DECLARATION

I hereby declare that this dissertation represents my own work. It has not previously been submitted for a degree, diploma or any other qualification at this or any other University.

Signed……

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Supervisor: Dr Lydia Korolova

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Co – supervisor: Dr Trevor Kaile.

ABSTRACT

Background: Diabetic nephropathy (DN) is a kidney disease that is a complication of diabetes. Pathogenesis of DN involves damage to the tiniest blood vessels which is followed by increased concentration of blood urea / creatinine and urine albumin excretion. DN is the leading cause of morbidity and mortality in patients with diabetes mellitus. Multiple factors and mechanisms such as interaction between hyperglycemia-induced metabolic and hemodynamic changes and genetic predisposition have been attributed to the development and outcomes of diabetic nephropathy. Diagnosis of DN in Zambia has been limited to the detection of elevated levels of creatinine, urea and urine albumin in the blood and urine respectively. We set out a comparative study to assess red blood cell distribution width (RDW) as a diagnostic marker of diabetic nephropathy in type 2diabetes mellitus patients.

Methods: A Structured questionnaire was used to capture age, sex, history of blood transfusion and cancer status of the participants. Urea, creatinine and urine albumin concentrations were measured and RDW determined in 122 type 2 diabetes mellitus patients and 61 non diabetic participants. Renal profile tests (creatinine, urea and urine albumin) were used as a proxy marker for diabetic nephropathy in type 2 diabetes mellitus patients. Patients with high renal profile tests (urea > 8.3 mmol/l, creatinine > 120µmol/l, urine albumin > 30mg/l) were considered to have diabetic nephropathy. This study was approved by the University of Zambia Biomedical Research Ethics Committee (Assurance No.FWA00000338, IRB00001131 of IOR0000774) and the ministry of health in Zambia.

Results: The results revealed that mean creatinine concentration for type 2 diabetes mellitus patients (750 $\pm$ 4.0 µmol/l) was significantly higher than control participants (250 $\pm$ 2.1 µmol/l) t – value 5.00; P – value = 0.003. The mean urea concentration for type 2 diabetes mellitus patients (4.2 $\pm$ 2.4 mmol/l) was significantly higher than control participants (2.2 $\pm$ 1.5 mmol/l). t – Value = 8.26; p – value 0.002.

The mean urine albumin concentration for type 2 diabetes mellitus patients (12.4 $\pm$ 3.3 mg/l) was higher than the control participants (12.2 + 2.9 mg/l) but the difference was not significant t – value 5.41; p – value 0.168. The mean RDW for type 2 diabetes mellitus patients (32.2 + 4.2 %) was significantly higher than the control participants (14.7 $\pm$ 3.8 %). t – value 7.58; p – value 0.001.The diagnostic performance of RDW and renal profile tests (urea, creatinine and urine albumin; standard proxy) were compared based on sensitivity, specificity, positive predictive value (PPV), negative predictive (NPV) and test efficiency.RDW was found to have sensitivity of 93%, specificity of 96%, PPV 97%, NPV 91% and efficiency of 94% which were very significant parameters to warrant the inclusion of RDW as one of the diagnostic markers of diabetic nephropathy.

Conclusion: Using diagnostic sensitivity, specificity, PPV, NPV and efficiency, it was found that RDW was a reliable and suitable biomarker for detecting diabetic nephropathy in type 2 diabetes mellitus patients.

DEDICATION

To my wife Ireen M. Nombwende and my daughters Leah and Dilnoza Nombwende, I owe it all to you.

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To Mrs Elina Malama for her invaluable help and guidance in compiling and typing this dissertation.

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TABLE OF CONTENTS

CONTENT **PAGE**

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS:

ACE - Angiotensin converting enzyme

ADP - Adenosine diphosphate

AGE - advanced glycosylation end product

ATP - Adenosine triphosphate

BMI - body mass index

DN - diabetic nephropathy

EDTA - ethylene diamine tetra acetic acid

ESRD - End stage renal disease

FBC - full blood count

FBS - fasting blood sugar

KGH - Kabwe General Hospital

MAPK - mitogen activated protein kinases

MCH - mean cell haemoglobin

MCHC - mean cell haemoglobin concentration

NO - Nitric oxide

OPD - Outpatient department

PKC - Protein Kinase C

RBC - red blood cell

RDW - red blood cell distribution width

ROS - Reactive oxygen species

TGF - Tumor growth factor

UAE - Urine albumin excretion

USA - United States of America

VEGF - Vascular epidermal growth factor

LIST OF ACRONYMS / DEFINITIONS

1. **Acute:** is a disease with either or both of:
    (a) A rapid onset, as in acute infection
    (b) A short course as opposed to a chronic course
2. **Anemia:** is a decrease in number of red blood cells (RBCs) or less than the normal quantity of hemoglobin in the blood.
3. **Epidemiology:** is the study (or the science of the study) of the patterns, causes, and effects of health and disease conditions in defined populations.
4. **Haemoglobin:** a conjugated protein, consisting of haem and the protein globin, that gives red blood cells their characteristic colour. It combines reversibly with oxygen and is thus very important in the transportation of oxygen to tissues
5. **Hemolysis**: (or **haemolysis**)—from the Greek αἷμα (aima, haema, hemo-) meaning "blood" and λύσις (lusis, lysis, -lysis) meaning a "loosing", "setting free" or "releasing" is the rupturing of erythrocytes (red blood cells) and the release of their contents (hemoglobin) into surrounding fluid (*e.g.*, blood plasma).
6. **Nephropathy:** disease of the kidneys.
7. **Diabetic nephropathy:** the nephropathy seen in later stages of diabetes mellitus, with first hyper filtration, renal hypertrophy, microalbuminuria, and hypertension, and later proteinuria and end-stage renal disease.
8. **Pathophysiology:** is the study of the changes of normal mechanical, physiological, and biochemical functions, either caused by a disease, or resulting from an abnormal syndrome
9. **Prognosis:** is a prediction of the chance of recovery or survival from a disease.
10. **Microvascular complications**: diseases affecting tiny blood vessels.
11. **Proteinuria**: an excess of serum proteins in the urine, as in renal disease or after strenuous exercise.

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SUPERVISOR'S CERTIFICATE

The dissertation of Grant Nombwende is ready for examination.

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CERTIFICATE OF APPROVAL.

This study dissertation entitled ***ASSESSMENT OF RED BLOOD CELL DISTRIBUTION WIDTH AS A BIOMARKER OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES MELLITUS PATIENTS REVIEWED AT KABWE GENERAL HOSPITAL*** by Grant Nombwende has been approved as partial fulfillment of the requirements for the award of the degree of Master of Science in Pathology (Hematology) by the University of Zambia.

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