REVIEW OF LITERATURE

Intraocular tension in Diabetes mellitus is important because
1. Chronic simple glaucoma may have a possible genetic connection with the disease
2. Secondary glaucoma may occur following rubeosis iridis
3. Hypotonia may occur in diabetic ketoacidosis.

Jain and Gill (1969) found that diabetic eyes had higher mean Intraocular pressure as compared to non diabetic eyes. Goel et al (1970) concluded that there is higher (10.6%) incidence of glaucoma in early and established cases of diabetes mellitus compared to 1.4% in general population and similarly more (15.8%) incidence of diabetes is seen in frank and latent cases of glaucoma. These cases show positive water drinking test and abnormal pressure rise on topical steroids. Diurnal variation of intraocular pressure must be taken into consideration the blood sugar levels and administration of insulin during the day as osmotic changes may bring about changes in pressure. Secondary rise of intraocular pressure in cases with rubeosis iridis is a terminal event.

Diabetic ketoacidosis is the only condition causing coma where there is a reduced intraocular pressure hence it is of diagnostic value. This is due to simultaneous salt and water depletion of acute onset metabolic acidosis and hyperosmolarity as it does not occur in conditions which only give rise to either salt and water deficit or metabolic acidosis or hyperosmolarity (non diabetic coma).

EPIDEMIOLOGY OF DIABETES MELLITUS

Increasing attention has been recently directed to Diabetes mellitus as a leading cause of blindness. The important fact is that prevalence and incidence of blindness due to diabetes is increasing and will probably continue to increase. The increase in blindness due to diabetes inspite of better medical treatment may be explained by the fact that the general population and life expectancy are increasing leading to a longer duration of disease. The longer duration gives rise to such complications as the potentially blinding diabetic retinopathy.

The true prevalence of diabetes mellitus in the general population is not known. The latest national health examination survey estimated the prevalence to be 18 per 1000 population.
while the last national health interview survey estimated the prevalence of diagnosed diabetes mellitus to be 14.5 per 1000 population.

**DIABETES MELLITUS AND BLINDNESS**

Caired et al (1969) have carried out a very thorough evaluation of the occurrence of blindness caused by diabetes mellitus based on hospital materials. They found that almost 2% of all diabetic persons were blind from retinopathy and 0.8% from other causes (cataract, glaucoma etc). Following a hospital series for a no. of years they found that diabetics with retinopathy have a considerable higher risk of developing blindness than diabetics without retinopathy. The percentage of diabetics among newly registered blind in the various blind registers varies from 7% (Sorsby 1966) to 23% (Vedet-Jensen 1962). Studies from U.S.A (Rogot et al 1966, Amos 1974, Khan & Hiller 1974) demonstrated that 10-13% of newly registered blind were blind because of diabetes mellitus.

Caired et al (1969) found incidence rates for blindness from diabetic retinopathy of 0.87 per 100,000 per year for men and women respectively. Khan and Hiller (1974) found a corresponding incidence rate of 1.5 per 100,000 per year for both men and women.

Caired et al (1969) in addition calculated that the relative risk for diabetics becoming blind from retinopathy was 11 times higher than the risk of blindness from all causes in background population further that the relative risk rose 30 times in diabetics with manifest retinopathy.

The duration of diabetes mellitus prior to the blindness was found to be shorter with high age at onset than with low age at onset. (Beetham 1963, Caired et al 1968)

**DIABETIC RETINOPATHY**

Diabetic retinopathy first described by Von Jaeger in 1855. Diabetic retinopathy has been divided into two large categories - Simple and proliferative. Approximately 10-18% patients with simple retinopathy progress to proliferative disease in a 10 year Period.

Mekenzie and Nettleship (1877) were the first to discover capillary aneurysm in a case of glycosuria. It was not until 1943 that Ballantyne and Lowenstein succeeded in providing that the...
earliest sign in diabetic retinopathy is the microaneurysm. Venous abnormalities are among the commonest manifestation of diabetic retinopathy.

Dilatation, irregularity and increased tortuosity of the retinal veins are all seen. Hemorrhages most commonly occurring in deeper layers of retina and hence round and regular in shape are also a relatively early feature of diabetic retinopathy (Ballentyne & Lowenstein 1943). The smaller ones may be difficult to differentiate ophthalmoscopically from a microaneurysm and the two are often grouped together as dots and blots. Hard and soft exudates also occur. Hard exudates are more common.

Manz (1876) and Nettleships (1888) first described new vascular formation with connective tissue develop from the retinal vessels, a most ominous state as the vision is then lost within a few years. New vessels formation are usually more marked in an area around the optic disc but they may occur in relation with retinal vessels anywhere between the disc and the periphery and are often multiple, particularly in vicinity of diseased retinal veins (Ballantyne 1946, Ballantyne and Michaelson 1947, G Scott 1951, Kornurup 1958 Larsen 1960).

E M. Kohner (1997) found that it is uncommon in IDDM to have retinopathy at the time of diagnosis of thier disease while significant retinopathy was present in about 20% of NIDDM patients. In IDDM patients no retinopathy develops during first 5 years thereafter progresses rapidly and by 15 years it reaches 90%. In NIDDM over 20% cases had retinopathy during first 5 years of diabetes but thier progression was slower.

Recurrent vitreous hemorrhages from the delicate new vessels are the most dramatic complication of proliferative retinopathy and for this reason a sudden loss of vision in a diabetic nearly always betrays the existence of neovascularisation. At the same time the connective tissue surrounding them increased in density and contracts into sheets or bands. The vision is greatly at risk caused due to the risk of traction bands thus formed leading to detachment of retina (Cartner 1950). The bands may also drag the retinal vessels out of their usual course and be a factor in the production of venous occlusion which commonly occurs. (Hanun 1938, Davenger 1961, Whittington 1964).
INCIDENCE OF DIABETIC RETINOPATHY

The general incidence of diabetes mellitus is high in it affects between 1.4 - 1.7 % of population. In 1921 immediately prior to the introduction of insulin found an incidence of 8.3 % of diabetic retinopathy among diabetics. (Wagner and W.Wilder 1921). In 1934 the incidence has risen to 17.7 % (Wagner et al 1934) and in 1945 29.6 % (Wagner 1945). At present time diabetic retinopathy may be expected to develop at least in 50 % of all the cases of diabetics.

In IDDM cases proliferative retinopathy develops in 60% cases in 20 years period while in NIDDM those cases treated with insulin 30% cases and without insulin treatment 20% cases develops retinopathy over 20 years (E.M.Kohner 1997).

HISTORY OF GLAUCOMA

Although attempts had been made to describe the condition of glaucoma earlier it was not till the beginning of 19th century that first excellent description of glaucoma with a raised intraocular pressure was given by Antoine - Pierr Demours (1818), G.J.Guthrie (1823) coined the term glaucoma.

Barkman (1938) using gonioscopy was responsible for a relatively satisfactory classification based on etiology i.e wide angle and narrow angle glaucoma (subsequently changed to open angle and closed angle glaucoma). In 1954 the international symposium on glaucoma provided the basis for the classification now in use (Duke Elder 1955).

Following the introduction of ophthalmoscope clinical observation on glaucomatous cup began to accumulate (Jackobson 1853, Jager 1854, Vongrafe 1854 - 57).

The observations were confirmed by the pathologic researches of Heinrich Muller (1856) who thought that changes were a mechanical pressure effect causing atrophy of the nerve fibres. Schnabel (1892) however put forward the opposite view claiming that the primary process is a neuritic atrophy leading to the formation of small empty spaces which finally coalesce (Cavernous degeneration) and the lamina cribrosa is not pushed back but pulled back by contraction of proliferated interstitial connective tissue. Elsing (1928) claimed that glaucomatous atrophy was due to reduction in capillary circulation confirmed histologically by Cristini (1950) and Keeler et al. (1966). It is believed that cavernous changes are not specific for glaucoma.
but are generally due to sclerotic vascular disease within the optic nerve and should be termed Ischemic optic Neuropathy.

The technique of tonography was introduced by Morton Grant (1950) following the use of electronic tonometer by Mores & Bruno (1950)

The study of visual field was started by Vongrafe (1855-69) who described paracentral scotomas in cases of glaucoma.

Glaucoma is a common disease and an extensive literature on its incidence has been built up over the past 50 years. Hallows and Grahm (1966) found that chronic simple glaucoma is 4-5 times greater than primary angle closure glaucoma. Bankes et al (1968) found that less than 1% of the population over 40 years of age have glaucoma. They found 0.71% chronic simple cases and 0.17% primary angle closure cases. Quigley and Addicks (1982) found that glaucoma affects 1·200 in the adult population. Primary open angle glaucoma comprises about 60% of all cases. (Becker shaffer 1983)

**SEX PREPONDERANCE OF GLAUCOMA**

In primary open angle glaucoma there is no marked sex difference although Carvill (1932) found a slight preponderance for males (54%) similarly Parkins and Jay (1960) found 56.5% males. The preponderance being more marked in patients under 50 years of age (68.2%) as compared to patients over 50 years (53.5%).

In angle closure glaucoma, the incidence in females is definitely higher than in males. Thus Holst (1947) found 64% females and Suda (1963) 62.4% females. The increased incidence of this disease in females may be related to the shallower depth of the anterior chamber in this sex (Torniquist 1956).

**AGE INCIDENCE OF GLAUCOMA**

Primary open angle glaucoma occurs commonly in the 7th decade. Its overall incidence increases rapidly from the age of 40-70 years and thereafter becomes less common.
The percentage of affected individuals in each decade varies in different surveys but all show the same trend. Thus Leydhecker in (1959) found 0.35% cases in the third decade, 0.65% in fourth, 1.45% in fifth decade, 2.84% in sixth and 4.48% in seventh decade. Bankes et al (1968) found 0.02% cases in the fifth decade, 0.31% in sixth decade, 0.9% in seventh, 2.82% in eighth and 10% in those over 80 years of age.

Primary angle closure glaucoma occurs a little earlier than primary open angle glaucoma.

**GENETIC TRANSMISSION OF GLAUCOMA**

Primary open angle glaucoma and primary angle closure glaucoma both are genetically transmitted conditions (Phelps 1974). In the majority of cases transmission occurs through two or more generations signifying an autosomal dominant transmission (Wardnberg 1950, Stankovic and Dergence 1967). In a few instance an autosomal recessive inheritance has been postulated (Wardenberg 1950, Becker 1960). X linked recessive transmission is exceptional (Sveinson 1959). The situation is further complicated by the observations that many of the associated parameters of glaucoma appear to be inherited in a multifactorial manner i.e cup-disc ratio of the optic nerve. The intraocular pressure and the facility of outflow are transmitted polygenetically (Armaly 1967, 1968). The anatomical predisposition to angle closure is also probably inherited polygenetically (Tornquist 1956, Paterson 1961).

**INCIDENCE OF GLAUCOMA IN DIABETES MELLITUS**

Some difficulties were always encountered in attempting to find adequate studies concerning the incidence of glaucoma in diabetes mellitus. In 1950 Palmer published a review of literature which included some of his own work. He stated that chronic simple glaucoma does not occur more frequently in diabetes mellitus than general population. In fact routine tonometry gives a lower average tension in diabetic persons. He included 416 patients of diabetes mellitus in his study. Waite and Beetham in 1935 reported a study of the visual mechanism in 2002 patients of diabetes mellitus using refraction peripheral fields, central fields, slit lamp examinations, fundoscopy and Schioz's tonometry (the type of calibration scale used was not mentioned) in which only 0.5% had clinical glaucoma (including primary and secondary). Leydhecs et al in an effort to determine normal intraocular pressure of 10000 normal people only 2.3% exceeded 20.5 mmHg and that in cases of tensions greater than this
glaucoma should be suspected and investigated Only 0.14 % exceeded that pressure of 26.5 mmHg and over are definitely pathological. Another study was conducted by J.R. Armstrong, R. K. Daily H.L. Dobson and L.J. Girard found that out of 393 diabetic persons 4.1 % had primary non congestive glaucoma and 1.8 % had secondary glaucoma. In a majority of cases diabetes was discovered before glaucoma. Goel et al (1970) concluded that there is a higher 10.6% incidence of glaucoma in early and established cases of diabetes mellitus compared to 1.4 % in general population and similarly more 15.8 % incidence of diabetes mellitus is seen in frank and latent cases of glaucoma. These cases show positive water drinking test and abnormal pressure rise on topical steroids. Secondary rise of intraocular pressure in cases with rubeosis iridis is a terminal event and treatment of these cases is usually unregarding.

**DIABETES AND PRIMARY OPEN ANGLE GLAUCOMA**

Armstrong et al (1960) reported that in a group of unselected diabetics the prevalence of open angle glaucoma was 40/1000 compared with a rate of 13/1000 in a control group. The other side of the coin the prevalence of diabetes in patient with open angle glaucoma is around 80:1000 (Liab et al 1967, Daves 1980). In affluent Societies published prevalence rates for diabetes are numerous but few allow age specific and sex comparisons to be made. Hamman (1983) has taken this into account and constructed a table of age adjusted prevalence rates from various sources.

While there may be an increased prevalence of open angle glaucoma in diabetes there is no compelling reason for asserting that there is increased prevalence of diabetes in open angle glaucoma. Any relationship that exists between diabetes and open angle glaucoma is not therefore as clean cut as has been claimed (Becker 1971).

The prevalence of glaucoma was investigated in an epidemiological study of diabetics traced by registration of prescription on insulin and oral hypoglycemic agents in Denmark (1983). Among 533 diabetics, 227 were treated by insulin and 306 by oral hypoglycemic agents treated. Among them the prevalence rate of primary open angle glaucoma and ocular hypertension was 6.0 % and 3.0% respectively. Open angle glaucoma was more prevalent in diabetics with macrovascular complications as compared in diabetics with microvascular (proliferation) complications.
In the Framingham Eye study, comprising persons above the age of 52 years, 2.7% of the population was found to have intraocular pressure of 25 mmHg or more, while 1.9% had glaucoma with visual field defects (Leibowitz et al. 1980). The men in the study had almost twice as high a prevalence of open angle glaucoma as women.

The frequency of open angle glaucoma will thus depend on the composition of the population with regard to age, sex and definition of glaucoma. Open angle glaucoma is said to occur in approximately 4% of diabetics (Armstrong et al. 1960). Relatively mild retinopathy has been observed in diabetics with increased intraocular pressure by a number of investigators. (Christiansons 1965, Jain and Luthra 1967, Shin et al. 1977)

**DIABETES AND PRIMARY CLOSED ANGLE GLOUCOMA**

Becker (1968) wrote that there appeared to be no association between diabetes and closed angle glaucoma prevalence. An observation that seems to be confirmed by a population study (Nielson 1983) which found one patient with closed angle glaucoma in a diabetic population.

**DIABETES MELLITUS AND OCCULAR HYPERTENSION**

Armaly (1969) during the follow up of a group of patients with ocular Hypertension discovered four who had developed field loss and all four demonstrated abnormal glucose tolerance test results. Wilensky et al. 1974 reported a similar experience consequently it became accepted that a combination of diabetes mellitus and ocular Hypertension represented an individual at particular risk.

Bankes (1967) using data obtained from the Bedford glaucoma survey found that the intraocular pressure in diabetic patients and pre-diabetics was no different from that in general population. Becker (1971) however recorded an increased mean intraocular pressure in diabetic patients with retinopathy. More recently Klein and Klein (1984) investigated a population of 2103 diabetic patients in Wisconsin and below age of 30 years the prevalence of ocular hypertension was 68/1000 in females and 59/1000 in males. Above age of 30 years the rates were 96/1000 and 73/1000 respectively, little different from the prevalence rates in population at large (Hollows and Graham 1966).
DIABETES MELLITUS AND RUBEOSIS IRIDIS

Rubeosis iridis almost always occurs secondary to some preexisting ocular or systemic disorder usually ischemic in nature. It is seen most often in patients with diabetes mellitus or following central vein occlusion. It is thought that retinal hypoxia is the common stimulus to the development of rubeosis iridis. Release of vasostimulating angiogenic substances from hypoxic retinal tissue has been postulated, leading to the growth of new vessels in the anterior segment of eye.

The rubeosis of diabetic retinopathy is almost always associated with retinitis proliferans and recurrent haemorrhages. Occasionally it is seen in eyes with remarkable good vision some 5% - 7% of diabetic patients develop iris neovascularisation. Not all of these cases progress to neovascular glaucoma. In Massden's series, approximately one fourth of these cases demonstrated regression of the iris neovascularisation. About one half of the cases remained unchanged for upto 5 years, while the remaining one - fourth progressed to neovascular glaucoma.

In epidemiological study conducted in Denmark (1983) among 533 diabetics (20) insulin and 306 (O H A treated) the prevalence rate of neovascular glaucoma was 2.13 % and 21.3 % were having proliferative retinopathy.

In another study conducted in Fyn (1985) the results were as follows. It was a retrospective study neovascular glaucoma was 2 % of them 2 were bilateral and 12 patients were having unilateral glaucoma.

DIABETIC RETINOPATHY AND INTRA OCULAR PRESSURE

A link between diabetes and glaucoma has long been suspected and glaucoma is usually common in diabetics. In a group diabetics have a higher intraocular pressure than normal individuals. However only occasional references in the literature consider a possible relationship between intraocular pressure and diabetic retinopathy. Weinstein had suggested that haemorrhages in diabetic fundus occur when dilatation of retinal capillaries is associated with intraocular pressure. Christianson have found higher pressure in eyes without retinopathy.
A study was conducted by Jain and Luthra (1964) in P.G.I. Chandigarh. In this study 100 unselected cases diabetic patients were examined and found that mean intraocular pressure in diabetic eyes is slightly higher than non diabetic eyes. However the difference is much more marked when eyes with retinopathy are compared with eyes of non diabetics. A significantly larger percentage of cases with retinopathy (31.6 %) shows intraocular pressure of less than 14 mmHg. This study supports the hypothesis that high intraocular pressure has some influence in delaying or preventing the retinopathic changes.

Arora and Prasad (1989) studied a total of 120 patients out of which 60 were diabetics and rest were normal forming a control group. Tonometry was done by a standard certified Schiotz tonometer. They reported that out of total 60 patients 46 (76.67 %) were of M.O. D. M., while juvenile onset diabetes constituted only 23.3 %. The mean intraocular pressure of diabetic eyes without retinopathy was 18.7 mmHg, while eyes with retinopathy was 19.99 mmHg. The significant finding was lower intraocular pressure 15.98 mmHg in proliferative retinopathy. They saw in different groups Viz 20.98 mmHg tension in grade I retinopathy, 21.99 mmHg in grade II and 22.18 mmHg in grade III while grade IV showed a lower level 15.98 mmHg.

**INTRA OCULAR PRESSURE AND FIELD DEFECTS IN DIABETES MELLITUS WITH GLAUCOMA**

Studies of diabetes mellitus with proven glaucoma cases indicate an increased susceptibility for progression of glaucoma damage at a lower intraocular pressure when compared with nondiabetic patients with glaucoma. (Becker & Shaffer 1971) It is not certain whether patients with ocular hypertension and diabetes mellitus share this increased susceptibility to field loss.

**INTRAOCULAR TENSION AND BLOOD SUGAR LEVEL**

Even since Hiene (1903) and Krause (1904) reported Hypotonia of the eye in diabetic coma, it has generally been accepted that severe hypotonia of eye often is seen during diabetic coma (Bannas 1932)
It is also known that when diabetic coma is treated with insulin normal intraocular pressure is restored. In diabetics a fall in intraocular pressure during hypoglycemia has been reported by Richter (1926), Wiechmann and Koch (1927) and Wiechmann (1930). According to Schmidt (1938), Toth (1938) and Cavka (1939) the intraocular tension in nondiabetics is not lowered during induced hypoglycemia.

Investigations on the intraocular pressure in diabetics and the possible correlation between the intraocular pressure and the state of diabetic retinopathy have not shown conclusive results (Gray 1933, Vila Ortez 1947, Weinstein 1949, 1951, Christianson 1961). These papers do not mention any correlation between intraocular pressure and the blood sugar fluctuations.

On theoretical grounds Philips (1946), Vila Ortez (1947), Weinstein (1951), Martin (1951), Krause (1953), Ashton (1958) and Larson (1960) all stressed how the development of diabetic retinopathy might be favoured by a changing or low intraocular pressure.

Martin (1951) found the variations in intraocular pressure over twenty four hours period was larger and more irregular in diabetics than in nondiabetics, but he was unable to correlate these variations with fluctuations in the blood sugar levels. In a single diabetic, Poos (1930) was able to correlate such variations in intraocular pressure with fluctuations in blood sugar levels.