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Renal cortex echogenicity increases degree of retinopathy in diabetes mellitus

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ABSTRACT

BACKGROUND

The number of people with diabetes mellitus (DM) is increasing due to population growth, aging, and increasing prevalence of obesity. Diabetic retinopathy and diabetic nephropathy are two main complications of DM. Some studies suggest a correlation between diabetic nephropathy and diabetic retinopathy. However, other studies found that renal cortex echogenicity is associated with chronicity of kidney disease and renal histopathology. The aim of this study was to determine whether there is a correlation between renal cortex echogenicity as determined by renal ultrasonography and degree of retinopathy as determined by funduscopy in subjects with DM.

METHODS

A cross sectional study was conducted on 41 DM subjects from September to November 2014. Data obtained by anamnesis, physical examination, and examination of ureum, creatinine, urinalysis, glycated hemoglobin (HbA1c), renal and urinary tract ultrasonography and funduscopy, were collected from all subjects. Blood samples were taken from the median cubital vein for biochemical measurements using COBAS automated analyzers. Normality of data distribution was tested using the Shapiro-Wilk test. To determine the relationship between variables the Spearman correlation test was used.

RESULTS

Using the Spearman correlation test, a strongly significant correlation was found between degree of renal cortex echogenicity and degree of retinopathy (r=0.773; p=0.0001). A significant relationship was also found for the degree of retinopathy with age (r=0.317; p=0.044), duration of diabetes mellitus (r=0.639; p=0.0001) and HbA1c (r=0.681; p=0.001).

CONCLUSION

This study found that renal cortex echogenicity increased the degree of diabetic retinopathy in diabetic subjects. Renal ultrasonography for patients with type 2 DM has a great role in diagnosing and grading diabetic retinopathy.

Keywords: Renal cortex echogenicity, retinopathy, subjects with diabetes mellitus

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INTRODUCTION

Various epidemiological studies have shown an increasing trend in the incidence and prevalence of diabetes mellitus type 2 (DM) in various parts of the world. The World Health Organization (WHO) predicts a substantial increase in the number of people with diabetes in the coming years. For Indonesia, the predicted increase will be from 8.4 million in 2000 to approximately 21.3 million in 2030.[1] Diabetic retinopathy (DR) and diabetic nephropathy (DN) are two main complications of DM. Approximately 40% of diabetic patients have renal involvement.[2] Diabetic nephropathy is the most common renoparenchymatous disease, accounting for 40% of cases of renal disease.

There are studies showing that ultrasonographically determined kidney size and cortex echogenicity are associated with chronicity and renal histopathology.[3,4] Increase in echogenicity is proportional to the increase in renal failure. After 5 years, approximately 25% of type 1 patients will have retinopathy. After 10 years, almost 60% have retinopathy, and after 15 years, 80% have retinopathy. Of type 2 patients over the age of 30 years who have a known duration of diabetes of less than 5 years, 40% of patients taking insulin and 24% of those not taking insulin have retinopathy.[5]

Proliferative DR and proteinuria secondary to DN are late complications of overt DN, usually occur 10 to 15 years after the establishment of the DM, and are closely related to each other. The relationship between DN and DR has been described, with the finding of an association between the presence of gross proteinuria in the basic examination and 96% increased risk of proliferative retinopathy.[6] There are some similarities in the appearance of DR and DN, both being microvascular disorders with microscopic evidence of thickening of the capillary basement membrane.[7] The pathophysiology of DN approximates that of DR, beginning with an increase in vascular permeability. Increased selective permeability for albumin in early DN is caused by the loss of polarity along the glomerular basement membrane and mechanisms of disorders of the eye because of the possibility of damage to the connections between the cells. The occurrence of proteinuria and proliferative retinopathy are both associated with poor glycemic control, duration of diabetes, and hypertension.[6,8]

Most of previous studies found a relationship between renal microvascular complications of diabetes characterized by microalbuminuria and the degree of retinopathy. However, to date no studies have been conducted linking renal cortex echogenicity with retinopathy. Some recent studies have proved that the presence of retinopathy may indicate risk of nephropathy.[6] Based on the above, the objective of this study was to determine the correlation between renal cortex echogenicity and the degree of retinopathy in diabetic patients.

METHODS

Research design

A cross-sectional study was conducted at H Adam Malik Hospital, Medan, between September and November 2014.

Research subjects

Subjects were recruited from the outpatient internal clinics, the inclusion criteria were: male or female subjects with DM, aged ≥18 years, being in stable condition and willing to participate in this research. Patients who were not willing to undergo the screening examinations, pregnant women, patients with anemia, hypertensive retinopathy, or other eye diseases (such as cloudiness of the eye) on funduscopy, were excluded from the study. Based on a significance level of 0.05 and power of 85%, the size of the sample was found to be 40.

Interviews

All subjects were interviewed using a questionnaire consisting of the subject's name, age, gender, duration of diabetes, smoker or non smoker status, a history of either disease in the patients and their families.

Measurements

The subject's weight was measured using Omron scales and height was determined by a Kenko height measuring instrument. A kidney and urinary tract ultrasound was carried out and classified as follows: Grade 0: normal (renal cortex echogenicity less than that of liver); Grade I: renal cortex echogenicity equal to that of liver; Grade II: renal cortex echogenicity more than that of liver, but less than that of the renal sinuses; Grade III: renal cortex echogenicity is equal to that of the renal sinuses. Direct fundoscopy was carried out and the results classified as normofunduscopy, non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

Laboratory analysis

Laboratory studies included ureum (mg/dL), creatinine (mg/dL), urinalysis, and glycated haemoglobin (HbA1c,%). Blood samples were taken from the median cubital vein for biochemical measurements using COBAS automated analyzers in the Clinical Pathology Laboratory of H. Adam Malik Hospital, Medan, Indonesia.

Statistical analysis

Normality of the data distribution was tested using the Shapiro-Wilk test. To determine the relationship between variables, the Spearman correlation test and Fischer's exact test were used. Statistical analysis was performed using SPSS, where $p<0.05$ was declared to be significant.

Ethical clearance

The study protocol was approved by the Health Research Ethical Committee of the Faculty of Medicine, Sumatera Utara University. All study subjects signed written informed consent after having been informed about the aims and benefits of the study.

RESULTS

This study involved 41 patients with diabetes mellitus (DM) who had met the inclusion and exclusion criteria. Most patients were female, comprising 22 people (53.7%). The mean age of the patients involved in this study was 62.49 ± 9.73 years. Respondents who were smokers was 12 people (29.3%) and 24 DM patients involved in this study had a family history of diabetes. Mean duration of diabetes for all patients was 10.71 ± 7.92 years (Table 1). Mean ureum and creatinine concentrations were 30.81 ± 12.4 mg/dL and 1.02 ± 12.4 mg/dL, respectively. Mean GFR value was 56.96 ± 21.65 mL/min. Mean body mass index (BMI) of the respondents was 24.82 ± 4.10 kg/m^2. The mean HbA1c concentration was 9.08 ± 1.97%. A total of 34 patients (82.9%) had +1 urinary protein (Table 1).

Table 1. Distributions of demographic characteristics and laboratory data (n=41)

Demographic characteristics	n (%)
Gender, n (%)	
Male	19 (46.30)
Female	22 (53.70)
Age (years)*	62.49 ±9.73
History of smoking, n (%)	
Yes	12 (29.30)
No	29 (70.70)
Family history, n(%)	
Yes	24 (58.50)
No	17 (41.50)
Laboratory data	
Duration of diabetes (years)*	10.71 ±7.92
Ureum (mg/dL)*	30.81 ± 12.40
Creatinine (mg/dL)*	1.01 ± 0.47
GFR (mL/min) *	56.96 ± 21.65
Body mass index (kg /m^2)*	24.82 ±4.10
HbA1c (%)*	9.08 ± 1.97
Proteinuria, n(%)	
Negative	6 (14.60)
+1	34 (82.90)
+2	1 (2.40)
Degree of retinopathy, n(%)	
Normal	4 (9.76)
NPDR	29 (70.73)
PDR	8 (19.51)
Renal cortex echogenicity, n (%)	
Grade 0	8 (19.51)
Grade I	21 (51.22)
Grade II	12 (29.27)

*Mean ± SD

Table 2. Correlation of age, laboratory data, and renal cortex echogenicity with the degree of retinopathy

	r	p
Age	0.317	0.044
Duration of diabetes	0.639	0.0001
Ureum	0.021	0.902
Creatinine	0.004	0.967
GFR	0.092	0.568
Body mass index	0.001	1.000
HbA1c	0.681	0.001
Proteinuria	0.179	0.264
Renal cortex echogenicity	0.773	0.0001

GFR= glomerular filtration rate; HbA1C= glycated hemoglobin

Using the Spearman correlation test, a strong and significant correlation was found between the degree of renal cortex echogenicity and degree of retinopathy (r= 0.773; p=0.0001) (Table 2). A weakly positive correlation was obtained between age and degree of retinopathy (r=0.317; p=0.044). Furthermore, the variables duration of diabetes and HbA1c had a moderate positive correlations of 0.639 and 0.681, respectively, with the degree of retinopathy (Table 2). Thus a longer suffering from diabetes results in a more severe degree of retinopathy. Similarly, a higher HbA1c concentration results in a more severe degree of retinopathy in patients with DM.

DISCUSSION

Diabetic retinopathy and diabetic nephropathy are two major microvascular complications of diabetes. Prevention of the occurrence of this complication is very necessary to reduce the morbidity and mortality of the number of people with diabetes that are quite large from year to year. This study aimed to determine the correlation between the degree of renal cortex echogenicity and degree of retinopathy in diabetic patients. This study found a significant and strongly positive correlation between the degree of renal cortex echogenicity and degree of retinopathy. The positive value of the correlation shows that the higher the degree of renal cortex echogenicity, the more severe the degree of retinopathy.

Results of previous studies showed an increase in renal cortex echogenicity in line with the increase in renal failure.[3,9] In addition, these studies also found that cortex echogenicity correlated positively with the parameters of renal histopathology, the significant one being glomerulosclerosis which is a glomerular lesion observed in diabetic nephropathy grades III and IV. Thus, apart from albuminuria, we can also predict the occurrence of renal microvascular complications in diabetic patients by assessing cortex echogenicity.

In our study, the mean duration of diabetes of the study subjects was 10.7 years, while according to the literature, patients suffering from diabetes for >10 years are likely to have stage III diabetic nephropathy (diabetic incipient nephropathy), and are already showing early signs of nephropathy such as microalbuminuria and thickening of the basement membrane.[2,10,11]

Most of previous studies searched for a relationship between diabetic kidney disease characterized by microalbuminuria and the degree of retinopathy, with a positive correlation being found in two studies. This correlation may be explained by assuming that the appearance of microalbuminuria is a sign of a general vascular dysfunction, including retinal vascular dysfunction.[12,13] In our study, 34 (82.9%) of the patients entering the study had proteinuria of +1, which could explain the positive correlation between the degree of cortex echogenicity and the degree of retinopathy. Albuminuria and associated complications appear to be primarly caused by enzymes with a susceptibility to hyperglycemia, that are involved in the metabolism of anionic components of the extracellular matrix (eg heparan sulfate proteoglycan).[12]

Thickening of the basement membrane, both in the retinal and glomerular capillaries, are seen in advanced stages of diabetic retinopathy and nephropathy. In addition to the above mechanisms, kidney damage may also accelerate retinopathy

where it is associated with higher levels of fibrinogen and serum lipoproteins.[14]

In the statistical analysis of the correlations of all basic characteristics and the degree of renal cortex echogenicity, two variables were found that had a significant correlation with the degree of renal cortex echogenicity, namely duration of diabetes and HbA1c. The positive correlation obtained between duration of diabetes and degree of kidney cortex echogenicity was of moderate, meaning that a longer duration of diabetes also increases the degree of cortex echogenicity. This is similar to the results of a study by Inassi et al.[15] which confirmed that the increasingly frequent occurrence of microproteinuria as a marker of diabetic nephropathy was associated with increased duration of diabetes. Similar results were observed in the studies of Chowta et al.[16] and Klein et al.[7]

Furthermore, the variable HbA1c correlated moderately with the degree of cortex echogenicity. Thus we concluded that the higher the concentration of HbA1c, the more severe the degree of cortex echogenicity in the diabetic patients in this study. The mean HbA1c concentration was 9.08%, indicating that the study subjects were in a state of poor glycemic control. This positive correlation was also found in a study by Java et al.[17] and can be explained by the mesangial extensions/expansions that are directly induced by hyperglycemia resulting in increased matrix production or matrix protein glycosylation. In vitro studies show that hyperglycemia stimulates mesangial cell matrix formation. Based on the data analysis looking for a correlation of all basic characteristics with the degree of retinopathy, there were three variables having a significant correlation with the degree of retinopathy, namely: age, duration of diabetes, and HbA1c. Meanwhile other variables, namely ureum, creatinine, GFR, BMI and proteinuria did not correlate significantly with the degree of retinopathy.

The correlation obtained between age and degree of retinopathy was a weak correlation, meaning that with age the degree of retinopathy will also increase. Furthermore, duration of diabetes and HbA1c had a moderate correlation with the degree of retinopathy. Thus we concluded that the longer the patient suffers from diabetes, the higher the degree of retinopathy. Similar findings were found in a study by Thomas et al.[18] who found that the incidence of referable retinopathy was positively and independently associated with the known duration of type 2 diabetes. For participants on dietary treatment with a duration of diabetes of less than five years, the cumulative incidence of referable diabetic retinopathy at one, two, and three years was 1.83, 3.66, and 5.45 per 1000 people, respectively.

Similarly, the higher the concentration of HbA1c, the more severe the degree of retinopathy in the diabetic patients in this study. Identical findings were found in a study by Ng et al.[19] where the investigators found a positive correlation between HbA1c levels and the degree of retinopathy. This can be explained by the mechanism of the increasing transduction activation of the diacylglycerol (DAG) - protein kinase C (PKC) pathway identified in the vascular tissue of diabetic animals, and in vascular cells exposed to a high glucose level. This would trigger abnormalities of the blood vessels, including changes in blood flow, extracellular matrix deposition, thickening of the basement membranes, increased permeability, and neovascularization. In addition it was that found the relation between hyperglycemia and apoptosis of capillary pericytes of the retina, where the pericytes containing glutathione, which acts as a basic defense against peroxidation, are reduced in conditions of high glucose. High glucose levels followed by fluctuations in glucose levels will trigger the death of retinal capillary pericytes.[17]

One limitation of this study is the relatively small sample size, involving only one health care center. Another limitation is that no histopathological examination and no quantitative assessment of albuminuria were carried out, since previous studies found that the

state of microalbuminuria (30-300mg/24 hours) could have predicted the occurrence of microvascular complications.[20]

The clinical implication of this study is that the retinopathy parameter can be used as a predictor of the start of nephropathy in diabetic patients, and vice versa. And it can improve the prevention and treatment as early as possible to reduce the worsening of the disease. Further studies are needed, using larger samples in multicenter settings, that include renal histopathology and quantitative albuminuria examination of the research subjects.

CONCLUSION

This study found that a higher degree of renal cortex echogenicity increased the degree of retinopathy in subjects with diabetes mellitus.

CONFLICT OF INTEREST

The authors who have taken part in this study declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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