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Relation of Calcium-Phosphate Levels and Severity of Diabetic Kidney Disease on Hypertension Case in Non-Dialysis Patients in Dr. Soetomo General Teaching Hospital, Surabaya, Indonesia

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Abstract

Diabetic kidney disease develops at approximately 40% of patients who are diabetic. Diabetic kidney disease is characterized by a decline in glomerular filtration rate (GFR). The diminished GFR arises phosphate retention which is a key early step in a pathologic cascade leading to vascular calcification and an increase in hypertension. The study aims to analyzed relation of calcium-phosphate levels and severity of diabetic kidney disease on hypertension case in non-dialysis patients and be able to inhibit the progression of diabetic kidney disease in non-dialysis patients by controlling calcium-phosphate levels and hypertension. Blood and urine samples were examined and recorded. Serum calcium and serum phosphate in blood sample, protein urea contents in urea sample and also hypertension were checked and examined. Serum creatinine used to determine severity level of disease using MDRD Formula. Data analysis was carried out using MARS 2.0 version and validated by SPSS software v.26 for Windows. With every increase in the severity of diabetic kidney disease, there was a decrease in calcium. Calcium levels dropped from 8.7 to 7.4 at the highest severity. The increase in the severity of diabetic kidney disease occurred starting at phosphate levels of 2.5 where the levels would increase along with the severity. Hypertension began to occur at the level 2 of severity. Every one increase in the severity, it was followed by an increase in hypertension of 0.7. Therefore, this study found that calcium-phosphate levels cause hypertension through the severity of diabetic kidney disease. Phosphate levels increase dan calcium levels decrease as the increase of the severity diabetic kidney disease.

Keywords: Diabetic kidney disease, calcium-phosphate levels, hypertension, non-dialysis patient.

Introduction :

Diabetic kidney disease develops at approximately 40% of patients who are diabetic[1]. Two main types of diabetes mellitus are classified into type-1 (autoimmune destruction of pancreatic β-cells and insulin dependent) and type 2 (Insulin resistance and deficiency)[2]. Type-2 diabetes accounts for about 75–85% of diabetes cases[3]. Diabetic kidney disease is a syndrome characterized by progressive increase in urinary albumin excretion and a decline in glomerular filtration rate (GFR), which occur in association with hypertension[4].

Diabetic kidney disease develops more than a decade after diabetes onset with the earliest sign as microalbuminuria (>30 mg/day), then progresses to macroalbuminuria (>300 mg/day) and decline in glomerular filtration rate (GFR), eventually terminating in ESRD[5]. Proteins present in the urine are toxic to the tubules and can result in tubular damage due to protein overloading of intracellular lysosomes, stimulation of inflammatory cytokine expression, and extracellular matrix protein production[6]. The diminished GFR arises phosphate retention which is a key early step in a pathologic cascade leading to vascular calcification[7].

Kidney is important organ in the regulation of mineral metabolism. Calcium and phosphate are minerals that are metabolized in the kidney[8]. Kidney regulates several hormones that regulate body metabolism include parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23)[9]. Hypocalcaemia leads to the increased

PTH production and secretion, then PTH rapidly increases renal calcium reabsorption and over hours even days, enhances osteoclastic bone resorption and liberates both calcium and phosphate from the skeleton[10].

High calcium-phosphate product and serum phosphate have been linked to risk of the incidence of vascular calcification[11]. Medial artery calcification emerges as an exceptionally strong predictor of mortality in patients with type 2 diabetes[12,13]. Aortic stiffness conveys impact of diabetes-enhanced cardiovascular mortality[13,14]. It is known that calcification of the vessel is associated with arterial stiffening is a major cause of isolated systolic hypertension in the elderly[15]. Functional impairment of vascular calcification is indicated by arterial stiffness which is mostly due to larger medial calcifications[16].

Diabetic kidney disease is seen to becoming epidemic in many countries and main cause of end-stage renal disease requiring dialysis[17]. Haemodialysis is an artificial renal replacement therapy with the aim of eliminating the remnants of metabolic products (protein) and correcting fluid and electrolyte balance disorders between the blood and dialysate compartments through semipermeable membrane that acts as an artificial kidney[18]. But there is still little evidence of effect of calcium-phosphate levels on hypertension cases due to the severity of diabetic kidney disease in non-dialysis patients. Further research is needed to answer the relevant questions of the said topic.

The study aims to analysis relation of calcium-phosphate levels and severity of diabetic kidney disease on hypertension case in non-dialysis patients. The aim of this study is to be able to inhibit the progression of diabetic kidney disease in non-dialysis patients by controlling calcium-phosphate levels and hypertension.

Materials and Methods :

Study Design and Participants :

This study was an observational analytic study with a cross sectional design which was carried out for 2 months at the outpatient polyclinic Dr. Soetomo Hospital, Surabaya, Indonesia. The study's subjects were diabetic kidney disease non-dialysis patients who underwent outpatient treatment at Dr. Soetomo Hospital, Surabaya, Indonesia. Criteria for participating patients were divided based on inclusion criteria (both male and female, aged 21-70 years and diabetic kidney disease non-dialysis patients who determined by observing the presence of albuminuria and the degree of diabetic kidney disease and undergoing outpatient treatment at the diabetes and kidney hypertension polyclinics Dr. Soetomo Hospital) and exclusion criteria (experiencing severe complications from diabetes and kidney that caused the subject to be hospitalized due to acute kidney injury). The study protocol was approved by Health Research Ethics Committee (HREC) of Dr. Soetomo Hospital, Surabaya, Indonesia (approval number; 1311/KEPK/VII/2019).

Data Collection :

Data collection was carried out by recording data from medical records and laboratory examination results from blood and urine samples of 59 patients into the registry of research subjects.

Analysis of Blood and Urine Samples :

The blood and urine samples obtained were analysed in the Clinical Pathology Laboratory of Dr. Soetomo Hospital, Surabaya, Indonesia for examination of pre-prandial blood sugar level, 2 hours post prandial, HbA1C, complete urine and also serums of creatinine, calcium and phosphate. Hypertension checks were carried out at the polyclinic Dr. Soetomo Hospital, Surabaya, Indonesia when the subjects had routine check-ups.

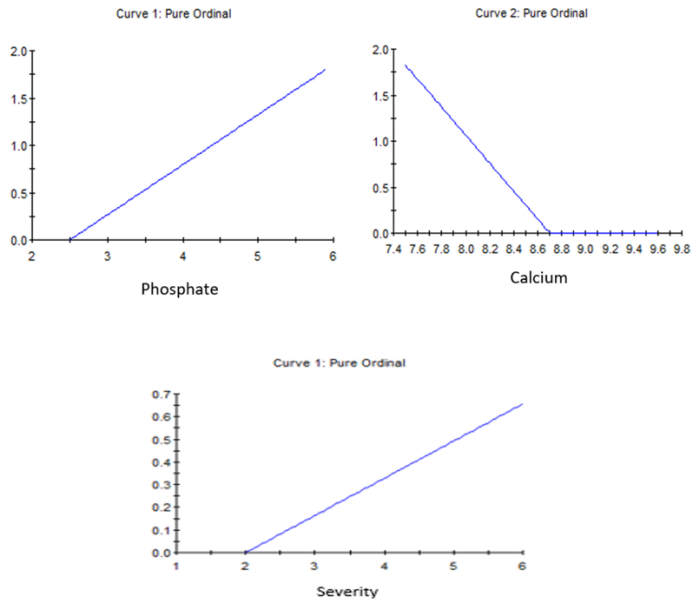
Data analysis :

Creatinine levels were included in the MDRD formula. The severity of the disease was carried out by MDRD Formula. Serum calcium levels, serum phosphate levels and hypertension were analyzed by statistical tests. Regression analysis was carried out. Data analysis was carried out using MARS v.2.0 and validated by SPSS v.26 for Windows.

Results and Discussion :

There was an indirect relationship of phosphate and calcium to hypertension through the severity of diabetic kidney disease. The relationship between calcium-phosphate to severity was shown by Y=2.921+0.530*BF1+1.522*BF3; BF1=max (0, PHOSPHATE-2,500); BF3=max (0,8,700-CALCIUM) equation. This equation meant that there was a linear relationship between calcium-phosphate and the severity if the calcium concentration was at least 7.4 and not more than 8.7. While the phosphate concentration at 2.5. The relationship between calcium and severity was shown by the opposite relationship, meant that the higher calcium the lower the severity. The relationship between phosphate and severity was shown by linear equation, meant that the higher the phosphate, the higher the severity. The relationship between severity and hypertension was shown by a linear relationship through Y=1.188+0.164*BF1; BF1=max (0, STADIUM-2,000) equation.

Figure 1. The results of phosphate and calcium to hypertension through the severity of diabetic kidney disease.



With every increase in the severity of diabetic kidney disease, there was a decrease in calcium. Calcium levels dropped from 8.7 to 7.4 at the highest severity. The increase in the severity of diabetic kidney disease occurred starting at phosphate levels of 2.5 where the levels would increase along with the severity of diabetic kidney disease with $p < 0.05$ and coefficient of determination (R^2) = 28%. Hypertension began to occur at the level of severity of 2, the higher severity of diabetic kidney disease, hypertension will increase. The severity of diabetic kidney disease affected hypertension, every one increase in the severity of diabetic kidney disease was followed by an increase in hypertension of 0.7.

Based on study that had been done, it showed that serum phosphate levels were strongly and independently related to the severity of diabetic kidney disease in non-dialysis diabetic kidney disease patients. The severity of diabetic kidney disease itself was related to the incidence of hypertension.

As the kidney function declines, serum phosphate levels rise and subsequently induce the development of hypertension. Cross-sectional studies in ESRD patients show that the presence of hyperphosphatemia was significantly associated with hypertension[19]. Hyperphosphatemia caused mineral deposition in the vascular wall (i.e., metastatic calcification) and this leads to arterial wall stiffened and vessel non-distensibility[13,14,15]. Increased arterial stiffness closely linked to increased risk of hypertension and an independent predictor of hypertension[20.] Arterial stiffening accelerates pulse wave velocity, thus widening pulse pressure and leading to hypertension[15].

The declining kidney function leads to deficiency of 1,25-dihydroxyvitamin D, the substance that serves to increase serum calcium by increasing ca absorption and resorption and also decreasing calcium excretion, because of the diminished activity of 1-α hydroxylase in the kidney as well as the increased of serum FGF-23 levels (direct inhibitor of 1-α hydroxylase activity). This leads to hypocalcaemia that, together with hyperphosphatemia, provide a powerful stimulus for PTH secretion and cause the secondary hyperparathyroidism[21].

Findings from experimental, mechanistic, observational and interventional studies suggest that PTH contributes to the regulation of aldosterone secretion in the zona glomerulosa of adrenal glands. The absolute aldosterone excess is related to the higher risk of development and progression of arterial hypertension[22].

This study obtained relation of calcium-phosphate levels and severity of diabetic kidney disease on hypertension case in non-dialysis patients and able to inhibit the progression of diabetic kidney disease in non-dialysis patients by controlling calcium-phosphate levels and hypertension.

Conclusion :

In summary, this study found that calcium-phosphate levels cause hypertension through the severity of diabetic kidney disease. Phosphate levels increase dan calcium levels decrease as the increase of the severity diabetic kidney disease. Diabetic kidney disease causes hypertension.

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CONFLICTS OF INTEREST :

The authors have no conflicts of interest to declare.

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