Metabolic disorder characterized by chronic hyperglycemia biology essay

Science, Biology

1. 1Diabetes mellitusDiabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia, that is, high blood glucose, due to derangement in carbohydrate, fat, and protein metabolism that are associated with absolute or relative deficiencies in insulin secretion, insulin action or both 1, 2. The insulin hormone is responsible for regulating blood glucose in blood. Diabetes is a chronic health condition that can lead to several other medical problems if not managed properly 3. Diabetic patients normally present symptoms such as polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) as a compensatory way of maintaining osmolarity in the body; and weight loss. In America, estimated new cases of diabetes diagnosed each day are 1, 800, or approximately 655, 000 new cases each year6. According to the World Health Organization (WHO), diabetes affects more than 170 million people worldwide, and this number will rise to 370 million by 2030 9, 10. In Zimbabwe, though there is lack of current statistics on the disease and its prevalence, diabetes is among the top five chronic conditions seen in the out-patients clinic. The latest survey was done in 2005 which noted that the prevalence of diabetes among the adult population was 10% with a large number of people not aware that they had raised blood sugar levels. Diabetes mellitus is classified primarily into Type I and Type II, which are the main groups. There are sub groups such as gestational diabetes, which is diabetes secondary to other diseases and conditions such as, following pancreatic surgery. Type I is the insulin dependent diabetes mellitus which is mainly idiopathic (cause unknown) or caused by autoimmune disorders. These disorders cause destruction of islets cells in the pancreas which synthesize the hormone insulin leading to an

absolute insulin deficiency. 4 This group comprises of less than 10% of patients who are diabetic 2, 3, 4. The onset is usually acute, developing over a period of a few days to weeks. Over 95 percent of persons with type I Diabetes mellitus develop the disease before the age of 25. Type II Diabetes mellitus arises from insufficient production of the hormone insulin from beta cells of the pancreas and in conditions where the peripheral receptors; primarily muscles, liver and fat tissue, do not respond adequately to normal insulin levels, a condition known as insulin resistance. 4 Instead of the body to convert glucose into energy, glucose backs up into the bloodstream causing hyperglycaemia. This group makes up about 90% of cases of diabetes and has a slow and insidious onset. 2, 11 It usually occurs in people who are over forty years of age, obesity, sedentary life style, poor diet, hypertension and have family history of diabetes. Type II Diabetes mellitus was formerly known as adult onset but now it is increasingly found in young people especially in the 21st Century. 3, 5 It is also common in women especially those with a history of gestational diabetes, which is defined as any degree of glucose intolerance which onset or first recognized during pregnancy. The epidemiological data shows that about 80% of Type II diabetic patients are considered to be obese, having a body mass index (BMI) greater than or equal to 30 kg/m2, whereas the other 20% are above their ideal weight or have a BMI of 25 to 29. 9 kg/m2. 7 Diet alone can be used as a way of controlling Type II diabetes or by a combination of medications (oral hypoglycemics or insulin), exercise, and diet. 8A study by the Nigerian National Non-Communicable Disease Survey, reported a prevalence rate of about 2. 2% for Diabetic mellitus and over 90% are Type II

diabetics in Nigeria. Epidemiological data shows there are increasing incidences of Type II Diabetic mellitus and diabetic patients are at an increased risk of developing complications such as: nephropathy, retinopathy, neuropathy and atherosclerosis 3, 8, 13. This has made it become a global health concern since about one third of Type II will eventually have progressive deterioration of renal function 10, 11.

1. 2 Kidneys

Kidneys are a pair of vital bean-shaped organs in the body, located at the rear of the abdominal cavity in the retroperitoneum just below the rib cage one on each side of the spine. In adults each kidney is about 10-14 cm in length, 6 cm in width and is 4 cm thick. Each kidney weighs about 150 grammes. The kidneys are one of the most important sophisticated organs in the body which mainly serve as a natural filter of the blood keeping the body chemically balanced. The basic structural and functional unit of kidneys is a nephron. It regulates the concentration of water and soluble substances like sodium salts by filtering the blood, reabsorbing water, glucose and amino acids and excrete wastes such as urea, creatinine, uric acid, ammonium, other acids, electrolytes and extra water. Thereby, regulating blood volume, blood pressure, levels of electrolytes and metabolites, and blood pH, which is a homeostatic function. 14 Each kidney has about a million functional nephrons. A normal person’s kidneys process about 150 litres of blood to sift out of the body about 1500 ml of waste products produced by metabolism processes daily15In addition to removing wastes in the body, the kidneys also release three important hormones: erythropoietin, which stimulates erythropoiesis in the bone marrow which is production of red blood cells;

renin, which is a key part of the renin-angiotensin-aldosterone system useful in regulating blood pressure and calcitriol, the active form of vitamin D, which helps maintain calcium for bones and for normal chemical balance in the body. There are also special cells in the kidneys that monitor oxygen concentration in the blood; if the levels get low (hypoxia) they stimulate production of erythropoietin to increase red cells for more oxygen uptake in the lungs (2-4). If the kidneys fail to remove wastes, they accumulate in the blood and the body, a condition called azotemia, damaging the body and most likely the kidneys themselves leading to renal failure (3-5). Diabetes mellitus often damages the kidneys especially when the disease is not controlled by keeping blood glucose levels within the normal range.

1. 3 Diabetic nephropathy

Diabetic nephropathy is a progressive kidney disease that arise as a complication of Diabetes mellitus. 16 Kidney damage usually start 2 to 5 years after onset of hyperglycemia 17. It is the most common cause of chronic kidney failure and End Stage Renal Disease (ESRD) throughout the world in both developed and emerging nations 16, 19. In 1991, it was estimated that diabetes accounted for 40% of the newly diagnosed cases of ESRD20. Normally 10 to 20 years after onset of overt nephropathy about 20% will progress to ESRD since the rate of fall is highly variable from individual to individual. 21, 22, 23The disease is progressive and is more frequent in men18 than in women because of differences in lifestyle and testosterone deficiency that is common in men who are diabetic. 37 Patients with Diabetes mellitus should be diagnosed early for nephropathy since they

are at a high risk, this will help them in preventing the development or progression of diabetic nephropathy. 24Kidney failure is described as a decrease in the estimated glomerular filtration rate. Problems frequently encountered in kidney malfunction include abnormal fluid levels in the body, deranged acid levels, abnormal levels of potassium, calcium, phosphate, haematuria (blood in the urine) and (in the longer term) anaemia (7).

Pathogenesis of diabetic nephropathy

The progression of diabetic nephropathy is divided into 5 stages, 26In stage I there is hyperfiltration, which is caused by the effects of hyperglycaemia. 26, 27, 28 Hyperglycaemia causes abnormal glycosylation of nephrotic proteins that induce abnormal cellular changes by signalling through receptors which are expressed by cells in the gromerulus. This glycosylation takes place non-enzymatically. This abnormal signalling disrupt important paracrine signalling between podocytes and endothelial cells required for normal maintenance of the filtration membrane, hence damaging nephrons. The glycated end products can also produce of oxygen radicals that also damage nephrons causing loss of functioning nephrons. The kidneys in healthy individuals try to compensate for damaged nephrons by increasing the Glomerular Filtration Rate (GFR) in order to maintain homeostasis. In order to do this, the kidney secretes intra-renal vaso-active hormones, such as prostaglandin E2, that preferentially dilate afferent arterioles and other hormones such as angiotensin and catecholamines constrict efferent arterioles. Each glomerulus therefore receives more blood at a higher pressure and therefore filters more fluid into tubules, hence hyperfiltration.

This in turn overworks and damages mesangial cell and glomerular basement membrane, and stimulates release of cytokines leading to further nephron loss and also systemic hypertension. Systemic hypertension, in the setting of a glomerulus with dilated afferent and constricted efferent arterioles and abnormal basement membrane permeability causes even greater degrees of glomerular pressure and injury 25. Hyperfiltration has been shown to be present in early phases of diabetes, may exist for several years. 25, 27, 28 Unfortunately, there are no symptoms during the hyperfiltration stage. However, with early detection, proper glycemic control and lowering blood pressure makes this stage reversible and also retards the onset and progression of diabetic nephropathy. 22, 26, 28 Hyperfiltration does not always predict the future development of kidney injury in diabetes. 26During stage II, the gromeruli begin to show damage by allowing small amounts of albumin to be excreted in the urine, known as microalbuminuria. Between 13% and 41% of people have microalbuminuria when first diagnosed with type II diabetes. 27, 28 Individuals may remain in this stage for several years by achieving proper control of blood glucose levels and blood pressure. 26 In this stage GFR begins to decrease as microalbuminuria appears. Although the overall GFR is decreased, the glomerular filtration rate per nephron is increased, and hyperfiltration injury continues. This leads to further nephron loss, glomerular and interstitial scarring, and progressive renal failure. However this stage is still reversible. Stage III is when diabetic nephropathy is first noticeable. 26, 28 There is accumulation of nitrogenous waste products in the blood above their normal ranges, which is known as azotemia, some of which are toxic. These products include creatinine and

Blood Urea Nitrogen (BUN). 26 Early detection at this stage is vital to preserve kidney function and to delay or prevent ESRD. 33 Type II diabetes patients may remain in this stage for several years with proper glycemic control. 26Stage IV is the point when kidney damage is irreversible and is usually known as advanced clinical nephropathy. 26 At this stage, due to decreased surface area in kidneys, they will no longer be capable of excreting toxins adequately to maintain homeostasis the body and accordingly there is a progressive increase in BUN and creatinine levels. 11, 29 Most people in this stage are hypertensive secondary to increased production of renin. Because hypertension accelerates the progression to ESRD, there is need for proper bloodpressure control. 30 If not treated at this stage; uremia and death will follow within 7 to 10 years. 31Stage V or ESRD, is when the kidneys fail to function, the overall GFR severely decreased, and hypertension continues to worsen. 32 During this final stage, the kidneys cannot excrete toxins; maintain fluid, pH, and electrolyte balances; or secrete important hormones (renin, vitamin D, and erythropoietin). As a result, a multitude of symptoms become apparent that involve most major organ systems in the body. 30 Patients are sustained by haemodialysis at this stage.

1. 4 Creatinine

Creatinine is a by-product of creatine, a product produced from muscle. Creatinine is filtered by the glomerulus; therefore, serum creatinine level can be used as an indirect measure of glomerular filtration. As GFR diminishes, there is a rise in plasma concentrations of serum creatinine. 11 At the early

stage of kidney disease, there is compensatory hypertrophy and hyperfiltration of the remaining healthy nephrons which keep creatinine within normal range. Apparent elevated creatinine levels are noticed when the GFR falls to about 60-70 ml/min. 33 Normal serum creatinine is usually 0, 6 - 1, 1 mg/dl for women and 0, 7 – 1. 3 mg/dl for men. 34

1. 5 Blood Urea Nitrogen

Blood Urea Nitrogen (BUN) is a waste product produced after protein metabolism excreted as urine. It is parameter to diagnose the functionality of the kidney 35. It is a quite sensitive indicator of renal disease, becoming elevated when renal function drops to around 25-50% of normal. 36 Normally urea is filtered out of the blood and controlled to a range of 8 -24 mg/dl for men and 6 – 21 mg/dl for women 34. hydration BUN and creatinine are the simplest way to monitor kidney function.

1. 6 Statement of problem

Diabetes mellitus has quickly become a global health problem due to rapidly increasing population growth, aging, urbanization and increasing prevalence of obesity and physical inactivity 33. Nephropathy is one of the complications caused by Diabetes mellitus and has also fatal tertiary complications. Diabetic nephropathy occurs approximately in one third of Type II diabetic patients 8, 11, 12 and is on the rise. Is treatment effectively managing the patients to reduce the risk of having complications?

1. 7 Aim and Objectives

1. 7. 1 Aim

To determine the prevalence of Diabetic Nephropathy in Type II Diabetic patients attending Parirenyatwa Diabetic Clinic.

1. 7. 2 Objectives

To evaluate creatinine and urea concentration in Type II diabetic patients attending Parirenyatwa Diabetic Clinic. To assess the progressive deterioration of renal function in type II diabetic patients attending Parirenyatwa Diabetic Clinic.

1. 8Hypothesis

Null hypothesis(H0): Less than one third of type II diabetic patients have elevated values of urea and creatinine . Alternative hypothesis(H1) : more than one third of type II diabetic patients have elevated values of urea and creatinine.

CHAPTER TWO : MATERIALS AND METHODS

2. 1 Materials

Refer to appendix

2. 2. Study site

The project was conducted at Parirenyatwa Group of Hospitals Diabetic Clinic.

2. 3 Study design.

A laboratory based cross-sectional study was carried out on the serum samples of diabetic patients attending the Diabetic Clinic at Parirenyatwa Group of Hospital (PGH).

2. 4 Study subjects

Inclusion criteria

Patients who have been documented as diabetics for at least 12 months who routinely attend Parirenyatwa Group of Hospitals Diabetic Clinic.

Exclusion criteria

Patients with a history of kidney problems and congestive cardiac failure were excluded from the study. Pregnant women, smokers and hyperlipidemics

2. 5 Ethical considerations

Permission to carry out the project was sought from authorities in charge of the Diabetic Clinic, the Consultant and the ward manager. Ethical approval was sought from the Joint research Ethics Committee of the College of Health Sciences and Parirenyatwa Group of Hospitals (JREC/346/12)

2. 6 Sample size

The sample size (n) was calculated to be 239 samples (refer to appendix for calculation) using the assumption that kidneys of one third of type II diabetic patients deteriorates in function.

Laboratory Methods

collection of sample

Residual samples left during routine testing of type II diabetic patients who have been on treatment for more than 12 months were used.

2. 7. 2 Sample identification and patient confidentiality

After permission from the Diabetic Clinic at Parirenyatwa Group of Hospitals, Public Health Laboratories and the ethical approval from Joint Research Ethics Committee of the College of Health Sciences was given, samples were collected and de-identified for confidentiality by giving numeric codes E001…, to E239[This is part of Ethical considerations].

2. 7. 3Procedure of the study

The batched samples were thawed only once and analysed for creatinine and BUN levels using the Mindray BS 120 chemistry analyser. The analyser was first calibrated and control samples were analysed before use. Control samples were made sure to be within their reference range for measure of analyser and reagents integrity. The samples were then run and results recorded for statistical analysis

2. 7. 4 Principle of tests

Estimation of plasma creatinine was done using modified Jaffe’s method 9-10. Serum urea was estimated using the Urease-glutamate Dehydrogenase, UV method.

The principle of Jaffe's method

Creatinine + Picric acid OH- Creatinine-picric acid complexAt an alkaline solution, creatinine combines with picric acid to form an orange-red colored complex. The absobency increase is directly proportional to the concentration of creatinine. This method is done using an absorbance of 510nm.

The principle of Urease-glutamate Dehydrogenase, UV method

Urea + 2H2O urease 2 NH4+ + CO2 2-α-Oxoglutarate +NH4+ + NADH GLDH L-Glutamate + NAD+ +H2OUrea is hydrolysed by urease, and one of the products, ammonia, helps to turn NADH to NAD+ with the catalysis of GLDH. The absorbency decrease is directly proportional to the concentration of urea. This is measured at 340nm.