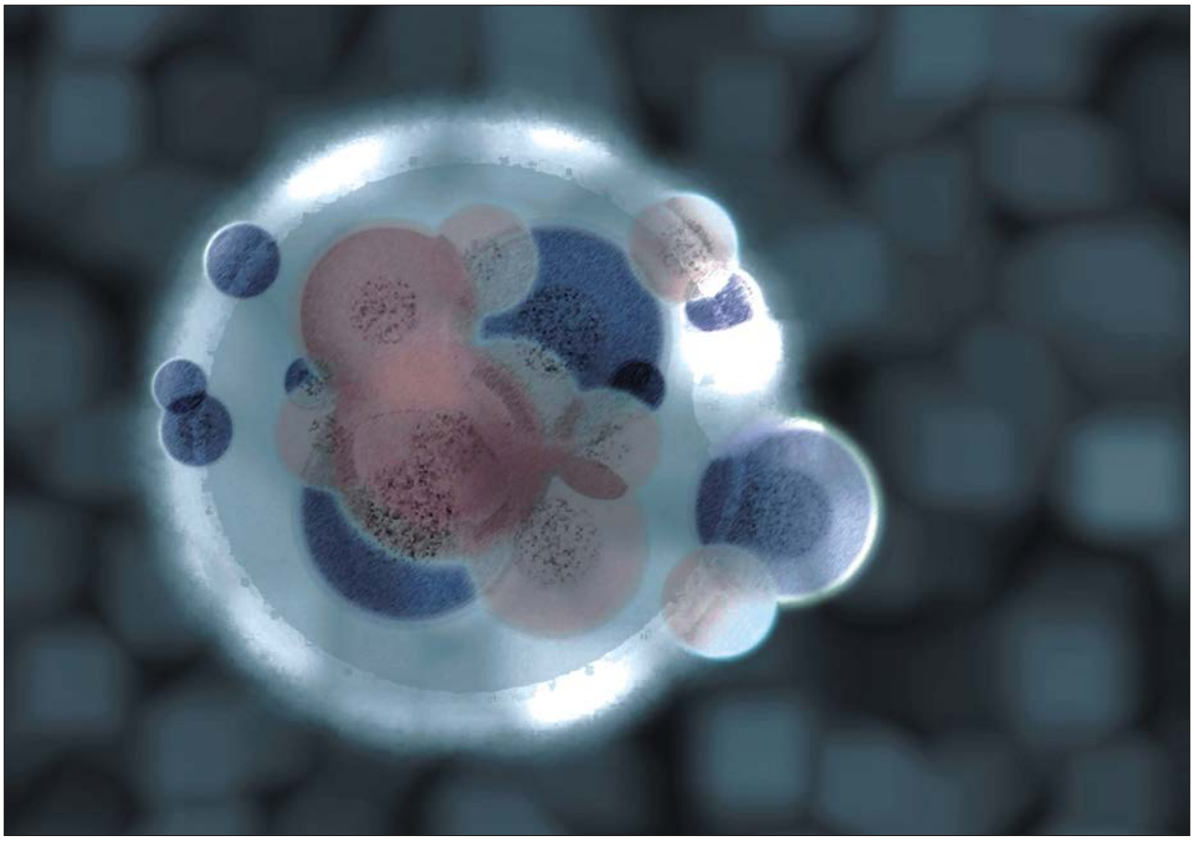

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# Microvascular Complications of Diabetes

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**Abstract:** Diabetes is a methabolic disease characterized by hyperglycemia, with high morbidity and mortility worldwide. Diabetic microvasular complications, which are considered as an important group of hyperglycemia imperfections, caused by increased endothelial permeability and can progress to severe impairments in several organs. Although diabetic nephropathy, neuropathy and retinopathy are the most common microvascular complications of hyperglycemia, it also affects choroid plexus. Here we briefly reviewed the characteristic and etiology of these complications emphasizing on cerebrospinal fluid.

**Key words:** Diabetes, nephropathy, neuropathy, retinopathy, choroid plexus, CSF

## INTRODUCTION

Diabetes Mellitus (DM) is a heterogeneous group of metabolic disease in which the body does not produce and/or utilize insulin (Alberti and Zimmet, 1998; Keecia *et al*., 2005; Abi-Chahin *et al*., 2009). Diabetes is going to become pandemic in the 21st century and its global prevalence is predicted to increase to more than 4% by 2030 (Wild *et al*., 2004).

Among the diabetes imperfections, microvascular complications are common in patients with type1 and type 2 diabetes and represent significant sources of morbidity and mortality (Schwarzenberg *et al*., 2007; Abi-Chahin *et al*., 2009).

Five risk factors that play important roles in the development of microvascular disease are hyperglycemia, individual susceptibility (Gerrits *et al*., 2008; Tarnow *et al*., 1998), hypertension (UK Prospective Diabetes Study Group, 1998), hyperlipidemia and obesity (Hendrick *et al*., 2002). The duration and severity of hyperglycemia are strongly correlated with the extent and rate of microvascular complications (Keecia *et al*., 2005; Bonney *et al*., 1995; Olsen *et al*., 2000).

Chronic hyperglycemia, which is considered as principal cause of microvascular complications such as nephropathy and neuropathy (Keecia *et al*., 2005; Peppa *et al*., 2003; Selvin *et al*., 2004; Sasase, 2006; Yen, 2010), can lead to chronic endothelial permeability; an early manifestation of endothelial dysfunction (Bonnardel-Phu *et al*., 1999; Dang *et al*., 2005; Algenstaedt *et al*., 2003) and kidneys, nervous system and ocular system (retina) impairment (Dandona *et al*., 2004; Lteif *et al*., 2005; Plante *et al*., 1995; Kukidome *et al*., 2006). Improving glycemic condition toward maintaining euglycemia is the most effective strategy for preventing microvascular complications (Yen, 2010) and substantially reduce the incidence of microvascular disease in diabetic patients (Selvin *et al*., 2004; Shichiri *et al*., 2000; Kukidome *et al*., 2006).

Although all diabetic cells are exposed to elevated levels of plasma glucose, hyperglycemic damage is limited to those cell types that are unable to down regulate glucose transport into the cell (e.g., endothelial cells), leading to intra-cellular hyperglycemia (Brownlee, 2001).

In the early stage of diabetes, intracellular hyperglycemia increases blood flow, vascular permeability and intra-capillary pressure (Brownlee, 2001), due to the decreased activity of vasodilators such as nitric oxide (Abi-Chahin *et al*., 2009), increased activity of vasoconstrictors such as angiotensin II (Schmieder *et al*., 2009) and endothelin-1 (Papadogeorgos *et al*., 2009) and permeability factors such as VEGF (Paques *et al*., 1997; Benjamin, 2001). Consequently, capillaries exhibit increased leakage in some organs. Hyperglycemia may also decreases the production of trophic factors in endothelial and neuronal cells (Russell *et al*., 1998). Connective Tissue Growth Factor (CTGF) has recently been shown to be over-expressed in kidney, myocardium and aorta in diabetic animals, implicating CTGF role in the pathogenesis of both microvascular and macrovascular diabetic complications (Brownlee, 2001).

Hyperglycemia results in mitochondrial ROS generation (Brownlee, 2005; Nishikawa *et al*., 2000; Kukidome *et al*., 2006), which induces oxidative stress through multiple pathways including polyol pathway (Gabbay, 1975), DAG/PKC pathway (Koya and King,

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1998; Nishizuka, 1992; Sasase, 2006), AGE formation (Brownlee *et al*., 1988; Brownlee, 1995) and hexosamine pathway (Nerlich *et al*., 1998; Schleicher and Weigert, 2000), that subsequently cause endothelial dysfunction and microvascular complications (Zhang and Gutterman., 2007).

## DIABETIC NEPHROPATHY (DN)

The DN, which is a major cause of illness and death in diabetic patients, leads to the end-stage renal disease (Czekalski, 2005; Ritz, 1999; Sumiyoshi *et al*., 2010). About 30% of type 1 and approximately 20 to 30% of type 2 diabetic cases develop diabetic nephropathy (Devi and George, 2008; Rossing *et al*., 1995; Bakris *et al*., 2000), which is characterized by persistent albuminuria and proteinuria, progressive reduction of GFR rate and increased morbidity and mortality due to cardiovascular diseases (Devi and George, 2008; Gross *et al*., 2005; Tarnow *et al*., 2000; Young *et al*., 2003; De Zeeuw, 2004). Long term diabetes and poor glycemic control are the most important risk factors for DN development (DCCT Research Group, 1993).

Although in all diabetic patients, GFR is initially normal or mildly elevated with no histological alterations, it progresses to produce thick glomerular basement membrane and expand to mesangial, followed by high glomerular capillary pressure and microalbuminuria. Without intervention, microalbuminuria typically may progresses to macroalbuminuria or proteinuria and overt diabetic nephropathy associated with decline in renal function (Fowler, 2008; Czekalski, 2005; Sumiyoshi *et al*., 2010). Only 30-45% of microalbuminuric patients develop overt proteinuria after more than 10 years (Caramori *et al*., 2000).

## ETIOLOGY

It has been suggested that advanced glycation end products (AGE) (Makita *et al*., 1991; Bucala *et al*., 1991), increase synthesis of cytokines and growth factors (Wolf, 2004; Brownlee, 2001) and diverse glucose metabolism into at least three metabolic pathways; the polyol, the protein kinase C (Park *et al*., 2000; Brownlee, 2001) and the hexosamine pathways (Brownlee, 2001), which are associated with the pathogenesis of DN. Vascular Endothelial Growth Factor (VEGF), which is an important growth factor involved in DN, is over-expressed at early stages of DN in both diabetic patients and diabetic animal models (Flyvbjerg, 2000; Khamaisi *et al*., 2003). It has aslo been shown that the blockade of VEGF bioactivity for 6 weeks abolish glomerular hyperfiltration in streptozotocin-induced diabetic rats (De Vriese *et al*., 2001).

Since the characteristic structural changes of diabetic nephropathy are accompanied by accumulation of AGEs, prolonged infusion of nondiabetic rats with AGEs has led to the development of similar morphological changes and significant proteinuria (Peppa *et al*., 2003). Likewise, AGE inhibitors such as aminoguanidine were able to prevent diabetic nephropathy in diabetic animal models (Peppa *et al*., 2003). Studies have also revealed that inflammation plays a crucial role in DN (Janssen *et al*., 2002; Okada *et al*., 2003; Shestakova *et al*., 2002); the migration of immune cells into the kidney is a crucial step in the progression of DN (Galkina and Ley, 2006).

## DIABETIC NEUROPATHY

Diabetic neuropathy, which is recognized as the presence of symptoms and/or signs of peripheral nerve dysfunction in diabetic patients (American Diabetes Association, 2007; Boulton *et al*., 1998a), is a common long-term complication of diabetes affecting up to 50% of patients (Huizinga and Peltier, 2007; Boulton, 2005). The risk factors of developing diabetic neuropathy are the duration and severity of hyperglycaemia (Boulton, 2005), high levels of serum lipids (Boulton, 2005; Rajbhandari and Piya, 2005) and high blood pressure (Boulton, 2005; Forrest *et al*., 1997). Hyperglycaemia, which increases endoneurial vascular resistance and reduces nerve blood flow, leads to endoneurial hypoxia and subsequently, inhibits axonal transport and nerve infarction (Ali, 2003).

Neuropathy, which is a significant source of disability in elderly diabetic patients (Simmons and Feldman, 2002), affect all peripheral nerves such as sensory (Boulton, 2005; Kannan, 2000), motor and autonomic (Boulton, 2005; Kannan, 2000) nerves. Neuropatheis may be focal or diffusable (Boulton, 2005; Kannan, 2000) and is classified as polyneuropathies and mononeuropathies (Boulton, 2007; Welles, 2003).

Mode of acute sensory neuropathy is relatively rapid (Boulton, 2007), while chronic sensory neuropathy is a length-dependant process (Welles, 2003). Diabetic peripheral neuropathy affects up to 50% of elderly type 2 diabetic patients (Boulton, 2005; Boulton *et al*., 2004; Cabezas-Cerrato, 1998) and more than 80% of amputations occur after foot ulceration or injury (Boulton, 2005; Katz *et al*., 2001).

Autonomic neuropathy affects all organs supplied by autonomic nerves (Bhadada *et al*., 2001) and can cause hypoglycemia unawareness, a condition in which people

no longer experience the warning symptoms of low blood glucose levels (Thomas and Tomlinson, 1993; Vinik and Erbas, 2001).

The trigger of diabetic neuropathy is hyperglycemia that appears to result in increased activity of the aldose reductase (polyol) pathway (Yagihashi *et al*., 2001; Simmons and Feldman, 2002), which leads to the accumulation of sorbitol and fructose (Tornlinson, 1989; Yagihashi *et al*., 2001), decreases free nerve myoinositol (Winegrade, 1987; Feldman and Vincent, 2004) and imbalances Nicotinamide Adenine Dinucleotide Phosphate (NADP) and its reduced form (Bhadada *et al*., 2001; Gingliano *et al*., 1996). Advanced glycation end-product pathway (Rajbhandari and Piya, 2005; Monnier *et al*., 1986; Vlassara *et al*., 1983) and hexosamine pathway (Vincent and Feldman, 2004; Feldman and Vincent, 2004) induce inappropriate activation of protein kinase C pathway (Simmons and Feldman, 2002; Rajbhandari and Piya, 2005; Vincent and Feldman, 2004) and formation of reactive oxygen species (Obrosova *et al*., 2001; Bhadada *et al*., 2001; Russell *et al*., 2002; Vincent *et al*., 2004), alter lipid metabolism (Stevensa *et al*., 2009) and lead to diabetes-induced defects in growth factors (Stevensa *et al*., 2009). Available evidence suggests that these various pathogenetic factors act synergistically (Feldman *et al*., 1997).

## DIABETIC RETINOPATHY (DR)

DR, which is defined as microangiopathy of retinal blood vessels, is one of the most common complications of diabetes that causes blindness in working-age individuals (Mohamed *et al*., 2007; Wild *et al*., 2004; Balasubramanyam *et al*., 2002). Damage is caused by both microvascular leakage and occlusion of the inner blood-retinal barrier (Watkins, 2003). Diabetic retinopathy is characterized by early vascular lesions including apoptosis of microvascular cells, formation of pericyte ghosts and the development of acellular capillaries (Mizutani *et al*., 1996; Hammes, 2005; Garg and Davis, 2009), which eventually lead to hypoxia, followed by impaired vision (Benjamin, 2001; Kramerov *et al*., 2006). Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes (Fong *et al*., 2004) and its prevalence increases with severity of hyperglycemia (Wong *et al*., 2008; DCCT Research Group, 1995; Kohner *et al*., 2001) and duration of diabetes (Klein *et al*., 1998, 1989). After twenty years of diabetes, almost all and more than 60% of patients with type 1, 2 diabetes will develop some degree of retinopathy, respectively (Fowler, 2008; Mohamed *et al*., 2007; Watkins, 2003; Balasubramanyam *et al*., 2002; Klein *et al*., 1984). Other risk factors for developing of DR include hypertension (Klein *et al*., 1998; Dharmalingam, 2003; Klein *et al*., 1995; Snow *et al*., 2003), family background (DCCT Research Group, 1997), hyperlipidemia (elevated triglycerides and reduced HDL cholesterol) (Kordonouri *et al*., 1996; Klein *et al*., 1991; Chew *et al*., 1996; Van Leiden *et al*., 2002; Klein *et al*., 2002), obesity, smoking and puberty (Kordonouri *et al*., 1996; Holl *et al*., 1998). DN can be generally classified into nonproliferative (background), proliferative and macular edema (Fowler, 2008; Mohamed *et al*., 2007; Watkins, 2003).

**Background retinopathy:** The first visible signs in background (nonproliferative) DR are microaneurysms, which are defined as small vascular dilatations that occur in the retina and small hemorrhages within the compact middle layers of the retina (Watkins, 2003; Garg and Davis, 2009). Hard exudates are caused by lipid deposition that typically occurs at the edge of microvascular leakage and may form a circinate pattern around a leaking microaneurysm (Fowler, 2008; Watkins, 2003).

Progressive capillary blockade is accompanied by ischaemia and hypoxia (Garg and Davis, 2009). Signs of ischaemia include large dark blot haemorrhages, venous beading (Garg and Davis, 2009), intra retinal microvascular abnormalities and white areas on the retina (cotton-wool spots) (Watkins, 2003).

**Preproliferative retinopathy:** Proliferative diabetic retionopathy occurs with more retinal ischemia and hypoxia, due to microvascular occlusion followed by production of compensatory chemical mediators (most notably VEGF). These mediators induce the growth of fragile new blood vessels, in term of abnormal neovascularization, at the inner surface of the retina, optic disc or iris (rubeosis iridis) (Watkins, 2003; Boulton *et al*., 1998b). If proliferation continues, these abnormal fragile vessels may bleed into vitreous and finally results in tractional retinal detachment and significant vision loss (Garg and Davis, 2009). The new blood vessels can also expand into the angle of eye anterior chamber and cause neovascular glaucoma (Aiello, 2003; Watkins, 2003; Schmieder *et al*., 2009).

**Diabetic macular edema:** Diabetic macular edema is the principal cause of visual deterioration in diabetic patients and caused by breakdown of the inner blood-retinal barrier (Weisbrod and Schwartz, 2009; Rajagopal *et al*., 2009). It can occur at any stage of DR (Garg and Davis, 2009) and is characterized by the accumulation of hard exudates on the macula (Watkins, 2003).

## PATHOGENESIS AND ETIOLOGY

Several biochemical mechanisms including the activation of polyol pathway (Fong *et al*., 2004; Nishimura *et al*., 1994), advanced glycosylated end products (AGEs) formation (Degenhardt *et al*., 1998; Balasubramanyam *et al*., 2002; Wautier and Guillausseau, 2001), increased hexosamine pathway flux (Nerlich *et al*., 1998; Schleicher and Weigert, 2000; Nakamura *et al*., 2001), activation of Protein Kinase C (PKC) (Mohamed *et al*., 2007; Shiba *et al*., 1993; Ways and Sheetz, 2000; Galvez, 2009) and oxidative stress (Balasubramanyam *et al*., 2002; Fong *et al*., 2004; Nakamura *et al*., 2001) lead to retinopathy development. These pathways are associated with the production and signaling of angiogenic factors such as Ang 2 (Schmieder *et al*., 2009) and growth factors including VEGF (Adamis *et al*., 1994; Boulton *et al*., 1998a; Aiello *et al*., 1994; Jardeleza and Miller, 2009; Rajagopal *et al*., 2009), IGF-I (Fong *et al*., 2004; Chew *et al*., 1995), PDGF (Geraldes *et al*., 2009), bFGF (Balasubramanyam *et al*., 2002), Ang2 (Schmieder *et al*., 2009), HGF/SF, PIGF (Balasubramanyam *et al*., 2002), TGF-β (Pena *et al*., 1994; Spranger *et al*., 1999) and PEDF (Dawson *et al*., 1999; Fong *et al*., 2004). Moreover, diabetes-induced tumor necrosis factor (TNFα) plays an important role in microvascular cell loss (Behl *et al*., 2008). Transcription factor FOXO1, which regulates cell death, inhibits cell cycle progression and modulates differentiation in various cell types (Accili and Arden, 2004; Burgering and Kops, 2002), plays an important role in diabetes-induced apoptosis and retinal micro vascular cell loss via a process mediated by TNF (Behl *et al*., 2009). Inhibition of FOXO1 by RNA interference technology reduces microvascular cell apoptosis in diabetic retinas *in vivo* and *in vitro* (Behl *et al*., 2009).

Hyperglycemia-induced intramural pericyte death and thickening of the basement membrane (Geraldes *et al*., 2009) lead to blood-retinal barrier breakdown, retinal capillary nonperfusion and microaneurysm formation (Pardianto, 2005; Watkins, 2003; Weisbrod and Schwartz, 2009).

## CHOROID PLEXUS (CP)

The CP is a leaf-like rich vascularized structure protruds into all four ventricles of the brain and produces cerebrospinal fluid (CSF). CP consists of many fenestrated capillaries and separated from the ventricles by choroid epithelial cells and ependymal lining of the ventricles. The external covering of CP acts as a barrier between blood and CSF; blood filters through CP and make CSF.

## CEREBROSPINAL FLUID (CSF)

CSF is a major part of CNS extracellular fluid (Brown *et al*., 2004). It fills all brains ventricles and subarachnoid space surrounding the brain and spinal cord (Carlson Neil, 2001).

CSF is separated from neuronal tissue by ependyma and pia, which line the ventricles and covers the external surface of the brain, respectively (Brown *et al*., 2004).

Circulation of CSF begins in the lateral ventricles and it flows into the third and forth ventricles. Then, it flows through a set of openings into the subarachnoid space, which encase the entire central nervous system and finally reabsorbed into the blood supply. The total volume of CSF is approximately 125 mL and its half-life is about 3 h (Carlson Neil, 2001). The CP weigh about 2 g in human, so that the rate of CSF secretion is approximately 0.2 mL $min^{-1}$ per g of tissue (Brown *et al*., 2004).

The composition of CSF influences neuronal activity, notably in the central chemoreceptors of the medulla oblongata, that control respiration by responding to changes in CSF pH (Brown *et al*., 2004).

CSF has a number of important functions; it provides mechanical support for the brain by reducing its net weights (Carlson Neil, 2001; Segal, 1993), it removes products of metabolism or synaptic activity and contribute to the stability of neuronal extracellular environment (Segal, 1993; Weaver *et al*., 2004) and acts as a route of communication within the CNS by carrying hormones and transmitters between different areas of the brain (Brown *et al*., 2004).

During fetal development, the brain normal growth depends on the CP-CSF nexus for a steady supply of micronutrients and trophic factors (Weaver *et al*., 2004).

Since CSF is extracted from blood (Carlson Neil, 2001), the compositions of plasma and CSF is very similar. However, in comparison with plasma, proteins have a greatly reduced concentration in the CSF (Brown *et al*., 2004) and the concentration of some ions such as $K^+$, $HCO_3^-$ and $Ca^{2+}$ is carefully regulated in CSF (Husted and Reed, 1976, 1977; Murphy *et al*., 1986).

Hemodynamics in the plexus acts as a significant factor in matching epithelial transport capacity and intimately connected CSF hydrodynamics. Autoregulation of blood flow normally stabilizes the supply of ions and water to the basolateral (plasma-facing) membrane of the epithelium (Weaver *et al*., 2004). In response to ischemia and augmented intracranial pressure, AVP and CBFGF-2, which are colocalized in the choroid epithelium, release from blood CSF barrier and help the repair of injured tissue and adjust CSF (Weaver *et al*., 2004).

**CSF secretion:** CP secrets $Na^+$, $Cl^-$ and HCO3$^-$ and mediate net absorption of $K^+$ from CSF to blood (Wright, 1978). There are net fluxes of other ions such as $Ca^{2+}$ and organic anions and cations across the CP,that play critical roles for the normal function of the CNS and contribute significantly to the osmotic gradient, which drives CSF secretion (Brown *et al*., 2004).

The basolateral membrane contains antiporters which are important for choroid plexus pH regulation and $Cl^-$-$HCO_3^-$ antiporters that move $Na^+$ and $Cl^-$ from plasma ultrafiltrate into choroid cells in the first step of CSF secretion. $HCO_3^-$ generated from carbonic anhydrase activity inside the cell, along with $Na^+$ and $Cl^-$ in the cytoplasm, are extruded into the ventricular CSF by primary ($Na^+$-$K^+$-ATPase pump) and secondary ($Na^+$-$K^+$-2$Cl^-$ cotransport) active transport mechanisms, as well as apical membrane channels (Brown *et al*., 2004; Weaver *et al*., 2004). The $Na^+$-$K^+$ ATPase pumps in the apical membrane are responsible for the export of $Na^+$ into CSF (Brown *et al*., 2004). The $Na^+$-$K^+$-2$Cl^-$ cotransporter is expressed on both basolateral and apical membranes of the choroid plexus (Plotkin *et al*., 1997).

$Na^+$-$K^+$ ATP-dependent transport is the main mechanism by which $K^+$ can be transported from CSF into epithelial cells against a large electrochemical gradient. In the mammalian CP, the Kv1 and Kir7.1 channels probably provide the major route for $K^+$ efflux. However, KCC4 may also contribute to $K^+$ efflux at the apical membrane. This recycling of $K^+$ is necessary to limit the transport of $K^+$ across the epithelium, so that CSF does not become denuded of $K^+$.

Furthermore, $Cl^-$ and $HCO_3^-$ diffuse down electrochemical gradients from cytoplasm to ventricular fluid via specific channels. A cardinal element in this transfer is the movement of $Cl^-$, which attains a concentration in CSF that is 20% greater than in plasma. To complete the secretory process, water follows the translocated ions 'osmotically' through protein structures in the membrane, i.e., aquaporin pores (AQP1) and cotransporters (Weaver *et al*., 2004). Biogenic amines, peptides and growth factors can alter ion transport and consequently CSF formation, usually in an inhibitory manner (Nilsson *et al*., 1992).

Although CSF production is not neurohumorally sensitive to a sudden rise in intracranial pressure, the fluid output by CP seems to be chronically responsive to feedback regulatory mechanisms involving growth factors and neuropeptides (Johanson *et al*., 1999; Hakvoort and Johanson, 2000; Chodobski and Szmydynger-Chodobska, 2001).

## EFFECTS OF DIABETES ON CP

Diabetes is a risk factor for abnormal CSF pressure in hydrocephalus (Casmiro *et al*., 1989; Krauss *et al*., 1996; Casmiro *et al*., 1989) that is caused by excessive retention or production of CSF within the CNS (Casmiro *et al*., 1989; Tehranipour *et al*., 2007). Length density of CP capillaries and the volume of lateral ventricles show significant increase in the newborns of hyperglycemic dams (Tehranipour *et al*., 2008). Furthermore, maternal hyperglycemia may increases the surface of CSF secreting epithelium by abnormal angiogenesis in CP, which leads to imbalance efflux of electrolytes at CSF- blood barrier and increases the ventricular volumes (Tehranipour *et al*., 2008, 2007). Diabetes can affect the blood-brain-barrier (BBB) permeability and leads to disturbance in ion transport and CSF homeostasis (Tehranipour *et al*., 2007).

Data obtained from experiments on diabetic animal models indicate the alteration of ion transporters expression (Jamicki *et al*., 1994) including $Na^+$-$H^+$ exchanger (Siczkowski *et al*., 1995; Dyck and Lopaschuk, 1998; Pierce *et al*., 1990), $Na^+$-$K^+$-2$Cl^-$ cotransporter (Michea *et al*., 2001) and $Na^+$-$K^+$-ATPase (Levy *et al*., 1986; Tehrani *et al*., 1990; Kumthekar and Katyare, 1992; Tesfamariam *et al*., 1993). Similar alterations are reported on perturbations in transport of various ions across the BBB in STZ induced diabetes; $Na^+$and $K^+$ uptake in rat BBB decreased, while $Cl^-$ and $Ca^{2+}$ transport did not alter (Jakobsen *et al*., 1987; Knudsen *et al*., 1986). It has been shown that in the CP of diabetic rats, the expression of α1-subunit of $Na^+$-$K^+$-ATPase, but not β1- or β2-subunits and $Na^+$-$K^+$-2$Cl^-$ cotransporter significantly increase. However, the activity of $Na^+$-$H^+$ exchanger reduces (Egleton *et al*., 2003) and application of $Na^+$-$K^+$-2$Cl^-$ inhibitors decreases CSF production (Egleton *et al*., 2003). Unlike plasma $K^+$, CSF $K^+$ level is maintained during hyperkalemia, which alternatively increases $Na^+$-$K^+$-ATPase α1-subunit expression in diabetic rat CP (Egleton *et al*., 2003; Klarr *et al*., 1997).

High blood glucose level can phosphorylate $Na^+$-$K^+$-ATPase α1-subunit, at serine and threonine residues, by protein kinase C, which may be linked with the down regulation of activity either by stimulating $Na^+$-$K^+$-ATPase endocytosis or inhibiting its enzyme activity (Chibalin *et al*., 2001). Conversely, insulin therapy increases the number of $Na^+$-$K^+$-ATPases and elevates its activity (Sweeney *et al*., 2001) via PKC and tyrosine kinase activity (Chibalin *et al*., 2001), as well as increasing $Na^+$-$H^+$exchanger activity via PKC-ξ (Egleton *et al*., 2003).

High blood glucose also inhibits $Na^+$-$K^+$-$2Cl^-$ activity through the protein kinase C mediated phosphorylation (Layne *et al*., 2001), while osmotic shock stimulates its activity via PKC-δ mediated phosphoelation (Egleton *et al*., 2003).

Since the alteration of transporters activity can alter the production of CSF, it is likely that in diabetic animals, the rate of CSF turnover will change and the ability of CP to compensate this alteration in brain extracellular fluid composition may reduce.

The assessment of electrolytes concentration in CSF of infants from diabetic mothers showed that electrolyte concentration in these animals was increased. Subsequently, CSF osmolality increased and finally resulted in too more water reabsorption. These effects could lead to brain disorders such as hydrocephalus (Tehrampour *et al*., 2007).

## PULMONARY COMPLICATIONS OF DIABETES

The reduction of lung function in diabetic patients (Goldman, 2003; McKeeve *et al*., 2005) may be due to alveolar tissue and capillaries disfunction (Chance *et al*., 2008) that lead to lung volume restriction (Davis *et al*., 2004), forced vital capacity (Hsia and Raskin, 2008) and loss of physiological reserves (Hsia, 2002). Hyperglycemia induces alveolar epithelial and capillary endothelial basal lamina thickening (Weynand *et al*., 1999; Vracko *et al*., 1979) and fibrosis (Farina *et al*., 1995), which result in reduced membrane diffusing capacity and pulmonary capillary blood volume (Chance *et al*., 2008) and restricted alveolar gas transport (Chance *et al*., 2008; Guvener *et al*., 2003; Mori *et al*., 1992) that cause pulmonary microangiopathy (Isotani *et al*., 1999) and 15-30% reduction of pulmonary capillary blood volume in young nonsmoker type 1 diabetic patients (Ramirez *et al*., 1991; Niranjan *et al*., 1997). Impaired alveolar gas transfer in type 1 diabetic patients signifies erosion of microvascular reserves (Chance *et al*., 2008).

Type 2 diabetes has also been linked to pulmonary dysfunction (Foster *et al*., 2010), lower spirometric indexes (Davis *et al*., 2004; Litonjua *et al*., 2005) and resting lung diffusing capacity for carbon monoxide (Asanuma *et al*., 1985; Weir *et al*., 1988), which may be correlate with glycemic control and extrapulmonary microangiopathy (Chance *et al*., 2008).

## CONCLUSION

Diabetic nephropathy, neuropathy and retinopathy are the most common microvascular complications of hyperglycemia and have been well characterized. Since recent reports reveal that hyperglycemia may also affect other microvascular systems, it is worth to pay more attentions on other specialized microvascular systems including CP, alveolar capillaries of lungs and hepatic microvasculature.

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