EYE AND RENAL COMPLICATIONS AMONG AFRICAN DIABETIC PATIENTS IN DAR ES SALAAM

BY

MILKA K.M. MAFWIRI, MD (DAR)

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PROF. J.L. F. SANGAWE
(SUPERVISOR)

DECLARATION

I hereby solemnly declare that this dissertation is my origional work and has never been submitted for a diploma or degree in any other University.

CANDIDATE'S SIGNATURE _____

DR. M.K.M. MAFWIRI, MD (DAR)

28 · 10 · 1990

DATE

SUPERVISOR'S SIGNATURE _____

PROF. J.L.F. SANGAWE

28 · 10 · 1990

DATE

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ABSTRACT

This study was conducted among 414 Tanzanian African diabetic patients attending the diabetic clinic at Muhimbili Medical Centre in 1988/89. The main objective was to study the prevalence of diabetic ocular and renal complications and associated risk factors.

The study revealed that the prevalence of diabetic retinopathy and cataract was higher than had previously been thought. The prevalence of other ocular lesions was similar to previous studies in Tanzania.

The overall prevalence rates of diabetic retinopathy, cataract and glaucoma were 50.5%, 47.8% and 4.8% respectively. The prevalence of optic atrophy was 1.7% while that of xanthelasmas was 1.0%. None of the patients had iridis, rubeosis iridis or diabetic ophthalmoplegia.

Among 387 patients on whom fundoscopy was done, 143(37.5%), 39(10.1%) and 14(3.6%) had background, preproliferative and proliferative diabetic retinopathy respectively. This was the highest prevalence of proliferative retinopathy yet reported in Africans. Diabetic retinopathy was significantly related to age ($P<0.001$), duration of diabetes ($P<0.0001$) and hypertension ($P<0.001$). There was however no relationship between diabetic retinopathy and smoking ($P>0.05$), alcohol consumption ($P>0.05$), serum cholesterol and triglycerides.

The prevalence and severity of diabetic retinopathy was significantly related to microalbuminuria ($P<0.001$), which occurred in 110(29.6%) of the study population.

Risk factors common to both diabetic retinopathy and nephropathy were age, duration of diabetes, raised serum creatinine level (>130μmol/L) and raised urine albumin excretion (>30μg/ml).

Blindness defined as inability to count fingers at 3 metres affected 24(5.8%) 19 of them being blinded by cataract. Patients with severe retinopathy and those with maculopathy had a significant reduction in vision compared to those free of retinopathy.

In conclusion, the prevalence of both diabetic retinopathy and cataracts are higher than previously reported. Although cataracts remain the major cause of blindness among diabetic patients, severe retinopathy and maculopathy may rival cataract as a cause of blindness in the years ahead. This may be concluded from the results of this study which show that both diabetic retinopathy and nephropathy are significantly associated with increasing survival of diabetic patients due to improved treatment and follow up of patients. Equipment for screening and treatment of patients with diabetic maculopathy, pre-proliferative and proliferative retinopathy are clearly required.

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INTRODUCTION

Tanzania, like all developing countries has a low per capital expenditure on health of less than US$ 1 per year. At present, the major challenges for the health sector in these countries is the control of malnutrition with its complications and infectious diseases. The ophthalmologist is faced with a big challenge of reducing morbidity and preventing blindness. The major causes of blindness in Dar es Salaam are cataracts and glaucoma. Other causes include corneal opacity, trauma, optic atrophy and macular degeneration.[1] Infectious diseases like trachoma and onchocerciasis are potentially blinding and affect a large number of people in Tanzania. Xerophthalmia is another blinding disease prevalent in Tanzania and other developing countries.

Apart from the above mentioned highly prevalent eye diseases, the blinding ocular complications of diabetes cannot be forgotten. These include diabetic retinopathy, diabetic cataracts and glaucoma. Among them, diabetic retinopathy and glaucoma have assumed a low profile because of their low prevalence rates. The experience of developed countries indicate that better living conditions, adoption of Western life styles and an increase in life expectancy leads to an increase in non-communicable diseases like diabetes mellitus with its macrovascular and microvascular complications.

For a country like Tanzania and other African countries, the low prevalence rates of such diseases as diabetic retinopathy has been a blessing to the health sector and to the diabetic population at large. This is in view of the lack of sufficient trained personnel and the huge financial expenses involved in securing facilities for diagnosis and treatment of this potentially blinding disease. Facilities for fluorescein angiography and photocoagualation are non-existent in many developing countries including Tanzania.

Many studies on diabetic retinopathy carried out in Africans before 1970 had reported prevalence rates of $<10\%$.[2,3,4,5,6]. One exception of these rates was the relatively high prevalence of 25% reported in urban South African Bantus.[7]

The low prevalence rates of diabetic retinopathy reported in African patients contrasted

with studies elsewhere especially the Western World. Kohner et al[8] noted that diabetic retinopathy has become the single most common cause of blindness in middle age in developed countries. In contrast to the low prevalence rates of diabetic retinopathy noted in earlier reports, a trend towards an increase has been observed in recent studies.[9,10,11,12,13] A similar observation has been reported in Japan.[14] More over, the results of the WHO Multinational Study on Microvascular disease showed that there were no differences of any magnitude between the participating centres in developed and developing countries in the frequency or severity of retinopathy when the important variable of duration of diabetes is taken into account.[15]

The prevalence of diabetes mellitus is probably increasing. At Muhimbili Medical Centre about 200 new patients are seen each year. The increase in the prevalence of diabetes may be due to the change in social economic structure among urban Tanzanians. In a study of non-communicable disease in Dar es Salaam it was observed that the urban African showed a high prevalence of hypertension and hyperlipidaemia.[20] A strong association between the development of diabetic retinopathy and high social-economic status on the one hand and to increased cholesterol levels in black Africans on the other have been reported.[6,10]

It also seems that diabetic patients are now living longer than they used to, due to provision of improved treatment and follow up. The prevalence rates of microvascular diabetic complications are known to increase with increasing duration of diabetes. The study highlights the magnitude of these microvascular complications of diabetes in the light of risk factors such as duration of diabetes, metabolic control of diabetes, and age. Other risk factors include smoking, alcohol consumption, serum cholesterol and triglycerides.

The association between clinical nephropathy and diabetic retinopathy has been reported both in the Western World[16,17] and in African diabetic patients.[6,11,13] However, probably due to lack of facilities, there are no reports on microalbuminuria and diabetic retinopathy among African diabetic patients. Elsewhere, microalbuminuria has been cited as a strong

predictor with respect to development of diabetic proliferative retinopathy and diabetic nephropathy[18,19].

The study was carried out to document the current prevalence of diabetic retinopathy and to relate it to diabetic nephropathy and other risk factors. The study also attempted to identify the patients at risk of developing proliferative retinopathy based on the presence of microalbuminuria. The prevalences of other ocular complications of diabetes were also studied.

2. OBJECTIVES

2.1 BROAD OBJECTIVES

To determine the prevalence of diabetic ocular complications and to relate diabetic retinopathy to diabetic nephropathy and other risk factors among Tanzanian African diabetic patients.

2.2 SPECIFIC OBJECTIVES

To determine:

1. The proportion of diabetics with diabetic eye disease: retinopathy, cataract, glaucoma, iritis, rubeosis iridis, optic atrophy, ophthalmoplegia, conjunctival microaneurysms and Xanthelasms.
2. The relationship between duration of diabetes and the prevalence of diabetic retinopathy.
3. The relationship between diabetes control and the prevalence of diabetic retinopathy and cataract.
4. The relationship between hypertension, smoking, alcohol consumption, serum cholesterol and triglycerides with the prevalence of diabetic retinopathy.
5. The proportion of diabetics with raised serum creatinine and the relationship between serum creatinine and diabetic retinopathy.
6. The proportion of diabetics with proteinuria and microalbuminuria and their relationship to diabetic retinopathy.

3. REVIEW OF LITERATURE

3.1 DIABETIC RETINOPATHY

Prevalence of diabetic retinopathy

Diabetic retinopathy is among the diabetic complications whose reported prevalences vary in different parts of the world. It has been suggested that African diabetics might be less vulnerable to complications of diabetes including retinopathy.[2,21]

While reviewing the pattern of diabetic complications in the tropics Tullouch[22] reported a prevalence of 3.3%. Subsequent studies in other African countries showed a similar low prevalence in comparison to European studies. Sharper[2] and Otim M.A.[23] reported approximately equal prevalences of 4.0%. Gelfand[3] found 4.1% retinopathy among Zimbabweans. In Nigeria, a study by Kinnear[4] showed that diabetic retinopathy was rare among Nigerians. This was further supported by Green wood and Taylor[5] and Osuntokun[6] who reported prevalences of 7.5% and 4.6% respectively.

Likewise Jackson,[7] while working among Bantus of South Africa revealed that diabetic retinopathy was uncommon among Bantus. A relatively higher prevalence was obtained in Kenya in which 52% of 115 diabetic patients attending the Kenyatta Hospital in Nairobi had diabetic retinopathy.[9] Retinal photography was used in assessment of retinopathy. The authors suggested that in spite of intraretinal microproliferative abnormalities, the fundus may appear harmless to many physicians who are not regular ophthalmologist and also lack the equipments needed for thorough fundus examination. This could result in falsely low prevalences.

Several studies on diabetic retinopathy have been done in Tanzania. The reported prevalences are not different from other African countries. Haddock[24] reported a prevalence of 5.2% among case notes of 116 African diabetic patients. Mhando and Yudkin[10] on a study of diabetic complications in 139 African diabetics reported a prevalence of 24.6%. Direct ophthalmoscopy was the method of assessment. A similar prevalence was obtained by Salim[25] in which 23.8% of 220 diabetic patients had retinopathy on ophthalmoscopy. Katenga[26] did direct and Indirect ophthalmoscopy

among 110 diabetic patients and reported a prevalence of 19.1% which is in agreement with the previous studies.

Lester[27] (1983) in Ethiopia found 7% of diabetic retinopathy. A more recent study in Central Africa among 600 African diabetic patients showed a prevalence of 34%.[11] In this study, the author used a standardized questionnaire and examination technique based on the WHO protocol for Diabetic Microangiopathy.[28] He suggested that the varying prevalences were due to the diversity of methods and criteria used in assessment of the presence of diabetic retinopathy.

In Developed countries such as U.S.A. diabetic retinopathy is rapidly becoming the single most important cause of blindness among the adult population. It accounted for 16% of registrations in patients aged 36-64 years.[29] The reported prevalences are therefore higher than those reported among African countries. Lundback[30] found 77% and Kornerup[31] found 47% among 1,000 patients in Stockholm. 33% retinopathy was found among 4,875 diabetic patients in Japan.[32] Safir[33] conducted a study among 65 juvenile onset diabetics by ophthalmoscopy. He revealed 45% affection.

However, some reports by researchers among Asians and Japanese reveal lower prevalences. Zimmet[34] studied retinopathy among Pima Indians and found 24.2% affection. Sasaki and associates[14] while reviewing the changing pattern of causes of death in Japanese diabetic patients pointed out that retinopathy like other diabetic complications was rare and mild among Japanese. However, a changing pattern showing an increase in incidence has been shown recently. These authors suggested that the change was presumably because of gradual change in the mode of living in recent years in Japan.

A more comprehensive study is the South Wisconsin Study in which Klein et al[35] in an epidemiological study took retinal photographs in 996 patients. 17.4% of them had retinopathy after 2 years of illness. The incidence rose to 95% after 15 years of illness.

Thus in general, reported prevalences in Africans are lower than in European studies. But a trend towards the increase in prevalence is evident in recent studies.[9,11,13]

Prevalence of proliferative retinopathy

Several studies in African diabetic patients have shown that proliferative retinopathy is rare in Africans. Mhando and Yudkin[10] found one patient with proliferative retinopathy out of 110 examined patients. A single patient with proliferative retinopathy was reported out of 600 examined.[11] A prevalence of 2.8% and 2.0% was found by Mengistu[12] among IDDM and NIDDM respectively. There was no patient with proliferative retinopathy among 377 diabetic patients examined by Erasmus et al.[13]

In Western Australia, 13% of those examined had proliferative retinopathy.[34]

Duration of diabetes and diabetic retinopathy

The prevalence of diabetic retinopathy increases with diabetic age. This is a world wide observation. In a study of ocular effects of juvenile onset diabetes, Safir[33] observed a rapid increase in the incidence of retinopathy, by 15-20 years 80% and at 25 years 100% of them had retinopathy. Similar observations were obtained by Katenga,[26] and Rolfe.[11] Klein et al[35] in an epidemiological study concluded that the duration of diabetes was strongly associated with severity and frequency of diabetic retinopathy.

Many patients diagnosed after 40 years have Non Insulin dependent Diabetes mellitus (NIDDM), and in 20% of these retinopathy may be present at diagnosis.[8,36] The proportion of retinopathy increases with increasing age at diagnosis[36] and with the duration of illness.[37]

In Insulin dependent Diabetes Mellitus (IDDM) however, retinopathy does not occur at diagnosis and is still uncommon (< 10%) after 5 years of illness.[36] Contrary to this view, in juvenile diabetic patients signs of microangiopathy have been demonstrated in 8 out of 37 patients aged 2 - 25 years who were on diabetic treatment for 2 - 17 years; by fluorescein angiography. The authors stress the possibility of occurrence of retinopathy even in the first years following onset of diabetes.[38]

In young children less than 10 years retinopathy is rare regardless of the duration of diabetes. This has been reported in many studies.[39,40] Growth hormone has been cited as a protective factor in these children.[35]

Hypertension and diabetic retinopathy

The rate of progression of both macrovascular and microvascular complications of diabetes increase when hypertension is present.[41] Retinopathy being a microvascular complication of diabetes has been cited by many workers to be aggravated by the presence of hypertension. Ballantine and Loewenstein[42] found hypertension in 50% of diabetic patients showing retinal changes. In a study of 100 diabetic patients in whom 50 had retinopathy and 50 without, mean blood pressures were significantly greater in those patients with retinopathy than those without .[36] A similar association had been recognised by Greenwood and Taylor.[5]

The almost universal association of retinopathy and raised systolic blood pressure emerged as an interesting feature in the WHO multinational study on microvascular disease.[15] More recent studies[11,35] continue to emphasize that hypertension is the most important factor for development of retinopathy.

On the contrary, hypertension has been noted by Dornan and his co-workers[43] to be an effect accompanying nephropathy than a factor contributing to the development of retinopathy. While investigating for risk factors protective against diabetic retinopathy, he found that a rise in diastolic pressure was found only after the development of nephropathy.

Forms of hypertension encountered in the diabetic[41]

There are several forms of hypertension encountered in the diabetic patient.

Essential hypertension This occurs in absence of renal disease and often is present very early, ie with the diagnosis of diabetes.

Systolic hypertension

1. Diabetic hypertension (diabetic nephropathy). Occurs in diabetic patients with diabetic nephropathy.
2. Hypertension associated with neuropathy (supine hypertension with orthostatic hypertension).

Cigarette smoking and diabetic retinopathy

Smoking is among the risk factors for development of proliferative retinopathy in diabetes. One might anticipate a relationship between smoking and retinopathy since smoking may cause tissue hypoxia by increasing blood carbon monoxide levels.[44] Additionally, smoking may lead to increased platelets adhesiveness.[44]

Several workers have studied and reported on the relationship between smoking and diabetic retinopathy. Paetkau and his colleagues[45] found in a subgroup of patients who had been having diabetes for more than 20 years that smoking increases the risk of developing proliferative retinopathy.

However, some subsequent studies have found no overall relationship between smoking habit and retinopathy.[47,48] Similar negative results were reported by Dornan et al.[43] Klein[35] found no relationship between the risk or severity of retinopathy and number of cigarettes smoked daily.

It therefore appears that the association between retinopathy and smoking has not been settled.

Diabetic control and retinopathy

The effect of diabetic control on development and progression of diabetic retinopathy has still not been clearly established.[8] In the early 70's it was argued that hyperglycemia and diabetes mellitus are unrelated and that the genetic factors were much more important for the development of late diabetic complications including retinopathy. However with time, more reports have come in favour of a positive association between poor control of diabetes and retinopathy. The strength of the association between higher glucose levels and worse retinopathy in humans was established in the long study by Pirart.[49] He studied 4,400 patients from 1947-1973. Subsequent reports have supported this observations.

Dornan et al[43] found that the mean blood glucose concentration were significantly lower in patients who remained free of retinopathy than in those who went on to develop retinopathy. He suggested that the development of both background and proliferative retinopathy is a function of the degree and duration of glyceamic exposure. These results

were further supported by Weber et al[50] who found the appearance of microaneurysms to be delayed by 4.5 years in young diabetic patients with good metabolic control. Glyceamic control was evaluated by serial measurements of glycosuria, post prandial blood glucose and HbA, and the number of ketoacidosis from the onset of diabetes to the time of the retinal examination. Katenga[26] and Erasmus et al[13] found poorly controlled patients to have more retinopathy than well controlled patients.

It is established that near normoglycaemia can now be obtained in large patient populations with either multiple insulin injections or continuous subcutaneous insulin infusions with insulin pumps.[51] These facilities have enabled workers to further study the effect of improved diabetic control on diabetic retinopathy. In a study of retinopathy during one year of tight blood glucose control, half of the patients in whom near normoglycaemia was achieved by continuous infusion and multiple injection showed a transient deterioration in retinopathy by developing soft exudates. It was suggested that a large and rapid fall in blood glucose concentration may promote deterioration of retinopathy.[52]

Similar results were obtained in the Steno study[53] which found morphological deterioration of retinopathy in the group with the best diabetic control. The Kroc collaborative study group[54] further supported this finding. Rolfe[11] found no difference in the degree of glycaemic control between those with and those without retinopathy.

Pathogenesis of diabetic retinopathy

Diabetic retinopathy is essentially a microangiopathy affecting the retinal pre-capillary arterioles, the capillaries and the venules. However, larger vessels may be involved. The retinopathy has features of both microvascular occlusion and leakage. Despite long and extensive research the pathogenesis of diabetic retinopathy is still a matter of much speculation.[55] There are many speculated factors which lead to the final clinical picture:

Aldose reductase is an enzyme which in the presence of high sugar concentration converts the sugar into its alcohol. These sugar alcohols increase the intracellular

concentration forcing water to diffuse into the cell, thus causing an electrolyte imbalance.[56] Like in the pathogenesis of cataracts in patients with galactosaemia and in experimental animals, diabetic retinopathy may be caused by aldose reductase mediated damage.[57] This view is supported by the finding of high concentration of aldose reductase in retinal pericytes and Schwann cells.

Platelet abnormalities: Investigators have shown that platelets in diabetic patients are abnormal in that they are stickier than those of non diabetics.[58] Once platelets adhere to the vessel wall, they secrete substances which cause further aggregation of platelets. Because of this, some investigators have postulated that abnormal platelet adhesion and aggregation causes focal capillary occlusion and focal areas of ischaemia in the retina which in turn are responsible for diabetic retinopathy.[59] This theory is supported by the fact that diabetic patients are sensitive to thromboxane and other aggregating factors. Thromboxane is a prostaglandin which is one of the most potent vasoconstrictor and platelet aggregating agent. It is produced during platelet coagulation. Furthermore, proliferative diabetic retinopathy has been reported in patients with severe platelet dysfunction.[60]

Other heamatological abnormalities seen in diabetics are increased blood viscosity, erythrocyte aggregation and decreased erythrocyte deformability.[61] These are possible causes of capillary occlusion.

Abnormal carbohydrate metabolism and growth hormone: A relationship between abnormal carbohydrate metabolism and growth hormone was evidenced by Hansen in 1971. He showed that rigid blood control of blood sugar levels normalized the hypersecretion of growth hormone in juvenile diabetics. Merimee[71] produced evidence that increased levels of growth hormone could be responsible for development of retinopathy in a study of dwarfs deficient in Human Growth Hormone. Further support for growth hormone as an aetiological factor for diabetic retinopathy was the favourable response to hypophysectomy in 65% of patients.[62]

Genetic factors: Card[63] and Pyke[64] presented conflicting evidence in a gene contributing to the aetiology of diabetic retinopathy. Evidence has been shown that, the genetic element in the pathogenesis of diabetic retinopathy may be strong in NIDDM but less strong in IDDM.[65] In a study of 48 IDDM and 37 NIDDM co-twins with diabetes for 9 years, 35 out of 37 pairs of NIDDM showed a similar stage of diabetic retinopathy. While among the 10 pairs of IDDM, 5 pairs showed marked variation within each other.

Microangiopathy: The heamodyanamic view. Studies done in IDDM have shown that there is generalized vasodilation in early diabetes.[66] The vasodilation is secondary to altered levels of vasoactive substances and altered vasomotor responsiveness. This vasodilation leads to increased capillary pressures and flows which initiate mechanisms leading to diabetic microangiopathy. High capillary pressure causes direct injury to the capillary wall which promote increased permeability to macromolecules in and around the capillary wall. This leads to endothelial thickening of the basement membrane which contribute to the genesis of diabetic capillary obstruction.[66]

This state of dilation of retinal arteries and veins has been reported to occur in diabetics in whom there are no signs of retinopathy.[67] And, it has been confirmed angiographically in newly diagnosed patients.[68]

It has long been shown that retinal capillary barrier function is disrupted at an early stage in diabetic patients. Fluorescein angiography studies have shown elevated fluorescein vitreous levels even before the development of retinopathy. This finding is not present in non diabetic patients.[69]

The cellular elements of retinal capillaries are of two types: endothelial cells and pericytes. The tight junction of the endothelial cells constitute the inner - retinal barrier as they prevent the passage of large molecules such as fluorescein from passing across the vessel wall. The pericytes are wrapped around the capillaries, are thought to be responsible for the structural integrity of the vessel wall. Normally, there is one pericyte for each endothetial cell. In diabetic patients there is a reduction in the number of pericytes which is thought to be responsible for distension of the capillary wall and

disruption of the blood - retinal barrier, leading to leakage of plasma constituents into the retina.[55]

In more advanced stages of diabetic retinopathy there is marked endothelial proliferation, microaneurysm formation and intravascular thrombosis. This thrombosis is associated with liberation of mitogenic factors from platelets thus predisposing capillaries to luminal obstruction.[70] There are also marked capillary dilation with endothelial proliferation. These widened capillaries are thought to be due to local hypoxia.

Clinical presentation of diabetic retinopathy

Several classifications have been adopted to classify diabetic retinopathy. The disease does not lend itself to classification since the various lesions do not follow one another in sequence and one or other of the fundamental changes may dominate the picture in the fundus. The accepted classification divides the lesions of diabetic retinopathy into 2 groups:

(a) Background retinopathy.

(b) Proliferative retinopathy.

Background retinopathy

Vascular lesions According to Lee and his colleagues[109] these are divided into venous abnormalities, arterial lesions, microaneurysms and capillary abnormalities.

(i) **Capillary dilation** These were first noted by Dosterhnis and Vink in 1967. They occur before capillary closure or microanerysms.

(ii) **Capillary closure** This leads to retinal ischaemia and further dilation of the capillary. Demonstrated by fluorescein angiography.

(iii) **Microaneurysms** These were originally noted by Mackenzie and Nettleship in 1877. They are common in the posterior pole and originate from the venous side of the circulation. Microaneurysms can be easily missed on ophthalmoscopy because they are ophthalmoscopically visible at 20 - 30 μ. Fluorescein angiography can identify them all. Microaneurysms may occur alone or with other signs of retinopathy. But even one only is

highly suspicious of diabetic retinopathy.[42] They may remain unchanged for months or years but with time they disappear. They are located in the inner nuclear layer of the retina.

(iv) **Arterial lesions** Generalized arteriosclerosis occurs more commonly in diabetics than in normal people. Further more diabetic retinopathy is frequently complicated by arteriosclerosis.[72] The larger arteries are narrow and irregular especially at their origin.[73] However it is common to find marked degrees of retinopathy without either generalized or focal retinal arteriosclerosis.[74]

(v) **Venous abnormalities** Uniform distension of the veins was first seen by Mylius[75] who found the arteriovenous ratio in diabetics to be 2:4 instead of 2:3. Distended veins are particularly seen in young diabetics when the diabetes is out of control.[76] In advanced diabetes mellitus, retinal venous dilatation and beading occurs.[77]

Extravascular lesions

(i) **Hard exudates** Hard exudates are characteristic of diabetic retinopathy. They are a collection of serum and glial-neuronal breakdown products with high lipid content extruded from retinal capillaries with increased permeability into the retinal tissue. They appear as white or yellowish deposits on ophthalmoscopy, either in clusters or circinate arrangement. Hard exudates may absorb spontaneously over a period of months either into the healthy surrounding capillaries or by phagocytosis of their lipid content. They may increase in size and develop cholesterol deposits.

(ii) **Cotton wool exudates** These represent microinfacts in the nerve fibre layer. Microinfacts are a result of retinal hypoxia due to microvascular occlusions. Factors leading to microvascular occlusion are thickening of the capillary basement membrane, capillary endothelial damage and proliferation and increased stickiness and aggregation of platelets.[8] They are not specific for diabetes; but were first recognised by Esmann et al[78] as one of the characteristic ophthalmoscopic feature of diabetic retinopathy. They appear in hypertensive retinopathy but there is predilection to the temporal half of the retina in diabetes. Cotton wool exudates fade in 6 to 8 months leaving no trace.[72] They are the first signs of proliferative retinopathy.

(iii) **Haemorrhages** Are due to extrusion of red blood cells from retinal capillaries. In diabetic retinopathy haemorrhages are typically round and occur in the compact retinal layers - outer - plexiform.[42] Flame shaped haemorrhages are relatively uncommon and follow the course of the nerve fibre layer. They are found in all stages of diabetic retinopathy.

Proliferative retinopathy

All lesions in proliferative retinopathy are caused by retinal ischaemia. Features of proliferative retinopathy include cotton wool spots, intraretinal and periretinal new vessel formation as well as fibrous retinitis proliferans. Venous changes including dilatation, beading, looping and segmentation of the blood column are important proliferative findings. Arteriolar narrowing and even obliteration may be seen.[55]

The new vessels are potentially reversible where as the fibrous retinitis proliferans is an irreversible end stage. Neovascularization is the hall mark of proliferative retinopathy. New vessels may proliferate on the optic nerve head and along the course of major vascular arcades. Over one quarter of the retina has to be non perfussed before new vessels appear.

The fibrovascular network becomes adherent to the posterior vitreous face and leaks plasma contents into the adjacent vitreous gel. With contraction of the vitreous, the fragile vessels are torn leading to vitreous haemorrhage.[79] Bleeding may occur into the vitreous gel (intragel haemorrhage), or more frequently into the retrohyaloid space (pre-retinal heamorrhage). Occasionally vitreous heamorrhage may be precipitated by severe physical exertion or strain, and direct ocular trauma. However, not infrequently bleeding occurs while the patient is asleep.

3.2 DIABETIC RETINOPATHY AND NEPHROPATHY

It was first shown by Kimmelstiel and Wilson[80] that certain long standing diabetic patients are liable to renal damage which in turn leads to hypertension. The triad of diabetic retinopathy, renal dysfunction and hypertension therefore makes up the syndrome of Kimmelstiel - Wilson. From the ophthalmic point of view, interest centres on the fact that

there is a close histological and biochemical similarity between the focal glomerular lesion and the retinal microaneurysm.[73]

Following the earlier reports by Kimmelstiel, interest in the relationship between renal and extrarenal microangipathy has been shown by several workers.

Relationship between retinopathy and nephropathy

Histological findings Wagener[81] found a close relationship between retinal and renal changes. He reported that retinopathy occurs in 80 - 90 per cent of patients with nephropathy. Day[82] concluded that several types of retinopathy are always associated with renal lesion. This conclusion was based on histological findings.

Laboratory findings The association between proteinuria and retinopathy in diabetes has been reported. Albuminuria was present in all 11 patients with retinopathy and diabetes of more than 10 years.[6] In 1985, after a study of 2166 diabetics in Gottenburq, Lindergard observed that microalbuminuria was highly associated with retinopathy. Rand et al[83] found that albuminuria and serum creatinine were higher in patients with proliferative retinopathy further supporting the association between retinopathy and nephropathy in diabetes. Koefed et al[17] studied the association between the incidence of diabetic retinopathy and the development of diabetic nephropathy in 110 Insulin dependent diabetes mellitus patients with persistent proteinuria. He compared these with 110 diabetic patients without proteinuria. The cumulative incidence of proliferative retinopathy was 74% in patients with clinical nephropathy and 14% in patients free of proteinuria. Background retinopathy was seen in 93% and 37% respectively. A higher albumin excretion was found in those patients with background retinopathy than those free of it in a study by Hockaday[19]. Further more, it has been concluded that even a slightly elevated UAE (Urinary Albumin Excretion) "microalbuminuria" is a strong predictor with respect to development of proliferative retinopathy.

However, despite reports showing that microalbuminuria predicts diabetic retinopathy, it should be stressed that there is an inconsistent relationship between retinopathy and

nephropathy. Patients with normal albumin excretion rate may show advanced retinal lesions, although more often there is a correlation. The opposite situation with completely normal retinae and nephropathy is more uncommon and suggests non diabetic renal disease.[84]

Duration of disease: Diabetic retinopathy and nephropathy share a common factor: their prevalence and severity increases with increasing duration of the diabetic state.[11,35,85] Thus diabetic nephropathy occurs non uniformly in long term diabetic patients and the cumulative incidence after 40 years is about 40 - 50%.[85] In these patients it takes between 5 and 20 years from the appearance of constant proteinuria to the development of end stage renal failure.[36] According to Maloney[86] and his colleagues retinopathy is always present in advanced diabetic nephropathy. And that most patients (80%) in renal failure from diabetes have proliferative retinopathy and between quarter and one third are blind at this stage.

Pathogenesis: Diabetic retinopathy and nephropathy are the microvascular complications of diabetes mellitus. The heamodyanamic theory on aetiology of diabetic microangiopathy relates the pathogenesis of diabetic nephropahy to diabetic retinopathy. Stalder and Schmid have shown that early stages of IDDM are characterised by pronounced glomerular hyperfiltration. Hyperfiltration has been pointed out to be responsible for the eventual development of glomerulopathy.[87] This view is supported by several lines of evidence: glomerulosclerosis also develops in clinical conditions affecting glomerular heamodyanamics like reduction of renal mass following unilateral nephrectomy.[88] Unilateral nephrectomy is a condition which increases the glomerular pressures and flows where as ipsilateral arterial stenosis limit the elevation of pressure and thereby reduce the risk of glomerulopathy. In the kidney, as an increasing number of glomeruli are destroyed adaptive increase in pressures and flows in relatively preserved nephrons lead to a self-perpertuating process of destruction.[87] Capillary damage could arise from direct mechanical injury, intracapillary coagulation and or increased transcapillary passage of macromolecules with deposition of proteineous material in the glomerular messangium.

A remarkably similar correlation between functional and morphologic alteration occur in the retinal microcirculation. As in the case of glomerular microcirculation heamodyanamic abnormalities can be detected in the retina many years before retinopathy becomes overt. Dilation of retinal arteries and veins occurs in patients with early IDDM in whom there is little or no sign of retinopathy.[89] Also like the glomerular microcirculation retinal vasodilatation has been shown to fluctuate with the state of metabolic control of the diabetic condition. Larsen[76] described marked venous dilatation in the retina of newly diagnosed IDDM patients a finding that could be reversed with restoration of euglycaemia. Likewise, Jutte[90] reported retinal venous dilatation in 43 among 100 young patients with IDDM as well as reversal of this abnormality with normalization of blood glucose levels. He further observed that the presence of dilated veins presages the development of severe retinal lesions. Patients with no venous dilatation appeared to have a better ophthalmologic prognosis.

The finding of asymmetric diabetic retinopathy in patients with unilateral reduction of retinal blood flow strongly supports the heamodyanamic theory on aetiology of microangiopathy in the retina.[91] Gay performed ophthalmodynamometry in 10 patients in whom unilateral diabetic retinopathy had been detected. They found reduced hydraulic pressure in the non-involved eye usually a consequence of ipsilateral partial carotid stenosis and normal or elevated pressure in the eye showing retinopathy. This finding is strongly reminiscent of clinical and experimental situation in which asymmetric glomerulopathy was seen in association with unilateral renal hypoperfusion.[92]

On the basis of heamodyanamic changes preceding the development of retinopathy, other investigators have commented that glaucoma decreases the incidence of diabetic retinopathy presumably by increasing the intraocular pressure and thus lowering the transmural hydraulic pressure gradient across the retinal capillaries.[93]

The sequency of events leading to development of proliferative retinopathy is likely to be similar to that observed in diabetic glomerulopathy. The retinal capillary barrier is disrupted at a very early stage in IDDM.[69] This was shown using vitreous fluorometry.

Fluorescein was detected in the vitreous in diabetic patients in contrast to non diabetics. At a more advanced stage, retinal capillaries allow the passage of large molecules. This finding is reminiscent of the increase messangial uptake of macromolecules in the glomeruli of diabetic rats.[94]

The early disruption of blood retinal barrier can be reversed with improved control of diabetes.[95] In this study 11 patients with IDDM were studied for 22 years. They all had abnormally elevated ocular fluorescein after fluorescein injection. After 5-9 months of vigorous metabolic control vitreous fluorescence levels were dramatically reduced in most patients. However, 2 patients who already had proliferative retinopathy showed no reduction in ocular fluorescence. This finding suggests that as in the glomerulus, transcapillary protein extravasation can no longer be reversed by strict metabolic control in advanced stages of microvascular disease.

3.3 DIABETIC NEPHROPATHY

Diabetic nephropathy is a term which encompasses all the lessons occurring in the kidney of patients with diabetes mellitus. These lesions include glomerulosclerosis (diffuse or nodular), arterionephrosclerosis, chronic intestial nephritis and papillary necrosis. Glomerular lesions are particularly common and account for the majority of abnormal clinical findings referable to the kidney. Diffuse diabetic glomerulosclerosis is the most common lesion.[96]

Incidence

About 1/3 of diabetic patients will develop proteinuria and eventually end stage renal failure.[97]

Pathogenesis

The cause of diabetic nephropathy is not known. Diabetic control is probably an important influence.[85] But the disease doesn't occur uniformly in long term diabetic and even after 40 years, the cumulative incidence is only 40-50%.[85] Microalbuminuria, defined as abnormally raised albumin excretion without clinical proteinuria is an excellent marker

of subsequent diabetic nephropathy.[97] Diabetic nephropathy manifests itself by intermittent traces of albuminuria (albustix positive) which gradually become constant and increase in amount with the development of hypertension and gradual reduction in glomerular filtration rate (GFR). This sequency of events takes between 5-20 years from the appearence of constant proteinuria to the development of end stage renal failure.[36] Furthermore, proteinuria is the hall mark of nephropathy and is found in both Non insulin dependent diabetes mellitus and Insulin dependent diabetes mellitus. It's overall prevalence in a large diabetic clinic is approximately 14%.[36]

Classification[97]

Classification of diabetic nephropathy is not agreed on but the current classification in use for IDDM includes 5 stages.

Stage 1: Initial hyperfiltration There is glomerular hyperfunction and hypertrophy, which are present at diagnosis of diabetes.

Stage 2: Silent Stage With normal urinary albumin excretion (UAE) but with structural lesion present. This stage may last for many years. Some patients may continue in this stage throughout their life. Occasionally in stress situation e.g. during episodes of very poor metabolic control or during moderate exercise, albumin excretion may increase but this is a readily reversible phenomenon.

Stage 3: Incipient diabetic nephropathy Is characterised by persisting micro-albuminuria. Patients with microalbuminuria have a very high risk of subsequent development of overt diabetic nephropathy. However, intervention may certainly be possible at this stage reversing both structural and functional changes.

Stage 4: Overt diabetic nephropathy is characterised by proteinuria, hypertension and subsequent fall in glomerular filtration rate (GFR).

Stage 5: End Stage Renal Failure is the clinical syndrome of uraemia, with generalised nephron closure and very low GFR.

Microalbuminuria in diabetic nephropathy

Microalbuminuria is defined as abnormally raised albumin excretion below the albustix

positive proteinuric range. Urinary excretion in young normal males and females is about 5 Ug/min and the excretion rate very seldom exceeds 12-15 Ug/min. Microalbuminuria is considered to be present when the UAE is grater than 20 Ug/min and less than or equal to 200 Ug/min (30-300 mg/24 hours).[97] Persistent microalbuminuria occurs in incipient diabetic nephropathy. There are reports that microalbuminuria is an excellent marker of subsequent overt diabetic nephropathy.[97] Most patients with persistent microalbuminuria (80% or more) will without intensified treatment develop overt diabetic nephropathy over the following decade.[97]

Other causes of microalbuminuria are episodic very poor metabolic control, physical exercise, urinary tract infection and non-diabetic renal disease.

3.4 CATARACTS

The prevalence of cataracts in diabetic patients

Several studies on the prevalence of cataracts in diabetics show minor differences. Pilbeam,[98] reported a prevalence of 3% being the lowest prevalence reported in Africa. 3 studies have been done in Nigeria with prevalences of 22%, 12.5% and 8.7%.[4,5,6] In Tanzania, Haddock (1964) reported 41% affection by cataracts in diabetics. A likewise higher prevalence was found by Katenga.[26]

Recent reports of 9% and 10.6% found by Lester,[27] Gillgv et al[99] and Rolfe[11] do not differ much from earlier reports. The diversity of methods and criteria used in diagnosis of cataracts could account for the discrepance between the low and high reported prevalence of cataracts in Africans.[11]

Patients with juvenile onset diabetes have a prevalence of cataracts varying from 2-50%.[5,37] Klein,[35] reported that among diabetics in Wisconsin, cataract was a significant cause of legal blindness in young onset diabetic persons second only to proliferative retinopathy. Cataract was also the most frequent cause of such severe visual loss in older onset persons. According to Rolfe,[11] cataract was a more frequent and an important cause of blindness than retinopathy in central Africa.

Senile cataracts have been found to be commoner in diabetic than non-diabetic patients.[100] Apart from the reported prevalence of cataracts, several workers have noted that cataracts are frequent in diabetics than in non-diabetics.[5,6,22,101] On the contrary Wite and Beetham[102] found no significant difference in the prevalence of cataracts between diabetics and non diabetics.

It has been noted that cataract extraction is more commoner in diabetics than in non diabetics by about 5%.[103] The difference between observed prevalence surveys and cataract extraction are due to the fact that lens opacities mature more rapidly in diabetics than in non diabetics.[37]

A sex difference in the prevalence of cataract has been reported by Burditt and card.[104] They found that cataracts were more frequent in females than in males. Furthermore, the progression of lens opacities is rapid in female than in males irrespective of age. Female patients present for cataract extraction more than male patients.[69,105]

The pathogenesis of cataract

The pathogenesis of cataract in diabetics has not been settled. However, 3 most accepted factors in the production of a true diabetic cataract are: disturbance in carbohydrate metabolism, osmotic hydration and development of hydration with consequent proteolysis.[106]

Studies on sugars have established that blood sugars like glucose, galactose or xylose lead to cataracts in young diabetic patients.[107] Similar studies with similar results were reported in animals.[108] Van Heyningen[108] described sugar alcohols: sorbitol, dulcitol and Xylitol in diabetic galactosaemic and xylose induced cataract. Furthermore, Van Heyningen showed that these sugar alcohols were formed from sugars the reaction being catalysed by Aldose reductase enzyme. Once formed these sugars can't easily get out of the cell thus causing osmotic hydration. The lens has high levels of aldose reductase.[106]

Support for these findings was given by subsequent workers who have shown that aldose reductase inhibitors given to diabetic rats delayed the onset and progression of cataracts.[110,111]

Transient cataracts in diabetic patients have been reported by Brown and Burman.[112]

Types of cataracts in diabetes

There are three recognized morphological types of cataract in diabetes:

i) **Snowflake cataract of O'Brien**

This is the true or juvenile diabetic cataract. It was described by O'Brien in 1943. It is typically composed of subcapsular opacities in the superficial layers of the anterior and posterior cortex. The snowflake cataract differs from other type of Lenticular opacities particularly in the location of the opacities in the subcapsular region. Chemically, the most significant change in these diabetic cataracts is an increase in sorbitol, glucose and fructose in the lens.[113] It is invariably bilateral.

ii) **Senile cataract**

This is indistinguishable in appearance from that in the non-diabetic patients.

iii) **Subcapsular lens opacities**

These are located in the anterior and posterior subcapsular region.

3.5 GLAUCOMA

Prevalence of glaucoma

It is generally accepted that the incidence of glaucoma in the general population is about 1-2%.

The association between glaucoma and diabetes has been cited by several workers. In a study of juvenile onset diabetics, using the applanation tonometer Safir[114] noted that 20% of diabetic patients had clearly abnormal tensions and 30% were suspiciously high. Becker[93] and his co-workers reported on intraocular pressure in diabetic patients and their response to topical steroids. They also confirmed the finding of elevated intraocular pressure in a large percentage of patients with juvenile onset diabetes. In another study, Safir[33] found 10% of definitely elevated intraocular pressure in diabetic patients.

On the other hand other workers have found no association of glaucoma and diabetes.[102,115]

Neovascular glaucoma, a form of secondary glaucoma, occurs frequently in diabetic patients with proliferative diabetic retinopathy and rubeosis iridis.[37] It was first pointed

out by Salus[116] that neovascularization of the iris in long term diabetic patients resulted in neovascular glaucoma. However, neovascular glaucoma of identical appearance may occur in patients with different diseases.[117]

During a 5 year period of observation of diabetic patients, neovascular glaucoma was found in 14 out of 58 eyes. The incidence of secondary glaucoma was found to be higher than that found in the general population by Amstrong.[118]

3.6 DIABETIC OPHTHALMOPLEGIA

The incidence of ophthalmoplegia in diabetics is rare.[119] It may occur in young diabetics.[120] But commonly occurs in elderly patients with latent diabetes. Waite Beetham[102] noted 0.4% of 2,000 diabetics having ophthalmoplegia.

Pathogenesis

The mechanism of diabetic ophthalmoplegia is not yet settled. Weinstein and Dogler[121] attributed the lesion to small vascular lesions in the brainstem. Studies by Jepson[122] among diabetic and non diabetics showed dilated posterior cerebral and superior cerebella arteries. He thought that the ophthalmoplegia in diabetes was due to pressure on the occulomotor nerve by these dilated arteries.

According to Asbury[123] diabetic ophthalmoplegia is due to a focal demyelination with minimal axonal degeneration. Demyelination occurs secondary to closure of intraneural arteriole.

Clinical presentation

Diabetic ophthalmoplegia is preceded by acute pain in and about the eye.[119] There is characteristic sparing of the pupil in diabetes.[124] This is because, diabetic microangiopathy may affect the vasa nervorum which supply the main trunk of the 3rd nerve, sparing the pia blood vessels which supply the pupillary fibres.[55] Recovery is predictable after several weeks and before 3 months.[125]

3.7 CONJUNCTIVAL MICROANEURYSMS

Conjunctional microaneurysms occur frequently in diabetic patients but they are not

pathognomonic of diabetes.[89] Microaneurysms were found in 55% of diabetic patients and in 4% of non-diabetic patients.[102] They were commoner in patients with retinopathy than those free of it.[102]

3.8 OPTIC NERVE DISORDERS IN DIABETES MELLITUS

Three problems have been cited to occur in the optic nerve in association with diabetes mellitus. These are increased susceptibility to tobacco amblyopia, acute optic neuritis and primary optic atrophy.

Waite and Beetham[102] found 14 eyes with tobacco alcohol amblyopia in 2,000 diabetic patients. Duke-Elder[100] considered the existence of acute optic neuritis in diabetes. He described this type of neuritis as affecting both sexes and all ages with long standing or severe uncontrolled diabetes. He further pointed out that there was rapid, painless and often bilateral loss of vision due to central scotoma. This clinical picture improved rapidly when diabetes was adequately controlled.

Waite et al[102] found over three times as many eyes with optic atrophy among diabetics (0.7%) as among non-diabetes (0.2%).

3.9 MACROVASCULAR AND MICROVASCULAR COMPLICATIONS OF DIABETES

Accelerated atherogenesis or macrovascular disease is recognised as one of the major concomitants of the diabetic condition in almost all areas of diabetic practice. Patients with diabetes are at an increased risk of coronary, peripheral vascular disease and cerebral vascular disease. These are the macrovascular complications of diabetes.[126] The risk factors for macrovascular disease include poor diabetic control, plasma cholesterol and high density lipoprotein cholesterol.[126]

It has been shown that ischaemic heart disease and perhaps atherosclerotic arterial disease generally vary widely in prevalence between different regional groups of diabetic subjects paticulary those living in Westernized and those in oriental environment. The prevalences are comparatively higher in Western World.

However, there is no suggestion that there are differences of any magnitude between oriental and Western World in the frequency or severity of retinopathy (microvascular disease) when the important variable of duration of diabetes is taken into account.[15] In this study, no African country was represented. It is interesting to study retinopathy in Tanzania Africans to see whether the prevalence and risk factor differ from other diabetic patients in the world.

4. MATERIALS AND METHODS

From August 1988 to April 1989 a total number of 414 diabetics were examined.

4.1 SELECTION OF PATIENTS

Tanzanian African patients attending the Muhimbili Medical Centre diabetic clinic were selected. These included:

a) All newly diagnosed diabetic patients attending the clinic. These were patients diagnosed within a period of 6 months before and 6 months after the commencement of the study.

ii) Special clinic patients: These were diabetic patients registered and followed up at the clinic since 1981 to 1987.

iii) Patients diagnosed before 1980.

Patients whose ocular examination was not completed were excluded from the study.

4.2 QUESTIONNAIRE

Basic information

For each patients a questionnaire was completed on which the following were recorded: name, age, sex, year of diagnosis of diabetes and hypertension. Clinical presentation at diagnosis (classical symptoms, routine exam, diabetic ketoacidosis, complications) and the duration of symptoms were recorded in weeks. Likewise, details of current treatment (diet, drugs, Insulin), family history of diabetes and hypertension, smoking and alcohol consumption were also included in the questionnaire. Patients case notes were consulted when patients were not sure of their answers.

Assessment of diabetic control

Diabetic control was assessed by dividing the total number of visits with those visits with glycosuria. Assessment of diabetic control was also done by the assay of serum fructosamine which is a method for determination of non-enzymatic glycation of serum proteins as an index of glycaemic control.

Body mass index

The weight and height were taken and the Body Mass Index calculated from the formula:

Body Mass Index = (Weight in Kg divided by the square of height in meters; ie BMI = $Wt(Kg)/Ht^2(m)$.

Blood pressure measurements

Both the diastolic and systolic blood pressures were taken using 12 x 22 cnf bladder applied 2-3 centimetres above the antecubital fossa. All readings were recorded to the nearest 2mmHg pressure, reading the calibration below the meniscus. Patients on treatment for hypertension and those with Blood pressure $\geq$160/95 mmHg were regarded as hypertensive.

Laboratory tests

Patients were then requested to submit urine samples which were examined for proteinuria. Blood samples were taken and examined for blood glucose. Other blood and urine samples were sent to Newcastle, United Kingdom for measurements of fructosamine, microalbuminuria, serum cholesterol and triglycerides and serum creatinine. Microalbuminuria was measured by radioimmunoassay. Serum triglyceride and cholesterol concentration were measured by a fluometric method using the Cobas Bio centrifugal analyser. Microalbuminuria - was defined as urinary albumin excretion of >30 μg per ml of urine.

Serum cretinine was considered elevated when it was >130 μmol per litre.

The albumin/creatinine ratio was calculated from the formular

$$\frac{\text{Alb} \times 1.73}{\text{Creatinine} \times 0.010115 \times m^2} = mg/g/m^2$$

Ocular examination

Ocular examination commenced with visual acuity using the Snellen and illiterate E charts for literate and illiterate patients respectively. Intraocular pressure was measured using the Schiotz tonometer after anaesthetizing the cornea. Intraocular pressures > 21 mmHg were considered glaucomatous. Presence or absence of xanthelasmas was noted.

Using the slit lamp the anterior segment was examined for: conjunctival microaneurysms, corneal opacities, hyphema, cells and flare in the anterior chamber, rubeosis and iris atrophy. The angle width was judged by the depth of the anterior chamber at the periphery. The presence or absence of the lens was noted. Gonioscopy was then done and the angle width ascertained.

Mydriatic drops (1% tropicamide) were then instilled into each eye. Slit lamp examination was repeated when pupillary dilatation was more than 3mm. The lens was examined for opacities and when present, lens opacities were specified whether cortical, nuclear, subcapsular or combined. The anterior vitreous was examined for vitreous heamorrhage.

Funds examination was done with both direct and indirect ophthalmoscope in a dark room. Patients whose retinae were not visible with the ophthalmoscope, the reason was recorded in the questionnaire. With the patient looking straight ahead, the optic disc was examined for size, shape and colour. Glaucomatous disc changes including cupping of the physiological cup and nasal shift of vessels were looked for and recorded. The disc was also examined for new vessels. While the patient was looking at the ophthalmoscope light, the macular was examined for exudates, heamorrhages and oedema. Vessels were traced from the disc to the periphery and information about venous dilatation, beading, microaneurysms and venous occlusion at the arteriovenous crossings noted. Heamorrhages were classified as 'blot' or 'dot' and flame shaped, while exudates were classified as being hard or soft. The number of different lesions were counted.

4.3 DEFINITION OF DIABETIC RETINOPATHY

Background diabetic retinopathy was defined as having microaneurysms, 'dot' and 'blot' heamorrhages, flame shaped heamorrhages, hard exudates and retinal or macular oedema.

Pre-proliferative diabetic retinopathy was defined as the presence of any findings in background retinopathy, cotton wool spots, doubtful new vessel formation and arteriovenous changes. These include venous dilatation and arteriolar narrowing.

Proliferative diabetic retinopathy was defined as occurring in an eye with any of the changes in background or pre-proliferative retinopathy and neovascularization of the disc or other parts of the retina.

4.4 DATA ANALYSIS

Data were analysed using the Statistical Package for the Social Sciences (SPSSPC). Comparisons were made using the Chi-squared test and the Student's t-test.

5. RESULTS

The data were initially analysed separately for patients on treatment with insulin and for patients not on insulin. There were no differences in the relationships between diabetic retinopathy and the other variables between those on insulin and those not on insulin. In this presentation therefore, the two types of diabetic patients have been pooled and analysed as one group.

5.1 DESCRIPTION OF THE STUDY POPULATION

Age distribution

Two hundred ninety three (70.8%) patients were in the age range 31 - 60 years. Patients with NIDDM were older than those with IDDM (table 1).

Table 1: Age distribution of 414 diabetic patients

Age (years)	No	%
1 - 15	6	1.4
16 - 30	37	8.9
1 - 45	125	30.2
46 - 60	168	40.6
61+	78	18.8
All ages	414	100

Sex

Of the 414 patients examined, 294 (71.0) were men.

Table 2. Distribution of the 414 patients by sex

Sex	No.	%
Male	294	71.0
Female	120	29.0
Total	414	100

Treatment for the diabetes

Most (56.0%) patients were on oral hypoglycaemic agents. Patients on insulin treatment were 149 (36.0%). Eight patients had just reported to the clinic and their treatment had not been decided upon (Table 3).

Table 3. Distribution of 414 diabetic patients by type of treatment

Treatment	No.	%
Diet only	25	6.0
Oral drugs	232	56.0
Insulin	149	36.0
Unspecified	8	2.0
Total	414	100

Duration of diabetes

One hundred patients (24.2%) were diagnosed to have diabetes within 6 months of the commencement of the study. Two hundred eighten (52.7%) patients were being followed up at the diabetic clinic for up to 8 years. Ninety-six (23.1%) patients had had diabetes for more than 10 years (Table 4).

Table 4. Distribution of 414 patients by duration of diabetes

Duration (years)	No.	%
< 1	100	24.2
1 - 8	218	52.7
> 10	96	23.1
Total	414	100

Smoking habit among the 414 patients

Only 10.6% of the study population were current smokers on the day of examination. 265 (64%) patients had never smoked (Table 5).

Table 5. Distribution of 414 patients by smoking habit

Cigarette smoking	No.	%
Non-smoker	265	64.0
Stopped smoking	105	25.4
Current smoker	44	10.6

Alcohol consumption

The prevalence of alcohol drinking on the day of examination was 17.4%. Most patients (58%) had never drunk alcohol (Table 6).

Table 6. Alcohol consumption among the 414 patients

Drinking habit	No.	%
Never	240	58.0
Stopped	102	24.6
Current drinker	72	17.4

5.2 PREVALENCE OF DIABETIC OCULAR LESIONS

Diabetic Retinopathy

Fundus examination was performed in 388 patients among 414 diabetics. The funds was not visible in either eye in 26 patients due to advanced cataract. Of the 388 patients, 196 (50.5%) had diabetic retinopathy. Background diabetic retinopathy was present in 143 (36.9%), pre-proliferative retinopathy in 39 (10.1%) and 14 (3.6%) patients had proliferative retinopathy (Table 7).

Microaneurysms were seen in one or both eyes in 63 (16.2%) patients. Haemorrhages appeared in 37 (9.5%) patients. Hard exudates were the most frequent presentation. They

diabetic retinopathy. Most hard exudates were scattered at the posterior pole. Twenty-four patients had hard exudates around the macular and two of them had macular oedema.

Table 7. The prevalence of diabetic retinopathy

Retinopathy	No.	%
None	192	49.5
Backgroud	143	36.8
Pre-proliferative	39	10.1
Proliferative	14	3.6
Total	388	100

Cataract

One hundred seventy-six (42.5%) patients at examination were found to have lens opacities of different severity. Eight of these had undergone cataract extraction in one or both eyes. Only 3 patients in the age group 16-30 had cataracts, in contrast to 36, 76 and 61 in the age groups 31-45, 46-60 and 61+ respectively. The proportion of diabetics with cataracts increased with increasing age of the patient (table 9a).

Table 8. Prevalence of ocular lesions other than retinopathy

Occular lesion	No.	%
Cataracts	176	42.5
Glaucoma	20	4.8
Optic atropy	7	1.7
Conjunctival microaneurysms	226	54.6
Xanthelasmas	4	0.9

Table 9a: The prevalence of cataract in 176 diabetic patients by age

Age (Years)	No	%
1 - 15	-	-
16 - 30	3	1.7
31 - 45	36	20.5
46 - 60	76	43.2
61+	61	31.7
Total	176	100.0

Most patients had subcapsular lens opacities followed by combined diffuse lens opacities as shown in table 9b. Twenty-six patients had total lens opacities obscuring funds view.

Table 9b. Type of cataract in 168 patients with cataracts

Type of cataract	No.	%
Subcapsular	79	47.1
Cortical	34	20.2
Nuclear	12	7.1
Combined	43	25.6
Total	168	100.0

Glaucoma

Among 414 patients, 20 (4.8%) patients were found to have elevated intraocular pressure of more than 24 mmHg. The rest of the patients had intraocular pressures of less than 21 mmHg. 50% of these patients were in the age group 46-60 years (table 8). Four patients were already on medical treatment for open angle glaucoma while one had undergone trabeculectomy in one eye. Two patients had secondary glaucoma. Glaucomatous optic atrophy with excavation of the physiological cup and nasal shift of vessels was seen in 4 patients.

Optic atrophy

Both optic discs were pale in 7 (1.8%) out of 388 examined patients. Four of these showed glaucomatous optic atrophy. Patients of different age groups were equally affected by optic atrophy (table 8).

Conjunctival microaneurysms

Two hundred twenty-six (54.6%) patients had conjunctival microanerysms, the proportion of affected patients increasing with increasing age (table 8).

Xanthelasmas

Four (0.9%) patients had xanthelasmas. Three of them had bilateral affection of the upper lid. One patient was affected in one upper lid.

Rubeosis Iridis

None of the examined patients had rubeosis iridis.

5.3 THE RELATIONSHIP BETWEEN DIABETIC RETINOPATHY AND SEVERAL FACTORS

Diabetic retinopathy and age

Table 10 presents the relationship between diabetic retinopathy and age. The prevalence and severity of diabetic retinopathy increased with increasing age. None of the patients below 30 years had diabetic retinopathy compared with 74.2% of those above 60 years. All patients with proliferative retinopathy were over 45 years of age. This relationship was statistically significant ($p < 0.001$).

Table 10. The distribution of diabetic retinopathy by age

	Age (years)					
	1 - 15 No. %	16 - 30 No. %	31 - 45 No. %	46 - 60 No. %	61 + No. %	Total
None	6 100	26 70.3	68 56.7	75 47.2	17 25.8	192
Background		10 27.0	46 38.3	63 39.6	24 36.4	143
Pre-proliferative		1 2.7	6 5.0	15 9.4	17 25.8	39
Proliferative				6 3.8	8 12.0	14
Total	6 100	37 100	120 100	159 100	66 100	388

$X^2 = 20.64$, $p < 0.001$

Duration of diabetes and diabetic retinopathy

Among 97 newly diagnosed patients, 45.4% had diabetic retinopathy. None of them had proliferative retinopathy. The prevalence and severity of diabetic retinopathy increased with increasing duration of diabetes, so that 47 (65.5%) patients with diabetes for more than 10 years had diabetic retinopathy. This same group comprised of 10 (71.4%) patients with proliferative diabetic retinopathy (Table 11). This relationship was statistically significant ($p<0.0001$).

Table 11. The distribution of diabetic retinopathy by duration of diabetes

	Duration of diabetes (years)			
Type of retinopathy	< 1 No %	1 - 8 No %	> 10 No %	Total
None	53 54.6	109 53.4	30 34.5	192
Background	39 40.2	74 36.3	30 34.5	143
Pre-proliferative	5 5.2	17 8.3	17 19.5	39
Proliferative		4 2.0	10 11.5	14
Total	97 100	204 100	87 100	388

$X^2 = 36.30$, $p<0.0001$

5.3.3 Hypertension and diabetic retinopathy

There was a strong relationship between hypertension and diabetic retinopathy (Table 12). There were 74 (17.9%) patients with blood pressure of $\geq$160/95 mmHg. Of the 388 patients, 72 (18.6%) patients had hypertension (blood pressure $\geq$160/95 mmHg). Fifty (69.4%) of the 72 patients with hypertension had retinopathy.

Table 12a. The prevalence of diabetic retinopathy in patients with and without hypertension

	Hypertension		
Retinopathy	Absent No %	Present No %	Total
Absent	170 53.8	22 30.6	192
Present	146 46.2	50 69.4	196
Total	316 100	72 100	388

$X^2 = 11.76$, $p<0.001$

Both the mean systolic and mean diastolic blood pressures were higher in patients with retinopathy compared to those without retinopathy (Table 12b).

Table 12b. Mean systolic and diastolic blood pressure in patients with and without retinopathy

	No.	Mean	SD	95% Confidence limits
Systolic:				
With retinopathy	196	140.8	26.45	137.3 - 144.3
Without retinopathy	192	133.9	23.86	130.2 - 137.2
Diastolic:				
With retinopathy	196	85.1	15.43	83.2 - 87.1
Without retinopathy	192	83.8	13.97	81.6 - 85.8

Cigarette smoking and diabetic retinopathy

Among smokers of 1-20 cigarettes per day 42 (47.4%) patients had diabetic retinopathy. 16 (44.4%) patients smoking 21-40 cigarettes per day had retinopathy while 6 (55.6%) of those patients smoking more than 40 cigarettes per day had diabetic retinopathy (Table 13). Of the 14 patients with proliferative retinopathy, 10 (71.4%) were non-smokers. There was no relationship between the prevalence and severity of diabetic retinopathy and the number of cigarettes consumed per day ($p > 0.05$).

Table 13a. The prevalence of diabetic retinopathy by number of cigarettes

Smoking (Cigarettes per day)	Retinopathy Absent No %	Present No %	Total No %
None smoker	131 49.6	133 50.4	264 100
1 - 20	34 44.7	42 55.3	76 100
21 - 40	23 59.0	16 41.0	39 100
41 - 60	4 44.4	6 55.6	9 100
Total	192	196	388

$X^2 = 9.09$, $p = 0.42$

The absence of a relationship between diabetic retinopathy and smoking was further shown in table 13b. One hundred thirty three (50.4%) of 264 non-smokers had diabetic retinopathy. Thirty-six (47.4%) patients who had smoked for a duration of 1-20 years had diabetic retinopathy. There was no significant increase in the prevalence of retinopathy with increase in duration of smoking ($p > 0.05$).

Table 13b. The prevalence of diabetic retinopathy by duration of smoking

Duration of smoking (years)	Retinopathy Present No %	Absent No %	Total No %
Non-smoker	131 49.6	133 50.4	264 100
1 - 20	40 52.6	36 47.4	76 100
21 - 40	18 45.0	22 55.0	40 100
41 - 60	3 37.5	5 62.5	8 100
Total	192	196	388

$X^2 = 11.71$, $p = 0.35$

Diabetic Control and diabetic retinopathy

Table 14a shows the relationship between retinopathy and diabetic control. The proportion of patients with different types of retinopathy did not differ between those, with 'good' and those with 'poor' diabetic control. There was no relationship between the prevalence or severity of retinopathy and degree of diabetic control ($P > 0.05$).

Table 14a: Relationship between diabetic retinopathy and diabetic control

Retinopathy Type	Diabetic Control: Good No %	Poor No %	Total No %
None	53 43.1	70 56.9	123 100
Background	35 39.3	54 60.9	89 100
Pre-proliferative	12 50.0	12 50.0	24 100
Proliferative	2 33.3	4 66.7	6 100
Total	102	140	242

$X^2 = 1.133,\ p = 0.7690$

The mean levels of serum fructosamine among patients with and without retinopathy are presented in table 14b. The mean serum fructosamine in patients with retinopathy were not significantly higher than those without retinopathy. There was also no difference between the different retinopathy groups. There was therefore no relationship between diabetic control and diabetic retinopathy ($P < 0.05$).

Table 14b: Mean levels of fructosamine (mmol/l) among patients with and without retinopathy

	Cases	Mean	SD	95% Confidence limits
Without retinopathy	155	3.88	1.43	3.64 - 4.11
Background retinopathy	120	4.28	1.57	4.01 - 4.54
Pre-proliferative retinopathy	32	3.78	1.45	3.26 - 4.30
Proliferative retinopathy	12	3.58	1.42	2.73 - 4.43

The mean levels of fructosamine among patients classified as having 'good' and 'poor' diabetic control by assessment of glycosuria are shown in table 14c. Patients classified as having 'poor' control by the glycosuria method had a higher mean fructosamine level compared to those classified as having 'good' control. The mean of 3.42 + 1.31 mmol/l among patients with 'good' control was significantly lower than that 4.28 + 1.57 mmol/l found in patients with 'poor' control ($P < 0.05$).

Table 14c: Mean levels of fructosamine (mmol/l) among patients classified as 'good' and 'poor' diabetic control by assessment of glycosuria

	Case	Mean	SD	95% Confidence limits
Good control	84	3.42	1.31	3.08 - 3.75
Poor control	126	4.28	1.64	4.01 - 4.56

Microalbuminuria and the prevalence of diabetic retinopathy

Table 15a presents the relationship between prevalence of diabetic retinopathy and microalbuminuria. Of 371 patients in whom urine albumin results were obtained, 110(29.6%) patients had albumin levels of more than 30 μg/ml. Among them, 118(45.2%) had diabetic retinopathy. Likewise only 37(20.6%) patients with albumin levels of more than 30 μg/ml had no retinopathy.

There were more patients with both microalbuminuria and retinopathy than with retinopathy alone. This relationship was statistically significant ($P < 0.001$).

Table 15a: The relationship between prevalence of diabetic retinopathy and microalbuminuria

	Microalbuminuria				
Retinopathy	Present		Absent		Total
	No	%	No	%	
Present	73	66.4	118	45.2	191
Absent	37	33.6	143	54.8	180
Total	110	100.0	261	100.0	371

$X^2 = 13.9$ P = 0.0000

Microalbuminuria and severity of diabetic retinopathy

The relationship between microalbuminuria and severity of diabetic retinopathy is shown in table 15b. Of 138 patients with background retinopathy 43(31.2%) had microalbuminuria. The number of patients with microalbuminuria among 39 patients with pre-proliferative retinopathy was 23(59.0%). However, 7(50%) patients with proliferative retinopathy also had microalbuminuria. Even though these patients with proliferative diabetic retinopathy were equally distributed between microalbuminuric and normoalbuminuric groups, 7(2.7%) out of 261 patients without microalbuminuria had proliferative diabetic retinopathy. This is in contrast to 7(6.4%) out of 110 patients with both microalbuminuria and proliferative retinopathy. The proportion of patients with microalbuminuria increased with the severity of retinopathy. This relationship was statistically significant ($P < 0.0001$).

Microalbuminuria and duration of diabetes

The proportion of patients with microalbuminuria increased with increasing duration of diabetes. In those patients who had diabetes for less than one year, 24(25.0%) had microalbuminuria compared to 55(26.4%) who had diabetes for up to 8 years. Thirty eight (41.8%) patients who had diabetes for more than 10 years had microalbuminuria (table 15d). Further analysis showed that the percentage of patients with microalbuminuria rose to 57.1%% for patients who had diabetes for more than 14 years.

Table 15b: The relationship between Severity of diabetic retinopathy and microalbuminuria

Retinopathy Type	Microalbuminuria Absent No	%	Present No	%	Total No	%
No Retinopathy	143	79.4	37	20.6	10	100.0
Background	95	58.8	43	31.2	138	100.0
Pre-proliferative	16	41.0	23	59.0	39	100.0
Proliferative	7	50.0	7	50.0	14	100.0
Total	261		110		371	

$X^2 = 26.14$ P = 0.0000

The mean level of albumin/creatinine ratio increased with increasing severity of diabetic retinopathy. However, it was not significantly higher among those with retinopathy than those free of it (table 15c). Further analysis showed that, the albumin/creatinine ratio was significantly related to severity of diabetic retinopathy. The mean rank for the albumin/creatinine ratio among patients without retinopathy was 155.5 while that for background, pre-proliferative and proliferative retinopathy respectively was 188.8, 226.7 and 259. This relationship was statistically significant (p=0.0000).

Table 15c: Mean albumin/creatinine ratio among patients with and without retinopathy

Retinopathy	No	Mean	SD	95% Confidence limits
Without retinopathy	174	727.9	531.2	-150.8 - 612.1
Background	133	79.4	256.7	46.5 - 282.8
Pre-proliferative	38	181.8	402.3	28.8 - 676.8
Proliferative	4	760.3	1583.2	-517.7 - 1483.3

Table 15d: Relationship between microalbuminuria and duration of diabetes

Microalbuminuria	Duration of diabetes (Years)					
	< 1		1-8		> 10	
	No	%	No	%	No %	Total
Present	24	25.0	55	26.4	38 41.8	117
Absent	72	75.0	155	73.6	53 58.2	278
Total	96	100.0	208	100.0	91 100.0	375

$X^2 = 8.42$ P = 0.0148

Microalbuminuria and age

The proportion of patients with microalbuminuria increased with increasing age of the patient. The proportion of patients with microalbuminuria in the age groups 16-30 years, 31-40 years and 46-60 years were 6(17.6%), 28(23.1%) and 50(31.3%) respectively. The proportion of patients with microalbuminuria in the age group 61 years and above was very high (41.9%). Two of the 6 patients in the age group 0-15 years had microalbuminuria. The relationship between microalbuminuria and age was significant ($P < 0.05$), as shown in table 15e.

Table 15e: Relationship between microalbuminuria and age

	Age group (Years)					
	0 - 15	16 - 30	31 - 45	46 - 60	61 +	
Microalbuminuria	No %	No %	No %	No %	No %	Total
Present	2 33.3	6 17.6	28 23.1	50 31.3	31 41.9	117
Absent	4 66.7	28 82.4	93 76.9	110 68.7	43 58.1	278
Total	6 100.0	34 100.0	121 100.0	160 100.0	74 100.0	395

$X^2 = 10.36$ P = 0.0347

Diabetic retinopathy and serum creatinine

There were 237(91.9%) patients with serum creatinine levels of less than 130 µmol/l. Of these patients, 124(52.3%) had no retinopathy while 88(37.1%) had background retinopathy. Twenty one (8.9%) and 4(1.7%) respectively had the severe types of retinopathy ie pre-proliferative and proliferative. The proportion of patients with high serum creatinine increased with the severity of diabetic retinopathy. Background retinopathy was present in 6.4% while pre-proliferative and proliferative occurred in 8.7% and 42.9% respectively. Many (52.4%) patients with high serum creatinine had diabetic retinopathy in contrast to 47.6% who had no retinopathy. This relationship was statistically significant ($P < 0.01$) as presented in table 16a.

Table 16a: Relationship between diabetic retinopathy and serum creatinine

	Serum Creatinine µmol/l		
Retinopathy	< 130	> 130	Total
Type	No %	No %	
No retinopathy	124 52.3	10 47.6	134
Background	88 37.1	6 28.6	94
Pre-proliferative	21 8.9	2 9.5	23
Proliferative	4 1.7	3 14.3	7
Total	237 100.0	21 100.0	258

$X^2 = 11.76$ P = 0.0082

Serum creatinine and diabetic retinopathy

Table 16b shows the mean concentration of serum creatinine (μmol/ml) among patients with and without retinopathy had the lowest mean serum creatinine while the highest levels were found in patients with proliferative retinopathy.

The difference between the two means was statistically significant ($P < 0.05$).

Table 16b: Mean serum creatinine (μmol/l) among patients with and without retinopathy

	Number	Mean	SD	95% Confidence Limits
Without retinopathy	131	84.29	48.49	73.99 - 94.88
Background retinopathy	93	83.65	25.26	71.41 - 95.88
Pre-proliferative retinopathy	23	93.12	28.70	73.5 - 117.74
Proliferative retinopathy	7	207.10	267.69	162.52 - 251.68

Serum cholesterol and diabetic retinopathy

The mean levels of serum cholesterol were not significantly different ($P < 0.05$) between those with retinopathy and those without. They were also not different between the different groups of retinopathy (table 17).

Table 17: Mean levels of serum cholesterol (mmols/l) in patients with and without retinopathy

	Number	Mean	SD	95% Confidence limits
Without retinopathy	170	3.67	1.20	3.49 - 3.86
Background retinopathy	138	3.90	125	3.69 - 4.10
Pre-proliferative retinopathy	38	3.86	1.23	3.66 - 6.06
Proliferative retinopathy	14	3.71	1.24	3.07 - 4.30

Serum triglycerides and diabetic retinopathy

The mean levels of serum triglycerides (mmol/l) were not significantly different ($P > 0.05$) between those patients with retinopathy and those without. Neither were these values different between the different groups of retinopathy (table 18).

Table 18: Mean levels of serum triglycerides (mmol/l) in patients with and without retinopathy

	Number	Mean	SD	95% Confidence limits
Without retinopathy	101	1.42	0.86	1.27 - 1.57
Background retinopathy	90	1.29	0.70	1.14 - 1.44
Pre-proliferative retinopathy	34	1.13	0.53	0.88 - 1.39
Proliferative retinopathy	9	1.32	0.87	0.82 - 1.82

6. DISCUSSION

6.1 AGE AND SEX DISTRIBUTION

Most studies carried out in African patients have been hospital based. They have shown that male diabetic patients predominate over female diabetic patients.[4,5,6,24-26] In Nigeria, Kinnear found that the number of male patients examined was twice as that of female patients. The reasons advanced for the predominance of male over female in these hospital based studies was that males in tropical Africa come to hospital more readily than females.[4] Greenwood and Taylor[5] showed similar findings. Rolfe[11] examined 372 men and 228 women. In the present study, 294 (71.0%) of the diabetic study group were males in contrast to 120 (29.0%) females. This is a male: female ratio of about 2.5:1. These findings are in agreement with previous workers.

Although this was a hospital based study, patients attending the diabetic clinic were included in the study as they came to the clinic. Considering the female preponderance over males in the Tanzanian population, the possibility of having more male than female diabetic patients in the Tanzanian population cannot be overlooked. Community based studies are required.

Kinnear found that most examined patients were in the age group 40-49 years. His findings did not differ much from those of subsequent workers. Thus in the studies by Haddock (1964) and Katenga (1983) the majority of patients were aged between 31-50 and 40-59 years respectively. Two hundred ninety-four (70.8%) of the patients in this study were in the age group of 31-60 years. Although the duration of diabetes is not considered in these data, these findings suggest that very few patients are diagnosed to have diabetes before 30 years of age. 6(1.4%) and 37(8.9%) patients were diagnosed to have diabetes mellitus below 15 and 30 years respectively in the present study. It is known that under the age of 30 years proliferative retinopathy starts to appear 10-15 years after the diagnosis of diabetes and develops ultimately in 25% of patients with IDDM. These are patients that need to be followed up as 25% of them will ultimately develop proliferative diabetic retinopathy.

6.2 RETINOPATHY

Prevalence of diabetic retinopathy

Studies done in African diabetic patients before 1970 showed prevalence rates of less than 10%.[2-6] This prompted some of the workers to suggest that African diabetic patients might be less vulnerable to complications of diabetes including retinopathy.[2,21] Subsequent workers have shown comparatively higher prevalences. Mhando and Yudkin[10] and Salim[25] reported approximately equal prevalences of 24.6% and 23.4% respectively. Katenga[26] found a similar prevalence of 19.1%. The highest prevalence rates reported in Africa include those of Steel[9] and Rolfe[11] in which 52% and 38% respectively had diabetic retinopathy. The present study recorded retinopathy in 196(50.5%) out of 388 patients. Of these patients 143(36.9%), 39(10.1%) and 14(3.6%) respectively had background, pre-proliferative and proliferative diabetic retinopathy.

The reasons advanced for the varying prevalence rates are several. Rolfe suggested that the varying prevalence rates were due to diversity of methods and criteria used in assessment of presence or absence of diabetic retinopathy. He used a standardized questionnaire and examination technique based on the WHO protocol for diabetic microangiopathy. The same questionnaire and examination technique was adopted in the present study. Few additions were made including the use of indirect ophthalmoscopy. Katenga[26] had likewise performed direct and indirect ophthalmoscopy. Steel[9] attributed the high prevalence (52.0%) recorded in his study to the use of retinal photography. He commented that inspite of intraretinal microproliferative abnormalities, the fundus may appear harmless to many physician who are not regular ophthalmologists. They may also lack the equipment needed for thorough fundus examination. This could result in falsely low prevalence rates. It has been found that retinal photography is sensitive in detecting diabetic retinopathy especially vasodilatation, beading and intraretinal microproliferative abnormalities. Studies have also shown that ophthalmologists' assessment by fundoscopy under mydriasis is a less sensitive method. Thus in a study comparing direct ophthalmoscopy and fundus photography among 1949 diabetic patients Moss et al[127]

found 86% agreement between ophthalmologists examination and retinal photographs for the presence or absence of retinopathy, non-proliferative and proliferative lesions. The disagreement was mainly in the milder forms of retinopathy, although there were 4 cases where proliferative lesions were not detected by the ophthalmologist (out of a total of 170). However, sensitivity is increased when indirect ophthalmoscopy is done, as in the present study. The high prevalence in this study could thus be related to the use of both direct and indirect ophthalmoscopy under mydriasis. The use of fundus photography could have resulted in an even higher prevalence.

In the study by Katenga, the duration of diabetes was shorter than in the present study. There were 27(24%), newly diagnosed patients, 52(47%) with a duration of 1-5 years and 31(29%) had had diabetes for more than 5 years. The present study had 96(23.2%) patients who had diabetes for more than 10 years. Among this subgroup 45 patient had diabetes for more than 14 years. So the high prevalence found in this study could also be attributed to the longer duration of diabetes in these patients.

In developed countries diabetic retinopathy is an important cause of blindness. Studies done in these countries show higher prevalence rates of 77%, 47%, 95%, 45%, 48% as reported by Lundback,[30] Kornerup,[31] Klein et al[35] Sagir[33] and Moriarty et al[128] respectively. The high prevalence obtained in this study together with the studies by Steel,[9] Rolfe[11] and Erasmus[13] suggest that diabetic retinopathy is probably not rare in Africans as suggested by earlier reports. A trend towards the increase is evident in recent studies. This tendency has also been observed in other parts of the world like Japan.[14]

The factors associated with diabetic retinopathy in the Western world including hypertension, duration of diabetes, proteinuria, microalbuminuria, metabolic control and age have been studied in the present study and the results are not different from those in European studies. This high prevalence probably represents a true picture of this microvascular diabetic complication in this community. The finding of 14 patients with proliferative retinopathy and 39 patients with pre-proliferative retinopathy calls for our awareness that in future visual disability due to proliferative retinopathy may assume public health importance. None of the studies done in Africans have reported such a high prevalence of proliferative retinopathy.[10-13]

Duration of diabetes and diabetic retinopathy

It has been a world wide observation that the prevalence of diabetic retinopathy increases with increasing duration of the diabetic condition.[11,12,26,35,36] The results in this study are similar. 57 (65.5%) patients with diabetes for more than 10 years had diabetic retinopathy compared to 44 (45.4%) and 96 (46.8%) of those with diabetes for less than one year and 1-8 years respectively. This shows that the prevalence of diabetic retinopathy increased with increasing duration of diabetes. This relationship was statistically significant ($P < 0.0001$). The relatively high prevalence of diabetic retinopathy among patients who had had diabetes for less than one year is attributed to the large number of NIDDM patients. 20% of these have retinopathy at diagnosis of diabetes.[36] The duration of diabetes in these patients is usually uncertain. Few years may elapse before they are diagnosed to have diabetes.

Following further analysis patients with retinopathy in the 3 different groups of duration of diabetes (Less than 1 year, 1-8 years, more than 10 years) showed an increasing proportion of patients with severe retinopathy (pre-proliferative and proliferative). Thus 12.0%, 22.0% and 27.0% were respectively having background, pre-proliferative and proliferative retinopathy. Despite being on constant follow up at the diabetic clinic, patients in the group of 1-8 years showed a similar trend. These findings clearly support the findings by Klein et al (1988) who concluded that the duration of diabetes was strongly associated with severity of diabetic retinopathy.

The relationship between hypertension and retinopathy

The relationship between hypertension and diabetic retinopathy is shown in table 12a. Among 387 patients on whom fundoscopy was done 72 (18.6%) had blood pressures of more than 160/95 mmHg or were on treatment for hypertension. The proportion of patients with both retinopathy and hypertension significantly exceeded those with retinopathy but without hypertension ($P < 0.001$). The mean systolic and diastolic blood pressures in patients with diabetic retinopathy were significantly higher than in patients without retinopathy ($P < 0.05$). This finding was also evident in the WHO Multinational

Study and in the study by Rolfe[11] in Zambia. The high blood pressure in patients with diabetic retinopathy is attributed to the effect of renal disease in raising the blood pressure. Dornan et al,[43] found that a rise in diastolic blood pressure was found only after the development of nephropathy. However, this study showed no relationship between microalbuminuria and hypertension. The hypertension in these patients may aggravate the ischaemic process already existing in the diabetic retina.

Smoking and diabetic retinopathy

A relationship between cigarette smoking and retinopathy was anticipated since smoking may cause tissue hypoxia by increasing carbon monoxide levels.[44] Smoking may lead to platelet adhesiveness thus exacerbating the problem of oxygen delivery to the tissues. In the present study group, most patient (64%) had never smoked while 103 (25.4%) had stopped smoking following medical advice. The number of patients smoking on the day of examination was only 44 (10.6%). The proportion of smokers is lower than that obtained in many centres in the WHO Multinational Study.[126] This probably suggests that African diabetic patients are not heavy smokers. A prevalence of 21.3% was found among African males in Dar es Salaam.[20]

The study further showed that there was no statistically significant increase in the prevalence of retinopathy with the increase in the duration of smoking ($P>0.05$). Also the mean duration of smoking was not significantly higher in patients with diabetic retinopathy than in those without ($P>0.05$). These data suggest that there is no relationship between smoking and diabetic retinopathy.

The absence of a relationship between cigarette smoking and diabetic retinopathy could be attributed to an examination bias because ascertainment of smoking was based on historical data. Having been advised against smoking by doctors, some patients might feel embarrassed to admit that they were still smoking against the doctors' advice. Such patients may also fail to reveal both the true number of cigarettes smoked per day and the duration of smoking. This is especially true for patients who feel that the doctor might be offended if they told the truth.

However, the history of smoking was taken before objective assessment of retinopathy was done. During this history taking the patient was not aware of the presence or absence of retinopathy. The lack of a relationship could mean that smoking does not contribute to the genesis or progression of diabetic retinopathy. The present finding are in agreement with other workers.[43,47,48]

Diabetic retinopathy and alcohol consumption

The present study also found no relationship between diabetic retinopathy and alcohol consumption.

Diabetic retinopathy and metabolic control of diabetes

The proportion of patients with and without retinopathy did not differ between the two groups of diabetic control (good and poor). Furthermore the proportion of patients with different grades of retinopathy did not significantly differ between the two groups ($P > 0.05$).

Diabetic metabolic control was also assessed by assay of serum fructosamine. The mean (SD) serum fructosamine of 3.9 (1.4) mmol/l found in patients without retinopathy did not differ from the means (SD) of 3.6 (1.4) mmol/l and 4.2 (1.5) mmol/l found among patients with proliferative and background retinopathy respectively.

Therefore both the assessment of metabolic control using the number of visits with glycosurias and that of serum fructosamine assay show an absence of a relationship between the state of metabolic control and diabetic retinopathy.

When the two methods of assessment of metabolic control were compared, it was found that patients classified as poorly controlled by the assessment of glycosuria also had high mean levels of serum fructosamine. The mean (SD) level of 4.28 (1.64) mmol/l fructosamine among poorly controlled patients is significantly higher than the mean (SD) of 3.42 (1.31) mmol/l found in patients with good control.

The findings in this study support those of previous workers who found no association between metabolic control and diabetic retinopathy in Africans.[11,26] They however

contradict the observation of workers elsewhere who have reported that diabetic retinopathy is associated with poor metabolic control of the diabetic condition.[43,49,50] Metabolic control can also be assessed by post prandial blood glucose[83] and HbA_1. However serum fructosamine assay, a recently introduced measure of mean blood glucose concentration is a technically easy and relatively inexpensive measurement which can easily be automated and large numbers of samples can be analysed with good precision.[129] It reflects glycation of serum proteins primary albumin. Thus it is better expressed in relation to total albumin concentration (umol fructosamine g^{-1} albumin). However, it has been found that expressing fructosamine values in absolute terms (mmol L^{-1}) or per gram albumin makes no difference except in those with very low albumin levels.

Thus the lack of an association can not be explained on the basis of different methods used in assessment of diabetic control. These findings and those by Rolfe[11] and Katenga[26] may suggest that glycaemic control is not an important factor in development and progression of diabetic retinopathy in Africans. On the other hand studies done in Africans have been cross-sectional studies. They do not reflect the true picture of glycaemic control in a particular patient year after year. The assessment of glycosuria in the present study was done over a period of 5 years except for those who were newly diagnosed and those with diabetes for less than one year. The problem encountered was the absence of case notes in some of the patients. Prospective studies are therefore needed.

6.3 DIABETIC RETINOPATHY AND DIABETIC NEPHROPATHY

Diabetic retinopathy and microalbuminuria

Among 371 patients in whom results for albumin were obtained 110 (29.6%) had albumin levels of more than 30 ug per ml of urine (microalbuminuria). This prevalence is higher than that found by Mogensen.[97] He found 13% of 267 patients having micro albuminuria. In his study patients with clinical proteinuria were excluded. In this study very few patients (19) were albustix positive for protein. The results for proteinuria did not correlate with the degree of microalbuminuria. This could have resulted from expired

albustix sticks which did not give a true result. Measurement of proteinuria by albustix is not a quantitative test. Further-more, because proteinuria can be intermittent, due to such factors as variable levels of exercise a single urine specimen may not provide an optimum representation of proteinuria.[130] This emphasizes the importance of serial measurements of albumin/clinical proteinuria over a specified period. The patients with albustix positive urine were thus not excluded from the analysis. If the upper limit of micro albuminuria was taken to be 299 ug per ml then only 4.3% patients would be albustix positive.

It has been observed that if single 24 hour samples are used, the prevalence of microalbuminuria (30-299 mg/24 hr) will be around 25%. If an over night urine collection or early morning urine sample is used, the prevalence is lower (13-15%). Reliable results have also been obtained in short-term collections[97]. The procedure of urine collection in this study was that of short term urine collection at the hospital.

Among 70 patients with hypertension only 25 (35.7%) had microalbuminuria while 45 (64.3%) had none. The relationship between microalbuminuria and hypertension was not significant ($P > 0.05$). Thus, though patients with hypertension were not excluded from the analysis of microalbuminuria and retinopathy, the lack of a relationship between microalbuminuria and hypertension show that most patients had microalbuminuria independent of hypertension. These findings contradict the findings by Berglund[131] who found an interesting correlation between the albumin excretion rate and blood pressure.

The albumin excretion rate has been reported to be lower in children[132] than in adults. Two of the 6 patients below 15 years and 6 (17.6%) patients in the age group 16-30 years had microalbuminuria respectively.

The prevalence of microalbuminuria increased with increasing age, the highest prevalence of 41.9% was found in the age group 61 years and above. This same age group included 17 (43.9%) and 8 (57.0%) of all patients with pre-proliferative and proliferative retinopathy respectively. The relationship between microalbuminuria and age was statistically significant ($P < 0.05$).

The duration of diabetes was significantly related to microalbuminuria ($P < 0.05$). Twenty

four (25.0%) patients among those who had diabetes for less than 1 year had microalbuminuria. There was a slight increase for those patients with diabetes for 1-8 years in whom 55 (26.4%) had microalbuminuria. However 41.8% of those patients with diabetes for more than 10 years had microalbuminuria. These proportions paralled the proportions of patients with diabetic retinopathy in different groups of duration of diabetes. Forty four (45.4%) and 96 (46.8%) of those who had diabetes for less than one year and 1-8 years respectively had diabetic retinopathy. A much higher proportion of patients with retinopathy was found in the age group 61 years and above.

The present finding on microalbuminuria and duration of diabetes contrasts with the observation by Marshal[132] who found no relationship between microalbuminuria and duration of diabetes.

Urinary albumin excretion is normal at the onset of diabetes even in the 30-40% who may later develop clinical nephropathy.[133] The high proportion of microalbuminuria in patients with diabetes for less than one year could be related to a larger number of patients with NIDDM whose duration of diagnosis is usually not exactly known at the time of diagnosis.

Studies in non-Africans have clearly pointed out that microalbuminuria is highly associated with diabetic retinopathy.[83] The results in this study agree with these workers. There are however no studies for comparison among Africans. Seventy three (79.4%) patients with microalbuminuria also had retinopathy in contrast with 45.2% patients without microalbuminuria. However, the finding of 45.2% patients with retinopathy among normoalbuminurics agrees with the observation by Agardh et al.[84] He observed that despite reports showing that microalbuminuria predicts diabetic retinopathy, it should be stressed that there is an inconsistent relationship between retinopathy and rephropathy. Patients with normal albumin excretion rate may show advanced retinal lesions although more often there is a correlation.

This study has further shown a highly significant relationship between microalbuminuria

and severity of diabetic retinopathy. Microalbuminuria was found in 37 (20.6%) patients without retinopathy. Forty three (31.2%) patients with background retinopathy had microalbuminuria in contrast with 23 (59.0%) patients with preproliferative retinopathy. 50% of patients with proliferative retinopathy also had microalbuminuria. The contrast in the proportion of patients with microalbuminuria between the different groups of retinopathy clearly shows that microalbuminuria is highly associated with severity of diabetic retinopathy.

Despite the fact that only 50% patients with proliferative retinopathy had microalbuminuria, 31.2% and 59.0% of patients with background and pre-poliferative retinopathy respectively will subsequently develop proliferative retinopathy. This is because microalbuminuria is a strong predictor with respect to development of proliferative retinopathy.[18,19]

The association between microalbuminuria and diabetic retinopathy was also studied using the albumin/creatinine ratio as a measure of microalbuminuria. The albumin creatinine ratio in spot urine gives a better indication of albumin excretion than 24 hour urine collection[134] because it gives a measure of albumin loss irrespective of glomerular filtration rate. However, the observations in this study show a highly significant association between the albumin creatinine ratio and microalbuminuria as assessed by measurement of albumin (ug per ml) in spot urine sample. The mean rank of albumin creatinine ratio in microalbuminurics was 312.5 in contrast to 140.8 in normoalbuminurics. The observation in this study compares well with findings by Cheta et al.[134] He reported that the albumin creatinine values obtained for NIDDM and IDDM significantly differed from the controls, but not from one another. He also noted that the values significantly correlated with duration of disease and the presence of such chronic complications as retinopathy. These findings indicate that patients with a high albumin creatinine ratio have or will later develop both proliferative retinopathy and retinopathy.

Diabetic retinopathy and serum creatinine

Serum creatinine levels have been reported to be higher in patients with retinopathy.[83] The present study has shown a significant relationship between diabetic retinopathy and the level of serum creatinine. Eleven (52.4%) patients with serum creatinine levels of more than 130 umol L^{-1} had retinopathy in contrast to 10 (47.6%) patients who had raised serum creatinine but no retinopathy. More over the proportion of patients with severe retinopathy (pre-proliferative and proliferative) is higher in those patients with higher serum creatinine levels compared to those who have low levels. The mean serum creatinine in patients with pre-proliferative and proliferative retinopathy was 93.12 umol $^{-1}$ and 207.10 umol L^{-1} respectively. This contrasted with mean serum creatinine of 84.2 umol L^{-1} and 83.6 umol $^{-1}$ in patients free of retinopathy and those with background retinopathy respectively. The highest mean serum creatinine (207.1 umol L^{-1}) was found in 74 patients with proliferative retinopathy reflecting long duration of diabetes and diabetic nephropathy. These results compare favourably with the study by Rand et al[83] who found that serum creatinine was high in patients with proliferative retinopathy.

Mean serum creatinine was also high in patients with microalbuminuria (99.5 μmol L^{-1}) than both the normoalbuminurics (83.2 μmol L^{-1}) and the study group (87.9 μmol L^{-1}). Mean serum creatinine among hypertensive patients differed significantly from those in normotensive patients. The findings support the observations by Kofoed-Enevoldsonet[17] on the simultaneous development of severe retinopathy and rephropathy. He suggested that pathogenic mechanisms leading to protein leakage in the kidney and severe retinopathy are similar.

6.4 DIABETIC RETINOPATHY AND SERUM CHOLESTEROL AND TRIGLYCERIDE

Raised serum cholesterol is a risk factor for diabetic macrovascular disease especially coronary heart disease (NIH consensus conference 1985). It however does not appear to be a risk factor for microvascular disease.[126]

The mean serum cholesterol level of 3.7 mmol L^{-1} found in patients without retinopathy

was lower than that found among patients with retinopathy. However, the difference was not statistically significant. This finding agrees with observation in other studies which found no association between cholesterol and microvascular disease.[15] Likewise serum triglyceride levels showed no association with diabetic retinopathy.

Serum cholesterol and triglyceride concentrations reflect the dietary habits of a particular subgroup of patients. Their lack of association with diabetic retinopathy suggests that this microvascular complication is unrelated to environmental factors such as diet unlike the macrovascular diabetic complications.

6.5 CATARACT

Prevalence

The reported prevalence of cataracts in African diabetics has varied from 1-38%.[2,4,11,12,24,27] Katenga[26] found an overall prevalence of 38%. Only 2.7% patients below 40 years had cataracts. Rolfe found 12% of diabetic study population affected by cataracts. These patients were older and had had diabetes for a longer period than patients without cataracts. Blindness due to cataracts in Rolfe's study was found in 25 (4.2%) patients.

In the present study, 176 (42.5%) patients were found to have lens opacities of different severity. 8 of them had undergone cataract extraction in one or both eyes. Most patients had subcapsular lens opacities. Twenty six patients had lens opacities obscuring fundus view - bilateral in 7 patients. Thirty (7.1%) diabetics below 40 years had cataracts. Three patients below 30 years had the true diabetic cataracts. They were bilateral in 2 of them. The proportion of diabetics with cataracts increased with increasing age.

The prevalence of 42.5% is higher than that found by earlier investigators. This is attributed to a high proportion (59.4%) of the diabetic study population being above 45 years of age. This is also the age for development of senile cataracts. Senile cataracts in diabetics appear at a younger age progress more rapidly to maturity them in non-diabetics.

In the study by Rolfe, the lens opacities were observed using the ophthalmoscope. This

could account for the low prevalence of 12.8% compared to the present study. In this study, patients were examined both by the ophthalmoscope and slit lamp biomicroscopy under mydriasis. Therefore, lens opacities of any magnitude could not be missed.

Blindness, defined as the inability to count fingers at three metres length affected 11 (2.3%) patients in one or both eyes. 8 (1.9%) were blinded by cataract. Another 24 (5.8%) of the diabetic study population could only count fingers up to 4 metres. Of these 16 were affected by cataracts. These findings are in agreement with the study by Rolfe[11] who observed that cataracts were a more important cause of blindness and visual disability than retinopathy.

6.6 GLAUCOMA

The association between glaucoma and diabetes has been cited by several workers. The finding of 20 (4.8%) with elevated intraocular pressure is in agreement with other studies.[33,93] Even though the proportion of 4.8% is lower than 20%[114] and 10%,[33] it is still higher than the prevalence of 1-2% found in the general population. The lower prevalence is attributed to the diversity of instruments for intraocular pressure measurements. The studies mentioned above had used the applanation tonometer which gives a better indication of the amount of intraocular pressure. The Schiotz tonometer was used in this study. The present study also agrees with the findings by Amstrong and associates[118] who found 4.1% of elevated intrascular pressure using the Schriotz tonometer in a larger group of diabetic patients.

The cut off point to classify the glaucomatous and non-gloucomatous patients also differs. In this study the cut off point was 21 mmHg. This intraocular pressure falls within 2 standard deviation (97.5%) of the normal population.[135]

Both the prevalence of glaucoma and cataracts increased with increasing age. There were 3 patients with primary open angle glaucoma and cataracts.

7.0 CONCLUSION AND RECOMMENDATIONS

This study has shown that the prevalence rates of diabetic retinopathy and cataracts are higher than it had previously been thought. The prevalence rates of other diabetic ocular lesions are in keeping with previous workers.

The study has also shown that diabetic retinopathy is significantly related to age, duration of diabetes, elevated serum creatinine and hypertension. No relationship was found between diabetic retinopathy and alcohol consumption, serum cholesterol and triglycerides and cigarette smoking habit. These findings are in keeping with studies in Non-Africans.

Another important observation was the association between diabetic retinopathy and microalbuminuria. The prevalence and severity of diabetic retinopathy were found to be significantly related to microalbuminuria. This finding supports the simultaneous development of retinopathy and nephropathy in Africans in Dar es Salaam just as studies elsewhere have revealed. Therefore microalbuminuria may be used to identify those of risk of developing both diabetic nephropathy and retinopathy.

Although cataracts remain a major cause of blindness among diabetic patients, the following findings in this study suggest that in future diabetic retinopathy may rival cataracts as a cause of blindness:

First and foremost is that the prevalence rates of diabetic retinopathy (including the blinding pre-proliferative and proliferative) are higher than it had previously been thought. Secondly, 31.2% patients with both background retinopathy and microalbuminuria will subsequently develop proliferative retinopathy. The increased survival of diabetic patients secondary to improved treatment and followup means an increase in the prevalence of diabetic retinopathy.

In view of these findings it is recommended that efforts should be made to secure equipment for screening and treatment of diabetic maculopathy, pre-proliferative and proliferative diabetic retinopathy. Equipment for screening those at risk of development of proliferative retinopathy and nephropathy are also important. Patients diagnosed to have diabetes mellitus should be examined by an ophthalmologist to establish baseline fundus findings. Thereafter regular fundoscopy should be done once a year.

8. SUMMARY

Four hundred and fourteen Tanzanian diabetic patients in Dar es Salaam were studied to determine the prevalence of diabetic ocular and renal complications and associated risk factors.

Males predominated (71%) over females (29%) diabetics. Most patients were aged between 31 and 60 years. Only 10.3% were below 30 years of age. Patients not on treatment with insulin were older than those receiving insulin.

The prevalence rate of diabetic retinopathy was 50.5%. Background diabetic retinopathy affected 37.5% while 10.1% had pre-proliferative retinopathy. Proliferative retinopathy was found in 3.6% of the study group. This prevalence is higher than previous reports in Africans. It is however, lower than many reports in European countries.

About 41.5% patients were poorly controlled. Many more patients on insulin tretment were poorly controlled than those not on insulin. The state of metabolic control of diabetes however did not appear to influence the prevalence of diabetic retinopathy. The mean serum fructosamine levels in patients with retinopathy did not differ from those free of it. When compared, assessment of diabetic control by counting the number of visits with glycosuria parallel the assay of fructosamine as a method of assessment of diabetic control.

The prevalence and severity of diabetic retinopathy increased with increasing duration of diabetes, being 65.5% in those with diabetes for more than 10 years. However, 45.4% patients had diabetic retinopathy at the diagnosis of diabetes mellitus. The majority of these had Non-Insulin dependent diabetes mellitus.

Despite constant follow up at the diabetic clinic, patients with diabetes for 1-8 years showed the same trend in the prevalence of diabetic retinopathy. This signifies that duration of diabetes is the most important factor in development of diabetic retinopathy.

Although 17.9% of the study group had hypertension, both hypertension and retinopathy occurred in 69.4% patients. Hypertension was found to be significantly related to diabetic retinopathy.

The prevalence of microalbuminuria was 29.6%. The proportion of patients with microalbuminuria increased with severity of diabetic retinopathy, the highest proportion being found in patients with pre-proliferative and proliferative retinopathy where 59% and 50% were affected respectively. Half of the patients with proliferative retinopathy and no microalbuminuria representing the proportion of patients who get advanced retinal lesions but with normal renal function. Microalbuminuria was significantly related to age, duration of diabetes and elevated serum creatinine. No relationship, was found between microalbuminuria and hypertension, serum cholesterol and triglycerides.

Serum creatinine were elevated in 8.1%. The mean serum creatinine levels were higher in patients with retinopathy than those free of it. The highest mean serum creatinine (207 μmol/l) was found in patients with proliferative retinopathy.

Risk factors common to both diabetic retinopathy and microalbuminuria were age, duration of diabetes and elevated serum creatinine. This finding signifies the simultaneous development of diabetic retinopathy and nephropathy.

Cataracts were found in 47.8% patients, the prevalence increased with increasing age. There was no relationship with diabetic control. The prevalence of glaucoma was 4.8%. Optic atrophy occurred in 1.7% patients. None of the patients had rubeosis iridis or diabetic ophthalmoplegia.

Blindness (in ability to count fingers at 3 metres) was found in 24 (5.8%) patients 19 being due to cataracts. Patients with maculopathy, pre-proliferative and proliferative retinopathy had a significant reduction in visual acuity compared to those free of it.

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