Microalbuminuria in Subjects with no History of Diabetes Mellitus and Hypertension: The Relationship with Hyperglycemia and High Blood Pressure at Non-Diagnostic Level

Fukashi ISHIBASHI, Kazufumi ISHIDA and Seiryo TAKASHINA

Department of Internal Medicine, Hiroshima General Hospital 1-3-3, Jigozen Hatsukaichi Hiroshima 738, Japan

ABSTRACT

1969 subjects underwent albumin index [A.I., urine microalbumin (mg/liter)/creatinine (g/liter)] in early morning urine, 75 g oral glucose tolerance test (OGTT), determination of plasma lipids (total cholesterol, triglyceride and high density lipoprotein-cholesterol) and a resting electrocardiogram. There was no history of treatment for diabetes mellitus and hypertension. The relationship between microalbuminuria, and hyperglycemia or high blood pressure at non-diagnostic level was examined. Then, plasma lipid levels or changes in electrocardiogram were correlated with the degree of microalbuminuria. Subjects were divided into 4 groups according to 75 gOGTT and into 3 groups according to blood pressure based on WHO definition, and A.I. was divided into 4 categories (0—9.9, 10.0—19.9, 20.0—49.9, and 50.0—199.9 mg/gCr).

Mildly or moderately enhanced microalbuminuria (A.I.) was found in subjects with hyperglycemia or high blood pressure at non-diagnostic level. In normotensive subjects, neither hyperglycemia in fasting nor after glucose challenge increased urine microalbumin above normal range, while in borderline hypertensives, diabetic glucose intolerance produced 2 and 3 fold increases respectively compared with normotensives. There was a linear increase in urine microalbumin in relation to the glucose intolerance in newly diagnosed hypertensives.

No correlation could be found between microalbuminuria and plasma lipid levels, while the prevalence of electrocardiographic changes increased 3 folds in group with the heaviest microalbuminuria compared with the other 3 groups excreting less microalbumin.

Key words: Microalbuminuria, Non-diabetics, Cardiovascular disease

Non-insulin dependent diabetes mellitus (NIDDM) patients with persistent microalbuminuria are recognized as having an increased mortality rate, especially from cardiovascular disease[1,6]. In NIDDM, enhanced microalbuminuria has been shown to be associated with electrocardiographic changes independent of other risk factors[4]. Although microalbuminuria has been evaluated as an early feature of diabetic nephropathy[5,7], it has also been found in non-diabetic subjects such as hypertensives[9]. However, the relationship between microalbuminuria and cardiovascular disease has not been investigated in subjects without known diabetes mellitus. Little is known about the influence of hyperglycemia and high blood pressure of non-diagnostic level or their coexistence on microalbuminuria. Also, no population study has elucidated the prevalence of microalbuminuria in newly-diagnosed diabetics and hypertensives.

In the present study, the relationship between hyperglycemia or high blood pressure at non-diagnostic level and microalbuminuria was examined. We also correlated the degree of microal-buminuria to plasma lipid level and the prevalence of changes in resting electrocardiogram.

SUBJECTS AND METHODS

1969 people underwent a health examination at the Health Control Division of Hiroshima General Hospital. They did not have a documented history of diabetes mellitus and hypertension, or renal diseases which might cause albuminuria. Subjects with proteinuria tested by dipstick were excluded from this study.

Fasting early morning urine was collected for the determination of microalbumin. Albumin index (A.I.) was calculated by dividing microalbumin content (mg/liter) by creatinine content (g/liter). A seventy-five gram oral glucose tolerance test (OGTT) was performed and venous samples were taken before and 2 hours after glucose challenge.

As shown in Table 1, subjects were divided into 4 groups according to 75 gOGTT as judged by WHO criteria [1: normal, 2: impaired glucose tolerance (IGT), 3: DM-1 (fasting plasma glucose, FPG < 140 mg/dl, 2 hour plasma glucose, 2 hr

Table 1. Grouping of subjects according to the results of 75 g oral glucose tolerance test (OGTT) and blood pressure based on WHO criteria. IGT: impaired glucose tolerance, DM: diabetes mellitus.

		75g OGTT				
		Normal	IGT	DM-I	DM-II	Total
Blood Pressure	Normal	669	625	41	14	1349
	Border. HT	148	214	22	8	392
	Hypertension	61	128	32	7	228
	Total	878	967	95	29	1969

Table 2. Grouping of subjects according to the degree of microalbuminuria. Albumin index (A.I.) 10.0 mg/gCr is approximately equal to urine albumin excretion rate (AER) 15 μg/min, and A.I. 200 mg/gCr is nearly equal to AER 300 μg/min. BMI: body mass index. Values are mean ± standard error.

Group of AI (mg/gCr)	Age (yrs. o.)	Number	Averaged AI (mg/gCr)	BMI (kg/m^2)
A (0 ~ 9.9)	54.2 ± 0.3	1884	1.9 ± 0.1	23.1 ± 0.1
B (10.0~ 19.9)	56.7 ± 1.7	49	14.0 ± 0.4	23.9 ± 0.4
C (20.0~ 49.9)	56.4 ± 1.8	24	31.7 ± 2.3	23.6 ± 0.5
D (50.0~199.9)	58.7 ± 2.9	12	93.1 ± 13.0	24.4 ± 1.1

PG≧200 mg/dl), 4: DM-II (FPG≧140 mg/dl, 2 hr PG≧200 mg/dl)]. Among them 124 subjects were newly-diagnosed as diabetics.

Based on blood pressures as defined by WHO, subjects were divided into 3 groups 1: normotensive, 2: borderline hypertensive, 3: hypertensive.

Subject grouping according to degree of microalbuminuria is presented in Table 2. Prevalence of excessive microalbuminuria was 4.3 % when A.I. over 10.0 mg/gCr was defined as an upper normal limit, and 1.8 % when over 20.0 mg/gCr was employed. There were no significant differences in body mass index (BMI, kg/m^2) and age among the 4 groups.

Blood pressure was measured with a mercury sphygmomanometer in patients at rest in a supine position. Urine microalbumin was measured by a nephelometric immunoassay using a monospecific antiserum to human albumin. PG was assayed by glucose oxidase method. Plasma cholesterol and triglyceride concentrations were measured enzymatically. High density lipoprotein (HDL) was isolated after precipitation of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) by MnCl$_2$ and heparin prior to cholesterol assay. Then, atherogenic index was calculated (T. cholesterol—HDL-cholesterol/HDL-cholesterol).

A resting 12-leads electrocardiogram was recorded and was coded by a trained observer using the Minnesota code. Abnormal Q wave, ST depression, negative T wave and complete left bundle branch block were designated as abnormal finding.

Data were presented as mean ± SEM and statistical analysis was performed by unpaired t test.

RESULTS

Fig. 1 shows the correlation between A.I. and
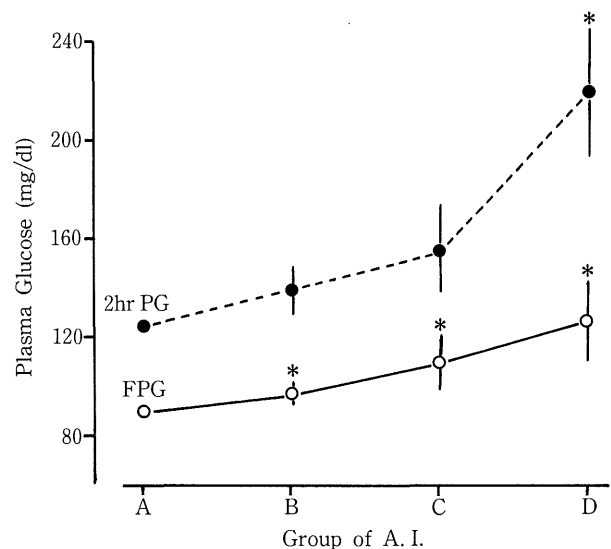
Fig. 1. Correlation between microalbuminuria and fasting plasma glucose (FPG) or 2 hour plasma glucose (PG) after glucose challenge. $*p < 0.05$ against group A.

FPG or PG 2 hours after glucose challenge. A diabetic pattern was found in subjects with the heaviest microalbuminuria (group D), while elevation in PG in the other 3 groups was small and not diagnostic of diabetes mellitus.

Fig. 2 delineates the correlation between A.I. and systolic blood pressure (SBP) or diastolic blood pressure (DBP). The elevation in SBP and DBP was small but significant, and weakly related with the degree of microalbuminuria. Blood pressure in the group with the heaviest microalbuminuria (group D) did not reach the diagnostic level of hypertension.

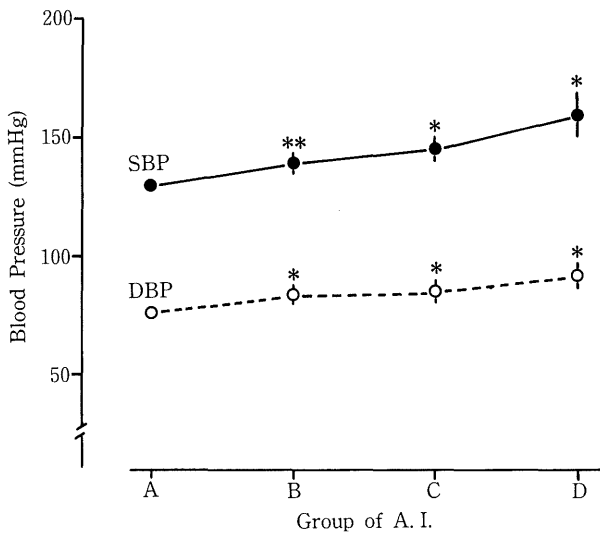Fig. 3 reveals the influence of coexistence of varying degrees of PG and blood pressure on A.I.

Fig. 2. Correlation between microalbuminuria and systolic blood pressure (SBP) or diastolic blood pressure (DBP). $*p < 0.05$, $**p < 0.01$ against group A.
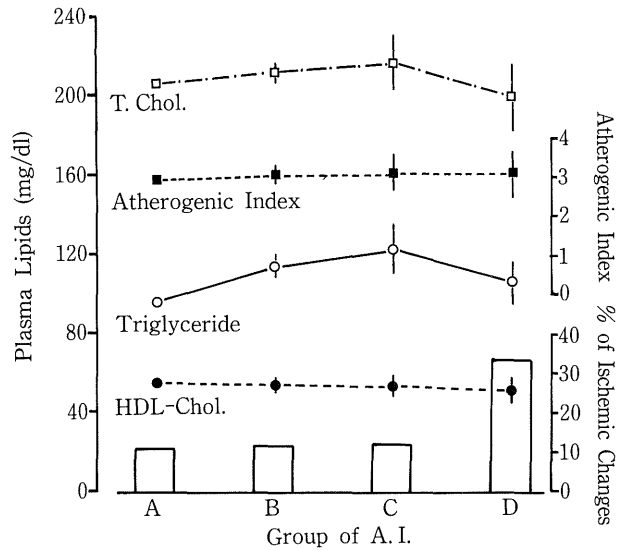

Fig. 4. Influence of microalbuminuria on total cholesterol (T. Chol.), triglyceride, HDL-cholesterol (HDL-Chol.), atherogenic index and prevalence of ischemic changes in resting electrocardiogram.
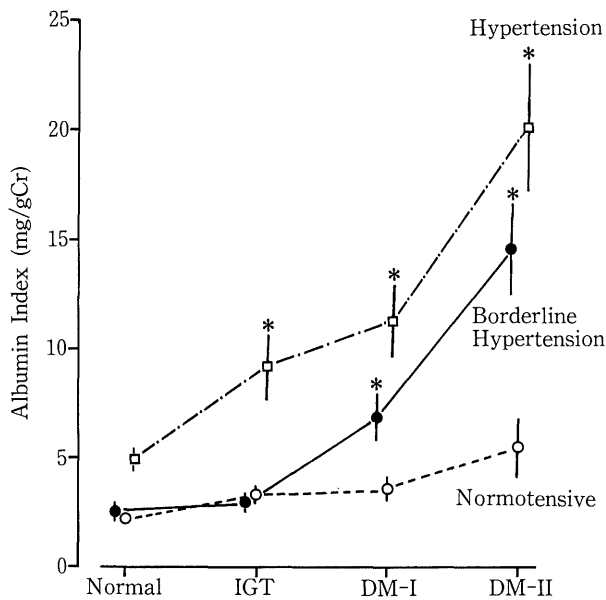

Fig. 3. Influence of coexistence of glucose intolerance and high blood pressure on albumin index. $*p < 0.05$ against normotensive group. Abbreviation as in Table 1.

lation to the degree of hyperglycemia.

Fig. 4 illustrates the correlation between the magnitude of microalbuminuria and plasma lipid levels. The increase in A.I. influenced neither plasma total cholesterol, triglyceride nor HDL-cholesterol. Furthermore, there was no significant difference in the atherogenic index among the groups with varying A.I. On the other hand, the prevalence of electrocardiographic changes increased 3 fold in subjects with the heaviest microalbuminuria.

DISCUSSION

Urine microalbumin has been considered to be the most reliable early marker of diabetic nephropathy[5,7] and can predict the prognosis of diabetics[10]. Since more than half of diabetics with excessive microalbuminuria died of cardiovascular disease in a shorter period of time after the development of persistent microalbuminuria than patients without it[10], it has been supposed that microalbuminuria promotes the process of macrovascular disease. Independent of other cardiovascular risk factors[4], increased urinary albumin excretion rate (AER) has been shown to be associated with ischemic electrocardiographic changes in NIDDM.

Microalbuminuria is also found in non-diabetic subjects, especially in the presence of essential hypertension[9]. Population study has demonstrated a weak correlation between albumin excretion rate and blood pressure[12]. However, little is known about the correlation between microalbuminuria and cardiovascular diseases.

In the present study, the influence of mild hyperglycemia and high blood pressure at non-diagnostic

in the subjects without a history of diabetes mellitus and hypertension. In normotensive subjects, A.I. increased minimally in relation to the degree of hyperglycemia, and remained within normal range (less than 10.0 mg/gCr) even in newly-diagnosed diabetes mellitus with fasting hyperglycemia (DM-II). Borderline hypertension definitely enhanced A.I. in newly diagnosed diabetics. On the other hand, hypertension by itself increased A.I. at the same level as fasting hyperglycemia alone, and increased A.I. in all glucose intolerant groups in re-

level and of their coexistence on microalbuminuria was investigated in subjects who had not been diagnosed or treated for diabetes mellitus and hypertension. Neither diabetic glucose intolerance with fasting hyperglycemia nor newly-diagnosed hypertension enhanced microalbuminuria above normal range. The concomitant presence of diabetic glucose intolerance and borderline hypertension significantly increased microalbuminuria, while hypertension increased it in subjects with IGT as well as diabetic glucose intolerance. These results indicate that the concomitant presence of mild hyperglycemia and high blood pressure at non-diagnostic level enhanced microalbuminuria more extensively than newly-diagnosed frank diabetes mellitus. Therefore, we must pay attention to glucose intolerance as well as blood pressure when evaluating microalbuminuria. The prevalence of excessive microalbuminuria was 4.3 % when A.I. over 10.0 mg/gCr was defined as upper normal limit, and was 1.8 % when over 20.0 mg/gCr was employed. Pima Indians have an extraordinarily high prevalence of NIDDM. A.I. in 2728 Pima Indians was determined and excessive albumin excretion (A.I. over 30 mg/gCr) was present in 8 % of subjects with normal glucose tolerance, 15 % with IGT and 47 % with NIDDM[8]. A much higher prevalence of excessive microalbuminuria in the Pima Indian might be due to their hereditary predisposition to NIDDM. In another population study[12], excessive microalbuminuria (AER more than 20 μg/min) was found to be 23 % in newly-diagnosed NIDDM and 9.4 % in non-diabetic subjects both higher than our results.

Little is known how microalbuminuria accelerates the process of cardiovascular disease in diabetics and in non-diabetics. In insulin dependent diabetes mellitus (IDDM) with excessive microalbuminuria, serum HDL-cholesterol was found to be lower than patients with normal microalbumin excretion, while there was no differences in total cholesterol, HDL-cholesterol, triglyceride and apoproteins[11]. On the other hand, Jensen et al[2] did not detect significant differences in serum cholesterol, triglyceride and HDL-cholesterol between IDDM with and without persistent microalbuminuria. No epidemiological study has sought to reveal the correlation between microalbuminuria and the risk factors of cardiovascular disease. The present study was not able to correlate microalbuminuria with plasma lipids in subjects without known diabetes mellitus and hypertension. On the other hand, ischemic changes in the electrocardiogram were found more frequently in the group with the heaviest microalbuminuria than in the other 3 groups. The highest blood pressure in this group by itself might produce ischemic changes in electrocardiogram. Recently, Yudkin et al[12] investigated the correlation between AER and cardiovascular diseases in non-diabetic subjects and concluded that excessive

microalbuminuria is an independent risk factor for cardiovascular disease when logistic regression including glucose intolerance, blood pressure, age and BMI was performed.

Microalbuminuria could accelerate the process of cardiovascular disease by mechanisms other than hyperlipidemia such as increased coagulation factors which was reported in IDDM with enhanced microalbuminuria[3]. These mechanisms involved in the development of cardiovascular disease might play a role in non-diabetic subjects.

REFERENCES

1. **Jarrett, R.J., Viberti, G.C., Argyropoulos, A., Hill, R.D., Mahmud, U. and Murrells, J.J.** 1984. Microalbuminuria predicts mortality in non-insulin-dependent diabetes. Diabetic Med. **1**: 17—19.
2. **Jensen, T., Stender, S. and Deckert, T.** 1988. Abnormalities in plasma concentrations of lipoproteins and fibrinogen in Type 1 (insulin-dependent) diabetic patients with increased urinary albumin excretion. Diabetologia **31**: 142—145.
3. **Jones, S.L., Close, C.F., Mattock, M.B., Jarrett, R.J., Keen, H. and Viberti, G.C.** 1989. Plasma lipid and coagulation factor concentrations in insulin-dependent diabetics with microalbuminuria. Br. Med. J. **298, No 6672**: 487—490.
4. **Mattock, M.B., Keen, H. and Viberti, G.C.** 1988. Coronary heart disease and urinary albumin excretion rate in type 2 (non-insulin-dependent) diabetic patients. Diabetologia **31**: 82—87.
5. **Miltenyi, M., Korner, A., Dobos, M. and Kammerer, L.** 1984. Changes in urinary protein excretion indicating the development of diabetic nephropathy. Diabetic Nephropathy **3**: 112—116.
6. **Mogensen, C.E.** 1984. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N. Engl. J. Med. **310**: 356—360.
7. **Mogensen, C.E.** 1987. Microalbuminuria as a predictor of clinical diabetic nephropathy. Kidney Int. **31**: 673—689.
8. **Nelson, R.G., Knowler, W.C., Petitt, D., Saad, M.F. and Bennett, P.H.** 1989. Urinary albumin excretion in normal and impaired glucose tolerance in Pima Indians. Diabetologia **32**: 521A.
9. **Parving, H-H., Jensen, H.A., Mogensen, C.E. and Evrin, P-E.** 1974. Increased urinary albumin-excretion rate in benign essential hypertension. Lancet **i**: 1190—1192.
10. **Schmitz, A.** 1988. Microalbuminuria and mortality in non-insulin-dependent diabetes, p.65—70, In C.E. Mogensen(ed.), The kidney and hypertension in diabetes mellitus, Martinus Nijhoff Publishing, Boston.
11. **Watts, G.F., Naumova, R., Slavin, B.M., Morris, R.W., Houston, R., Kubal, C. and Shaw, K.M.** 1989. Serum lipids and lipoproteins in insulin-dependent diabetic patients with persistent microalbuminuria. Diabetic Med. **6**: 25—30.
12. **Yudkin, J.S., Forrest, R.D. and Jackson, C.A.** 1988. Microalbuminuria as a predictor of vascular disease in non-diabetic subjects. Lancet **ii**: 530—533.