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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Tight junction disruption and the pathogenesis of the chronic complications of diabetes mellitus: A narrative review

Ma Ludivina Robles-Osorio, Ernesto Sabath

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Abstract

The chronic complications of diabetes mellitus constitute a major public health problem. For example, diabetic eye diseases are the most important cause of blindness, and diabetic nephropathy is the most frequent cause of chronic kidney disease worldwide. The cellular and molecular mechanisms of these chronic complications are still poorly understood, preventing the development of effective treatment strategies. Tight junctions (TJs) are epithelial intercellular junctions located at the most apical region of cell-cell contacts, and their main function is to restrict the passage of molecules through the paracellular space. The TJs consist of over 40 proteins, and the most important are occludin, claudins and the zonula occludens. Accumulating evidence suggests that TJ disruption in different organs, such as the brain, nerves, retina and kidneys, plays a fundamental pathophysiological role in the development of chronic complications. Increased permeability of the blood-brain barrier and the blood-retinal barrier has been demonstrated in diabetic neuropathy, brain injury and diabetic retinopathy. The consequences of TJ disruption on kidney function or progression of kidney disease are currently unknown. In the present review, we highlighted the molecular events that lead to barrier dysfunction in diabetes. Further investigation of the mechanisms underlying TJ disruption is expected to provide new insights into therapeutic approaches to ameliorate the chronic complications of diabetes mellitus.

Key Words: Tight junctions; Blood-brain barrier; Diabetic neuropathy; Blood-retinal barrier; Diabetic retinopathy; Diabetic nephropathy

Core Tip: Chronic complications of diabetes mellitus constitute a major public health problem. Tight junctions are epithelial intercellular junctions, and their main function is to restrict the passage of molecules through the paracellular space. TJ disruption plays a fundamental pathophysiological role in the development of diabetic chronic complications. Increased permeability of the blood-brain barrier and the blood-retinal barrier are related to development of diabetic neuropathy and diabetic retinopathy.

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INTRODUCTION

Tight junctions (TJs) are epithelial intercellular junctions located at the most apical region of cell-cell contacts. TJs serve two main functions: (1) Gate function, which restricts the passage of molecules through the paracellular space; and (2) Fence function, which confers cell polarity by preventing the movement of solutes and proteins between the apical and basolateral plasma membrane. Additional functions in cell-signaling processes, cell proliferation and gene expression have been identified[1].

At a molecular level, the TJs consist of over 40 proteins including members of the four-pass trans-membrane proteins that are part of the occludin and claudin families. TJs are also composed of cytoplasmic proteins, such as members of the zonula occludens (ZO-1,-2,-3) family, which connect TJs to the cytoskeleton by binding to actin filaments[2] (Figure 1).

Claudins are 21-28 kDa proteins and consist of four transmembrane domains, two extracellular loops, amino- and carboxyl-terminal cytoplasmic domains, and a short cytoplasmic turn. Claudins interact with the ZO-family of scaffolding proteins *via* their cytoplasmic region and are an essential component of the TJs regulating assembly and permeability[2].

Occludin is a 65 kDa protein that interacts with other TJ proteins such as membrane-associated guanylate kinase-scaffolding proteins. Occludin is expressed in endothelial and epithelial tissues, and its expression is regulated by different tyrosine and threonine kinases such as the non-receptor tyrosine kinase c-Yes and the protein kinase C (PKC). Madin-Darby Canine Kidney (MDCK) cells that express terminally truncated occludin have an increase in the paracellular permeability but preserve the formation of TJ strands[3]. However, occludin null mice did exhibit defects in certain organs, and histological abnormalities were found in several tissues including hyperplasia of the gastric epithelium, brain calcifications and testicular atrophy, suggesting an unknown role of occludin in the homeostasis of these organs[4].

The ZO proteins (members of the membrane-associated guanylate kinase family) are scaffolding proteins that bind and regulate the expression of cytoplasmic (cytoskeleton) and transmembrane components of the TJs. ZO proteins regulate gene transcription, cell proliferation and claudin polymerization. Phosphorylation of these proteins by the PKC and tyrosine kinases regulates TJ permeability and assembly. ZO-1 depletion in MDCK and endothelial cells lead to TJ disruption, delayed formation of TJs and reorganization of the actin and myosin cytoskeleton[5]. Maintenance of the cellular barriers and regulation of the transepithelial permeability to prevent diffusion of small molecules and bacteria to specific organs such as brain and retina is essential to keep the homeostasis at these organs.

Type 2 diabetes mellitus (DM) is a chronic disease that has reached epidemic proportions. Chronic hyperglycemia (CH) combined with defects on insulin secretion and action impair the microvasculature and activate intracellular signaling pathways, eventually leading to diabetic nephropathy (DN), retinopathy and neuropathy with significant negative effects on the quality of life and life expectancy[6].

Many studies have demonstrated that TJ disruption and increased leakage of water, solutes and proteins is associated with development of diabetic chronic complications [diabetic eye disease (DED), diabetic neuropathy and DN][7,8]. Therefore, this review aimed: (1) To summarize the normal structure of the TJs at the different barrier structures (brain, nerves, retina and kidney); (2) To describe the pathophysiological changes caused by DM leading to TJ disruption and increase in paracellular permeability that are associated with the chronic complications; and (3) To summarize these findings with the clinical consequences and pharmacological treatments used in the management of these complications.

SEARCH STRATEGY

This systematic review was conducted according to the 2021 guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[9]. Both authors (MLRO and ES) systematically searched PubMed, Google Scholar and the Reference Citation Analysis (<https://www.referencecitationanalysis.com/>) databases to identify published articles from 1978 to December 2022 describing the role of TJs and the chronic complications of DM. Seminal references from selected articles were also searched and included. Both authors independently reviewed the database search results, assessed the

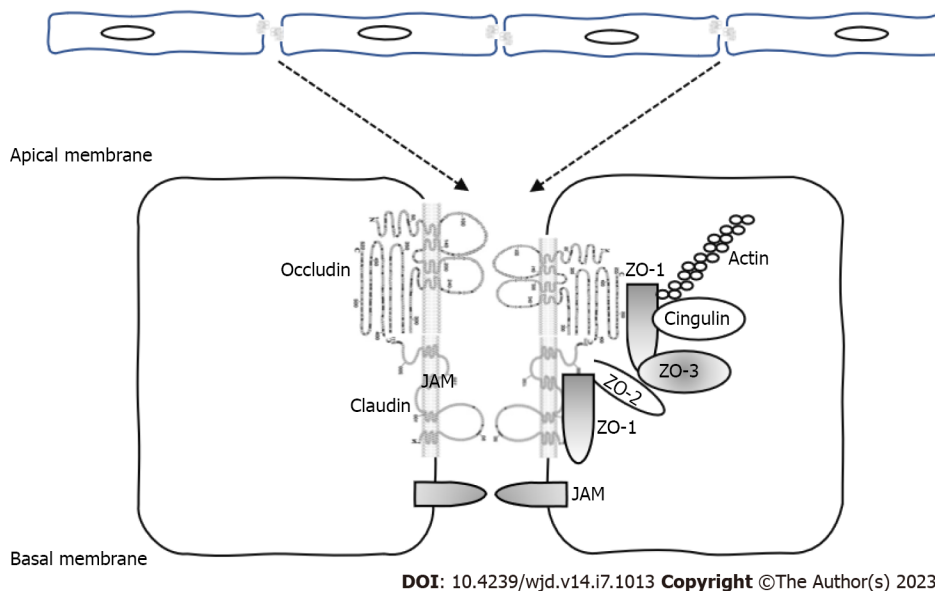


Figure 1 Molecular organization of the tight junctions. Claudins, occludin and junctional adhesion molecules are the major integral membrane proteins of tight junctions (TJs). Claudins form TJ strands, corresponding to membrane kissing points. TJ-associated membrane proteins are localized at apical cell-cell junctions by interacting with the zonula occludens family of scaffolding proteins, serving as links between TJs and the actin cytoskeleton. JAM: Junctional adhesion molecules; ZO: Zonula occludens.

titles, evaluated the abstracts and considered the study for full review. The search was performed combining the texts “tight junction” OR “occludin” OR “ZO (zonula occludens) proteins” OR “claudin” OR “blood retinal barrier” OR “brain-blood-barrier” OR “glomeruli” OR “renal tight junctions” with “diabetes mellitus” OR “diabetic retinopathy” OR “diabetic neuropathy” OR “diabetic nephropathy.” Only articles written in English were included (Figure 2). For the final analysis we evaluated 109 research papers.

DM AND TJ DISRUPTION

DM, TJs and nervous system disease

The blood-brain-barrier (BBB) and the blood-nerve-barrier (BNB) are highly selective semipermeable barriers that regulate the exchange of water and solutes between the blood and the nerve tissue. Both the BBB and the BNB play important roles in maintaining the integrity of the nervous system, and many recent reports suggest that their breakdown drives a cascade of pathogenic events leading to many nervous system diseases[10].

DM and increased permeability of the BBB: Numerous epidemiological studies have shown that DM is an important risk factor for central nervous system (CNS) disorders such as stroke[11], mild cognitive impairment and dementia[12]. The underlying causes related to these complications are multifactorial and are not well understood, although it is now evident that BBB damage adversely affects CNS homeostasis and function[10] (Figure 3).

The BBB consists of a confluent layer of non-fenestrated endothelial cells that tightly regulate the movement of molecules between the blood and the nervous system. Its basic structure is formed by the TJs located between the endothelial cells. The brain capillaries are shielded by pericytes and the foot processes of the astrocytes. These cells are important for the secretion of proteins that forms the basement membrane. The BBB is permeable to small molecules and lipid-soluble proteins, but receptor-mediated transcytosis is required by large molecules to enter the nervous system[13].

The endothelial TJs of the BBB are formed by the transcellular proteins claudins, occludin and junctional adhesion molecules. The loss of claudins increases barrier permeability, suggesting that this family of proteins are particularly important for barrier function. Claudins -1, -3, -5 and -12 take part in the formation of TJs between the endothelial cells [14]; claudin-5 is the most abundant claudin at the BBB and is a critical regulator of brain endothelial cell permeability. In claudin-5 knockout mice the blood vessels of the brain showed normal development and morphology, but the size-selectivity of the BBB was impaired allowing diffusion of small molecules[15].

Occludin is highly expressed at the BBB but does not appear to be essential to barrier function, as occludin-deficient mice have normal BBB permeability. ZO-1, ZO-2 and ZO-3 cross-link the claudins and other TJ proteins to the endothelial cytoskeleton[16]. Increased permeability of the BBB has been demonstrated in both type 1 DM[17] and type 2 DM[18,19], and significant efforts have been made to identify the molecular mechanisms related to BBB breakdown in DM.

Huber *et al*[20] demonstrated a progressive increase in the BBB permeability to small molecules in mice with streptozotocin-induced DM; the midbrain was particularly susceptible to DM-induced microvascular damage. Insulin administration attenuated BBB disruption during the first few weeks of treatment. However, as DM progressed the microvascular damage occurred even if hyperglycemia was controlled.

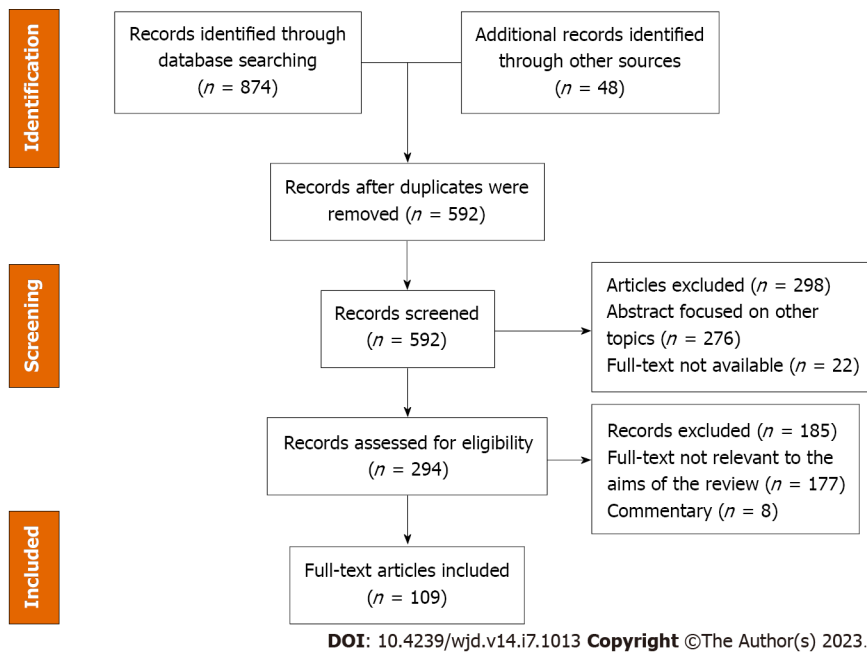


Figure 2 Study flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

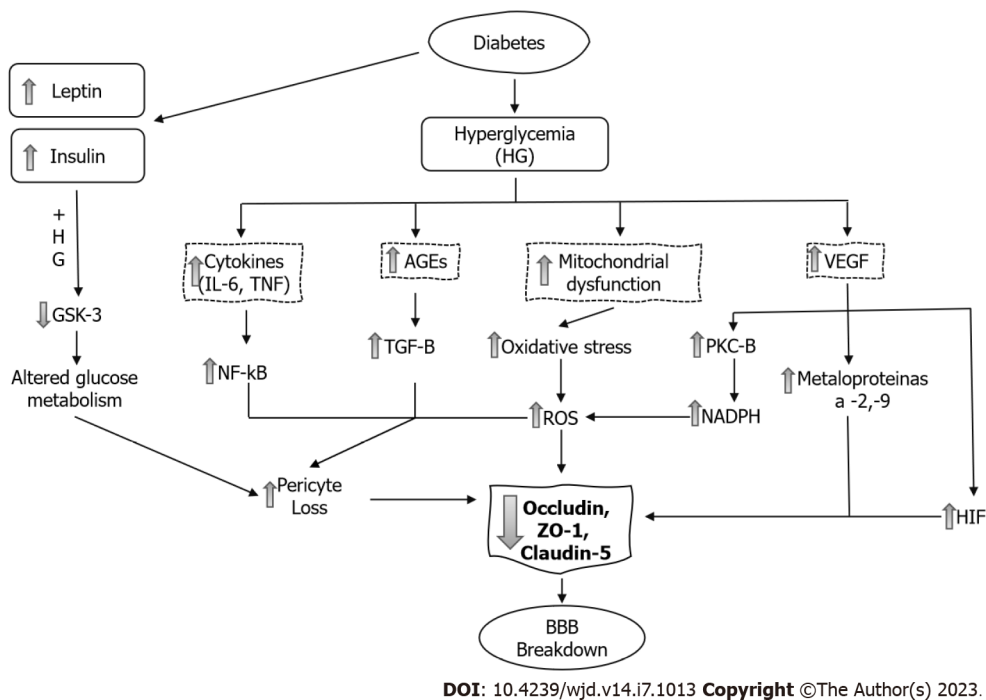


Figure 3 Mechanisms of blood-brain-barrier dysfunction in diabetes mellitus. AGE: Advanced glycation end-product; BBB: Blood-brain-barrier; GSK-3: Glycogen synthase kinase 3; HG: Hyperglycemia; HIF: Hypoxia-inducible factor; IL-6: Interleukin 6; NADPH: Nicotinamide adenine dinucleotide phosphate; NF-κB: Nuclear factor-kappa B; PKC-β: Protein kinase C; ROS: Reactive oxygen species; TGF-β: Transforming growth factor; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; ZO-1: Zonula occludens.

There are many proposed mechanisms by which DM leads to pericyte loss and BBB breakdown. Hyperglycemia causes mitochondrial dysfunction and synthesis of reactive oxygen species (ROS) and increases oxidative stress, activation of nuclear factor-kappa B (NF-κB) and the synthesis of inflammatory cytokines[21]. In pericytes and endothelial cells, both hyperglycemia and formation of advanced glycation end-products (AGEs) downregulate the TJ proteins claudin-5, ZO-1 and occludin. There is also a significant increase in the amount of occludin and claudin-5 on the membrane-bound extracellular vesicles[22]. This allows greater influx of blood components into the perivascular space.

Hyperglycemia also stimulates the synthesis of vascular endothelial growth factor (VEGF), increasing both angiogenesis and vascular permeability. Downstream, VEGF activates PKC-β, causing an increase in nicotinamide

adenine dinucleotide phosphate-oxidase and an increase in ROS formation. VEGF increases the activation of different matrix metalloproteinases (MMP-2 and MMP-9). These mechanisms increase brain barrier permeability through the decrease in occludin expression and phosphorylation[23].

The hypoxia-inducible factor-1 (HIF-1) is a transcriptional factor that activates cellular adaptation to hypoxia. High glucose upregulates the transcriptional activity and protein level of HIF-1 α in brain endothelial cells. In addition, it increased the paracellular permeability and diminished the expression of the TJ proteins occludin and ZO-1[24].

The development of cognitive impairment in diabetic rats was associated with an increase in the BBB permeability. These rats showed an increase in brain levels of interleukin (IL)-6 and a decrease in occludin and claudin-5 expression [25].

Recent studies suggested that many factors other than hyperglycemia, like insulin and leptin, have a pathophysiological role increasing BBB permeability[26]. Insulin crosses the BBB using a saturable transporter, affecting brain functions through mechanisms largely independent of glucose utilization. Insulin transport across the BBB is highly regulated and altered in obesity, starvation and DM[27].

Insulin receptor signaling regulates the integrity of the BBB *via* inactivation of glycogen synthase kinase 3, a key enzyme in many cellular functions, specifically regulating glycogen synthesis and blood glucose levels. Administration of insulin alone increases BBB resistance, but the combined administration of high glucose/high insulin synergistically impairs TJ integrity[28].

Some drugs have been shown to have effects on BBB structure and function. Statins are known to improve endothelial cell function, and simvastatin treatment improved the barrier function in cerebral tissue of diabetic rats[29]. Administration of valsartan (AT1R antagonist) to db/db mice ameliorated BBB leakage. This finding suggested that neurovascular protection can be obtained blocking the AT1-receptor mediated signaling pathways[30]. Exogenous administration of exendin-4, a glucagon-like peptide 1 agonist that crosses the BBB, reverses the functional changes and restores levels of TJ proteins[31].

In many CNS disorders the BBB integrity is compromised, and treatment with glucocorticoids improves the tightness of the BBB[32]. However, there are no reports about its effects on diabetic animal models.

Diabetic neuropathy and increase permeability of the BNB: Diabetic polyneuropathy (DPN) is the most common chronic complication, with a prevalence of 30%-50%. The duration of DM and HbA_{1c} levels are major predictors of DPN. Other risk factors consistently associated with DPN are hypertriglyceridemia, hypertension, abdominal obesity, low high-density lipoprotein levels, smoking and alcohol ingestion[33].

The BNB is localized in the microvessels of the endoneurium or perineurium, and consists of endothelial cells, pericytes and the basement membrane (Figure 4). TJs are an essential component of the BNB cellular architecture to restrict the paracellular flow into the endoneurial milieu and are constituted by occludin, ZO-1 and claudins. Cells of the perineurium express claudin-1, -3 and -19, whereas the endoneurial vessels express claudin-5[34].

There are many mechanisms involved in the axonopathy associated with DPN. Hyperglycemia increases sorbitol pathway activity, reduces myo-inositol nerve content, induces mitochondrial dysfunction with an increase in the synthesis of free radical species and activates metalloproteinases. The formation of AGEs increases protein glycosylation and Schwann cell injury[35].

Initial studies on the effects of hyperglycemia on BNB structure and permeability were controversial as some initial studies conducted in streptozotocin-diabetic rat models did not show increased permeability to large molecules, even in experiments performed with exposition to severe hyperglycemia[36,37]. Other studies showed severe impairment and increased permeability of the BNB[38]. More recent studies showed that the BNB was leaky for small but not for large molecules. Even though no gross changes in TJ proteins were observed, there was a downregulation in the expression of claudin-1[39]. In human subjects with type 1 DM an increase in the extravasation of albumin and immunoglobulin G through the BNB has been demonstrated[40].

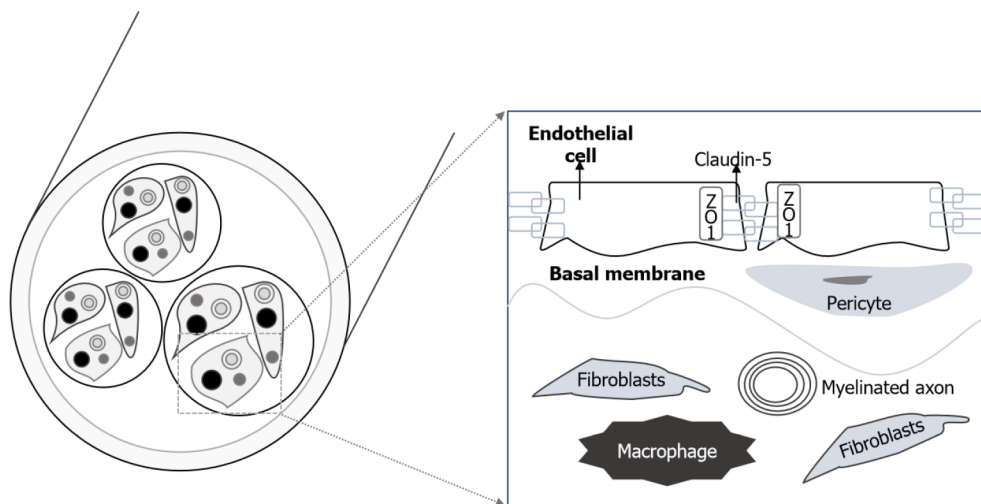
Pathological BNB breakdown leads to an increase in the paracellular leakage of potentially harmful molecules into the nerve tissue and the upregulation of adhesion molecules on the vessel walls to permit the transcellular entry of inflammatory cells to the endoneurium initiating a local inflammatory cascade. Inflammation, endoneurial hypoxia and pericyte degeneration are some of the mechanisms associated with BNB disruption[13]. AGE exposition induces basement membrane hypertrophy and disrupts the BNB by increasing autocrine VEGF and transforming growth factor- β signaling. Claudin-5 synthesis was also significantly reduced[41].

The consequences of the breakdown of the BNB are the access of hematogenous cells and inflammatory molecules to the endoneurium. These phenomenon take part in the local inflammatory cascade generating neuropathic pain[42]. Unfortunately, there are no effective treatments for this complication. Current analgesics have limited beneficial impact alleviating neuropathic pain, and other than glucose and metabolic control there are no disease-modifying therapies[35].

TJ disruption in the physiopathology of DED

DED is the most common microvascular complication of DM and manifests as vascular disease with vessel proliferation [diabetic retinopathy (DR)] and vascular leakage (diabetic macular edema). The latest prevalence data from a pooled analysis estimated a prevalence of 35%, and this prevalence increased with DM duration. The most important risk factors associated with DED are CH, age, cholesterol levels and high blood pressure[43].

The retina is the innermost, light-sensitive layer of tissue of the eye that turns light energy from photons into three-dimensional images. The blood-retina barrier (BRB) separates the retina from the systemic circulation to regulate the flow of water, electrolytes, nutrients and metabolic waste products. The BRB is composed of both an inner barrier (iBRB) and an outer barrier (oBRB)[44].



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Figure 4 Blood-nerve-barrier and cellular structure of the endothelial cells and tight junctions. ZO: Zonula occludens.

The iBRB is composed of retinal vascular endothelial cells (REC) that line the retinal vasculature, which originates from the central retinal artery and supplies the inner retinal layers. The iBRB has some transport properties because substances from the blood can cross it by transcellular (caveolae-mediated transport) and paracellular transport (dependent on TJs). Intercellular TJs are crucial for the formation of endothelial barriers, as they regulate paracellular diffusion[44].

Claudins are the main determinants to regulate TJ properties. Claudin-5 is the most abundant claudin isoform in the BRB and is essential for the maintenance of the iBRB integrity[45,46]. Claudin-5 interacts with the PDZ domains of ZO-1 to cross-link the transmembrane proteins to the cytoskeleton. ZO-1 has an important role to maintain the iBRB permeability as loss of ZO-1 disrupts TJs and increases the barrier permeability[47]. Claudin-1 is also expressed in TJs on REC and is an important component of these structures to keep the barrier function[48].

The oBRB consists of the choroid, Bruch's membrane and the retinal pigment epithelial cells. The retinal pigment epithelial cells are a group of epithelial cells divided into apical and basolateral sides. The apical surface is in direct contact with the photoreceptors, and the basolateral side acts as a barrier that interacts with the capillaries of the choroid layer. The TJs of the RPE are located at the apical surface and are mainly responsible for maintaining oBRB integrity. The oBRB is essential for the survival of the photoreceptors by supporting the absorption of out of focus light, the retinal adhesion and the transport of retinoids and other nutrients[49].

Effects of DM on iBRB: Clinical studies strongly suggest that diabetic macular edema is the result of abnormal fluid accumulation as a consequence of the breakdown and vascular leakage of the iBRB. The predominant molecular mechanisms leading to iBRB breakdown include hypoxia and the direct effects of glucose on the endothelium, activation of VEGF and other intracellular signaling transduction pathways (such as PKC) and the triggering of inflammatory factors like tumor necrosis factor alpha, prostaglandins and toll-like receptor 4 (TLR-4)[50] (Figure 5). Hypoxia activates PKC and directly affects the TJs redistributing occludin and ZO-1[51]; hypoxia is also a key factor to induce the synthesis of VEGF.

VEGF has an important role in the homeostasis of endothelial cells as is an important regulator of vascular permeability, migration and cell proliferation. CH and oxidative stress upregulate VEGF- α and VEGF- β , which induces retinal neovascularization and vascular leakage. In the retina, VEGF is mainly expressed in Müller cells, endothelial cells, astrocytes, RPE cells and ganglion cells. However, recent studies suggest that Müller cell-derived VEGF induces retinal neovascularization, vascular leakage and inflammation playing a major causative role in DR[52].

The process whereby VEGF induces paracellular permeability involves binding to its receptor VEGFR-2 and activation of both the Src family cytoplasmic tyrosine kinases and PKC- β . Tyrosine kinases of the Src family are critically involved in TJ regulation through occludin and ZO-1 tyrosine phosphorylation[53,54]. VEGF also decreases occludin expression[55] and induces occludin serine-threonine phosphorylation through a mechanism mediated by activation of PKC- β . PKC- β is the most crucial PKC isoform that regulates the retinal microvascular permeability[56], and administration of PKC inhibitors prevented this increase in permeability[57]. Endothelial cells with the phosphorylation-resistant Ser490 to Ala form of occludin have preserved TJ organization and reduced VEGF-induced permeability[58].

Hyperglycemia increases the permeability of the REC through decreasing the levels of both ZO-1 and occludin[49]. The expression of claudin-1 and -5 is also decreased[59]. The formation of AGEs also decreases the expression of occludin, ZO-1 and ZO-2 in REC increasing permeability. Interestingly, the administration of silver-nanoparticles inhibited AGE-induced permeability by increasing the expression of the TJ proteins[60].

The increase of intracellular glucose leads to an increase in the synthesis of diacylglycerol, the main endogenous activator of PKC[61]. PKC regulates the function of TJ proteins through the phosphorylation of serine and threonine amino acids. The pathologic effects of PKC activation are mediated through increased vascular permeability, disruption of nitric oxide regulation, increased leukocyte adhesion to vessel walls, changes in blood flow, overexpression of VEGF and increased oxidative stress[62].

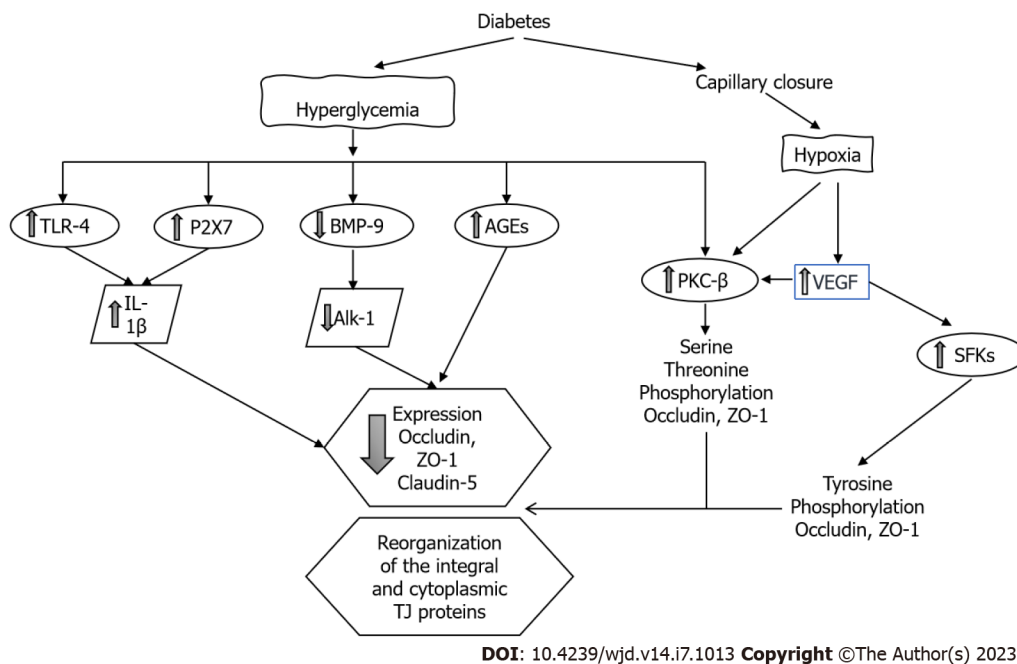


Figure 5 Mechanisms of blood-retina-barrier dysfunction in diabetes mellitus. AGEs: Advanced glycation end-products; Alk-1: Activin-like kinase receptor type I; BMP-9: Bone morphogenetic protein 9; IL-1: Interleukin 1 beta; P2X7: Purinergic receptor; PKC-: Protein kinase C beta; SFK: Src family of cytoplasmic proteins; TJ: Tight junction; TLR-4: Toll-like receptor 4; VEGF: Vascular endothelial growth factor; ZO-1: Zonula occludens 1.

High glucose impairs other signaling cascades in retinal endothelial cells. The bone morphogenetic protein 9/activin receptor-like kinase 1 signaling cascade is necessary to maintain the endothelium integrity; this system is impaired in endothelial cells exposed to hyperglycemic conditions. A decrease in bone morphogenetic protein 9 and alterations in the activin receptor-like kinase 1 cascade contributes to increasing vascular permeability through the disruption of the occludin junctions[63].

Many cell components of the retina including the REC and the RPE express the purinergic receptor (P2X7R). It has been shown that activation of the P2X7R by hyperglycemia has a role in the breakdown of the BRB. Activation of the P2X7R induces the release of IL-1 β . IL-1 β reduces the transendothelial electrical resistance by decreasing the expression of claudin-5 and ZO-1. These effects were inhibited with the exogenous administration of an P2X7R antagonist[64].

β -adrenergic receptors regulate TLR-4 signaling in the retina, and inhibition of TLR-4 significantly reduces retinal barrier permeability. The exogenous administration of forskolin (a PKA agonist) or compound 49b (β -adrenergic receptor agonist) to retinal endothelial cells restored the high glucose-associated decrease in ZO-1 and occludin through the inhibition of the TLR-4 inflammatory cascade[65]. Histamine increases paracellular permeability and reduces the expression of the TJ protein ZO-1 in cultures of retinal endothelial cells[66].

Angiopoietin 1, derived from pericytes, is known to be an antipermeability factor in the vascular system. Angiopoietin 1 has also been proven to have a protective effect on BRB *via* inhibiting VEGF-induced retinal vascular leakage[67].

Hydrocortisone increases barrier properties of the retinal endothelial cells. Hydrocortisone increases the occludin content, decreases occludin phosphorylation and promotes the TJ assembly. These changes decrease water and solute endothelial permeability[68].

Effects of DM on oBRB: The role of the oBRB in the pathophysiology of the macular edema has gained importance in recent years. Recent evidence suggests that the TJs of RPE cells are also compromised in DR and may contribute to macular edema. Leaky TJs would dissipate the chloride gradient that RPE uses to pump fluid out of the retina[69]. Treatment of RPE cells with tumor necrosis factor alpha or IL-1 decreased transendothelial electrical resistance, increased permeability and altered the expression or content of TJ molecules[70].

Villarroel *et al*[71] studied the effects of high glucose concentration in ARPE-19 cells; there was a reduction of permeability with overexpression of claudin-1 and no changes in ZO-1 or occludin. These findings suggested that hyperglycemia per se is not the only factor accounting for the impairment of the oBRB in DR but requires the release of cytokines and ROS to induced damage and increase permeability[72]. At higher glucose exposure, the ARPE-19 cells increased miR-132 expression and decreased the expression of occludin and increased cell permeability[73].

High glucose induces a loss of Na-K-ATPase function impairing the transport of water from the subretinal space contributing to the development of macular edema[74]. Erythropoietin (EPO) is upregulated in DR. EPO overexpression has been found in both the RPE and neuroretina of diabetic eyes. EPO maintains the oBRB integrity through downregulation of HIF-1 α and JNK signaling, thus upregulating ZO-1 and occludin expression in RPE cells[75]. Although VEGF has an important role in the pathogenesis of this disease, the RPE has mechanisms for maintaining low concentrations of VEGF in the retinal space. Peng *et al*[76] showed that VEGF and anti-VEGF drugs (bevacizumab, ranibizumab) have no effects on the TJs of RPE cells.

TJ and diabetic kidney disease

Diabetic kidney disease or DN is the leading cause of end-stage kidney disease[77]. CH leads to structural, metabolic and hemodynamic changes in the renal glomeruli and tubules, but the pathophysiology of the DN is complex and still poorly understood. CH activates the renin-angiotensin system and increases the activity of PKC, ROS formation and many cytokines and transcription factors that result in structural and functional abnormalities in the kidney[78]. However, the effects of hyperglycemia on the renal TJs have received little interest, except for the important focus on the podocyte slit diaphragms (SD).

TJs are necessary for the proper function of glomeruli and tubules and are the most important structures involved in the paracellular transport of water and solutes. The transepithelial electrical resistance and the complexity of the TJ increases from the proximal to the collecting tubule as does the expression of ZO-1, ZO-2 and occludin[79]. The distribution of claudins through the glomerular endothelium and tubules form selective pores and barriers for water and electrolytes such as sodium, potassium, magnesium, calcium and chloride[80].

The distribution and localization of claudins varies along the nephron. In the glomerular endothelium, claudin-5 forms a barrier for high molecular weight proteins. In the proximal tubule (leaky epithelium), claudin-2 forms a pore for sodium and potassium ions. In the thick ascending limb, claudin-14, -16 and -19 regulate the paracellular reabsorption of calcium and magnesium. In the renal collecting duct (tight epithelium), claudin-4 is expressed (together with claudin-3, -7 and -8) and is the major modulator of the paracellular chloride pathway[81].

Aldosterone is the main hormonal stimulus of sodium reabsorption in the distal segments of the nephron by increasing the expression and activity of the epithelial sodium channel. Recent evidence has shown that aldosterone also has a role regulating the paracellular flow of sodium. Aldosterone phosphorylates claudin-4 and increases claudin-8 expression. These mechanism in the distal nephron are aimed to prevent the luminal back-flux of reabsorbed sodium as well to reinforce the paracellular chloride reabsorption pathway[81,82].

Effects of DM on TJs of the glomerulus: The glomerulus is a highly specialized structure that functions as an efficient filtration barrier that restricts passage of large molecules but remains highly permeable to water and small molecules. The glomerulus is composed by a network of capillaries, mesangial cells, podocytes and the Bowman's capsule. The blood is filtered across the fenestra of the glomerular endothelial cells (GEC) and the other components of the glomerular filtration barrier yielding a fluid composed of water plus soluble substances that accumulates at the Bowman's capsule to enter the renal tubules[83].

The GECs form the first cellular barrier, and the TJs between cells are important for maintaining capillary permeability. Injury to the GECs with disruption of the TJs increases its permeability and induces inflammatory cell infiltration, podocyte damage, albuminuria and progression of kidney disease[84]. High glucose decreases the expression of occludin and translocates ZO-1 to the cytoplasm by activation of RhoA (a member of the family of small GTPases)/ROCK1 system. Simvastatin inhibits the RhoA/ROCK1 signaling, increases occludin expression and restores ZO-1 localization. In db/db mice simvastatin decreases albuminuria by suppressing the RhoA/ROCK1 system[85]. AGEs significantly increase the permeability of GEC monolayers through activation of MMP-2 and MMP-9, which downregulate the expression of occludin and claudin-5[86].

Glomerular podocytes (Figure 6) are highly differentiated cells that cover the glomerular capillaries and have a characteristic morphology with numerous foot processes. The formation of SD between the foot processes serves as a final filtration barrier and is composed by many transmembrane proteins such as nephrin, podocin, Nephr1 and Fat1. Podocyte damage causes disruption of the filtration barrier, proteinuria and glomerulosclerosis[87].

During the early stages of embryonic development the TJs connect immature podocytes, but in mature stages they disappear along with the widening of the intercellular spaces and the appearance of SD[88]. TJ proteins such as occludin, claudin-5 and ZO-1, but not claudin-1, have also been found in the SD of the mature podocytes. Their expression and localization are altered in glomerular diseases[89].

DN and other diseases with nephrotic proteinuria are characterized by the loss of the filtration slit, appearance of TJ-like structures and the presence of multiple membrane "fusion" points between the foot processes. This finding has been called the SD to TJ transition and is mediated by the upregulation of claudin-1 in podocytes[90-92].

In normal conditions, claudin-1 is usually absent from podocytes but present in the glomerular parietal cells. In DN, claudin-1 is upregulated in parietal cells and extended ectopically to podocytes[90]. The presence of claudin-1 led to podocyte effacement and albuminuria, presumably through the activation of the β -catenin/Snail signaling system and pathological interactions with nephrin and podocin, which disrupts the SD[92].

Sirtuin-1 (Sirt1) is an NAD(+)-regulated deacetylase with numerous known positive effects on cellular functions, and accumulating evidence shows that Sirt1 plays a crucial role in the pathogenesis of DN[92]. Hasegawa *et al*[93] found reduced expression of Sirt1 in the proximal tubules and higher expression of claudin-1 in glomeruli in streptozotocin-induced diabetic mice, which led to morphological changes on podocytes and albuminuria. Overexpression of Sirt1 in these mice inhibited the rise of claudin-1 and morphological changes. In kidney biopsy samples from subjects with DN, lower expression of Sirt1 and higher expression of claudin-1 were correlated with higher levels of albuminuria. Altogether, these data indicate a protective role of Sirt1 in glomerular and tubular injury.

Claudin-5 has been classified as a cation barrier and is expressed throughout the plasma membrane of podocytes. Molina-Jijón *et al*[82] reported that early DN decreases the expression of claudin-5 in glomeruli. This finding was attributed to an increase in oxidative stress and was associated with changes in the localization of ZO-1. Administration of all-trans retinoic acid ameliorated these changes[94]. Spironolactone prevented depletion of claudin-5 in glomeruli, suggesting a role of aldosterone in the regulation of claudin-5 expression and function[82].

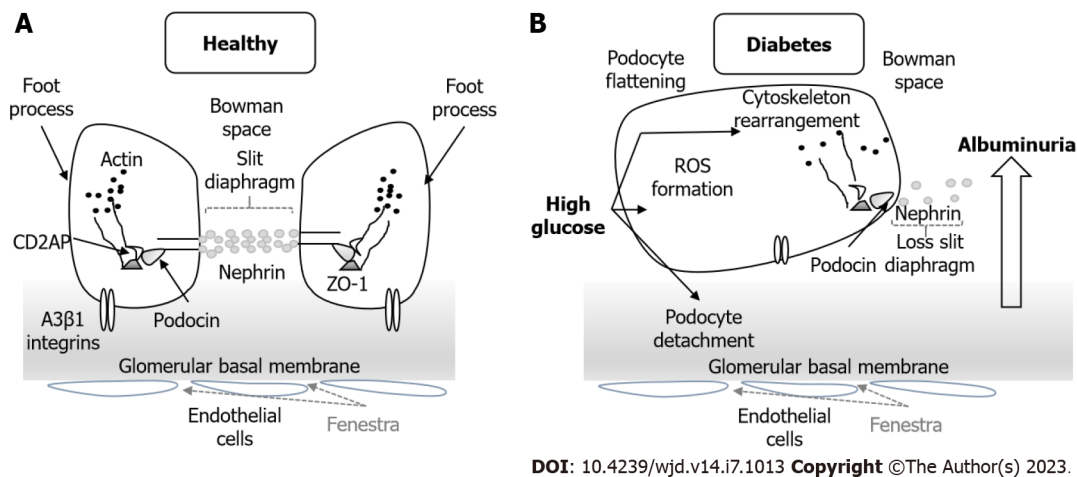


Figure 6 Podocyte structure. A: Normal structure of the podocyte with the morphology of the foot process and the slit diaphragm; B: In diabetic nephropathy the podocyte structure and slit diaphragm are injured with slit diaphragm disruption, podocyte detachment and cytoskeleton rearrangement. These changes lead to albuminuria and progressive kidney disease. ROS: Reactive oxygen species; ZO: Zonula occludens.

Sun *et al*[95] showed that claudin-5 deletion reduced ZO-1 expression and nuclear translocation of ZO-1-associated nucleic acid-binding protein, followed by activation of the WNT signaling pathway that led to podocyte injury and dysfunction. ZO-1-associated nucleic acid-binding protein is a member of a family of DNA-binding proteins that regulate the expression of genes involved in proliferation and other nuclear signaling processes[96].

As previously stated, the scaffolding protein ZO-1 helps to maintain the permselective properties of the glomerular capillary wall. Experimental proteinuria is associated with cellular redistribution of this protein in the glomeruli, and administration of lisinopril [angiotensin converting enzyme (ACE) inhibitor] prevented these changes[97]. In glomeruli exposed to high glucose ZO-1 expression decreased, was redistributed from the podocyte membrane to the cytoplasm and inhibited serine and tyrosine phosphorylation. Administration of angiotensin II type 1 receptor blockers attenuated these changes[98]. An increase of bradykinin levels associated with the use of ACE-inhibitors also prevented ZO-1 changes[99]. These findings explain some of the beneficial effects of drugs acting on inhibition of the renin-angiotensin system.

Modulation of claudins and other TJ-SD proteins remains a key area of research from a clinical and therapeutic point of view. Many current drugs such as ACE inhibitors and simvastatin have a positive effect on these proteins limiting the glomerular injury and progressive kidney disease. Other potential drugs are shown in Table 1. Further research is necessary to develop specific drugs that target these proteins to evaluate their effect on glomerular cells.

Effects of DM on TJs of the renal tubules and tubular transport: The renal tubules and specifically the proximal tubule are uniquely susceptible to a variety of metabolic and hemodynamic factors associated with DM. The development of tubule-interstitial injury is an important risk factor associated with progressive diabetic kidney disease. In early stages of DN, tubular hypertrophy with thickening of the basal membrane is observed, but in advanced stages tubular atrophy with interstitial fibrosis is more prominent[100]. Studies on the effects of DM on tubular TJs are scarce.

The exposition of MDCK II cells to high glucose induced a decrease in the TJ content of claudins-1 and -3, a significant increase in claudin-2 and a decrease in the expression of occludin and ZO-1 junctional content. These changes decreased transendothelial electrical resistance and increased TJ permeability[101]. Claudin-2 expression in the proximal tubule decreased in streptozotocin-induced diabetic rat models[102,103]. The administration of spironolactone and all-trans retinoic acid prevented the decrease in claudin-2 and occludin in proximal tubules by decreasing oxidative stress[82,94].

The consequences of these tubular cell TJ changes on kidney function or progression of kidney disease are currently unknown.

IMPLICATIONS

TJs have an important role in maintaining organ homeostasis and are highly selective structures that regulate the paracellular exchange of water and solutes. Altered TJs have an important role in the pathogenesis of the chronic complications of DM. Identification of the mechanisms that lead to TJ disruption will provide better tools for prevention and treatment of these complications in people with DM.

An area of particular interest is the measurement of TJ proteins on plasma and its correlations with clinical outcomes. Halbgebauer *et al*[104] found significantly increased levels of plasma claudin-5 in trauma patients with hemorrhagic shock that were positively correlated with lactate levels and blood transfusions. These findings indicate that a breakdown of TJ barriers can be related with clinical outcomes in this group of patients. In other diseases, such as bipolar disorders [105] and chronic migraine[106], claudin-5 plasma levels have been found to be significantly higher than in healthy subjects. There are no studies about plasma levels of TJ proteins and clinical outcomes in diabetic patients. This is an area

Table 1 Drugs used to decrease proteinuria and progressive kidney disease and their effects on slit diaphragms /tight junction proteins

| Drug | Type | Mechanism of action |
|------------------|---|---|
| Spirolactone[82] | Mineralocorticoid inhibitor | Decrease oxidative stress Prevent decrease of claudin-5 in glomeruli Prevent decrease of claudin-2 and occludin in PT |
| Simvastatin[85] | Inhibits HMG-CoA reductase | Inhibit RhoA/ROCK1 signaling Increase occludin expression Restore ZO-1 localization |
| atRA[94] | Retinoid | Decrease oxidative stress Prevent decrease of claudin-5 in glomeruli Prevent decrease of claudin-2 and occludin in PT |
| Lisinopril[97] | ACE inhibitor | Preserve glomerular ZO-1 distribution |
| Irbesartan[107] | Antagonist Ang II receptor | Avoid nephrin depletion on SD |
| Sitagliptin[108] | Inhibits DPP-4 | Decrease levels of mitochondrial ROS, ameliorate reduction of claudin-5 in GEC |
| Sinomenine[109] | Alkaloid isolated from the root of <i>Sinomenium acutum</i> | Attenuate ROS level, tight junction dysfunction and RhoA/ROCK activation |

ACE: Angiotensin converting enzyme; Ang: Angiotensin; atRA: All-trans retinoic acid; DPP-4: Dipeptidyl peptidase 4; GEC: Glomerular endothelial cells; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; PT: Proximal tubule; ROS: Reactive oxygen species; SD: Slit diaphragms; ZO: Zonula occludens.

of opportunity for early detection of chronic complications in diabetic subjects.

New findings about the pathophysiology of TJs on the retina, nervous system and kidney may advance the development of delivery systems of insulin and other drugs by targeting these structures.

CONCLUSION

TJs are essential to the integrity and function of the epithelial and endothelial barriers in the retina, nervous system and kidney. Disruption of these structures contributes to the pathophysiology of the chronic complications in DM. There are many mechanisms of TJ disruption in DM, and hyperglycemia triggers many of the mechanisms that induce TJ disruption. Activation of PKC phosphorylates ZO-1, occludin and claudin increasing the permeability of the TJ; an increase in the oxidative stress, activation of metalloproteinases, synthesis of AGEs and hypoxia induces changes on TJ proteins increasing permeability in these barriers. Claudin-5 is an essential component of the BBB and BRB. A better understanding of the functions of these protein may allow better diagnosis and treatment to prevent injury at these organs.

In the kidney, hyperglycemia induces podocyte detachment and changes in the morphology and function of the SD that leads to albuminuria and progressive kidney disease. More research is required to identify the role of TJ disruption with clinical outcomes in diabetic subjects. Future studies should be directed to develop drugs that target TJ proteins to prevent disruption of these barriers and to improve drug delivery to these organs.

The main limitation of this review was the lack of clinical studies conducted on humans, as most of studies were carried out in animal and cellular models. This increases the difficulty for translating whether the molecular changes and severity of the TJ disruption are associated with worse clinical outcomes.

FOOTNOTES

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