Research Article

Glycocalyx Failure Across The Diabetic Gut-Kidney-Brain Axis: A Three-Barrier Model of Albuminuria and Cognitive Vulnerability

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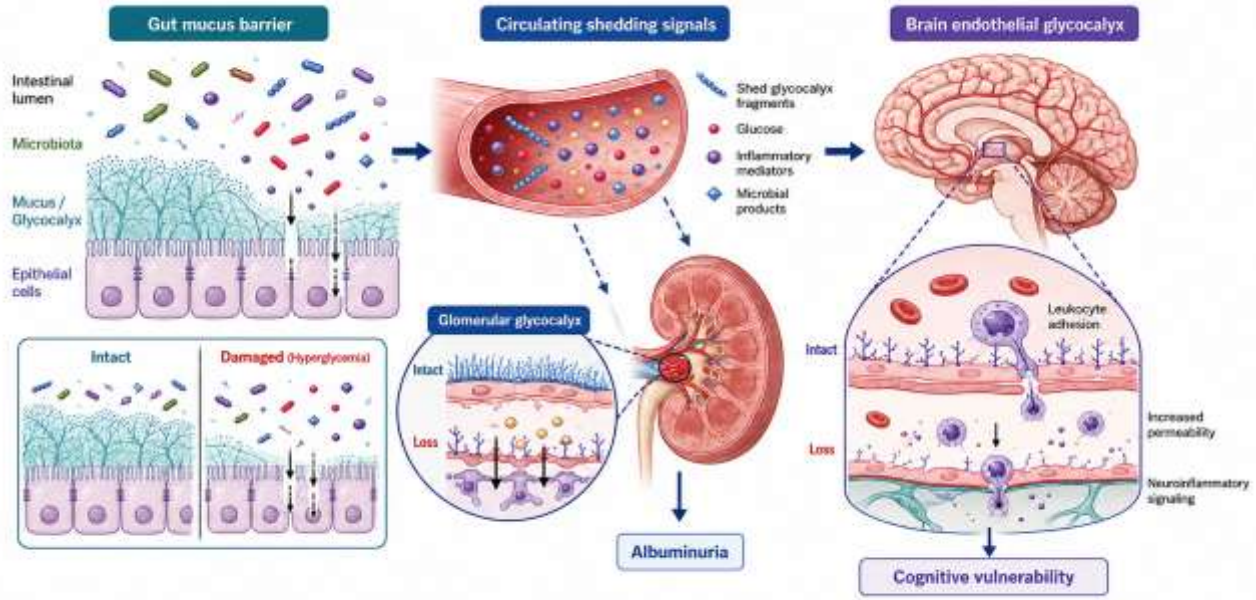
Abstract

Diabetes injures multiple biological interfaces, yet intestinal permeability, albuminuria and neurovascular dysfunction are usually interpreted as separate complications. This review develops a three-barrier glycocalyx framework linking the intestinal mucus-epithelial surface, the glomerular endothelial glycocalyx and the brain endothelial glycocalyx without assuming that a continuous causal pathway has already been demonstrated in humans. Across these interfaces, carbohydrate-rich surface layers regulate steric and charge exclusion, mechanotransduction, leukocyte adhesion and access of circulating or luminal molecules to the underlying cells. Hyperglycaemia, oxidative and inflammatory stress, abnormal shear and glycocalyx-degrading enzymes can perturb these functions. Human evidence is strongest for intestinal barrier abnormalities in diabetes, systemic endothelial glycocalyx loss and the association of glycocalyx shedding with albuminuria. Brain-endothelial glycocalyx data are mechanistically compelling but remain dominated by experimental and disease-adjacent studies. Albuminuria is associated with cognitive and neuroimaging outcomes, but it is not an organ-specific readout of cerebral glycocalyx injury. We therefore propose a falsifiable programme combining direct or validated measures of each barrier, circulating shedding products, renal phenotyping, blood-brain barrier imaging and domain-level cognition in longitudinal cohorts. Glycocalyx preservation is a promising pharmacological concept, but target engagement at one vascular bed cannot be presumed to restore another. The framework converts parallel observations into testable cross-barrier hypotheses while preserving the boundaries of current evidence.

Keywords: albuminuria; blood-brain barrier; diabetic kidney disease; endothelial glycocalyx; intestinal barrier; syndecan-1

Graphical Abstract:



Highlights

- Diabetes may injure three distinct glycocalyx-bearing interfaces.
- Glomerular glycocalyx evidence is stronger than brain translation.
- Circulating shedding markers are not organ-specific.
- Albuminuria links kidney and brain risk but does not prove mediation.
- Longitudinal barrier-specific measurements are required.

1. Introduction

The luminal surface of a vessel is not bare endothelium. A hydrated layer of proteoglycans, glycoproteins, glycosaminoglycans and adsorbed plasma constituents covers the endothelial surface [1]. Direct visualization studies show that this layer is structurally dynamic [2]. Its physiological roles include permeability control and mechanotransduction [3]. Anti-adhesive and anti-inflammatory functions are particularly important during vascular stress [4]. Disease-associated hyaluronan shedding can destabilize the layer [5], while diabetic vascular injury alters hyaluronan-dependent protection [6]. Syndecan-4 turnover provides a further route through which the surface can be remodelled [7]. These properties are especially relevant in diabetes, where biochemical stress and microvascular injury occur simultaneously across organs.

The glycocalyx is often discussed as a single entity, although its architecture and function depend on the local biological environment [1]. Differences in flow, permeability, molecular composition and neighbouring cells make direct extrapolation between organs unsafe [3]. Evidence obtained from one vascular bed therefore cannot be treated as direct evidence for another [4]. This distinction is especially important for the gut, kidney and brain, where carbohydrate-rich surfaces face microbial, filtration and neurovascular environments, respectively. The organ-specific structures and evidence are examined in the sections that follow.

The co-occurrence of intestinal barrier disturbance, albuminuria and cognitive vulnerability provides a clinical rationale for an interface-level framework, but it does not establish a continuous causal pathway. Glycocalyx-dependent permeability, mechanotransduction and cellular adhesion offer a common biological vocabulary [3]. Inflammatory injury can perturb these functions across vascular beds without implying that one organ initiated the other [4]. The three-barrier model developed here therefore separates direct human observations from experimentally supported mechanisms and from relationships that still require longitudinal validation. Its scope is deliberately narrower than broad gut-kidney-brain narratives and focuses on claims that can be tested with organ-resolved measurements.

2. Literature scope and evidence appraisal

PubMed/MEDLINE was searched through July 2026 using combinations of diabetes, diabetic kidney disease, glycocalyx, mucus, mucin, intestinal permeability, microbiota, glomerular endothelium, albuminuria, heparanase, hyaluronidase, syndecan, blood-brain barrier, neurovascular unit and cognition. Direct human measurements and longitudinal observations were prioritized, followed by mechanistic studies addressing a defined barrier component. Foundational articles were retained when they established structure, measurement or causal perturbation. Review articles were used for scope and competing interpretations, not as substitutes for primary evidence.

Evidence was classified as direct human measurement, human association, experimental mechanism, method study or interpretive synthesis. A claim is termed causal only when exposure manipulation, target engagement and barrier outcome were linked in the same model. Albuminuria is treated as a renal and systemic microvascular phenotype, not a surrogate for brain-endothelial glycocalyx loss. Plasma syndecan-1, hyaluronan and heparan-sulfate fragments are treated as shedding-associated markers with limited organ specificity. The complete PubMed metadata, claim links and evidence classification are provided in the accompanying evidence register.

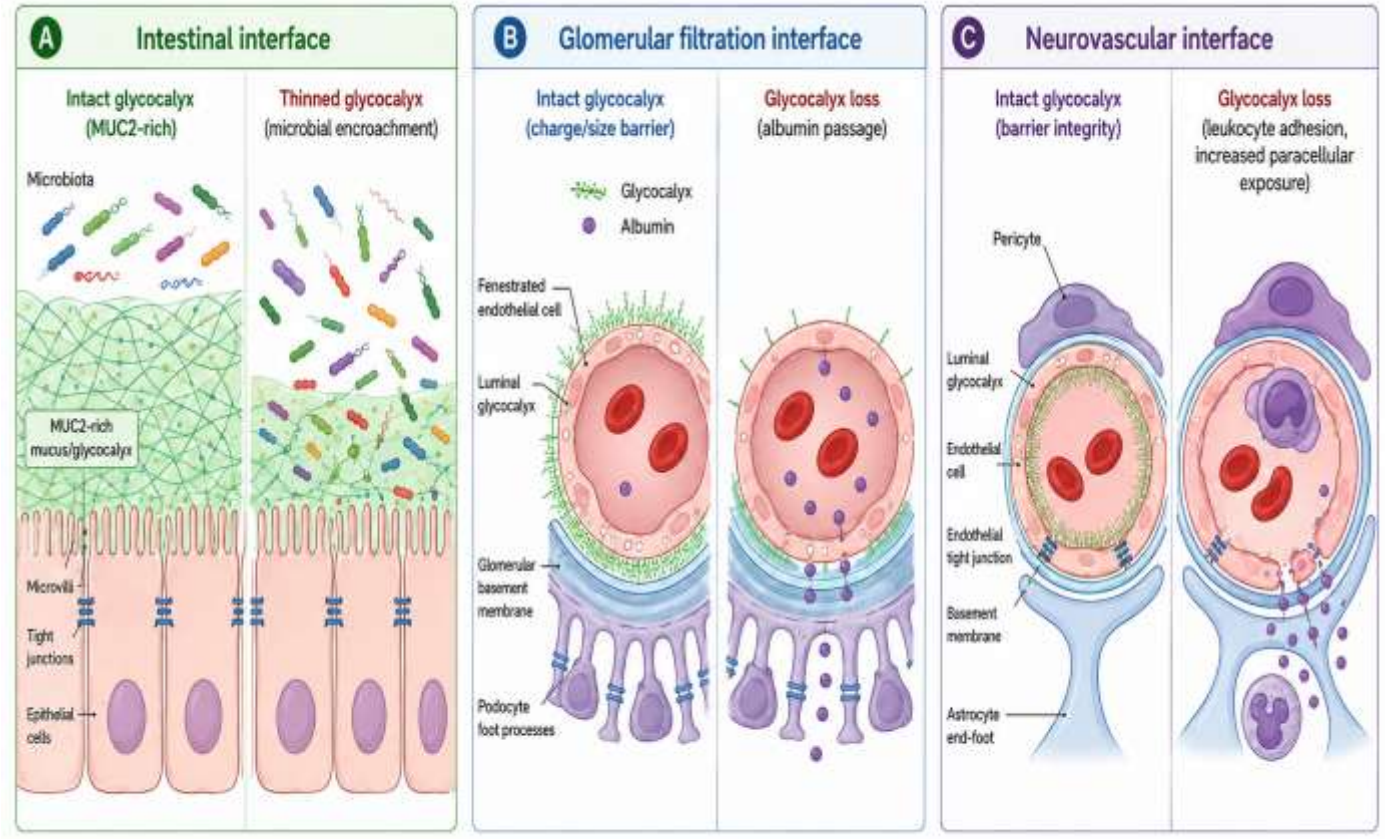
The structural and functional contrasts between the three interfaces are summarized in Table 1. Figure 1 provides the corresponding intact versus injured visual comparison.

Table 1. Comparison of the three glycocalyx-bearing interfaces

Interface	Principal surface layer	Core functions	Human anchor	Main interpretive limit
Intestinal	MUC2-rich mucus and epithelial glycocalyx [8]	Microbial separation; chemical barrier; host-microbe signalling	Microbial encroachment, permeability and mucus	Mucus, junctions and permeability are related but non-identical

			abnormalities in diabetes [13]	
Glomerular	Fenestrated endothelial glycocalyx within the filtration barrier [19]	Albumin restriction; charge/size selectivity; shear sensing	Systemic glycocalyx loss and syndecan-1 association with albuminuria [31]	Albuminuria also reflects podocyte, basement-membrane, tubular and haemodynamic processes
Brain endothelial	Luminal glycocalyx of the neurovascular unit [38]	Barrier exclusion; anti-adhesion; receptor organization; mechanosensing	BBB and neurovascular abnormalities in diabetes; direct glycocalyx evidence remains mainly experimental [46]	Circulating shedding markers are not brain specific

Figure 1. The three glycocalyx-bearing barriers.



Notes: Intestinal mucus/epithelial glycocalyx, glomerular endothelial glycocalyx and brain endothelial glycocalyx share barrier and signalling functions but differ in composition, environment and measurement. The intact-versus-injured comparisons are conceptual and do not imply a proven serial causal pathway.

3. Barrier-specific glycocalyx injury in diabetes

3.1. Intestinal mucus and the epithelial surface

In the colon, polymeric MUC2 organizes a mucus network that separates most bacteria from the epithelial surface while permitting metabolite exchange and immune communication [8]. The small-intestinal barrier has a distinct mucus architecture, faster turnover and closer integration with antimicrobial peptides, epithelial junctions and nutrient transport [9]. These surfaces should therefore be described as related mucosal systems rather than a single uniform glycocalyx.

Human data support the relationship between dysglycaemia and reduced microbial-epithelial distance. In colonoscopic specimens, microbiota encroachment correlated with fasting glucose and glycated haemoglobin [10]. Experimental work showed that hyperglycaemia can directly reprogramme intestinal epithelial cells through glucose metabolism and impair junctional containment, increasing dissemination of microbial products [11]. In people with type 1 diabetes, altered mucus-layer features were reported alongside dysbiosis and immune abnormalities [12]. A 2026 endoscopic impedance study extended human evidence by linking in situ permeability measurements with hyperglycaemia, mucosal microbiota and short-chain fatty-acid biology [13]. These studies do not establish that mucus damage causes kidney or brain injury, but they justify measuring the intestinal interface directly in cross-organ cohorts.

Faecal community composition is often used as a proxy for barrier repair, although it cannot establish restoration of the mucosal surface. Diabetes-focused reviews support a relationship among reduced short-chain-fatty-acid production, intestinal permeability and complications [14]. Broader metabolic disease analysis shows that tissue bacteria and permeability changes may be causes, consequences or parallel responses [15]. Systemic inflammation provides an additional context in which gut permeability findings must be interpreted [16]. Dietary fibre and fat can modify mucus and junctional biology [17], but the response depends on baseline ecology and disease context. A cross-sectional study in cognitively impaired participants connected microbiota features with barrier measurements [18], although temporality and diabetes-specific mediation remain unresolved.

3.2. Glomerular endothelial glycocalyx and albumin handling

The glomerular filtration barrier comprises fenestrated endothelium and its glycocalyx, glomerular basement membrane and podocyte slit diaphragms. Enzymatic removal of endothelial surface carbohydrates increases albumin flux, demonstrating that the glomerular glycocalyx is functionally restrictive rather than decorative [19]. High glucose altered heparan-sulphate content and increased albumin passage across human glomerular endothelial monolayers without requiring overt junctional disruption [20]. In small human studies, systemic and sublingual glycocalyx dimensions were reduced in type 1 diabetes and were lowest in participants with microalbuminuria [21].

Clinical interpretation extends beyond the traditional charge-barrier model. Endothelial surface properties contribute directly to albumin handling [22]. Early diabetic kidney disease also involves basement membrane, podocyte, tubular and haemodynamic processes [23]. Experimental diabetic kidney disease identifies several shedding pathways. Matrix metalloproteinase inhibition reduced syndecan-4 loss, restored glycocalyx coverage and attenuated albumin permeability [24]. Hyaluronidase-1 deficiency preserved endothelial function and glomerular barrier properties in early experimental diabetes [25]. Endothelin-1 stimulated podocyte heparanase release and reduced glomerular heparan sulphate in an experimental model [26]. Heparanase has broader relevance to kidney injury and inflammatory signalling [27]. Its contribution to glycocalyx disruption and proteinuria has also been examined directly [28]. Glomerular hyaluronan has context-dependent structural and signalling functions [29].

Several interventions provide target-level support without yet establishing a class effect in humans. Mineralocorticoid-receptor antagonism preserved the glomerular endothelial glycocalyx and reduced albuminuria in diabetic rats, and enzymatic glycocalyx degradation negated the benefit [30]. In a human cross-sectional study, serum syndecan-1 was higher in type 2 diabetes and independently associated with albuminuria [31]. Systemic heparanase inhibition protected the endothelial glycocalyx in an experimental diabetes model [32]. Adiponectin restored glomerular barrier properties in a mouse model of type 2 diabetes [33]. Heparanase-2-derived proteins and peptides showed renal protection in experimental disease [34]. Angiotensin-converting-enzyme inhibition preserved the peritubular capillary glycocalyx in experimental diabetic nephropathy [35]. These findings support druggable biology, but albuminuria remains a composite outcome and systemic shedding markers remain non-localizing. The association of glycocalyx injury with albuminuria and cardiovascular risk supports this caution [36]. Evidence from other vascular disorders likewise shows that systemic permeability markers are not organ specific [37].

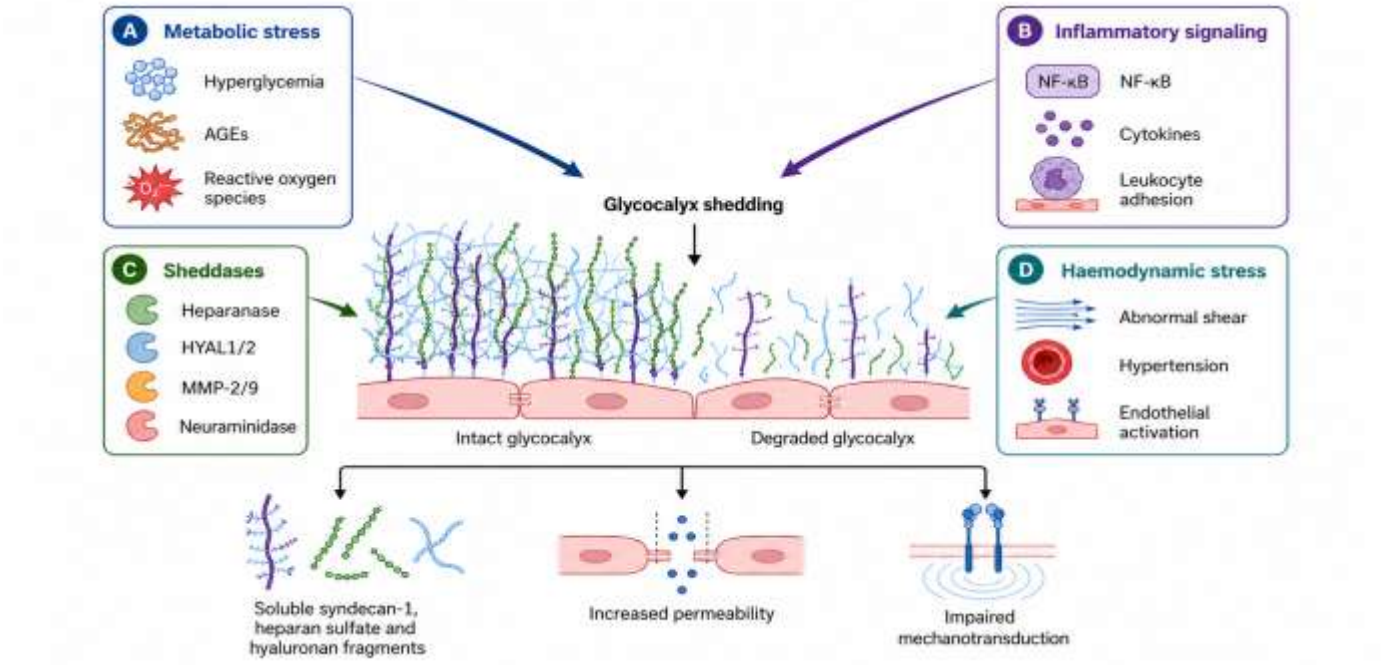
3.3. Brain endothelial glycocalyx and neurovascular integrity

The brain endothelial glycocalyx is the first blood-facing layer of the extended neurovascular unit. It contributes physical and electrostatic exclusion, shear sensing, anti-adhesive signalling and organization of endothelial receptors [38]. Recent experimental work identified age- and disease-associated loss of brain endothelial mucin-domain glycoproteins; restoring core mucin-type O-glycans improved barrier function and reduced neuroinflammation and cognitive deficits in aged mice [39]. This work establishes biological importance, but it is not a diabetes trial and does not validate circulating glycocalyx markers as brain-specific readouts.

A focused review has proposed that brain-endothelial glycocalyx damage may contribute to enlarged perivascular spaces in obesity, metabolic syndrome and type 2 diabetes [40]. Diabetes-related blood-brain barrier injury is supported by experimental and clinical literature, including endothelial junctional change, pericyte dysfunction, inflammation and altered transport [41]. In diabetic mice, neurovascular-unit disruption was attenuated by a mitochondrial carbonic-anhydrase inhibitor [42], while earlier studies linked impaired neurovascular coupling to diabetes-associated cognitive dysfunction [43]. Contemporary human-oriented synthesis likewise identifies neurovascular coupling as a plausible contributor to cognitive decline [44].

Retinal imaging has been associated with cognition, barrier disruption and neuroinflammation in diabetic mice [45], suggesting that accessible microvascular beds may provide convergent rather than brain-specific information. Emerging human studies combine circulating and imaging markers of blood-brain barrier disruption in diabetic cognitive impairment [46]. Experimental MYDGF treatment has attenuated barrier breakdown and cognitive deficits [47], but such intervention studies demonstrate model-specific rescue, not the proposed gut-kidney-brain mediation. The neurovascular extracellular matrix shapes barrier behaviour beyond the glycocalyx [48]. Haemorrhagic complications of diabetes further illustrate the contribution of cellular and haemodynamic injury [49]. Figure 2 integrates these metabolic, inflammatory, enzymatic and haemodynamic routes while retaining the limits of organ-level inference.

Figure 2. Glycocalyx shedding network in diabetes.



Notes: Metabolic, inflammatory, enzymatic and hemodynamic stresses can converge on surface-layer loss. Evidence for individual nodes varies by organ and model; circulating fragments do not identify their tissue of origin.

3.4. Functional convergence across anatomically distinct barriers

The three barriers share broad functions that include spatial exclusion, charge-dependent interactions, mechanochemical signalling and control of cellular adhesion [3]. Their implementation nevertheless differs. Intestinal mucus is continuously secreted and hydrated at a host-microbial interface, where mucin glycans also participate in microbial nutrition and recognition [8]. The glomerular endothelial glycocalyx is exposed to filtration forces and operates within a multilayer barrier whose endothelial, basement-membrane and podocyte components are functionally coupled [19]. The cerebral endothelial glycocalyx forms part of a low-permeability vascular interface supported by specialized transport systems and neurovascular cells [38]. Consequently, an intervention that protects one surface cannot be assumed to reach or rebuild the others.

This anatomical distinction changes how circulating biomarkers should be interpreted. Plasma hyaluronan can increase during endothelial shedding, but its concentration also reflects systemic matrix turnover and clearance [5]. Soluble syndecan-1 is likewise not specific to a single vascular bed or epithelium [31]. Heparan-sulphate fragments may exert biological effects, yet their circulating concentration does not locate the tissue in which cleavage occurred [27]. The review therefore uses the term shared shedding phenotype when the organ source is unresolved and reserves organ-specific injury for tissue, imaging or functionally localized evidence.

A similar rule applies to permeability. Intestinal probe recovery measures transepithelial passage under assay-specific conditions [13]. Albuminuria reflects renal albumin handling across the glomerular barrier and downstream tubular processes [22]. Contrast-based blood-brain barrier imaging interrogates a different substrate, vascular territory and time scale [46]. Concurrent abnormalities could identify a clinically vulnerable phenotype, but these measurements cannot be pooled into a universal barrier score without prospective calibration.

4. Clinical rationale for a cross-barrier model

Albuminuria is the strongest clinical bridge presently available, but it is an epidemiological bridge rather than proof of glycocalyx continuity. Reviews of the diabetic kidney-brain axis describe albuminuria as a marker of renal injury and systemic microvascular dysfunction associated with cognitive outcomes [50]. In American Indian participants, albuminuria related to cognition and MRI markers of cerebrovascular disease [51]. Prospective data in people with diabetes and preserved renal function linked albuminuria with cognitive decline [52]. ACCORD-MIND evaluated brain-volume findings in adults with type 2 diabetes and albuminuria [53], while broader synthesis supports an association with mild cognitive impairment and dementia [54].

Not all cohorts give identical results. The Maastricht Study evaluated eGFR, albuminuria and domain-specific cognitive performance [55], while a systematic review and meta-analysis found an overall association between albuminuria and cognitive impairment or dementia across heterogeneous populations [56]. Longitudinal US data linked kidney measures with incident cognitive impairment [57], and the Rancho Bernardo study provided prospective evidence in older adults [58]. Confounding by age, hypertension, small-vessel disease, education, anaemia and cardiovascular disease remains substantial. None of these studies measured intestinal mucus, glomerular glycocalyx and brain-endothelial glycocalyx concurrently.

The three-barrier hypothesis, therefore makes a deliberately conditional prediction: a subset of people with diabetes may display concordant barrier injury because common metabolic and vascular exposures affect anatomically distinct interfaces. Albuminuria is associated with cognitive and neuroimaging abnormalities in several human cohorts, but these observations do not establish a continuous glycocalyx-mediated pathway from gut to kidney to brain [50]. The model should therefore be evaluated against vascular-common-cause and organ-specific alternatives rather than treated as an established disease sequence.

4.1. Plausible routes of cross-barrier propagation

Hyperglycaemia is a plausible shared exposure because experimental studies show that it can directly alter intestinal epithelial integrity [11], glomerular endothelial glycocalyx properties [20] and blood-brain barrier biology [42]. Oxidative stress, advanced glycation, inflammatory signalling and glycocalyx-cleaving enzymes may amplify injury, although their relative contribution is unlikely to be identical at each interface [4]. Haemodynamic stress is particularly relevant to vascular beds, whereas diet and microbial ecology have more immediate effects at the intestinal surface [17]. These pathways support biological plausibility, not proof that injury progresses through the three organs in a fixed order.

Heparanase, hyaluronidases, matrix metalloproteinases and neuraminidases are plausible convergence nodes, but their relative contribution is not established across all three organs. Kidney experiments provide direct evidence for MMP-mediated syndecan loss [24]. HYAL1 has been linked experimentally to early glycocalyx and endothelial injury [25]. Heparanase has the clearest renal evidence for a broader enzymatic pathway [27]. Brain and intestinal studies more often measure downstream permeability, mucus organization or neurovascular function rather than the same enzyme panel. A rigorous evaluation should therefore measure enzymatic activity and tissue localization rather than assume a universal sheddase signature.

Microbial translocation could connect intestinal containment failure with systemic vascular activation, as experimental work has detected tissue-associated bacteria in metabolic disease models [15]. Shed glycocalyx constituents may also participate in inflammatory signalling rather than behaving only as inert degradation products [5]. Neither mechanism has yet been shown to transmit a complete gut-kidney-brain glycocalyx sequence in humans. Future studies should distinguish these candidate mediators from correlated consequences of obesity, reduced kidney function and generalized endothelial injury.

5. Measuring glycocalyx injury across organs

No single assay can identify whole-body glycocalyx integrity. Plasma syndecan-1, heparan sulphate and hyaluronan are affected by synthesis, shedding and clearance. Sublingual videomicroscopy estimates red-cell penetration into the perfused boundary region and provides an indirect systemic microvascular measure [59]. Studies in diabetic patients demonstrate sublingual microvascular abnormalities [60], while cross-sectional atherosclerosis work illustrates associations between sublingual glycocalyx measures and vascular disease [61]. Methodological reviews emphasize acquisition, analysis and physiological limitations [62]. A biomarker panel should therefore combine orthogonal readouts rather than label one circulating concentration as “glycocalyx damage”.

For the gut, preferred measures include histological mucus thickness or microbial-epithelial distance when tissue is available, together with validated permeability probes and endoscopic barrier assessment [13]. For the kidney, urine albumin-to-creatinine

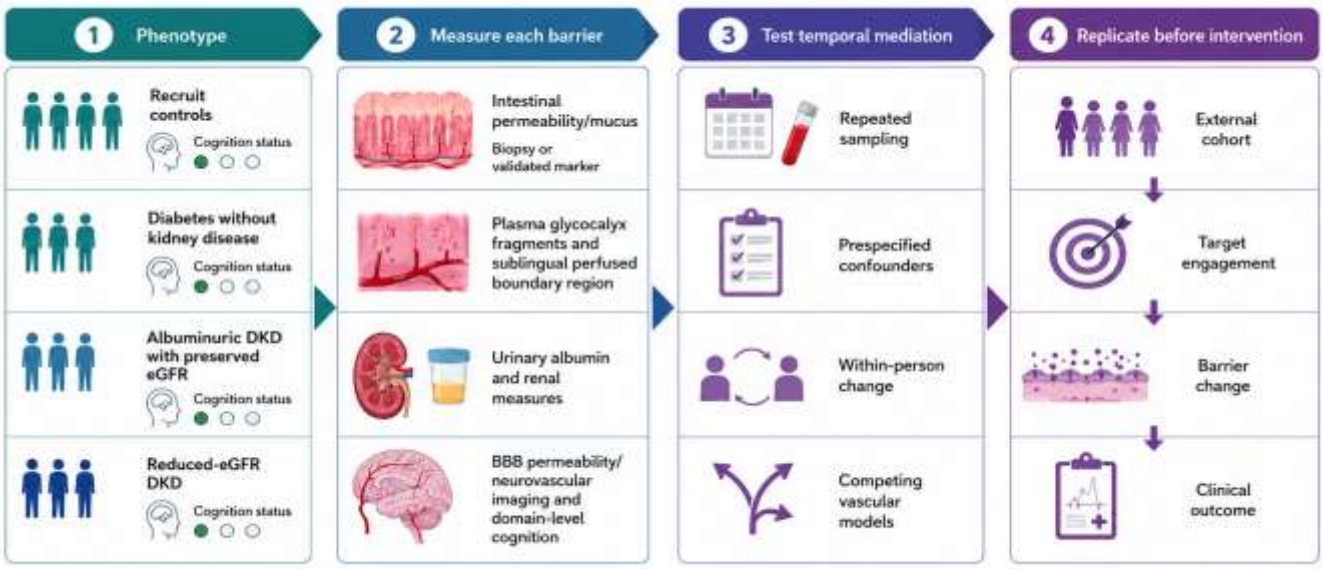
ratio should be combined with eGFR and, in mechanistic studies, a direct or tissue-localized glycocalyx measure because albuminuria alone is not glycocalyx-specific [31]. For the brain, dynamic contrast-enhanced MRI, validated blood biomarkers and neurovascular testing interrogate complementary aspects of barrier function, but none is a direct universal measure of cerebral glycocalyx integrity [46]. Sublingual glycocalyx imaging can provide a systemic vascular phenotype, although it cannot identify the injured organ [59].

Table 2 aligns the principal human evidence with the conclusions that each study design can reasonably support. A minimum validation study should prespecify control, diabetes without CKD, albuminuric DKD with preserved eGFR and reduced-eGFR DKD groups. Cognition should be assessed across executive function, attention, processing speed and memory, with the principal measurements repeated longitudinally. Figure 3 translates these requirements into a staged sequence of temporal testing, mediation, target engagement and replication.

Table 2. Human evidence anchors and interpretation boundaries

Evidence anchor	Study type	What it supports	What it does not prove
Colonic microbial encroachment and dysglycaemia [10]	Human cross-sectional biopsy	Association between glucose dysregulation and microbial-epithelial distance	Kidney or brain mediation
In situ intestinal permeability in type 2 diabetes [13]	Human method/mechanistic study	Feasible direct barrier phenotyping linked to microbiota and glucose	Long-term cognitive or renal causality
Glycocalyx damage with microalbuminuria [21]	Small human comparison	Systemic/microvascular glycocalyx loss tracks albuminuria	Glomerular source of every circulating marker
Serum syndecan-1 and albuminuria [31]	Human cross-sectional cohort	Shedding-associated marker relates to albuminuria	Organ source or mediation
Albuminuria and cognitive outcomes [56]	Human cohorts and synthesis	Albuminuria marks higher cognitive/cerebrovascular risk	Brain glycocalyx injury
Brain glycocalyx restoration [39]	Experimental ageing model	Brain endothelial glycans can be manipulated with functional consequences	Efficacy in diabetic humans

Figure 3. Falsifiable validation roadmap.



Cross-barrier association must be followed by temporal ordering, mediation, organ-specific target engagement and external replication. Failure at any checkpoint should refine or reject the unified model.

5.1. A multimodal phenotyping strategy

A pragmatic protocol can be organized into three tiers. Tier 1 is scalable phenotyping: glycated haemoglobin, ambulatory blood pressure, eGFR, urine albumin-to-creatinine ratio, medication, sleep, body composition, plasma syndecan-1, hyaluronan and heparan-sulphate fragments, plus a standardized cognitive battery. Tier 2 adds barrier-focused measures: intestinal permeability or endoscopic impedance, faecal and mucosal sampling, sublingual videomicroscopy, dynamic contrast-enhanced brain imaging and neurovascular reactivity. Tier 3 provides mechanistic localization in nested subsets through biopsy material, endothelial cell assays, targeted glycomics or spatial analysis.

Repeated sampling is important because circulating shedding products and permeability measurements vary with biological state and sampling conditions. Protocols should therefore standardize fasting status, recent exercise, acute inflammatory illness, hydration, dialysis timing where applicable and medication exposure. These variables should be recorded prospectively and included in a prespecified analysis plan rather than adjusted after outcome inspection.

Organ specificity should be tested, not asserted. Investigators can compare circulating markers with tissue-localized or organ-functional measures, use multivariable latent-variable models and examine whether a proposed systemic shedding factor explains independent variance across interfaces. A marker that tracks only albuminuria may remain clinically useful for kidney risk but should not be promoted as a pan-barrier biomarker.

6. Therapeutic implications and evidentiary thresholds

Preserving the glycocalyx could, in principle, influence permeability, inflammation and maladaptive mechanosensing at the same time. Current therapeutic strategies focus on limiting oxidative stress, enzymatic shedding and endothelial activation [63]. Hyaluronan preservation represents a related approach in diabetic vascular disease [64]. However, a compound that lowers albuminuria or plasma syndecan-1 cannot be described as a three-barrier therapy unless it changes prespecified organ-level measures.

Clinical pharmacology provides preliminary signals. Twelve-month treatment with glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors or their combination was associated with changes in endothelial glycocalyx and vascular measures in type 2 diabetes [65]. Growth-factor pathways have been explored for glycocalyx restoration in diabetic nephropathy [66], and atrasentan has been reported to stabilize endothelial glycocalyx-related properties [67]. Sphingosine-1-phosphate can inhibit syndecan-1 shedding in experimental endothelium [68]. Dietary glycocalyx-precursor supplementation has also been evaluated in type 2 diabetes [69]. These studies vary in design and do not establish cognitive benefit through glycocalyx mediation.

Visceral adiposity has been associated with glycocalyx degradation in people with and without type 2 diabetes [70]. Cardio-renal risk factors also influence glycocalyx measures in type 1 diabetes [71]. Retinal evidence supports diabetes-related surface-layer injury in an accessible microvascular bed [72]. Experimental hyaluronidase exposure further links retinal glycocalyx loss with diabetes [73]. Cardiac experiments show that glycocalyx restoration can improve organ-specific function without establishing cross-organ mediation [74]. Together, these findings support systemic vulnerability while emphasizing the non-specificity of circulating markers. Endothelial CXCR2/NF-kB signalling provides an additional inflammatory-shedding pathway in experimental diabetic kidney disease [75]. A human probiotic-and-fibre trial in type 1 diabetes with albuminuria measured intestinal and endothelial markers [76], but strain-level efficacy and three-barrier mediation were not established. A recent experimental study linked canagliflozin, a microbiota-derived metabolite and glomerular endothelial injury [77]; it should be treated as hypothesis-generating until independently reproduced. Modern turnover models indicate that glycocalyx shedding can represent regulated remodelling as well as irreversible destruction [78]. Translation should therefore assess both loss and resynthesis.

A credible mechanism-linked trial requires a proximal target, a direct target-engagement marker, a barrier-specific intermediate and a clinical endpoint in temporal order. Improved cognition without a measured brain-interface change may still be clinically valuable, but it does not validate glycocalyx mediation. Conversely, lower shedding markers without renal, neurovascular or functional benefit may reflect altered clearance or turnover rather than repair.

7. Experimental evaluation of the three-barrier model

The initial test of the model should be observational and longitudinal rather than an efficacy trial. The proposed protocol would standardize fasting status, medication exposure and blood pressure at each visit. Intestinal barrier phenotyping can include a validated permeability assay, with endoscopic impedance reserved for centres with the required expertise [13]. A plasma shedding panel should be interpreted alongside an organ-localized renal phenotype because circulating syndecan-1 is not tissue specific [31]. Sublingual perfused boundary region can provide a systemic microvascular measure but cannot identify the affected organ

[59]. Neurovascular imaging and domain-level cognition should be acquired together because available blood and imaging markers interrogate complementary, not interchangeable, aspects of brain-interface injury [46]. Missingness, assay batch and centre effects should be defined in the statistical analysis plan.

We propose a directed acyclic graph that separates hyperglycaemia, obesity, blood pressure, kidney function, medication, sleep and small-vessel disease as potential confounders, mediators or modifiers. The primary analysis should emphasize within-person trajectories rather than isolated cross-sectional correlations. A mediation analysis would require the candidate barrier change to precede the downstream phenotype and should avoid adjustment for consequences of the mediator. External replication should precede development of diagnostic thresholds.

Table 3 defines the observations that would support, refine or challenge the proposed model. Concordant worsening across all three interfaces would support a shared vulnerability phenotype but would not establish directionality. Intestinal change preceding circulating shedding and subsequent renal or cerebral change would be temporally compatible with propagation, although intervention evidence would still be required. Poor agreement between circulating markers and organ-level measures would challenge biomarker validity because circulating glycocalyx fragments are not inherently organ specific [62]. Clinical improvement without a corresponding barrier change would argue against glycocalyx mediation while preserving the clinical result.

Table 3. Results that would support, refine, or falsify the three-barrier model

Finding	Interpretation	Decision for model
Three barrier measures worsen together	Shared vulnerability phenotype	Support association; direction remains unresolved
Gut change precedes circulating shedding and organ change	Temporal compatibility with propagation	Proceed to mediation and mechanistic testing
Circulating marker changes without organ-level change	Marker may reflect another vascular bed or altered clearance	Reject organ-specific inference
Albuminuria improves without brain-interface change	Renal benefit without cerebral mediation	Do not claim three-barrier rescue
Cognition improves without barrier change	Clinical benefit through another mechanism	Glycocalyx mediation falsified
Independent cohort fails to reproduce cross-barrier pattern	Model lacks transportability	Refine or abandon unified phenotype

Note: This author-developed decision framework is informed by the evidence summarized and cited in Table 2.

7.1. Prespecified analysis and independent replication

The primary analysis should be declared before outcome inspection. We propose testing whether within-person change in a validated intestinal-barrier measure predicts subsequent change in a prespecified renal or brain-interface measure beyond glycaemia, blood pressure and baseline kidney function. Secondary analyses may examine circulating shedding markers as candidate mediators. The analysis plan should identify the selected markers in advance, control multiplicity and include internal resampling; exhaustive searching for the most favourable pathway should not be permitted.

Competing models deserve equal status. A vascular-common-cause model predicts parallel renal and brain changes driven by blood pressure or small-vessel disease without intestinal mediation. A kidney-clearance model predicts accumulation of circulating fragments as eGFR falls, even if shedding is unchanged. An organ-specific model predicts weak cross-barrier correlation after common risk factors are controlled. Comparing these alternatives is more informative than testing only whether each pairwise correlation is non-zero.

Replication should use a second centre with harmonized acquisition but a different population. Before an intervention trial, the programme should demonstrate reproducible effect direction, acceptable test-retest reliability and temporal precedence of the candidate intermediate. A subsequent intervention should have a defined proximal target, with prespecified adherence, target-engagement and barrier-response measures. Randomization and appropriate negative-control or rescue analyses would then test whether target engagement, rather than nonspecific clinical improvement, accounts for the observed barrier response.

8. Recent advances and future research priorities

8.1. Direct measurement and spatial localization

Recent work is moving the field beyond indirect systemic surrogates. Real-time endoscopic impedance has enabled in situ assessment of intestinal permeability in people with type 2 diabetes and linked the measurements to hyperglycaemia and mucosal microbial features [13]. Human data also associate serum syndecan-1 with albuminuria, although the circulating marker does not reveal its tissue of origin [31]. Brain glycocalyx research has advanced through disease-focused synthesis of endothelial surface loss and neurovascular dysfunction [39]. Blood and imaging biomarkers are now being combined in diabetic cognitive impairment, but direct measurement of the human brain endothelial glycocalyx remains unavailable in routine practice [46]. The next methodological advance should pair circulating markers with tissue, imaging or functionally localized measurements in the same participants.

8.2. Longitudinal validation across the three interfaces

Cross-sectional concordance cannot distinguish common exposure from true cross-barrier propagation. Future cohorts should obtain repeated intestinal, renal and neurovascular measurements under standardized metabolic and haemodynamic conditions. The ProFOS study illustrates the feasibility of measuring intestinal and endothelial markers in people with type 1 diabetes and albuminuria, while also showing that multiorgan measurement does not by itself establish mediation [76]. Experimental work linking canagliflozin, a microbiota-dependent metabolite and glomerular endothelial injury offers a tractable mechanistic lead that requires independent human validation [77]. Because shedding can reflect regulated turnover as well as irreversible damage, future studies should measure both surface loss and resynthesis over time [78].

8.3. Mechanism-linked intervention studies

Intervention studies should proceed only after reproducible temporal relationships have been established. Existing clinical observations with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors suggest that endothelial glycocalyx measures can respond during diabetes treatment [65]. Dietary supplementation with glycocalyx precursors provides another clinically testable strategy [69]. Neither approach currently demonstrates restoration of all three interfaces or cognitive benefit through glycocalyx mediation. A definitive trial should prespecify a proximal target, confirm target engagement, demonstrate change in an organ-resolved barrier measure and test whether that change precedes the clinical outcome. Null mediation findings should be reported even when the treatment remains clinically beneficial.

9. Evidence gaps and limitations

The term glycocalyx covers structurally different surfaces. Intestinal mucus is secreted into a microbial lumen [8], whereas glomerular and cerebral glycocalyces face blood under distinct haemodynamic and transport conditions [19]. Circulating shedding products are therefore not inherently organ-specific [62]. Intestinal permeability, albuminuria and blood-brain barrier imaging also measure different substrates and cannot be treated as interchangeable outcomes [46]. These distinctions limit causal inference from cross-sectional concordance.

The literature is heterogeneous in diabetes type, disease stage, assay and treatment. Narrative evidence mapping cannot provide pooled effect estimates, and several proposed protective strategies remain supported mainly by experimental or early clinical evidence [63]. The three-barrier framework is consequently a testable synthesis rather than a demonstrated clinical pathway. Its value depends on prospective studies that include direct measurements, temporal ordering and explicit comparison with competing explanations.

10. Conclusions

Diabetes can disturb carbohydrate-rich surface layers at intestinal, renal and neurovascular interfaces, but the evidence does not yet establish one continuous gut-to-kidney-to-brain causal chain. The glomerular endothelial glycocalyx has the strongest organ-specific mechanistic connection to albuminuria. Human intestinal-barrier evidence is improving, whereas brain-endothelial glycocalyx translation remains largely experimental. Albuminuria and systemic shedding markers can enrich risk phenotypes but cannot localize cerebral injury. A three-barrier programme based on direct measurement, temporal ordering, competing models and target engagement offers a way to test the hypothesis without converting biological plausibility into premature clinical certainty.

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