Proteinuria and Ischemic Stroke in Diabetes.

البيلة البروتينية و السكتة الدماغية الذاوية لدى مرضى السكري.

Dr. Riadh al- Saigh M.B.Ch.B,D.M, F.I.C.M.S (med.),C.A.B.M.(med.), F.I.C.M.S(nephrology). Depat.of Med.Coll.of Med., Uni.of Kerbala.
Prof .Adnan M.Al-Jubori M.R.C.P.(UK).Deparment of Med. Coll.of Med.,Uni. Of Baghdad.

Key wards: WHO=World Health Organization, OR=odd ratios,95%CI= 95% confidence intervals,SBP= systolic blood pressure, DBP=diastolic blood pressure, GBM=glomerular basement membrane,NS=not significant,FBG=fasting blood glucose,

خلاصة البحث:

المقدمة:

البيلة البروتينية هي عامل خطورة مستقل لامراض الجهاز القلبي الوعائي في مرضى الزرب السكري اللاانسوليني .ان الهدف من هذه الدراسة هو تقييم العلاقة بين البيلة البروتينية و السكتة الدماغية الذاوية لدى مرضى الزرب السكري الانسوليني و كذلك لتحديد فيما اذا كانت البيلة البروتينية هي عامل خطورة مستقل لحصول السكتة الدماغية الذاوية.

طرق العمل:

اجرينا دراسة حالات مقارنية على خمسة و ثلاثين(اثنين و عشرين امراة و ثلاثة عشر رجلا) مريضا مصابا بداء السكري و سكتة دماغية ذاوية لاول مرة بسبب انسداد شرياني خثري ،و مائة و خمسة مرضى مصابين بداء السكري اللانسوليني بدون سكتة دماغية ذاوية (سبعين امراة و خمس و ثلأثين رجلا).لقد كان كلى الفئتين من المرضى متوافقين في الجنس والعمر و مدة الاصابة بداء السكري .لقد استعملت معايير منضمة الصحة العالمية لتاكيد تشخيص السكتة الدماغية الذاوية المؤكدة او المحتملة. البيلة البروتينية في هذه الدراسة هي معدل الزلال خلال اربع و عشرين ساعة وتساوي خمس و سبعين الى سبعمائة و خمسين غرام باليوم الواحد. ان عوامل الخطورة المشتملة في هذه الدراسة هي التدخين،فرط ضغط الدم الانقباضي او الانبساطي او كلاهما،معامل كتلة الجسم ،كوليسترول مصل الدم الاجمالي، فرط ضغط الدم و البيلة البروتينية.

النتائج:

لقد كانت النتائج فرط ضغط الدم الانقباضي: النسبة المبهمة= ١ و مدى الثقة ٩٥ ٪=١،١- ٣,٨ و قيمة ب=٠,٠٣ ؛ فرط ضغط الدم الانبساطي النسبة المبهمة= ٢,٣ و مدى الثقة ٩٥ ٪=٠,٩٨ ـ ٣,٨ و قيمة ب<٠,٠٠٠١؛ سكر الدم في حالة الصوم (مليغرام بالديسيلتر من الدم)< ٢٠١ مليجرام/ ديسيلتر: النسبة المبهمة=٢ و مدى الثقة ٩٥ ٪=١,١-٤,١ و قيمة ب=٠,٠٤؛البيلة البروتينية: النسبة المبهمة=١٩,٤ و مدى الثقة ٩٥ ٪=٩٤,٦ و قيمة ب=٠,٠٠٥.

الاستنتاجات:

ان دراسة الحالات المقارنية عندنا تعطي ادلة بان البيلة البروتينية هي عامل خطورة مستقل لحصول السكتة الدماغية الذ اوية لدى مرضى الزرب السكري اللانسوليني.

Summary

Background and Purpose:

Proteinuria is an independent risk factor for cardiovascular disease in patients with type 2 diabetes mellitus. The aim of this study was to assess the relationship between proteinuria and ischemic stroke in subjects with type 2 diabetes mellitus, and to determine whether proteinuria is an independent risk factor for ischemic stroke.

Background and Purpose:

We performed a case-control study of 35 patients with type 2 diabetes (22 women and 13 men) with first-ever ischemic stroke due to thrombotic arterial occlusion, who were considered cases, and 105 patients with type 2 diabetes (70 women and 35 men) without stroke, matched by gender, age, and diabetes duration, as a control group.World Health Organization (WHO) criteria for a verified definite or possible stroke were used to ascertain the diagnosis of ischemic stroke. For the purpose of this study, proteinuria was defined as a 24-hour urinary protein excretion rate of >075 and <750 mg/day. Risk factors included in this study were: smoking, high blood pressures (systolic, diastolic or both), elevated body mass index, high fasting serum total cholesterol, hyperglycemia, and proteinuria.

Results:

Patients with ischemic stroke had higher proteinuria proportion and systolic and diastolic blood pressures. Frequencies of antihypertensive treatment and the types of the antihypertensive drugs used were similar in subjects with and without ischemic stroke. In multivariate logistic regression analysis, the odd ratios (ORs) and 95% confidence intervals (CIs) for the variables identified as risk factors for stroke were as follows: high systolic blood pressure(SBP),(OR= 2.0; 95% CI= 1.1 to 3.8; P=0.03); high diastolic blood pressure(DBP), (OR= 2.3; 95% CI= 0.98 to 3.8; P<0.0001); fasting blood glucose(FBG) >201 mg/dl (OR= 2; 95% CI= 1.1 to 4.1; P=0.04); proteinuria (OR= 19.4 ; 95% C1= 9.0 - 44.6; P=0.005).

Conclusions:

This case-control study gives evidence that proteinuria is an independent risk factor of ischemic stroke in patients with type 2 diabetes mellitus.

Introduction:

The incidence atherosclerotic vascular disease such as stroke is higher in patients with type 2 diabetes mellitus than in non diabetic patients.[1]The cardiovascular risk has been found to be associated with an increased urinary protein excretion rate. [2] Clinical proteinuria is an ominous development in a subject with diabetes. It leads to a decline in the glomerular filtration and premature cardiovascular mortality.[3]Albuminuria is a strong predictor of renal disease progression[4], premature death of cardiovascular origin, [5] and foot ulcers in patients with type 2 diabetes mellitus.[6-7] the relationship between microalbuminuria and cardiovascular disease mortality in patients with type 2 diabetes mellitus is well established [8]. Determination of risk factors for ischemic stroke is the basis for stroke prevention strategies. [9-11]

Pathogenesis of proteinuria in diabetes mellitus.

Early in the course of diabetes, the glomerular basement membrane (GBM) widens and may reach three to four times its normal thickness.Glycosylation of the GBM appears to make it less prone to degradation, and there is also some evidence for increased type IV collagen synthesis.[12] Structurally, the increased GBM thickness is associated with a loss of heparan sulfate proteoglycan, the principal negatively charged constituent in the GBM that provides the charge barrier to prevent protein from escaping into bowman's space.Experimentally,several studies suggest that this may be mediated by glucose induced advanced glycation end products and glucose induced activation of protein kinase C.[12]

Proteinuria and atherosclerosis.

Patients with proteinuria already manifest potentially atherogenic changes, including increased levels of low density lipoprotein cholesterol, fibrinogen and Von willebrand factor; the latter perhaps signaling widespread alterations in endothelial function.[13] Type 2 diabetic patients with proteinuria have a more generalized transscapillay escape rate for albumin than type 2 diabetic patients without proteinuria. [13]

Proteinuria and cerebrovascular disease:

Azotemic diabetic patients sustain a sharply increased attack rate for cerebrovascular accidents (stroke), transient ischemic attacks, and altered intellect due to decreased cerebral perfusion resulting from macrovasculopathy of the cerebral arteries. [13]Once end stage renal disease therapy is initiated; deaths related to cerebrovascular disease are about twice as common in those with diabetes. Diabetes compounds the risk of stroke and transient ischemic attack, not only by promoting cerebral parthenogenesis but also by aggravating other risk factors including hypertension, heart disease, and dyslipidemia. Diabetic stroke patients are younger, and sustain higher mortality than do age and gender

matched non-diabetic stroke patients. Regression analysis of multiple factors indicates that diabetes is second only to hypertension as a risk factor for stroke, and is followed in order by heart disease and smoking. .[13]

Renal protein handling:

In normal individuals; the daily urinary protein excretion, averages 40-80 mg, and the upper limit of normal ranges from 75-150 mg. Urinary protein is a mixture of plasma proteins that cross the filtration barrier and non-plasma proteins that originate in the tubules and lower urinary tract. Of the total, albumin constitutes 30%-40%, IgG 5%-10%, light chains 5% and IgA 3%. Tamm-Hosfall protein, a glycoprotein not found in plasma, is the most abundant in normal human urine and constitutes the remainder. Large molecules such as IgM normally are not detected in the urine. .[13]

Definition of proteinuria:

Proteinuria >150 mg/24 hours is abnormal and can result from a number of mechanisms:

1- Glomerular proteinuria: results from leakage of plasma protein through a disturbed glomerular filtration barrier.

2-Tubular proteinuria: results from failure of tubular reabsorption of low molecular weight plasma proteins. Tubular proteinuria virtually never exceeds 2gm/24 hour's.

3-Overflow Proteinuria: results from filtration of proteins usually immunoglobulin light chain when they are present in excess in the circulation.[13]

Measurement techniques for urinary albumin:

A variety of methods available to quantify total urine protein irrespective of the type of protein. Although these tests are extremely useful in screening for proteinuria, they detect an abnormal concentration of the total urine protein. not an abnormal excretion rate. Therefore, they might be positive in patients with low urine volume even if the excretion rate is normal and they may be negative in patients with high urine volume if the excretion rate is elevated. For more definite evaluation and management of patients with proteinuria. Quantitative protein analysis of 24 -hours urine samples or calculation of the urinary protein to creatinine ratio must be undertaken[13].These techniques include:

1-Random urine samples.

The urinary albumin: creatinine ratio in the first voided; early morning samples has the best correlation with measurement of the timed overnight urine sample.[13]

2-Short term collection.
Multiple short-term collections over one hour to a few hours can be used in patients when reliable and complete voiding can be ensured. If glomerular filtration rate measurement is done, the urinary albumin excretion may be determined in the same samples. If the albumin concentration is low, bovine albumin may be added to the test tubes to minimize absorption.[13]

3-Twenty-four hours urine samples:
Routine 24 hours urine collection can be used in hospitals or in outpatient clinics where 24 hours urine sampling has become clinical practice. Many patients, when properly instructed, are able to provide complete collections, but in many cases difficulties may arise especially because of poor patient's compliance. Measurement of urine creatinine output, can, however; vary with intake of cooked meat. Furthermore, measurement based on a 24 hours sample may show great irregularity due to a number of variables, such as physical and metabolic control. [13]

4-Overnight urine collection:
Usually this ensures urine collection at rest and with low solute intake. Creatinine excretion can be used as a control, and multiple urine collection is advisable. [13]

Patients and methods.

Design and setting.

After obtaining informed consent from the patients, a case control study was performed. Cases and controls were recruited from Medical City, Baghdad Teaching Hospital, and Department of neurology tenth floor, over a period of 17 months starting from to June 2003 to January.

Patients:

consecutive type 2 diabetes mellitus Iraqi subjects with first stroke due to thrombotic arterial occlusion were considered cases and compared with a control group of type 2 diabetes mellitus subjects without stroke (volunteer medical staff and patients relatives without stroke), who were matched by age, gender, and duration of diabetes. A control to case ratio of 3:1 was aimed .The study includes 35 cases and 105 controls.
In this study patient with type 2 diabetes mellitus were defined as:
1- Diabetics who are treated by diet alone.
2-Those on Diet combined with oral hypoglycemic drugs.
3- Those on Insulin treatment and onset of diabetes after the age of 40 years and a body mass index ≥ 30 kg/m^2 at the time of examination [14].

The WHO criteria for verified definite or possible stroke were used in the ascertainment of the diagnosis of first-ever ischemic stroke, which was defined

as a clinical syndrome consisting of neurological symptoms persisting >24 hours [15], and confirmed by an area of low density on CT scan of the head. [11] Subjects with a history of previous stroke were excluded. We performed the physical examination and made the clinical diagnosis under supervision of neurologist in the tenth floor, Neurological Department of Baghdad Teaching Hospital, Medical City. Stroke due to intracranial or subarachnoid hemorrhage and cerebral infarction associated with a major cardiac source of emboli or with significant atherosclerotic disease in an appropriate extracranial artery were excluded. Furthermore, subjects with the following diseases were excluded:

1-Heart failure.
2-Non diabetic renal disease.
3-Acute febrile illness.
4-Urinary tract infection.
5-Overt proteinuria (>750 mg/day).
6-Those receiving treatment with angiotensin –converting enzyme inhibiters, Angiotencin receptors blockers or pentoxiphylin.

When 50 cases were obtained, we had identified 175 potential control patients 130 of them fulfilled the matching criteria, which was done by sex, age and duration of the diabetes. Forty five patients were excluded as being control for mismatching in; age (4 patients), mismatching in diabetes duration (7 patients) ,inadequacy of urine sampling (14 patients), gross proteinuria > 750 mg/day in (15 patients) ,and loss of follow up in (5 patients).At this step of the process, we lost 15 patients in case groups because of death in (3 patients) ,proteinuria >750 mg and less than 75mg/day in (6patients) and inadequacy of 24 hours urine sampling in (6 patients). We exclude 25 patients from the control group to make the ratio of case to control 1:3, finally 35 cases and 105 controls were included.

Risk factors included in this study were[14]:

1-Smoking. (Current smokers were defined as subjects who smoke one or more cigarettes or pipe a day. Former smokers were defined as subjects who stopped smoking before the baseline examination. Non smokers were patients who described themselves as never having smoked. A positive history of smoking included current and former smokers.)

2- Blood pressures (systolic and diastolic that were measured twice in the right arm after ten minutes rest while the patient was in the supine position by using mercurial sphygmomanometer recording phase one systolic and phase five diastolic. One examiner performed all blood pressure readings. Arterial hypertension was defined according to the WHO criteria: SBP>140 mm-Hg or DBP>90 mm-Hg or both, or if antihypertensive treatment was being prescribed with normal readings of blood pressures.

3-High body mass index (BMI=body weight in kg/square of height in m^2) >30 kg/m^2.

4-Raised fasting serum total cholesterol >200mg/dl.
5-High fasting blood glucose >201mg/dl.
6-Proteinuria=057-750 mg/day.

These were assessed in each patient by a standardized questionnaire, physical examination, and laboratory evaluation.

Measurements:

Plasma glucose and cholesterol levels were measured after twelve hours fasting.Proteinuria was measured, on a 24-hour urine collection, by precipitation with 3% sulfosalicylic acid and determination of turbidity by measuring absorbency at a wave length of 540 mm with a spectrophotometer. The measurement was done in the Teaching Laboratory of Medical City Teaching Hospital. The collection of urine was done in hospital for most of the patients with stroke either by regular collection or by the urine bags for those who had indwelling Foley's catheter. The inadequate samples of` urine was discarded.

For the purpose of this study. Proteinuria was defined as a 24hour urinary protein excretion rate >075 and <750 mg/day assessed at 2 separate occasions in each patient, with a 7-day interval between measurements *(Values were taken as such to overcome the problems of unavailability of tests for microalbuninuria since the later is in the range of 030-300 mg/ day and urine albumin constitutes 40% of the normal urine protein. The use of 3%sulfosalcylic acid is because of its high sensitivity to urine albumin compared with urine globulin.)*Urinary creatinine excretion was measured to ascertain the adequacy of the 24 hours urine collection, considering as a normal range 16 to 26 mg/kg per day in men and 12 to 24 mg/kg per day in women.

Statistical analysis.

Comparison between the two groups was made with the unpaired Student t (Mann-Whitney U) test for numeric variables and for differences among proportions, by calculating the OR, the relationship between proteinuria and stroke was estimated. Multivariate logistic regression analysis was performed to determine the independent effect of proteinuria on stroke. Differences were considered statistically significant at $P<0.05$. [16]

Results

One hundred forty patients, 35 cases (22 women and 13 men) and 105 controls (70 women and 35 men) were included. The average age was 50.7±5.3 years versus 53.2±6.8 years (P value =not significant NS, unpaired Student t test) and the average duration of diabetes 9.6±5.9 years versus 9.6±6.6 years (P=NS, Mann-Whitney U test), for the subjects with and without stroke, respectively. Prevalence of hypertension among patients with

stroke was of 50.7%.Antihypertensive treatment was similar among subjects with and without stroke. Antihypertensive drugs used in subjects with and without stroke were B-blockers (52% and 64%), calcium channel blockers (30% and 35%), thiazides (4.5% and 3.5%), and others (3.5% and 1%), respectively. For the men, the mean±SD for the following variables were hypercholesterolemia= 238.2±100, S.B.P= 138±19 mm-Hg, D.B.P= 89+12.2mm-Hg. For women the mean ± SD were hypercholesterolemia= 236.8±115, S.B.P= 140±14, D.B.P= 85-12.1. The frequency of hypertension and anti hypertensive drugs treatment was similar among men and women. More men (45.5%) than woman (5.2%) were smokers ($P \leq 0.0001$, Chi^2 test).Proteinuria was identified in (40) out of (140) total subjects (28.5%). 28/35 (80%) of cases group and 12/105 (11.4%) of control group ($P<0.0001$, by Chi^2 test).

The vast majority of the patients had other vascular risk factors. These included:

1. Age ≥ 60 years (in 52.7%).
2. Obesity (BMI ≥ 30 kg/m^2, 31.3%).
3. Diabetes duration ≥10 years (36.8%).
4. Arterial hypertension (52.7%).
5. Smoking (18.0%).
6. Hypercholesterolemia (58.1 %).

The main characteristics of the target population are presented in table 1.

Table 1: Characteristics of type 2 diabetes mellitus patients:

Characteristics	**with stroke n=35***	**without stroke n=105***	**P value**
1-BMIkg/m^2	27.3 ±18.0	27.2± 5.0	ns**
2-SBP mm-Hg	143.8 ± 18	133.2 ± 20.4	0.01**
3-DBP mm-Hg	94.2 ± 12.4	83.5 ± 12.2	0.0001**
4-FBG mg/dl	189 ± 83.6	176.4 ± 63.7	ns**
5-Total fasting cholesterol mg/dl	226.9 ± 100	242.3 ± 138	ns**
6-proteinuria (075-750mg/day)	134.4 ± 104.8	43.8 ± 80.5	0.005***

*Values are expressed as mean ±SD, **by unpaired student t test, ***By Mann Whitney U test.

Subjects with and without stroke had similar BMI and smoking. About half (20/35) of the patients with stroke had higher SBP, DBP (S.B.P >140mm Hg and D.B.P >90 mm-Hg). Both frequencies of antihypertensive treatment and drugs used were similar among subjects with and without ischemic stroke.1 patients with stroke have proteinuria and high blood pressure at the same time. Because more than half of the target population had elevated fasting glucose, and fasting

total cholesterol serum levels, to determine the association of these variables with stroke, a controlled standardized studies are required.Bivariate analysis demonstrated that proteinuria, elevated blood pressure and fasting blood glucose≥201 mg/dl are significantly associated with stroke ($P<0.05$, Chi^2 test), see table 3-2.To determine which factors were independently associated with the risk of stroke, multivariate logistic regression analyses were performed. High systolic/diastolic pressures, fasting glucose =201 mg/dl, and proteinuria remained as an independent predictors for stroke. The ORs (with 95% CIs and P values) for the factors were as in table 2

Table 2: Bivariate analysis of the relationship between vascular risk factors and ischemic stroke in type 2 diabetes mellitus Subjects:

Risk factors	With stroke n=35	Without stroke n=105	OR	95%CI
Age>60 years	50.7%	53.2%	0.9	0.5-1.7
Gender, male/female	62.9%/37.1%	66.6%/33.4%	0.9	0.5-1.7
BMI>30kg/m^2	30.2%	29.9%	1.02	0.45-2.2
Cigarette smoking	23.7%	16.0%	1.6	0.68-3.5
Diabetes duration>10 years	36.8%	36.0%	1.6	0.5-1.9
History of arterial hypertension	43.91%	56.0%	0.85	0.4-1.8
Hypertension duration >10 years	10.00%	14.0%	0.7	0.19-1.92
SBP>140 mm- Hg	45.85%	29.46%	2.0	1.1-3.8*
DBP>90 mm- Hg	56.1%	36.0%	2.28	0.98-3.8*
Fasting blood glucose(FBG) >201mg/dl	68.0%	50.0%	2.0	1.1-4.1*
Total cholesterol>200 mg/dl	58.0%	58.3%	1.0	0.5-1.8
Proteinuria= 075-750 mg/day	80%	11.4%	19.9	9.0-44.6*

*P value <0.05

Discussion:

Stroke is a special problem that is particularly tragic because of the potential for a life time of disability [17] and the high risk of death. [18-20]

Our findings showed that proteinuria >075 and <750 mg/day is a marker of stroke in patients with type 2 diabetes mellitus. This supports the hypothesis that significant proteinuria reflects a more generalized vascular process, which is consistent with a Miettinel and Haffner et al report that based on a 7-year follow-up and showed that proteinuria is a predictor for ischemic stroke in non diabetic and diabetic subjects. [9] This study determined the total urinary protein excretion but didn't qualitatively assess the albumin concentration**.** Thus we can assume that the patients, who had proteinuria, might excrete urinary

albumin as well. If we had quantitatively measured the albumin excretion rate, our findings concerning its relationship with stroke might have been even stronger. It has been proposed that proteinuria is associated with an increase of both albumin and fibrinogen transcapillary escape rate, which reflects widespread vascular damage[7] or endothelial dysfunction. [21] Furthermore, proteinuria has been shown to be related to increased extra vascular coagulation, which leads to an increased release of vonWillebrand factor, contributing to the formation of microthrombi and platelet plugs, followed by areas of no perfusion. [7, 21-23] High systolic and diastolic blood pressures are risk factors associated with stroke, [9, 18-20] a relationship that was demonstrated in our study. It is well known that diabetic patients have an increased risk of both hypertension and death from ischemic stroke. [18] It has been previously reported[18] that some of the effects of hypertension status as well as duration of the risk of stroke can be attributed to factors other than high blood pressure itself. In this matter, although several antihypertensive drugs have adverse effects on glucose control and lipid profile[24-25] ,the relationship between hypertension and stroke risk is under debate. [18] In this respect, studies[18, 26] have demonstrated that there may be no possible advantage to a particular glucose control in diabetic subjects. Gall and coworkers[14] showed SBP to be an independent risk factor for the relative rate of increase of the urinary albumin concentration slope. Higher mean arterial blood pressure was also risk factor for the development of an abnormally increased rate of urinary albumin excretion in the Pima Indians. The same group also reported that high blood pressure before the development of diabetes predicts proteinuria after the onset of type 2 diabetes mellitus in Pima Indians.[14]Because angiotensin converting enzyme inhibitors and angiotensin receptor blockers modify albuminuria; in this study the subjects who received these drugs were not included. Furthermore, we have not evaluated the effects of different treatment modalities for hypertension on the risk of stroke. A certain degree of hyperglycemia (severe) plays a role in stroke whereas a milder one is innocuous[9.27-28], see table 3-I (FBG) and table 2 (FBG) > 201.The importance of hyperglycemia with respect to macrovascular disease is controversial. Hyperglycemia is related to atherogenic lipoprotein changes and is also a procoagulant state. Hyperglycemia can cause the following: [29]

1-Decrease prostacyclin synthesis.
2-Increase fibrinogen formation.
3-Accelerates production of vonWillebrand factor.
4-Cause glycosylation of proteins in the artery wall.

These conditions, which are related to poor metabolic control, can cause atherosclerosis, which could contribute to increase the risk of stroke. Regarding this concern, further studies are needed to determine whether activation of the coagulation system is the cause or the result of vascular disease in poorly controlled diabetic subjects. Because aging and duration of diabetes have previously been reported as strong predictors of stroke [18,30] and

proteinuria, [7] we controlled for these variables by matching for age and duration of diabetes (table 3-2).Thus, these risk factors do not differentiate between stroke and non-stroke patients.

Given the compared samples. This study demonstrated no association between smoking and hypercholesterolemia with stroke. The absence of an association between smoking and stroke probably was because the narrow range of diabetic smokers made the statistical power low. Similarly, Lehto et al[29] reported a low prevalence of smokers along diabetic subjects and a lack of association between smoking and risk of stroke in such patients. On the other hand, the relationship of serum cholesterol with the excess risk of stroke in subjects with type 2 diabetes mellitus is not constant.[31-32] Davis et al[33] reported , in patients with newly diagnosed type 2 diabetes recruited to the United Kingdom Prospective Diabetes Study, that dyslipidelia was not significantly associated with stroke. On the other hand. Gall et al [14] found that the concentration of cholesterol, both initially and during a five years of follow up was found to be related to the development of abnormally increased urinary albumin excretion rates in Pima Indians who had had diabetes for more than ten years. Although many of the changes in plasma lipoproteins associated with renal disease are believed to be caused by renal dysfunction, hyperlipidemia, however, may be associated with the development of glomerular injury.Lehto et al [29] showed that hypercholesterolemia is the most common lipid abnormality in patients with type 2 diabetes mellitus. The level of total cholesterol may be elevated, and High-Density Lipoprotein cholesterol is often decreased. Although lipid abnormalities have been shown to be associated with cerebral atherosclerosis, data on the relationship between dyslipidemia and stroke are limited.Lehto et al[29] found a dose - response relationship between total cholesterol, HDL cholesterol and triglycerides and the risk of stroke events in type 2 diabetes mellitus subjects. This is due to that triglyceride level has been shown to correlate with plasminogen activator inhibitor-1,which is the main regulator of fibrinolytic activity in the blood.Plasminogen activator inhibitor-1 is increased in type 2 diabetes mellitus patients with coronary heart disease and ischemic stroke.

Conclusion and recommendations:

The implication of our findings is that proteinuria >075 and <750 mg/day) is an independent and a strong marker of stroke in subjects with type 2 diabetes mellitus. The significance of recognizing the relationship of proteinuria to stroke is that it is a modifiable and easily identifiable risk factor. We recommend further studies to prove that proteinuria is a marker of macro vascular complications or that decreasing urinary protein excretion could delay the occurrence of ischemic stroke.

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