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The Effect of Intranasal Desmopressin Spray on Basal and Total Tear Secretions in Healthy Subjects

Faustina Kemdinum Idu*[1], Gladys Ovigue George[1], Leonard F. Obika[2]
[1]Department of Optometry, Faculty of Life Sciences, [2] Department of Physiology, College of Medical Sciences University of Benin, P.M.B 1154, Benin City, Nigeria.

Summary: Many hormones have been implicated in dry eye syndrome. This study was carried out to investigate the effects of antidiuretic hormone (ADH) on tear secretion. Fifty (50) healthy male and female volunteers between the ages of 21 and 70 years were studied. They were given exogenous ADH in the form of intranasal desmopressin spray (DDAVP). Total and basal tear secretions were assessed using the Schirmer strip at baseline and at 30 minutes intervals for a period of 180 minutes after the nasal administration of 10 µg desmopressin spray into each nostril. Blood samples were taken before and 60 minutes after desmopressin administration for the determination of plasma osmolality and plasma ADH concentrations. Results showed a significant reduction ($p<0.001$) in the means of total and basal tear secretions from baselines of 20.04 ± 1.19 and 14.64 ± 1.00 mm/5mins to 12.80 ± 0.75 and 9.68 ± 0.72 mm/5mins peak reductions respectively. The peak reduction was observed at 90 minutes assessment time after desmopressin administration. The difference in mean total tear secretions between males and females were statistically significant ($p < 0.05$). The difference in mean plasma osmolality before and 60 minutes after desmopressin administration was not statistically significant. However, there was a significant increase ($p<0.05$) in mean ADH concentration after DDAVP administration. It is concluded from this study that exogenous ADH reduces tear secretion in man with associated increase in ADH concentration but no change in plasma osmolality.

Keywords*:* Tears, Desmopressin, Osmolality, Antidiuretic hormone, Schirmer strip, Lacrimal gland

**Address for correspondence:* faustina.idu@ gmail.com

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INTRODUCTION

Antidiuretic hormone (ADH) also known as arginine vasopressin in humans is a peptide consisting of nine amino acids (nonapeptide) produced in the supraoptic and paraventricular nuclei of the hypothalamus, transported to and stored in the posterior pituitary. ADH is responsible for increasing water absorption in the collecting ducts of the kidney nephron which confers its major role in the regulation of water balance (Nielsen *et al*, 1993). ADH is also known as vasopressin because of the vasopressor effect at pharmacological doses.

Desmopressin is a synthetic analogue of the natural pituitary hormone-ADH or better still; it is a synthetic replacement for vasopressin. Compared to vasopressin, desmopressin's first amino acid has been deaminated, and the arginine at the eighth position is in the *dextro* rather than the *levo* form. It is also known as 1- desamino (8 - D- arginine) vasopressin (DDAVP). Desmopressin works by binding to the ADH receptors in the kidneys, which mimics the effect of natural ADH and this reduces the production of urine *(*den Ouden *and* Meinders, 2005). Desmopressin is degraded more slowly than vasopressin, and requires less frequent administration. In addition, it has little effect on blood pressure, while vasopressin may cause arterial hypertension.

The preocular or precorneal tear film is a thin film of tears covering the anterior surface of the cornea. The preocular tears form a film between the inside of the lids and the cornea when the eyes are closed and remain as a film over the cornea for a limited time after the lids are opened [usually greater than 15 seconds] (Whikehart, 2003). The tear film performs several important functions which can be divided broadly into optical, metabolic support, protective and lubricative functions. Complete tear film is essential for the health and function of the eye (Walcott, 1998). Normal tear film dynamics require adequate production of tears, retention on the ocular surface, and balanced elimination. Disruption of any of these components can lead to the condition of dry eye (Tomlinson and Khanal 2005). Dry eye syndrome also known as "keratoconjunctivitis sicca" occurs when there is reduced tear production, unstable tears or excessive tear evaporation and it is the most common disorder of the tear film. Keratoconjunctivitis sicca (KCS) refers to a dry eye primarily resulting from aqueous tear deficiency (Lemp, 1980). Dry eye syndrome is believed to be one of the most common ocular problems in the United States of America (Schaumberg *et al*., 2003).

Many hormones, for example, sex hormones have been implicated in dry eye syndrome, and the presence of antidiuretic hormone in the lacrimal gland of the rat has been documented immunohisto-chemically (Djeridane, 1994). There are conflicting results in the few available data on the effects of ADH on tear dynamics. Turkcuoglu, (2006) in his preliminary study on the effects of desmopressin on aqueous secretion of the lacrimal gland showed that desmopressin decreases the lacrimal glands aqueous secretion. Kurasawa *et al.* (2005) however reported that exogenous ADH increases tear fluid secretion in rats via ADH V1a receptors.

The aim and objectives of this research were to investigate the effect of antidiuretic hormone (ADH) on tear secretion, determine if the effect of ADH on tear secretion is dependent on gender and also determine the plasma concentrations of ADH following intranasal desmopressin administration.

MATERIALS AND METHODS

This study was carried out in the Department of Optometry, University of Benin, Benin City, Nigeria. The study included Fifty (50) apparently healthy volunteers between the ages of 21 and 70 years, comprising 27 males and 23 females. These included staff and students of the University of Benin, Benin City, and staff of Specialist Hospital Benin City, Nigeria.

The study procedure was well explained to each participant and informed consent was obtained from all of them. The study was approved by the ethics committee of the Specialist Hospital, Benin City and was performed in accordance with the guidelines of the Declaration of Helsinki.

Inclusion criteria

The subjects included in the study were males and females within the age range of 21 and 70 years, healthy subjects with no history of systemic diseases and ocular diseases, subjects who wore contact lenses and those who were using any form of topical or systemic medication within 30 days were excluded from the study.

General procedures

A brief case history was taken to provide information on subjects' ocular health and general health. Visual acuity test was carried out using the standard Snellen's chart. The slit lamp biomicroscope (Zeiss, USA) was used to examine the external segment of the eye to rule out ocular surface and anterior segment abnormalities. The monocular direct Ophthalmoscope (Keeler, UK) was used to examine the internal structures of the eye to rule out diseases of the posterior segment. Blood pressure was measured with U-MEC mercurial sphygmomanometer and Sprague stethoscope (Model No 112) to rule out hypertensive patients from the research study.

Subjects who met the inclusion criteria were recruited for the study.

Data collection

With each subject comfortably seated in the examination room, the baseline measurements of total and basal tear secretions were taken as described below. Blood samples of each subject were then taken for determination of baseline plasma osmolality and plasma concentration of ADH. Blood was drawn from the ante-cubital vein of each subject into chilled EDTA specimen bottles for determination of plasma ADH concentration, into lithium heparin bottles for determination of plasma sodium and potassium concentrations and into sodium oxalate bottles for the determination of plasma urea and glucose concentrations.

After 10 minutes rest, a spray dose of 10 µg was administered into each nostril (as described below) giving a total of 20 µg per subject. Thirty (30) minutes after administration of DDAVP, blood pressure measurements, total tear secretion and basal tear secretion were taken and were repeated at 30 minutes interval until 180 minutes.

One hour post administration of desmopressin nasal spray, which is the time for the most effective serum concentration of desmopressin (Den Ouden and Meinders, 2005), blood samples were taken again for determination of plasma osmolality and plasma concentration of ADH.

Samples were sent to the laboratory within 30 minutes of collection.

Measurement of tear secretions

Total tear secretion

Total tear secretion was measured by Schirmer test (without anaesthetic) and it was done monocularly (right eye only) (Turckuoglu, 2006). The subject was comfortably seated and was instructed to look up. The lower eyelid was gently pulled down, the bent hooked end of the Schirmer strip was then placed at the junction of the middle and outer two third of the lower eyelid taking care not to touch the cornea or lashes. The subject was then instructed to close the eye. The time of insertion was noted and after 5 minutes the strip was removed and the wetted portion of the strip from the notch towards the flat end was measured in mm and recorded. Length of wetting of less than 10mm in five minutes was considered low tear secretion.

Basal tear secretion

After 10 minutes of rest, one drop of local anaesthetic (0.5% tetracaine) was instilled into the lower conjunctival fornix of the left eye (OS) and the above procedure repeated. This value gave the basal tear

secretion rate. Length of wetting of less than 10mm in five minutes was considered low tear secretion.

Intranasal application of Desmopressin (DDAVP) Nasal Spray 0.1mg/ml

Desmopressin which is a synthetic analogue of ADH was used in this study.

Desmopressin (DDAVP) Nasal Spray (Ferring, GmbH, Germany) contains desmopressin acetate at a concentration of 0.1mg/ml. Each ml contains 0.1mg desmopressin acetate equivalent to 0.089 mg DDAVP (desmopressin). The vial is equipped with a snap-on, tamper-proof precompression pump which gives a spray dose of 10 µg desmopressin acetate.

The pump of the spray was primed by pressing downwards until an even spray was obtained. This was to ensure that the spray delivered 10 µg each time it was pressed. The protective cap was then removed and it was ensured that the end of the tube inside the bottle was totally submerged in the liquid.

The head of the subject was tipped back slightly while the applicator was inserted into the nostril. A spray dose of 10 µg was administered into each nostril giving a total of 20 µg per subject.

Hormonal Assay

Plasma concentrations of ADH were assessed using Assay Designs' arginine Vasopressin Enzyme Immunoassay (EIA) kit Ann Arbor, MI. Catalog No. 900-017, Lot No. 08040908.

Plasma osmolality

Plasma osmolality was estimated by the summation of urea, glucose and twice sodium and potassium as shown below.

Calculated osmolality (mOsmol/kg) = 2 Na + 2 K + Glucose + Urea (all in mmol/L) (Purssell *et al.*, 2001).

Flame photometry was used for the estimation of sodium and potassium in plasma, urease method was used for the estimation of urea while glucose oxidase method was used for the estimation of glucose in the number of samples.

Statistical analyses

Results are presented as means and standard error of means. All data obtained in this study were analyzed using SPSS 17.0, SPSS Inc., Chicago, IL, USA. and STATGRAPHICS Centurion XVI, Dayton, OH, USA. Pre desmopressin and post desmopressin results were analyzed using the paired *t* - test to determine the effects of desmopressin on plasma osmolality and plasma ADH concentration using SPSS 17.0. Unpaired *t* – test was used to determine significant differences in means of tear secretions in males and females (SPSS 17.0). Analysis of variance (ANOVA) was used to determine the effects of desmopressin on tear secretion across different assessment times, and Fisher's least significant difference (LSD) was used to identify the highest significant mean differences. (STATGRAPHICS 5.1). Significance was declared when probabilities values were, $p < 0.05$.

RESULTS

The mean age of subjects in the total population was 40.75 ± 2.61, (males =42.11 ± 2.52, females =39.39 ± 2.71). As shown in fig.1, there was a gradual reduction in total tear secretion from baseline value of 20.04 ± 1.19 mm/5mins which showed a significant reduction at 90 minutes with a mean of 12.80 ± 0.75 mm/5mins (p<0.001). Thereafter, there was a gradual increase with a mean of 19.30 ± 1.11 mm/5mins at 180 minutes. Similarly, there was a significant difference in mean basal tear secretion across different assessment time, (P< 0.001) with peak reduction at 90 minutes with a mean of 9.68 ± 0.72 mm/5mins from baseline of 14.64 ± 1.00 mm/5minutes. There was also a gradual increase of up to 13.82 ± 0.95 mm/5mins at 180 minutes (Fig.2)

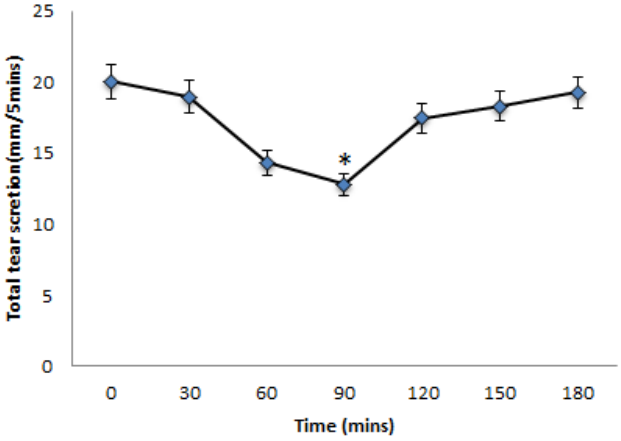

Fig.1: Mean total tear secretion at baseline and at different assessment times after desmopressin administration in the total population. * p<0.001

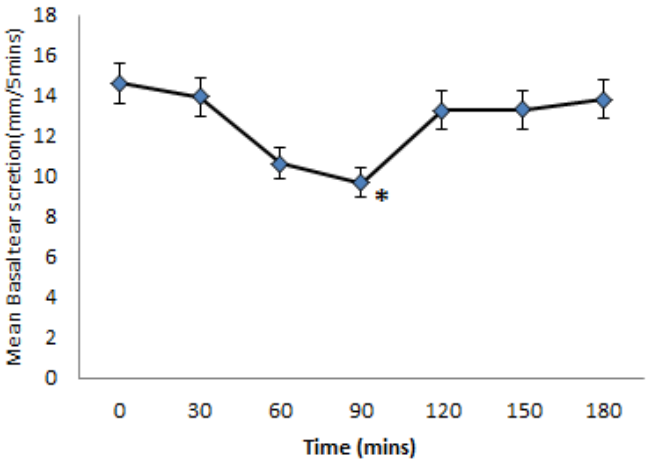

Fig.2: Mean basal tear secretion at baseline and at different assessment times after desmopressin administration in the total population. * p<0.001

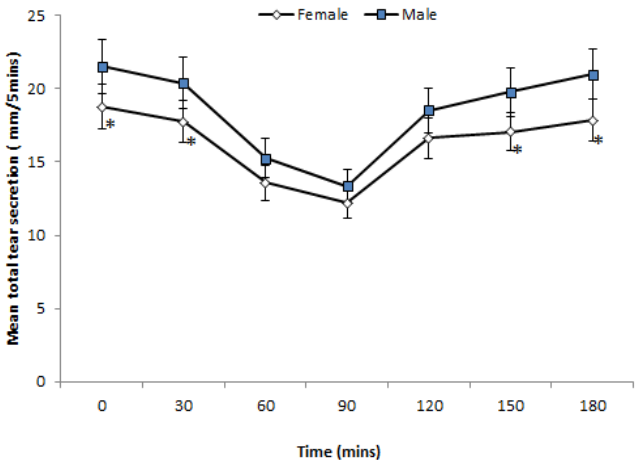

Fig.3: Mean total tear secretion at baseline at different assessment times after desmopressin administration in males and females

Table 1: Mean Basal tear secretion at baseline and at different assessment times after desmopressin administration in males and females

Time (mins)	Mean Basal Tear Secretion (mm/5minutes)	
	Males (n=27)	Females (n=23)
0	15.60±1.47	13.81±1.37
30	15.13±1.50	12.88±1.30
60	11.47±1.15	9.88±1.07
90	10.30±0.99	9.14±1.04
120	14.34±1.44	12.37±1.27
150	14.17±1.44	12.59±1.28
180	14.73±1.43	13.03±1.29

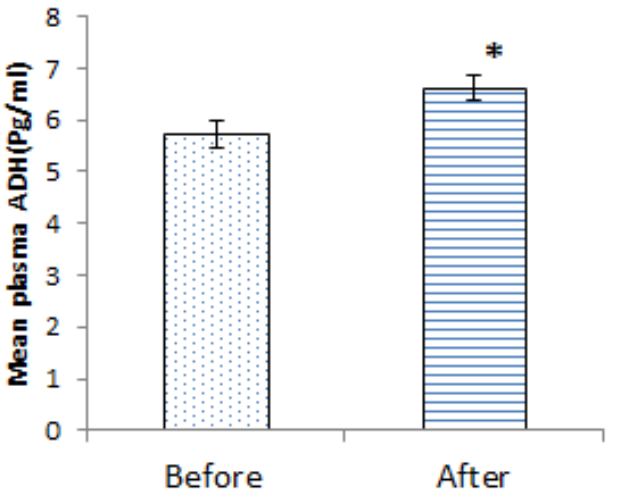

Fig. 4: Mean plasma ADH before and after desmopressin administration in total population. *p < 0.001

The total tear secretions in female subjects were significantly decreased (p <0.05) at baseline, 30 minutes, 150 minutes and 180 minutes when compared with the male subjects (fig 3). However there was no difference in the basal tear secretions of the two genders (table 1).

As shown in fig 4, mean plasma ADH concentration increased significantly from baseline value of 5.72 ± 0.25 pg/ml to 6.62 ± 0.25 pg/ml after

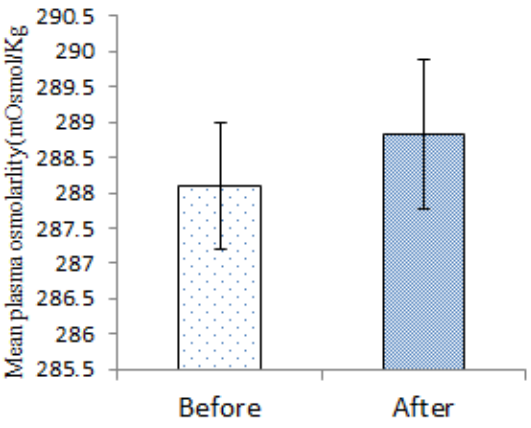

Fig.5: Mean plasma osmolality before and after desmopressin administration in total population

DDAVP (p < 0.001) and there was no significant difference in mean plasma osmolality before (288.09±0.89 mOsmol/Kg) and after (288.83±1.06 mOsmol/Kg) DDAVP administration (fig 5).

DISCUSSION

Complete tear film is essential for the normal health and function of the eye (Walcott, 1998). Normal tear film dynamics require adequate production of tears, retention on the ocular surface, and balanced elimination. Disruption of any of these components can lead to the condition of dry eye (Tomlinson and Khanal 2005).

In the present study, desmopressin intranasal spray significantly reduced the total and basal tear secretions with a peak reduction at 90 minutes after administration as shown in Figures 1 and 2. This finding is consistent with the findings of Turkcuoglu, (2006) who reported a decrease in lacrimal aqueous secretion after the administration of intranasal desmopressin in humans. They however suggested further studies to be able to identify the mechanism of action responsible for this decrease. Kurasawa, *et al*., (2005) however reported an increase in tear fluid secretion following an intravenous administration of ADH in rats. They demonstrated that a selective V_{1a} receptor antagonist reduced tear secretion in the same animal models. They therefore implicated the V_{1a} receptors for this increase in tear secretion.

It has been reported that peptide agents and humoral factors all play a role in modulating the processes of tear secretion from the lacrimal glands (Dartt, 1989). Studies by Affinitio, *et al*., (2003) have demonstrated that sex hormones play an important role in the secretory functions of the main lacrimal gland. A variety of medications for various conditions are known to be inhibitory to tear production. These drugs comprise of ganglion blockers, hypnotics and sedatives, antihistamines oral contraceptives, etc. (Van Haeringen, 1997; Crandall and Leopold, 1979). The lacrimal gland is tubulo-

acinar with large number of secretory acini. There are also myoepithelial cells closely associated with the secretory cells which squeeze the secretory products down the tubule. In normal tear secretion of the lacrimal gland, water a major secretory product of the lacrimal gland moves from the interstitial spaces into the lumen where it is mixed with other secretary products. The movement of water is driven by osmosis which depends on the movement of ions from the acinar cells into the lumen of the gland (Crandall and Leopold, 1979). The acinar cell surface membrane is differentiated into apical domain which contain water channels, aquaporin 5, which facilitate the movement of water across the epithelium, and the basolateral membranes which contain large numbers of $Na^+ – K^+$ pump which maintain the usual gradients that are seen in all cells. The movement of ions into the lumen will osmotically drive the movement of water into the aquaporin water channels into the lumen to maintain the osmotic balance (Walcott, 1998). Tearing is a form of water loss. ADH conserves water by preventing water loss from the body by reabsorption of water through the Kidneys.

The mechanism for the reduction of tear secretion by ADH is not well understood (Turkcuoglu, 2006). However, since desmopressin is a V_2 agonist, with its main function being antidiuresis, we hypothesized that it brings about its action by increasing the permeability of the apical and basolateral membranes of the acinar cells thereby pulling water from the lumen into the interstitium. This therefore brings about the reduction in tear secretion. This result therefore suggests that ADH does not only reduce water loss through the kidney, it also does it through reducing water loss in the form of tear secretion.

The peak reduction in tear secretion was observed at 90 minutes after which there was a gradual rise in tear secretion which almost reversed to the baseline values. This observation is consistent with the reports that DDAVP intranasal spray reaches a peak plasma concentration at about 1 – 1.5 hours (Harris, (1989). This observation suggests that the effect of desmopressin may be within 180 minutes in the ocular tissues. This is also consistent with the reports of Bitchet *et al*, (1988) who found out that the effect of DDAVP on mean arterial blood pressure reversed back to normal over the following 60 – 90 minutes. These observations show that desmopressin reduced the secretions of both the main lacrimal gland and accessory lacrimal glands as the main lacrimal gland is responsible for reflex tears while the accessory glands of Krause and Wolfring are responsible for basal tears.

The observation of reduction in tear secretion by desmospressin suggests that it predisposes to dry eye Syndrome, Keratoconjunctivits Sicca (KCS). This condition occurs when there is reduced tear production, unstable tears or excessive tear evaporation. Keratoconjunctivitis sicca is a dry eye primarily resulting from aqueous tear deficiency (Walcott, 1998; Lemp, 1995). Aqueous-deficient dry eye is due to a lack of tear secretion from the lacrimal glands.

The significantly lowered total tears secretion observed in this study is consistent with the reports of other researchers who reported decreased tear secretions in women compared to their male counterparts and the higher prevalence of dry eye syndrome amongst women (Schaumberg *et al*, 2001). The female gender has been identified as a risk factor for dry-eye development (Caffary *et al*, 1996). These reporters related this high prevalence to the findings that 90% of the individuals with primary or secondary Sjogren's syndrome are women, and that these auto immune disorders are among the most frequent causes of aqueous-deficient dry eye. It has been documented that the onset of dry eye is very common during menopause and may result from the loss of hormonal support (Gupta, 2006). In humans, tear production is correlated with serum prolactin and sex steroids hormone levels prior to and during menopause (Mathers *et al*, 1998). These findings are consistent with the findings of Idu and Oghre (2010) who reported a decrease in tear secretion of females compared to males.

The results of this research showed a significant increase in plasma ADH concentration from baseline levels after desmopressin administration. DDAVP intranasal spray is absorbed from nasal mucosa into plasma. The time to peak effect is 1 – 1.5 hrs (Harris, 1989). Vilhardt and Lundin, (1986) in a study comparing the biological effect and plasma concentration of DDAVP after intranasal and peroral administration to humans, reported that 11.3% of the dose of DDAVP through intranasal administration appeared in the blood thereby significantly increasing the plasma ADH level from baseline values. Chiozza *et al*, (1998) in a study of evaluation of ADH before and after treatment with desmopressin in a group of enuretic children reported a significant increase in plasma ADH levels at the end of treatment. These findings suggest a good bioavailability of desmopressin in plasma following intranasal administration.

This study showed no significant change in plasma osmolality after desmopressin administration at the concentration used for this study. This observation is consistent with the findings of Wallace *et al*, (1988). Wong *et al*, (2003) also reported that DDAVP tablet had no effect on plasma osmolality and plasma electrolyte levels (found no significant difference in osmolality, sodium or potassium levels between pre and post infusion of DDAV in human subjects).

In conclusion, this study showed a significant reduction in both total and basal tear secretions. This

reduction was however transient as the tear values returned to almost baseline values at 180 minutes. This demonstrates that antidiuretic hormone (ADH) reduces tear secretion hence, the use of medications containing ADH agonists may predispose users to dry eye syndrome.

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REFERENCES

Affinitio, P., Di Spiezio Sardo, A. and Carlo, C.(2003). Effects of hormone replacement therapy on ocular function in postmenopause. Menopause. 10: 482-487.

Bitchet, D.G., Razi, M., Lonergan, M, Arthus M.(1988). 1– desamino (8 – D – arginie) vasopressin (DDAVP) decreases blood pressure and increases pulse rate in normal Individuals. Thromb. Haemost. 60(2):348-9.

Caffery, B., Puchter, D., Simpson, T (1996). The prevalence of dry eye in contact lens wearers part 2 of the Canadian dry eye epidemiology study. (CANDEES). Invest. Ophthalmol. Vis. Sci. 37: S72.

Chiozza, M.L., Plebani, M., Scaccianoce, C., Biraghi, M., Zacchello, G. (1998). Evaluation of antidiu-retic hormone before and after long-term treatment with desmopressin in a group of enuretic children. Br. J. of Urol. 81 (3) : 53 – 55.

Crandall, D.C., Leopold, I.H. (1979). The influence of systemic drugs on tear constituents Ophthalmology. 86: 115 – 25.

Dart, D.A. (1989). Signal transduction and control of lacrimal gland protein secretion: A review. Curr Eye Res. 8: 619 – 636.

den Ouden, D.T and Meinders, A.E. (2005). Vasopressin: Physiology and clinical use in patients with vasodilatory shock: A review. Neth. J. Med. 63:4-13.

Djeridane, Y.(1994) Immunohistochemical evidence for the presence of vasopressin in the rat harderian gland, retina and lacrimal gland. Exp. Eye. Res. 77: 347-354.

Gupta P.D. (2006). Patho-Physiology of lacrimal glands in old age. Inter. Dig. Organ. sci. infor. 1: 1-8.

Harris, A.S. (1989). Clinical experience with desmopressin: Efficacy and safety in central diabetes insipidus and other conditions. The Journal of Pediatrics 114 (2) 711 – 718.

Idu, F.K. and Oghre, E. (2010). Tear secretion and tear film stability in Nigerians with non-insulin dependent diabetes mellitus. S. Afr. Optom. 69 (3) :140-145.

Kurasawa, T., Naito, A., Ohtake, Y. and Shirasawa, E. (2005)**.** Exogenous Arginine Vasopressin Increases Tear Fluid Secretion Via Vasopressin V_{1a} Receptors in Rats. Invest. Ophthalmol. Vis. Sci.46:E-Abstract4407.

Lemp, M.A. (1980). Tear deficiencies In: Clinical Ophthalmology T. D. Duane, ed. Hagerstown; M. D. Harper and Row.

Lemp, M.A. (1995) Report of the National Eye institute/industry workshop on clinical trials in dry eyes. CLAO J., 21: 221 – 32.

Mathers, W. D., Lane, J. A. and Zimmerman, M. B. (1996). Tear film changes associated with normal aging. Cornea, 15: 229 – 234.

Mathers, W. D., Stovall, D., Lane, J. A. (1998). Menopause and tear function: The influence of prolactin and sex hormones on human tear production. Cornea, 17: 353 – 358.

Nielsen, S., DiGiovanni, S. R., Christensen, E. I., Knepper, M. A. and Harris, H. W. (1993). Cellular and subcellular immunolocalization of vasopressin-regulated water channel in rat kidney. Proc. Natl. Acad. Sci. USA. 90: 11663–11667.

Purssell, R. A., Pudek, M., Brubacher. J and Abu-Laban, R.B. (2001). Derivation and validation of a formula to calculate the contribution of ethanol to the osmolal gap Ann Emerg Med. 38 (6): 653–659.

Schaumberg, D. A., Buring, J.E., Sullivan, D. A. and Dana, M. R. (2001). Hormone replacement therapy and the prevalence of dry eye syndrome. JAMA. 286: 2114-2119.

Schaumberg, D.A., Sullivan, D.A., Buring, J.E., Dana, M.R. (2003). Prevalence of dry eye syndrome among US Women. Am. J. Ophthamol. 136:318-326.

Tomlinson, A. and Khanal, S. (2005). Assessment of tear film dynamics: quantitative approach. The Ocular Surface. 3(2): 81-95.

Turkcuoglu,,P. (2006). The effect of Desmopressin on aqueous secretion of the lacrimal glands. F.U. Saglik Bil. Dergisis. 20: 115-118.

Van Haeringen, N.J. (1997). Aging and the lacrimal system. Br.J. Ophthalmol . 81: 824-826.

Vilhardt, H. and Lundin, S. (1986). Biological effect and plasma concentrations of DDAVP after intranasal and peroral administration to humans. General Pharmacology: The Vascular System. 17 (4): 481 – 483.

Walcott, B. (1998). The Lacrimal gland and it's veil of tears. News Physiol. Sci. 13: 97 – 103.

Wallace, I., Moolchandani J., Krupin, T., Wulc, A. and Stone, R. A. (1988). Effects of systemic desmopressin on aqueous humour dynamics and rabbits. Invest. Ophthalmol.Vis. Sci. 29: 406 – 410.

Whikehart, D.R. (2003). Water and Ocular fluids. In: Biochemistry of the eye, 2nd ed. Philadelphia: Butterworth-Heinemann. pp 7-11.

Wong, A.Y.C., Irwin, M.G., Hui,T.W.C., Fung, S.K.Y., Fan, S.T. and Ma, E.S.K. (2003). Desmopressin does not decrease blood loss and transfusion requirements in patients undergoing hepatectomy. Canadian Journal of Anesthesia 50: (1) 14 – 20.