well as conceptual and methodological limitations. Rather than acting through a single pathway or within a single tissue to produce a uniform outcome, insulin has tissue-specific effects, which are dynamically and differently regulated. This complexity reflects the diverse biological actions of insulin across multiple organs and the context-dependent nature of insulin sensitivity, which varies according to numerous factors, such as nutritional status, physical activity, circadian rhythm, endocrine and metabolic interorgan crosstalk, and others [1–4]. In addition, baseline insulin sensitivity is likely influenced by genetic susceptibility, developmental programming and epigenetic mechanisms [5–7], which may contribute to inter-individual differences in the propensity to develop chronic insulin resistance across the life course. Consequently, fundamental questions remain regarding how insulin resistance develops, why it manifests differently across organs and among individuals, and how it contributes to downstream metabolic and cardiovascular complications.

In September 2025, the editors of *Diabetologia, Diabetes* and *Diabetes Care* convened an Expert Forum in advance of the 61st Annual Meeting of the EASD. Its purpose was to review the state of research on insulin resistance, clarify key concepts and definitions, and critically assess areas in which knowledge is limited or contested and ripe for further investigation. Drawing on evidence from molecular biology, physiology, clinical research and epidemiology, the authors aimed to develop a more integrated and precise framework for understanding insulin resistance. Insights from the forum were summarised in a symposium at the EASD meeting and are described in greater detail in this article. A central conclusion emerging from these discussions is that insulin resistance is best understood not as a single disease entity, but as a dynamic, multidimensional biological phenotype arising from interactions among genetic susceptibility, metabolic stress and tissue-specific adaptive and maladaptive responses.

This conceptual framework is summarised in Fig. 1. Insulin sensitivity changes continuously in response to physiological demands such as fasting, exercise, pregnancy, circadian rhythm and illness, enabling coordinated substrate partitioning across the body. Under these physiological conditions, transient reductions in insulin sensitivity represent adaptive and reversible components of metabolic flexibility rather than pathological dysfunction. In susceptible individuals, however, sustained positive energy balance, altered adipose tissue function, chronic inflammation, ectopic lipid accumulation, endocrine perturbations and other metabolic stressors may exceed adaptive capacity, promoting persistent insulin resistance. Over time, this persistent insulin resistance drives progressive dysfunction across multiple organs. Importantly, these processes do not develop uniformly but differ among tissues and affected signalling pathways, and respective biological responses, as well as among individuals. These differences underlie the considerable heterogeneity in metabolic phenotypes and disease trajectories. This perspective provides a conceptual framework for understanding the remarkable heterogeneity of insulin resistance and its contribution to cardiometabolic disease (Fig. 2). Throughout this review, we discuss these concepts, focusing on evidence in humans wherever possible and incorporating findings from preclinical models only where they provide important mechanistic insights into human insulin resistance.

## Overview of insulin resistance

### Definitions of insulin sensitivity and insulin resistance

Insulin has widespread metabolic and physiological effects in numerous tissues. However, regardless of the tissue or outcome studied, insulin sensitivity in general can be derived from the relationship between insulin dose or concentration and a defined response to insulin. As shown in Fig. 3, a shift of the dose/concentration–response curve to the right defines a reduction in insulin sensitivity, whereas a reduction in the maximal effect defines insulin responsiveness [8]. Indeed, insulin resistance, as observed in chronic metabolic diseases such as type 2 diabetes and, to a lesser extent, type 1 diabetes, results from both impaired insulin sensitivity and reduced responsiveness [9–11]. Fundamentally, insulin resistance is a quantitative measure describing how responsive a cell, tissue or whole organism is to the action of insulin.



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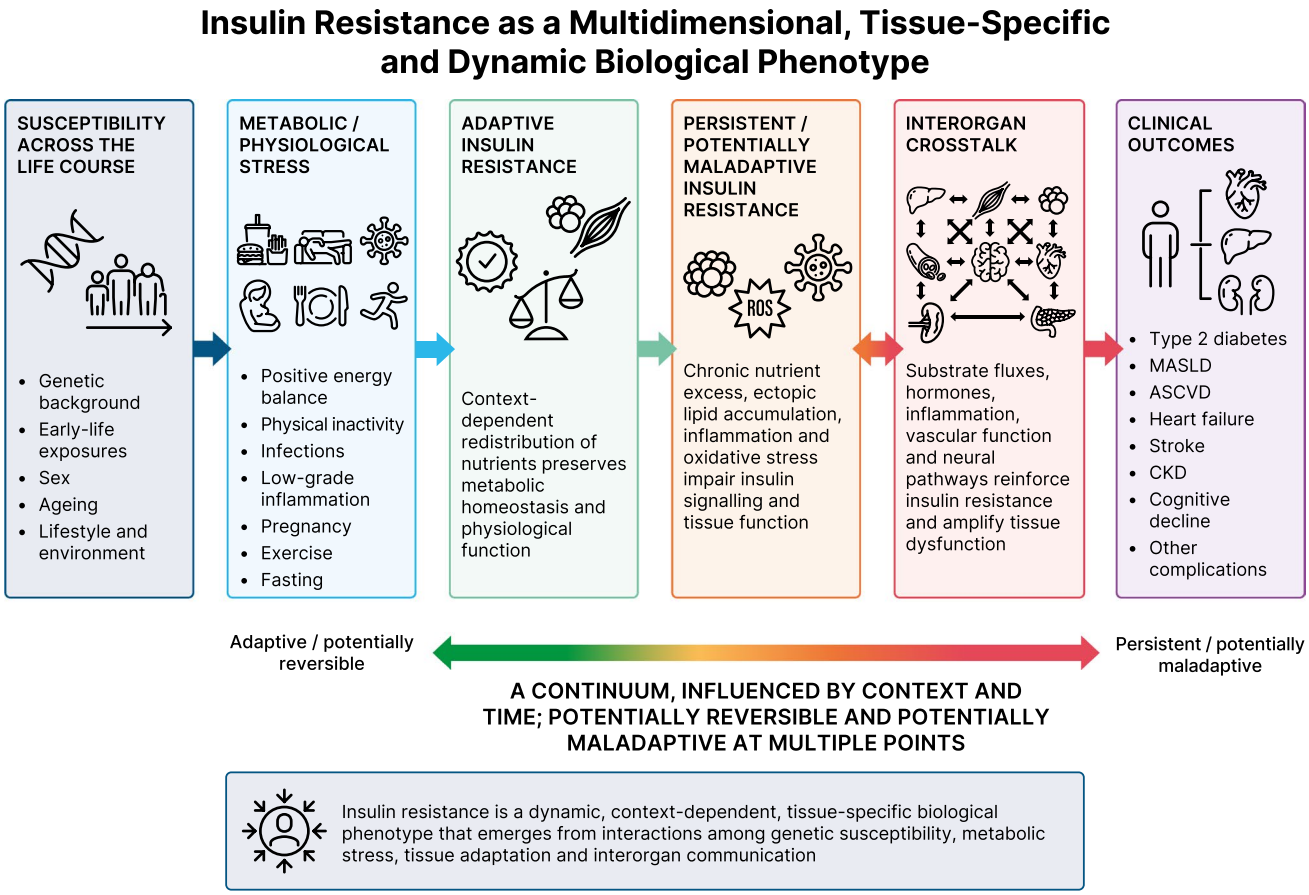


**Fig. 1** A working model of insulin resistance as a dynamic multidimensional biological phenotype. Insulin resistance is not a single disease entity, but rather arises from interactions among genetic susceptibility, metabolic and physiological stressors and tissue-specific adaptive and maladaptive responses. Insulin sensitivity changes continuously in response to physiological demands such as fasting, exercise, pregnancy, circadian rhythm and illness; under these conditions, transient reductions in insulin sensitivity represent adaptive, reversible components of metabolic flexibility that enable coordinated substrate partitioning rather than pathological dysfunction. In susceptible individuals, sustained positive energy balance, altered adipose tissue function, chronic inflammation, ectopic lipid accumulation, endocrine perturbations and other stressors may exceed this adaptive capacity, driving persistent, potentially maladaptive insulin resistance. Over time, interorgan crosstalk among liver, muscle, adipose tissue, heart, kidney, brain and pancreas reinforces and amplifies tissue dysfunction, which does not develop uniformly but varies by tissue, signalling pathway and individual, ultimately contributing to clinical outcomes, including type 2 diabetes, MASLD, atherosclerotic CVD (ASCVD), heart failure, stroke, CKD and cognitive decline. The gradient bar reflects this continuum, spanning from adaptive/reversible to persistent/maladaptive states. This figure is available as part of a downloadable slideset

In clinical practice and translational studies, insulin sensitivity is mostly assessed as a measure of a specific biological response to a given concentration of insulin. High insulin sensitivity indicates that relatively low concentrations of insulin are sufficient to produce the response in question, whereas low insulin sensitivity implies that higher insulin concentrations are required to achieve the same response (Fig. 3). Insulin resistance is defined as a reduced biological response to a given amount of insulin. Accordingly, the interpretation of insulin resistance depends on both the tissue and response examined and the method used to assess insulin action (discussed in more detail later).

Importantly, insulin resistance is a graded and context-dependent phenomenon that can vary within an individual by tissue, signalling pathway and biological readout. For example, insulin resistance in a key glucose-regulating tissue is likely to result in greater insulin action in other insulin-sensitive tissues. This, in part, reflects differing dose–response characteristics, in which modest global insulin resistance preferentially impairs insulin target tissues with low insulin sensitivity while sparing highly insulin-sensitive ones. As a result, in any individual, one tissue can be classified as insulin resistant, whereas another tissue may be highly insulin sensitive.

## Complexity of insulin resistance

The term insulin resistance is most commonly used in relation to the outcome of glucose metabolism and therefore has



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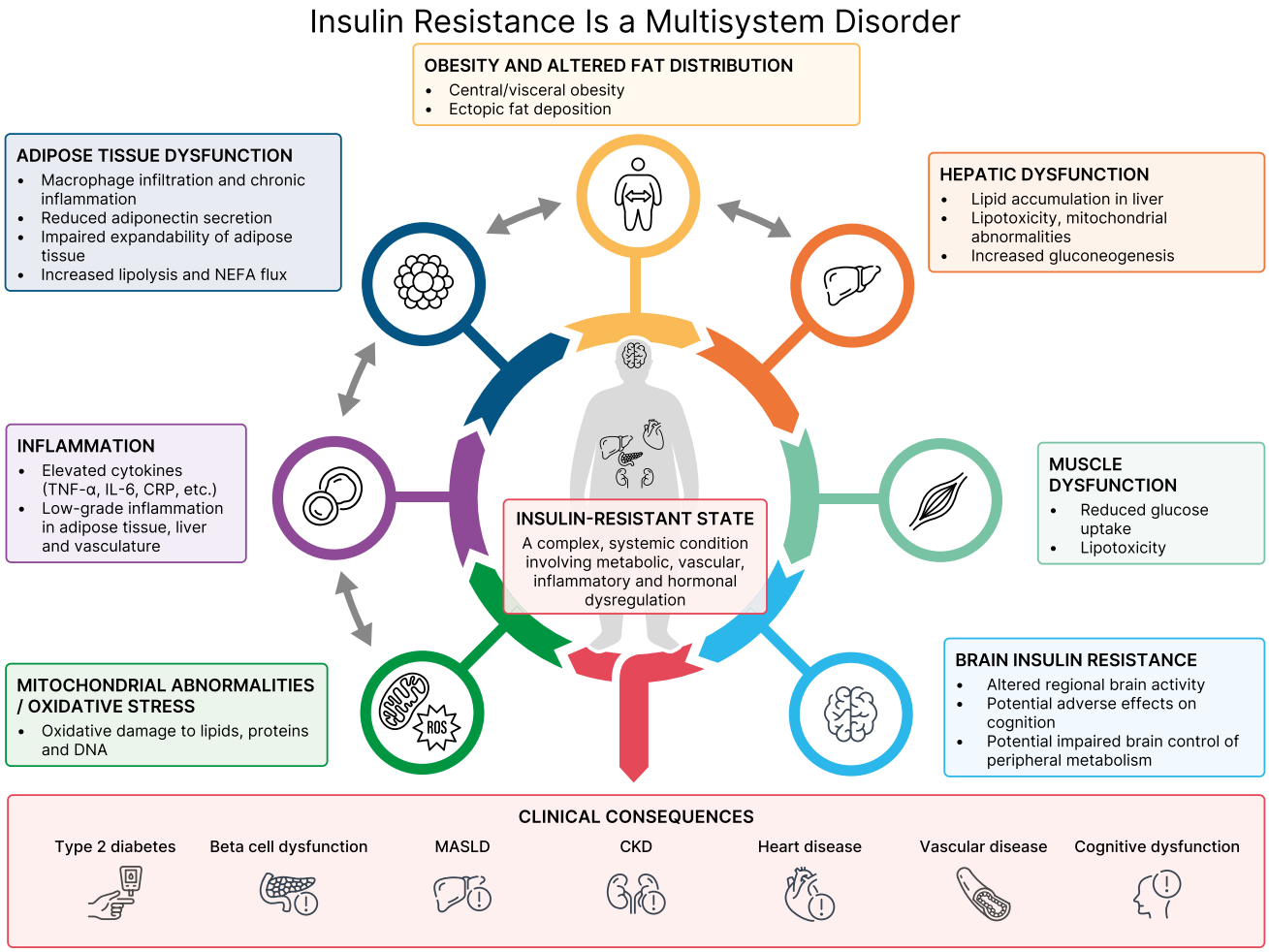


**Fig. 2** The insulin-resistant state is a systemic disorder. Insulin resistance is a complex condition characterised by impaired insulin signalling in different organs, including the liver, muscle and adipose tissue, leading to reduced glucose uptake, increased hepatic glucose production and metabolic dysfunction. It is closely associated with adipose tissue dysfunction, ectopic fat deposition, hepatic steatosis, lipotoxicity, oxidative stress, chronic low-grade inflammation, endothelial dysfunction, obesity with altered fat distribution, and dysfunction of other organs, including the brain, pancreas and vasculature. Together, these interconnected abnormalities contribute to the development and progression of type 2 diabetes, MASLD and CVD. CRP, C-reactive protein. This figure is available as part of a downloadable slideset

often been conceptualised as a single, uniform defect and commonly inferred from elevated fasting glucose or insulin levels. However, this oversimplified view masks important complexity. As will be discussed in detail below, insulin sensitivity differs substantially among tissues such as the liver, skeletal muscle (hereafter referred to simply as muscle), adipose tissue, kidney, brain and heart, as well as among specific biological processes, including glucose uptake, suppression of hepatic glucose production or lipolysis, lipogenesis, protein synthesis and cell growth [11–22]. In addition, insulin sensitivity is not static but rather varies throughout the day and is continuously modulated by physiological states such as nutritional status, physical activity, pregnancy, illness and disease progression, as well as environmental factors [1, 3, 23–29]. Consequently, the term 'insulin resistance' often encompasses a diverse set of adaptive, maladaptive, transient and chronic responses rather than a single, well-defined pathophysiological condition.

Furthermore, a single cell, tissue or organism often exhibits multiple responses to insulin, and these responses do not necessarily share the same sensitivity. For example, in the liver, the ability of insulin to suppress fasting endogenous glucose production (EGP) is impaired in individuals with MASLD, while the dose–response for insulin–EGP is similar but shifted to the right [16, 30]; at the same time, the capacity to stimulate fat oxidation or de novo lipogenesis in



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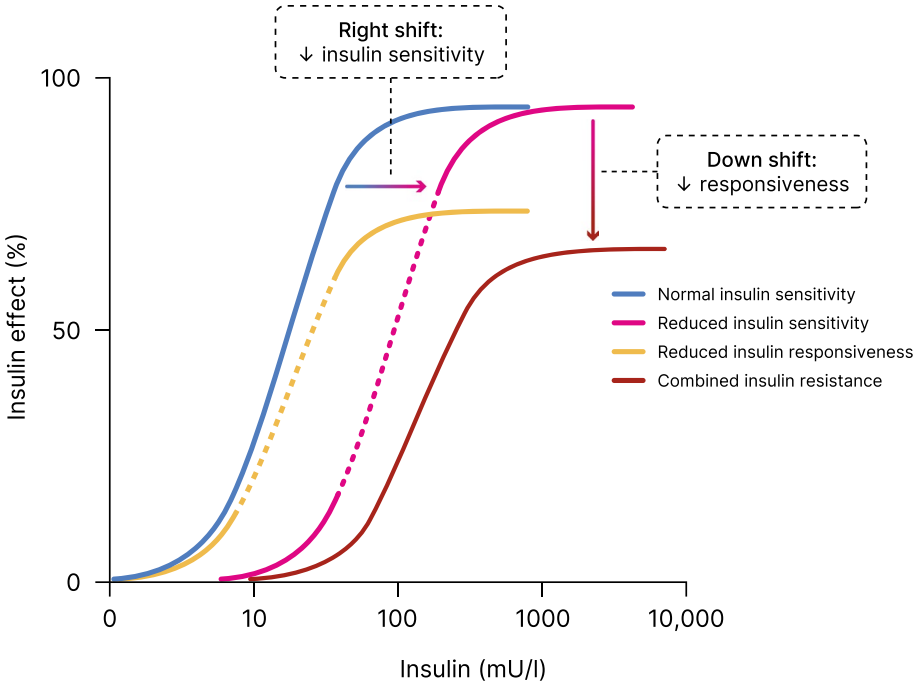


**Fig. 3** Model of concentration-dependent effects of insulin. The *x*-axis shows the insulin concentration and the *y*-axis shows the target-tissue-specific effect expressed as a percentage of the maximum effect under physiological insulin-sensitive conditions (blue line). A shift of the dose/concentration–response curve to the right defines a reduction in insulin sensitivity per se (pink line), whereas a reduction in the maximal effect defines insulin responsiveness (yellow line). Depending on the effect and tissue examined, common insulin resistance, as in obesity or type 2 diabetes, mostly comprises both abnormalities (brown line). Based on [8], adapted from a figure originally published in [379], with permission from Elsevier. This figure is available as part of a downloadable slideset

hepatocytes remains relatively preserved in those individuals [30–33]. This phenomenon sometimes has been referred to as 'selective insulin resistance' but it may result from differences in metabolic fluxes unrelated to insulin signalling, further complicating the understanding of insulin resistance.

It is important to distinguish the normal, temporary and reversible variability in insulin sensitivity from the progressive, persistent impairment of insulin sensitivity that defines chronic insulin resistance. Chronic insulin resistance is characterised by sustained alterations in tissue responses to insulin and compensatory hyperinsulinaemia (e.g. in obesity and type 2 diabetes). Over time, these changes can exceed adaptive capacity and contribute to dysfunction across multiple organ systems [34, 35], as discussed in greater detail below. Hence, insulin resistance is best viewed as a multidimensional biological phenotype that varies across tissues, signalling pathways, metabolic processes and physiological contexts, rather than as a single pathological entity. These observations illustrate that insulin resistance is not a uniform defect but rather a dynamic, tissue-specific biological phenotype shaped by metabolic context and interorgan communication (Fig. 1).

## Measurement of insulin resistance

Because insulin resistance is not a singular defect, but rather a context-dependent and highly variable attenuation of the biological actions of insulin, quantifying insulin resistance requires explicit definition of the organ under study, the (mainly metabolic) outcome, the prevailing insulin exposure and the characteristics of the population examined. Most established in vivo methods are centred on glucose metabolism and therefore provide limited information on other biologically relevant actions of insulin, including effects on lipid and protein metabolism.

### Assessment of whole-body insulin sensitivity

Although insulin action can be assessed for different effects of insulin (e.g. on glucose, lipid or protein metabolism), most current approaches to the measurement of whole-body insulin sensitivity in vivo are based on quantification of the effect of defined or prevailing insulin concentrations on a metabolic action of insulin, mainly on glucose uptake and/or production. Simple tests rely on the relationship between



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circulating glucose and insulin/C-peptide or circulating triglycerides, HDL-cholesterol, or combinations thereof, in the fasted state. Homeostasis model assessments such as HOMA-IR or the quantitative insulin-sensitivity check index (QUICKI) have been used frequently [36, 37] but rely on adequate insulin secretion and are therefore less reliable in conditions of fasting hyperglycaemia due to insufficient insulin secretion [36, 37]. Nevertheless, HOMA-IR performs well in recent-onset overt diabetes and its phenomic subtypes [38–40]. Indices from dynamic tests, such as the insulin sensitivity index (SI), glucose effectiveness (SG) from frequently sampled IVGTTs, rate constant for plasma glucose disappearance during an ITT (KITT), oral glucose insulin sensitivity (OGIS) index [41, 42] and Stumvoll insulin sensitivity index (ISI) [43] from OGTTs, more resemble the pathophysiological effect of insulin on whole-body glucose metabolism. However, their interpretation differs by test type; IVGTT-derived indices are influenced by endogenous insulin secretion and insulin clearance, whereas OGTT-derived indices estimate peripheral insulin sensitivity from the dynamic glucose–insulin relationship and require consideration of the underlying model, glycaemic state and population studied. Insulin clearance itself may also be altered in diabetes and this can affect both fasting and postprandial insulin concentrations [44, 45].

Thus, despite its complexity and resource intensity, the hyperinsulinaemic–euglycaemic clamp (HEC) is the gold-standard method for quantifying insulin sensitivity in humans [8, 36, 37, 46]. Under steady-state hyperinsulinaemia, the glucose infusion rate required to maintain euglycaemia, corrected for the glucose space (i.e. the rate of whole-body glucose metabolism [*M* value]), provides an estimate of whole-body insulin-stimulated glucose disposal [46]. However, the *M* value depends on the predefined insulin dose and the glycaemic target (i.e. normoglycaemia/euglycaemia or isoglycaemia). Additionally, its interpretation depends critically on insulin clearance, which can substantially influence the achieved steady-state insulin concentrations, the degree of suppression of EGP (predominantly of hepatic origin) and the method used to normalise glucose disposal for body size [47]. Only when EGP is completely suppressed will the *M* value provide an accurate measure of the peripheral glucose disposal rate (GDR) (mainly in muscle) because residual EGP contributes to circulating glucose and is not accounted for by the exogenous glucose infusion rate alone. However, residual EGP can be quantified only through the use of labelled glucose tracers and in their absence the *M* value may underestimate total insulin-stimulated glucose uptake [12, 36, 37]. Although *M* values and GDRs are commonly expressed relative to body weight, normalisation to lean (fat-free) body mass is generally more appropriate because insulin-stimulated glucose uptake occurs predominantly in muscle, and individuals with obesity may have a disproportionately lower muscle mass relative to body weight [48]. Therefore, when comparing insulin sensitivity across heterogeneous cohorts, the *M* value is preferably expressed per unit of lean body mass and normalised to the achieved steady-state plasma insulin concentration (I), a calculation known as the M/I ratio (metabolised glucose divided by mean plasma insulin concentration).

The surrogate indices derived from fasting or OGTT measurements correlate, but only moderately, with HEC-derived measures and these correlations may vary with the experimental setup, HEC protocol, glycaemic state and population studied [45, 49, 50]. This context dependence is illustrated by pregnancy, during which commonly used glucose- and insulin-based OGTT indices may fail to fully capture the expected reduction in insulin sensitivity, whereas incorporation of NEFA measurements can improve estimation in this physiological state [51]. Therefore, surrogate indices require careful interpretation, and the methodological choice fundamentally influences the biological inference drawn. In a meta-analysis of commonly used OGTT-based surrogate measures [50], OGIS showed a pooled correlation of $r$=0.70 with the HEC, whereas both the Matsuda index and the Stumvoll ISI showed pooled correlations of $r$=0.67. Fasting surrogate indices generally performed less well, including QUICKI ($r$=0.61), log HOMA-IR ($r$=−0.60) and HOMA-S ($r$=0.57). These pooled estimates were derived from heterogeneous populations, including healthy individuals and people with obesity and diabetes, and should therefore be interpreted as general performance estimates rather than universally applicable values. Thus, fasting and OGTT-derived indices can be useful for large-scale studies and also for repeated assessments where HEC studies are not feasible, but they should not be interpreted as direct or tissue-specific measurements of insulin action.

### Clinical implications

In routine clinical practice, insulin resistance is generally inferred from the overall metabolic phenotype rather than measured directly. Clinical features such as acanthosis nigricans, visceral adiposity, hypertriglyceridaemia, low HDL-cholesterol, MASLD, polycystic ovary syndrome (recently proposed to be renamed polyendocrine metabolic ovarian syndrome [PMOS]) or unexpectedly high insulin requirements may suggest impaired insulin action, although none is specific. Among laboratory surrogate indices, HOMA-IR is the most widely used because it requires only fasting glucose and insulin concentrations; however, it remains an indirect estimate whose interpretation depends on endogenous insulin secretion, insulin clearance, assay characteristics, glycaemic state and population context [36, 39, 52].

For routine clinical practice, measuring C-peptide may offer advantages over insulin quantification. It is secreted



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equimolarly with endogenous insulin, undergoes negligible first-pass hepatic extraction, has a longer plasma half-life and can be used to assess endogenous secretion in individuals receiving exogenous insulin [53]. HOMA2-IR (https://www.rdm.ox.ac.uk/about/our-facilities-and-units/DTU/software/homa) can be calculated using either fasting insulin or fasting C-peptide concentrations. However, C-peptide concentrations are strongly influenced by renal function, and substantial between-assay variability currently still limits the transferability of thresholds and results across laboratories [54, 55]. Accordingly, indices based on insulin and C-peptide must always be interpreted together with the clinical phenotype and should complement, rather than replace, clinical judgement when assessing insulin resistance in routine practice.

## Assessment of organ-specific insulin sensitivity

As discussed above, insulin has tissue-specific actions, and insulin resistance can appear differently in different tissues (Table 1, Fig. 2). Because whole-body measures of insulin sensitivity do not capture such differences, we discuss in the sections below the current methodologies available to assess tissue-specific insulin sensitivity.

### Muscle

The standard HEC provides the most direct quantification of peripheral (mainly muscle) insulin action on glucose disposal, particularly when glucose disposal is normalised to lean body mass using the M/I ratio [37]. Physiologically, insulin primarily promotes glucose transport, thereby facilitating intracellular glucose phosphorylation as well as glycogen synthesis and glucose oxidation [56–59].

During HEC studies, accurate assessment of muscle glucose uptake depends on achieving a stable steady-state insulin concentration sufficient to suppress EGP as completely as possible, so that muscle accounts for ~70–80% of insulin-stimulated glucose uptake from the circulation (i.e. whole-body GDR) [12, 56, 60]. Importantly, the insulin dose used influences the relative contribution made by muscle vs liver to whole-body glucose disposal. Lower insulin infusion rates may lead to lower hepatic glucose deposition as glycogen and to incomplete suppression of hepatic glucose production in individuals with marked insulin resistance [12, 37, 61]. The most frequently used insulin dose of 1 mU (kg body weight)$^{-1}$ min$^{-1}$ (~40 mU [m$^2$ body surface area]$^{-1}$ min$^{-1}$) allows for almost complete EGP suppression in insulin-sensitive individuals [12, 46] but not in severely insulin-resistant individuals, who will require insulin infusion rates up to 120 mU m$^{-2}$ min$^{-1}$ to overcome the impact of EGP on whole-body GDR assessments [47, 62].

In conditions of muscle insulin resistance, insulin-stimulated glucose uptake is reduced, contributing predominantly to postprandial hyperglycaemia [20, 63, 64]. However, although muscle is classically regarded as the major site of postprandial glucose disposal, tracer and arteriovenous balance studies indicate that only a fraction of ingested glucose is stored in muscle, with a substantial proportion being oxidised or released as glycolytic intermediates and significant uptake also occurring in splanchnic tissues. These findings highlight that the metabolic fate of glucose is distributed across multiple pathways and tissues rather than being dominated by muscle glycogen storage hyperglycaemia [64].

Although surrogate indices such as OGIS, the Matsuda index and HOMA-IR provide useful estimates of whole-body insulin sensitivity, they should not be interpreted as direct measures of muscle insulin action. Studies using non-invasive $^{13}C/^{31}P$ magnetic resonance spectroscopy (MRS) allow for direct monitoring of muscle metabolism and have shown that individuals with type 2 diabetes have reduced insulin-stimulated glucose transport and phosphorylation, which can be increased with higher insulin doses, while muscle ATP synthase flux remains independently impaired [65]. Although the decreased insulin-mediated glucose disposal frequently and inversely correlates to intramyocellular lipid content (IMCL) in sedentary humans [66–69], accumulation of bioactive lipid intermediates, rather than neutral lipid storage, associates with inhibited muscle insulin signalling in humans [20, 70, 71]. Of note, this relationship is modified by physical fitness and exercise training [72–74], which may even protect against lipid-induced insulin resistance (Lipo-IR) [75, 76].

Beyond glucose metabolism, insulin exerts anabolic effects in muscle by suppressing proteolysis and amino acid release during fasting and promoting amino acid uptake and protein synthesis in the postprandial state. In insulin-resistant muscle, increased proteolysis and impaired amino acid uptake favour elevation of circulating amino acids, which can serve as gluconeogenic substrates, thereby increasing hepatic glucose production and further exacerbating systemic insulin resistance [77, 78].

### Liver

Aside from various other metabolic effects, insulin suppresses EGP, which is mostly, but not exclusively, accounted for by the liver. Insulin-mediated suppression of hepatic glucose production results not only from direct effects (inhibition of gluconeogenesis and glycogenolysis; promotion of glycogen synthesis) but also from indirect effects (inhibition of release of NEFAs and glycerol from adipose tissue), which favour gluconeogenesis by allosteric regulation or, for glycerol, by serving as substrate [20, 79, 80]. Insulin also concurrently regulates hepatic lipid metabolism by



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**Table 1** Overview of tissue-specific insulin action and possible assessment of insulin resistance in humans

| Tissue | Physiological insulin action | Insulin resistance: key features | Assessment | | |
|---|---|---|---|---|---|
| | | | Direct methods | Proxies (often not tissue-specific) | Possible biomarkers (often indirect and not specific) |
| Muscle | Promotes glucose uptake (GLUT4), glycogen synthesis and glucose oxidation | Reduced insulin-stimulated glucose uptake, impaired GLUT4 translocation, lipid-induced signalling defects | HEC: *M* value, M/I; tracer-based glucose uptake; IVGTT: glucose effectiveness | OGTT-derived indices (e.g. Matsuda index, OGIS, Stumvoll ISI, KITT, fasting insulin) | Intramyocellular lipids (in non-trained individuals), DAGs, ceramides |
| Liver | Suppresses EGP and regulates lipid metabolism (↑ lipogenesis, ↓ fatty acid oxidation) | Impaired suppression of glucose production with relatively preserved or increased lipogenesis, increased VLDL secretion | Low-dose HEC with isotopic tracers (EGP suppression), MRS-based flux measurements | HOMA-IR, HIRI | Liver fat (MRI/MRS), circulating triglycerides/VLDL |
| Adipose tissue | Suppresses lipolysis and promotes triglyceride storage and adipokine secretion | Increased lipolysis, elevated circulating NEFAs, ectopic lipid deposition, adipokine dysregulation | Clamp with NEFA suppression, tracer-based inhibition of lipolysis, microdialysis | Adipo-IR, Lipo-IR, fasting NEFAs | Circulating NEFAs, adiponectin, leptin, inflammatory cytokines |
| Brain | Modulates appetite, neuronal activity and central coordination of whole-body metabolism | Altered brain insulin signalling, impaired regulation of food intake, impaired modulation of whole-body metabolism, unhealthy body fat distribution, potential unfavourable impacts on cognition | Intranasal insulin with neuroimaging (functional MRI, PET) | Peripheral indices (limited validity) | Possibly epigenetic signatures [342]<br>Characteristics of extracellular vesicles |
| Vasculature | Stimulates NO production and promotes vasodilation | Impaired NO signalling, endothelial dysfunction, relative preservation of mitogenic signalling | Forearm plethysmography with insulin infusion | Flow-mediated dilation | NO metabolites, endothelin-1, inflammatory markers |
| Heart | Regulates substrate selection, favouring glucose use in the fed state | Shift toward fatty acid oxidation, increased oxygen demand, lipotoxicity | Fluorodeoxyglucose PET under insulin stimulation (HEC) | Systemic indices | Myocardial glucose uptake, lipid accumulation |
| Kidney | Regulates sodium handling and contributes to gluconeogenesis | Preserved sodium reabsorption, contribution to hypertension, altered renal metabolism | Limited (experimental tracer approaches) | Systemic indices | Albuminuria, markers of sodium handling, hyperfiltration/renal haemodynamic measures |

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suppressing fatty acid oxidation, stimulating lipogenesis and favouring lipid storage [81–83].

Hepatic insulin resistance manifests as impaired insulin-mediated suppression of EGP [12, 84], which is a principal determinant of fasting hyperglycaemia [80]. As discussed above, hepatic insulin resistance has classically been described as a form of selective insulin resistance in which impaired suppression of EGP coexists with relatively preserved or even enhanced lipogenesis [82, 85]. However, preserved lipogenesis does not necessarily indicate intact hepatic insulin signalling but may instead result from increased substrate delivery from adipose tissue when insulin-mediated suppression of lipolysis is impaired [20, 33, 81, 86]. Hepatic insulin resistance is often linked to adipose tissue insulin resistance, which is a feature of adipose tissue dysfunction, increases lipolysis and thereby elevates NEFA and glycerol fluxes toward the liver, promoting gluconeogenesis [20, 79–81]. Increased NEFA flux to the liver enhances synthesis of triglycerides and lipotoxic species, which impairs insulin-mediated suppression of EGP [87–89], particularly in the context of inadequate hepatic fatty acid oxidation [90]. These observations point to abnormal adipose tissue–liver crosstalk in insulin-resistant states, involving ambient insulin levels, substrate flux and hepatic glucose, lipid and energy metabolism.

Assessment of hepatic insulin sensitivity requires single low-dose or, even better, stepped (i.e. increasing low doses) insulin clamp protocols combined with isotopic tracer dilution ($^{3}$H-, $^{2}$H- or $^{13}$C-labelled glucose) to simultaneously assess for GDR and the rate of glucose appearance ($R_a$), with the latter allowing quantification of EGP [37]. Without tracer-determined EGP, interpretation of glucose infusion rates and *M* values may obscure hepatic contributions because they reflect integrated whole-body glucose metabolism rather than liver-specific insulin action. In insulin-resistant states where EGP may not be fully suppressed, the uncorrected *M* value may underestimate whole-body insulin sensitivity because residual EGP is not accounted for. Of note, HEC studies using low insulin doses, hyperglycaemic conditions or simultaneous exposure to insulin secretagogues (e.g. triglycerides, NEFAs or amino acids) can stimulate insulin secretion and, in turn, hepatic insulinisation [91–93]. Correct assessment of hepatic and peripheral insulin sensitivity therefore may require co-infusion of insulin and somatostatin to block endogenous insulin secretion, particularly in protocols in which endogenous insulin secretion may be stimulated.

HOMA-IR [39] and the fasting hepatic insulin resistance index (HIRI) [94] provide fasting surrogate estimates of hepatic insulin resistance based on basal insulin–glucose relationships, whereas the OGTT-derived HIRI [95] incorporates the early postprandial glucose and insulin responses during an OGTT and therefore better reflects the dynamic regulation of hepatic glucose production. Nevertheless, none of these indices directly quantifies insulin-mediated suppression of EGP; this requires tracer-based assessment during controlled insulin exposure [96].

Using istopically labelled glucose, fasting hepatic insulin resistance can be quantified from the product of fasting EGP and fasting plasma insulin concentrations [12, 95, 97]. More detailed analysis of hepatic glucose fluxes became possible by non-invasive $^{13}$C/$^{31}$P MRS along with labelled glucose and/or $^{2}$H-labelled $H_2O$, which enables assessment of glycogen synthesis, glycogenolysis and gluconeogenesis as well as ATP synthesis. These studies, combined with ex vivo analyses of liver biopsies, directly identified the reduction in net glycogen synthesis, excess gluconeogenesis and impaired mitochondrial plasticity in insulin-resistant humans [98–100]. In addition, genome-scale metabolic models integrating transcriptomic and metabolomic data from liver biopsies have been used to estimate intracellular metabolic fluxes, with validation against tracer-based measurements [80].

### Adipose tissue

Although insulin also stimulates adipose tissue glucose uptake [60, 101], insulin action in adipose tissue is defined primarily by suppression of lipolysis (i.e. NEFA release) and promotion of lipid storage and NEFA re-esterification [12, 14, 83]. As described above, adipose tissue insulin resistance is characterised by inadequate suppression of lipolysis, resulting in elevated circulating NEFAs that contribute to hepatic gluconeogenesis, VLDL-cholesterol production, and ectopic lipid deposition in muscle and liver [81, 97, 102]. Because impaired suppression of adipose tissue lipolysis can occur early in the development of systemic insulin resistance, adipose tissue insulin resistance may represent an important upstream contributor to hepatic and muscular metabolic dysfunction. Adipose tissue dysfunction not only comprises adipose tissue insulin resistance, but also has additional consequences such as imbalanced release of adipokines, which via interorgan crosstalk are believed to play a role in the development and progression of whole-body insulin resistance [4].

Adipose tissue insulin sensitivity can be assessed during low-dose or stepped clamp protocols from the suppression of plasma NEFA levels [12, 103, 104]. Alternatively, the adipose insulin resistance index (Adipo-IR) is calculated from the product of fasting concentrations of insulin and NEFAs and provides a useful surrogate of adipose tissue insulin resistance [26]. However, circulating NEFAs are an imperfect estimate of lipolysis because they can be retained and re-esterified intracellularly to triglycerides or can be released to the plasma pool by lipase-mediated hydrolysis of VLDL triglycerides as NEFA spillover [105–107]. Thus,



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importantly, although plasma NEFAs largely reflect adipose tissue lipolysis in the fasting state, during the postprandial period a significant contribution arises from spillover of fatty acids derived from lipoprotein triglyceride hydrolysis, further limiting their utility as a direct marker of lipolytic flux [105–107]. A better measure of lipolysis is obtained by the rate of appearance of glycerol (using labelled glycerol) derived by adipocyte triglyceride hydrolysis [108], whereas insulin resistance can be estimated using Lipo-IR, which is the product of insulin and the rate of appearance of labelled glycerol instead of NEFAs [109]. Of note, the validity of these indices outside of their fasting time is limited because NEFA concentrations and lipolysis are influenced by circadian variation, recent food intake and overall metabolic context [83]. As with muscle and liver, dynamic assessments better reflect insulin action than fasting measures alone, especially in adipose tissue, where lipolysis is context dependent.

Circulating adipokines, especially adiponectin, might be used as a surrogate biomarker for systemic and tissue-specific insulin resistance. Adiponectin release is reduced in the presence of adipose tissue dysfunction, and its levels are positively correlated with insulin sensitivity measured by HEC, reflecting both peripheral (muscle) and hepatic insulin sensitivity [110]. Beyond its metabolic signalling, adiponectin is independently associated with better NO bioavailability and lower vascular oxidative stress, contributing to reduced endothelial inflammation by restoring endothelial NO synthase (eNOS) coupling. Interestingly, this relationship appears to be bidirectional; vascular oxidative stress itself upregulates adiponectin expression in perivascular adipose tissue through a peroxisome proliferator-activated receptor (PPAR)-γ-dependent mechanism [111]. Thus, monitoring changes in adiponectin levels provides an integrated estimate of both tissue-level insulin sensitivity and vascular risk, making it an endocrine marker at the intersection of metabolic restoration and cardiovascular protection.

The stimulatory effect of insulin on glucose uptake in adipocytes gives rise to glycerol 3-phosphate, which, as a substrate of triglyceride synthesis, also contributes to lipid metabolism in adipose tissue [14]. The contribution of adipose tissue to peripheral glucose uptake has been emphasised, but studies using positron emission tomography (PET) have shown that individuals with muscle and liver insulin resistance also display impaired glucose uptake in adipose tissue [60], and this can also be depot-specific [112].

The interdependence of adipose, hepatic, muscle and brain insulin action underscores the systemic nature of insulin resistance. Elevated NEFA flux links adipose dysfunction to hepatic and muscle impairments by promoting accumulation of lipotoxic compounds and release of hormones and cytokines, whereas altered brain-derived signals may further contribute to these peripheral processes, illustrating how tissue-specific defects converge into whole-body insulin resistance [13, 19, 20, 81, 113, 114].

### Non-classical tissues

**Brain** Insulin receptors are widely expressed throughout the central nervous system, and insulin is actively transported from the blood across the blood–brain barrier [115, 116]. In contrast to classical insulin-sensitive tissues such as muscle, brain glucose uptake is largely insulin independent [115]. Insulin primarily modulates neuronal activity, appetite regulation and the central coordination of whole-body metabolism [19] and plausibly also influences cognitive processes [115, 117]. Human evidence derives mainly from intranasal insulin interventions, which deliver insulin predominantly to the brain [118], and from neuroimaging studies demonstrating insulin-induced changes in regional brain activity [119], metabolic effects in the periphery after nasal insulin administration [19] and associations between peripheral insulin resistance and altered regional brain glucose metabolism [120, 121]. Brain-derived signals likely reach metabolic tissues in the periphery through the autonomic nervous system [114].

However, standardised clinical measures of brain insulin resistance are lacking, and peripheral indices such as HOMA-IR do not reliably reflect brain insulin signalling [122]. Thus, although brain insulin action is physiologically established and likely influences systemic metabolism, adiposity and body fat distribution [19], its clinical contribution and quantification in humans remain incompletely defined.

**Vasculature** In the vasculature, insulin regulates not only vascular tone but also the delivery of insulin and nutrients to metabolically active tissues. The vascular endothelium is therefore not merely a passive barrier between the circulation and insulin-responsive cells but rather an active component of insulin action in other tissues. In endothelial cells, insulin activates the PI3K–Akt pathway, leading to eNOS activation and NO production that results in vasodilation and recruitment of the muscle microvasculature. These responses increase tissue perfusion and the endothelial exchange surface available for insulin and glucose delivery and thereby contribute to insulin-stimulated glucose disposal [123–125].

Before reaching classical metabolic cells such as myocytes or adipocytes, insulin must cross the capillary endothelium. A concentration gradient between plasma and muscle interstitial fluid, together with the delayed metabolic response to circulating insulin, indicates that transendothelial transport can limit the rate of insulin action [126, 127]. Thus, insulin delivery to muscle depends on both



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microvascular recruitment and endothelial permeability. Experimental studies support regulated transendothelial transport that involves vesicular and caveolae-associated processes, although the relative contributions of receptor-dependent and receptor-independent pathways in humans remain unresolved [128, 129].

Vascular insulin resistance can therefore impair peripheral insulin action through complementary mechanisms. Reduced PI3K–Akt–eNOS signalling lowers NO bioavailability, limits vasodilation and microvascular recruitment, and may restrict insulin access to the tissue interstitium. In contrast, MAPK-dependent signalling is often relatively preserved, particularly in the presence of compensatory hyperinsulinaemia, favouring endothelin-1 production, adhesion-molecule expression, inflammation and vascular smooth-muscle cell growth, hence promoting atherosclerotic changes [130–132]. This pathway-selective model is useful but it should not be interpreted as an absolute separation between metabolic and mitogenic signalling because both pathways are interconnected and their effects depend on vascular cell type, insulin exposure and metabolic context. Thus, vascular insulin resistance may both amplify metabolic insulin resistance by limiting insulin delivery and directly contribute to endothelial dysfunction, arterial stiffness, hypertension and atherosclerosis.

Assessment of vascular insulin effects requires distinction between general endothelial function and vascular responses specifically induced by insulin. Flow-mediated dilation predominantly assesses shear-stress-induced, NO-dependent conduit artery function and is not insulin specific. Forearm plethysmography can quantify insulin-mediated changes in limb blood flow when combined with intra-arterial insulin administration or HEC, whereas contrast-enhanced ultrasound assesses insulin-induced microvascular recruitment [124, 125, 133]. Besides the achieved insulin concentrations, these measurements are influenced by BP, sympathetic tone, glucose level, circulating substrates and (subclinical) inflammation. Accordingly, impaired flow-mediated dilation or reduced basal blood flow alone should not be equated with vascular insulin resistance.

**Heart** Cardiac insulin signalling regulates substrate selection, favouring glucose use in the postprandial state [134]. In cardiac insulin resistance, myocardial metabolism shifts toward increased fatty acid oxidation [134, 135], potentially increasing oxygen demand and contributing to lipotoxic processes and ultimately diastolic dysfunction [135]. Cardiac insulin resistance has also been linked to coronary artery disease, mediated by lipotoxicity [136, 137]. Assessment of myocardial insulin sensitivity is largely restricted to research settings using PET [138, 139], and no established heart-specific proxies exist. Consequently, clinical inference primarily relies on systemic indices rather than direct measurement.

**Kidney** Beyond its systemic effects, insulin modulates renal sodium handling, glomerular haemodynamics and gluconeogenesis [131, 140] in multiple cell types, including podocytes, mesangial cells and tubular epithelial cells [131, 140]. Disruption of these pathways contributes to albuminuria, hyperfiltration and progressive kidney injury. Insulin resistance is common in chronic kidney disease (CKD) and associates with hypertension and increased cardiovascular risk [17]. The metabolic effects of insulin may be selectively impaired, whereas its stimulatory effects on tubular sodium reabsorption can be relatively preserved [131, 140], contributing to salt-sensitive hypertension [141] and volume expansion.

Direct quantification of renal insulin sensitivity in humans remains limited [17]. Current measures of insulin-mediated renal glucose metabolism are derived from older arteriovenous catheterisation/tracer studies and a more recent [$^{18}$F] fludeoxyglucose PET approach [142]. This study estimated that hyperinsulinaemia increased total and cortical renal glucose uptake by approximately 84% and 73%, respectively, whereas insulin-stimulated renal glucose uptake was reduced in individuals with obesity. Hence, clinical interpretation still relies largely on systemic indices and clinical correlates rather than validated kidney-specific measures.

## Tissue-specific differences: mechanisms and manifestation

From the discussion above, it is evident that insulin resistance manifests differently across tissues because each tissue plays a distinct metabolic role (Fig. 2). Muscle, responsible for most glucose uptake after meals, becomes insulin resistant mainly as a result of lipid-induced defects in insulin signalling and impaired GLUT4 translocation [15]. In contrast, the liver and adipose tissue have their greatest impact during the fasted state, when hepatic insulin resistance, driven by inflammation, fat accumulation and endoplasmic reticulum stress, prevents insulin from suppressing gluconeogenesis [80]. Insulin resistance in adipose tissue primarily impairs the ability of insulin to inhibit lipolysis, raising circulating NEFAs that worsen whole-body metabolic dysfunction and promote lipotoxicity and insulin resistance in other tissues [26, 80]. These defects arise in part from the accumulation of lipid intermediates (e.g. diacylglycerols [DAGs] and ceramides) and compromise postprandial glucose disposal [71, 143, 144]. Moreover, different fat depots show different degrees of insulin responsiveness. Visceral adipose tissue is intrinsically more lipolytic and more prone to inflammation than subcutaneous fat, making it more susceptible to insulin resistance and a stronger contributor to metabolic dysfunction [13, 97, 145]. It has also been shown that having increased visceral and liver fat is associated with insulin resistance in liver, muscle and adipose tissue [97, 146].



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Additional organs, including the heart, brain, vasculature and endothelium, can also develop insulin resistance through oxidative stress, inflammation or mitochondrial abnormalities (Table 1). These varied mechanisms explain why insulin resistance does not occur uniformly but rather reflects each tissue's specific metabolic demands and vulnerabilities.

Priorities for future research into the measurement of insulin resistance are summarised in the text box.

### Future research priorities: measurement of insulin resistance

- Further standardise current protocols for clamp tests, OGTT evaluation and mixed-meal tests.
- Develop minimally invasive, validated methods to assess tissue-specific insulin sensitivity, and also insulin sensitivity in non-classical organs, for use in epidemiological cohorts and clinical trials.
- Develop a consensus definition and measurement approaches for insulin resistance in non-classical tissues.
- Standardise insulin clearance assessments and incorporate insulin clearance into phenotyping.
- Integrate tracer-based assessments incorporating imaging and multiomics approaches to assess insulin actions beyond glucose metabolism, including alterations in lipid and amino acid metabolism and their tissue-specific regulation.
- Harmonise organ-selective surrogate indices with mechanistic measures across populations.

## Plasticity of insulin sensitivity and factors that induce change

Insulin sensitivity has profound interindividual variation, with high insulin sensitivity in exercise-trained healthy individuals [23, 75, 147] and severe insulin resistance in individuals with inadequately managed type 2 diabetes [26, 44, 148, 149]. However, there is also marked interindividual variation in insulin sensitivity among both young, healthy people [150] and people with recent-onset, well-managed type 2 diabetes [151]. Insulin sensitivity also varies within a single individual in response to nutritional status, environmental factors, diurnal fluctuations and periods of normal physiological stress such as pregnancy [1, 3, 24, 28, 115, 152], indicating that it can also be viewed as an adaptive response rather than a uniformly pathological state.

This dual nature is important to acknowledge: a transient, context-dependent insulin resistance (e.g. during fasting or in pregnancy) evidently serves a physiological purpose (e.g. redirecting glucose toward specific metabolic demands), whereas chronic insulin resistance, as observed in obesity and type 2 diabetes, appears to be an extension of this mechanism that becomes maladaptive when the underlying stressor is not resolved. Reconciling these two perspectives has direct implications for when and how insulin resistance should be targeted therapeutically.

### Acute plasticity of insulin sensitivity

Insulin sensitivity is higher in the morning than in the evening. This is especially apparent in hepatic insulin sensitivity, which is further decreased in people with MASLD [27], although this diurnal variation may be blunted in people with obesity and diabetes [153–155]. Diurnal variation in insulin sensitivity also becomes apparent when people undergo circadian misalignment, such as during shiftwork or when crossing time zones (i.e. when experiencing jet lag). Indeed, a 3.5 day misalignment protocol induced by a 12 h rapid shift of the behavioral cycle has been shown to result in a marked decrease in insulin sensitivity, mainly in muscle, as measured with the gold-standard HEC [156]. This rapid induction of insulin resistance is accompanied by changes in substrate metabolism, increased lipolysis, and hepatic de novo lipogenesis [27, 155] and favouring of PPAR-related fatty acid metabolism in muscle. This finding suggests that lipid fluxes play a role in diurnal variation in insulin sensitivity [156].

The high degree of plasticity is also apparent in the rapid effects of changes in nutritional status and physical activity on insulin sensitivity in humans, with fatty acid metabolism again being an important determinant. In the fed state, enhanced insulin sensitivity in key metabolic tissues facilitates glucose uptake and storage and suppresses the release of NEFAs from adipose tissue. However, during prolonged fasting, there is a reduction in insulin sensitivity in glucose-consuming tissues such as muscle. Indeed, acute fasting for up to 60 h rapidly increases insulin resistance by up to 50%, accompanied by a marked increase in circulating fatty acids and ectopic disposition of lipids in liver and muscle [157–160].



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The rapid induction of insulin resistance by fasting is thought to have evolutionary relevance. It allows humans to survive under conditions of food scarcity, when the body's limited glycogen stores in muscle must be spared for those tissues that depend on glucose for oxidation, such as the brain [161]. Switching to fatty acid metabolism by drawing on much larger bodily stores is an efficient survival strategy. These coordinated adjustments in insulin sensitivity represent adaptive regulation rather than pathological dysfunction. They are a core component of metabolic flexibility (i.e. the capacity of an organism to match fuel oxidation to fuel availability) [34, 35] and extend to other physiological states, including stress, illness (e.g. fever and dehydration), pregnancy and hormonal fluctuations.

However, not only the lack of food intake but also the macronutrient composition of the meal can acutely induce insulin resistance. It has been shown that a single high-energy, fat-rich meal can reduce whole-body and hepatic insulin sensitivity [162], again linking excessive fatty acid metabolism to acute insulin resistance. Lipid infusion resulting in supraphysiological NEFA levels was shown to reduce muscle glucose transport/phosphorylation and glycogen synthesis, reflecting insulin resistance [163–165]. This process was strongly related not only to the accumulation of ectopic lipids in muscle and liver but also to insulin secretion [166].

Conversely to acute induction of insulin resistance, insulin sensitivity can also be increased rapidly, with the most pronounced effect resulting from an acute bout of exercise [2]. This effect leads to an enhanced capacity for glucose uptake into muscle, facilitating the glucose oxidation needed for efficient ATP production for exercise. Mechanistically, this enhanced post-exercise muscle insulin sensitivity is mediated by AMPK and its phosphorylation of TBC1D4 on Ser711 [167, 168]. It is also well known that glucose uptake is directly induced by muscle contraction independently of insulin [169]. Multiple studies have addressed the role of AMPK in this contraction-induced glucose uptake without reaching a clear consensus. However, recent studies indicate that AMPK mediates increased glucose uptake immediately after, but not during, the contraction [170]. The molecular mechanisms underlying glucose uptake during contraction are not fully understood but are likely pleiotropic and complex [171].

Responses to prolonged exercise training (vs an acute bout of exercise) in the setting of insulin resistance are inherently variable. Reversal of insulin resistance has been associated with improvements in cardiorespiratory fitness (CRF) and muscle mitochondrial capacity [172] but has also been observed without such changes [173]. Mitochondrial abnormalities and insulin resistance have been linked even in individuals matched for age and BMI [65, 174] but they have also been dissociated when accounting for confounding factors such as CRF [147]. Thus, this connection remains a topic of debate. Ambient hyperglycaemia has also been identified as a potential regulator of the exercise response in the setting of insulin resistance [175]. Moreover, recent evidence indicates that exercise-induced improvements in insulin sensitivity are heterogeneous and may depend on baseline metabolic status, with insulin-resistant individuals exhibiting variable responsiveness to training interventions [176].

Taken together, these examples show that insulin sensitivity is highly plastic and can change rapidly in response to acute changes in nutritional status or physical activity or as a result of circadian disruption. They further illustrate that, under normal conditions, insulin sensitivity is a physiological mechanism that allows the body to adjust to changes in substrate supply and demand.

## Chronic plasticity of insulin sensitivity

Whereas acute insulin resistance can be part of important physiological adaptations, as described above, chronic insulin resistance can lead to metabolic conditions such as MASLD and type 2 diabetes. Obesity, and in particular visceral adiposity, is strongly associated with and may contribute causally to chronic insulin resistance, although the evidence remains predominantly observational and the causal relationship continues to be debated [177, 178]. In this setting, insulin resistance is often interpreted as a response to a sustained mismatch between substrate supply and oxidative capacity.

The deposition of lipids with subsequent increases in lipid mediators outside of adipose tissue appears to be a major determinant that links obesity to insulin resistance. Indeed, accumulation of fat in the muscle, liver and heart is associated with reduced insulin sensitivity in those tissues, and emerging evidence suggests that the pattern of lipid partitioning across organs, rather than isolated ectopic fat accumulation alone, contributes to interindividual differences in insulin sensitivity, insulin secretion and future diabetes risk [179, 180]. The key molecular mechanisms linking ectopic fat accumulation to tissue-specific insulin resistance, including lipid-activated protein kinases, are discussed below (see 'Current understanding of insulin signalling networks'). Additional factors influencing the degree to which lipids induce insulin resistance have been reviewed elsewhere [181, 182] and include different lipid



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species, their subcellular location and the balance between lipid accumulation and oxidative capacity. This balance is exemplified by endurance-trained athletes, who have a high degree of insulin sensitivity despite frequently having large amounts of muscle triglyceride and other lipid species. This enhanced insulin sensitivity is thought to reflect the athletes' high fat-oxidative capacity [72, 75, 183–187].

Chronic determinants of insulin resistance extend beyond obesity and fat accumulation and include circadian regulation, hormonal influences, age-related changes and even pregnancy. Chronic insufficient sleep impairs insulin sensitivity independently of changes in adiposity [188]. Conversely, in adolescents at high risk for type 2 diabetes, extending sleep by just 1 h per night was found to improve insulin sensitivity, highlighting the bidirectional and adaptable nature of sleep-dependent metabolic regulation [189]. Chronic sleep disruption and circadian misalignment influence metabolic tissues through circadian clock-regulated transcriptional programs. Restoring circadian alignment improves rhythmic control of hepatic gluconeogenesis [190] and may influence lipolysis and adipokine secretion in adipose tissue, as well as mitochondrial abnormalities and GLUT4 trafficking in muscle.

It has also been shown that insulin sensitivity declines with age, which can contribute to the age-associated declines in lean body (mostly muscle) mass and physical activity [191]. However, these changes are strongly influenced by lifestyle and body composition. Lifelong exercise training can prevent age-induced decline in insulin sensitivity [192], suggesting that ageing per se does not affect insulin sensitivity. Nevertheless, hormonal fluctuations, including age-related declines in growth hormone, sex steroids and incretins, also modulate insulin sensitivity across tissues, affecting glucose uptake, lipolysis and EGP.

Pregnancy is another example of this natural, physiological stress-induced chronic insulin resistance [152]. Numerous factors such as placental hormones, obesity, inactivity, unhealthy diet and genetic and epigenetic contributions influence insulin resistance in pregnancy. Most importantly, pregnancy-induced insulin resistance is largely transient; most pregnant individuals resume normal insulin sensitivity quickly after delivery and the removal of the placenta, restoring homeostasis [24, 193].

Sex also influences insulin sensitivity, and women, in general, are more insulin sensitive than men, although this difference at least in part depends on factors such as body composition, hormonal and pregnancy status and assessment methodology. However, sex differences may dissipate after the onset of menopause, again highlighting the strong hormonal influence on insulin sensitivity. Sex hormones, including androgens, have been shown to modulate insulin sensitivity, although their effects seem to be dependent on sex and context [194, 195]. In addition, differences in body fat distribution and amount of lean body mass can also influence insulin sensitivity. Notably, early alterations in insulin sensitivity are accompanied by sex-dependent patterns of hyperinsulinaemia, suggesting that compensatory insulin responses differ between men and women, even at initial stages of insulin resistance [196]. In molecular investigations of muscle tissues obtained from men and women, large differences in the proteome were found between sexes, with women exhibiting a greater reliance on lipid metabolism and men showing a higher reliance on glucose metabolism [197].

Together, these observations illustrate that insulin sensitivity across the life course reflects the interplay between metabolic load, tissue capacity and regulatory factors, rather than a single unifying mechanism.

## Insulin resistance in different diabetes subgroups

Type 2 diabetes is characterised by insulin resistance and arises when the pancreas is not able to secrete sufficient insulin to overcome reduced insulin action; yet, the degree of insulin resistance varies among people with diabetes. Although insulin resistance classically has been associated with type 2 diabetes, people with type 1 diabetes can exhibit a similar degree of insulin resistance alongside the beta cell failure that is a hallmark of the disease. Furthermore, insulin sensitivity can vary by a factor of ten or more in both type 1 and type 2 diabetes.

Recently, adults with newly diagnosed diabetes have been categorised by clustering analysis into subgroups based on phenomic variables such as age at diagnosis, BMI, $HbA_{1c}$ and measures of insulin resistance and beta cell function, helping especially to categorise the highly heterogeneous population with type 2 diabetes. The most common subgroups are severe insulin-resistant diabetes (SIRD), characterised by low insulin sensitivity (i.e. high insulin resistance), and mild obesity-related diabetes, characterised by moderate insulin resistance. Additional subgroups include mild age-related diabetes, severe insulin-deficient diabetes and severe autoimmune diabetes [198]. A study using the Botnia clamp to determine insulin sensitivity and insulin secretion showed a two- to threefold variation in insulin sensitivity among these subgroups [38]. These observations suggest that future stratification may evolve beyond composite clinical phenotypes towards direct characterisation of tissue- and pathway-specific insulin resistance, potentially providing a more biologically grounded framework for precision medicine in metabolic diseases.

Priorities for future research into the plasticity of insulin sensitivity are summarised in the text box.



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## Future research priorities: plasticity of insulin sensitivity

- Identify molecular determinants of the plasticity of insulin sensitivity in different tissues.
- Develop biomarkers to classify poor vs strong responder phenotypes for therapeutic approaches such as exercise.
- Clarify the independent effects of age and body composition on insulin resistance.
- Map genetic-, sex- and population-level differences in insulin sensitivity to specific metabolic pathways and tissue responses.
- Determine which tissues are most amenable to reversal of insulin resistance and how to combine treatments for whole-body benefit.
- Understand interactions among glucose, lipid and amino acid metabolism in driving and reversing insulin resistance.
- Elucidate differences in insulin resistance mechanisms between type 1 and type 2 diabetes.
- Perform deep metabolic phenotyping of diabetes subgroups to reveal the factors responsible for variation in insulin sensitivity.

## Consequences of chronic insulin resistance

In the insulin-resistant state, pancreatic beta cells increase insulin secretion in an attempt to preserve euglycaemia, leading to compensatory hyperinsulinaemia [44]. However, the temporal sequence of this process is not fully resolved [196, 199, 200], and some have suggested that hyperinsulinaemia may not only compensate for insulin resistance but also contribute to its development or amplification [201–203], at least in some tissues. Over time, this interplay may increase secretory demand on beta cells and ultimately promote beta cell dysfunction.

As insulin resistance becomes persistent and increasingly maladaptive, the coordinated regulation of glucose and lipid metabolism progressively deteriorates (Fig. 1). Altered substrate partitioning and interorgan communication amplify metabolic dysfunction, creating a self-reinforcing cycle that promotes cardiometabolic disease. In the liver, insulin resistance leads not only to inappropriate glucose production but also to increased lipogenesis and VLDL secretion [16, 33], while in muscle, it leads to reduced glucose uptake, contributing to both fasting and postprandial hyperglycaemia [20, 204]. In adipose tissue, reduced insulin action is associated with reduced insulin-induced inhibition of lipolysis and higher circulating NEFAs [205]. These changes in turn promote ectopic lipid deposition in the liver, muscle and other organs, further reducing insulin action, exacerbating insulin resistance in these tissues [97, 206, 207] and thereby promoting a cycle of metabolic deterioration.

The clinical consequences of insulin resistance, and/or the dysfunction that leads to it, are widespread. Chronic insulin resistance is associated with low-grade inflammation, oxidative stress and mitochondrial abnormalities [208]. Review articles have described how excess lipid accumulation and lipotoxic signalling can also activate inflammatory pathways, impair cellular energy metabolism and increase susceptibility to tissue damage [13, 20]. Clinically, these processes manifest as lipid accumulation, most prominently hepatic steatosis and visceral adiposity [145, 207], as well as hypertension, dyslipidaemia and an excess risk for CVD [25].

Beyond classical metabolic disorders such as type 2 diabetes, obesity, MASLD and hypertension, insulin resistance has also been linked to a wider range of clinical conditions, including CKD [17], PMOS [209, 210], sarcopenia [211] and certain neurodegenerative diseases [115]. Evidence is also accumulating that hyperinsulinaemia and insulin resistance are strongly associated with increased risk for certain cancers [212, 213], probably due to mitogenic actions of insulin. However, clinical evidence of these actions in humans suggests complex processes in need of further elucidation [214–216]. Although the causal pathways linking insulin resistance to these conditions are not yet fully understood, the strength and consistency of these associations highlight the broad systemic impact of impaired insulin action. Together, these observations support the concept that persistent insulin resistance is not confined to isolated organs but represents a systemic biological phenotype arising from dysregulated interactions among metabolic tissues.

Understanding the molecular mechanisms by which insulin transmits its signal is essential for understanding how insulin resistance develops. Defects at different levels of the insulin signalling cascade may differentially impair specific biological responses, providing a mechanistic basis for the tissue- and pathway-specific manifestations of insulin resistance discussed throughout this review.



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Priorities for future research into the consequences of chronic insulin resistance are summarised in the text box.

### Future research priorities: consequences of chronic insulin resistance

- Clarify mechanisms and functional/clinical impacts of organ-selective insulin resistance.
- Define the temporal sequence of insulin resistance across organs and pathways, including the order in which adipose, hepatic, muscle and non-classical tissue abnormalities emerge.
- Continue available and establish new longitudinal cohorts with repeated gold-standard measurements.
- Define determinants of interindividual variability and reversibility of insulin resistance.

## Current understanding of insulin signalling networks

Physiological studies of insulin sensitivity have concentrated on the regulation of glucose and lipid metabolism, and molecular studies have revealed broad and interconnected regulatory signalling networks. Defects at different network nodes can alter distinct biological outputs in a tissue-, pathway- and insulin-dose-dependent manner. This section focuses on mechanisms that may explain heterogeneous insulin resistance in humans, while distinguishing findings supported by human studies from those derived mainly from model systems.

### Mechanisms of insulin receptor activation

The insulin receptor, a member of the receptor tyrosine kinase family, is a preformed, disulfide-linked dimer [217]. In the absence of a ligand, the receptor adopts an inactive inverted V-shaped conformation that separates the intracellular kinase domains from each other (Fig. 4a). The receptor dimer has four insulin-binding sites: two primary, high-affinity sites (site-1s) and two secondary, lower-affinity sites (site-2s) (Fig. 4b) [218, 219]. Progressive binding of insulin to these sites causes the extracellular domains of the receptor to rearrange from asymmetrical Γ- and T-shaped states toward a symmetrical T-shaped conformation, bringing the intracellular kinase domains together for *trans*-autophosphorylation (Fig. 4a, b) [219–223]. Functional studies with complementary insulin analogues with selective defects in site-1 or site-2 binding showed that the analogue retaining site-1 binding produced partial receptor activation, whereas the analogue retaining site-2 binding was insufficient to activate the receptor. Combining the two analogues enhanced receptor activation, supporting synergistic engagement of site-1 and site-2 for optimal receptor activation [221]. Whether all four sites are occupied at physiological insulin concentrations remains uncertain, and current structures do not fully resolve how extracellular conformations couple to intracellular kinase states. These limitations matter conceptually because receptor occupancy and conformation may influence signalling strength or bias; however, their contribution to common human insulin resistance has not been established. We therefore use receptor structure to define plausible regulatory mechanisms rather than as a proven cause of common, polygenic insulin resistance associated with obesity and type 2 diabetes.

### Two interconnected axes of the insulin signalling network

The activated insulin receptor recruits IRS- and SHC-family adaptors, organising signalling through two highly interconnected axes: the PI3K–Akt pathway and the Ras–MAPK/ERK pathway (Fig. 4c). These are useful organising frameworks rather than discrete ‘metabolic’ and ‘mitogenic’ pathways, because their outputs overlap and depend on cell type, insulin concentration, time and subcellular location. Membrane lipid composition and fluidity may influence receptor mobility and nanoscale clustering, while receptor and adaptor proteins may form higher-order signalosomes or condensate-like assemblies that shape signalling amplitude and duration.

#### PI3K–Akt pathway

The PI3K–Akt axis is central to insulin’s regulation of carbohydrate, lipid and protein metabolism (Fig. 4c) [56]. After receptor activation, IRS1/2 are recruited to the insulin receptor and phosphorylated on multiple tyrosine residues [224, 225]. IRS1/2 are also subject to serine/threonine phosphorylation by multiple kinases, which can modulate signal strength and duration.

Class I PI3K binds phosphorylated IRS1/2 [226] and converts phosphatidylinositol 4,5-bisphosphate ($PIP_2$) into phosphatidylinositol 3,4,5-trisphosphate ($PIP_3$), which recruits PDK1, mTORC2 and Akt to the plasma membrane. This spatial restriction enables sequential phosphorylation



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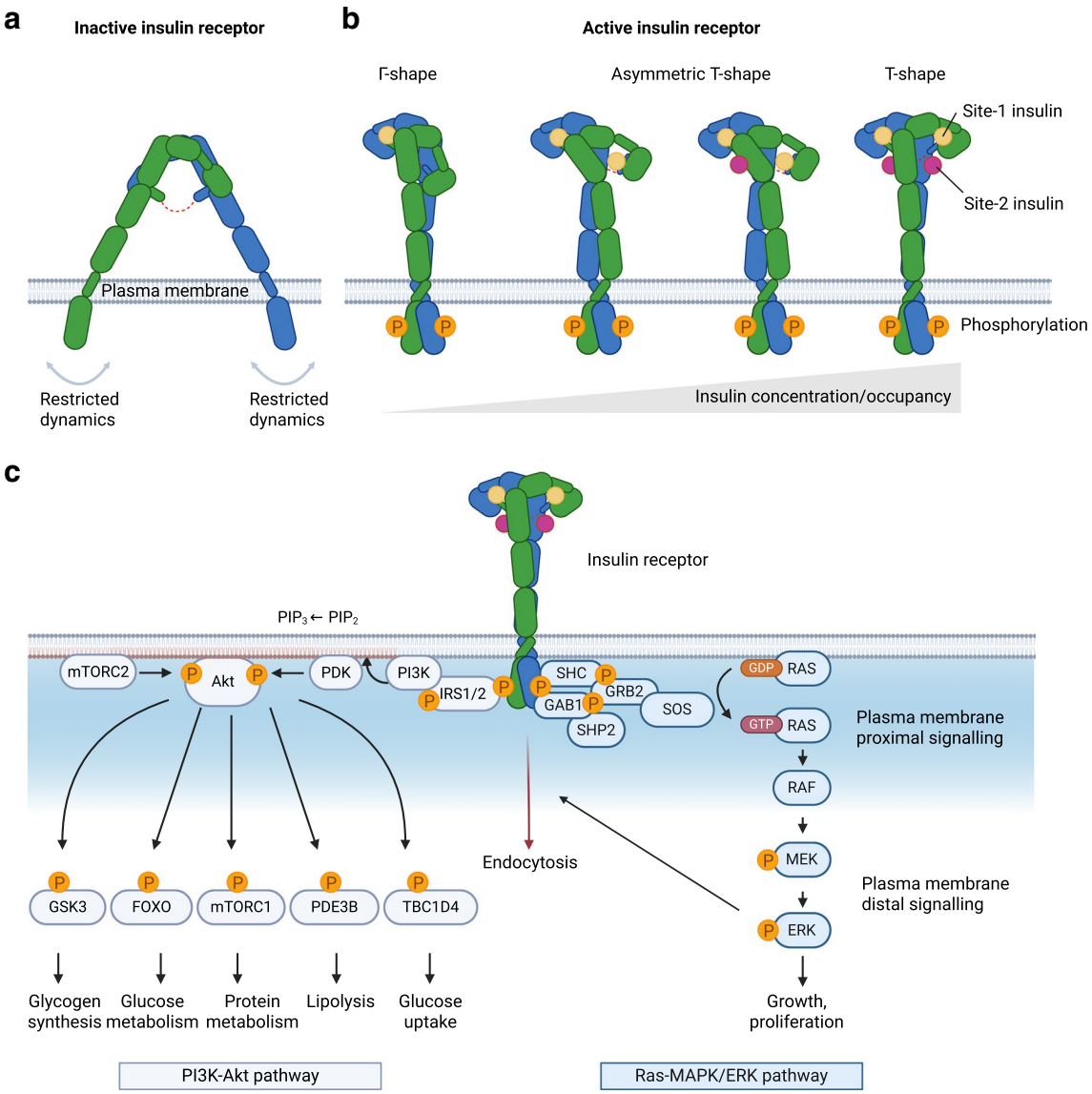


**Fig. 4** Insulin-dependent activation and signalling of the insulin receptor. Insulin binding to the inactive insulin receptor (**a**) induces a large conformational change that promotes efficient *trans*-autophosphorylation. Depending on insulin concentration, the receptor adopts multiple active conformations (**b**). One protomer of the insulin receptor is shown in green and the other in blue. Insulin bound to site-1 is depicted in yellow, and insulin bound to site-2 in purple. 'P' indicates *trans*-autophosphorylation of the insulin receptor. The red dotted lines indicate disulfide-linked αCT segments. The activated insulin receptor initiates two major signalling pathways (the PI3K–Akt pathway and the Ras–MAPK/ERK pathway) that regulate metabolism, growth and proliferation (**c**). Created in BioRender. Choi, E. (2026) https://BioRender.com/2t6u5jk. This figure is available as part of a downloadable slideset

of Akt by PDK1 [227] and mTORC2 [228] at Thr308 and Ser473, respectively [229], resulting in full Akt activation. Akt regulates more than 300 substrates involved in glycogen synthesis (via GSK3), glucose metabolism (via FOXO), protein metabolism (via mTORC1 regulators), lipolysis (via PDE3B) [230] and glucose uptake (via TBC1D4), among others [231]. Numerous excellent reviews describe this pathway in greater depth [232–234].

In muscle and adipose tissue, GLUT4 trafficking is a major distal output of insulin signalling. Akt-dependent phosphorylation of TBC1D4 and, particularly in muscle, TBC1D1 relieves Rab-GAP-dependent restraint on Rab-family small GTPases, promoting the surface delivery of GLUT4-containing vesicles [235–237]. In muscle, Rac1-dependent actin remodelling provides an additional input into GLUT4 delivery and insulin-stimulated glucose uptake



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[238, 239]. Reduced GLUT4 abundance or defects in these distal trafficking steps can limit insulin-stimulated glucose uptake despite relatively preserved proximal Akt signalling [240–242]. Human genetic evidence is provided by the *TBC1D4* p.Arg684Ter loss-of-function variant, which causes severe muscle insulin resistance and markedly reduced insulin-stimulated muscle glucose uptake [242, 243].

#### Ras–MAPK/ERK pathway

The Ras–MAPK/ERK signalling pathway has traditionally been associated with cell growth, proliferation and differentiation. This pathway is initiated through protein–protein interactions at the insulin-activated insulin receptor (Fig. 4c) [244–247]. Insulin receptor-bound IRS1/2 and SHC recruit downstream effector proteins such as GRB2 and SHP2. These adaptors facilitate the association of the guanine nucleotide exchange factor SOS with the insulin receptor complex. SOS catalyses GDP–GTP exchange on Ras, thereby initiating the Raf–MEK–ERK kinase cascade. SHP2 activity is crucial for stabilising a productive signalling complex that ensures efficient Ras–GTP loading. In addition to IRS1/2 and SHC, the adaptor protein GAB1 is also recruited to the activated insulin receptor, providing further docking sites for GRB2 and SHP2 and amplifying MAPK pathway assembly.

In insulin-resistant states, compensatory hyperinsulinaemia may overstimulate relatively preserved growth-related outputs, a possibility relevant to vascular remodelling and cancer risk, although direct causal evidence in humans remains incomplete [212, 213, 248–251]. Although often presented as separate cascades, the PI3K–Akt and Ras–MAPK/ERK pathways are interconnected branches of a broader insulin signalling network, with shared components, extensive crosstalk, feedback regulation and overlapping biological outputs. This integrated view is more useful than assigning each biological response to a single linear pathway.

### Spatiotemporal and tissue-specific regulation

Insulin receptor internalisation is tissue dependent and regulates insulin clearance, receptor recycling and signal duration [252–254]. In addition, insulin must first traverse the vascular endothelium to reach its target tissues, and impaired transendothelial insulin transport has been proposed as another mechanism contributing to insulin resistance [255, 256]. Although the quantitative contribution of impaired insulin delivery to human insulin resistance remains incompletely defined, these observations suggest that insulin action may be regulated not only at the level of intracellular signalling but also through tissue insulin delivery. Once insulin reaches its target cells, receptor internalisation represents another layer of spatiotemporal regulation that differs across tissues. Clathrin-mediated uptake predominates in hepatocytes [257, 258], whereas caveolin-dependent internalisation has been implicated in adipocytes [259, 260]. Evidence for signalling by internalised insulin receptors is strongest in rodent hepatocytes, where receptor–insulin complexes can remain catalytically active and signalling proteins redistribute to endosomal compartments [261, 262]. By contrast, disrupting dynamin-dependent endocytosis in 3T3-L1 adipocytes did not materially impair acute insulin receptor signalling or insulin-stimulated GLUT4 exocytosis [263]. Evidence in muscle remains limited.

Thus, receptor internalisation should not be assumed to create a universal signalling compartment; its relative contribution to signalling vs clearance is likely tissue and context dependent. Nevertheless, this raises the intriguing possibility that insulin signalling persists within intracellular organelles, where it could locally influence mTORC1 activation at the lysosome. Testing this hypothesis will require insulin receptor trafficking-defective cellular or animal systems capable of distinguishing plasma membrane-initiated signals from post-endocytic signalling events.

## Molecular aspects of insulin resistance

#### Lessons from mutations in insulin signalling pathways

Rare monogenic disorders are not models of common type 2 diabetes but, as genetically defined human data, they reveal the relative importance of individual insulin signalling nodes, tissue context, lipid partitioning and pathway selectivity. Individuals with insulin receptor loss of function exhibit profound whole-body insulin resistance with extreme hyperinsulinaemia. Whereas a complete loss of insulin receptor function reduces life expectancy to <2 years, underscoring the overall importance of insulin action, individuals with impaired insulin receptor function are protected from the atherogenic dyslipidaemia and MASLD typical of common insulin resistance, and they have normal hepatic de novo lipogenesis [264]. In contrast, insulin resistance resulting from *AKT2* defects is associated with marked liver steatosis and dyslipidaemia, implying that the metabolic consequences of insulin resistance are strongly influenced by tissue context and the level at which signalling is disrupted [264, 265].

These disorders also demonstrate pathway selectivity; impaired outputs can coexist with preserved pathways that are overstimulated by compensatory hyperinsulinaemia [266, 267]. Phenotypes such as acanthosis nigricans



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and hyperandrogenism further help distinguish effects of impaired insulin action from those of marked hyperinsulinaemia. Together, these observations support a network model of insulin resistance, rather than a uniform block in signalling.

### Mechanisms of impaired insulin action in type 2 diabetes

Type 2 diabetes is rarely caused by coding defects in the canonical insulin signalling pathways. Most type 2 diabetes susceptibility loci implicate pancreatic islet biology and beta cell function, whereas genetic signals related more specifically to insulin resistance often implicate adipose storage capacity, body fat distribution and lipid partitioning. These observations support a systems-level phenotype, in which the reduced ability of insulin to mediate metabolic and other endpoints may in part be adaptive and shaped by polygenic susceptibility, ageing, sustained positive energy balance and ectopic lipid accumulation [268–272].

In common obesity-associated insulin resistance, sustained positive energy balance and elevated lipid availability can promote the accumulation of DAGs and ceramides in key insulin-responsive metabolic tissues, including liver, muscle and adipose tissue; however, these lipid species impair insulin action through distinct signalling mechanisms. In the liver, the DAG-mediated activation of novel PKCε has been linked to impaired insulin receptor activation and downstream IRS2–PI3K signalling [273, 274]. In muscle, DAG accumulation has been associated with impaired insulin action, including through activation of PKCθ, which promotes IRS1 serine phosphorylation and reduces insulin-stimulated IRS1–PI3K signalling, particularly in lipid-infusion models [70]. Mitochondrial abnormalities have also been described in insulin-resistant muscle and may further contribute to impaired substrate handling [71]. In adipose tissue, reduced insulin-stimulated IRS1 tyrosine phosphorylation and PI3K–Akt activation, together with site-specific serine/threonine phosphorylation that attenuates IRS function, are associated with impaired suppression of lipolysis and GLUT4-mediated glucose uptake [275–277]. Nutrient- and stress-responsive kinases, including novel PKCs, JNK, S6K and IKK, can phosphorylate IRS proteins at specific sites, linking cytokines and lipid signals to changes in pathway amplitude, duration and feedback.

Mechanisms underlying ceramide-induced impairment of insulin signalling appear distinct from those underlying DAG-induced impairment. Several foundational cell-based studies used the short-chain, cell-permeable analogue C2-ceramide to implicate protein phosphatase 2A-mediated Akt dephosphorylation and PKCζ-dependent impairment of Akt membrane recruitment [278–280]. However, C2-ceramide differs from endogenous long-chain ceramides in cellular localisation and metabolism and can be remodelled through the salvage/recycling pathway into endogenous ceramide species [281]. In human studies, not all ceramide species are associated with insulin resistance in the same way. Associations differ according to the individual ceramide or dihydroceramide species measured, the tissue examined and the lipid's subcellular localisation; consequently, total ceramide content may obscure biologically relevant species- and compartment-specific relationships. Because most human evidence is associative, the causal contribution of individual ceramide species to muscle insulin resistance and MASLD remains uncertain [278, 282–285].

In addition to lipids, branched-chain amino acids and other nutrient signals may also engage mTORC1–S6K feedback [286, 287]. More broadly, insulin resistance should not be equated with failure of proximal IRS–Akt signalling. In mouse models, substantial reductions in Akt activity can be buffered by pathway redundancy and signalling 'spareness,' whereas distal outputs such as GLUT4 trafficking also depend on Rab- and Rho-family small GTPases [15, 288–290]. This helps to explain why some responses to insulin remain intact in insulin-resistant states, whereas others are blunted.

Human phosphoproteomic and proteomic studies further indicate that proximal Akt signalling can remain relatively preserved, whereas distal, tissue-specific outputs, including mTORC1-linked signalling and mitochondrial pathways, are altered [22, 291]. Selective post-receptor defects may be further exacerbated by IRS1/2-directed negative feedback mechanisms, including protein and lipid phosphatase activity and inhibitory serine/threonine phosphorylation of IRS1/2 by kinases such as mTORC1 and S6K1. These mechanisms can reduce signal amplitude, shorten pathway residence time and promote desensitisation [81, 292–295]. Pathway-selective disruption of insulin signalling supports the concept that compartment-specific alterations, including potential endosomal or lysosomal insulin receptor signalling, may contribute to altered insulin action in metabolic disease. Although the capacity of the beta cell to secrete insulin may be relatively fixed, the ability of target tissues to respond to insulin is highly dynamic, responding to changes in body weight, diet and exercise. Future studies incorporating different insulin doses, tissues and time courses are needed to explore direct in vivo insulin action in people with different degrees of insulin sensitivity and to translate these findings to actionable, more personalised, interventions with clinically relevant outcomes.

Priorities for future research into insulin signalling are summarised in the text box.



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## Future research priorities: insulin signalling

- Determine how distinct ligand-bound stoichiometries and receptor conformations encode signalling specificity, pathways bias and divergent trafficking fates across cell types.
- Elucidate how membrane fluidity, lipid composition and metabolic state reshape receptor activation, signalling complex assembly, nanoscale organisation and coupling to downstream signalling networks.
- Explain how dynamic receptor clustering, signalosome assembly, phase separation and higher-order architectures regulate signal amplitude, duration and qualitative outcomes beyond ligand binding alone.
- Discover how endosomal and other intracellular insulin receptor pools generate sustained, spatially compartmentalised or qualitatively distinct signalling programmes.
- Develop a more complete characterisation of insulin-induced changes in global phosphorylation patterns and other post-translational modifications across various insulin doses and time points in different tissues, in both insulin-sensitive and insulin-resistant states.

## Pharmacological treatment of insulin resistance: an unmet need

Many of the currently available diabetes treatment options that are helping people with diabetes and/or obesity to maintain or improve their metabolic function and consequently reduce their risk for comorbidities have a direct or indirect impact on insulin resistance. However, current treatments only partially address the underlying pathophysiology of insulin resistance, are often limited in efficacy, or have been associated with unwanted side effects, which limit their potential clinical benefit [85]. This raises the question of whether we are addressing the needs of people with diabetes in the right way. To determine what types of new therapies we need to develop, we must first better understand the nature of insulin resistance itself and also consider what current treatments offer in terms of reducing insulin resistance, based on their mechanisms of action.

### Available pharmacological treatments

The cornerstones of treating type 2 diabetes are lifestyle interventions, including dietary approaches and physical activity and pharmacotherapies. See 'Acute plasticity of insulin sensitivity' above for a discussion of the effects of exercise on insulin sensitivity. Existing diabetes therapies that also affect insulin resistance include metformin, PPAR-γ activators, sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists. All of these therapies are approved as glucose-lowering treatments, with varying efficacy. Some have been associated with additional benefits in preventing, slowing the progression of, or treating comorbidities, including obesity and cardiovascular, kidney and liver complications.

PPAR-γ activators act directly on their nuclear receptor target and represent one of the most pharmacologically established classes of insulin-sensitising agents [296–299], whereas most other drugs act more indirectly to reduce insulin resistance. Pioglitazone has been shown to improve adipose tissue insulin resistance, increase adiponectin and reduce lipolysis [300–302] and this, in turn, reduces the overflow of fatty acids to several organs, thereby reducing visceral, liver and cardiac fat [113, 297, 298, 303, 304] despite the increase in subcutaneous adipose tissue [297, 298, 304]. Pioglitazone not only reduces ectopic fat and lipotoxicity but also stimulates muscle glucose uptake and increases AMPK activity [301]. Moreover, pioglitazone reduces hepatic glucose production and gluconeogenesis [297, 300], thus improving insulin sensitivity in these organs as well as in the heart, where it reduces cardiac fat and improves cardiac function [297].

These tissue-level effects on insulin sensitivity translate into meaningful clinical benefit, as demonstrated by the ACT NOW (Actos Now for the Prevention of Diabetes) study, which followed participants with impaired glucose tolerance (IGT) for progression to diabetes or reversion to normal glucose tolerance after treatment with pioglitazone or placebo [296]. This study revealed that improvements in insulin sensitivity, insulin secretion and beta cell function were associated with higher final glucose tolerance status (normal glucose tolerance > IGT > type 2 diabetes) in people receiving pioglitazone, with improved beta cell function emerging as the main mechanism whereby pioglitazone improves glucose tolerance and prevents diabetes [296].

Newer PPAR agonists are emerging as insulin-sensitising agents. Lanifibranor, a pan-PPAR (α/γ/δ) agonist, has been shown in a phase 2 clamp-based study to restore hepatic insulin sensitivity to near normal and improve muscle insulin sensitivity to near normal, alongside enhanced adipose tissue function, including a doubling of plasma adiponectin



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levels, in people with type 2 diabetes and MASLD [305]. Several highly selective PPAR modulators and non-adipogenic structural derivatives are in development with the aim of enhancing tissue-specific insulin sensitisation while minimising adipogenic side effects.

Beyond direct insulin sensitisers, two newer drug classes developed primarily for type 2 diabetes and obesity have also emerged as important indirect modulators of insulin sensitivity. GLP-1 receptor agonists and GLP-1-based co-agonists induce substantial weight loss along with improvements in insulin sensitivity and beta cell function. This is thought to be predominantly due to loss of weight and fat mass. Whether this mode of action also exerts clinically relevant weight-independent insulin-sensitising effects remains an area of active investigation. Head-to-head data indicate that the dual GIP/GLP-1 receptor agonist tirzepatide produces greater improvements than semaglutide or dulaglutide in insulin sensitivity, as determined with HOMA-IR [306, 307]. This greater improvement may, at least in part, reflect additional insulin-sensitising actions of GIP receptor activation in adipose tissue, although the relative contribution of direct GIP signalling vs greater weight loss remains incompletely understood. Supporting this pathway, a post hoc exploratory analysis of the SYNERGY-NASH trial revealed that individuals achieving histological resolution of metabolic dysfunction-associated steatohepatitis (MASH) exhibited greater reductions in the Adipo-IR alongside robust increases in circulating adiponectin [308].

SGLT2 inhibitors, which act through a distinct, glucosuria-driven mechanism, have also been shown to improve insulin sensitivity across multiple tissues. Clamp-based studies have shown that SGLT2 inhibitor treatment increases muscle glucose uptake, indicating improved peripheral insulin sensitivity, while acutely increasing endogenous (hepatic) glucose production and lipolysis. With chronic dosing, these effects are accompanied by a shift in substrate use towards increased fatty acid oxidation, thereby potentially reducing lipotoxicity [309–311]. SGLT2 inhibitors also improve vascular insulin sensitivity, with empagliflozin enhancing insulin-mediated skeletal and cardiac muscle microvascular perfusion in people with type 2 diabetes [312]. Furthermore, preliminary evidence suggests that empagliflozin may improve brain insulin responsiveness [313], although the clinical relevance of these findings remains to be established.

Comparative trial data further support prioritising insulin sensitisation over insulin secretagogue-based approaches. The Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) randomised clinical trial addressed the efficacy of four types of glucose-lowering treatments with different mechanisms of action (long-lasting man-made insulin, sulfonylureas, GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors) for their effects on insulin resistance and beta cell function over 5 years when added to metformin [314]. The study revealed a loss of glycaemic regulation and progressive beta cell dysfunction with all four treatments [314]. Earlier, ADOPT (A Diabetes Outcome Progression Trial) found that monotherapy with metformin or the PPAR-γ activator rosiglitazone led to more effective insulin sensitisation and slower decline of beta cell function than monotherapy with a sulfonylurea [315]. These data together led the GRADE investigators to suggest that improving insulin sensitivity could reduce the functional demand on beta cells to secrete insulin, helping to preserve the function of beta cells and maintain glycaemic management [314].

Collectively, these agents illustrate that meaningful improvement in insulin sensitivity can be achieved through mechanisms distinct from classical insulin receptor- or PPAR-γ-mediated pathways, highlighting that insulin sensitisation can be achieved by targeting multiple aspects of metabolic dysfunction rather than insulin signalling alone. Their broad efficacy across the spectrum of cardio-kidney metabolic disease underscores the centrality of insulin resistance as a therapeutic target. Table 2 provides an overview of the known insulin sensitisation mechanisms of action, target tissues and efficacy profiles of these treatments.

These observations further emphasise the need for new insulin sensitisers that selectively restore tissue-specific beneficial insulin action while preserving physiological adaptive insulin resistance where it remains beneficial.

## The changing treatment landscape

The diabetes treatment paradigm, as well as major treatment goals, has evolved over the past decade. According to type 2 diabetes treatment guidelines, the first-line treatment is now flexible and should be individualised, and novel drugs with non-glycaemic beneficial effects can be considered as first-line therapy based on an individual's medical history and comorbidity risk profile [316]. However, in clinical practice, existing treatments often are still being used in a one-size-fits-all approach. This approach is being challenged because it has become clear that diabetes is not a homogeneous disease but rather one in which the underlying pathophysiology differs among individuals. For example, a subgroup of adults with newly diagnosed diabetes was found to differ not only in insulin resistance and beta cell function but also in susceptibility to diabetes-related complications, with individuals in the SIRD subgroup at high risk for diabetes-related CKD despite having only moderately elevated $HbA_{1c}$ [198]. These observations suggest that risks for complications reflect differences in underlying pathophysiology beyond glycaemic state alone and support the concept that future therapeutic strategies should increasingly move beyond the one-size-fits-all approach and instead target the



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**Table 2** Current diabetes treatments and their mechanisms of action, efficacy and beneficial effects on comorbidities

| Therapy | Mechanism of action | Glycaemic efficacy | Beneficial effects on comorbidities |
|---|---|---|---|
| Metformin | Main sites of action: liver, muscle and gut [343]<br>Mechanisms [344, 345]:<br>• Decreases hepatic glucose production<br>• Increases muscle glucose uptake<br>• Reduces inflammation<br>• Alters gut microbiota<br>Benefits:<br>• Improves hepatic and peripheral insulin sensitivity<br>• Lowers fasting glucose levels<br>• Is weight neutral or induces mild weight loss<br>• Improves the lipid profile | Reduces $HbA_{1c}$ by 10.9–21.9 mmol/mol (1–2%) and FBG by 2–3 mmol/l (36–54 mg/dl) [343, 346] | • Decreases ASCVD [347]<br>• Reduces microvascular complications [348, 349] |
| PPAR-γ activators | Main sites of action: adipose tissue, liver and muscle [304]<br>Mechanisms [296–299, 304, 350]:<br>• Sensitise directly to insulin by binding to nuclear PPAR-γ receptors, leading to transcriptional changes that increase adiponectin<br>• Reduce ectopic fat<br>• Restore IRS-1–PI3K–Akt signalling in muscle and liver<br>Benefits:<br>• Strongly sensitise to insulin, especially in muscle, adipose tissue and liver<br>• Improve the lipid profile<br>• Redistribute fat to subcutaneous depots | Reduce $HbA_{1c}$ by 3.3–23.0 mmol/mol (0.3–2.1%) [351] | • Improve MASH [350]<br>• Lower the risk of MACE in people with prediabetes or diabetes [352] |
| SGLT2 inhibitors | Main site of action: kidney (proximal tubule) [353]<br>Mechanisms:<br>• Increase glucosuria<br>• Reduce glucotoxicity and hyperinsulinaemia<br>• Induce weight loss<br>• Increase lipid oxidation<br>• Reduce visceral fat<br>Benefits:<br>• Indirectly improve insulin sensitivity by reducing glucose load and via weight loss<br>• Restore tubuloglomerular feedback, reduce intraglomerular pressure and natriuresis, and improve proximal tubular metabolism<br>• Reduce glucotoxicity and uric acid levels<br>• Reduce oxidative stress and improve endothelial function indirectly via haemodynamic and metabolic relief | Reduce $HbA_{1c}$ by 3.3–10.9 mmol/mol (0.3–1%) depending on agent and population [354–356] | • Provide cardioprotection (reduced hospitalisation for heart failure)<br>• Provide kidney protection [357, 358] |



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**Table 2** (continued)

| Therapy | Mechanism of action | Glycaemic efficacy | Beneficial effects on comorbidities |
|---|---|---|---|
| GLP-1 receptor agonists | Main sites of action: pancreas, brain, heart and kidney [359–361]<br>Mechanisms:<br>• Reduce glucotoxicity by stimulating glucose-dependent insulin secretion<br>• Induce weight loss [362]<br>• Reduce adiposity by suppression of appetite via central satiety pathways (hypothalamic neurons)<br>Benefits:<br>• Improve peripheral insulin action by enhancing glucose uptake in muscle and IRS-1–PI3K–Akt signalling cascade in adipose tissue [363]<br>• Protect beta cells and reduce hyperinsulinaemia by lowering glucose load and improving beta cell function<br>• Confer anti-inflammatory and adipokine effects by reducing systemic inflammation and oxidative stress [364] | Reduce $HbA_{1c}$ by 5.5–21.9 mmol/mol (0.5–2%) depending on agent and baseline $HbA_{1c}$ levels [365] | Semaglutide:<br>• Decreases body weight<br>• Provides cardioprotection in individuals with ASCVD and heart failure<br>• Provides kidney protection<br>• Has efficacy in MASH for improving liver histology<br>• Improves lipid values and metabolite levels [366–368] |
| Dual GIP/GLP-1 receptor agonist tirzepatide | Main sites of action: pancreas, brain, heart and kidney [369]<br>Mechanisms [360, 370]:<br>• Combines the appetite suppression of GLP-1 with glucose-lowering via the adipose tissue effects of GIP<br>Benefits:<br>• Decreases visceral fat and improves systemic insulin sensitivity<br>• Promotes lipid storage in subcutaneous fat rather than in ectopic depots, reducing lipotoxicity and improving insulin responsiveness<br>• Decreases fasting insulin and HOMA2-IR and improves markers of insulin sensitivity adiponectin, IGFBP-1 and IGFBP-2 [307] | Reduces $HbA_{1c}$ by 19.8–28.6 mmol/mol (1.8–2.6%) and decreases FBG by 0.8–3.3 mmol/l (15–60 mg/dl) [371–374] | • Lowers risk for MACE and improves the cardiometabolic profile<br>• Reduces adverse kidney events, improves kidney function and lowers albuminuria<br>• Induces MASH resolution and fibrosis improvement [375–378] |

ASCVD, atherosclerotic CVD; FBG, fasting blood glucose; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis

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dominant pathophysiological mechanisms, including the distinct forms of insulin resistance, that underlie diabetes in individuals.

Importantly, biologically distinct metabolic subgroups can also be identified before the onset of overt diabetes [317]. These subgroups differ markedly in their risks for diabetes, complications and mortality [318], indicating that clinically relevant heterogeneity precedes the diagnosis of diabetes and is not merely a consequence of hyperglycaemia. Individuals with IGT, impaired fasting glucose or borderline elevated $HbA_{1c}$ who progress to overt diabetes frequently progress into distinct diabetes subtypes, further supporting the concept that distinct pathophysiological trajectories exist long before diabetes diagnosis [317].

The aforementioned subclassification of diabetes by Ahlqvist et al [198] has been reproduced by different groups in European [38, 319–324] and non-European [320, 325–327] cohorts, clearly demonstrating the heterogeneity of the disease and identifying differences in risks for complications. The data-driven hard-clustering approach used in these studies, which assigns individuals to a single diabetes subgroup, has been followed by soft-clustering approaches, through which individuals are recognised to possess features from more than one cluster. In the Innovative Medicines Initiative's DIRECT (Diabetes Research on Patient Stratification) study, soft clustering of individuals with newly diagnosed type 2 diabetes based on 32 clinical variables identified four quantitative archetypes, reflecting the contribution of various aetiological processes to the disease phenotype and further emphasising the heterogeneity of the disease [328].

Subclassification of individuals without diabetes or with prediabetes can identify early pathophysiological alterations that increase the risk for diabetes and its complications. The Portuguese PREVADIAB2 (Prevalence of Diabetes 2) study, which included individuals with normoglycaemia, prediabetes and diabetes, classified individuals into four subgroups (insulin resistant, liver sensitive, pancreas glucose sensitive and insulin deficient) and found sex-specific lipidomic patterns even before diabetes onset [329]. Subclassification of individuals at increased risk for type 2 diabetes in the TUEF/TULIP (Tübingen Family Study and Tübingen Lifestyle Program) cohort using both phenotypic measures and polygenic risk for type 2 diabetes identified six subgroups, including one showing an insulin-resistant phenotype, high risk for CKD and elevated mortality [318]. These studies indicate early metabolic heterogeneity and also underscore the need for improved insulin resistance treatment strategies that likely will have the potential to protect against diabetes-related CKD.

Both systemic and kidney cell insulin resistance contribute to diabetes-related CKD [140], and podocytes have been shown to develop insulin resistance in diabetic mice [330]. Podocyte insulin resistance may play a role in the development of CKD in diabetes, as transgenic deletion of insulin receptors specifically in podocytes in mice leads to features of CKD in the setting of normoglycaemia [331]. Identification of the central drivers of insulin resistance in podocytes and other kidney cells that contribute to diabetes-related CKD would be of great interest and would clarify disease mechanisms and guide design of interventions.

Subgrouping may also help in choosing therapies, as revealed by an approach using continuous variables integrated into a regression model yielding continuous measurements of various outcomes. This approach showed that sex and obesity are associated with glycaemic response to specific medications [332]. However, before clinical implementation of diabetes subgroups, we need more refined subclassification approaches combining clinical phenotype-based and genetic subgroups, followed by replication studies and demonstration that the subgroups have clinical significance [333]. Further understanding of the drivers of disease progression in such refined subgroups may facilitate the development of better treatments and prevention strategies for type 2 diabetes and its complications.

## Strategies aiming towards new insulin-sensitising therapies

The growing recognition that insulin resistance is biologically heterogeneous emphasises the need for a more detailed understanding of the tissue-, pathway- and process-specific mechanisms underlying impaired insulin action. Such mechanistic insights are essential for moving beyond current treatment approaches, which largely improve insulin resistance indirectly, towards therapies that target the underlying biological defects more precisely. As our understanding of the molecular basis of insulin resistance continues to evolve, new opportunities are emerging to identify and selectively target the pathways responsible for impaired insulin action, while preserving beneficial physiological insulin signalling.

Additionally, new approaches such as the variant-to-function (V2F) strategy are being implemented to identify new targets for drug design, and specific modulation of insulin receptor activity are under investigation. Below, we highlight several emerging strategies that may ultimately enable the development of next-generation insulin sensitisers.

### Target identification by deep phenotyping

Slieker et al [334] carried out a multiomic assessment, including clinical variables, metabolomics, lipidomics and proteomics, in a subset of individuals from three different



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cohorts. The results revealed that there are molecular phenotypic differences among the different diabetes subgroups and, as a consequence, potential pathways that may be responsible for increased susceptibility to diabetes-related CKD and its progression in the SIRD subgroup. The omics profile in these individuals suggested that they had genetically greater beta cell function, increased levels of amino acids associated with insulin resistance (e.g. tryptophane and its metabolites, such as kynurenic acid) [335] and increased levels of lipids with different subclasses of DAGs and triglycerides. Similarly, the protein signature confirmed the dysregulation of proteins involved in the insulin signalling pathway and, in addition, dysregulation of proteins known to be associated with diabetes-related CKD, such as cystatin C.

Other studies have used plasma to identify small, non-coding RNAs and microRNAs to reveal specific profiles for the SIRD subgroup, increasing the understanding of and providing biomarkers for insulin resistance [336, 337]. The limitation of these analyses, however, is their focus on plasma, leaving the tissue-specific pathophysiology of insulin resistance undetermined.

Performing further deep phenotyping of tissues central to the development of insulin resistance will allow the identification of key pathways that may lead to targets for drug discovery purposes. These could potentially lead to novel treatments that offer better efficacy and safety profiles for individuals with SIRD in a precision medicine approach.

#### Target identification by the V2F strategy

The V2F approach is another strategy to expanding disease understanding that could lead to identification of novel pathways and targets at the cellular and tissue level [338, 339]. This approach aims to characterise the functional impact of variants identified through genome-wide association studies (GWASs). Given the large number of genetic variants that have been associated with disease, and with diabetes in particular, a major challenge has been to define how these disease-associated genetic variants can be translated into mechanistic insights that explain the increased risk for the disease or its underlying pathophysiology. The V2F strategy combines various methodological approaches to integrate genetic variants identified by GWASs, including non-coding variants typical for type 2 diabetes, with understanding of how gene activities are regulated in the different metabolic tissues and translated to the control of cellular function and morphology to give rise to the different disease phenotypes.

This approach has been exemplified by recently reviewed work on metabolic tissues highlighting both the feasibility and challenges of the strategy [338, 339]. For any particular cellular system, it is important to select the specific readout, given the many functions of the cell type under study. Thus, selecting the right conditions, mimicking either health or a disease environment, and using the most appropriate methodological approaches are all essential.

The feasibility of this approach has already been demonstrated by studies identifying causal genes and pathways involved in insulin action. For example, rare coding variants in *TBC1D4* identified in the Greenlandic population linked defective insulin-stimulated GLUT4-mediated glucose uptake in muscle to an increased risk for type 2 diabetes [243]. Applying a V2F approach across the different key organs known to drive insulin resistance, together with an expanded understanding of the molecular phenotypes in diabetes subgroups, will highlight biological pathways that regulate insulin sensitivity and could thus help to identify potential drug targets.

#### Direct modulation of insulin receptor activity

Future work must also address the need for direct insulin sensitisers or insulin receptor agonists (i.e. molecules that directly modulate the insulin receptor and its downstream signalling), identify the characteristics such treatments should have, and determine whether such treatments would offer improved efficacy and safety compared with currently available medications, including insulin. Several key questions remain to be answered. How might we address the fact that insulin sensitivity is not the same in all tissues or among all individuals? Will insulin sensitisation requirements further differ by comorbidities?

Previous attempts to deliver pure insulin sensitisation via molecules that directly modulate the insulin receptor have encountered challenges due to selectivity (inability to bias the signal towards metabolic activity and away from cell growth/proliferation activity), lack of understanding of structural elements in a disease-state- or organ-specific approach, or simply a lack of efficacy. Improved understanding of the structural conformation of the insulin receptor at different activation stages has facilitated the design of molecules that activate insulin signalling in the metabolic arm of the signalling pathway and tune down the insulin-stimulated growth- and proliferation-promoting pathway. For example, a recent work introduced synthetic insulin receptor agonists that alter the conformation of the insulin receptor, leading to selective activation of downstream signalling [340]. Although these agonists need further development for potential therapeutic use, they were shown to effectively lower blood glucose in mice and could be further modulated to target desired tissues specifically.

Collectively, treating insulin resistance is clearly an unmet need, so how can we best proceed toward meeting it? The previously described introduction of subgroups of diabetes based on clinical variables, with further refinements



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and coupled with genetic information and new biomarkers, could help to direct existing treatments to individuals who will benefit the most from them. In addition, we can take advantage of the knowledge collected from lifestyle interventions with known insulin-sensitising effects, such as exercise and weight loss interventions, to increase our understanding of the tissue-specific enhancement of insulin sensitivity. This information could also be coupled with new machine-learning models to predict the effectiveness of a given treatment or the development of complications, thus aiding clinical decisions [341]. The development of new, improved therapeutic options will require multidimensional, innovative approaches to identify new targets and lead compounds and design new true insulin sensitisers with better safety profiles than current PPAR-γ activators. These efforts should take into account the tissue-specific features and functional consequences of insulin resistance to ensure optimal outcomes.

Priorities for future research into insulin sensitisation are summarised in the text box.

### Future research priorities: new approaches to insulin sensitisation

- Increase understanding of the pathophysiology of insulin resistance in different tissues.
- Decide whether different drugs are needed to target insulin resistance in different tissues and what the clinical impacts of such drugs are likely to be.
- Determine whether true insulin sensitisers would deliver improved efficacy and safety profiles compared with existing treatments.
- Identify new drug targets and lead compounds to design true insulin sensitisers.
- Evaluate whether de novo-designed insulin receptor agonists will have clinical application for the treatment of insulin resistance.

## Conclusion

Insulin resistance is not a static or uniform condition; rather, it is a complex, tissue- or substrate-specific and dynamic phenomenon. Although it historically has been viewed through a glucocentric lens as a simple failure of glucose uptake, modern research has revealed a far more nuanced landscape defined by selective signalling impairments and varied organ responses. The distinction between adaptive physiological variability, such as the changes seen during fasting or exercise, and the maladaptive, persistent state of chronic insulin resistance is fundamental to understanding metabolic disease progression.

Moving forward, the integration of molecular insights such as asymmetrical receptor signalling and spatiotemporal dynamics with clinical observations will be vital. By shifting towards a more precise framework that accounts for individual variability and pathway-specific defects, we can better address the systemic impact of insulin resistance. Ultimately, resolving the current conceptual and methodological limitations highlighted by the 2025 *Diabetologia, Diabetes* and *Diabetes Care* Expert Forum will be imperative to developing targeted, more effective therapeutic strategies for type 2 diabetes, MASLD and the broader spectrum of metabolic and cardiovascular complications.

**Supplementary Information** The online version contains a slide-set of the figures for download available at https://doi.org/10.1007/s00125-026-06853-9.

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