Vasopressin Contribute to the Renal Disorder in Insulin-Depending Diabetes Mellitus (IDDM)

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Abstract: Background: diabetes is a condition in which the body does not make enough insulin or cannot use normal amount of insulin, as a result it lead to high blood sugar level, which lead to decrease of kidney function. Diabetic nephropathy represents a major complication of diabetes mellitus and the origin of this complication is poorly understood. Serum arginine vasopressin (AVP) is elevated in type 1 Diabetes mellitus and contribute to progression of chronic renal failure. The current study investigate the hypothesis that AVP hormone play a crucial role in the onset and aggravation of the renal complications of Diabetes mellitus. Methods: one of the major complications of diabetes mellitus is a progressive nephropathy that develops in about thirty females patients with insulin–depending diabetes mellitus IDDM within 15-60 years (after the onset the disease and leads in most cases to different stage of renal failure) and 15 from healthy control groups the samples was obtaining from the Al-Hussein Teaching Hospital and AL-Indian public Hospital in addition some of the samples obtained from some of the specialist diabetes within three months. Enzyme link immunosorbent assay (Elisa system) was used to measured serum vasopressin level among patients with IDDM and healthy controls groups, and factors that are known to be abnormal in early type 1 diabetes mellitus also were assessed including glucose, urea (resulting from liver metabolism), and serum creatinine clearance (an index of glomerular filtration). Result: at the end of the study research revealed the mean of serum vasopressin value in patients with DM was significantly higher in hyperglycemic compared with healthy control (55.5 ± 3.6 and 3.22 ± 1.8), respectively, and the value of probability p = 0.0001 and the result show higher concentration of urea in patients (56.46 ± 3.05mg/dl) compared with controls (27.86 ± 1.5mg/dl) with (p=0.0001). And higher concentration of creatinine in patients (1.56 ± 1.66mg/dl) compared with controls (0.83 ± 0.08mg/dl) with (p=0.003). And during hyperglycemia showed an apparent hypersecretion of vasopressin correlation with higher concentration of urea and creatinine (p<0.0001) conclusions: The current study suggest that AVP may be due to develop the complication of diabetic nephropathy, and future possible therapeutic target for its prevention. All results explained according the influence of AVP on renal function and liver metabolism.

Key words: vasopressin, diabetes mellitus, thirst, hyperglycemia, polyuria, diabetic nephropathy, hyperfiltration, urinary concentrating ability, aquaporin.

INTRODUCTION

Diabetes mellitus often referred to as diabetes-is a condition in which the body either does not produce enough, or does not properly respond to, insulin, a hormone produced in the pancreas. Insulin enables cells to absorb glucose in order to turn it into energy. This causes glucose to accumulate in the blood (hyperglycemia), leading to various potential complications. (Rother, KI, 2007; L.M. Tierney, et al., 2002) the classical symptoms of DM are polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger) in diabetes mellitus the urine flow rate is increased and the fluid turnover in the body is accelerated because of the glucose–induced osmotic diuresis. Presently most persons with type 1 diabetes take insulin injections. Symptoms may develop quite rapidly (weeks or months) in type 1 diabetes. When the glucose concentration in the blood is raised beyond its renal threshold reabsorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst. (Cooke, DW, Plotnick L., 2008) Insulin–depending Diabetes mellitus (IDDM) is characterized by hyperglycemia, with thirst and polyuria secondary to a glycosuric diuresis. However, the mechanism of the polyuria is complex and not simply due to an osmotic Diuresis resulting from the large solute load of urinary glucose (Brodsky, WA, et al., 2000). Secretion of the antidiuretic hormone vasopressin (AVP) in response to osmotic stimuli in type 1 diabetes(Thompson, CJ., et al., 2009; Thompson, CJ., et al., 2004; Zerbe, RL, 2005). It has been suggested that chronic hyperglycemia may cause a form of partial nephrogenic diabetes (8). This suggests the presence of renal resistance to the antidiuretic actions of AVP in type 1 diabetes and suggests that the degree of resistance to AVP is a consequence of poor glycemic control. Diabetic nephropathy represents a major complication of diabetes mellitus (DM), and the origin of this
complication is poorly understood. Arginine vasopressin (AVP) also known as vasopressin or antidiuretic hormone (ADH) is a peptide consisting of nine amino acids. The amino acid sequence of arginine vasopressin is (Cys-Tyr-phe-Gln-Asn-Cys-pro-Arg-Gly) with the cysteine residues forming a sulfur bridge lysine vasopressin has a lysine in place of the arginine. This hormone controls the reabsorption of molecules in the tubules of the kidney by affecting the tissues permeability. It plays a key role in homeostasis, and the regulation of water, glucose and salt in the blood (Caldwell, HK, Young, WS. III, 2006). One of the most important roles of AVP is to regulate the body's retention of water; it is released when the body is dehydrated and causes the kidneys to conserve urine, thus concentrating the urine and reducing urine volume (Walum, H., et al., 2008).

Vasopressin (VP), which is elevated in type 1 DM, has been shown to increase glomerular filtration rate and contribute to progression of chronic renal failure (Baylis PH and Thompson CJ., 1999).

The effects of VP on glomerular filtration rate (GFR), albuminuria, and kidney hypertrophy are thought to result, indirectly, from its antidiuretic activity and the ensuing alterations in tubulo-glomerular feedback control of glomerular haemodynamics (American Diabetes Association, 1998; Bouby, N., et al., 2006; Bankir, L., Kriz, W., 1995; Bankir, L., et al., 1999). In addition to its renal effects, VP also may influence vascular resistance through V1a receptors, expressed in smooth muscle cells. V1a receptors are also abundantly expressed in the liver (Michell, R.H., et al., 2001; Barberis, C., 1998) and VP was shown to stimulate glycogenolysis, gluconeogenesis, and ureagenesis in isolated perfused liver or hepatocyte suspensions, in the same way as does glucagon (Hems, D.A Whitton P.D., 2003; Patel, T.B., 2000).

MATERIAL AND METHOD

After 2 week period of begin the experiment serum samples was collected from forty five females subjected (mean age 36.26 yr. (range 15-60yr.). Mean duration of diabetes 4.2yr range (1-11yr). To evaluated levels of arginin vasopressin (AVP) hormone and concentrations of sugar, urea and creatinine. The forty five females groups were divided into two groups. Thirty females for patients with insulin–depending diabetes mellitus (IDDM) were recruited from the outpatient department of participating hospitals and fifteen females nondiabetic controls groups were recruited from health staff. Analysis serum arginin vasopressin was measured with enzyme link immunoassorbent assay ELISA system (BECKMAN –USA). By used ELISA vasopressin kit obtain from (CUSABIO-BIOTECH co, ltd.). The minimum and maximum level of vasopressin detectable was (10, 80 pg/dl) respectively from all patients with IDDM, but for controls the minimum and maximum level was (0.3, 5 pg/dl) respectively.

The concentration of sugar, urea and creatinine was measured with (spectro UV-Ultrasensitive BEAM-8 AUTO CELL UVs-2800)(LAMBOMED,INC-USA), all chemical and standard solution that used to measurement concentration of fasting blood sugar, urea and creatinine was highest grade and we obtained from (RANDOX-UK). The normal ranging of fasting blood sugar is (80-120 mg/dl), serum urea is (18-40 mg/dl), serum creatinine is (0.7-1.4 mg/dl).

All statistical analyses in studies were performed using SPSS version 15.0 for Windows (Statistical Package for Social Science, Inc., Chicago, IL, USA). Descriptive analysis was used to show the mean and standard deviation of variables. The significance of difference between mean values was estimated by Student T-Test. The probability P< 0.05 = significant, P> 0.05 = non-significant. Correlation analysis was used to test the linear relationship between parameters. NOVA test was used to show the differences between variables of differentiated groups.

Results:

Study 1: Renal response to vasopressin in IDDM patients and nondiabetic control. A significantly higher means of AVP levels occurred in patients with IDDM than in control groups (Table-1).

In this table we can see that the value of vasopressin hormone in IDDM patients was (55.5±3.6 pg/dl) while in nondiabetic control groups (3.22±1.8 pg/dl) with (p<0.0001). and the table show higher concentration of urea in patients (56.46±3.05mg/dl) compared with controls (27.86±1.5mg/dl) with (p<0.0001). And higher concentration of creatinine in patients (1.5±1.66mg/dl) compared with controls (0.83±0.08mg/dl) with (p<0.003).

Study 2: the correlation between hyperglycemia and the hyper secretion of vasopressin, correlation between vasopressin and level of urea and creatinine.

In this study we can see the rise of serum vasopressin was associated with increased of concentration of urea and creatinine. And the table 3 shown the correlation coefficients between the vasopressin ,urea and creatinine in patients with IDDM with (p<0.0001). A possible mechanism is proposed that could explain how the vasopressin–induced intrarenal recycling of urea (which contributes to improvement in urinary concentration) administration, could indirectly depress the tubuloglomerular feedback and hence increased creatinin (an index of GFR). An increased concentration of an osmotically active solute in the thick ascending limb oh henle’ s loop could enable a lower Nacl concentration to be achieved at the macula densa by reducing the osmotically drive.
water leakage in this nephron segment. This mechanism could explain the increased of urea and creatinin seen in various pathophysiologic situations such as chronic vasopressin infusion, high protein intake, severe burns and diabetes mellitus (Bankir, L., et al., 1999).

### Table 1: The means, number of cases, minimum, maximum and standard error in both control and patients:

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age</th>
<th>FBG</th>
<th>urea</th>
<th>creatinine</th>
<th>AVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Mean</td>
<td>36.2667</td>
<td>85.6000</td>
<td>27.3667</td>
<td>1.5480</td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Minimum</td>
<td>19.00</td>
<td>69.00</td>
<td>18.00</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Maximum</td>
<td>55.00</td>
<td>112.00</td>
<td>39.00</td>
<td>1.43</td>
<td>5.00</td>
</tr>
<tr>
<td>Std. Error of Mean</td>
<td>2.80215</td>
<td>3.79825</td>
<td>1.53022</td>
<td>0.8419</td>
<td>3.5456</td>
</tr>
<tr>
<td>Patient</td>
<td>Mean</td>
<td>40.0667</td>
<td>321.3000</td>
<td>56.4667</td>
<td>1.5887</td>
</tr>
<tr>
<td>N</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Minimum</td>
<td>18.00</td>
<td>224.00</td>
<td>38.00</td>
<td>.60</td>
<td>10.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>60.00</td>
<td>423.00</td>
<td>109.00</td>
<td>5.40</td>
<td>80.00</td>
</tr>
<tr>
<td>Std. Error of Mean</td>
<td>2.06277</td>
<td>9.17933</td>
<td>3.05382</td>
<td>.16665</td>
<td>3.60128</td>
</tr>
</tbody>
</table>

### Table 2: the correlation coefficients between age, FBG, urea, creatinin, and vasopressin and other parameter.

<table>
<thead>
<tr>
<th></th>
<th>AGE</th>
<th>FBG</th>
<th>UREA</th>
<th>CREATININ</th>
<th>AVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>1</td>
<td>0.206</td>
<td>0.385*</td>
<td>0.343</td>
<td>0.485**</td>
</tr>
<tr>
<td>FBG</td>
<td>0.206</td>
<td>1</td>
<td>0.446*</td>
<td>0.343</td>
<td>0.626**</td>
</tr>
<tr>
<td>UREA</td>
<td>0.385*</td>
<td>0.446*</td>
<td>1</td>
<td>0.807**</td>
<td>0.492**</td>
</tr>
<tr>
<td>CREATININ</td>
<td>0.324</td>
<td>0.343</td>
<td>0.807**</td>
<td>1</td>
<td>**</td>
</tr>
<tr>
<td>AVP</td>
<td>0.485**</td>
<td>0.626**</td>
<td>0.637**</td>
<td>0.492**</td>
<td>1</td>
</tr>
</tbody>
</table>

*correlation is significant at p<0.05 compared with control groups
**Correlation is significant at p<0.0001 compared with control groups

**Discussion:**

The data from these studies have shown that people with type 1 diabetes are less able than nondiabetic controls to effect antidiuresis and concentrate urine in response to a compare able rise in serum AVP concentration (Lise Bankir, et al., 2001; L. Zerbe, et al., 1999). AVP appears to be inversely related to glycemic control, in that failure to concentrate urine was most marked in those patients who had chronically poorglycemic control. In addition, the reversal of resistance to AVP by short term good glycemic control provides further evidence that the impaired ability to concentrate urine in poorly controlled IDDM is a function of chronically poor glycemic control, rather than a reflection of renal pathology. The role of insulin in the return of renal sensitivity to AVP after improved glycemic control is interesting (DeFronzo, RA., 1981) and data show that insulin can enhance water transport, most probably by stimulating glucose transporters to act as water channels, but possibly by enhancing AVP-mediated water reabsorption. We have also shown for the first time that the severity of renal resistance to the antidiuretic actions of AVP was inversely proportional to the degree of glycemic control. Thus those diabetic subjects with the poorest glycemic control had the least ability to concentrate urine in response to the intravenous infusion of AVP. The demonstration that renal resistance to AVP occurs at physiological plasma concentrations of the hormone indicates that this impaired antidiuresis is likely to have clinically significant effects but our data in IDDM suggest a potential mechanism (Mckenna, K., et al., 2000; Mckenna, K., et al., 2000) We have shown that urinary concentrations of aquaporin-2, the vasopressin-sensitive water channels that promote tubular water reabsorption, are lower in patients with IDDM than in the control group despite comparable plasma AVP concentrations. The failure to recruit aquaporin-2 was more marked in patients with chronically poor glycemic control. (Knepper, MA, et al., 2000) The clinical implications of the renal resistance to AVP is transient. (McKenna, K., et al., 1999) The clinical implications of the renal resistance to AVP in subjects with poorly controlled diabetes mellitus are clear. Poor glycemic control renders the kidneys relatively insensitive to the main homeostatic mechanism that limits water excretion, namely, AVP-stimulated antidiuresis. People with poorly controlled IDDM will therefore be less able to compensate for dehydrating illnesses, Renal resistance to AVP, caused by failure of aquaporin-2 recruitment, may therefore contribute to the propensity for patients with poor glycemic control to develop more marked dehydration and poorer outcome from diabetic ketoacidosis. These results are agreement with those obtained from others investigators (Lise Bankir, et al., 2001; Dongun, K., 2004; Ichinose, K., 2007) vasopressin hormone plays crucial roles in the onset and aggravation of the renal complication and several disturbances observe in diabetes mellitus.
**Conclusion:**

Arginin vasopressin influence of renal function and liver metabolism, it is possible it assume that this hormone might contribute in perturbations in renal and metabolism complication observe in diabetes mellitus. Vasopressin is elevation in type 1 DM understanding the consequences of this elevations thus be important prevention of the renal complication of diabetes mellitus.

**REFERENCE**


