STRATIFICATION OF PATIENTS WITH DIABETES INTO RISK CATEGORIES FOR FOOT ULCERATION

A study of ambulatory patients presenting at the diabetic outpatient clinic, Kenyatta National Hospital

INVESTIGATOR

Dr. Eric Mugambi Nturibi

SUPERVISORS

1) **Dr. C.F. Otieno**
2) **Dr. T.O. Kwasa**
3) **Dr. K. Acharya**
4) **Dr. G.O. Oyoo**

DECLARATION

THIS DISSERTATION WAS SUBMITTED FOR EXAMINATION WITH OUR APPROVAL AS SUPERVISORS:

SIGNED : .....

DR. C.F. OTIENO, SENIOR LECTURER, Department of Medicine and Clinical Therapeutics, University of Nairobi

SIGNED : .....

DR. T.O.O. KWASA, SENIOR LECTURER, Department of Medicine and Clinical Therapeutics, University of Nairobi

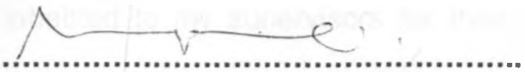
SIGNED : .....

DR. K. ACHARYA, LECTURER, Department of Medicine and Clinical Therapeutics, University of Nairobi

SIGNED : .....

DR. G.O. OYOO, LECTURER, Department of Medicine and Clinical Therapeutics, University of Nairobi

I certify that this dissertation is my own original work and has not been presented for a degree at any other university.



Dr. Eric Mugambi Nturibi, MB chB

ACKNOWLEDGEMENT

I thank God the Almighty for the good health and sustenance that he has benevolently provided till the present day.

I am indebted to my supervisors for their selfless assistance and guidance that pointed me in the right direction, all the way from protocol development to the submission of the complete dissertation.

I am grateful to the Director and staff of Kenyatta National Hospital for their approval of the study and in particular the staff of the diabetic clinic for their enormous assistance.

Finally I would like to convey my deepest gratitude to my family and close friends who stuck with me through those difficult moments.

Thank you all and God bless you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES & GRAPHS

LIST OF ABBREVIATIONS

AB (P) I	–	Ankle Brachial (Pressure) Index
AGES	–	Advanced Glycosylation End Products
BMI	–	Body Mass Index
BP	–	Blood Pressure
CVA	–	Cerebrovascular Accident
DBP	–	Diastolic Blood Pressure
DM	–	Diabetes Mellitus
DNA	–	Deoxyribonucleic Acid
HBA1C	–	Glycosylated Hemoglobin
IWGDF	–	International Working Group on the Diabetic Foot
LDL	–	Low Density Lipoprotein
LEA	–	Lower Extremity Amputation
NDS	–	Neurological Disability Score
OR	–	Odds Ratio
P	–	P Value (Significant When P<0.05)
PAD	–	Peripheral Arterial Disease
PKC	–	Protein Kinase C
PREV	–	Prevalence
QSART	–	Quantitative Sudomotor Axon Reflex Testing
RBS	–	Random Blood Sugar
REDOX	–	Reduction – Oxidation
ROS	–	Reactive Oxygen Species
SBP	–	Systolic Blood Pressure
SD	-	Standard Deviation

TCOT	-	Trans Cutaneous Oxygen Tension
TGF-B	–	Transforming Growth Factor B
VPT	–	Vibration Perception Threshold
Vs	-	Versus

ABSTRACT

BACKGROUND

Patients with Diabetes mellitus are at a higher risk of lower extremity complications as compared to their non-diabetic counterparts

OBJECTIVE

To stratify patients with Diabetes mellitus into risk categories for foot ulceration

DESIGN

Cross sectional descriptive study over five months

SETTING

Diabetic outpatient clinic, Kenyatta National Hospital

SUBJECTS

Ambulatory subjects with Diabetes mellitus without active foot lesions

RESULTS

A total of 218 patients with Diabetes were studied. 58% were females. The mean (SD) age of the study population was 58.6 (8.9) years and that of men was 59.6 (9) years. The mean (SD) duration of diabetes in males was 16.6 (4.4) years while that in females was 15.9 (4.3) years. The mean (SD) random blood sugar in males was higher than that in females, 13.13 (3.9) mmols/l versus 10.86 (2.9) mmols/l respectively. Males had a mean (SD) body mass index of 25.48 (3.5) kg/m^2 while females had a mean (SD) body mass index of 26.07 (2.9) kg/m^2. 64% of the participants were on oral hypoglycaemic agents, 15% were on insulin, 13% were on the combination of insulin and oral hypoglycaemic agents and 8% were on dietary control only. Males had a higher mean (SD) systolic blood pressure than females; 140.1 (16) mmhg versus 134.8 (20.4) mmhg. 23% of the study participants had a history of cigarette smoking, 96% of whom were males. 37% of the study subjects

had a history of alcohol intake, 80% of them being males. The prevalence of previous foot ulceration was 16% while that of previous amputation was 8%. Neuropathy was present in 42% of the study subjects and was significantly associated with age, male gender, duration of diabetes, random blood sugar, systolic blood pressure and the presence of foot deformity. Peripheral arterial disease was present in 12% and showed significant association with male gender. Foot deformities were observed in 46% of study subjects and were significantly associated with age, male gender, and presence of neuropathy. Only 39% of subjects had received foot care education, while only 12% had had their feet examined at the clinic at least once. 90% of the subjects had unsuitable shoes on shoe examination. Subsequently 57% were categorised into IWGDF group 0 – no neuropathy, 10% were placed in group 1 – neuropathy alone, 16% were put in group 2 – neuropathy plus either peripheral arterial disease or foot deformity and 17% were placed in risk group 3 – previous foot ulceration/amputation.

CONCLUSION

One third (33%) of diabetic patients were found to be at high risk for future foot ulceration (IWGDF groups 2 and 3) and thus there is need for setting up a special podiatric centre for referral of high risk patients. Long term prospective studies to determine outcomes in the various risk categories should be carried out locally.

1. INTRODUCTION

Diabetes Mellitus is a chronic, multi-systemic, and often debilitating disease caused by either a deficiency of insulin, or resistance to the action of insulin in peripheral tissues.

By the year 2010 it is estimated that 221 million people will be affected with diabetes globally. [1] It is also thought that the life time risk of developing a foot ulcer in a diabetic patient (type 1 or 2) is approximately 15%. [2]

Diabetic foot ulcers are responsible for frequent and prolonged admission periods[3]. Ramsey et al estimated the cost of foot ulcers in the diabetic patient to be almost $28000 for the two years after diagnosis of the ulcer. [4]

Clinical epidemiological studies suggest that foot ulcers precede ~85% of non traumatic lower extremity amputations (LEA) in individuals with diabetes[4]. Once amputation has been performed, the prognosis for the patient has often been poor, with 9% to 20% of diabetic individuals undergoing a new (ipsilateral) or second leg (contralateral) amputation during a second hospitalisation within 12 months of the first amputation. The five year mortality following amputation has been found to be between 39%-68% in various studies. [5-7]

In a 1999 study on Diabetic foot ulcer disease, Nyamu found the prevalence of diabetic foot ulcers at Kenyatta National Hospital to be 46/1000 diabetic patients, and that diabetic foot ulcers accounted for 12% of all diabetic admissions. Nyamu further alluded to the burden of morbidity attributable to diabetic foot ulcers with the

finding that the mean ulcer duration was 17 weeks and that 50% of patients presented with Wagner stage 2 ulcers whilst 25% had advanced Wagner stage 4 ulcers.[8]

It is thus evident that diabetic foot ulcers are a cause of potentially preventable morbidity, tragic sequelae, notably lower extremity amputation with its grave socio-economic consequences, and mortality.

Regrettably, several reports indicate that adequate examinations relevant to foot ulceration are often not performed in diabetic patients.[9-10] In his study, Nyamu found that only 23% of patients with diabetic foot ulcers had undergone a preceeding examination of the feet at the clinic prior to the onset of ulceration.[8]

This may be explained by the fact that although most clinicians are aware of the strong association between diabetes, foot wounds and low extremity amputations, they may lack a clear understanding of the most important criteria to include in a screening examination.[11]

Furthermore with the increasing number of patients with diabetes, it is impractical to provide in depth preventive foot services for every patient with the disease owing to constraints in both medical personnel and other podiatric resources.[12-13]

2. LITERATURE REVIEW

A wide body of literature suggests that ulceration and amputation rates are similar in both type 1 and type 2 Diabetes.[21,26,27,28] This implies that more factors other than age of onset and duration of diabetes are responsible for the causation of foot ulcers.

The principal risk factors for ulceration and lower extremity amputation among patients with diabetes include neuropathy, altered foot bio-mechanics, foot deformity, peripheral vascular disease, and previous ulcerations or lower extremity amputation. [14-20]

Non-foot related risk factors include male gender, long duration of diabetes, poor glycemic control, hypertension, dyslipidemia, and microvascular complications.[16, 21-24] Patients with diabetes who are on dialysis for end stage renal disease have 10 times more risk for lower extremity amputation than other patients with diabetes.[25] This either reflects the role of longer duration of disease hence presentation of patients with multiple organ pathologies, or indicates an important role for dialysis in the worsening of neuropathy± peripheral arterial disease.

Among the risk factors, Lehto and Litzelman et al concluded that the best predictors of future limb amputation are a history of previous ulcer, the presence of neuropathy, peripheral arterial disease and poor glycemic control.[29-30] However, in their evaluation of practical criteria for screening patients at high risk for diabetic foot ulceration, Lawrence et al reported that although vascular and renal disease

may result in delayed wound healing, they were not significant risk factors for the development of ulceration. [32]

A recent concept that has attracted much attention is the role of microvascular abnormalities in the causation of diabetic foot ulcers. Indeed microvascular abnormalities with regard to impaired tissue oxygenation have been found in individuals without detectable macrovascular disease. Impaired cutaneous oxygenation as measured by trans-cutaneous oxygen tension (TCOT) was reported to be the strongest risk factor for the development of diabetic foot ulceration [OR 57.87] in a case control study of patients with Diabetes from the Seattle veterans affairs medical centre. However, the authors noted that this measurement was impractical in the clinical setting. [31]

Prospective studies have verified the role of clinically defined foot deformity in the causation of foot ulcers. [15] By contributing to abnormal foot bio-mechanics, it is thought that high pressure areas are created on some areas which later develop ulceration. Claw foot deformity in particular, has been found in association with diabetic plantar ulcers.[12] Limited joint mobility is thought to contribute to ulceration in much the same fashion as foot deformity. However, Fernando et al demonstrated that limited joint mobility and in extension high foot pressures only cause ulceration in the susceptible neuropathic foot. [34]

That, high foot pressures, the common final pathway to both foot deformity and limited joint mobility, are positively associated with diabetic foot ulcer occurrence, was demonstrated by a prospective study of 135 clinic/emergency room patients in whom foot pressures were measured by an expensive and clinically impractical

device. the optical pedobaragragh. [33] Moreover, a multicentre prospective study investigating screening techniques to identify people at high risk for foot ulceration found that the best specificity for a single test in detecting those at risk for foot ulceration was offered by foot pressures, as compared to either the Neurological Disability Score or the Monofilament. [32]

The local data appears to correlate well with literature from around the world. In his study on diabetic foot ulcer disease at Kenyatta National Hospital, Nyamu found both genders to be equally afflicted with foot ulcers. This may indicate that male may not be a substantial risk factor for foot ulceration in our setting. Foot deformities were commoner in patients with advanced neuropathy ($p<0.05$), hammer toe deformity being noted in 39%. The mean duration of diabetes in the study subjects was 7.98± 6.86 years. Clinically detectable neuropathy was present in more than three quarters (78%) of study subjects. Macrovascular disease as detectable clinically was present in half (52%) of the study participants with 17% lacking palpable lower extremity peripheral pulses. Good glycemic control as defined by HbA1c <7% was present in less than a fifth (18%) of the study participants. Two thirds (67%) of patients with diabetes enrolled in the study were found to be either known hypertensives or to have a blood pressure greater than 140/90 mmHg. [8]
Risk categorization has been reported to play a major role in the identification and subsequently efficient management of persons with diabetes as clinicians who are aware of high risk foot conditions are more likely to refer at-risk patients for preventive services.

In their 32 month evaluation of a risk categorization scheme for lower-extremity problems that incorporates the Semmes-Weinstein 5.07 monofilament and a simple

exam to stratify patients who were followed in a primary-care setting into risk groups for plantar ulceration and lower-extremity amputation, Najarian et al observed that incident rates of ulcers and lower extremity amputations correlated positively with increasing risk category ($p<0.00001$) with all amputations occurring in the higher risk groups. [37]

Moreover, screening with risk stratification and targeting interventions for high risk patients has been associated with 25%-60% reductions in lower extremity amputation rates in population based studies. [35-38]

The consensus classification of the International Working Group on the Diabetic Foot differs from earlier classification systems because clinicians and researchers from various parts of the world and from various fields of work were involved in its conceptualisation. The goal of the consensus classification system was to achieve global consistency in adequate diagnostic, preventive and therapeutic strategies, through the use of simple diagnostic tools. In their study, Armstrong et al set out to compare the sensitivities and specificities of 3 sensory perception testing instruments: They found that Vibration Perception Threshold (VPT) testing and lack of perception at 4 or more sites using the monofilament had a significantly higher specificity than the neuropathy score. When modalities were combined, particularly the monofilament plus either VPT, or neuropathy score. there was a substantial increase of specificity with little or no diminution in sensitivity.[39] However, the consensus criteria does not specify which default methods should be used to measure neuropathy and angiopathy. The choice of instrument is therefore largely dictated by local availability and cost effectiveness.

In their 3 year prospective study to determine the effectiveness of the International Working Group Criteria, Edgar et al found the Diabetic foot risk classification system of the International Working Group on the Diabetic Foot (IWGDF), to be effective as a tool for predicting ulceration and subsequent amputation. A total of 225 patients were stratified into 4 risk categories namely: Group 0 – No neuropathy; Group 1 – Neuropathy but neither Deformity nor Peripheral Arterial Disease; Group 2 – Neuropathy and either deformity or peripheral arterial disease; Group 3 – previous foot ulceration/ Lower Extremity Amputation. Subsequently, during 3 years of follow up, ulceration developed in 5.1, 14.3, 18.8 and 55.8% of the patients in the three groups respectively ($p<0.001$). All amputations were found in groups 2 and 3(3.1 and 20.9%, $p<0.001$) [40]

2.1 ROLE OF NEUROPATHY

It is estimated that Neuropathy is present in over 80 percent of diabetic patients with foot ulcers. Diabetic Poly-neuropathy is primarily a symmetrical sensory neuropathy, initially affecting the distal lower extremities. With disease progression, sensory loss ascends and, when reaching approximately mid-calf, appears in the hands. This gradual evolution causes the typical "stocking-glove" sensory loss. This pattern reflects preferential damage according to axon length; the longest axons are affected first. Motor involvement with frank weakness occurs in the same pattern, but only later and in more severe cases.

The earliest signs of diabetic neuropathy probably reflect the gradual loss of integrity of both large myelinated and small myelinated and unmyelinated nerve fibers: Loss of vibratory sensation and altered proprioception reflect large-fiber loss. Impairment of pain, light touch and temperature is secondary to loss of small fibers. Decreased or absent ankle reflexes occur early in the disease, while more widespread loss of reflexes and motor weakness are late findings.

Neuropathy promotes ulcer formation by decreasing pain sensation and perception of pressure, by causing muscle imbalance that can lead to anatomic deformities, and by impairing the microcirculation and the integrity of the skin. Distal motor axonal loss results in atrophy of intrinsic foot muscles and an imbalance between strength in toe extensors and flexors. This ultimately leads to chronic metatarsal-phalangeal flexion (claw-toe deformity) which shifts weight to the metatarsal heads. This weight shift results in formation of calluses that can fissure, become infected and ulcerate.

Healing may be delayed or difficult to achieve, particularly if infection penetrates to deep tissues and bone and/or there is diminished local blood flow. [41] In addition, the loss of sensation to a joint may result in a chronic, progressive, and destructive arthropathy.[r] Diabetes is now the most common cause of neuropathic (Charcot) arthropathy in the Western world.

In 1988, a group of Diabetologists and Neurologists proposed the San Antonio Consensus criteria for the diagnosis of Diabetic Polyneuropathy. Before that, the diagnosis was largely based on subjective findings on the clinical examination. *APPENDIX 3* San Antonio Consensus Criteria

Though the San Antonio criteria are thorough and well reproducible, they are not suited for routine clinical use. This need for simplified criteria led to the development of simple screening tests such as the Neurological Disability Score. UK Screening Test, and the Michigan University Screening Test. [42-44]

Peripheral autonomic nerve dysfunction may be manifest as changes in the texture of the skin, edema, venous prominence, callus formation, loss of nails, and sweating abnormalities of the feet.

The association between peripheral autonomic denervation and the resultant effects on the peripheral vasculature was recognized as early as 1941, when it was noted that diabetic patients with neuropathy had similar peripheral vasomotor reflexes as non-diabetic patients after sympathectomy.[45] Moreover, diabetic patients with neuropathic foot ulceration have greater impairment of heart rate variation than

patients with neuropathy with no foot ulcers thus adding support to the role of autonomic dysfunction in the pathophysiology of diabetic ulcers.[46]

Peripheral autonomic neuropathy may be a prerequisite for the development of foot ulceration.[47] Though human studies are yet to confirm it, animal studies have suggested that autonomic neuropathy alone can precipitate plantar ulceration.[48]

Peripheral autonomic neuropathy is thought to contribute to several other symptoms such as aching, pulsation, tightness, cramping, dry skin, pruritus and the development of Charcot arthropathy. In this condition fractures can occur spontaneously and are followed by progressive bone disorganisation with an increased risk of secondary ulceration.

Sweating is diminished or absent; as a result, the skin of the feet remains dry and has a tendency to become scaly and cracked, thereby allowing infection to penetrate below the skin. Lack of autonomic tone in the capillary circulation causes shunting of blood from arteries directly into veins, bypassing the tissues that need nutrition. This results in a foot that feels warm and has distended veins and bounding pulses.

Despite these apparent signs of adequate perfusion, the foot is vulnerable to local "microvascular" gangrene, will heal very poorly and slowly, and will be less able to resist infection.

High peripheral blood flow can cause weakening of the bones in the foot, thereby predisposing to fractures.

Peripheral autonomic neuropathy can be detected by direct microelectrode recording of postganglionic C fibers. This specialized technique is not yet available for routine diagnosis.[49]

Galvanic skin responses, on the other hand, are available and offer a simple measure of the presence of sympathetic innervation in the hands and feet. This technique, however, does not reliably detect more subtle degrees of sympathetic denervation.[50]

More recently, quantitative sudomotor axon reflex testing (QSART) has become widely utilized for the detection of early peripheral sympathetic denervation.

Measurement of vascular responses in the foot is an alternative method to detect peripheral sympathetic denervation. Thermal-induced vasoconstriction (rather than the normal vasodilatation) reflects vascular denervation and is present only in those patients with both autonomic and somatic neuropathy. Impairment of local axon reflex dilatation is thought to reflect depletion of local vasoactive neuropeptides.[51]

The role of alteration in the skin blood flow regulation in the development of foot ulceration is being evaluated. Although peripheral autonomic neuropathy correlates poorly with motor nerve dysfunction, motor nerve conduction velocity is decreased in patients with other evidence of small fiber damage, particularly loss of thermal sensation.

2.2 ATHEROSCLEROPATHY IN DIABETES

Peripheral arterial disease is one of the manifestations of atherosclerosis. Both type I and II diabetes are powerful and independent risk factors for coronary arterial disease, stroke and peripheral arterial disease.[52-54]

Hyperglycemia induces a number of alterations at the cellular level of vascular tissue that potentially accelerate the atherosclerotic process.[55]

Animal and human studies have elucidated three major mechanisms that encompass most of the pathological alterations observed in the diabetic vasculature.

Non-enzymatic glycosylation of proteins and lipids interferes with their normal function by disrupting molecular conformation, altering enzymatic activity, reducing degradative capacity, and interfering with receptor recognition. In addition, glycosylated proteins interact with a specific receptor present on all cells relevant to the atherosclerotic process, including monocyte-derived macrophages, endothelial cells, and smooth muscle cells. The interaction of glycosylated proteins with their receptor results in the induction of oxidative stress and pro-inflammatory responses. Interactions between glucose and reactive amino groups of circulating or vessel wall proteins (Schiff bases), results in the formation of the more stable Amadori-type early glycosylation products. Equilibrium levels of Schiff base and Amadori products (the best known of which is hemoglobin A1C) are reached in hours and weeks, respectively.[56]

Some of the early glycosylation products on long-lived proteins (e.g. vessel wall collagen) continue to undergo complex series of chemical rearrangement to form advanced glycosylation end products (AGEs). Once formed, AGE-protein adducts are stable and virtually irreversible. Although AGEs comprise a large number of chemical structures, carboxy-methyllysine-protein adducts are the predominant AGEs present in vivo.[57 58]

AGEs accumulate continuously on long-lived vessel wall proteins with aging and at an accelerated rate in diabetes.[59] The degree of non-enzymatic glycation is determined mainly by the glucose concentration and time of exposure. However, another critical factor to the formation of AGEs is the tissue microenvironment redox potential. Thus, situations in which the local redox potential has been shifted to favor oxidant stress result in a substantial increase in the formation of AGEs.[60-63]

AGEs promote atherosclerosis through either receptor mediated or non receptor mediated mechanisms:

Receptor Mediated Mechanisms

- Promoting inflammation
- Secretion of cytokines such as TNF-α, IL-1
- Chemotactic stimulus for monocyte-macrophages
- Induction of cellular proliferation
- Stimulation of PDGF and IGF-I secretion from Monocytes and possibly Smooth Muscle Cells.
- Endothelial dysfunction

- Increased permeability of Endothelial Cell monolayers
- Increased pro-coagulant activity
- Increased expression of adhesion molecules
- Increased intracellular oxidative stress

Non-Receptor Mediated Mechanisms:

- Collagen cross linking
- Enhanced synthesis of extra-cellular matrix components
- Trapping of LDL in the subendothelium
- Glycosylation of subendothelial matrix which quenches nitric oxide
- Functional alterations of regulatory proteins
- βFGF glycosylation reducing its heparin binding capacity and its mitogenic activity on endothelial cells
- Inactivation of the complement regulatory protein CD59
- Lipoprotein modifications
- Glycosylation of LDL
- Reduced LDL recognition by cellular LDL receptors
- Increased susceptibility of LDL to oxidative modification

Hyperglycemia induced oxidative stress promotes both the formation of advanced glycosylation end products and PKC activation.

Protein Kinase C activation increases the expression of transforming growth factor β (TGF-β), which is one of the most important growth factor regulating extra-cellular

matrix production by activating gene expression of proteoglycans, and collagen and decreasing the synthesis of proteolytic enzymes that degrade matrix proteins.

Increased expression of TGF-β is thought to lead to thickening of capillary basement membrane – one of the early structural abnormalities observed in almost all tissues in diabetes.[64-66]

Oxidative stress implies a loss of redox homeostasis with an excess of ROS by the singular process of oxidation. Both redox and oxidative stress may be associated with an impairment of antioxidant defensive capacity as well as an overproduction of ROS.

It has been known for some time that ROS are detrimental and toxic to cells and tissues as a result of injury to lipids, nucleic acids, and proteins. Mechanisms of damage include:

1) Lipid peroxidation of membranes (loss of membrane function and increased permeability) and generation of lipid auto-peroxidation reactions

2) DNA damage leading to mutation and death

3) Cross linking or vulcanization of sulf-hydryl rich proteins (leading to stiff aged proteins specifically collagen of the extra-cellular matrix).[70]

Hyperglycemia can increase oxidative stress through several pathways:

A major mechanism appears to be the hyperglycemia-induced intracellular reactive oxygen species (ROS), produced by the proton electromechanical gradient generated by the mitochondrial electron transport chain and resulting in increased production of superoxide.[67]

A second mechanism involves the transition metal catalyzed auto-oxidation of free glucose, as described in cell-free systems. Through this mechanism, glucose itself initiates auto-oxidative reactions and free radical production yielding superoxide anion (O2 -) and hydrogen peroxide (H_2O_2)[68]

The third mechanism involves the transition metal-catalyzed auto-oxidation of protein-bound Amadori products, which yields superoxide and hydroxyl radicals and highly reactive di-carbonyl compounds.[69]

There is also evidence that hyperglycemia may compromise natural antioxidant defences. Under normal circumstances, free radicals are rapidly eliminated by antioxidants such as reduced glutathione, vitamin C, and vitamin E. Reduced glutathione content,[70,71] as well as reduced vitamin E[72,73], have been reported in diabetic patients. Plasma and tissue levels of vitamin C[74,75] are 40–50% lower in diabetic patients compared with non-diabetic subjects.

2.3 ROLE OF FOOT DEFORMITY

Foot deformities, equinus, limited joint mobility, and previous foot amputation are thought to contribute to foot ulceration because they are more likely to create areas exposed to constant pressure and because they cause bio-mechanical abnormalities that are related to increased foot pressures. In addition there is evidence that after a partial foot amputation, patients with diabetes are at a greater risk of these types of foot deformities and subsequent foot ulcers developing.[76]

3. STUDY JUSTIFICATION

Diabetic foot ulcers can be prevented through identification of modifiable risk factors and consequent stratification of persons with diabetes into risk categories.

Allocation of appropriate intervention modalities in high risk diabetic patients has been shown to decrease the rate of re-ulceration by up to 60% and lower extremity amputation by up to 85%.[13] By applying a well validated risk stratification system to patients with diabetes, it will be possible to identify the proportion of patients in each risk category.

In a health care system grappling with competing priorities, the importance of identifying high risk patients cannot be overemphasised. This will enable allocation of resources and implementation of aggressive medical care in populations in which they will have the greatest impact.

In this era of expensive gadgetry, it is gratifying to identify a situation where a careful patient history, focussed examination and simple tools will provide key medical information.

The study will help augment primary prevention campaigns by identifying and targeting the groups of patients who are likely to derive the most benefit from such campaigns.

This information will help shape health policy, and it is hoped this will translate into a reduction of morbidity and mortality attributable to foot ulceration in persons with diabetes.

For instance, if 75% of persons with diabetes seen at Kenyatta National Hospital were in the highest risk category, policy makers would shift more emphasis toward protecting the high risk foot from injury through patient education, protective footwear, and routine podiatric care whereas if the majority of patients were in the low risk category, the major objective would be prevention of neuropathy and peripheral vascular disease through interventions that focus on glycemic control, lipid regulation, blood pressure management and smoking cessation.

4. STUDY OBJECTIVES

4.1 BROAD OBJECTIVE

- To stratify persons with diabetes into risk categories that will predict the likelihood of future foot ulceration

4.2 SPECIFIC OBJECTIVES

1) To determine the prevalence of clinically detectable neuropathy among ambulatory persons with diabetes seen at the outpatient clinic

2) To determine the prevalence of peripheral arterial disease among persons with diabetes attending the outpatient clinic

3) To establish the prevalence and describe the types of foot deformities among persons with diabetes attending the outpatient clinic

4) To establish the level of knowledge on foot care among persons with diabetes attending the outpatient clinic

5. METHODOLOGY

5.1 Study design

Cross Sectional, Descriptive

5.2 Study population/ site

Ambulatory Diabetic patients seen at the Diabetic Outpatient Clinic, KNH

5.3 Study period

September 2006 – February 2007

5.4 Inclusion criteria

- All ambulatory diabetic patients over 13yrs old seen at the diabetic outpatient clinic

5.5 Exclusion criteria

- Any patient with active foot ulcer
- Any patient with a history of bilateral leg amputation (since they are at no further risk of future foot ulceration)
- Any patient failing to give consent to participate

5.6 Sample selection and size

Since the International Working Group on Diabetic Foot stratification criteria considers presence of Neuropathy as a prerequisite for risk of ulceration, the prevalence of Neuropathy among diabetic patients at KNH was inferred from a recent study at KNH by Mwenda et al. Their study revealed Neuropathy in 28% of study subjects.[77]

This figure is also similar to that observed in the multicentre study of prevalence of diabetic peripheral neuropathy in the United Kingdom Hospital clinic population by Young MJ.[78]

The sample size required will be:

$$n = \frac{z^2 \, p \, (q)}{d^2}$$

Where: n = required sample size

z = z score of required confidence interval (95%)

p= likely value of parameter

q=1-p

d=Relative permissive error in this case (0.05)

$$n = \frac{1.645^2 \, (0.72) \, (0.28)}{0.05^2} = 218$$

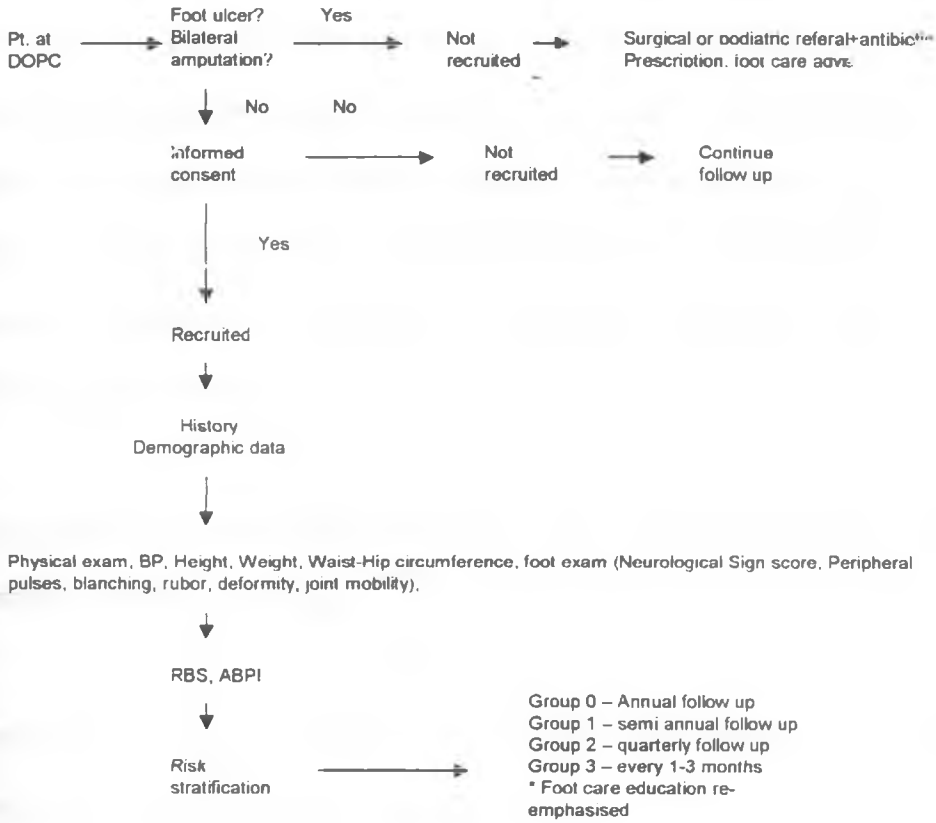
Therefore n = 218 patients

The sample size selection was carried out through *systematic sampling* of eligible subjects.

5.7 Screening and recruitment

Figure 5.71

Flow of patients



Recruitment procedure

Depending on the number of patients seen at the diabetic clinic on a particular day, on average 20-30, concealed numbers (1-30) were offered to the patients who had come for the clinic.

Every third patient (i.e. 3, 6, 9, 12, 15, 18, 21, 24, 27, and 30) was offered to participate till the required sample size was attained. Inclusion/ exclusion criteria were then applied. On average, 6 patients per day were recruited.

For each recruited patient, the demographic history was taken and where necessary the patient's record book was consulted. Likewise, where available, data regarding the patient's glycemic control, lipid control, urine micro-albumin testing, retinopathy and current treatment regimes was inferred from the patient's record book. A simple questionnaire was then administered to the patient to inquire about previous ulcerations, amputations, symptoms of peripheral vascular disease, neurological symptoms, and basic knowledge on foot care.

A physical examination was then carried out. The general condition was assessed as good, fair or sick-looking.

Height was measured against a vertical scale to the nearest half centimetre, with the patient standing erect and without shoes.

Weight was measured to the nearest half kilogram with the patient in light clothing, without shoes and using a standard weighing chair in the clinic.
BMI was calculated as the weight in kilograms divided by the square of the height in metres and the degree of obesity classified as follows: [79]

Table 5.71

BMI (KG/M^2)	Degree of Obesity
- <25	Non obese
- 25-29.9	Overweight
- 30-39.9	Obese
- >40	Very obese

Blood pressure was measured with the patient in the supine position after a rest period of 5 minutes. The arm was comfortably supported at about heart level. A standard adult cuff (bladder length 30-35cm and width of 12cm) was applied to the arm. The brachial pulse was identified and the cuff inflated until it was no longer palpable, and then to a further 10mmHg beyond this point. A stethoscope was applied to the brachial artery. The cuff was then deflated slowly until regular heart sounds could just be heard. This was recorded to the nearest 2mmhg as the systolic pressure. The cuff was then deflated further until the sounds disappeared. The point at which the sounds just disappeared was recorded as the diastolic pressure. The blood pressure was recorded as the mean of two readings taken at five minute intervals. Hypertension was defined as per the 2003 European Society of Hypertension criteria:

Table 5.72

CATEGORY	SYSTOLIC BP (MMHG)	DIASTOLIC BP (MMHG)
Optimal	<120	<80
Normal	<130	<85
High Normal	130-139	85-89

Hypertension		
- Stage 1	140-159	90-99
- Stage 2	160-179	100-109
- Stage 3	≥ 180	≥ 110
Isolated Systolic Hypertension	≥ 140	<90

The feet were then examined as follows:

Inspection

The patient was observed while walking from one end of the examination room to the other and any abnormality of gait due to pain or deformity recorded

With the patient standing, the feet and the ankles were inspected for hind foot deformities (valgus/varus), pes planus, pes cavus, toe deformities(hallux valgus, claw toe, mallet toe, hammer toe) and prominent metatarsal heads.
With the patient supine, the condition of the nails and skin was noted as was the presence of swellings. The presence of callosities was recorded. The presence of high risk lesions such as fungal infections was also recorded.

Palpation

The hind-foot, mid-foot and fore-foot were palpated to accurately localise any tenderness, swelling or deformity.

The passive range of movement of the ankle joint (normal dorsiflexion 10^0 plantar flexion 30^0) was then noted and graded as normal or restricted.

The range of mobility of the sub-talar and mid-tarsal joints was then assessed by observing the active and passive range of inversion and eversion of the heel (normal composite range of movement 30^0 - inversion, 20^0 - eversion). This was recorded as normal, or restricted.

The individual toes were assessed to identify any restriction of movement, and this was recorded as normal or restricted.

The posterior tibial pulse and the dorsalis pedis were then assessed and graded as normal, reduced or absent. With the patient in the supine position the posterior tibial pulse was palpated 2 cm below and 2cm behind the medial maleolus. The dorsalis pedis was palpated in the middle of the dorsum of the foot just lateral to the tendon of extensor hallucis longus.

The presence of blanching on elevation, rubor on dependance and delayed capillary refill was then assessed. The examined limb was elevated for 30 seconds and blanching assessed through comparison with the other foot. The patient was then asked to sit up and the limb lowered to a dependant position. The time of appearance of reactive hyperaemia was noted and recorded as prolonged if longer than ten seconds. Slight pressure was then applied on the nail beds and pulps of the toes until pallor was seen, then released. The refill time (disappearance of pallor) was noted and considered prolonged if longer than two seconds.

Neurological Exam

For each foot the Achilles tendon reflex was tested using a standard patella hammer and a standard technique and scored as:

- Absent (2 points for each foot)
- Present with reinforcement (1 point for each foot)
- Present without reinforcement (0 points)

Vibration sense was tested using a 128HZ tuning fork over the lateral and medial maleoli and the perception graded as:

- Normal (0 points)
- Absent or reduced (1 point for each foot)

Pressure sensation was then tested. A 5.07 (10-g) monofilament was placed at a right angle to the skin on the plantar surface of the foot; pressure was then increased until the filament buckled, indicating that a known amount of pressure had been applied. The patient was asked if he or she felt the pressure induced by the monofilament. This was done at six points on the foot and recorded as normal or abnormal.

Pinprick sensation was assessed on the feet using a disposable pin and graded as:

- Normal – (0 points)
- Absent or reduced – (1 point for each foot)

Temperature sensation was assessed using a cold tuning fork after immersion in cold water, on the dorsum of the feet and the sensation graded as:

- Normal – 0 points
- Reduced (1 point for each foot)

The Neurological Disability Score was then determined:

0 to 2 — no neuropathy

3 to 5 — mild neuropathy

6 to 8 — moderate

9 to 10 — severe

The score was doubled in patients with previous unilateral foot amputation.

A hand held doppler probe was then held over the three pedal arteries (posterior tibial, dorsalis pedis, perforating peroneal) in turn while a blood pressure cuff wrapped around the ankle was inflated. The pressure at which the doppler signal disappears was recorded as the systolic pressure in the artery as it passed under the cuff. The ratio of the highest pedal pressure to the highest brachial artery pressure determined by the doppler method was recorded as the Ankle Brachial Pressure Index and interpreted as follows:

>1.30	-	Non compressible vessel
0.91-1.30	-	Normal
0.41-0.90	-	Mild-Moderate Peripheral arterial disease
0.00-0.40	-	Severe Peripheral arterial disease

A random blood sugar level was then determined by pin prick using a standard glucometer.

RISK STRATIFICATION

Patients were then placed into one of the following risk categories:

Table 5.73

GROUP	CATEGORY
0	No neuropathy
1	Neuropathy present Deformity absent PAD absent
2	Neuropathy present, plus either Deformity or PAD or both
3	Previous ulcer Previous amputation

6. DATA ANALYSIS

Data was collected into a specially designed pro-forma and coded before input into a statistical computer package (SPSS version 12)

Descriptive statistics were applied to continuous and categorical data from which measures of central tendency and proportions were derived.

Inferential statistics were applied to determine associations between age, gender, blood sugar, measures of obesity and Neuropathy / peripheral arterial disease/ foot deformity.

Where comparisons were made a p – value of less than 0.05 was taken to be significant.

7. ETHICAL CONSIDERATIONS

The study was approved by the Department of Internal Medicine, University of Nairobi, and the Kenyatta National Hospital Ethical Review Board

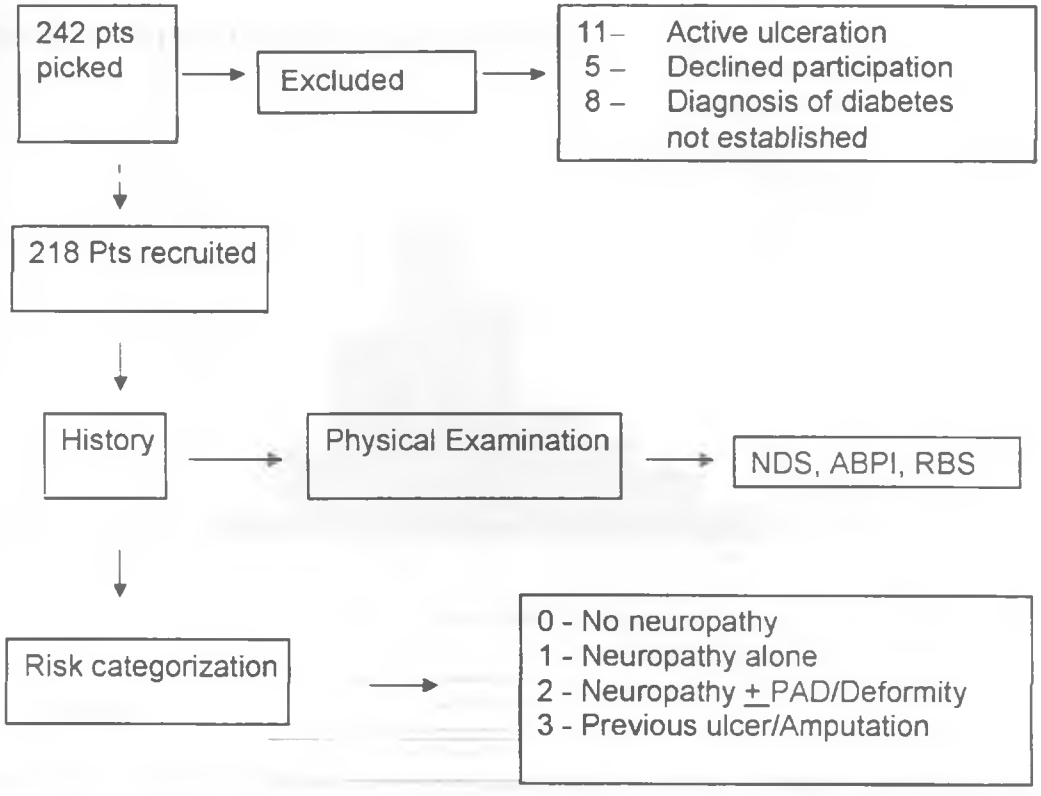
The objectives and purposes of the study were clearly explained to eligible participants in a language suitable to them prior to inclusion into the study APPENDIX 2

Appropriate interventions were offered to the study participants as indicated by clinical and laboratory parameters. At the end of each interview and clinic examination session, diabetic education specifically targeting foot care was re-emphasised.

The full cost of the study was met by the Principal Investigator.

8. RESULTS

FLOWCHART OF STUDY METHODS



For all study subjects foot care advice was given
NDS - Neurological Disability Score, ABPI - Ankle Brachial Pressure Index, RBS - Random Blood Sugar

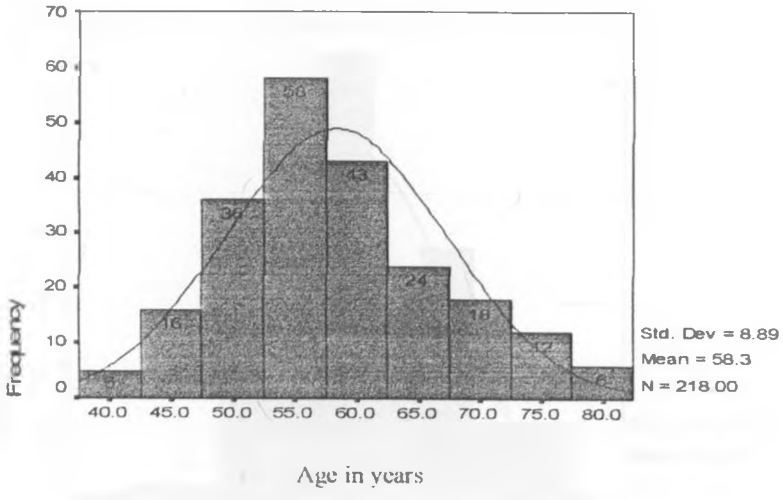
Although prospective subjects with bilateral leg amputation were excluded, since they would be at no further risk for new foot ulceration, no such subject was seen during the screening of subjects for participation into the study. The subjects excluded were as shown above: 11 had active ulceration, 5 declined participation and in 8, the diagnosis of diabetes had not been established.

8.1 BASELINE CHARACTERISTICS

8.1.1 Age

The mean age of the study participants was 58.3 ±8.89 years old. Males were older with a mean age of 59.6±8.95 years old as compared to a mean age of 57.5± 8.77 years old in the female participants.

Graph 8.1.1 Age distribution of study subjects

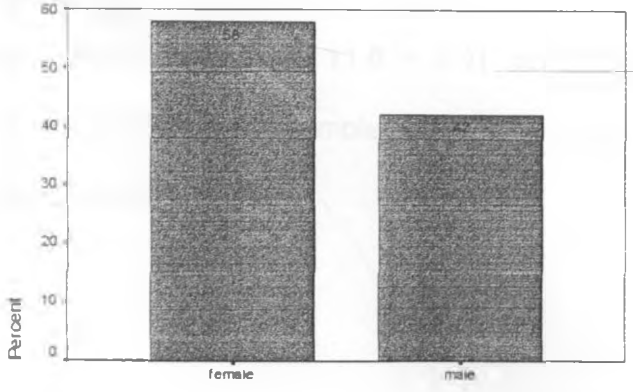


Age in years

8.1.2 Gender

Males accounted for 42% of the study participants while females comprised 58% The Male: Female ratio was 1:1.38.

Graph 8.1.2 Gender distribution of study subjects

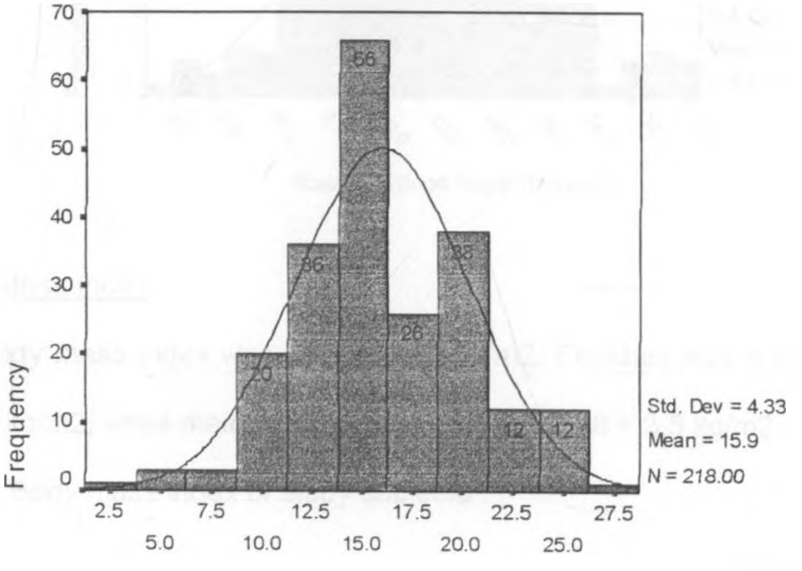


Gender

8.1.3 Duration of diabetes

The mean duration of diabetes in the study group was 15.9± 4.33 years. Females had a shorter mean duration of 15.5± 4.23 years as compared to males who had a mean duration of 16.6+ 4.4 years.

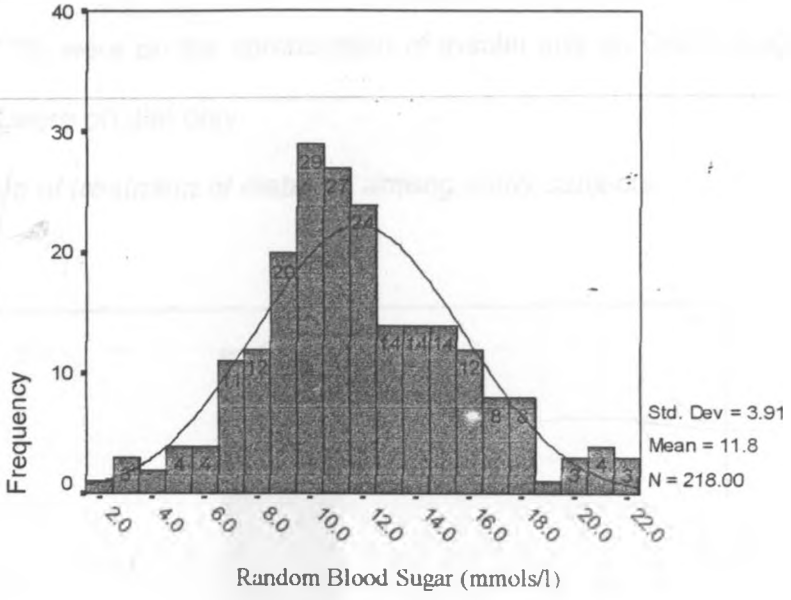
Graph 8.1.3 Duration of diabetes among study subjects



8.1.4 Random blood sugar

The mean Random Blood Sugar was 11.8 + 3.91 mmols/l. In males the mean random blood sugar was 13.126 + 4.7mmols/l while in females it was 10.864 +2.87. This is demonstrated graphically below:

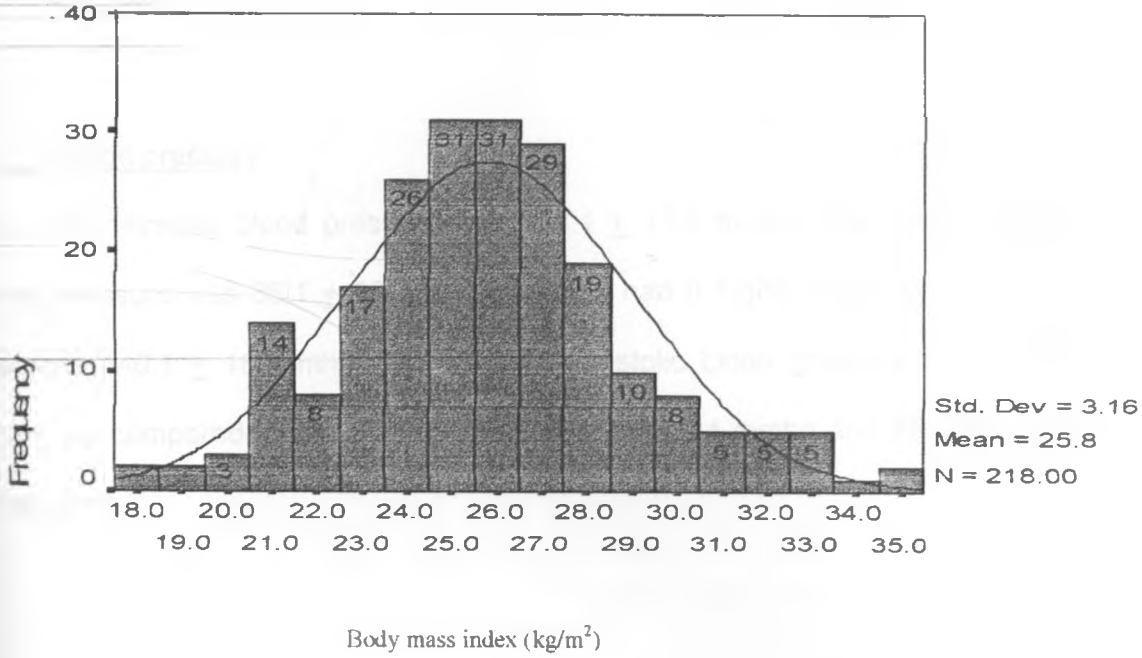
Graph 8.1.4 Random blood sugar of study subjects



8.1.5 Body Mass Index

The mean body mass index was 25.8 + 3.16 kg/m2. Females had a mean BMI of 26.07 + 2.87 kg/m2, while males had a mean BMI of 25.48 + 3.5 kg/m2.

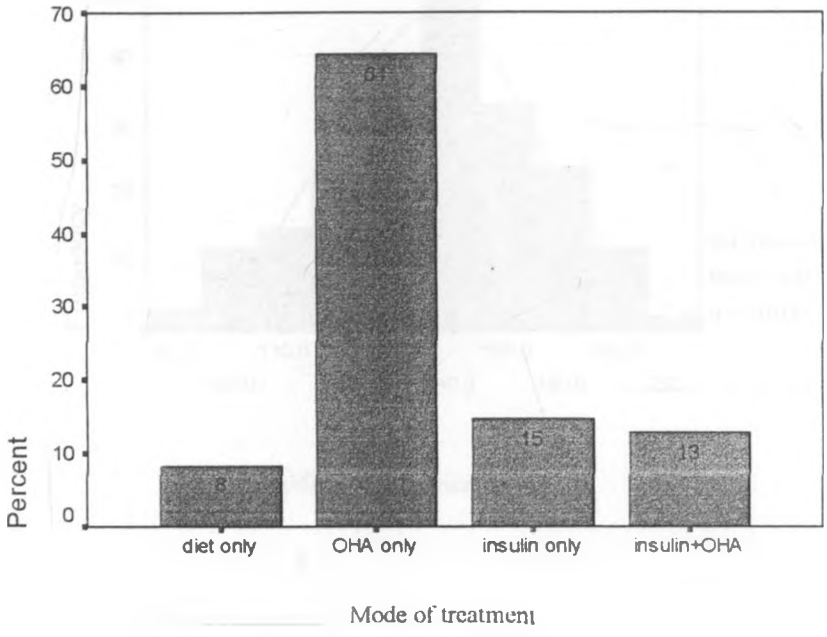
Graph 8.1.5 Body mass index of study subjects



8.1.6 Mode of treatment

64% of the study participants were on Oral Hypoglycemic Agent therapy. 15% were on insulin while 13% were on the combination of Insulin and an Oral hypoglycemic agent (OHA). 8% were on diet only.

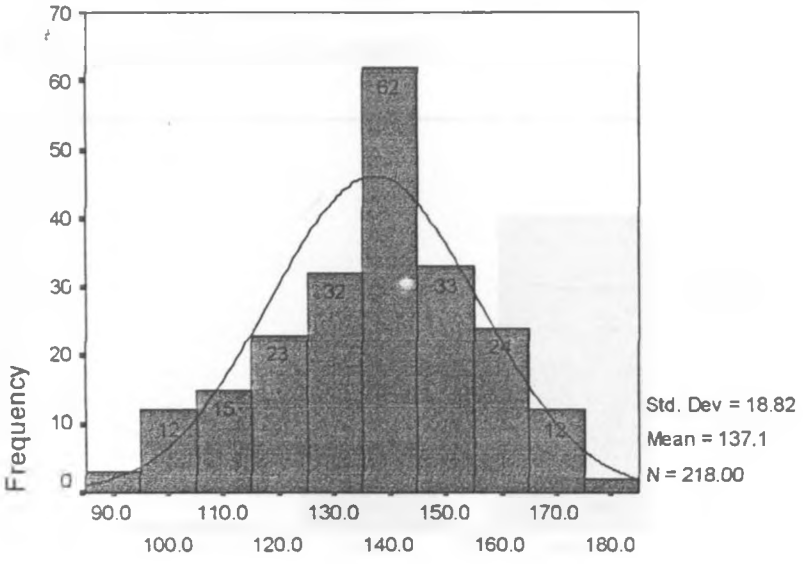
Graph 8.1.6 Mode of treatment of diabetes among study subjects



8.1.7 Blood pressure

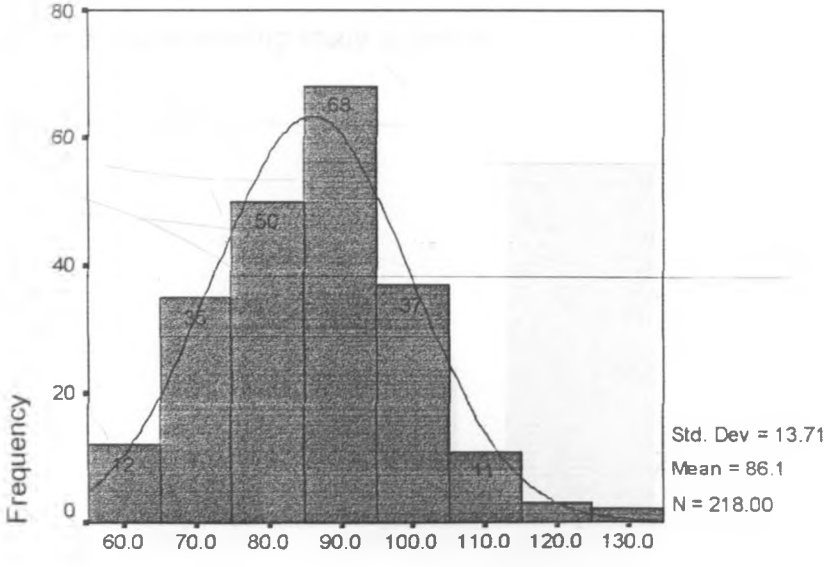
The mean systolic blood pressure was 137.1 ± 18.8 mmhg. The mean diastolic blood pressure was 86.1 ± 13.7 mmhg. Males had a higher mean systolic blood pressure 140.1 ± 16 mmhg, and a higher diastolic blood pressure 87.5 + 12.6 mmhg as compared to females who had 134.8 + 20.4 mmhg and 85.06 + 14.45 respectively.

Graph 8.1.71 *Systolic Blood Pressure among study subjects*



Systolic blood pressure (mmhg)

Graph 8.1.72 *Diastolic Blood Pressure among study subjects*

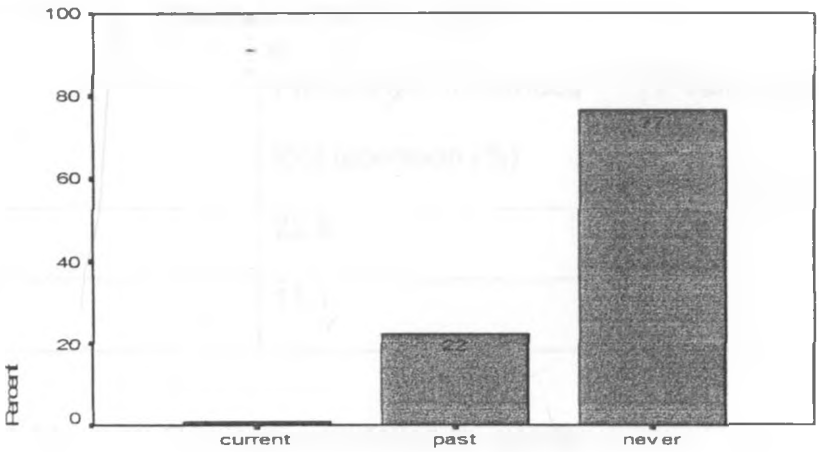


Diastolic blood pressure (mmhg)

8.1.8 Smoking

The vast majority of the study participants had never smoked a cigarette (77%), 22% were past smokers, and 1% of the participants were current smokers. 98.4% of the females had never smoked as compared with 47% of the males.

Graph 8.1.8 Smoking status of study subjects

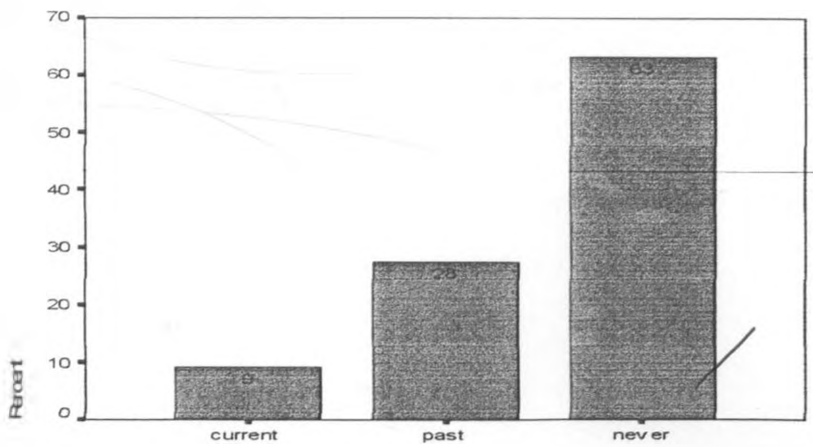


Smoking status

8.1.9 Alcohol

63% of study subjects had never taken alcohol. 28% were past partakers while 9% were still taking alcohol. Males were more likely to have a history of past or current alcohol intake as were females. (74% vs. 9.5%)

Graph 8.1.9 Alcohol intake among study subjects



Alcohol intake

8.1.10 Previous ulcer / Amputation

The prevalence of previous foot ulceration was 16% while the prevalence of previous amputation was 8%. Male gender was strongly associated with foot ulcers and amputations.

Table 8.1.10 Previous ulcer vs. gender

Gender	Prevalence of previous foot ulceration (%)	P value (chi square)
Male	22.8	0.020
Female	11.1	

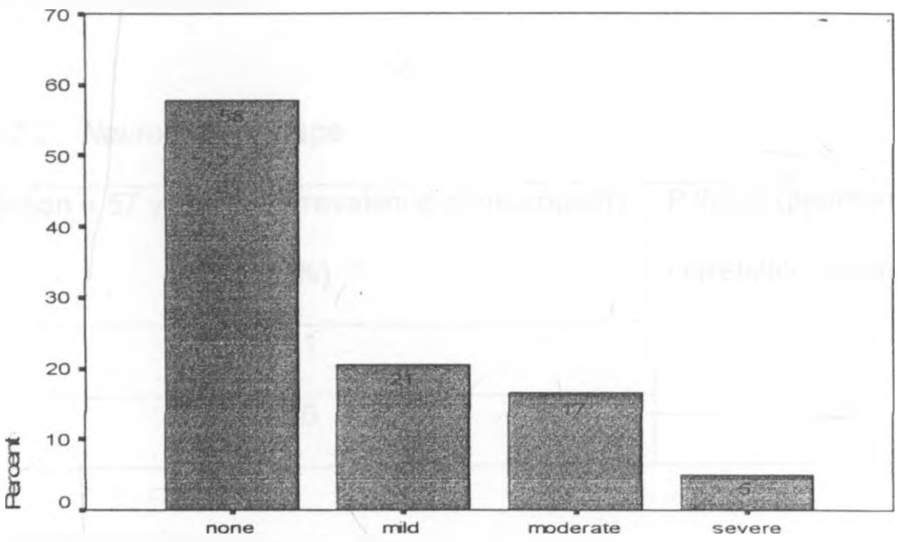
Table 8.1.11 Previous amputation vs. gender

Gender	Prevalence of previous foot amputation (%)	P value (chi square)
Male	13.1	0.028
Female	4.8	

8.2 NEUROPATHY

The prevalence of neuropathy, as defined by a neurological disability score of >2 was 42%.

Graph 8.2 Prevalence and Grade of neuropathy among study subjects



8.2.1 Neuropathy vs. Gender

Males were more likely to have neuropathy than were females. This association was statistically significant with a p – value of 0.01.

Table 8.2.1 Neuropathy vs. gender

Gender	Prevalence of neuropathy (%)	P value (chi square)
Male	58	0.01
Female	16	

8.2.2 Neuropathy vs. Age

The prevalence of neuropathy increased with increasing age. This relationship was statistically significant on statistical analysis with a p – value of 0.041. This is illustrated in the table below:

Table 8.2.2 Neuropathy vs. age

Age (Median = 57 years)	Prevalence of neuropathy (%)	P value (pearson correlation, bivariate)
< 57	31	0.041
> 57	56	

8.2.3 Neuropathy vs. Duration of Diabetes

The prevalence of neuropathy among the study subjects increased with duration of diabetes. The prevalence was 30% in those with duration of diabetes of less than 16 years as compared to 61% in those with duration of diabetes more than 16 years. The relationship was statistically significant.

Table 8.2.3 Neuropathy vs. duration of diabetes

Duration of Diabetes (median = 16 yrs)	Prevalence of neuropathy (%)	P value (pearson correlation, bivariate)
< 16	30	0.014
> 16	61	

8.2.4 Neuropathy vs. Random Blood Sugar

The prevalence of neuropathy increased with increases in the random blood sugar. The relationship between random blood sugar and neuropathy was statistically significant with a p value of 0.011. This is illustrated in the table below:

Table 8.2.4 Neuropathy vs. random blood sugar

Random Blood Sugar (median = 11.2 mmols/litre)	Prevalence of neuropathy (%)	P value (pearson correlation, bivariate)
< 11.2	39	0.011
> 11.2	45	

8.2.5 Neuropathy vs. Systolic Blood Pressure

There was a statistically significant increase (p=0.034) in the prevalence of neuropathy with rise in the systolic blood pressure. The prevalence of neuropathy was 37% in those with a systolic blood pressure less than 140mmhg while it was 50% in those with a pressure more than 140 mmhg.

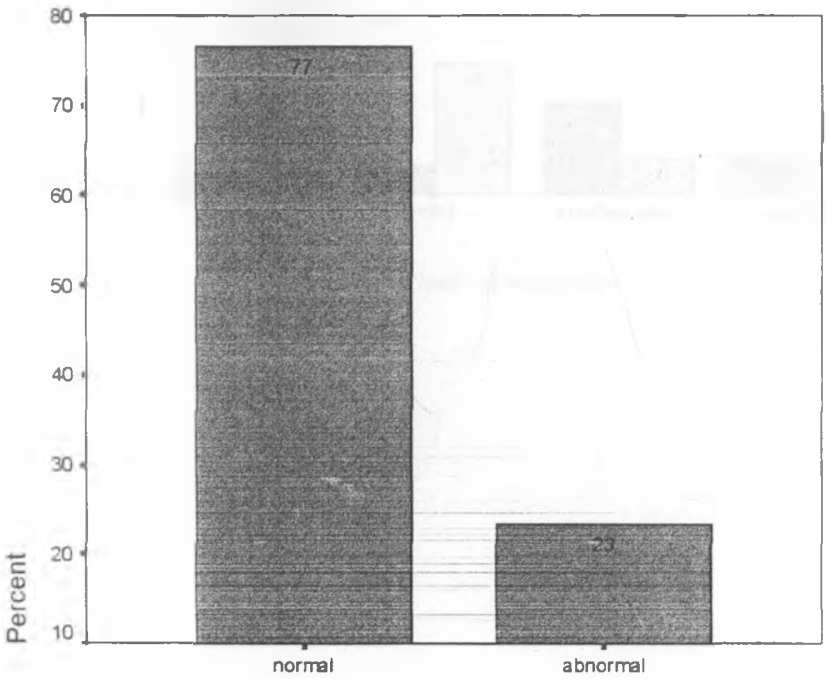
Table 8.2.5 Neuropathy vs. systolic blood pressure

Systolic Blood Pressure (mmhg)	Prevalence of neuropathy (%)	P value (chi square)
< 140	37	0.034
> 140	50	

8.2.6 Monofilament Test

77% of study subjects had a normal monofilament test while 23% had an abnormal response on the test.

Graph 8.2.6 Monofilament testing in study subjects

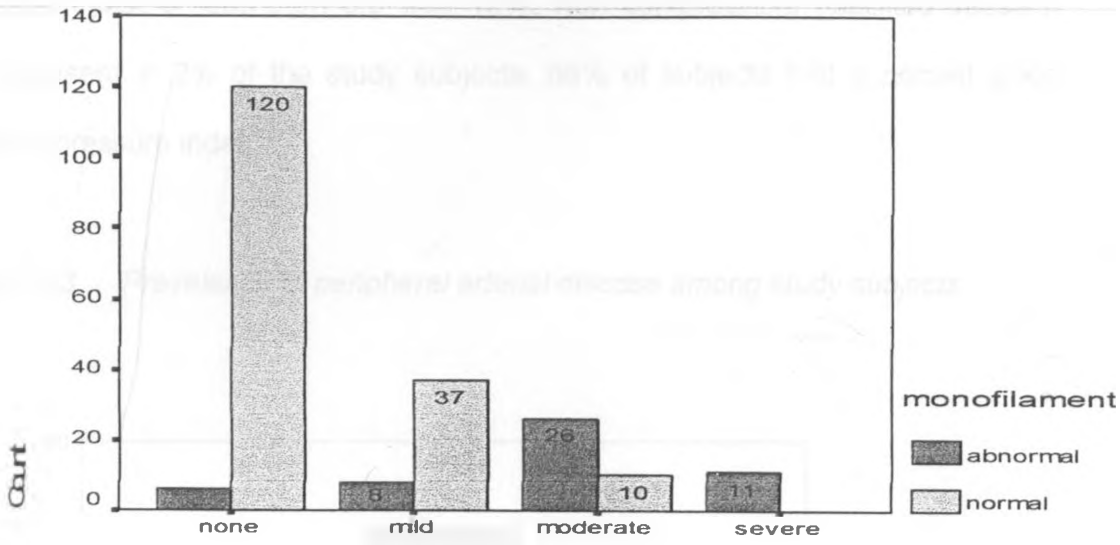


Result of monofilament testing

8.2.7 Monofilament vs. Neuropathy

The monofilament was able to accurately detect severe neuropathy assuming the NDS to be the 'gold' standard, in all cases of severe neuropathy (NDS 9-10). However false negatives, and false positives occurred at lower grades of neuropathy. This is illustrated below:

Graph *8.2.7 Monofilament testing vs. Neurological Disability Score*

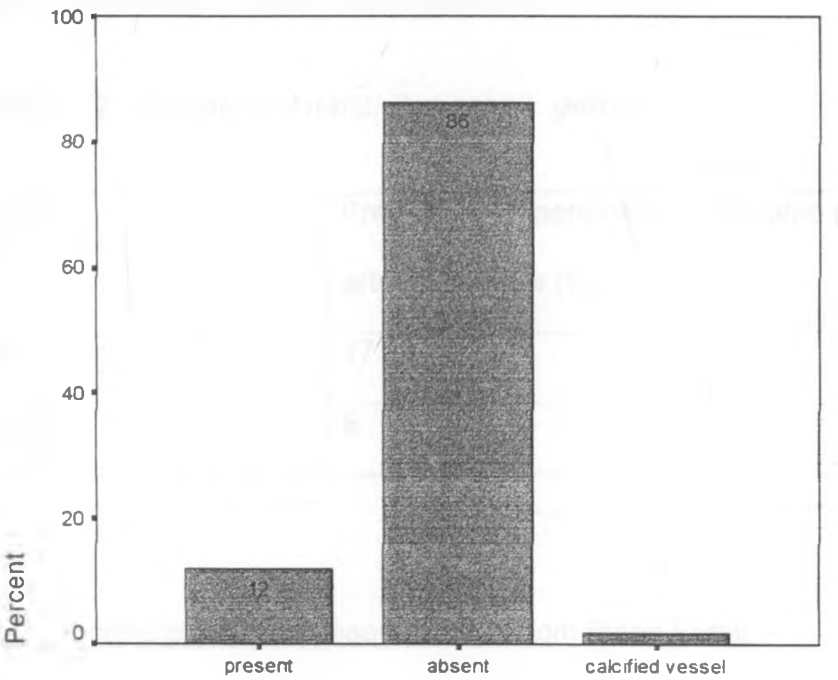


Grade of neuropathy

8.3 PERIPHERAL ARTERIAL DISEASE

The prevalence of peripheral arterial disease as defined by an ankle brachial pressure index of less than 0.9 was 12%. Non compressible (calcified vessels) were present in 2% of the study subjects. 86% of subjects had a normal ankle brachial pressure index.

Graph 8.3 Prevalence of peripheral arterial disease among study subjects



8.3.1 Peripheral Arterial Disease vs. Age

There was a trend towards increased prevalence of peripheral arterial disease with age but this was not statistically significant (p value = 0.063). This is illustrated in the table below:

Table 8.3.1 Peripheral Arterial Disease vs. age

Age (median = 57 years)	Prevalence of peripheral arterial disease (%)	P value (chi square)
< 57	58	0.063
> 57	16	

8.3.2 Peripheral Arterial Disease vs. Gender

Male gender was associated with increased prevalence of peripheral arterial disease and this association was significant (p = 0.001)

Table 8.3.2 Peripheral Arterial Disease vs. gender

Gender	Prevalence of peripheral arterial disease (%)	P value (chi square)
Male	17	0.001
Female	8	

8.3.3 Peripheral Arterial Disease vs. Random Blood Sugar

The relationship between peripheral arterial disease and random blood sugar did not attain statistical significance. However, the mean Random Blood Sugar in the study subjects with peripheral arterial disease was 13.1 mmols/ litre as compared to 11.8 mmols/ litre in subjects without peripheral arterial disease.

Table 8.3.3 Peripheral Arterial Disease vs. random blood sugar

Peripheral arterial disease	Random Blood Sugar (mmols/litre)	P value (chi square)
Present	13.1	0.233
Absent	11.8	

8.3.4 Ankle Brachial Index vs. Body Mass Index (BMI)

Subjects with an ideal BMI of less than 25 had a higher Ankle Brachial Index than patients with a BMI of more than 25, i.e. 1.04 vs. 1.01 respectively (p=0.138)

Table 8.3.4 Body Mass Index vs. Ankle Brachial Index

Body Mass Index (kg/m^2)	Mean Ankle Brachial Index	P value (paired samples T test correlation)
<25	1.04	0.138
>25	1.01	

8.3.5 Peripheral Arterial Disease vs. Systolic Blood Pressure

Patients who were hypertensive (SBP>140MMHG) had a higher ABI than patients who were normotensive (SBP<140MMHG) i.e. 1.03 vs. 1.02. However this difference was not statistically significant (p = 0.407).

Table 8.3.5 Systolic Blood Pressure vs. Ankle Brachial Index

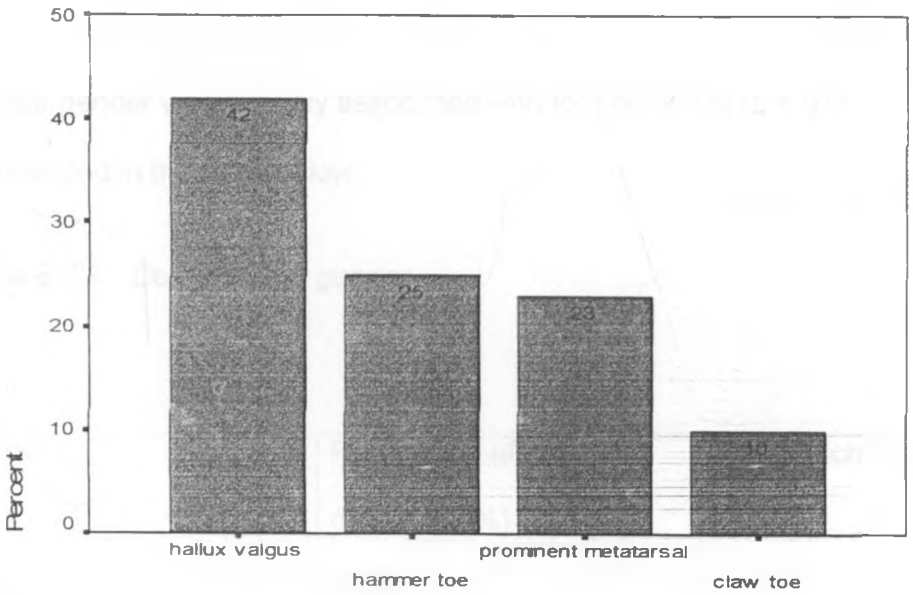
SBP(mmhg)	Mean ABI	P value (paired samples T test correlation)
<140	1.03	0.407
>140	1.02	

8.4 FOOT DEFORMITY

The prevalence of foot deformity was 46%. Of the deformities the most common deformity was hallux valgus (42%) followed by hammer toe (25%) and prominent metatarsal heads (23%) . Claw toe deformity accounted for 10% of foot deformities.

See appendix 4 (figures: 1 - 4)

Graph 8.4 Types of foot deformity among study subjects



8.4.1 Deformity vs. Age

There was a significant association between foot deformity and increasing age (p value=0.012). The prevalence of foot deformities in study subjects above the median age of 57 years was 57% in comparison to 34% in subjects younger than the median age of 57 years.

Table 8.4.1 Deformity vs. age

Age (median = 57 years)	Prevalence of foot deformity (%)	P value (chi square)
< 57	34	0.012
> 57	57	

8.4.2 Deformity vs. Gender

Female gender was strongly associated with foot deformity (p = 0.001). This is represented in the table below:

Table 8.4.2 Deformity vs. gender

Gender	Prevalence of foot deformity (%)	P value (chi square)
Male	44.6	0.001
Female	46.8	

8.4.3 Deformity vs. Neuropathy

Patients with neuropathy were more likely to also have foot deformity. The prevalence of foot deformities in subjects with neuropathy was 63% as compared to 34%, in subjects without neuropathy. The association between neuropathy and foot deformity was statistically significant (p = 0.049)

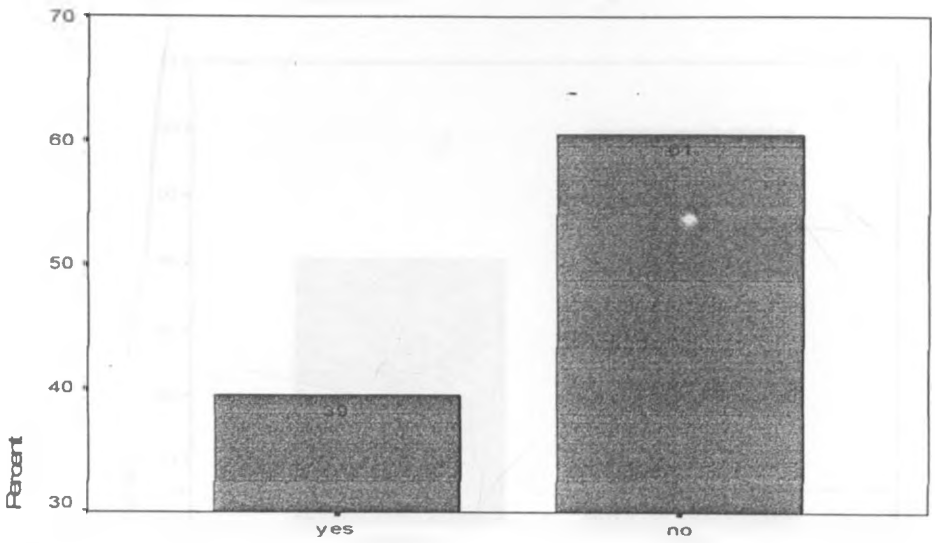
Table 8.4.3 Deformity vs. neuropathy

Neuropathy	Prevalence of foot deformity (%)	P value (chi square)
Present	63	0.049
Absent	34	

8.5 FOOT CARE

Only 39% of study participants had received foot care education at the clinic.

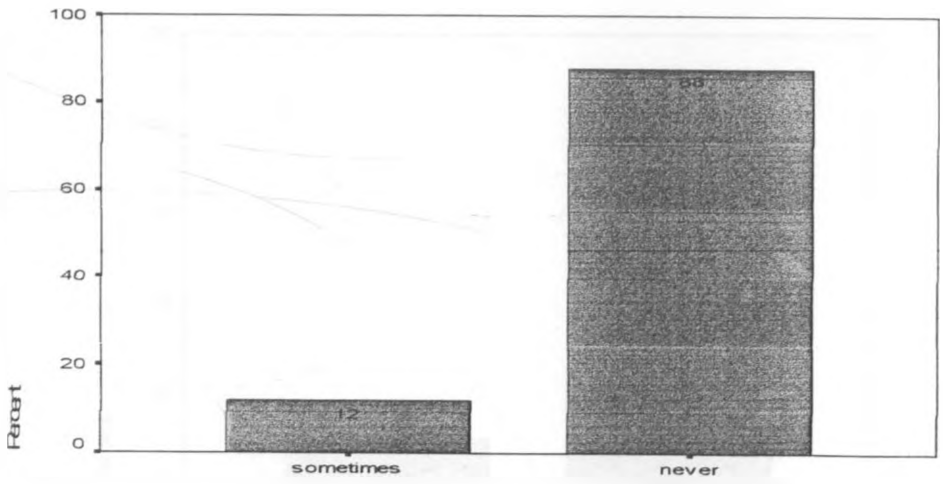
Graph 8.5 foot care knowledge among study subjects



Received any education on foot care?

Only 12% of subjects had had their feet examined at least once in the clinic.

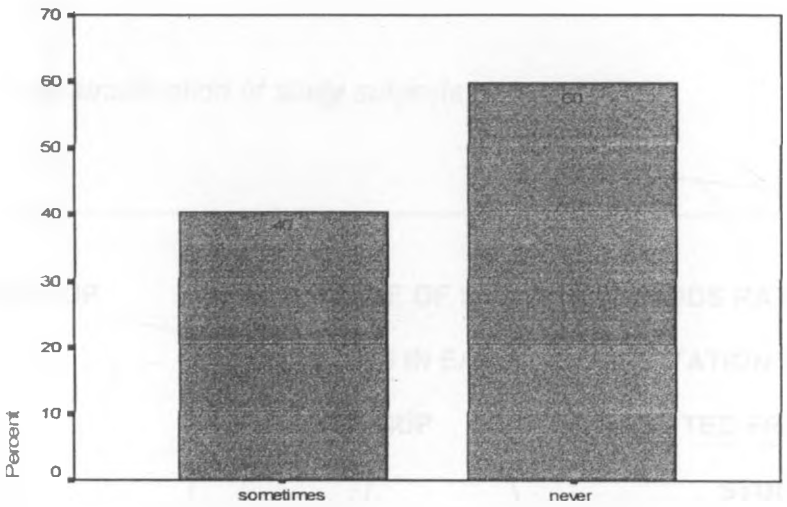
Graph 8.5.1 foot examination at the clinic



Have your feet ever been examined at the clinic?

40% of the study subjects reported having walked outdoor barefoot on occasion after the diagnosis of diabetes was made.

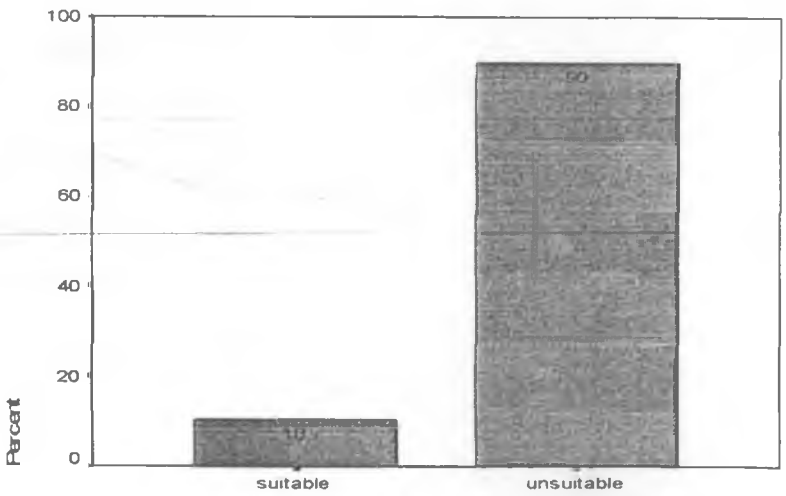
Graph 8.5.2 proportion of subjects who reported having walked outdoors barefoot following the diagnosis of diabetes



Walked outdoors barefoot?

90% of the participants in the study had unsuitable shoes on the shoe exam.

Graph 8.5.3 Shoe examination among study subjects



Suitability of shoes on examination

8.6 RISK STRATIFICATION

The study participants were stratified into risk categories for diabetic foot ulceration based on the criteria devised and recommended by the international working group on the diabetic foot (IWGDF).

Table 8.6 Risk stratification of study subjects

IWGDF GROUP	PERCENTAGE OF STUDY SUBJECTS IN EACH GROUP	ODDS RATIO FOR AMPUTATION after 3 years ADAPTED FROM IWGDF STUDY
0 NO NEUROPATHY	57	0
1 NEUROPATHY ALONE	10	1.7
2 NEUROPATHY PLUS EITHER PAD OR DEFORMITY	16	12.1
3 PREVIOUS ULCER/ AMPUTATION OTHER THAN BILATERAL LEG AMPUTATION	17	36.4

9. DISCUSSION

The prevalence of neuropathy in this study was 46%. Neuropathy was assessed through the use of the Neurological Disability Score. Using the same tool, Mwendwa et al [77] found a prevalence of 28% among newly diagnosed diabetics at Kenyatta National Hospital. However the mean duration of diabetes in their study group was 10.3 months in comparison to 15.9 years in this study. The mean age of the study population in Mwendwa et al was 53.7 years old as compared with the older age group in the present study with a mean of 58 years old. Also the current study had more males i.e. (42%) vs. (37%) in Mwendwa et al. Male gender has been shown to be strongly associated with neuropathy. Thus, the older age group, larger number of males, coupled with the increased duration of diabetes could have contributed to the higher prevalence of neuropathy in this particular study. The prevalence of neuropathy has been shown to vary widely among countries. Inter observer variations have also occurred within similar populations. For instance, in South Africa. Gill (1995) found a prevalence of 42%, whilst Levitt (1997) found a prevalence of 28%. In Sudan, Elmadhi (1991) found a prevalence of 32% where as Elbagir (1995) showed the prevalence to be 37%. In Tanzania, Mhando (1980) concluded that neuropathy was present in 32% of his study population. Wikhlad (1997) reported the prevalence in Tanzania to be 28%. In Zambia, Rolfe (1988) found neuropathy in 31% of his study group while Lester (1991) in Ethiopia reported the prevalence of neuropathy as 36%. [80] Data from the west ranges from 11.7% in France (Delcourt 1998) [80], 27.8% in the San Louis Diabetic Study [81], 28% in EURODIAB [82], 60% in turkey [83], and 66% in the Rochester Study [84] . A recent study reported from the middle-east found a high prevalence of 82% in Iran. [85]

The varying prevalence has been attributed to the lack of a consensus on how to define neuropathy and the methods used in determining its presence. In some studies, only symptomatic scores were done, while in others, clinical examination tools were employed. Yet other studies performed nerve conduction testing and electromyography. Also in some studies, subjects with other causes of neuropathy were excluded while this was not the case in other studies. Thus direct comparison between studies has been made virtually impossible owing to the above reasons.

In this study male gender was found to be significantly associated with neuropathy ($p = 0.01$). This has been shown before in previous studies both locally (Mwendwa 2005) [78] and in large multi centre controlled studies like the DCCT [86] and the San Luis valley Diabetic study [81]. Pickett (1992) [87] showed that females have higher nerve conduction speeds than males.

Age was significantly associated with neuropathy in this study. Virtually all studies of neuropathy in diabetics have shown an increased prevalence with age.

The duration of diabetes has also been shown to be significantly associated with the prevalence of neuropathy. In this study the association was significant with a p value of 0.014.

Although studies that have demonstrated the strong link between poor glycemic control and neuropathy have used the hbA1c as the marker for glycemic control, this study was able to demonstrate that in our population the random blood sugar is significantly associated with neuropathy ($p = 0.011$). The DCCT showed a 60% reduction in the incidence of neuropathy among type 1 diabetic subjects in the group randomized to intensive glycemic control. In type 2 diabetics the UKPDS [88] estimated that each 1% reduction in the hba1c was associated in a relative reduction of 35% on all micro-vascular complications.

In this study, the prevalence of neuropathy was significantly increased with rise in systolic pressure (p = 0.034). The EURODIAB [82] found that hypertension was associated with an odds ratio of 1.92 (p<0.0001) of incident neuropathy. The UKPDS [88] reported that all microvascular outcomes were reduced by between 24-56% by modest BP reduction to a mean of 144/82mmhg.

The prevalence of peripheral arterial disease was 12%. The tool used was the Ankle Brachial Pressure Index as determined by the Doppler method. Currently there are no published studies from Kenya on the prevalence of peripheral arterial disease among diabetics without foot ulcers. Nyamu (1999) [8], using clinical assessment of pulses, blanching on elevation and dependant rubor, found a prevalence of 52% in patients with diabetic foot ulcers. In Sudan, Elbaghir (1995) reported a prevalence of 10%. Wikblad (1997) in Tanzania found a prevalence of 12%. Levitt (1997) in South Africa and Niang (1994) in Senegal reported prevalence values of 8% and 28% respectively [80]. In the USA, the NHANES 2000 [89] estimated peripheral arterial disease to be present in 9.5% of the survey subjects. In the UK, the Edinburg Artery Study [90] estimated the prevalence to be as high as 20.1%.

In this study the association between peripheral arterial disease and age did not reach statistical significance although there was a trend towards increased prevalence with increasing age.

Male gender was significantly associated with peripheral arterial disease (p=0.001). Since the pathogenesis involves atherosclerosis, this finding is in keeping with published evidence that shows a strong link between male gender and atherosclerotic manifestations such as myocardial infarction and cerebro-vascular disease. A positive association between peripheral arterial disease and random blood sugar could not be demonstrated in this study. It is interesting to speculate

that HBA1C levels which are a marker of longer term control might have been linearly associated with peripheral arterial disease. Although it has been shown that advanced glycemic end products may have a role in the pathogenesis of peripheral arterial disease in diabetics, [91] very few controlled studies have investigated the association between glycemic control and peripheral arterial disease. The Atherosclerosis Risk in Communities study [92] found a positive, graded, and independent association between A1C and PAD risk in diabetic adults. This association was stronger for clinical (symptomatic) PAD, whose manifestations may be related to microvascular insufficiency, than for low ABI. Although the mean Ankle Brachial Index was lower for patients with a BMI of more than 25kg/m^2, the association between Ankle Brachial Index and Body Mass Index was not statistically significant ($p = 0.138$). No published well controlled studies thus far have demonstrated an unequivocal link between BMI and ABI. Systolic blood pressure was not associated with Ankle Brachial Index in this study ($p = 0.407$). The Edinburg Artery Study [90] showed that raised SBP was associated with an odds ratio of 1.22 of developing peripheral arterial disease. The study concluded that increased mean levels of Systolic Blood Pressure and triglycerides may help to explain the higher prevalence of PAD in diabetic subjects compared with that in normal glucose tolerance patients.

The prevalence of foot deformities in this study was 46%. Female gender had a significant statistical association with foot deformities ($p = 0.012$). Females have generally been shown to have more foot deformities [93, 94] likely owing to the use of foot wear with restricted toe boxes and high heels. In our local setup, particularly in the rural areas, women are engaged in cultivation, fetching of firewood and water, and other activities that may result in accumulation of deformities particularly where

they walk barefoot or wear inappropriate footwear. However, Abbas in Basra has recently documented male gender as a risk factor for foot abnormalities in his study population [95]. It is likely that foot deformities as a whole are more determined by gender roles as opposed to gender per se. However, the higher risk deformities, i.e. claw toe, hammer toe and prominent metatarsals were more frequent in males and thus this may explain the increased prevalence of foot ulcers in men. As expected, deformity was significantly associated with advancing age which no doubt provides a greater opportunity for acquisition and accumulation of deformities. An important finding in this study that was also shown by Nyamu (1999) [8] is the significant association between foot deformity and neuropathy. Although it is generally held that neuropathy, by causing imbalance between the toe flexors and extensors may ultimately lead to claw toe deformity and hence areas of increased plantar pressure, this ultimately progressing to ulceration, very few studies have investigated the role of neuropathy in the causation of foot deformity. Carine et al (2004) [96], in their study published in Diabetes care, concluded that although important relationships between motor nerve conduction deficit and muscle weakness were demonstrated, it was still not clear whether abnormal nerve function, leading to a decrease in muscle strength, could be responsible for the development of foot deformities.

This study confirms that foot care education is still not well disseminated to diabetic patients. The discrepancy between the number of study subjects that had received foot care education (39%) and the number that had had foot exam (12%) suggests that the diabetes educators may be making gains in the provision of important foot care information but that owing perhaps to staffing constraints; they are unable to literally examine the feet. An easy to use tool like the monofilament might be well

applicable in such a setting as it would quickly identify the high risk foot as demonstrated by this study. Risk categorization also would have a role, because once performed at baseline the clinician can easily identify who requires quarterly, semi-annual, or annual examinations. Moreover there is need for setting up a specialized well staffed foot centre that would deal with patients noted to have anomalies on initial screening. Although the shoe exam has not been standardized, majority of the foot wear was inadequate in terms of material, size, toe box, in- sole, outer-sole, and whether laced or not. Only 20% had shoes that were suitable in all the above respects.

10. CONCLUSIONS

1. More than one third of diabetics (33%) are at high risk for future foot ulceration:

- 16% of them are in group 3 of the Working Group criteria, which represents presence of Neuropathy and either deformity or peripheral arterial disease.

- 17% of the subjects at high risk have had a history of previous foot ulceration/ amputation.

2. The 5.07 (10g) monofilament is an effective tool in the identification of severe grades of neuropathy

11. RECOMMENDATIONS

1. Development of an easy to use protocol, incorporating the monofilament, for screening foot examination in the outpatient clinic.

2. Setting up of a specialized podiatric centre where diabetic patients with high risk feet can be referred and followed up with provision of specialized foot wear for those at the highest risk category

3. Long term prospective studies should be carried out in a similar population locally to determine the odds ratio of ulceration in the different risk categories since these may differ from studies done in the west

12. STUDY LIMITATIONS

The financial implications of the large sample size required for this study made it impossible to carry out a number of laboratory tests relevant to persons with diabetes. However, since the ultimate aim of the study was to identify patients likely to have foot ulceration, the presence of peripheral arterial disease, for instance, is in itself sufficient for this assessment and thus one might not require preliminary lipid testing to decide on the risk status. There are patients with deranged lipids but intact peripheral vessels. From the perspective of a foot ulcer, it is perhaps more relevant to first determine whether peripheral vascular disease is present then later when intervention is contemplated assess the causative factors.

Likewise Neuropathy is an end result of poor glycemic control among other factors. Therefore its presence would be indicative of poor glycemic control in the vast majority of patients with neuropathy. Therefore it is not necessary to do HBA1c testing for initial screening of patients at risk of diabetic foot. The presence of other microvascular abnormalities i.e. retinopathy and nephropathy may indicate that neuropathy may be present as well. However, the presence of neuropathy can often be inferred from simple tools at a single visit. This is the main argument of the International Working Group on the Diabetic foot and the principal investigator: That foot saving information can often be gotten from simple, easily available and tools. Delays while sending the patient for multiple investigations may be costly. These few limitations were partly offset by the fact that most clinic attendees have well kept records where longer term BP, Glycemic, Lipid control could be assessed. Treatment regimes, eye examinations and urine micro-albumin status were all part of this well kept archive. This information was captured as accurately as possible.

13. REFERENCES

1. Bjork S. The cost of diabetes and diabetes care. *Diabetes Res Clin pract* 2001; **1(suppl) :** S13-S18
2. Jeffcoate, WJ, Harding, KG. Diabetic foot ulcers. *Lancet* 2003; **361:** 1545-1548
3. Graves EJ. National Hospital Discharge Survey, Annual Summary. *Vital and Health Statistics* 1990 ; **13:** 1992-1996
4. Ramsey, SD, Newton K, *et al.* Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care* 1999; **22:** 382-385
5. Reiber GE. Pecoraro RE. Koepsell TD. Risk factors for amputation in patients with diabetes mellitus: a case-control study. *Ann Intern Med* 1992: **117:** 97-105
6. Miller AD, Van Buskirk A, Verhok W, Miller ER. Diabetes related lower extremity amputations in New Jersey, 1979 to 1981. *J Med Soc New Jersey* 1985; **82:** 723-726
7. Nelson RG, Ghodes DM, Everhart JE: Low extremity amputations in NIDDM: 12 yr follow up sudy of pima indians. *Diabetes care* 1988; **11:** 8-16
8. Nyamu PN, Otieno CF, Amayo EO. McLigeyo SO. Patterns of diabetic foot ulcers at Kenyatta National Hospital. *East Afr. Med. J.* 2003; **80:** 36-43
9. Kenny, SJ, Smith, PL, Goldschmid, MG, *et al.* Survey of physician practice behaviors related to diabetes mellitus in the U.S. *Diabetes Care* 1993; **16:** 1507-1509
10. Peters, AL, Legorreta, AP, Ossorio, RC, Davidson, MB. Quality of outpatient care provided to diabetic patients. A health maintenance organization experience. *Diabetes Care* 1996; **19:** 601-603

11. Pecoraro RE. Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care* 1990; **13:** 513-521.

12. Eckman MH, Greenfield S, Mackey WC. Foot infections in diabetic patients: decision and cost effectiveness analysis. *JAMA*. 1995; **273:** 712-720

13. Edmonds M.E. Improved survival of the diabetic foot. The role of a specialised foot clinic. *QJM* 1986; **60:** 763-771

14. Pram H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care* 2000; **23:** 606-611.

15. Rith-Najarian S, Stoluski T, Gohdes D. Identifying diabetic individuals at high risk for lower extremity amputation in a primary health care setting: a prospective evaluation of simple screening criteria. *Diabetes Care* 1992; **15**: 1386-1389.

16. Litzelman DK, Marriott DJ, Vinicor F. Independent physiological predictors of foot lesions in patients with NIDDM. *Diabetes Care* 1997; **20:** 1273-1278.

17. Fernando DJ, Masson EA, Veves A, Boulton AJ. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. *Diabetes Care* 1991; **14:** 8-11.

18. Reiber GE, Pecoraro RE, Koepsell TD. Risk factors for amputation in patients with diabetes mellitus: a case-control study. *Ann Intern Med* 1992; **117:** 97-105.

19. Walters DP, Gatling W, Mullee MA, Hill RD. The distribution and severity of diabetic foot disease: a community study with comparison to a non-diabetic group. *Diabetic Medicine* 1992; **9:** 354-358.

20. Kumar S, Ashe HA, Parnell LN, *et al.* The prevalence of foot ulceration and its correlates in type 2 diabetic patients: a population-based study. *Diabetic Medicine* 1994; **1:** 480-484.

21. Moss SE, Klein R, Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care* 1999; **22:** 951-959.

22. Klein R, Moss SE, *et al.* The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Intern Med* 1992; **152:** 610-616.

23. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Risk factors predicting lower extremity amputations in patients with NIDDM. *Diabetes Care* 1996; **19:** 607-612.

24. Lee JS. Lu M, Lee VS, Russell D, Bahr C, Lee ET. Lower-extremity amputation: incidence, risk factors, and mortality in the Oklahoma Indian Diabetes Study. *Diabetes* 1993; **42:** 876-882.

25. Eggers P, Gohdes D, Pugh J. Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. *Kidney International* 1999; **56:** 1524-1533.

26. Borssen B, Bergenheim T, Lithner E. The epidemiology of foot lesions in diabetic patients aged 15-50 years. *Diabetic Medicine* 1990; **7:** 438-444.

27. Selby JV, Zhang D. Risk factors for lower extremity amputation in persons with diabetes. *Diabetes Care* 1995; **18:** 509-516.

28. Humphrey LL, Palumbo PJ, Butters MA, *et al.* The contribution of non-insulin-dependent diabetes to lower-extremity amputation in the community. *Arch Intern Med* 1994; **15:** 885-892.

29. Litzelman, DK, Marriott, DJ, Vinicor, F. Independent physiological predictors of foot lesions in patients with NIDDM. *Diabetes Care* 1997; **20:** 1273-1275.

30. Lehto, ST, Rönnemaa,T, Pyörälä, K, et al. Risk factors predicting lower extremity amputation in patients with NIDDM. *Diabetes Care* 1996; **19:** 607-608

31. Mcneely MJ. The independent contributions of neuropathy and vasculopathy in foot ulceration. How great are the risks? *Diabetes Care* 1995; **18:** 216-219

32. Lawrence A. Lavery. *et al.* Practical criteria for screening patients at high risk for diabetic foot ulceration. *Arch Intern Med* 1998; **158:** 157-162

33. Veves A. *et al.* Risk of foot ulceration in diabetic patients with high foot pressure: A prospective study. *Diabetologia* 1995; **35:** 660-663

34. DJ Fernando, Veves A, AJ Boulton. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. *Diabetes Care* 1996;**19**: 613-615

35. Del Aguila MA, Reiber GE, Koepsell TD. How does provider and patient awareness of high-risk status for lower-extremity amputation influence foot-care practice? *Diabetes Care* 1994; **17:** 1050-1054.

36. Gohdes D, Schraer C, Rith-Najarian S. Diabetes prevention in American Indians and Alaska natives: where are we? *Diabetes Res Clin Pract* 1996; **34(suppl):** S95-S100.

37. Rith-Najarian S, Branchaud C, Beaulieu O, Gohdes D, Simonson G, Mazze R. Reducing lower extremity amputations due to diabetes: application of the staged diabetes management approach in a primary care setting. *Journal of Family Practice* 1998; **47:** 127-132.

38. Schraer CD, Adler AI, Mayer AM, Halderson KR, Trimble BA. Diabetes complications and mortality among Alaska natives: 8 years of observation. *Diabetes Care* 1997; **20:** 314-321.

39. David G. Armstrong, Lawrence Lavery. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. *Arch of Intern Med* 1998; **158:** 289-292.

40. Edgar J, Lawrence L. Effectiveness of the Diabetic Foot risk classification system of the International Working Group on the diabetic foot. *Diabetes care* 1996; **19:** 617-620.

41. Partanen J, Niskanen L, Lehtinen J, *et al.* Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Eng J Med* 1995; **89:** 333 – 337.

42. American Diabetes Association, American Academy of Neurology. Consensus statement: Report and recommendations of the San Antonio conference on diabetic neuropathy. . *Diabetes Care* 1988; **11:** 592-595.

43. Young MJ, Boulton AJ, Macleod AF, *et al.* A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993; **36:** 150-154.

44. Feldman EL, Stevens MJ, Thomas PK, *et al.* A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994; **17:** 1281-1283.

45. Wilkins RW, Kolb LC. Vasomotor disturbance in peripheral neuritis. *Am J Med Sci* 1941; **202:** 216 -218.

46. Aso Y, Fujiwara Y, Inukai T, Takemura Y. Power spectral analysis of heart rate variation in diabetic patients with neuropathic foot ulceration. *Diabetes Care* 1998; **21:** 1173-1177.

47. Edmonds ME, Nicolaides K, Watkins PJ. The importance of autonomic neuropathy in the etiology of diabetic neuropathic foot ulceration. *Diabetologia* 1981; **21:** 506-508.

48. Deanfield JE, Daggett PR, Harrison MJ. The role of autonomic neuropathy in diabetic foot ulceration. *J Neurological Science* 1980; **47:** 203-205.

49. Fagius J. Microneurographic findings in diabetic polyneuropathy with special reference to sympathetic nerve activity. *Diabetologia* 1982; **23:** 415-417.

50. Shahani BT, Halperin JJ, Boulu P, Cohen J. Sympathetic skin response: a method of assessing unmyelinated axon dysfunction in peripheral neuropathies. *J Neurolog Neurosurg Psych* 1984; **47:** 536-538.

51. Stevens MJ, Edmonds ME, Douglas SL, Watkins PJ. Influence of neuropathy on the microvascular response to local heating in the human diabetic foot. *Clinical Science* 1991; **80:** 249-251.

52. American Diabetes Association. Consensus Statement: Role of cardiovascular risk factors in prevention and treatment of macrovascular disease in diabetes. *Diabetes Care* 1993, **16:** 72-78.

53. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993 **16:** 434-444.

54. Schwartz CJ, Valente AJ, Sprague EA, Kelley JL, Cayatte AJ, Rozek MM. Pathogenesis of the atherosclerotic lesion. Implications for diabetes mellitus. *Diabetes Care* 1992, **15:** 1156-1167.

55. Nishikawa T, Edelstein D, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000 ; **404:** 787-790.

56. Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N Eng J Med* 1988; **318:** 1315-1321.

57. Ikeda K, Higashi T, Sano H, Jinnouchi Y, Yoshida M, Araki T, Ueda S, Horiuchi S. N epsilon - carboxymethyl lysine protein adduct is a major immunological

epitope in proteins modified with advanced glycation end products of the Maillard reaction. *Biochemistry* 1996, **35:** 8075-8083.

58. Reddy S, Bichler J, Wells-Knecht KJ, Thorpe SR, Baynes JW. N epsilon-carboxymethyl lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteins. *Biochemistry* 1995, **34:** N10872-10878.

59. Giardino I, Edelstein D, Brownlee M. BCL-2 expression or antioxidants prevent hyperglycemia-induced formation of intracellular advanced glycation endproducts in bovine endothelial cells. *J Clin Invest* 1996; **97:** 1422-1428.

60. Fu MX, Knecht KJ, Thorpe SR, Baynes JW. Role of oxygen in crosslinking and chemical modification of collagen by glucose. *Diabetes* 1992; **41(Suppl 2):** 42-48.

61. Dunn JA, Ahmed MU, Murtiashaw MH, Richardson JM, Walla MD, Thorpe SR, Baynes JW. Reaction of ascorbate with lysine and protein under autoxidizing conditions: formation of N epsilon- carboxymethyl lysine by reaction between lysine and products of autoxidation of ascorbate. *Biochemistry* 1990; **29:** 10964-10970.

62. Schmidt AM, Hori O, Brett J, Yan SD, Wautier JL, Stern D. Cellular receptors for advanced glycation end products. Implications for induction of oxidant stress and cellular dysfunction in the pathogenesis of vascular lesions. *Arterioscler Thromb* 1994; **14**: 1521-1528.

63. Schmidt AM, Yan SD, Wautier JL, Stern D. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. *Circ Res* 1999; **84:** 489-497.

64. Feener EP, King GL. Vascular dysfunction in diabetes mellitus. *Lancet* 1997; **350(Suppl 1):** SI 9-13.

65. Ishii H, Jirousek MR, Koya D, Takagi C, Xia P, Clermont A, Bursell SE, Kern TS, Ballas LM, Heath WF, Stramm LE, *et al.* Amelioration of vascular dysfunctions in diabetic rats by an oral PKC beta inhibitor. *Science* 1996; **272:** 728-731.

66. Koya D, King GL: Protein kinase C activation and the development of diabetic complications. *Diabetes* 1998; **47:** 859-866.

67. Oberley LW. Free radical and diabetes. *Free Radical Bio Med* 1988; **5:** 113-124.

68. Wolff SP: Diabetes mellitus and free radicals. Free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. *British Medical Bulletin* 1993; **49:** 642-652.

69. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. *Diabetes* 1999; **48:** 1-9.

70. Yoshida K, Hirokawa J, Tagami S, Kawakami Y, Urata Y, Kondo T. Weakened cellular scavenging activity against oxidative stress in diabetes mellitus: regulation of glutathione synthesis and efflux. *Diabetologia* 1995; **38:** 201-210.

71. Dominguez C, Ruiz E, Gussinye M, Carrascosa A. Oxidative stress at onset and in early stages of type 1 diabetes in children and adolescents [see comments]. *Diabetes Care* 1998; **21:** 1736-1742.

72. Sano T, Umeda F, Hashimoto T, Nawata H, Utsumi H:. Oxidative stress measurement by in vivo electron spin resonance spectroscopy in rats with streptozotocin-induced diabetes. *Diabetologia* 1998; **41:** 1355-1360.

73. Karpen CW, Cataland S, O'Dorisio TM, Panganamala RV. Production of 12-hydroxyeicosatetraenoic acid and vitamin E status in platelets from type I human diabetic subjects. *Diabetes* 1985; **34:** 526-531.

74. Chen MS, Hutchinson ML, Pecoraro RE, Lee WY, Labbe RF. Hyperglycemia-induced intracellular depletion of ascorbic acid in human mononuclear leukocytes. *Diabetes* 1983; **32**: 1078-1081.

75. Yue DK, McLennan S, Fisher E, Heffernan S, Capogreco C, Ross GR, Turtle JR. Ascorbic acid metabolism and polyol pathway in diabetes. *Diabetes* 1989; **38**: 257-261.

76. Lavery LA et al. Increased foot pressures after great toe amputation in diabetes. *Diabetes Care* 1995; **18:** 1460-1462.

77. Mwendwa FM, Otieno CF, Amayo EO, Kayima JK, Otieno P. Risk factor profile and the occurrence of microvascular complications in type 2 Diabetes at KNH. *East Afr Med J.* 2005; **82(suppl):** S 163-172.

78. Young MJ. Prevalence of diabetic peripheral neuropathy in the United Kingdom Hospital clinic population. *Diabetologia* 1993; **36:**150-154

79. Report of WHO convention Geneva, 1999, *WHO technical report* series 894

80. Sobngwi E *et al.* Diabetes in Africa. *Diabetes Metab* 2001*;* **27:** *628-634.*

81. Franklin GM, Kahn LB, *et al.* Sensory neuropathy in non insulin dependent diabetes mellitus, San Luis Valley Diabetes study. *Amer j. Epidemiology* 1990; **4:** 633-643.

82. Tesfaye S, Chaturvedi N. Prospective study on diabetic complications in type I diabetics. *N Engl J Med.* 2005; **352:** 341-350.

83. Malik M. Risk factors for diabetic foot. *Turk j. sci.* 1999; **2:** 34-36.

84. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study *Neurology* 1993; **43:** 817-824.

85. Isfahan Endocrinology and Metabolism Research Group: Peripheral neuropathy in type 2 diabetes mellitus in Isfahan, Iran. Prevalence and risk factors; *ISSN No. 1606-7754,* 2006; **14:** 1-3.

86. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Eng J Med* 1993; **329:** 977-986.

87. Pickett, J.B. Motor conduction velocity – faster in women. *Diabetologia* 1982; **23:** 544-548.

88. American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. *Clinical diabetes* 1999; **17:** 2180-2184.

89. Elizabeth S, Thomas P. Prevalence of and Risk Factors for Peripheral Arterial Disease in the United States (1999-2000), *Circulation* 2004; **110:** 738-743.

90. Andrew S, amanda J. Role of Systolic Blood Pressure and Plasma Triglycerides in Diabetic Peripheral Arterial Disease, The Edinburgh Artery Study, *Diabetes care* 1999; **22:** 453-458.

91. Annunziata L, Francesco P. Advanced Glycation End Products and Antioxidant Status in Type 2 Diabetic Patients With and Without Peripheral Artery Disease, *Diabetes Care* 2007; **30:** 670–676.

92. Elizabeth S, Keattiyo A. HbA1c and Peripheral Arterial Disease in Diabetes, The Atherosclerosis Risk in Communities study. *Diabetes Care* 2006; **29:** 877–882.

93. Holewski J. Prevalence of foot pathology and lower extremity complications in a diabetic outpatient clinic, *Journal of Rehab Research and Development* 1989; **26:** 35-44.

94. Ledoux R. Relationship between foot type, foot deformity, and ulcer occurrence in the high-risk diabetic foot, *Journal of Rehab Research and Development* 2005; **42:** 665–672.

95. Abbas M, Husam J. Foot Abnormalities in Diabetics, Prevalence & Predictors In Basrah, Iraq. *Pak J Med Sci* 2006; **22:** 229-233.

96. Carine H, Van S. Muscle Weakness and Foot Deformities in Diabetes Relationship to neuropathy and foot ulceration in Caucasian diabetic men, *Diabetes Care* 2004; **27:** 1668-1673.

14. APPENDICES

14.1 APPENDIX 1

STUDY PROFORMA

(Tick as applicable)

DEMOGRAPHIC DATA

Patient No.	Age	Gender M / F		Married? Yes	No	Usual Residence

Education level 0	1^0	2^0	3^0	Smoking history Never	Past	Current	Current Alcohol use Yes	No	Occupation

MEDICAL HISTORY
Diabetes

Year of diagnosis (diabetes)	Duration of diabetes	Mode of Treatment None	Diet only	OHA	Insulin	Compliance? Yes	no

Previous foot ulceration Yes	No	*Previous amputation* Yes	No

Other co-morbidity

Renal Disease Yes	No	Hypertension Yes	No	Heart Disease Yes	No	CVA Yes	No

Other medications/ treatment modalities

Anti-hypertensive Yes	No	Lipid lowering Yes	No	Anti-proteinuric Yes	No	Dialysis Yes	No	Eye laser? Yes	No

FOOT CARE: KNOWLEDGE, EDUCATION, PRACTICE

Have you ever received any education on foot care?	Yes	No

Are your feet examined whenever you visit the clinic?	Always	Sometimes	Never

How often do you inspect your feet?	Daily	Every1-7 days	>7 days

How often do you specifically clean your feet?	Daily	Other: specify

Do you regularly trim your nails? If yes, what instrument do you use?	Yes	No

Do you walk outdoors without shoes?	Always	Sometimes	Never

Do you inspect shoes before putting them on?	Yes	No

Do you exercise? If yes, what kind of shoes do you use when exercising?	Yes	No	

VISION

Do you experience any visual difficulties	Yes	No	Spectacles

PERIPHERAL VASCULAR DISEASE

On walking do you suffer from calf, thigh or buttock pain (cramp like) which is relieved by rest and recurs on resumption of walking?	Yes	No

Are you woken up at night by pain in the foot?	Yes	No

Do you experience pain in the leg at rest?	Yes	No

NEUROPATHY SYMPTOMATIC SCORE

	Symptom	Points
What is the sensation felt?	*burning, numbness, or tingling*	2
	fatigue, cramping, or aching	1

What is the location of symptoms?	Feet	2
	calves	1

Have the symptoms ever awakened you at night?	Yes	1

What is the timing of symptoms?	Worse at night	2
	present day and night	1

How are symptoms relieved?	walking around	2
	Standing	1

Total symptom score: 0 to 2 — normal, 3 to 4 — mild, 5 to 6 — moderate, 7 to 9 — severe

CLINICAL PARAMETERS

Height (m)	Weight (kg)	BMI (kg/m2)	Waist (cm)	Hip (cm)	Waist/Hip ratio	BP(mmhg)

FOOT EXAM

PARAMETER	**RIGHT FOOT**				**LEFT FOOT**			
Deformity [Absent(1)/ Present(2)]	Fore	mid	Hind		Fore	Mid	Hind	
Specify deformity								
Joint mobility[Normal(1)/Restricted(2)]	Fore	mid	Hind		Fore	Mid	Hind	
Pulses (Bounding, Normal, Weak, Absent)	B	N	W	A	B	N	W	A
Capillary refill	Normal	Delayed			Normal	Delayed		
Blanching on elevation	Yes	No			Yes	No		
Dependent rubor	Yes	No			Yes	No		
Achilles tendon reflex	Absent	Present Reinforced	Present Unreinforced		Absent	Present Reinforced	Present Unreinforced	
Vibration sense	Normal	Abnormal			Normal	Abnormal		
Pressure sensation	Normal	Abnormal			Normal	Abnormal		
Pinprick sensation	Normal	Abnormal			Normal	Abnormal		
Temperature sensation	Normal	Abnormal			Normal	Abnormal		
Other high risk lesions:	Tinea	Ingrown nail	Callus	Fissured skin	Tinea	Ingrown nail	Callus	Fissured skin

SHOE EXAM:

Material	( )	**Leather=1, canvas=2, plastic=3, other=4**
Size	( )	**Suitable=1, unsuitable=2**
Toe Box	( )	**Suitable=1, unsuitable=2**
Sole	( )	**Suitable=1, unsuitable=2**
Insoles	( )	**Suitable=1, unsuitable=2**

BLOOD SUGAR

RBS	

14.2 APPENDIX 2

PATIENT INFORMATION AND CONSENT FORM

Diabetes mellitus is a disease that affects multiple organ systems. Persons with Diabetes are at a higher risk of foot ulceration than persons without diabetes.

Once foot ulcers develop, they are often difficult to treat and take long periods of time to heal. The ulcers prevent one from taking part in normal day to day activities and when severe may result in admission to hospital. In some cases where early recognition and treatment was not offered, diabetic ulcers have resulted in the loss of a lower limb or part of the limb.

Diabetic foot ulcers can be successfully prevented. The aim of this study is to screen persons with Diabetes for well known factors that substantially increase the risk for foot ulceration.

You will then be placed in a risk category that indicates the likelihood that you might develop a foot ulcer in the near future.

We shall then offer recommendations that will enable you to reduce your risk for foot ulceration.

If you agree to take part in the study, a full medical history will be taken and physical examination done. A Random Blood Sugar level will be determined by standard pin-prick.

The procedures involved are part of the normal clinical care of all diabetic patients and constitute no adverse risk to you.

You shall be advised of the results of any tests done and these will be shared with your primary doctor. Where this is required, standard care will be offered in accordance with the procedures and protocols of Kenyatta National Hospital.

All information obtained will be strictly confidential and will not be revealed to other persons without your prior consent.

The quality of medical care given to you in this hospital will not be compromised by your refusal to participate in this study.

Participation in the study is voluntary and you are free to withdraw at any time.

I .... of .....understand the above and give my consent to participate in the study.

Signed ..... Date .....

I confirm that I have adequately explained to the patient the above.

Investigator ..... Date.....

14.3 APPENDIX 3

San Antonio Consensus Criteria [42]

- **Subclinical neuropathy**
  - Abnormal electrodiagnostic tests
    - **Decreased nerve conduction velocity**
    - **Decreased amplitude of evoked muscle or nerve action potentials**
  - Abnormal neurologic examination
    - **Vibratory and tactile tests**
    - **Thermal warming and cooling tests**
    - **Other**
  - Abnormal autonomic function tests
    - **Abnormal cardiovascular reflexes**
    - **Altered cardiovascular reflexes**
    - **Abnormal biochemical responses to hypoglycemia**
- **Clinical neuropathy**
  - Diffuse somatic neuropathy
    - **Sensorimotor or distal symmetrical sensorimotor polyneuropathy**
      - ***Primarily small-fiber neuropathy***
      - ***Primarily large-fiber neuropathy***
      - ***Mixed***
  - Autonomic neuropathy
    - **Cardiovascular autonomic**
    - **Abnormal pupillary function**
    - **Gastrointestinal autonomic neuropathy**
      - ***Gastroparesis***
      - ***Constipation***
      - ***Diabetic diarrhea***
      - ***Anorectal incontinence***
    - **Genitourinary autonomic neuropathy**
      - ***Bladder dysfunction***
      - ***Sexual dysfunction***
  - Focal Neuropathy
    - **Mononeuropathy**
    - **Mononeuropathy multiplex**
    - **Amyotrophy**

14.4 APPENDIX 4

DEFINITION OF TERMS

Diabetic patient

Patient on follow up at the diabetic outpatient clinic with a diagnosis of 'Diabetes Mellitus' following standard criteria

Foot ulcer

Any wound in the foot of a diabetic patient

Lower limb amputation

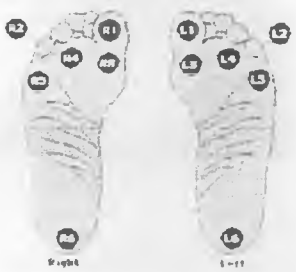
Below-knee or above-knee amputation. Does not include partial trans-metatarsal amputations or digit amputations

Neuropathy

Defined as a Neurological Disability Score of > 2

Insensate foot

Inability to feel the 5.07 (10g) monofilament in any of six recommended areas of the foot:



Peripheral arterial disease

Ankle Brachial Index of less than 0.9 using the Doppler method

Foot deformities

Common abnormalities in foot structure encountered during the study are illustrated below:

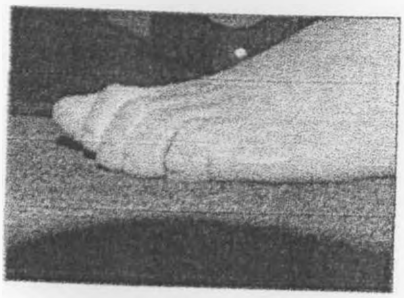


Fig. 1hammer toe

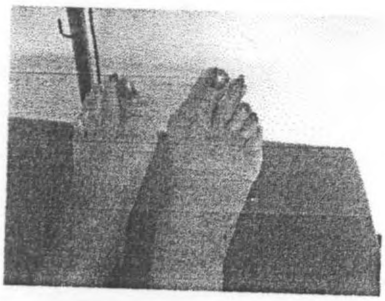


Fig 2. hallux valgus

Fig. 3 claw toe

Fig. 4 prominent metatarsals