

**RETINOPATHY, NEPHROPATHY,
NEUROLOGICAL COMPLICATIONS AND RISK
PROFILE OF RECENTLY DIAGNOSED TYPE 2
DIABETES MELLITUS AT KENYATTA NATIONAL
HOSPITAL.**

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COMPLICATIONS AND RISK PROFILE IN RECENTLY
DIAGNOSED TYPE 2 DIABETICS AT KENYATTA NATIONAL
HOSPITAL.**

**A DISSERTATION PRESENTED IN PART FULFILLMENT
FOR THE DEGREE OF MASTER OF MEDICINE
(INTERNAL MEDICINE) , UNIVERSITY OF NAIROBI.**

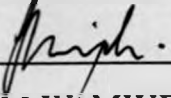
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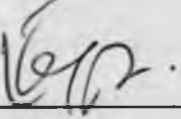
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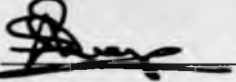
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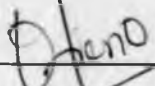
I declare that this is my own original work and has not been published elsewhere or presented for a degree in any other university.

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DEDICATION

This work is dedicated to my husband, Nzambu, whose love and support has been unfailing even on the worst of days, and to my parents who have taught me that nothing worth having comes easy.

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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
NDDG	National Diabetes Data Group
WHO	World Health Organization
NIDDM	Non Insulin Dependent Diabetes Mellitus
IDDM	Insulin Dependent Diabetes Mellitus
FPG	Fasting plasma glucose
DNA	Deoxyribonucleic acid
KNH	Kenyatta National Hospital
UKPDS	United Kingdom Prospective Diabetes Study
ROS	Reactive oxygen species
ACE	Angiotensin Convertase Enzyme
HbA1c	Glycated haemoglobin fraction
LDL-C	Low density lipoprotein cholesterol
HDL-C	High density lipoprotein cholesterol
MODY	Maturity onset diabetes of the young
DNA	Deoxyribonucleic acid
tRNA	transcription ribonucleic acid
Na/K ATPase	Sodium / potassium adenosine triphosphatase
AGE	Advanced glycosylated end products
GBM	Glomerular basement membrane
ESRD	End stage renal disease
UAER	Urinary albumin excretion rate
UACR	Urinary albumin to creatinine ratio
GFR	Glomerular filtration rate
BMI	Body mass index
NDS	Neurological disability score
ECG	Electrocardiogram
NCEP	National Cholesterol Education Programme
OHA	Oral hypoglycemic agents

ABSTRACT

Background: Type 2 diabetes is an increasingly important health problem in Kenya. As type 2 diabetes is characterised by a variable period of metabolic abnormalities prior to clinical diagnosis, microvascular complications may be present at or soon after the diagnosis of diabetes. The microvascular complications cause significant morbidity and even mortality yet their development and progression is largely preventable through modification of associated modifiable risk factors such as smoking, dyslipidemias, hypertension and hyperglycaemia. Their most effective management is therefore through primary and secondary intervention measures. There is no local data as to the prevalence of these complications and risk factors in the recently diagnosed type 2 diabetics.

Objectives: The aim of this study was to determine the prevalence of diabetic retinopathy, polyneuropathy, autonomic neuropathy and microalbuminuria as a marker of nephropathy in type 2 diabetic patients, and the prevalence of some associated risk factors within 2 years of the clinical diagnosis of diabetes.

Materials and methods: This was a cross sectional descriptive study undertaken in the diabetic outpatient clinic of Kenyatta National Hospital. Type 2 diabetic patients were recruited and underwent a clinical evaluation and screening for retinopathy, polyneuropathy, autonomic neuropathy and nephropathy. Laboratory tests undertaken were fasting blood sugar, glycated haemoglobin A1c, lipid profile, serum creatinine and a semiquantitative microalbuminuria assay.

Results: 100 patients were studied. The mean age of the patients was 53.7 ± 9.3 years. Family history of diabetes and hypertension was present in 48% and 24% of the patients respectively. 28% of the patients had a smoking record although current smokers were 7%. Obesity was frequently seen with 66% classifying as obese and this was preponderant in females ($p < 0.05$). Hypertension was noted in 50% of which 24% were newly detected, none of the hypertensives was achieving optimal blood pressure control. Ideal glycaemic control was being achieved in only 29% of the patients. Dyslipidemias were also frequently observed. Diabetic polyneuropathy was present in 28%, autonomic neuropathy in 27%, albuminuria in 26% and retinopathy in 7%. Over 50% of the patients presented with at least one complication.

Conclusion: The prevalence of microvascular complications is already quite high at or soon after diagnosis of type 2 diabetes in our patients. They have also a high prevalence of associated modifiable risk factors. Prevention strategies are warranted and justified by the high prevalences at primary, secondary and tertiary levels.

INTRODUCTION

Diabetes Mellitus is a term applied to a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (1). In 1997 the American Diabetes Association (ADA) proposed a new classification system (1) that tends to shift the focus more to etiological rather than the purely clinical criteria which are characteristic of the World Health Organization (WHO) / National Diabetes Data Group (NDDG) classification of 1980 (2). This divides diabetes mellitus into four categories namely : (i) Type 1 Diabetes mellitus is characterized by beta cell destruction usually due to immune mediated mechanisms and eventually leading to absolute insulin deficiency, (ii) Type 2 defines the individuals with predominant insulin resistance and relative rather than absolute insulin deficiency, (iii) Gestational Diabetes and (iv) other specific forms.

Of these various types of diabetes the most frequently encountered are type 1 and type 2 diabetes mellitus, with the latter having a much higher prevalence. In the United States of America (USA), of the 8 million diabetics diagnosed it is estimated that 90-95% are type 2 diabetics (3). In the last decades type 2 diabetes mellitus has been rapidly emerging as a major health threat in populations from both developed and developing countries (4). This global epidemic of type 2 diabetes mellitus has a projected morbidity and mortality of enormous magnitude. It is only about 50 years ago when the teaching was that diabetes is a rare occurrence in the African with Dubois in 1944 stating " diabetes is rare in the African. I do not remember ever having made the diagnosis" and in 1950 Trowell in

Kampala, Uganda was noted as stating that not only was diabetes rare but also that there were no known complications in Africans (5).

As type 2 diabetes is a disease which becomes clinically apparent later in life, by the time it is diagnosed it has usually had a long preclinical, undiagnosed course. This is because the hyperglycemia develops gradually and initially is not severe enough for the patient to detect the symptoms of hyperglycemia. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. In type 2 diabetes the progression towards tissue damage may start even prior to diagnosis as the detrimental metabolic influences precede clinical diagnosis. Various studies have shown that during this period of undiagnosed and hence untreated diabetes, tissue damage continues so that at diagnosis the presence of chronic complications is already present. In the United Kingdom Prospective Diabetes Study (6) amongst the type 2 diabetic patients, 1% had evidence of Q wave myocardial infarction, 5 % peripheral vascular disease, 19 % retinopathy , 12 % neuropathy and 11% microalbuminuria at the time of diagnosis of diabetes.

At whatever age diabetes is diagnosed, life expectancy is reduced due to chronic complications, and the quality of life may be severely impaired by angina, stroke, blindness, renal failure and neuropathy. Looking at our own population no studies so far have looked at the complication burden of the newly diagnosed type 2 diabetics. Most of the studies done have been cross sectional taking into consideration all diabetics irregardless of age or classification type. Kioy in 1984 (7) found a prevalence of 42% of clinical neuropathy in the 31 patients assessed and 22% with autonomic neuropathy. The prevalence of retinopathy in subjects studied over time at Kenyatta

National Hospital (KNH) has been found to vary, with 34% in 1986 by E. Mubia (8) who assessed 77 patients, 32% in 1982 by PJ Onyango (9) who had a sample size of 42 patients and in 1977, 55%, by Steele et al (10) who looked at 234 patients. In 1976, MS Abdullah (11) demonstrated a prevalence of diabetic renal involvement in 46% of the diabetic population in attendance at KNH. Ngugi in 1989 (12), found overt nephropathy to be present in 15.8% of the 359 diabetic patients screened, with 12.9% of non insulin dependent diabetes mellitus (NIDDM) patients presenting with macroproteinuria within 5 years of diagnosis. Twahir later in 1994 (13) found a prevalence of microalbuminuria in 40.6% of the 79 type 2 patients assessed. Nyamu in 1999 (14) found that of the 4.6% of the diabetics in his study that had diabetic foot ulcers, 78% also had clinical neuropathy, while Onyango (15) found that from 1981-1986, 29.6% of all non-traumatic amputations at KNH were secondary to diabetes.

It is evident today as exemplified by the above data that diabetes is in fact very much a reality in our local environment and with it come the complications that contribute significantly to the morbidity of diabetes.

Microvascular disease as reflected by retinopathy, nephropathy and neurological complications are easily detectable using clinical and simple laboratory techniques even in their earlier stages. It has also been shown that the early diagnosis and management of these conditions have an enormous effect in the reduction of morbidity and mortality from the same, since it is at their early stages when they are most amenable to treatment. The early recognition and control of modifiable risk factors would also have the same effect thus leading to an improvement in the quality of life in our diabetic patients which is the ultimate goal for those involved in the care of the diabetic patient.

CLASSIFICATION

The classification of diabetes mellitus has been difficult mainly due to the limited knowledge on etiopathogenesis. Especially as it becomes more apparent that what we call diabetes mellitus actually encompasses a number of heterogeneous syndromes that are characterized by a continuum of metabolic changes secondary to insufficient insulin action and by various tissue changes referred to as the chronic complications of diabetes (16). The classification proposed by the NDDG and endorsed by the WHO in 1980 (2) comprises five categories of Diabetes mellitus : (i) Insulin Dependent Diabetes Mellitus (IDDM), (ii) Non-Insulin Dependent Diabetes Mellitus (NIDDM), (iii) Malnutrition Related Diabetes Mellitus, (iv) Gestational Diabetes and (v) other specific forms of Diabetes. In this classification the terms Type I and Type II were also proposed as synonyms for IDDM and NIDDM respectively. This has been the classification system used for many years and is based on clinical criteria. The diagnostic cut off point for plasma glucose concentrations in this classification was set at a fasting plasma glucose (FPG) $> 7.8\text{mmol/L}$, or a 2 hour post-prandial or post oral glucose tolerance test (2hr PG) of $> 11.1\text{mmol/L}$.

In 1997 the American Diabetics Association (ADA) proposed a new classification system that tends to shift the focus more to etiological rather than purely clinical criteria (1). This divides diabetes mellitus into four categories namely : (i) Type 1 Diabetes mellitus which is characterized by beta cell destruction, usually due to immune mediated mechanisms and eventually leading to absolute insulin deficiency, (ii) Type 2 defines the

individuals with predominant insulin resistance and relative rather than absolute insulin deficiency, (iii) Gestational Diabetes and (iv) other specific forms. This also saw the diagnostic cut-off point revised with the current cut-point set at FPG >7.0 mmol/l and 2hr PG >11.1 mmol/l based on the observation that this new diagnostic cut-point represents a serious metabolic abnormality that is associated with complications (1).

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus shows heterogeneity in numerous aspects. While there are strong genetic factors in the development of type 2 diabetes, as evidenced by the importance of a positive family history as a risk factor for the development of the same, numerous modifiable risk factors have also been identified. These include the development of obesity and decreased physical activity (17,18). Although the pathogenesis of type 2 diabetes mellitus is not fully understood, it is clear that at least three factors are important: a genetic predisposition to the disease, a decrease in the action of insulin in insulin sensitive tissues, and a defect in pancreatic beta cell function. Conditions associated with the development of insulin resistance greatly increase the risk of developing type 2 diabetes, and chief amongst these are obesity and advancing age. Insulin resistance and hyperinsulinemia are also associated with hypertension, hypertriglyceridemia, decreased high density lipoprotein cholesterol (HDL-C) and increased risk of atherosclerosis and cardiovascular disease (19-21).

There are five major hypothesis for the pathogenesis of type 2 diabetes:

1. Genetic : The suggestion of a susceptible genotype may be inferred from the finding of higher concordance rates for type 2 diabetes amongst

monozygotic twins compared to dizygotic twins (22,23). Empirical risk calculations to 80 years of age also reveal a 40-60% risk of developing type 2 diabetes in siblings and first degree relatives of patients with diabetes, and a risk of 80% in offspring where both parents have type 2 diabetes (24). There also exist populations that have an extraordinary high prevalence of type 2 diabetes such as the Pima Indians (25).

A number of genetic abnormalities have been associated with type 2 diabetes, involving genes with products of metabolic importance such as glycogen synthetase and glucokinase variants and abnormal insulin, or genes of unknown significance such as mitochondrial DNA deletions (26).

Candidate genes that might contribute to either insulin resistance or insulin deficiency have been studied with functional mutations being identified that account for the disease phenotype in a small number of these patients. The first mutations to be associated with type 2 diabetes were those of the insulin receptor gene, this was found in several syndromes associated with extreme insulin resistance such as Leprechaunism, Rabson-Mendenhall syndrome and Type A insulin resistance (27). In these syndromes homozygosity for insulin receptor mutations is associated with severe insulin resistance, but heterozygous subjects often have more modest degrees of insulin resistance which may be consistent with the more common diagnosis of type 2 diabetes. Patterns of type 2 diabetes that are consistent with a dominant mode of inheritance have been known to exist since the description of maturity onset diabetes of the young (MODY), which appears in about half the cases to be associated with a single gene defect and subsequent glucokinase mutations (28). A further genetic susceptibility factor has been defined in mitochondrial DNA which results in a combination of diabetes and deafness from an adenine to guanine mutation in position 3243 of

leucine tRNA (28). Again the role of this mutation in the common type 2 diabetes is probably minimal. These initial attempts to characterize the genetic factors involved in the pathogenesis of type 2 diabetes have identified a number of rare genetic factors which may contribute to the disease. While in all cases the inheritance pattern has been simple there still seems to be marked heterogeneity in the mechanism by which glucose intolerance may be produced. The challenge still remains to identify and characterize genetic factors that may contribute to larger groups of type 2 diabetes.

2. Environmental adaptation: Neel in 1962 proposed the theory of a 'thrifty genotype' (29) which would result in a selective survival advantage in times of fluctuating food supplies by allowing storage in times of plenty. He argued that the thrifty genotype then became detrimental when food supplies were abundant leading to increased obesity and non-insulin dependent diabetes mellitus. Wendorf and Goldfine (30) later proposed that selective muscle insulin resistance might represent a phenotypic expression of a thrifty genotype redirecting glucose uptake from muscle to adipose tissue and thus predisposing to obesity. More recently Hales and Barker (31) proposed that nutritional deprivation in utero which impairs the development of the fetal pancreas predisposes to diabetes later in life. They suggested that NIDDM is mainly the result of environmental factors and that genetic factors play a very minor role in its development. They termed this the 'thrifty phenotype'. Various studies have been carried out showing an association between low birth weight, which is a reflection of intrauterine malnutrition, and impaired glucose tolerance in different populations (32,33). This association could in some cases be explained by a genetically determined reduced fetal growth rate, such that the same genotype

responsible for type 2 diabetes mellitus may lead to retarded fetal growth. On the other hand an unfavourable uterine environment may increase the risk of type 2 diabetes later in life by deleterious effects on organ development and maturation during critical periods in early life. An alternative hypothesis is that of the 'surviving small baby genotype' (34), proposing that the genetic predisposition to insulin resistance may represent the selective survival advantage, and the low birth weight observed is a reflection of the selective survival of these low birth weight infants genetically susceptible to developing diabetes.

3. Pancreatic amyloid : In 1901 Opie observed a hyaline material in postmortem histological preparations of pancreatic islets from diabetic patients. The protein responsible was later realized to be a 37 amino acid peptide and was called amylin or islet pancreatic amyloid. Amyloid deposits are found in the pancreas of more than 90% of patients with type 2 diabetes and even small deposits are associated with extensive beta cell damage (35). This material which is found outside the surviving beta cells of the morbid islet and near the islet's small blood vessels is also found within beta cell lysosomes. Amylin is secreted from beta cells together with insulin and may also be found in minute concentrations in plasma. There is evidence of a paracrine influence within the islet inhibiting the release of insulin (36). Amylin also has vasodilatory properties and may be important in inhibiting islet blood flow leading to ischemic islet damage. However whether the deposition of amyloid is a primary or secondary influences in beta cell failure is questionable.

4. Beta-cell Overstimulation : Overstimulation of beta cells is associated with secretion of more proinsulin per unit of insulin secreted. This relative hyperproinsulinemia was initially thought to represent an end stage of severe

hyperglycemia due to beta cell overstimulation that would increase the demand on an islet with decreasing ability to respond, leading to premature release of incompletely processed granules. Further evidence did not support this theory and it seems more probable that there is a constitutional proinsulin defect in type 2 diabetes that leads to inappropriate release of proinsulin which further contributes to the development of hyperglycemia (35). Type 2 diabetes is commonly associated with obesity and one hypothesis is that the overstimulation that may lead to inappropriate proinsulin release, may occur during the period of excessive food intake during the development of obesity. However whether obesity precedes glucose/insulin disturbance in type 2 diabetes or whether the basic abnormality itself generates obesity remains to be defined.

5. Role of environment and lifestyle: It has long been demonstrated in most societies that there is a higher prevalence of type 2 diabetes in urban populations as compared to rural populations. It is also well documented that moderate degrees of weight reduction and increased levels of physical activity are associated with decreases in postprandial and fasting glucose levels, improved insulin sensitivity and improved plasma insulin concentrations in type 2 diabetics (17,18,37). Weight reduction and increased physical activity are also associated with improvement of several other cardiovascular risk factors including reduction in blood pressure, and improvement in lipid profiles (37), with physical inactivity being associated with the development of insulin resistance and decreased glucose tolerance and regular physical activity having a protective effect (38). These data suggest that lifestyle interventions to decrease the development of obesity and increase physical activity may be beneficial in subjects who are at risk

for developing type 2 diabetes, while at the same time reducing the risk factors for the development of vascular disease in the established diabetic.

PATHOGENESIS OF MICROVASCULAR COMPLICATIONS

Damage to the microvascular circulation plays a central role in the development of the long term complications of diabetes, leading to a specific microangiopathy which is characterized histologically by basement membrane thickening in capillaries, arterioles and venules (39). The pathogenesis of diabetic microangiopathic complications is definitely multifactorial and remains poorly understood to date.

Role of Hyperglycemia

Hyperglycemia is the common culprit in the initiation and progression of diabetic microvascular disease. The demonstration that improved glycemic control may reverse initial nerve conduction abnormalities, microalbuminuria and delay or prevent progression of retinopathy validates its permissive role (40). Various mechanisms have been suggested in which hyperglycemia may lead to the functional and structural abnormalities characteristic of these complications. With hyperglycemia there is increased activation of the polyol pathway in which excessive glucose is shunted by the high aldose reductase into the formation of sorbitol and fructose. This has long been recognized and studied as one of the major metabolic pathways involved in diabetic neuropathy, nephropathy and retinopathy (39,41,42). Accumulation of sorbitol would lead to alteration of cellular osmotic effects with subsequent cellular edema. It may also result in

compensatory depletion of other important osmolytes such as myo-inositol and taurine. This depletion in myo-inositol is in part responsible for concomitant reduction in Na / K ATPase activity. In the nerves this reduced Na /K ATPase activity has the effect of reducing motor nerve conduction velocity as the rate of inward sodium current is slowed due to the elevated intracellular sodium level (41). A similar myo-inositol dependent defect in pump function has been identified in the retinal epithelial layers, in the vascular smooth muscle of the aorta and within the glomerulus (43,44). The polyol pathway is also linked to oxidative stress as aldose reductase requires NADPH as a cofactor thus its activation will impact on the recycling of glutathione (GSH) from oxidised glutathione and hence on the synthesis of nitric oxide (39,45).

Another potential pathway for glycemic induced injury is via the formation of advanced glycosylated end-products (AGE's) (42,45,46). In the process of non enzymatic glycation, sugars initially react with free amino groups of proteins, lipids or nucleic acids to form reversible glycation products. With time these undergo chemical rearrangement with dehydration, fragmentation and cross linking reactions to form advanced glycosylation end products. These AGE's accumulate throughout the body. Protein glycation itself may give rise to oxygen free radicals. In addition AGE's may stimulate growth factor release from activated macrophages resulting in smooth muscle cell proliferation and vascular occlusion (46). It has also been suggested that peripheral nerve myelin modified by AGE's is identified as foreign and scavenged by the macrophages via putative AGE specific receptors. This may contribute to the segmental demyelination seen in diabetic neuropathy. Axonal cytoskeletal proteins and Schwann cells are not spared, and the glycation of components which are essential to tubular structure,

maintenance, axonal transport and nerve fibre regeneration are affected. This alteration of axonal structures results in slowed transport, axonal atrophy and degeneration while the glycation of laminin of the Schwann cell has been shown to result in reduced fibre regeneration capacity (45). This glycation also involves glomerular basement membranes interfering with its breakdown, turnover rate and predisposing to its thickening, similarly it may predispose to mesangial matrix accumulation (42). The glycation of glycoproteins present in the basement membranes may also account for changes in the permeability properties of the same. The activation of receptors for AGE's which are present on the surface of macrophages and their binding would therefore induce the release of cytokines, vascular adhesion molecules and other factors which contribute to the tissue injury (46).

Role of Oxidative Stress

Diabetes is a state of increased oxidative stress due to both a higher production of reactive oxygen species (ROS) as well as an impaired antioxidant capacity (47,48). Increased production of ROS leads to increased peroxidation of lipid membranes, proteins and DNA with important cellular, functional and structural implications. A notable target for increased pro-oxidant activity in diabetes is the vascular system in part explaining the increased propensity for atherogenesis and cardiovascular disease. In microvascular complications, oxidative stress affects the endothelial cell function and vascular reactivity contributing to impaired blood flow and tissue oxygenation (46).

One of the affected systems is the renin angiotensin system in diabetics. The vascular renin angiotensin system appears to be upregulated in several

vascular systems and circulating plasma angiotensin converting enzyme activity have been shown to be increased in both diabetic animals and patients (49,50). Another vasogenic agent increased by the oxidative effects is endothelin-1, both endothelin-1 and angiotensin are potent vasoconstrictors and therefore probably contribute to a reduction in the peripheral nutritive blood flow resulting in endoneural hypoxia. That this is probably an important factor in the development of diabetic neuropathy is supported by the experimental data demonstrating that blockade of the renin angiotensin system via angiotensin converting enzyme (ACE) inhibitors or angiotensin-1 receptor antagonists reduces impaired blood flow, endoneural oxygenation and nerve conduction velocity in diabetic rats (45), this has also been shown to prevent the resistance to ischaemic conduction failure and restore the blunted regenerative capacity of nerve fibres. Endothelium dependent vessel relaxation is also affected by the oxidative stress which has been shown in animal studies to be prevented by a variety of radical scavengers such as tocopherol, dimethylthiourea and acetylcysteine (51).

Role of Trophic Factors

Cell culture experiments in vitro have demonstrated that insulin has a trophic effect stimulating the proliferation of capillary endothelial cells, pericytes and vascular smooth cells (39). In most patients with type 2 diabetes there is a relative hyperinsulinemia and basement membrane producing cells appear to respond to insulin leading to increases in type IV collagen and decrease in heparan sulphate synthesis (39), the latter being important in maintaining the fixed negative charge which is an important determinant of selective permeability. Abnormal synthesis and availability

of neurotrophins or neuroprotective factors have also been implicated in the pathogenesis of diabetic neuropathy. Of these the most important appears to be Nerve Growth factor which has been used with some success in small clinical trials in improving thermal perception (52).

Role of Essential Fatty Acids

Production of vasoactive prostanoids is altered in diabetes with studies reporting an increase in prostacyclin, prostaglandin E₂, F₂ and thromboxane (53-56,45). This may be attributed to a decrease in both the Δ -5 and Δ -6 desaturase activity in the diabetic state. The depressed desaturation particularly in the liver is probably due to a combination of hyperglycemia, hypoinsulinemia and oxidative stress. The consequences of the impaired desaturation are reduced tissue and plasma concentrations of linoleic acid and arachidonic acid with impaired synthesis of cyclooxygenase products such as vasodilatory and antiplatelet aggregation prostaglandins which leads to increased vascular tone and decreased blood flow (45).

RISK FACTORS

Duration of diabetes. The incidence of all microvascular complications has been shown to increase with duration of type 2 diabetes (6,57-60). The influence of duration in these studies appears greater than that of age, gender or type of diabetes. However in the Rochester study (58) when patients with NIDDM were matched for years after diagnosis, those diagnosed after the age of 50yrs had a higher prevalence and degree of microalbuminuria than did those diagnosed before the age of 40yrs. The later age of diagnosis may suggest a longer duration of preclinical metabolic abnormalities exerting their deleterious effects on the kidneys.

While the age at diagnosis was not found to be one of the factors that influenced the progression of microalbuminuria in the UKPDS it was found to be a factor in the progression of neuropathy and retinopathy (6). Previous studies have shown a major decline in motor and sensory nerve conduction as well as autonomic nervous system function during normal aging (61). This is an important confounding variable that must be taken into consideration when assessing the type 2 diabetic population which by definition are generally of an older age group. However even controlling for age and sex, Pfeiffer et al found type 2 diabetics within 2 years of diagnosis to have significantly abnormal autonomic function compared with the controls (62).

Genetics. It appears that there are separately inherited risks that determine if patient develops nephropathy or not. This is supported by the fact that only about 50% of patients ever develop diabetic nephropathy irregardless of the metabolic status or duration of disease, and by the observation of familial clustering (63,64). This latter aspect has been observed in Pima Indians the majority of which have type 2 diabetes. Pettitt found that in this population, proteinuria was present in 14% of diabetic offspring in whom neither parent had proteinuria, 23% in whom one parent had proteinuria and in 46% in whom both parents had proteinuria (64). This genetic predisposition for nephropathy has been linked to polymorphisms of the ACE, angiotensinogen and angiotensin receptor genes (65,66). However further studies, although demonstrating a better response to ACE inhibitors in those with the double insertion genetic variation of the ACE gene, and a more accelerated progression of disease in those with the double deletion genotype, have not shown these to be important factors in initiating nephropathy (65). Certain HLA-DR types have been linked with the development of diabetic

retinopathy (67). No studies have shown any genetic markers associated with neuropathy.

Gender. Male sex seems to confer a specific risk in the development of diabetic nephropathy and neuropathy (59,68). However this may only play a minor role as most studies do not report any gender disparities. It has been proposed that this maybe related to hormonal effects (69).

Hyperglycemia. Persistent hyperglycaemia is probably the most important risk factor. Intensive blood glucose control was shown in the UKPDS to be both safe and highly beneficial in reducing the incidence of diabetic microvascular complications (40). This is directly in keeping with the pathogenetic role of hyperglycaemia in the development of the same as previously noted.

Hypertension. Hypertension, even before the onset of diabetes, is a common finding in type 2 diabetes. Systolic blood pressure was shown to be related to the rate of decline of glomerular filtration rate by Nielsen et al (70). Several studies have shown hypertension to be related both to the development and progression of diabetic nephropathy (71,72,73). Similarly strict blood pressure control has been shown to reduce the incidence and progression of renal disease in type 2 diabetics (74,75). A similar association has been noted as regards the development and progression of diabetic retinopathy and neuropathy (74,76).

Dyslipidemia. The active role of lipids in the progression of diabetic renal disease is largely speculative. Type 2 diabetes is already associated with lipid abnormalities as part of the 'metabolic syndrome'. With the onset of renal disease further abnormalities in the lipid profile may be observed. It is hypothesised that these play an active role in the nephrotoxicity and thereby in progressive renal injury (77). The increase in the glomerular basement

membrane (GBM) in diabetic nephropathy would lead to the loss of lipoprotein activators resulting in hyperlipidemia. Circulating LDL binds to glycosaminoglycans in the GBM and increases further its permeability. This would lead to filtered lipoprotein accumulating in mesangial cells and stimulating them to proliferate and produce excess basement material leading to a vicious cycle of events. Apolipoprotein also precipitates in the tubules initiating or aggravating tubulo-interstitial disease. The association between dyslipidemia and nephropathy differs in various studies with some showing an association while others do not. The presence of dyslipidemias has also been linked to the other microvascular complications with some studies showing a greater prevalence of retinopathy in patients with dyslipidemia (78).

Smoking. Smoking may confer a risk in as much as it causes vasoconstriction, impaired platelet function, abnormal regulation of coagulation and transient hypertension thus accelerating vascular damage. Cigarette smoking has been associated with progression of nephropathy in type 2 diabetes. A study on the Danish population (79) of newly diagnosed type 2 diabetics found that heavy albuminuria was more common in smokers (8%) and former smokers (7%) than in non smokers (2%). In type 1 diabetes a significantly higher proportion of smokers (14%), compared to non-smokers (3%), progressed to persistent microalbuminuria in a study by the Microalbuminuria Collaborative Study group (80). The association with retinopathy has also been proposed (81,82), these findings are inconclusive as other studies have not shown any significant association (83,84).

DIABETIC NEPHROPATHY

Diabetic nephropathy is a leading cause of end stage renal disease accounting for half of all end stage renal disease (ESRD) cases in the USA (85). At Kenyatta National Hospital diabetics comprise 21% of the 91 patients with ESRD currently undergoing dialysis in the Renal Unit (KNH records). Diabetic nephropathy is caused primarily by advanced glomerulosclerosis, the renal expression of renal microangiopathy. The key pathological changes seen are an accumulation of extracellular material resulting in concomitant development of peripheral basement membrane thickening and mesangial expansion associated with a significant reduction in glomerular filtration area. A clinical diagnosis of diabetic nephropathy can be made in a patient with diabetes on the basis of persistent albuminuria >300mg/24hrs, presence of retinopathy and in the absence of any clinical or laboratory evidence of other renal or urinary tract disease (73).

Once initiated the natural course of diabetic nephropathy is one of progressive decline in renal function. Therefore the most effective strategy to prevent diabetic nephropathy should be directed toward the detection and management of the disease at an early stage of development, that is, when it is known to be more amenable to treatment, and towards identifying and controlling modifiable risk factors (73).

Several stages have been described in the development of diabetic nephropathy, and although they apply more strictly to type 1 diabetes they

are also used for the classification of type 2 associated diabetic nephropathy.

These are (42) :

Stage 1: Renal Hyperfunction and hypertrophy: in this stage there is an increase in the glomerular filtration rate (GFR) with concomitant increase in renal size. Although type 2 patients have not been studied as intensively as type 1, studies suggest that GFR may not be increased in most of these patients and neither is renal hypertrophy a salient feature.

Stage 2: Clinical latency: this is a 'silent' stage characterized by the development of renal lesions mainly glomerular, which progress without any clinical signs.

Stage 3: Incipient Nephropathy: in this stage urinary albumin excretion rate (UAER) is persistently elevated with persistent microalbuminuria hence being the main feature, at the same time there is a gradual increase in blood pressure so that at this stage the common finding is that of blood pressure levels that are slightly to moderately increased. At this stage the GFR also begins to decline.

Stage 4: Overt Nephropathy: this is the classic clinical entity characterized by permanent proteinuria, increased blood pressure, and fall in GFR.

Stage 5 : Renal failure: this final stage corresponds to end stage renal failure with uraemia.

Thus the earliest stage at which diabetic nephropathy may become apparent is Stage 3 where microalbuminuria is used as a marker. In the early work by Morgensen (86,87), it was retrospectively demonstrated that microalbuminuria is a predictor of nephropathy in diabetic subjects, although with a lower predictive power for type 2 than type 1. This observation has since been confirmed by other authors (88,89).

Retrospective as well as prospective studies have demonstrated that both microalbuminuria and macroalbuminuria are associated with increased mortality not only from renal disease but also from cardiovascular disease suggesting that this may be also considered a marker of more widespread vascular damage. This relationship of increased mortality with microalbuminuria has also been demonstrated in the non diabetic population (90). Hence microalbuminuria is not only an independent predictor of renal disease but is also an important marker of progressive atherosclerotic disease and premature death in the type 2 diabetic population.

Microalbuminuria may often be detected in type 2 diabetic patients at the time of clinical diagnosis and although there may be a decline in the prevalence with dietary and oral hypoglycemic intervention there are those patients who will remain microalbuminuric thus documenting that renal changes may be found early in the course of type 2 diabetes.

Urinary albumin excretion rate (UAER) is the main parameter used in diabetic patients for the clinical evaluation of early or incipient diabetic nephropathy. With microalbuminuria being defined as a UAER of 20-200 mcg/min. If this is found consistently then the patient is defined as having incipient diabetic nephropathy (86).

There is considerable intraindividual variability of UAER, and there may be confounding factors that need to be taken into account when assessing microalbuminuria (91). There is a diurnal variation with UAER being higher in the daytime than at night thus ideally use of a 24hr urine specimen.

Physical exercise is also known to cause transient increases in the UAER, as is the presence of urinary tract infections, acute febrile illnesses, acute ingestion of water, hematuria, menstruation, vaginal discharge and

pregnancy. Hence in the evaluation of microalbuminuria these factors must be taken into account and attempts made to reduce their influences such as the collection of early morning urine specimens or 24hr urine specimens. There have been various studies attempting to define and standardize the method of urine collection and subsequent measurement of microalbuminuria. Although most studies have used the timed 24hr urine collection this has noted to be clearly impractical in outpatient settings and for epidemiological studies in some settings. The assessment of single random urine specimens has been found to have a high predictive value for the development of overt nephropathy (92). The use of urinary albumin to creatinine ratio (UACR) has been validated as an alternative measure of UAER (93,94) with the advantage that it is easier to execute in the outpatient setting as it requires a single random urine specimen, thus making it a more cost effective and efficient method. It correlates well with the UAER with a kappa statistic of 0.92 (94). Microalbuminuria in this case is defined as UACR of 30-300 mcg/mg. More recently reagent strips have been devised to detect microalbuminuria, these use untimed samples and albumin concentration is usually expressed in mg/l with a cutoff at 20mg/l. One such test the Micral II has been found to have a high sensitivity of 95%, a specificity of 93%, the predictive value of a positive test is 97% and of a negative one 88% as compared to UAER determined by the nephelometric method (95,96).

DIABETIC RETINOPATHY

Diabetic retinopathy is a major cause of visual disability in the population. Approximately 60% of type 2 diabetics develop retinopathy during the course of their illness and 10% of these will develop proliferative disease (97). At the time of diagnosis the prevalence of retinopathy has been found to be between 10 - 28% (98,99,6). Studies done on the Kenyan diabetic population give figures of overall prevalence between 32-55% (8-10).

The pathogenesis of diabetic retinopathy like that of the other diabetic complications is almost certainly multifactorial.

Pathologically the first changes to be seen is in the retinal capillaries with thickening of the basement membrane even up to five times the normal thickness which is associated with increases in laminin and type IV collagen. The pericytes surrounding the capillaries reduce in number and are gradually lost with some of the nuclei remaining as 'ghosts' and the normal 1:1 ratio of pericytes to endothelial cells may fall as low as 1:18. The endothelial cells degenerate and may either be lost or may proliferate in situ forming microaneurysms. Later small vessels may be occluded with formation of small collateral channels at the edges of the enlarging avascular areas, and abnormal capillaries may bud to form new vessels which often grow forward into the vitreous itself and being fragile may spontaneously bleed. The so called soft exudates are plaques composed of glial cells, glial fibres and cytooid bodies, while the hard exudates are irregular punched out holes in the outer plexiform layer of the retina where lost retinal elements are replaced by a hyaline substance

Retinopathy is classified into three major groups of background pre-proliferative and proliferative retinopathy.

Simple or background retinopathy is the mildest form of diabetic retinopathy and in itself not vision threatening and may not necessarily progress to the more advanced stages. The characteristic feature of background retinopathy is the microaneurysms which are seen on retinal examination as red dots on white light view. These saccular dilatations are thought to form either from local distension of the retinal capillary as a result of vessel wall weakness or from the partial fusing of adjacent arms of capillary kinks. The other features of background retinopathy are small retinal haemorrhages, retinal exudate and cotton wool spots. The retinal exudates represent areas of focal vascular leakage and when present in proximity to the macula can be vision threatening and require urgent laser therapy.

Pre-proliferative retinopathy is associated with an increase in the size and number of lesions seen in background retinopathy and in addition intraretinal microvascular abnormalities are seen at this stage. Changes also appear in larger vessels especially in the retinal veins which show characteristic venous 'loops'. The risk of progression to proliferative retinopathy may be as high as 50% within a year (99) and laser treatment is advisable at this stage

Proliferative retinopathy is characterized by neovascularization and occurs when about 25% of the retinal capillary bed perfusion is compromised. Although the exact mechanism is unknown it is thought that the ischaemic retina produces diffusible blood vessel growth factors in an attempt to rejuvenate perfusion. The new vessels are however fragile and tend to bleed easily leading to vitreal haemorrhage. Fibrous overgrowth is an accompanying feature and as it increases the traction forces within the retina

it predisposes to retinal detachment and at this stage the only hope of salvaging vision would be with vitreoretinal surgery.

The management of diabetic retinopathy falls into three phases, that of prevention, screening and treatment. Efforts to prevent retinopathy should be guided by knowledge on the risk factors that contribute to the development of the same. Prime on the list is the glycaemic control and hypertension. Other risk factors mentioned previously may also play a role. Diabetic retinopathy has also been noted to rapidly progress with anaemia and pregnancy such that attention may be warranted in these conditions (100,101).

Screening for retinopathy is justified by the high incidence of the condition, the resultant morbidity and the possibility of early and beneficial intervention. This is best carried out by an ophthalmologist and involves visual acuity testing and fundoscopic examination on dilation of pupils. Retinal photography allows for objective analysis and follow up documentation of the condition. Among other methods which may supplement the basic ophthalmoscopy examination are the use of fluorescein angiography and slit-lamp bio-microscopy, however these are specialized techniques not advocated for screening.

The mainstay of therapy is laser photocoagulation, which may reduce by 90% severe visual impairment associated with proliferative retinopathy when intervention is timely (102,103).

DIABETIC NEUROPATHY

Diabetic neuropathy is a descriptive term referring to a demonstrable disorder either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy (104). The neuropathic disorder includes manifestations of the somatic and or autonomic parts of the peripheral nervous system resulting in a number of neurological syndromes of which the most common is distal symmetric polyneuropathy.

Diabetic neuropathy is the single most frequent cause of neuropathy worldwide. Prevalence figures vary depending on the employed definition. In newly diagnosed type 2 diabetics prevalence of clinical polyneuropathy has been reported between 2 - 15% (40,104-6). In a study on Kenyan diabetic patients (7) the prevalence of clinical neuropathy was 42% while those with electrophysiological nerve abnormalities as evidenced by nerve conduction studies was 80%. In the same study 22% had evidence of autonomic neuropathy.

The presence of neuropathy is associated with significant morbidity, including recurrent foot infections and ulceration, necessitating amputation, impotence, gastropathy and sudden death in individuals with cardiovascular autonomic neuropathy.

The diabetic neuropathies may be classified into four main groups (107), polyneuropathies, autonomic neuropathy and mononeuropathies and proximal motor neuropathy.

Diabetic distal symmetric polyneuropathies: there are two forms, one which consists of an acute and rapidly reversible physiologic dysfunction

associated with hyperglycemia, and the second a chronic symmetrical distal polyneuropathy which is predominantly sensory and may involve both large and small fibres. The latter is not only the most frequent of the diabetic neuropathies but also potentially the most debilitating in terms of morbidity. The presence of sensory loss in these patients leads to an increased tendency to unaverted foot trauma, and improper weight distribution, this combined with a compromised peripheral vascularization and increased propensity to infections in the diabetic patient, increases the risk for chronic foot ulcerations and infections which may end up with amputations. At Kenyatta National Hospital (15) about 30% of the amputations between 1981-86 were secondary to diabetic foot, second only to major trauma.

The assessment of polyneuropathy may rely on different methodologies or a combination of these. Namely :

1. Clinical measures - studies have shown a close correlation between clinical manifestations of diabetic polyneuropathy and neuropathological abnormalities however as clinical measures lack precision reliability may be enhanced by using a dichotomous measure to achieve higher degrees of reproducibility. Neuropathic symptoms do not comprise adequate criteria for diagnosis and grading of polyneuropathy as they have been found to have a poor correlation with the degree of nerve damage (107,108).
2. Morphological and biochemical assessments - although nerve biopsies have demonstrated an array of biochemical and morphological abnormalities they are not recommended in the evaluation of human diabetic neuropathy save in specific studies designed to increase the understanding of basic etiopathogenesis or effect of therapeutic agents.

3. **Electrodiagnosis** - these are very useful in evaluating various disorders including not just the polyneuropathies but also the mononeuropathies. Nerve conduction studies primarily reflect functional status of large myelinated sensory and motor nerve fibres in the upper and lower limbs, however normal results do not rule out neuropathy. Nerve conduction abnormalities are however reported in up to 80-100% of patients with diabetes and the clinical relevance then of a positive test is questionable. Electromyography may reveal partial denervation in intrinsic foot muscles as an early sign of diabetic neuropathy and needle studies may also detect focal or asymmetric clinical findings not detectable by conduction studies.
4. **Quantitative sensory testing** - sensory examination may be undertaken using quantitative probes which detect various thresholds, they have the advantage of being sensitive, highly reproducible and noninvasive, however being fairly new there is an incomplete degree of standardization or validation for some.

A research classification for diabetic neuropathy was drawn up at the San Antonio conference in 1988 and reviewed in 1992 (104) with various recommendations of criteria to be used in different research settings on diabetic neuropathy with various combinations of the above. Thus for natural history epidemiological studies it was recommended that a simplified clinical examination with a scoring system be used with or without limited nerve conduction studies.

Diabetic Autonomic Neuropathy - this may manifest as dysfunction of different organ systems e.g. cardiovascular, gastrointestinal, genitourinary, sudomotor and ocular. The symptoms while being important in the individual patient are difficult to evaluate and quantify because they are

often nonspecific. The presence of autonomic dysfunction increases the risk of silent myocardial infarctions, sudden death and unaverted hypoglycemic attacks as well as causing other disturbances which while not immediately life threatening may impact negatively on the life of a diabetic such as frequent diarrhoea, impotence and incontinence.

Several objective tests have been proposed for the assessment of autonomic dysfunction which measure end organ responses to the activation of neural reflex arcs. Of these the most suitable for routine screening or monitoring the progression of autonomic neuropathy are the non invasive tests which have been shown to be reliable and reproducible as well as having a prognostic value. These are :

1. Tests of heart rate control (mainly parasympathetic) evaluating the heart rate response to valsava manoeuvre, deep breathing or standing.
2. Test of blood pressure control (mainly sympathetic) evaluating the blood pressure response to standing or tilting and/or sustained hand grip.
3. Tests of sudomotor control i.e. temperature induced sweating or chemically induced sweating.

Other test modalities such as invasive tests or other biochemical, physiological or pharmacological studies although useful may not be generally available or ideal for routine screening or progress monitoring.

The San Antonio Panel (104), hence recommended that for the assessment of autonomic neuropathy the following be adhered to :

- symptoms relating to autonomic neuropathy should not be by themselves considered as markers for it's presence
- non-invasive tests should be used as specific markers of autonomic neuropathy if end organ failure and other important confounding factors

such as concomitant illness, drug use and age are taken into account, and these should include both tests of sympathetic and parasympathetic function.

Diabetic mononeuropathies: These include spontaneous neuropathies which usually involve the third, fourth, sixth or seventh cranial nerves these are of rapid onset and there is presumably a vascular component. The entrapment neuropathies usually manifest as median carpal tunnel syndrome. In the limbs lesions of the ulna, radial and peroneal nerves may occur at sites of external pressure. These neuropathies are all more common amongst diabetic patients and probably represent an increased vulnerability of an already compromised peripheral nervous system.

Proximal Motor neuropathy: Also known as diabetic amyotrophy this is a condition that involves the lower motor neurones of the lumbosacral plexus presenting with severe pain, parathesias, weakness and muscle wasting of the upper legs.

JUSTIFICATION

Type 2 Diabetics comprise about 90% of the total diabetic population and is a disease which is becoming increasingly more important in the developing countries and the Kenyan population is not exempt from this trend. Being a chronic disease that is associated with long term complications, it results in higher morbidity and mortality rates in those affected. The complications of Type 2 diabetes mellitus are determined by events occurring both before and after the onset of the clinical disease and the risk of developing and progression of the late complications is not only related to the duration and control of hyperglycaemia, but is also dependent on other risk factors some of which are modifiable. In other populations microvascular complications and modifiable risk factors have been documented at the time of diagnosis. As type 2 diabetes is a condition where the interplay between genetic, biophysical and environmental parameters are evident, it follows that different populations may have different characteristics as regards both the characteristics of the patients as well as their risk factors and subsequent complication development.

This study is aimed at providing this baseline data as regards the local type 2 diabetic population at the time or shortly after diagnosis as this data is lacking. It is hoped that the data on the prevalence of risk factors and chronic complications at diagnosis or shortly thereafter in our local population may aid primary healthcare providers and policy makers to formulate a more focused, aggressive and timely approach towards both primary and secondary intervention in the management of this potentially debilitating disease.

STUDY OBJECTIVES

MAIN OBJECTIVE

To study the prevalence of retinopathy, nephropathy and neuropathy and the prevalence of some of the associated risk factors in type 2 diabetic patients shortly after diagnosis at the Kenyatta National Hospital.

SPECIFIC OBJECTIVES

1. To determine some clinical characteristics (i.e age at diagnosis, family history of diabetes, anthropometric measurements and mode of glycaemic control) in the patients with recently diagnosed Type 2 diabetes mellitus patients presenting to KNH.
2. To determine the prevalence of retinopathy, neuropathy and nephropathy by screening methods in recently diagnosed Type 2 diabetes mellitus patients.
3. To determine the prevalence of related risk factors namely smoking habit, hypertension, dyslipidemia, quality of glycaemic control and age at diagnosis in the population under study.

DESIGN AND METHODS

STUDY DESIGN: This was a descriptive cross - sectional study.

STUDY SITE : The study was conducted at the diabetic out-patient clinic of the Kenyatta National Hospital, Nairobi.

STUDY POPULATION : All patients attending the diabetic clinic in whom a clinical diagnosis of diabetes had been made within the preceding 24 months.

SAMPLING : Primary screening of all patients seen in the diabetic outpatient clinic was carried out by the attendant clinicians and consecutive patients fitting the inclusion criteria were then referred to the investigator.

Inclusion criteria :

1. Newly diagnosed diabetics who were diagnosed to have diabetes mellitus as per WHO or NDDG guidelines, or those with a prior diagnosis and already on treatment as was evidenced by clinic records.
2. Patients whose duration since clinical diagnosis of diabetes mellitus did not exceed two years.
3. Patients who were not on insulin treatment, or if on insulin treatment had an age at diagnosis of ≥ 40 yrs and a BMI ≥ 30 kg/m.
4. Patients with no prior history of ketosis and with no ketonuria as per clinic records and urine dipstick examination.
4. Patients willing to participate in the study and give informed written consent to the same effect (Appendix I).

Exclusion criteria.

1. Any history of current steroid use.
2. Patients with Gestational diabetes or diabetes in pregnancy.
3. Patients who on history taking and physical examination may have been found to have concomitant medication or illnesses that maybe responsible for neuropathy or that may have interfered with biochemical assays.

(Appendix II)

SAMPLE SIZE ESTIMATION:

As there are no local studies on prevalence of microvascular complications at diagnosis data from studies done mainly in the developed countries show a prevalence of diabetic retinopathy, nephropathy and neuropathy at diagnosis which ranges from about 10-21% .

The expected prevalence was hence approximated at 15% and a confidence level of 90% was used to calculate the sample size using the formula:

$$N = \frac{Z_{1-\alpha/2}^2 \cdot P(1-P)}{d}$$

Where :

P = anticipated prevalence (15%) = 0.15

$Z_{1-\alpha/2}$ = number of standard errors from the mean = 1.96

d = precision required on either side = 0.05

$$N = 1.96 * 0.15 * 0.85 = 99$$

(0.05)

Therefore sample size was estimated at 99 patients.

MATERIALS AND METHODS

For all patients recruited a history was obtained. This included demographic data pertaining to current age, gender, age at diagnosis, usual residence, level of formal education and occupation, where possible age was confirmed with national identity card but in some cases this was not possible and an estimate of age was sometimes used. In the medical history attention was paid to prior diagnosis of hypertension or treatment with anti hypertensive agents.

Any history of poorly healing foot ulcers, non traumatic amputation, renal disease or dialysis and that of myocardial infarction, angina pectoris or intermittent claudication was also noted, as that of any other concomitant disease. Smoking habit was also recorded with details on duration and quantity being noted and subsequently the cigarette-pack years calculated as cigarettes per day / 20 . years smoked. A family history both for diabetes mellitus and hypertension was also sought and it was noted if this was in a first degree relative or not.

Symptoms consistent with peripheral sensory or autonomic neuropathy were noted, namely loss of sensation, numbness and parasthesias for the former and history of impotence, bladder dysfunction, nocturnal diarrhoea and postural dizziness for the latter.

Information on prior and current medications both for diabetes and any other condition were noted, and a record of all current regular medications and dosages was made.

A physical examination was then carried out.

Weight was measured to the nearest half kilogram (kg) with the patient in light clothing and no shoes using a standard weighing chair in the clinic. The

height was measured against a vertical scale while the patient had no shoes and recorded to the nearest half centimetre (cm). Waist circumference was measured as the minimum circumference between the costal margins and the iliac crests, while the hip circumference was taken as the circumference measured at the level of the great trochanteric prominences, where these were not palpable then the greatest gluteal circumference was measured. These circumferences were both measured to the nearest 0.5cm. From this data the Body Mass Index (BMI) was then determined being calculated as : $BMI = \text{weight (kg)} / \text{height (m)}$, and degree of obesity classified as (109):

BMI kg/m	DEGREE OF OBESITY
< 25	Non-obese
25 – 29.9	Grade 1
30 – 39.9	Grade 2
> 40	Grade 3

Weight/ Hip circumference ratio was determined and android obesity defined as a waist / hip ratio > 0.85 for females and > 1.0 for males (109).

Blood pressure was measured with the patient in the supine position after a rest period of 5 minutes by the normal manual technique using an adult cuff and the systolic blood pressure recorded on the appearance of the first sounds, (Korotkoffs phase 1), while the diastolic pressure corresponded to the disappearance of the sounds, (phase 5), two such readings were made with readings being taken from the top of the meniscus and expressed to the nearest 2mmHg, the blood pressure was then expressed as a mean of the two readings. The patient was defined as having hypertension if found to have a systolic blood pressure of $\geq 140\text{mmHg}$ and / or a diastolic blood pressure of $\geq 90\text{ mmHg}$ or if normotensive but previously diagnosed as having

hypertension and on antihypertensive medication. Hypertension was grouped into categories according to the JNC VI criteria as below (110) :

BLOOD PRESSURE mmHg	DEGREE OF HYPERTENSION
< 130 / 85	Nil
130 -139 / 85-89	Borderline
140 -159 / 90-99	Grade 1
160 - 179 / 100 -109	Grade 2
> 180 / 110	Grade 3

If the diastolic and systolic blood pressures fell into different grades then the highest of the two determined the grade of hypertension. The patient would then assume a standing position and the blood pressure recorded again after 1 minute in the same manner. Orthostatic hypotension was defined as a drop in systolic pressure of ≥ 20 mmHg or a drop in diastolic pressure of ≥ 10 mmHg upon assuming the erect posture.

Neurological assessment was undertaken and the following were noted :

Vibration sense : using a 128Hz tuning fork over the lateral and medial malleoli, this was graded as normal or abnormal.

Pain : assessed using a disposable pin and graded as normal or abnormal.

Touch : light touch sensation was assessed using a cotton wisp and graded as normal or abnormal.

Temperature : sensation was assessed using a cold tuning fork (after immersion in cold water) on the dorsum of the feet and graded as normal or abnormal.

The achilles deep tendon reflexes were examined using the standard technique and the presence or absence of each reflex noted, where necessary with reinforcement.

For the definition and grading of peripheral neuropathy the Neurological Disability Score (NDS), (107,108,111) was then determined as follows:

Sensation	normal	abnormal
vibration	0	1
pain	0	1
temperature	0	1
Ankle reflex	0	1 (reinforced) 2 (absent)

This was applied to both lower limbs and scored as :

NDS	DEGREE OF POLYNEUROPATHY
0 – 2	Nil
3 – 5	Mild
6 – 8	Moderate
> 9	Severe

For assessment of autonomic function the Valsava test and beat to beat heart variation ratio from lying to standing was assessed on electrocardiographic (ECG) monitoring. The ECG monitoring commenced with the patient in the resting supine position and extended to include monitoring upon assuming an erect posture. The lying to standing RR 30:15 ratio was then determined i.e the ratio of the heart rate at the 30th beat after standing to that at the 15th, and an abnormal ratio defined as ≤ 1.00 (112). The Valsava test was performed with the patient rested for 10 mins prior to the test. ECG monitoring was resumed and the patient asked to blow into a modified sphygmomanometer maintaining a pressure of 40mmHg for 15secs. The ratio

of the highest heart rate during the rest period after the test, to that of the lowest during the test period was considered abnormal if ≤ 1.1 (112).

Autonomic neuropathy was then noted as present if any two of the three autonomic function parameters were positive (i.e. Valsava's test, lying to standing RR ratio or orthostatic hypotension).

Assessment of retinopathy was undertaken by an ophthalmologist using direct ophthalmoscopy without dilatation and with dilated pupils using 1% cyclopentolate eye drops and the retinal changes classified as normal, background, pre-proliferative retinopathy and proliferative retinopathy (Appendix III):

In addition visual acuity was assessed.

Nephropathy: For the assessment of nephropathy an early morning urine sample of 10mls was taken. A dipstick urinalysis was performed noting the presence of ketones, and for protein, leucocytes and nitrites as indices of infection. If the latter two were found present then the patient was considered as having a urinary tract infection and subsequent albuminuria test considered non valid, the patient was referred for microscopy, culture and sensitivity and appropriate treatment offered. The microalbuminuria was determined using Micral-II strips which gave semi-quantitative values of nil, 20mg/l, 50mg/l and 100mg/l.

All patients were examined in the morning having fasted for at least 8hrs and a fasting blood sugar obtained. Subsequently 8mls of venous blood was drawn from the ante-cubital veins, 3mls of which was placed in an EDTA bottle and sent for HbA1c assay while the other 5mls was put in a plain bottle and sent for fasting lipid profile and serum creatinine levels.

Predicted creatinine clearance was also calculated from the serum creatinine value measured, using a modified Cockcroft-Gaults formula (113) as follows:

Males :

$$\text{Creatinine clearance in ml/kg per 70kg} = \frac{(145 - \text{age in years}) - 3}{\text{Serum creatinine in mg/dl}}$$

Female:

$$\text{Creatinine clearance in ml/kg per 70kg} = \frac{0.85 (145 - \text{age in years}) - 3}{\text{Serum creatinine in mg/dl}}$$

HbA1c was assayed and the degree of glycemic control classified as :

$$\begin{array}{ll} \leq 7\% & = \text{ideal} & 8 - 8.9\% & = \text{fair} \\ 7 - 7.9\% & = \text{good} & > 9\% & = \text{poor} \end{array}$$

Fasting blood sugar was also assessed and control classified as :

$$\begin{array}{ll} \leq 5.9 \text{ mmol/l} & = \text{ideal} & 8-9.9 \text{ mmol/l} & = \text{fair} \\ 6 - 7.9 \text{ mmol/l} & = \text{good} & > 10 \text{ mmol/l} & = \text{poor} \end{array}$$

Dyslipidemia was assessed using the cholesterol oxidase and esterase calorimetric method. While total cholesterol, HDL cholesterol and triglycerides were determined directly, LDL-C was derived using Friedwalds formula (114). Lipid abnormalities were classified using two criteria, the NCEP and the ADA whose cut-off values respectively are :

	NCEP	ADA
hypercholesterolaemia (mmol/l)	≥ 5.2	≥ 4.2
hypertriglyceridemia (mmol/l)	≥ 1.7	≥ 2.3
high LDL-C (mmol/l)	≥ 3.4	≥ 2.6
low HDL-C (mmol/l)	≤ 0.9	≤ 0.9 males, < 1.15 females

The methodology of the individual biochemical analysis is given in appendix (iv).

ETHICAL CONSIDERATIONS

Before undertaking the study approval was sought and granted from the Kenyatta National Hospital Ethical Committee.

All patients received prior information as to the nature of the examination, its purposes and procedures it would entail. They were further informed that participation was on a voluntary basis and no health care would be withheld to those who declined to participate. Similarly witnessed informed written consent was necessary prior to recruitment of any patient into the study.

The clinical examination and laboratory measures that were undertaken are those proposed in the routine standard care of all diabetic patients. The primary care clinician was informed of all results of the clinical and biochemical evaluations, similarly appropriate interventions were offered as the need arose.

DATA ANALYSIS

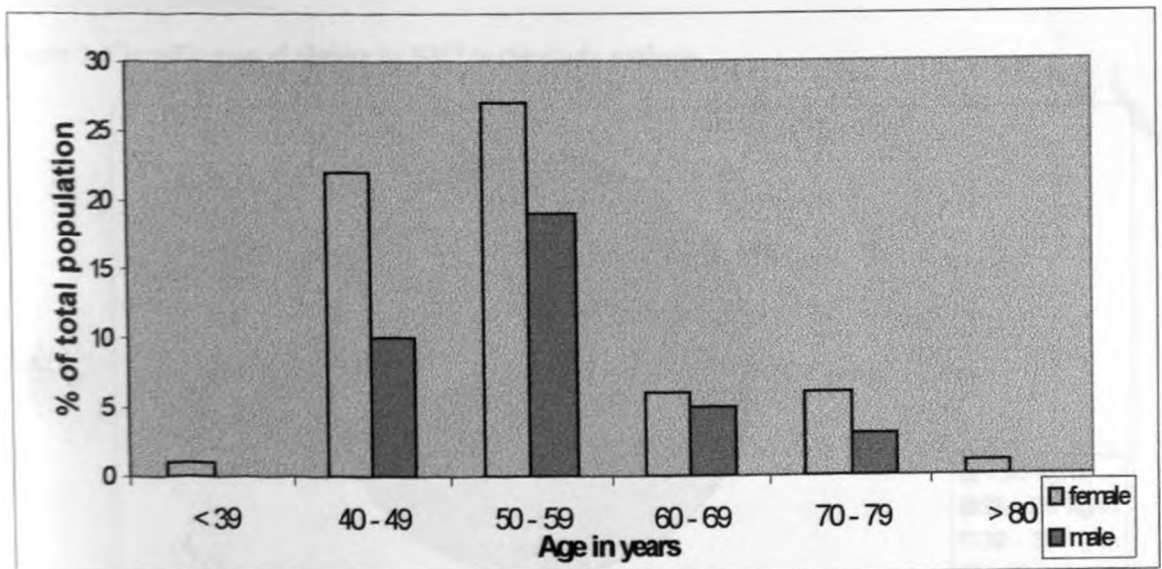
Data was entered into a data analysis proforma - appendix (v), and subsequently entered into the SPSS computer software system. All statistical analysis was carried out using the same system. Means and standard deviations were calculated and any significance between different groups determined by the Mann-Whitney test. Association between the complications and proposed risk factors was evaluated using the Chi-squared Pearson test.

RESULTS

139 patients seen in the diabetic clinic between June 2000 and January 2001 satisfied the inclusion criteria and were referred for recruitment. Of these, 28 patients failed to turn up for their appointments. Of the 111 patients seen, 1 did not fulfill the criteria for classification as diabetic, 1 patient had concomitant chronic obstructive pulmonary disease while another was excluded as was on phenytoin treatment for longstanding epilepsy. Of the remaining 108 recruited 8 were excluded from the final analysis as they did not complete the clinical workup and hence had incomplete data.

Of the 100 patients studied, 63% were female and 37% were male, giving a male to female ratio of 1:1.7. The mean age of the study population was 53.7 ± 9.3 years with a range of 34 - 80 yrs. The mean age for males was 54.9 ± 8.8 yrs while that of females was 53.2 ± 9.6 yrs, there was no significant difference in the mean age between the males and females ($p > 0.05$). The age and gender distribution of the patients are shown in figure 1.

Figure 1. Age and gender distribution of the study population.



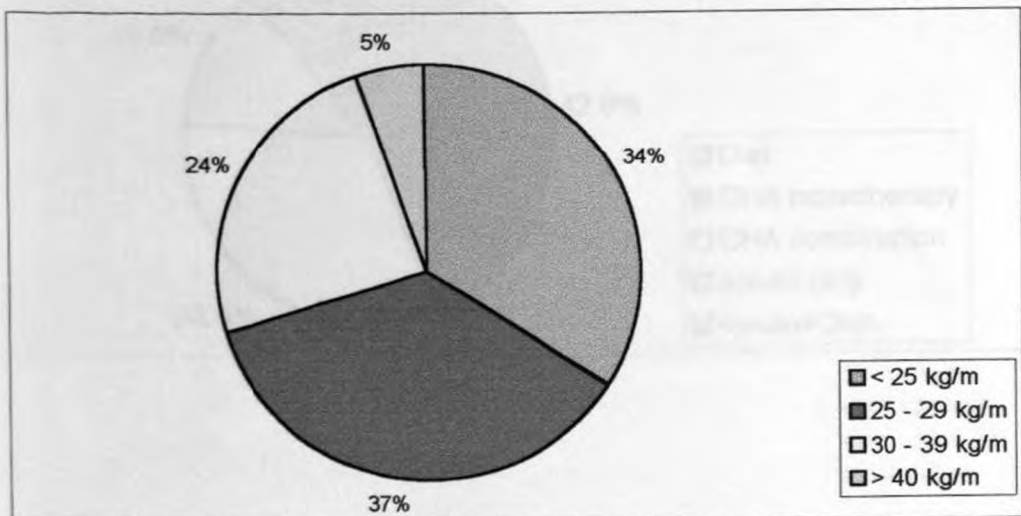
The mean duration of diabetes from the time of clinical diagnosis was 10.3 ± 7.5 months.

Of the patients seen 78% of these were urban dwellers mainly from Nairobi. There was a family history of diabetes mellitus present in a first degree relative in 38% while another 10 % of the patients had a family history of diabetes in another relative. A family history of hypertension was present in 24% of the patients.

Most of the male patients had a smoking history (73%). Current smokers were 7% of the study population while 21% were ex smokers, there was only one female ex-smoker.

The mean body mass index was 27.8 ± 6.0 kg/m with a range of 13.5 - 49 kg/m. 66% of patients were classified as obese, of which 37% had grade I obesity, 24% grade II and 5% had grade III obesity. Obesity was more marked amongst the females with a mean BMI of 28.9 ± 6 kg/m as compared to a male mean BMI of 25.9 ± 5.7 kg/m ($p = 0.017$). Abdominal adiposity was present in 41% of the patients and was more prevalent in the female population.

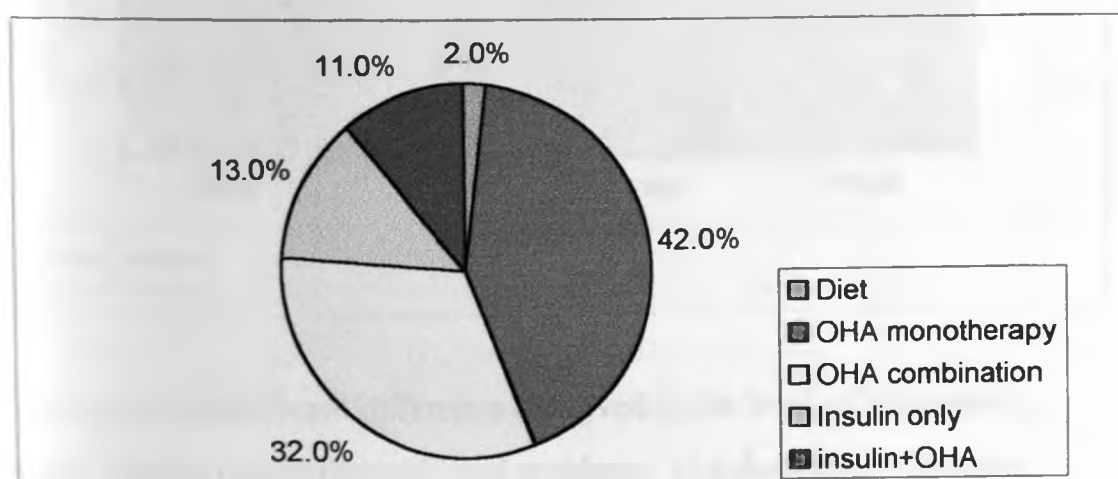
Figure 2. Classification of obesity by BMI in the study patients.



Hypertension was present in 50% of the patients, of these 52% (n=26) had a prior diagnosis of hypertension and were on treatment, while in 48% (n=24) high blood pressures were detected at the time of inclusion into the study. Of those patients with a prior diagnosis of hypertension, this had preceded the diagnosis of diabetes in 54% (n=14) cases. There was a strong association between a family history of hypertension and the presence of hypertension ($p=0.005$). 68% of the patients were in the category of grade 1 hypertension, 22% grade 2 while 10% had grade 3 hypertension. None of the patients who were already on treatment were well controlled ($BP \leq 130/85$ mmHg).

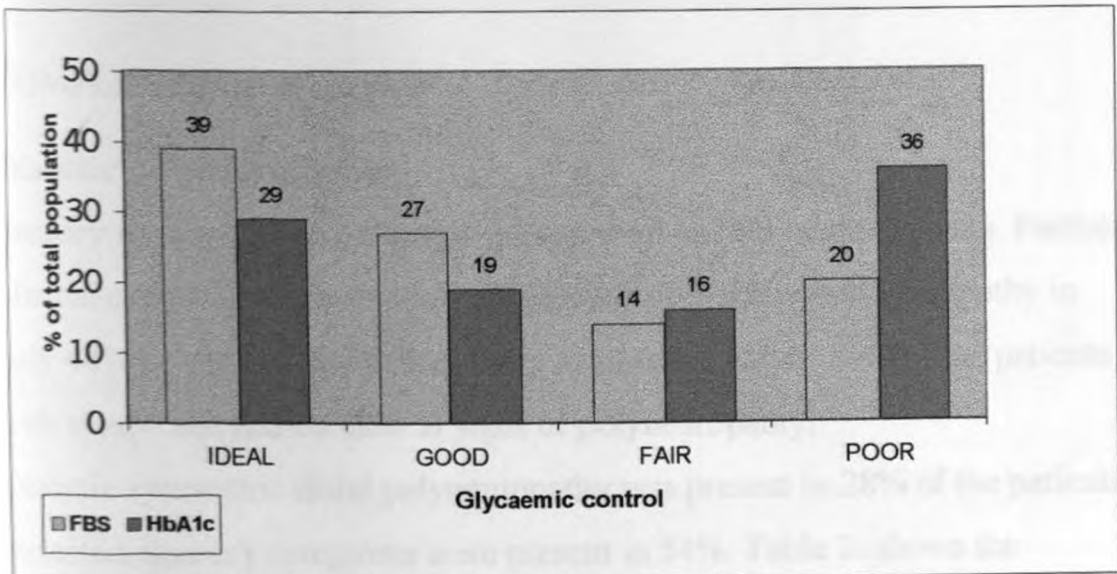
74% were on oral hypoglycemic agents (OHA's) as the mode of therapy for glycaemic control while 13% were on insulin only, 11% were on a combination of insulin and OHA's and only 2% were on dietary management alone. (Fig.3).

Figure 3. Treatment for glycaemic control in the study patients.



The mean HbA1c was $8.5 \pm 2.3\%$ while that of fasting blood sugar was 7.5 ± 3.9 mmol/l. Using the HbA1c as a measure of glycaemic control 48% of the patients had ideal to good control (HbA1c $\leq 7.9\%$), while 36% were poorly controlled (HbA1c $\geq 9.0\%$). Using the fasting blood sugar as a measure of glycaemic control a higher prevalence of 68% was found for those with ideal to good control (FBS < 8 mmol/l) and a lower prevalence of poor control of 20%, (FBS > 10 mmol/l). The classification of glycaemic control as measured by HbA1c and by FBS tended to show little agreement with a kappa value of 0.26, Fig.4 compares the frequencies obtained using the two measures.

Fig.4 Classification of patients level of glycaemic control using HbA1c and Fasting blood sugar as measures.



There was no significant difference observed in the level of glycaemic control between the urban and rural residents. The duration of diabetes although limited in this study, also did not influence the level of glycaemic control.

The mean total cholesterol was 5.1 ± 1.0 mmol/l, mean HDL-C 1.8 ± 0.5 mmol/l, mean LDL-C 2.4 ± 0.9 mmol/l and mean triglyceride levels 1.5 ± 0.8 mmol/l amongst the study patients. Lipid abnormalities were classified using two systems, the older NCEP criteria and the newer ADA criteria. The prevalence of dyslipidemia using both criteria is shown in Table 1.

ADA criteria	% of population	NCEP criteria	% of population
Total cholesterol > 4.2 mmol/l	82	Total cholesterol > 5.2 mmol/l	50
HDL-C < 0.9 mmol/l - male < 1.15 mmol/l-females	9	HDL-C < 0.9 mmol/l	1
LDL-C > 2.6 mmol/l	35	LDL-C > 3.4 mmol/l	17
Triglycerides > 2.3 mmol/l	12	Triglycerides > 1.7 mmol/l	50

Table 1. Abnormalities in lipid profiles of recently diagnosed type 2 diabetic patients using the NCEP and ADA criteria.

COMPLICATION PROFILE

Diabetic polyneuropathy

Sensory neuropathic symptoms were reported in 34% of the patients. Further clinical examination established a diagnosis of diabetic polyneuropathy in only 44% of the patients with sensory symptoms, while 56% of the patients with symptoms had no clinical signs of polyneuropathy.

Diabetic symmetric distal polyneuropathy was present in 28% of the patients recruited, sensory symptoms were present in 54%. Table 2. shows the distribution of neuropathic symptoms. Using the neurological disability score 18% had mild neuropathy, 5% moderate and 5% severe disease, the mean NDS of the patients with neuropathy was 5.25.

Table 2. Distribution of sensory and autonomic symptoms in the study population.

Symptom	Frequency
Numbness	26
Paraesthesia(pins and needles)	21
Pain	21
Postural dizziness	8
Difficulty with micturation or incontinence	2
Impotence	9
Nocturnal diarrhoea	2

The characteristics of the patients with and without diabetic polyneuropathy is shown in Table 3. with means comparison using the Mann Whitney test. The mean age of patients with polyneuropathy and mean cholesterol levels tended to be significantly higher than those of their counterparts ($p=0.009$ and $p=0.02$ respectively). With Pearsons chi-squared test a significant association was seen between male gender, history of smoking and polyneuropathy ($p=0.032$ and $p=0.039$ respectively). Diabetic polyneuropathy in these patients was also significantly associated with *hypertriglyceridemia ($p=0.013$) and *high LDL-C levels ($p=0.015$) while no significant association was noted with age, glycaemic control or other lipid abnormalities.

Means	Polyneuropathy present (n=28)	Polyneuropathy absent (n=72)	p value
Age (yrs)	57.1 + 8.0	52.5 + 9.5	0.009
HbA1c %	8.8 + 2.5	8.6 + 2.2	0.55
T Cholesterol mmol/l	5.5 + 1.0	4.9 + 1.0	0.02
HDL-C mmol/l	1.9 + 0.5	1.8 + 0.5	0.35
LDL-C mmol/l	2.9 + 0.9	2.3 + 0.9	0.05
Triglycerides mmol/l	1.6 + 0.9	1.5 + 0.7	0.32

Table 3 Comparison of variables between patients with and without polyneuropathy

* ADA criteria

Autonomic Neuropathy

Autonomic neuropathy was found in 27% of the patients. Abnormalities in the Valsava test were more common while orthostatic hypotension was rare at 6%. All the patients who had orthostatic hypotension also had an abnormal lying to standing ratio and an abnormal Valsava test ratio.

Table 4. shows the frequency of abnormalities in the various tests .

No significant association was noted between autonomic neuropathy and the presence of hypertension, level of glycaemic control, dyslipidemias, smoking status or age at diagnosis of diabetes in this study population.

Abnormal 30:15 RR ratio	Abnormal Valsava Ratio		Total
	Yes	No	
Yes	27	1	28
No	6	66	72
Total	33	67	100

Table 4. Frequency of abnormal Valsava ratio and lying to standing 30:15 RR ratio in the study population.

Nephropathy

Albuminuria as a marker for nephropathy was present in 26.3% (n=26). Of these 96% (n=25) had microalbuminuria while only 4% (n=1) had macroalbuminuria. Only one patient was excluded from this analysis due to the evidence of a urinary tract infection. Of the microalbuminuric patients, 46.2% had values in the lower range of 20mg/l, 42.3% intermediate range of 50mg/l and 11.5% in the higher 100 mg/l range. The mean serum creatinine in the microalbuminuric patients was $82.8 \pm 26.2 \mu\text{mol/l}$, the difference between the serum creatinine or calculated creatinine clearance in those with

and without microalbuminuria was not statistically significant. The only patient with macroalbuminuria had a serum creatinine of 138 $\mu\text{mol/l}$ and a calculated creatinine clearance of 49.9 ml/min/70kg. However those patients with hypertension had significantly lower mean creatinine clearance of 84.7 ± 21.4 ml/min/70kg, as compared to those without hypertension, 103 ± 26.9 ml/min/70kg ($p=0.0005$). The characteristics of the variables in patients with and without microalbuminuria are shown in table 5. With the chi-squared test the only significant association noted was between male gender and microalbuminuria ($p=0.043$). A tendency towards association of microalbuminuria and smoking was noted but this did not achieve statistical significance ($p=0.064$).

Means	Albuminuria present (n=26)	Albuminuria absent (n=73)	p value
Age (yrs)	52.0 + 8.6	54.0 + 9.6	0.90
HbA1c %	8.5 + 2.3	8.6 + 2.3	0.97
FBS mmol/l	7.9 + 5.0	7.5 + 3.7	0.75
SBP mmHg	143 + 27	136.2 + 18.7	0.27
DBP mmHg	87.2 + 16.2	83.3 + 13.1	0.26
T.Cholesterol mmol/l	5.2 + 0.7	5.0 + 1.1	0.42
HDL-C mmol/l	1.8 + 0.5	1.8 + 0.5	0.69
LDL-C mmol/l	2.5 + 1.0	2.4 + 0.9	0.90
Triglycerides mmol/l	1.7 + 0.7	1.5 + 0.8	0.43
Creatinine clearance ml/min/70kg	96.9 + 31.9	93.1 + 24.1	0.84

Table 5. Comparison of variables between albuminuric and non-albuminuric patients

Retinopathy

Retinopathy was present in 7.1% (7) of the patients of whom none had proliferative disease, 2 had pre-proliferative disease and 5 had background retinopathy. The small number of patients limited any useful analysis however no significant associations were noted.

Only 42% of the patients had no complication at all, while 22% had more than one of the complications present. Figure 5 shows the overall prevalence of complications while table 6 shows the association between the complications observed in this study population.

Figure 5. Prevalence of complications in the study population.

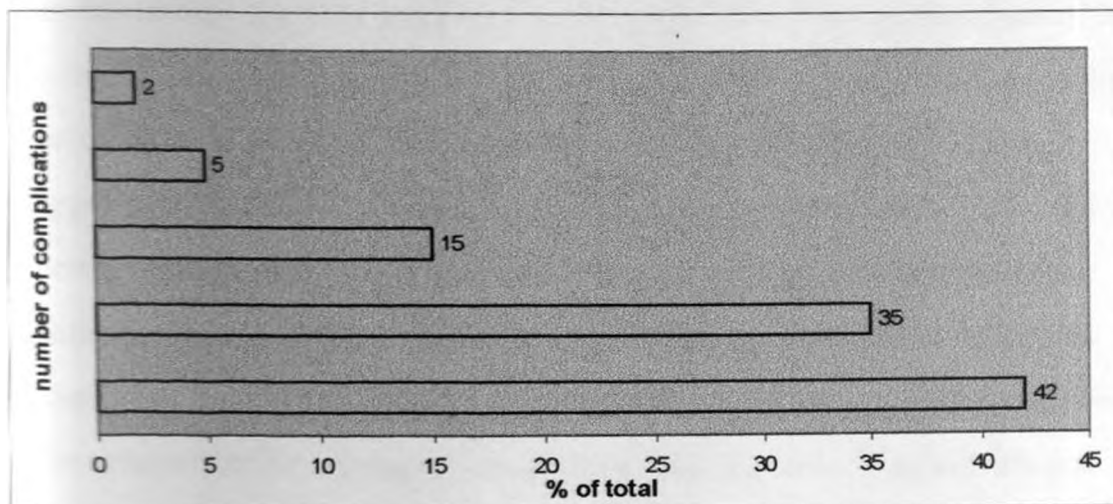


Table 6. Association between the complications.

Complication (frequency)	None	Polyneuropathy	Autonomic neuropathy	Autonomic + Polyneuropathy
None	42	13	11	3
Albuminuria	10	5	5	3
Retinopathy	1	0	1	2
Albuminuria + retinopathy	1	0	0	2

DISCUSSION

Type 2 diabetes is becoming an increasingly important health concern in the developing countries (4). The increased morbidity and mortality that it carries makes it a very pertinent health care issue. Prior to the onset of frank symptomatic hyperglycemia there will have been a long period estimated between 4-7yrs (98) of undiagnosed metabolic disturbances such as hyperinsulinemia, insulin resistance and glucose intolerance (117). This prediabetic phase of the disease process is such that at diagnosis some patients will already present with complications. Most of the long term morbidity is as a result of the microvascular complications of diabetes and the most effective management strategy focuses on early diagnosis and management of associated modifiable risk factors. So far there have been no local studies that have looked at the burden of microvascular complications at the time or soon after diagnosis and the baseline characteristics of our newly diagnosed type 2 diabetic population.

Of the type 2 diabetic patients evaluated in this study there was a male to female ratio of 1: 1.7. This may reflect a gender difference in health seeking behaviour of the population under study, rather than a true gender disparity as other studies on diabetics conducted in the same centre have not reflected the same (7-14). However it is of note that many countries do have a higher female prevalence of type 2 diabetes (118). This may be partially explained by the longer life expectancy in the female population, but it would also suggest that there maybe risk factors for the development of diabetes that maybe specific to the female population. Parity was not assessed in this

study but pregnancy per se is a state of glucose intolerance (119), and one hypothesis is that frequent pregnancies may confer repeated and excessive stress on the beta pancreatic cells without allowing for a sufficient recovery time in between pregnancies, this may place highly multiparous females at an increased risk for developing diabetes. Another possibility is that weight gain acquired from previous pregnancies could place females at a greater risk for developing diabetes. If confirmed then this may form an additional high risk category and provide an opportunity for early screening for glucose intolerance and diabetes, and for primary prevention strategies in this subgroup.

Most of the patients in this study were urban residents. Although there may have been a bias introduced by the location of the study site within an urban environment, the prevalence of diabetes in urban areas has been noted to be higher than that in rural populations (4). Whether the same is true in this population cannot be concluded from this study. However the increasingly 'westernised' lifestyles in the urban populations may put them at a higher risk of developing type 2 diabetes (4, 38, 120).

The mean age of patients studied was 53.7 ± 9.3 years and the mean duration since clinical diagnosis was 10.3 ± 7.5 months. The mean age at diagnosis compares well with that found in other studies on newly diagnosed type 2 diabetics (6,121).

A positive family history of diabetes mellitus was elicited in 48% of the patients and in about 80% of them, diabetes was present in a first degree relative. This familial clustering of type 2 diabetes has been observed in

other studies and supports the hypothesis that genetic factors may have an important role (20,22,24,122). However this clustering that is observed may also be due to environmental factors other than genetics alone. The record of a positive family history for hypertension amongst those patients with hypertension was statistically significant ($p=0.005$). This may be a reflection of biased familial clinical records, more so with a 'silent' disease such as hypertension, such that the history may come out only when searched for by another member suffering from the same. However, although there is no direct pattern of inheritance for hypertension, genetic factors probably polygenic, do have a role to play. Both hypertension and type 2 diabetes are conditions that cluster, and more so with age (117,123). This may suggest that there is an interplay between the polygenic factors and environmental influences that interact to cause both these conditions.

More than two thirds of the male population in this study were or had been smokers. Current smokers were recorded as 7%. A possibility of under reporting smoking habit is common amongst patients and this prevalence may have been higher. The male predominance reflects the cultural acceptability associated with male smokers and not with female smokers, however as urbanization causes changes in cultural values we may see a gradual change in this trend. The only complications that were associated with a smoking history, polyneuropathy and nephropathy, were the same in which a significant difference was noted as pertained to gender, being more prevalent among the male population. Hence the apparent association with smoking may reflect an increased risk conferred by male gender. However smoking per se may confer an increased risk in as much as it impairs platelet

function, results in abnormalities of coagulation and causes vasoconstriction resulting in endothelial damage.

The patients in this study tended to be leaner, with a mean body mass index of 27.8 ± 6.0 kg/m, than those observed in the western populations (6). This is probably a reflection of the socio-economic and lifestyle differences, however the predisposition to obesity may also be genetically determined. The use of BMI cut-off values that have been based on these different populations may not reflect the true risk strata in our patients. The higher prevalence of obesity and of abdominal obesity in the female population is not unique to this study and has been noted elsewhere (124). This may be explained by the fact that this population is generally post menopausal. The female obesity noted may be associated with increase in central adiposity possibly due to weight gained from previous pregnancies. This study however did not control for parity. As obesity and especially abdominal adiposity are established risk factors for type 2 diabetes this finding may contribute to a higher prevalence of diabetes amongst the female population.

Using the JNC VI Criteria for the diagnosis of hypertension, there was a high prevalence of 50%, of hypertension amongst the study patients. Half of these were detected at the time of examination. Considering that the treatment target for high blood pressure in diabetics is slightly lower at 130/85mmHg if this were to be used as the cut-off to define hypertension in this study group then the prevalence would be even higher at 67%. An accepted limitation is that the blood pressures were taken in one sitting and hence there may have been some false positives due to "white-coat hypertension". The prevalence observed in this study is however lower than

that found amongst local diabetic patients who had a longer duration of disease, in the study by Twahir (13) where mean duration of diabetes was 7.0 ± 5.3 years hypertension occurred in 58.2% of the patients, and in the study by Nyamu (14) where the mean duration of diabetes was 7.98 years this was 67%, although in the latter these were patients with established complications. These findings may reflect a rising incidence of hypertension with increasing duration of diabetes and with advancing age of the patients. None of our patients already on treatment was achieving target levels of blood pressure control. This may reflect the difficulty in patients compliance especially where the disease is chronic and relatively asymptomatic or suboptimal prescription. The current guidelines on hypertension classification and treatment goals have recently been challenged by a group of American statisticians (125) who suggest that the mortality risk does not increase at the levels advocated by the JNC VI guidelines, but that this impacts at much higher levels than those advocated for treatment. Further studies to clarify this important issue are awaited.

While mass screening for diabetes may not be cost-effective, there are those patients who are at a high risk for developing diabetes and in whom screening for the same may be considered. Among these risk factors are age > 40yrs, abdominal obesity, hypertension, hyperlipidemia and a family history of diabetes. Forty-eight percent of the patients in this study had a positive family history of diabetes. There was also high prevalence of obesity seen in our patients of 62% with 41% having abdominal obesity both of which were more prevalent amongst the females as compared to the male population. Hypertension was also frequently observed (50%). This clustering of risk factors in this particular population of recently diagnosed

diabetics may suggest a reason to reconsider the issue of screening high risk patients for type 2 diabetes within our population.

Most of the patients, about 70%, were found to have a suboptimal glycaemic control as evaluated by HbA1c, with 36% of the study population having poor control. The measure of control using HbA1c and that using FBS were found to vary, where FBS tended to underestimate the proportion of patients with poor control. A single blood sugar measurement is inadequate to assess the glycaemic control of a patient as this a fluctuating variable relating to timing of medications, quantity and quality of feeds, and the duration since last meal. As regards the timing of the blood sugar measurements a fasting blood sugar tends to obtain a falsely low starvation blood sugar as the time of measurement would usually exceed the patients physiological fasting time. Random blood sugars which can then be assessed taking into consideration the post prandial duration maybe a better alternative. This study did not for logistic reasons take post prandial blood sugar measurements. As FBS is the main parameter used to assess glycaemic control in our diabetic clinic this maybe an important limitation in affording patients the appropriate measures to optimize glycaemic control. The level of glycaemic control was not influenced by the duration of diabetes, this was probably because the target population were fairly uniform as regarded duration of diabetes as per the study design.

Applying the current ADA recommended criteria for dyslipidemia there was a very high prevalence of high total cholesterol of 81% with relatively low prevalence of high triglycerides at 12%, and low HDL-C at 9% , while high LDL-C was present in 35%. While diabetes is associated with high total cholesterol, LDL-C and low HDL-C, the typical diabetic dyslipidemia is

characterised by hypertriglyceridemia (126). The low prevalence observed here of hypertriglyceridemia is similar to that observed in the African American diabetic population compared to their Caucasian counterparts who were characterized by a lower prevalence of hypertriglyceridemia but a higher prevalence of high risk LDL-C levels (127). In the presence of lower triglyceride levels then the relatively higher HDL-C levels are not surprising as these two are inversely correlated. Unfortunately we do not have local data on lipid levels in the non diabetic population with which to compare the high levels of total cholesterol found in our patients. However in the study by Nyamu (14) on diabetics with foot ulcers 30% had hypercholesterolemia, 36% had low HDL, 16% high LDL and hypertriglyceridemia was present in 34%. While the patients seen in that study had a longer duration of disease and presented with an advanced complication, the use of different cut-off values may also be responsible for part of the difference observed. This then raises the issue of risk stratification within our own environment rather than relying on classifications based on data derived from populations that are subject to different environmental and genetic influences and hence may not be representative of the local situation.

Seven percent of the patients in this study were found to have non proliferative diabetic retinopathy. This prevalence is lower than the 19.2% found in the newly diagnosed diabetics of the UKPDS (6). Retinopathy at diagnosis has been reported as low as 3% amongst the Pima Indians (60), while other African studies have given different figures ranging from Uganda where the prevalence within 5 years of onset was found to be 5.5% (128) and 12.7% in Nigeria (128), while in Tanzania the prevalence of retinopathy in a group of unselected patients with duration of diabetes ranging from 0-24yrs was 25% (130). Other local studies have reported a

prevalence between 35 - 55% in diabetics with a duration of disease of more than 10 years (8-10). Various studies suggest that glycaemic control and duration of diabetes are the most important risk factors with hypertension, dyslipidemias and cigarette smoking also being implicated (6, 60, 76, 81,84, 131). Most of these factors were prevalent in our population yet the prevalence of retinopathy was relatively low and no association was noted between any of these factors and the presence of retinopathy. While the small numbers may have limited a detailed analysis it is quite likely that the duration of diabetes plays a major role in interplay with these traditional risk factors and others such as genetic factors. The role of duration of disease is supported by the higher prevalence of retinopathy seen in the local population with longer duration of disease (8-10).

The prevalence of micro- and macro-albuminuria in this study was 25% and 1% respectively. The prevalence of microalbuminuria in this group of patients is higher than that found in other studies. The UKPDS (6), found microalbuminuria in 11%, while a Danish study (132) found a prevalence of 22% in patients with duration of diabetes of less than 4years. Twahir (13) reported a prevalence of microalbuminuria in 40.5% of the type 2 patients seen at KNH with a mean duration of 7.0 ± 5.3 years, Ngugi (12) reported macroalbuminuria in 15.8% of the total patients in his study. The prevalence of albuminuria both micro- and macro- albuminuria has been shown to increase with duration of disease (58,68). In this study a single urine screening was undertaken and this was not repeated to confirm the result. This may have introduced some false positives as this is a test that could be altered by many variables such as exercise, posture and infections (91), however attempts were made to eliminate these confounders.

It is also well established that improvement of glycaemic control in the acute stage can reduce the albumin excretion rate (91). As the majority of our patients were fairly newly diagnosed and as shown did not have optimal glycaemic control this may have contributed to the higher prevalence, however the expected association between microalbuminuria and glycaemic control was not present. The mean HbA1c although not different in the group with and without microalbuminuria, was still elevated at about 8.5%. There was no association between the microalbumin and serum creatinine levels or calculated creatinine clearance. This is not surprising as the clinical stage of nephropathy at which one finds microalbuminuria, stage 3, is usually the transition between the early stages of hyperfiltration and the subsequent falling GFR (42), such that the GFR at this stage is usually within normal. This further emphasizes on the role of microalbuminuria as an early marker of nephropathy as the creatinine clearance is only altered at a later stage in the natural course of diabetic nephropathy. A significant association was however noted between hypertension and creatinine clearance where the patients with hypertension had a significantly lower mean creatinine clearance of 84.7 ± 21.4 ml/min/70kg as compared to those without hypertension, 103 ± 26.9 ml/min/70kg. The association between hypertension and creatinine clearance may be interpreted in two different ways. Either that the patients with lower creatinine clearance and hence some element of renal failure, whether due to diabetes or other causes, is responsible for the raised blood pressure, or that the renal dysfunction is secondary to the hypertension itself. Either way this association would then place the hypertensive patients at a higher risk for progression of diabetic nephropathy. Although essential hypertension maybe associated with microalbuminuria (133), blood pressure is apparently not a major contributor

to microalbuminuria in early type 2 diabetes as there was no difference in this between the patients with and without microalbuminuria. This was also seen in Twahir's study (14). Mattock et. al (134) demonstrated a correlation only for diastolic blood pressure in the male population and two large Danish studies also failed to show any strong association between systolic blood pressure and urinary albumin in type 2 diabetes (132). Hypertension has however been associated with the deteriorating renal function as reflected by progression of proteinuria and decline in GFR over time (70). Hence we would expect that those patients with a high prevalence of poorly controlled hypertension would be at an increased risk of progressive diabetic nephropathy.

Male gender was significantly associated with microalbuminuria. This is a finding that has come out in other studies suggesting that male gender per se is an independent risk factor for the development of renal microangiopathy (68). Although it is suggested that androgens may play an active role in promoting diabetic microangiopathy (69) it may also be possible that the differences in lifestyle, health habits and general attitude to healthcare may condition this.

Lipoprotein abnormalities are common in type 2 diabetics and may be aggravated by the onset of microalbuminuria. In this population no association was seen between microalbuminuria and lipids or lipoproteins. This finding is similar to that of Niskanen et al (135) who found no difference in those patients at diagnosis with and without microalbuminuria but found that abnormalities were significantly increased in the microalbuminuric group at a 5 year follow up. The mechanisms by which lipid abnormalities develop in microalbuminuric patients is not clear, in the nephrotic syndrome lipoprotein synthesis is increased in response to albumin

loss. The lipid abnormalities may also be related to increased renal toxicity (77) so that a vicious cycle ensues.

Surprisingly the relationship between albuminuria and retinopathy was not significant and the former had a prevalence three times that of retinopathy. This may suggest that other factors, possibly genetic and environmental, account for the more accelerated development of renal microangiopathy compared with the retina. This discordance has been observed in other studies, with Marshall et al (136) reporting 60% of their proteinuric patients had no retinopathy and Schmitz et al (137) reported 62%. This finding is important to consider in the diagnosis of diabetic nephropathy where the finding of retinopathy has been an important major criteria in determining if one is dealing with diabetic nephropathy or another cause of proteinuria in type 2 diabetic patients. This may be relevant in our population where other conditions may be responsible for nephropathy and hence in the absence of retinopathy would have to be excluded. Further studies may help to answer this question on the histological and functional correlates of microalbuminuria in our type 2 diabetic population.

The prevalence of neuropathy, combined peripheral and autonomic was found to be the highest of the complications found to be 48%. In this study an attempt was made to adhere to the ADA recommendations and a validated modified scoring system was used. Peripheral neuropathy was found to be the most common complication present in 28% of the patients, against that of 12.1% found in the UKPDS at diagnosis (6). Kioy (7) found a prevalence of 42% on unselected diabetics evaluated using clinical criteria, this was higher at when supplemented with nerve conduction studies at the same centre. The relatively high prevalence found in this study may reflect

the possibility of a high incidence of other causes of nerve abnormalities within the general population. The type 2 diabetic population is generally, as was seen even in this study, an elderly population. Aging is associated with slower nerve conduction and abnormalities of the autonomic nervous system particularly as pertains to parasympathetic function (61). This age-related slowing of nerve conduction may provide a background for diabetic peripheral neuropathy. This would be consistent with the finding in this study of a significantly higher mean age in the patients with polyneuropathy. Given that the study population was fairly uniform as regards duration, the effect of duration of diabetes on the incidence of peripheral neuropathy could not be assessed. That other risk factors maybe important in diabetic neuropathy is suggested by the Steno-2 trial (138) where multifactorial intervention on the traditional factors was shown to be beneficial in retarding all microvascular complications of diabetes except for neuropathy. One of the factors that could account for the high prevalence of peripheral neuropathy in this environment is subclinical malnutrition especially as pertains to thiamine and pyridoxine deficiency. This may be particularly so in the diabetic who is keen to follow dietary advice on low carbohydrate diet and minimizes the intake of starch and cereals, foods that are rich in thiamine. Indeed these vitamin deficiencies have been found to play an important role in patients with diabetic polyneuropathy in Dar es Salaam (139), similarly thiamine levels were found to be low in 80% of Japanese NIDDM patients (140).

Peripheral neuropathy in this study was significantly associated with male gender a finding similar to that in other studies (141, 59). It has been observed that men have a normally slower nerve conduction than females and this may render them more susceptible (142). In experimental diabetic

neuropathy disturbances of sorbitol and myoinositol have also been noted to be sex hormone dependent (69).

A high prevalence of autonomic neuropathy was also found. There was a higher prevalence of abnormality in the tests that evaluate predominantly parasympathetic function, i.e Valsava test and lying-to-standing heart rate. This is in keeping with the finding of a background age-related nerve dysfunction which affects more the parasympathetic system than the sympathetic system, and may put these individuals at a higher risk for earlier expression and progression of diabetic neuropathy through a cumulative effect.

A high prevalence of autonomic neuropathy in the local diabetic population was also found in a study by Chokwe (143) who found a prevalence of 62% in unselected diabetic patients with a mean duration of 5.5 ± 5 years. While the association between polyneuropathy and autonomic neuropathy did not attain statistical significance at least one third of the patients in either group had both the complications present. Hence one form of neuropathy may not be used to predict the presence of the other. This is despite the proposed similar pathogenetic mechanisms which suggests that there are other factors as yet undefined that influence the development of these neuropathic complications.

The impact of duration of diabetes while being established for peripheral neuropathy has been controversial as far as autonomic neuropathy is concerned. Straub et al (144) found that while the prevalence of retinopathy, nephropathy and polyneuropathy were correlated with duration of disease, autonomic neuropathy was not, and suggested that the lesion maybe more

functional than structural and may even be present prior to the development of diabetes.

While attempts were made clinically to exclude other conditions that may have contributed to the presence of autonomic neuropathy we cannot rule out that some of these were present. This is more so in an elderly population that frequently has comorbid conditions with poly-pharmacotherapy and may not recall these medications some of which may impact on the tests undertaken. In this Kenyan population where HIV disease has reached epidemic proportions we cannot rule out that some patients may have had preclinical disease. Onchwari (145) reported a prevalence of autonomic neuropathy of 100% amongst AIDS patients at KNH. This is probably much less frequent in the subclinical phase of HIV infection (146) and hence would have contributed little if at all as a confounder in these study patients.

Lipid abnormalities were also significantly associated with peripheral neuropathy. While there is a role of lipid mediated damage to the vasa nervorum via lipid peroxides, another important consideration in patients with peripheral neuropathy is concomitant peripheral vascular disease of which dyslipidemia is well known risk factor. In the face of neuropathy the addition of macrovascular disease would greatly increase the incidence of diabetic foot and associated amputations. Onyango (15) noted that there is a high rate of diabetic-related lower limb amputations at KNH of 30%.

Considering the special handicaps that our patients may have such as access to health care, emphasis must again go back to primary and secondary prevention.

No association was found between glycaemic control, smoking and hypertension and the studied complications. Glucose homeostasis is now a confirmed primary risk factor and the absence of any association here was surprising. The duration of exposure to hyperglycaemia may then be of great necessity in the evolution of microvascular complications. A single elevated indice such as HbA1c, which gives an estimate of glycaemic levels in the preceding 4-8 weeks, such as undertaken in this study would not reflect the true long term glycaemic status. The periods of hyperglycaemia and the extent of this in these patients prior to and after their clinical diagnosis therefore remains unknown and may be a major determinant.

STUDY LIMITATIONS

The study population comprised only out patients who were referred for recruitment through the diabetic outpatient clinic. Some of these were lost to follow up during this recruitment procedure, as a result data on the patients who were not selected is limited.

The study excluded in-patients, who would probably have presented with acute or chronic complications as a primary presentation. Hence the study cannot be representative of the entire recently diagnosed type 2 diabetic population.

For the diagnosis of type 2 diabetes an operational definition was used. No clause was included for those patients on insulin to have had a prior period of treatment on OHA's. This consideration was made as most of the newly diagnosed diabetics coming from the wards would be on initial insulin control prior to conversion to oral hypoglycaemics. It is recognised that this may have led to the misdiagnosis of a few patients who may have been type1 of late onset. However considering the low prevalence of latent

autoimmune diabetes in adults this was not considered an important confounder.

Due to fiscal and temporal constraints simple screening methods were used to identify the prevalence of complications. Hence more specific tests such as fluorescein angiography, nerve conduction studies, quantitative and serial microalbuminuria, were not used. All the measures however used, while they may need confirmation for individual diagnosis, are those recommended for preliminary screening for microvascular complications and hence have good predictive values.

A cross-sectional study such as this was would not be adequately equipped to make any causal associations between the complications observed and the risk factors due to the very nature of the study design. This issue would best be addressed with case-cohort prospective studies.

CONCLUSION

Microvascular complications were present in 57% of the type 2 diabetics within 2 years of clinical diagnosis in this study. The prevalence of diabetic polyneuropathy was 28%, autonomic neuropathy 27%, albuminuria 26% and retinopathy 7%.

The recently diagnosed type 2 diabetics also had a high prevalence of associated risk factors. Glycaemic control was less than ideal in 71%, hypertension was present in 50%, none of whom were achieving target blood pressure control. Lipid abnormalities were present in over 80% of the patients. About 60% of the patients had some degree of obesity most of whom were female, and more than 70% of the male population had a history of smoking.

RECOMMENDATIONS

1. All type 2 diabetics should undergo comprehensive screening for microvascular complications, even when asymptomatic, at the time of diagnosis and periodically thereafter.
2. Greater efforts should be made in controlling glycaemia, hypertension, dyslipidemias and obesity in newly diagnosed diabetics.
3. Screening of high risk individuals for type 2 diabetes is warranted considering the high prevalence of complications at diagnosis.
4. There is a need for prospective studies to identify the actual role of these and other possible risk factors in the development and progression of microvascular complications within our environment.

APPENDIX (I)**CONSENT FORM**

I _____, consent to participate in the study on diabetic complications and risk factors. I do this with full understanding of the purposes of the study and the procedures it will entail which include a clinical examination, ECG monitoring, blood tests for glucose, HbA1c, creatinine, fasting lipid profile and urine for albumin levels which have been explained to me by Dr Mwendwa.

Signature of patient, _____

Signature of witness, _____

Date, _____.

APPENDIX (II)

The following drugs have been associated with polyneuropathy hence any patient found to be on treatment with the same will be excluded from the study :-

- Isoniazid - Metronidazole
- Hydralazine - Nitrofurantoin
- Amiodarone - Nucleoside analogues
- Dapsone - Disulfiram
- Phenytoin - High dose pyridoxine

Any patient who has already been diagnosed to have any of the following medical conditions which may be responsible for polyneuropathy will be excluded :-

- Chronic liver disease - Hypothyroidism
- HIV infection - Chronic obstructive lung disease
- Carcinoma - Acromegaly
- Lymphoma - Multiple myeloma
- Alcohol abuse

The following drugs and medical conditions may be associated with errors in the biochemical assays and will hence be excluded :-

- Cimetidine - Hemoglobinopathies
- Methotrexate - Hemolytic anaemias
- Lead poisoning - Hyperuricemia
- Febrile illness - Alcohol abuse

APPENDIX (III)**Stage Classification of diabetic retinopathy on fundoscopic examination.**

1. **Simple (background) diabetic retinopathy** : presence of dot and blot haemorrhages, soft and / or hard exudates.
2. **Pre-proliferative diabetic retinopathy** : characterised by the presence of large soft exudates larger than one disc diameter or small but multiple soft exudates, superficial retinal haemorrhages (flame like or striated), diffuse retinal edema and / or markedly dilated veins.
3. **Proliferative retinopathy** : presence of new vessels and venous reduplication seen as loop formation and string-of -beads like veins.

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APPENDIX (IV)**BIOCHEMICAL ANALYSIS**

Dipstick urinalysis were undertaken on a mid stream specimen of urine using the Combur 10 test strips (Boehringer Mannheim). This assessed the presence of ketones, leukocytes, protein, nitrite, glucose, and pH of urine.

Serum creatinine was assessed by the Jaffe method using a RA 100 machine.

Urine albumin was assayed using the Micral II test strips (Boehringer Mannheim) This is a gold labelled optically read immunoassay and gave a semiquantitative assessment as negative, ca.20mg/l, ca. 50mg/l, and ca.100mg/l.

HbA1c was assessed on a blood specimen of 2mls in EDTA using the calorimetric end point method. An Abbott kit was used.

Lipid profiles was assayed using the Chod Pap end calorimetric method and the RA 100 machine . The total cholesterol, triglycerides and HDL-C were assayed directly while the LDL-C was derived using Friedwalds formula (114):

$$\text{LDL-C} = (\text{total cholesterol} - \text{triglycerides}/2 - \text{HDL-C}) \text{ mmols/l}$$

APPENDIX (Va)**STUDY PROFORMA**

Registration No. : _____

Date of examination : _____

Date of Birth (month , year) : _____ , _____

Date of diagnosis of diabetes (month , year) : _____ , _____

SOCIO-DEMOGRAPHIC CHARACTERISTICS

1. Gender 1=male 2=female

2. Ethnic group : _____

3. Usual residence : _____

4. Usual occupation : _____

5. Level of formal education

1 = none

2 = primary school

3 = secondary school

4 = tertiary level

5 = adult education

PAST MEDICAL HISTORY

6. Have you ever been told by a healthworker that you have hypertension?

1=yes 2=no

If yes in what year? _____

7. Have you ever been told by a healthworker that you have kidney disease?

1=yes 2=no

If yes in what year? _____

8. Have you ever been told by a healthworker that you have diabetic eye disease?

1=yes 2=no

If yes in what year? _____

9. Have you ever had diabetic foot ulcers?

1=yes 2=no

If yes what year did the first foot ulcer occur? _____

10. Have you ever suffered from any other serious illnesses in the past ?

If so please specify :

FAMILY HISTORY

11. Did or do any of your relatives suffer from diabetes?

1=yes 2=no

12. If yes specify :

1 = parent 3 = sibling
2 = both parents 4 = other (_____)

13. Did or do any of your relatives suffer from hypertension?

1 = yes 2 = no

14. If yes specify:

1 = parent 3 = sibling
2 = both parents 4 = other (_____)

SMOKING HABITS

15. What is your current smoking status ?

1 = never been a smoker
2 = ex-smoker
3 = current smoker

16a. If ex smoker or current, when did you start (yr) ? _____

b. When did you stop smoking (yr)? _____

c. Approximately how many cigarettes did or do you smoke per day? _____

CURRENT MEDICATIONS

17. Are you currently on any of the following medications? 1=yes 2=no 3=don't know

Oral hypoglycaemic agents (specify drug and dose)

Insulin treatment (specify formulation and dose)

Blood pressure lowering drugs(specify drug and dose)

Drugs for any cardiac condition (specify drug and dose)

Oral contraceptives or oestrogens (specify drug and dose)

Cortisone or related steroids (specify drug and dose)

Blood lipid lowering drugs (specify drug and dose)

Any other drug taken regularly (at least once a day -specify drug and dose)

SYMPTOMS

Grade the presence of symptoms as : 1=yes 2= no 3=don't know

18. Sensation : have you frequently in the last six months :

- a. Had any numbness in the feet?
- b. Had any prickly sensations in the feet?
- c. Had any deep or burning pains of the legs?

19. Autonomic : have you frequently in the last six months :

- a. Felt faint or dizzy on standing up?
- b. Had any trouble controlling your bladder?
- c. Had any trouble with nocturnal diarrhoea?

20. Impotence (males only) : have you in the last six months :

- a. Had any problems with sexual intercourse?
- b. Had any problems obtaining or sustaining an erection ?

PHYSICAL EXAMINATION

21. Height (cm) : _____

22. Weight (kg) : _____

23. Hip circumference (cm) : _____

24. Waist circumference (cm) : _____

25. Sitting blood pressures (mmHg)

1st reading _____

2nd reading _____

AUTONOMIC FUNCTION

26. Lying blood pressure after 5mins.(mmHg) :
 Systolic _____
 Diastolic _____
27. Standing blood pressure , after 1 min. standing (mmHg) :
 Systolic _____
 Diastolic _____

NEUROLOGICAL EXAMINATION

28. Are there any foot ulcers present ?
 1=yes 2= no
29. Are ankle reflexes : 1 = normal 2 = present+reinforcement 3 = absent
 -right ankle
 -left ankle
30. Vibration perception (medial malleolus) 1= normal 2 = abnormal
 -right foot
 -left foot
31. Nociceptive perception (pin-prick) 1 = normal 2 = abnormal
 -right leg
 -left leg
32. Temperature sensation 1 = normal 2 = abnormal
 -right leg
 -left leg

EYE EXAMINATION

33. Visual Acuity (1.0-0.1)
 1 = 6/6 - 6/18 2 = 6/24-6/60 RE LE
 3 = CF 5m- CF 3m 4 = < CF 3m 5 = blind eye (NPL)
34. Is pupillary dilatation 6mm or more? 1=yes 2=no RE LE
35. Is retinal detail easily visible? 1=yes 2=no RE LE
36. If retinal detail is not easily visible is it because of : RE LE
 1 = poor pupillary dilatation 6 = corneal opacity

- 2 = lens opacity
 3 = vitreous opacity /haemorrhage
 4 = glaucoma
 5 = combination of 2&3
 7 = eye absent
 8 = other

37. Are there any haemorrhages present? 1 = yes 2 = no RE LE
38. Are there any exudates ? 1=yes 2=no
 - Soft exudates: RE LE
 - Hard exudates: RE LE
39. Are there any new vessels ? 1=yes 2=no RE LE
40. Has there been any previous laser treatment?
 1=yes 2=no RE LE
41. Does the patient have diabetic retinopathy?
 1 = yes 2 = no RE LE
42. If yes, what type? RE LE
 1 = background 2 = preproliferative
 3 = proliferative 4 = retinopathy with complications

*RE = right eye , LE = left eye

LABORATORY DATA

Fasting blood sugar _____
 Microalbumin _____
 Glycated HbA1c. _____
 Total cholesterol. _____
 HDL-C. _____
 Triglycerides _____
 Calculated LDL-C. _____
 Serum creatinine. _____
 Calculated creatinine clearance _____

APPENDIX (Vb)**DATA ANALYSIS PROFORMA**

Registration no. _____

KNH IP no. _____

1a. Age (yrs) _____

1b. Age at diagnosis. _____

2. Duration of diabetes (mths) _____

3. Gender 1 = male 2 = female

4. Ethnic group _____

5. Usual residence _____

RISK FACTORS

6. What is the BMI? _____

a. Is the patient obese? 1 = yes 2 = no

b. What is the degree of obesity? 1 = mild 2 = moderate 3 = severe

7. W/H ratio _____

a. Does the patient have android obesity? 1 = yes 2 = no

8. Dyslipidemia

a. What is the total cholesterol? _____

b. What is the HDL-C? _____

c. What is the LDL-C? _____

d. What is the Triglyceride? _____

9. Hypertension.

a. What is the mean systolic BP? _____

b. What is the mean diastolic BP? _____

c. Does the patient have hypertension? 1 = yes 2 = no

d. If yes is this: 1 = newly diagnosed 2 = prior to diagnoses of DM
3 = at time or after diagnoses of DM

e. Family history of hypertension : 1 = present 2 = absent

f. If present is it with a first degree relative? 1 = yes 2 = no

10a. Family history of diabetes: 1 = present 2 = absent

b. If present is it with a first degree relative? 1 = yes 2 = no

11. Glycemic control.

a. What is the HbA1c? _____

b. What is the level of control? 1 = ideal 2 = good 3 = fair 4 = poor

c. What is the fasting blood sugar? _____

12. Cigarette Smoking

- a. Smoking: 1= current smoker 2 = ex smoker 3 = neither
 b. If either 1 or 2 how many pack yrs smoked ? _____

COMPLICATIONS

- 13a. Does the patient have symptoms of neuropathy? 1 = yes 2 = no
 b. If yes, are these 1 = sensory 2 = autonomic?
 c. What is the NDS? _____

- 14a. Does the patient have clinical DM polyneuropathy ? 1= yes 2= no
 b. Is this 1 = mild 2 = moderate 3 = severe?

15

- a. On Valsava test - What is the ratio of the highest HR during the rest period / lowest HR during the valsava manouvre _____
 b. Is this abnormal ? 1 = yes 2= no _____
 c. On the lying to standing test-What is the 30:15 RR ratio? _____
 d. Is this : 1= normal(>1.04) 2=borderline (1.01-1.03) 3= abnormal(<1.0)
 e. Does the patient have orthostatic hypotension? 1=yes 2=no
 f. Does the patient have autonomic neuropathy 1 =yes 2=no

16. Nephropathy

- a. Does the patient have microalbuminuria ? 1 = yes 2 = no
 b. If yes at what level? 1 = ca.20mg/l 2 = ca.50mg/l 3 = ca.100mg/l
 c. Does the patient have macroalbuminuria? 1 = yes 2 = no

- 17 a. What is the serum creatinine? _____
 b. What is the calculated creatinine clearance? _____

- 18a. Does the patient have diabetic retinopathy? 1 = yes 2 = no
 b. Is this, 1 = background 2 = preproliferative RE
 3 = proliferative 4 = complicated LE

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