

# Diabetes Mellitus and Renal Aquaporins (AQPs)



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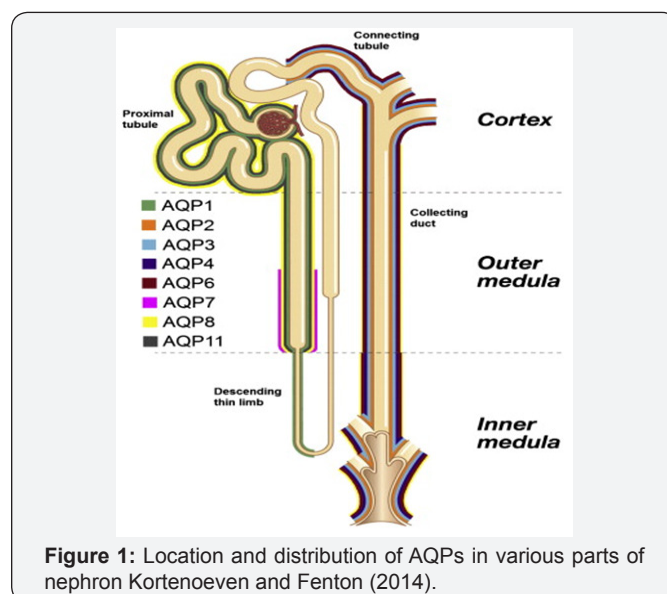
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## Introduction

Diabetes mellitus is defined by the elevation of fasting blood sugar and fasting and it is a disease characterized by impaired carbohydrate, lipid and protein metabolism. The frequency of diabetes has become a rapidly growing public problem and threatening the whole world Satman et al. [1]. The number of diabetics in the world was 194 million in 2003, and this number is reported to reach 246 million in 2007 Satman [2]. It is estimated that this number will increase further International Diabetes Federation (2013). According to estimates, before 2025, the number of diabetics will rise to over 380 million [3]. According to the TURDEP-I study in Turkey, there were a total of 5 million diabetics in 2002. According to the TURDEP-II study results, the rate of diabetic patients in Turkey was increased to 13.7 in 2010, while 7.8% in 2002. This data are shows that diabetes mellitus is a health problem that need to be meticulously focused. Diabetes mellitus causes damage to many organs and tissues. Renal damage induced by diabetes is one of them [4].

In the nephropathy and polyuria in the kidney are disturbing the body water balance. Intracellular, intercellular and extracellular water rates are kept in constant balance with homeostatic mechanisms [5]. Cells are surrounded by cell membranes called plasma membranes that separate the intracellular and extracellular area. The cell is tasked with providing the necessary conditions for the survival of the hostile lifestyle. The water can be passed by simple diffusion the plasma membrane, but the rapid and intensive passage of water is thanks to special channels for this work. The passage from the plasma membrane of water has been a topic of interest to researchers for many years. In 1993, Smith et al. [6] identified the water channel known as CHIP28 on the plasma membrane of erythrocytes (1993). In 1991, Preston and colleagues has showed as a water channel molecule the CHIP28 [7]. In 1993, Fusihimi [8] and his colleagues identified another form that served as a water channel in the renal collecting duct [8]. Agre and colleagues has give the aquaporin (AQP) name to water channel proteins [9]. Later years, studies have determined that

in the cell membrane of mammals found 13 different channels. These channels are named as AQP0-AQP12 [10]. These channels have been identified in many tissues such as kidney, lung, liver, brain and secretory gland [11].



**Figure 1:** Location and distribution of AQPs in various parts of nephron Kortenoeven and Fenton (2014).

As the studies progressed, it was determined that these channel proteins are varied in function, structure and phylogenetics. For example: AQP3, AQP7 and AQP9 passes in glycerol as much as in water. For this reason they are also called aquaglyceroporins [12]. AQP1, AQP2, AQP4 and AQP5 pass only the water. AQP5 is commonly found in tears, duodenal, pyloric and intestinal glands. In the kidney, at least 8 types such as AQP1, AQP2, AQP3, AQP4, AQP6, AQP7, AQP8 and AQP11 have identified [13] (Figure 1). From the AQP1 passes Approximately 109 water molecules. Aquaporins are very important because they provide fluid exchange between placenta and fetal membranes. They are tasked in cerebrospinal fluid formation during normal brain development. Before implantation, the blastocyst is filled with liquid released during the developmental phase of trophectoderm epithelium around the cavity [14-16].

AQPs, which are found in many parts of the organism and play a very important role in water balance, also have important roles in kidney tissue. In the various parts of the nephron, is the functional unit of the kidney have been identified the different APQs [16].

AQP1, consisting of 269 amino acids, forms 3% of the total membrane proteins in the kidney. AQP1 provides water reabsorption from tubule epithelial cells in proximal and descending Henle's thin convolutions [17-19]. It has been determined that there is a decrease in polyuria and urine concentrating ability in experimental AQP1 deficient mice. AQP1 insufficiency is maintained water reabsorption in the proximal tubule by compensating with AQP7. It has determined that AQP1 is also found in the proximal tubule, of apical and basolateral membrane of epithelial cells of the descending Henle. AQP2, which is 271 amino acids in length, is localized to the apical membrane of the parent cells of the collecting tubules. Vasopressin is attached to the V2 receptor at the basolateral membrane of the collecting tubule parent cell and is stimulated with adenylyl cyclase by activation of protein G3, which is guanosine triphosphate binding protein. Activated adenylate cyclase increases cyclic adenosine monophosphate (cAMP) synthesis. cAMP binds to the regulatory subunit of protein kinase A (PKA) and the catalytic unit of the PKA becomes active. As a result, the phosphorylation of AQP2 in intracellular vesicles is increased. AQP2 moves through the apical membrane through microtubule motor proteins. AQPs stick to the apical membrane through various receptors (VAMP2, syntaxin-4, NSF) and exocytosis comes into play.

At this stage, the passage into the cell from the tubule lumen of water is provided. Then, the AQP2 turns cell into from apical membrane cell and the water is taken in by endocytosis. Activation of promoter regions the cAMP responsive substance binding protein in the AQP2 gene is achieved by PKA and thereby increasing the synthesis of AQP2. AQP3, consisting of 292 amino acids, is found in the basolateral membrane of the parent cells of collecting tubules and AQP3 provides passage of water to the interstitial space in this region. Also, AQP3 is responsible for the passage of the urea as well as the water. It has been suggested that AQP3 has activity under the AVP effect. AQP4, which is 301 amino-acidic, is found on the basolateral membrane of collecting tubules in the medulla. AQP4 provides the transmission into the interstitial space from the tubule cells of the water. AQP6 and AQP7 occurs of 276 and 269 amino acids, respectively. AQP6 is found in the renal cortex and medullary and AQP7 is present in apical membranes of the renal cortex.

The functions of AQP6 and AQP7 have not yet been fully obtained. As previously mentioned, AQP7 provides reabsorption of water from the proximal tubules in the inadequacy of AQP1, which prevents the inadequacy of this to reflect on the clinic of this situation. A variety of studies have identified the alteration of diabetes mellitus expression in AQP2, which has a significant

relative in water metabolism [20]. Earlier, diabetic polyuria was thought that was originated from an osmotic diuresis as a result of hyperglycemia. However, recent studies have reported that polyuria is caused by AQPs and especially this is due to the decrease of AQP2 expression. It is thought that in the osmotic diuresis is shaped by the increase of blood vasopressin level. It has been previously determined that AQP2 plays a role in vasopressin-mediated water absorption in the kidney [21-23]. It was determined that the expression of AQP2 and AQP3 was increased in STZ-induced diabetes mellitus in mice [24].

## Conclusion

For this reason, many researchers have been curious about the effects of various drugs on APQ2 and AQP3 excretion in the regulation of polyuria [25-27].

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