Microalbuminuria and cardiovascular risk

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Summary

The term ‘microalbuminuria’ has been introduced to describe a measurable increase in urine albumin excretion, which is still within normal total urine protein excretion levels. Many data suggest that microalbuminuria is of value as an index of vascular damage, especially in hypertension and diabetes, and there is increasing information on its associations with traditional cardiovascular risk factors and its prognostic value. The association between microalbuminuria and peripheral markers of endothelial damage or dysfunction, such as von Willebrand factor, suggests the possibility that microalbuminuria may be a simple, cheap and easy index of endothelial abnormalities in cardiovascular disease. Nevertheless, further information on the value of microalbuminuria in other atherosclerotic vascular complications, such as ischaemic heart disease, stroke and peripheral artery disease is still needed.

Introduction

The various components of urinary protein excretion are useful indicators of renal function. The biggest fraction of protein excreted in normal urine consists of Tamm-Horsfall protein, which originates from renal tubular cells. Low-molecular-mass plasma proteins (insulin, parathormone, lysozyme, β2 microglobulin, trypsinogen) are easily filtered through the glomerular basement membrane and reabsorbed by tubular cells, and thus an increase in their urinary excretion indicates tubular damage. On the other hand, medium-size (40–150 kDa) plasma proteins are precluded almost completely from glomerular ultrafiltrate and therefore any detection in urine of these proteins indicates alteration of the glomerular barrier. Proteins such as albumin, transferrin, immunoglobulin G, caeruloplasmin, α1-acid glycoprotein and the HDL particles are typical examples of the latter category.

Albumin is the major constituent of abnormal protein excretion in the urine. The usual screening method for the detection of proteinuria is the dipstick (for example, ‘Albustix’) which has a sensitivity of 150–300 mg/l. However, even with a five-fold increase of albumin excretion, the total urine protein (as detected by Albustix) may remain within normal range, and so increased levels of albuminuria may be undetected. Nevertheless, such changes may have pathological significance. For example, Viberti et al. showed in 1982 that increased albumin levels, even within the ‘normal’ proteinuric range, may herald the onset of nephropathy in insulin-dependent diabetes mellitus (IDDM) patients, whilst Parving et al. reported in 1974 that increased urine albumin excretion (UAE) can be found in poorly-controlled hypertensives. The term ‘microalbuminuria’ was therefore introduced to describe such an increase in urine albumin excretion, which was still within normal total urine protein levels.
Microalbuminuria: normal variations

The term ‘microalbuminuria’ was introduced by Viberti et al. to refer to a subclinical rise in UAE > 30 mg/24 h in patients with IDDM. The definition has also been applied to patients with essential hypertension; although the same as that used in diabetes, this definition may not be necessarily correct. It would be more relevant to study UAE in a large background population with exactly the same techniques and procedures as in essential hypertensive patients, and to define abnormal albuminuria as the level above (say) the 95th percentile. For example, in a study from the general population with 5670 subjects (using random urine samples) in New Zealand, the 97.5th percentile concentration of UAE was 28 mg/l for men and 29 mg/l for women.

The UAE rate can vary highly from day to day, by up to 40%. Early-morning urine specimens have been reported to have smaller variations, but large variations in morning and night specimens have previously been noted. Measurement of the 24-h urine collection has probably the lowest variability. In one study, for example, the coefficients of variation in daily, overnight and 24 h urine collections were 50%, 58% and 44%, respectively. Due to this wide variation, more than one urine collection has been advocated as necessary before convincingly labelling a patient as ‘microalbuminuric’.

Other factors should also be taken into account when evaluating patients for microalbuminuria (MAL). For example, normal variations in UAE can occur with exercise, with increased diuresis and within 24 h, being higher during day than night. The latter diurnal variation could be the result of greater activity during the day or higher blood pressure values throughout day time, or could simply be due to a true circadian rhythm in excretion rates.

Furthermore, gender and obesity are also factors which play a role. In a large population study from New Zealand, body mass index (BMI) was found to correlate positively with UAE, but only for subjects of European ethnicity, and only for BMI values > 25.9 kg/m² for men and > 28.9 kg/m² for women, with no differences between sexes. By contrast, a study of 1046 non-diabetic subjects found slightly higher UAE values in men compared with women, and also an inverse correlation between UAE and height. On the other hand, no significant correlation between BMI and UAE was found in an American study of 1298 non-diabetics. Ethnicity may be another important factor in UAE rates. For example, subjects of Asian origin (Maori and Pacific natives) have been found to have greater UAE values than those of European origin. In addition, the correlation of UAE and blood pressure is greater in Black than in White subjects, consistent with the greater cardiovascular risk in Black subjects, even with mild increases of blood pressure, when compared with Whites.

Age correlates positively with UAE in both normo- and hypertensives, perhaps due to a degree of nephrosclerosis that accompanies age (which is greater in hypertensives). By contrast, a negative correlation was noted between UAE and age in the population study from New Zealand, which was attributed to the progressive reduction of glomerular filtration rate (GFR) with age. Finally, an increased UAE rate has been reported in the erect position and during exercise in both normo- and hypertensive subjects.

Microalbuminuria: methods of evaluation and measurement

Several methods are used for measuring UAE, such as nephelometry, immunoturbidimetry, immunoassay with latex bodies, radial immunodiffusion, fluoroimmunoassay, and enzyme immunoassay. Urine albumin is stable at room temperature, so urine specimens can even be sent by post. Urine specimens can be stored in the fridge at −4 °C for 8 weeks, although for periods longer than 2 weeks the addition of preservative (sodium azide) is advocated.

An important issue in measuring urine albumin is the high variability in the measurements within and between laboratories. In a study which was designed to estimate existing variability, aliquots with albumin concentrations at or near the normal range were sent to five laboratories; the assays used were immunoturbidimetry, enzyme immunoassay, fluoroimmunoassay, and zone immunoelectrophoresis. Variability was equally attributable to differences in precision of individual immunoassays and to variation within each laboratory; however, total variance between laboratories ranged between 43.8% to 51.4%, while that due to within-laboratory variance ranged between 48.6% to 56.2%, with the immunoturbidimetric method having the greater variability.

Microalbuminuria: physiological and pathological considerations

The glomerular transmembrane transport of albumin depends upon several factors: the electric charge and size of the molecule, membrane status and specific renal hemodynamics. The fractional clearance of albumin, which is defined as the fraction of albumin clearance to filtration rate, is normally very low (<0.1%) due to the negative charge and to the
comparatively large molecular size of albumin (with a molecular mass of 69 kDa). However, albumin excretion is altered in many physiological and pathological situations.

Hypertension

In hypertension, specific haemodynamic conditions may lead to increased albumin transmembrane escape. For example, the basic findings in hypertensives are low renal plasma flow (RPF) and increased renal vascular resistance, with maintenance of the glomerular filtration rate (GFR), suggesting an increase in the filtration fraction (FF). This can be attributed either to the unimpeded transmission of systemic blood pressure within the glomerulus, or to increased post-glomerular vasoconstriction (of the efferent arteriole). However, Hollenberg et al. showed that the reduction in RPF is at least a partly functional phenomenon, since dopamine, phenolamine and acetylcholine can reverse it.

In addition, pharmacological inhibition of the action of angiotensin II causes renal vasodilatation in hypertensives. Small doses of angiotensin II normally causes renal vasoconstriction in hypertensives, but this does not appear to be the case in normotensives. This might mean however that sensitivity to angiotensin II infusion is higher in hypertensives than normotensives. Increased sensitivity to angiotensin II has also been documented in normotensive subjects with positive family history of hypertension, since a reduction of RPF and GFR after infusion of this peptide was greater than in the control group. Angiotensin II is considered to maintain GFR (although RPF is reduced) through selective constriction of the efferent arterioles, thus increasing the intraglomerular hydraulic pressure and leading to increased membrane permeability to protein. In two studies, infusion of angiotensin II increased proteinuria in rats, and either increased intraglomerular pressure or an increase of membrane permeability, perhaps due to an increase of membrane pore size, are the suggested mechanisms.

These pathophysiological mechanisms are closely correlated with clinical observations. Higher GFR values have been documented in a microalbuminuric group of hypertensive patients when compared with a normoalbuminuric group. Another study in hypertensive subjects showed that microalbuminuric subjects had higher plasma renin activity levels after being given captopril, when compared to normoalbuminurics. Renal vasodilatation was also less prominent in hypertensive microalbuminurics after captopril, compared with hypertensive normoalbuminurics. The latter findings indicate that a state of intrarenal vascular dysfunction exists in hypertensives.

Hyperfiltration may also be present in 10–15% of newly hypertensive patients. In some studies ‘renal functional reserve’, that is, the ability of the kidney to increase RPF and GFR through renal vasodilatation after a protein meal, has been used to assess the hyperfiltration status. It has been reported that renal functional reserve was reduced in hypertensives with normal renal function and in offsprings of hypertensive subjects. These observations suggest that hyperfiltration was already present even before a protein meal intake, resulting in the kidney being unable to increase the GFR further after the protein meal. On the other hand, other studies do not seem to confirm these conclusions.

Indeed, blood pressure levels correlate significantly with UAE in hypertensives and probably in normotensives. Both office systolic and diastolic, as well as 24-h systolic and diastolic blood pressure levels, have been shown to correlate with UAE in hypertensives. Although some studies have shown a correlation with UAE, this relationship is only with 24-h blood pressure measurements and not with single office values, with a regression coefficient for this association ranging from 0.32 to 0.62. The strongest correlations are seen when 24-h blood pressure measurements were used, suggesting that the 24-h ambulatory blood pressure monitoring is more reliable than casual measurements in evaluating early target-organ damage. Hypertensive subjects without the normal night time fall in blood pressure (‘non dippers’) have higher UAE values when compared to hypertensives with dipping (‘dippers’).

Several studies in general (unselected) populations or in non-diabetic populations have shown either positive correlations between UAE and systolic or diastolic blood pressures, or a lack of any correlation. However, these studies were heterogeneous and had different urine collection methods, including morning or casual or overnight or 24-h urine collections. In the largest population study from New Zealand involving 5349 subjects, using morning specimen collections, a positive correlation was noted only with diastolic blood pressures above 78.8 mmHg.

Diabetes and insulin resistance

MAL has been established as a major risk factor for the evolution of overt nephropathy and other micro- and macroangiopathic complications in patients with both insulin-dependent and non-insulin-dependent diabetes. High intraglomerular pressure, hyperfiltration and increased GFR have been documented
in the early stages of nephropathy secondary to IDDM, and are accompanied by MAL.\textsuperscript{65} It is also well recognized that a significant association exists between UAE and peripheral insulin resistance. In the diabetic Munich Wistar rat model, administration of insulin normalized glomerular capillary pressure, suggesting that glomerular hypertension (and subsequent increased UAE) in diabetes may be related to insulin deficiency rather than glomerular hypertrophy.\textsuperscript{66} Insulin resistance has also been associated with increased renal sodium reabsorption.\textsuperscript{67} These observations suggest that hyperinsulinemia may be one causal factor for the development of MAL.

In a study of 333 treated hypertensives, UAE was found to correlate with BMI, waist-to-hip ratio, fasting insulin levels and sum of insulin levels at times 0, 30, 60, 90 and 120 min during an oral glucose tolerance test (OGTT).\textsuperscript{68} In another study of 25 hypertensives and 20 controls undergoing an OGTT, microalbuminuric hypertensives had higher values of insulin area-under-the-curve values, when compared to 15 normoalbuminuric hypertensives.\textsuperscript{47}

The above studies suggest that there is an association between MAL and hyperinsulinemia, and presumably insulin resistance in hypertensive patients. The precise pathophysiological link between MAL and hyperinsulinemia per se is, however, obscure. It is possible that both these phenomena are genetically determined and co-segregate in the same patient, or that hyperinsulaemia may cause hypertension and MAL, perhaps by altering membrane permeability and causing renal damage; alternatively, they may both be a consequence of the same (as yet unknown) pathogenetic factor.\textsuperscript{69}

**Miscellaneous**

Several other diseases or pathological situations are associated with MAL. In cases of patients suffering from burns, trauma,\textsuperscript{70} muscle ischaemia or pancreatitis high values of UAE have been reported during the acute phase, which remain high especially if septic or respiratory complications occur.\textsuperscript{71} MAL has been reported during exacerbations of inflammatory bowel disease\textsuperscript{72} and rheumatoid arthritis,\textsuperscript{73} and remissions of these conditions are often followed by normalization of UAE. These observations suggest that UAE may perhaps behave like an acute-phase reactant. The postulated mechanism of albumin leakage through the kidney in such diseases is that there is increased microvascular permeability secondary to increased circulating inflammatory mediators, such as the cytokines.\textsuperscript{72} MAL may thus reflect either the direct effect of cytokines on the renal matrix or indirect effects mediated through an inflammatory cell infiltrate into the affected kidney.\textsuperscript{72}

MAL in pregnant women during the third trimester may be an early predictor of pre-eclamptic complications.\textsuperscript{74} Finally, other conditions, such as exacerbations of psoriasis have been reported to correlate with UAE independently of sex, age and blood pressure.\textsuperscript{73}

**Microalbuminuria and cardiovascular risk**

**Hypertension and endothelial dysfunction**

The association between MAL and cardiovascular risk has been closely studied in hypertensives. However, the prevalence of MAL in hypertension varies in different studies from 11\%\textsuperscript{47} to 40\%\textsuperscript{76} or greater, depending upon the number of patients studied, severity of hypertension, age, race and coexistence of renal impairment.\textsuperscript{77}

Correlations between UAE and several cardiovascular risk factors have been observed in hypertensive patients. For example, hypertensives with MAL have higher left ventricular mass than normoalbuminurics.\textsuperscript{50,52} In a further study with 74 patients with untreated hypertension, there was a positive correlation between left ventricular mass and UAE, but only in men and not in women.\textsuperscript{77} Hypertensives with other risk factors such as smoking or hyperlipidemia show greater target organ damage in patients with MAL, with cardiovascular disease being 50\% higher in microalbuminurics.\textsuperscript{68} The levels of UAE were also significantly correlated with body mass index and waist to hip ratio, which have recognised associations with cardiovascular risk.\textsuperscript{68}

The thickness of the intima and media layers of the carotid artery is higher in microalbuminuric hypertensives in comparison to normoalbuminuric hypertensives and normotensive controls.\textsuperscript{78} In the same study, other cardiovascular risk factors, such as total cholesterol, triglycerides, lipoprotein (a), insulin area-under-the-curve and glucose area-under-the-curve, were significantly more prevalent among microalbuminuric patients.

In a large study of 11 343 non-diabetic hypertensives from a general population sample, the prevalence of MAL was 30\%.\textsuperscript{79} The analysis showed that microalbuminurics (compared to normoalbuminurics) had a higher prevalence of hyperlipidemia (57.4\% vs. 52.2\%), coronary artery disease (31\% vs. 22.4\%), peripheral vascular disease (7.3\% vs. 4.9\%), myocardial infarction (7\% vs. 4\%) and stroke (5.8\% vs. 4.2\%). In addition, MAL was a risk factor which was independent of age, duration of hypertension and degree of blood pressure elevation.

MAL has also been regarded as a marker of generalized endothelial damage. The latter is the
basis of the Steno hypothesis, where that the transmembrane passage of albumin (which is negatively charged) is facilitated when the production of heparan sulphate (the main negatively charged molecule in the glomerular basement membrane) is reduced; poor glycaemic control inhibits the enzyme N-deacetylase (which is responsible for heparan sulphate production). Transcapillary albumin leakage is not confined only to the glomerulus but may occur also in the retina and other vascular beds. In support of this, increased transcapillary escape of albumin has been observed in hypertensives, contributing to the development of MAL, and hypertensives with MAL have increased levels of von Willebrand factor, an established marker of endothelial dysfunction, when compared to hypertensives with normal UAE and with normotensive controls. Furthermore, in a Japanese study where several markers of endothelial dysfunction were investigated in a group of 61 elderly hypertensives, the microalbuminuric subgroup showed significant elevations of activated Factor VII (FVIIa), von Willebrand factor and thrombomodulin, compared with a normoalbuminuric group and a group of patients with ‘white coat’ hypertension. The increased levels of such markers might account for the higher cardiovascular risk in hypertensive patients with MAL. A further assumption of the hypothesis that MAL is an index of endothelial dysfunction is that a widespread transcapillary escape of albumin and other plasma proteins not only occurs at the capillary level but also in other parts of the vascular tree (such as the coronary vessels) thus triggering or contributing to the atherosclerotic process.

However, not all the evidence is fully supportive of generalized vascular or target-organ damage in microalbuminuric patients. For example, where direct vasodilatation of the forearm vascular tree after infusion of acetylcholine and nitroprusside was measured in hypertensives and normotensives, there were no significant differences in the type and degree of vascular response between micro- and normoalbuminuric hypertensives. Furthermore, in a prospective follow-up of 345 non-diabetic hypertensive men with several risk factors, it was observed that the increased risk for cardiovascular events occurred only in patients with UAE above 100 mg/12 h, corresponding to macroalbuminuria rather than MAL. Results from the HARVEST study in 870 young hypertensives (up to 45 years old) reported that no significant correlation existed between left ventricular mass and UAE, suggesting that in the initial phase of hypertension, renal and cardiac involvement do not occur in a parallel fashion.

Overall, although it is generally accepted that the presence of raised UAE levels increases the risk for hypertensive complications, not all the questions have been fully answered.

### Blood lipids

Some studies, particularly in hypertensives, imply that MAL is accompanied by higher levels of blood lipids. For example, UAE has been significantly correlated with serum triglyceride levels (even on a multivariate analysis) and VLDL, triglycerides and lipoprotein (a). A large study of 11 343 non-diabetic hypertensives also reported that the microalbuminuric subgroup had a higher prevalence of hyperlipidaemia in comparison to normoalbuminurics (57.4 vs. 52.2%). Another report of 12 patients with salt-sensitive hypertension found higher levels of UAE, HDL, LDL and lipoprotein (a) when compared with patients with salt-resistant hypertension. By contrast, another study of 313 hypertensives found no relationship between various lipid components and MAL.

### Obesity

Obesity is considered to be a well-recognized risk factor for increased morbidity and mortality, usually from cardiovascular complications. It has been postulated that high intake of food, including protein, can lead to renal hyperfiltration and renal impairment. Consistent with this hypothesis, proteinuria and focal glomerulosclerosis have been reported in obese patients, with strong correlations between BMI and UAE, and between BMI and kidney volume. A correlation of UAE with waist-to-hip ratio and insulin levels has also been noted in hypertensive men and in obese healthy subjects. These findings imply that MAL may be one of the metabolic abnormalities that accompany central-type obesity; these have been included together as part of the insulin resistance syndrome (‘syndrome X’).

### Retinopathy

In hypertensive subjects, an increased prevalence of hypertensive retinopathy has been reported in microalbuminuric patients. In another study of 84 poorly-controlled hypertensives, the prevalences of retinopathy in patients with irreversible MAL (n=12), patients with reversible MAL (n=27) and patients with normoalbuminuria (n=45) were 85%, 33% and 31%, respectively. The significantly higher prevalence of retinopathy in patients with irreversible (after short intensive therapy) MAL was considered to be compatible with the hypothesis that MAL is a marker of widespread diabetic microangiopathy.
Smoking

Smoking correlates positively with UAE in patients with IDDM on univariate analysis, but not on multivariate analysis. This suggests that smoking probably plays a minor role in the evolution of diabetic nephropathy.

In the general population, however, a positive correlation between smoking and UAE was found in the New Zealand study. Smoking status also did not appear to contribute to UAE variation in three groups of hypertensives, once von Willebrand factor levels were taken into account.

Smoking appears to be an important link between MAL and endothelial damage or dysfunction in diabetics. Increased von Willebrand factor levels, an index of endothelial damage, have been demonstrated in smokers irrespective of their blood pressure.

Effects of treatment strategies

MAL can be altered by therapeutic interventions, particularly in hypertensive subjects. Indeed, the positive correlation between blood pressure levels and MAL implies that lowering of blood pressure could reduce UAE levels as well. This has been substantiated by several studies, using different antihypertensive drugs. An unanswered issue, however, is whether different classes of antihypertensive drugs exert different and specific actions in the kidney.

Bianchi et al. studied hypertensives with four different classes of drugs (chlorothalidone, atenolol, nitrrendipine and enalapril) given in random order. By contrast, some reports suggest that the calcium antagonists, such as isradipine had no significant influence on UAE. These studies suggest that angiotensin-converting-enzyme (ACE) inhibitors had a more specific capacity to reduce UAE compared to other antihypertensive drugs. This favourable effect may be a consequence of the decrease in intraglomerular pressure, and glomerular permeability or selectivity.

By contrast, in another study mild hypertensives were treated with 12-week courses of doxazosin, felodipine, metoprolol and ramipril, and all four drugs reduced both blood pressure and UAE to the same extent. The reduction of blood pressure per se had beneficial effects on UAE levels, irrespective of specific drug actions. The authors therefore suggest that in patients with mild hypertension but without elevation of the filtration fraction (as is usually the

Table 1  Microalbuminuria: normal variations

<table>
<thead>
<tr>
<th>Parameters influencing UAE rate</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erect position</td>
<td>Increased UAE rate</td>
</tr>
<tr>
<td>Exercise</td>
<td>Increased UAE rate</td>
</tr>
<tr>
<td>Increased diuresis</td>
<td>Increased during day time</td>
</tr>
<tr>
<td>Day/night time</td>
<td>Higher in Black and Asian (Maori and Pacific natives) compared to Caucasians</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Uncertain, possibly positive correlation</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Possibly positive correlation</td>
</tr>
<tr>
<td>Age</td>
<td>Uncertain, possibly higher in men</td>
</tr>
</tbody>
</table>

Table 2  Microalbuminuria in various cardiovascular disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relationship to severity of disease</th>
<th>Effect of treatment</th>
<th>Prognostic value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Probably positive</td>
<td>Reduction in excretion</td>
<td>Unclear; probably marker of cardiovascular and renal complications</td>
<td>Significance of reversibility is unknown</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Positive relationship</td>
<td>Reduction in excretion</td>
<td>High prognostic value for both renal and cardiovascular disease</td>
<td>Established risk factor for renal and cardiovascular complications. Established significance of reversibility</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Uncertain</td>
<td>Lack of data</td>
<td>Lack of data</td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>Uncertain</td>
<td>Lack of data</td>
<td>Lack of data</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Uncertain</td>
<td>Lack of data</td>
<td>Lack of data</td>
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</tr>
</tbody>
</table>
case with younger hypertensives), no special and expensive antihypertensive treatment (such as ACE inhibitors) is required, in contrast to diabetic patients with MAL. A recent Finnish study in 1069 patients showed that even 7 years of effective treatment of hypertensive patients eventually resulted in normalization of initial increased UAE levels and a decrease in renal vascular resistance, with no change in GFR compared with control subjects. Large prospective randomized trials are needed to investigate whether reduction of MAL reduces the long-term cardiovascular risk.

Microalbuminuria and cardiovascular risk in the general population setting

Yudkin et al. in 1988 were the first to report that, in non-diabetic subjects, UAE significantly correlated with prevalence of atherosclerotic arterial disease with odds ratio (OR) of 6.38, especially the risk of peripheral vascular disease (with OR of 7.72). Damsgaard et al. also reported a decreased survival rate in 216 microalbuminuric non-diabetics when compared to normoalbuminuric subjects. In the large population study from New Zealand, the parameters that correlated positively with UAE in a multivariate regression model were BMI, diastolic pressure, smoking, sex and ethnicity, with Asians having greater risk than subjects of European origin. The strongest risk factor found for developing MAL was in fact the existence of hyperglycaemia and impaired glucose tolerance.

The different prevalence of MAL among different ethnic groups has been attributed to genetic and dietary factors as well as smoking and drinking habits, but may in part be associated with the different cardiovascular risk in different ethnic groups. In the San Antonio Heart Study, for example, which studied 316 non-diabetics of Spanish origin with regard to several cardiovascular risk factors and UAE, subjects with MAL had lower HDL levels and higher blood pressure levels, triglycerides, and the sum of insulin measurements at times 0, 30, 60 and 120 min during an oral glucose tolerance test (OGTT). An increased prevalence of myocardial infarction was also noted in this group.

Similar results were drawn from the Mexico City Diabetes Study, where amongst 1298 non-diabetic subjects, those with MAL had lower HDL cholesterol and higher triglycerides, fasting glucose and 2-h insulin levels during OGTT when compared to normoalbuminurics. A recent Finnish study in 1069 non-diabetic subjects also found that high UAE values correlated with coronary morbidity and mortality (with OR of 5.93 and 3.39, respectively) and the coexistence of MAL and hyperinsulinaemia was an even stronger cardiovascular risk factor. Finally, an British study of 1046 White non-diabetics reported a positive correlation between UAE with blood pressure (in men) age, impaired glucose tolerance and a negative correlation with height.

The evidence therefore suggests that even normotensive non-diabetic microalbuminuric subjects have a more atherogenic profile and tend to be more insulin-resistant than normoalbuminurics. Measurement of UAE in the general population can thus be helpful in the evaluation of patients with cardiovascular risk.

Conclusion

Changes in MAL in various cardiovascular disorders are likely to be more than an epiphenomenon. Data suggest that it is of value as an index of vascular damage, especially in hypertension and diabetes, and increasing information on its associations with traditional cardiovascular risk factors and its prognostic value is becoming available. The association between MAL and peripheral markers of endothelial damage or dysfunction suggests the possibility that MAL may be a simple, cheap and easy measure of endothelial abnormalities in cardiovascular disease. This opens the possibility of assessing various treatment modalities, for example, antihypertensive drugs, and their effects in reversing MAL. Nevertheless, further information of the value of MAL in the investigation of other atherosclerotic vascular complications, such as ischaemic heart disease, stroke and peripheral artery disease is still necessary.

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