

# MICROALBUMINURIA AND ITS ASSOCIATION WITH SUBCLINICAL ATHEROSCLEROSIS IN THE MEXICAN MESTIZO POPULATION: THE GEA STUDY

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## ABSTRACT

**Background:** Microalbuminuria is an early marker of atherosclerosis. Ethnic differences for both conditions have been reported. We studied microalbuminuria prevalence and its association with coronary artery calcification as an early atherosclerosis marker in a Mexican-Mestizo population free of diabetes and hypertension (healthy), as well as in hypertensive and diabetic subjects. **Methods:** In 1,472 adults (53.3 ± 9.4 years old, 50.3% women), anthropometric measurements, fasting blood glucose, and lipid profile were determined. A spot urine sample was used to quantify the albumin-to-creatinine ratio and to define microalbuminuria (20–200 mg/g in men, and 30–300 mg/g in women). A coronary artery calcification score was obtained by electron-beam computed tomography and subclinical atherosclerosis was defined as a score > 0. **Results:** Overall microalbuminuria prevalence was 9.3% (5.4% in healthy, 11.6% in obese, 12% in hypertensive, and 25% in diabetic subjects). Compared to “healthy” subjects without microalbuminuria, those with microalbuminuria had a ~3-fold higher prevalence of coronary artery calcification > 0, while normal-high albumin-to-creatinine ratio (OR: 1.8; p < 0.05) and microalbuminuria (OR: 2.6; p < 0.001) was independently associated with coronary artery calcification > 0 only among diabetic subjects. **Conclusions:** Microalbuminuria and high-normal albumin-to-creatinine ratio were independently associated with subclinical atherosclerosis, suggesting that they may confer a higher risk of future cardiovascular events. (REV INVES CLIN. 2016;68:262-8)

**Key words:** Coronary artery calcium. Microalbuminuria. Subclinical atherosclerosis.

## INTRODUCTION

Kidney disease increases the risk of cardiovascular and all-cause mortality<sup>1,2</sup>. A moderate decrease in kidney function is also associated with subclinical atherosclerosis<sup>3</sup>. In studies performed in different populations,

microalbuminuria (MA), which is known to be associated with kidney disease, has been associated with an increased incidence of coronary artery disease (CAD) events, and elevated risk of all-cause and CAD mortality in diabetes mellitus (DM) and hypertensive (HT) patients, as well as individuals without these clinical

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conditions<sup>4</sup>. The association between urinary albumin excretion and CAD has been observed at albumin-to-creatinine ratios even below 30 mg per gram of creatinine, a value usually used to define microalbuminuria<sup>5,6</sup>.

Coronary artery calcification (CAC) is a specific marker of the presence and magnitude of atherosclerosis<sup>7</sup>. This marker strongly correlates with histologically atherosclerotic plaque area<sup>8</sup>. Moreover, CAC may be a predictor of future coronary events in asymptomatic patients<sup>9</sup> and may be identified and quantified rapidly, easily, and non-invasively using computed tomography<sup>10</sup>. Several studies have found an association between MA and subclinical atherosclerosis, defined by the presence of CAC<sup>10</sup>. However, ethnic variations in the prevalence of CAC<sup>11-14</sup> as well as albuminuria<sup>15,16</sup> suggest that the degree of this association depends on the analyzed population. There have been no studies that analyze the relationship between MA and subclinical atherosclerosis in Mexico. For this reason, our objective was to investigate the prevalence of MA and its association with subclinical atherosclerosis defined by the presence of CAC in a “healthy” (no evidence of DM or HT) Mexican-Mestizo population as well as type 2 diabetic and hypertensive patients.

## METHODS

This investigation is part of the “Genetics of Atherosclerosis Disease” (GEA, for its initials in Spanish) study, designed at the National Institute of Cardiology Ignacio Chavez to examine the genomic basis of CAD and to evaluate its relationship with traditional and emerging cardiovascular risk factors in an adult Mexican population. The study included a group of 1,000 patients with CAD and a control group of 1,500 individuals without CAD, who were all between the ages of 35-75 years and residents of Mexico City. Subjects from the control group were volunteers with no clinical or family history of CAD, who attended the blood bank of the National Institute of Cardiology Ignacio Chavez or were invited via written messages placed in social service centers. Exclusion criteria included a history or clinical evidence of cancer, liver or kidney disease, or corticosteroid use. Urine samples were unavailable in 28 participants; therefore this report includes only 1,472 control subjects. The GEA study was approved by the Ethics and Research Committee of the National Institute of Cardiology Ignacio Chavez following

the guidelines of the Declaration of Helsinki. All subjects who participated in the study signed an informed consent form.

## Clinical methods

Every participant was asked to complete a standardized questionnaire containing demographic information, personal background of cardiovascular risk, dietary habits, physical activity, alcohol and tobacco consumption, and use of medications. Weight (kg) and height (m) were recorded and body mass index (BMI) calculated as kg/m<sup>2</sup>. Waist circumference was measured at the midpoint between the bottom of the lowest rib and the iliac crest with an approximation of 0.5 cm. Blood pressure was measured three times using a Welch Allyn digital sphygmomanometer after at least five minutes in a resting position. The average of the last two measurements was used for the analysis.

## Laboratory procedures

Each participant was told to avoid vigorous exercise or smoking the morning of the study and there should be no evident infections during the previous two weeks. Venous blood samples were collected after a 12-hour fasting and 20 minutes in a resting position. K<sub>2</sub>EDTA (1.8 mg/ml) plasma or serum were prepared by centrifugation at 4° C at 2,500 rpm for 20 minutes. Total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) concentrations were measured in plasma, while uric acid and creatinine were determined in serum within three days after obtaining the sample. The measurements were made in a Hitachi 902 automated analyzer (Hitachi LTD, Tokyo, Japan) using enzymatic-colorimetric reagents (Roche Diagnostics, Mannheim, Germany). The reproducibility and reliability of the lipid and lipoprotein determinations were evaluated periodically by the Lipid Standardization Program of the Centers for Disease Control and Prevention (LSP-CDC, Atlanta, GA, USA). Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula as modified by De Long, et al. Albuminuria was determined in a spot urine sample that was kept at -70° C (boric acid 10 mg/ml) until analyzed by immunonephelometry in a BN ProSpec® nephelometer (Dade Behring, Marburg GmbH, Germany). Creatinuria was determined by the Jaffe method in a Hitachi 902 automated analyzer (Hitachi LTD, Tokyo, Japan). Renal function was estimated with the

glomerular filtration rate (GFR)<sup>17</sup>, using the following formula:  $\text{MDRD GF (ml/min/1.73 m}^2\text{)} = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742^{\text{(women only)}}$ .

## Computed tomography study

Coronary artery calcification and visceral (VAF) and subcutaneous (SAF) abdominal fat were quantified using an axial computed tomography scan. We used a 64-channel multidetector scan (Somatom Sensation, Siemens) to obtain the images that were subsequently interpreted by a specialized radiologist. The VAF was quantified as described by Kvist, et al.<sup>18</sup>. The Agatston method was used to quantify CAC<sup>19</sup>. Subclinical atherosclerosis was considered to be present when CAC levels exceeded zero Hounsfield units (CAC > 0).

## Cardiovascular risk factor definitions

To classify the degree of albuminuria, we used the albumin/creatinine ratio with the following cut-off points<sup>20</sup>: normal albuminuria (< 10 mg/g in men and < 15 mg/g in women), normal-high (10 to < 20 mg/g in men and 15 to < 30 mg/g in women), microalbuminuria (20 to < 200 mg/g in men and 30 to < 300 mg/g in women), and macroalbuminuria (> 200 mg/g in men and > 300 mg/g in women). Hypertension was defined with systolic and/or diastolic blood pressure readings  $\geq 140/90$  mmHg, or the use of antihypertensive medication. Impaired fasting glycemia was defined as fasting glucose levels between 100 and 125 mg/dl, while diabetes was considered when glucose levels were  $\geq 126$  mg/dl, when there was a previous diagnosis, or the patient used hypoglycemic treatment.

## Statistical analysis

General characteristics of the population were reported as mean  $\pm$  standard deviation, median (interquartile range) or prevalences. Comparisons were performed using ANOVA, Kruskal-Wallis or chi-squared, as appropriate. Coronary artery calcification > 0 and the degree of albuminuria were analyzed as simple prevalence. To identify the independence of the association between these variables, a logistic regression analysis adjusted for age, gender, VAF, uric acid, LDL-C, HDL-C and glomerular filtration rate was performed. All  $p < 0.05$  values were considered statistically significant. Statistical analysis was performed using SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

Our investigation included 1,472 subjects (50.3% women), with an average age of  $53.3 \pm 94$  years and BMI of  $28.5 \pm 4.4$  kg/m<sup>2</sup>. Hypertension was identified in 25%, DM in 13.0%, and obesity in 31.7% of the population studied. Overall MA prevalence was 9.3%: 12.0% in subjects with HT, 25% in those with DM, 11.6% among obese, and 5.4% in "healthy" subjects. Clinical and biochemical characteristics of the population stratified by albuminuria concentration are shown in table 1. Age, proportion of men, BMI, and waist circumference increased gradually and significantly as the value of urinary albumin increased. It is worth noting that the highest values of waist circumference present in MA subjects was determined by excess VAF, given that SAF showed no statistically significant differences across groups. In general, subjects with normal-high albuminuria and MA had a more adverse cardiometabolic profile than those with normal degree of albuminuria. This profile was characterized by an HT prevalence twice as high, and a DM prevalence 3-4-times higher. These subjects also presented higher LDL-C, TG, and uric acid levels, as well as lower HDL-C concentrations. This adverse cardiometabolic profile was associated with a higher prevalence of subclinical atherosclerosis (23.7 vs. 33.8 and 51.5%;  $p < 0.001$ ).

The association between microalbuminuria and subclinical atherosclerosis (Fig. 1) was analyzed separately: "healthy" subjects (panel A), DM patients (panel B), and HT patients (panel C). As expected, DM and HT patients had a CAC > 0 prevalence twice as high as the "healthy" subjects and this prevalence increased gradually and significantly as albuminuria concentrations increased in all three groups ( $p < 0.0001$ ). The independence of this association was investigated through a logistic regression analysis (Table 2) adjusted for age, gender, VAF, uric acid, LDL-C, HDL-C, GFR, and patients receiving angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers ( $n = 128$  and  $82$ , respectively). To exclusively analyze the effect of albuminuria, in each group, subjects with normal albuminuria were considered as the reference group. In healthy subjects, the independent risk of subclinical atherosclerosis was three times as high for subjects with MA. In DM patients, normal-high albuminuria was associated with an independent risk, 1.8-times higher, while MA showed a risk 2.6-times higher. These associations were not independent for HT patients (Table 2).

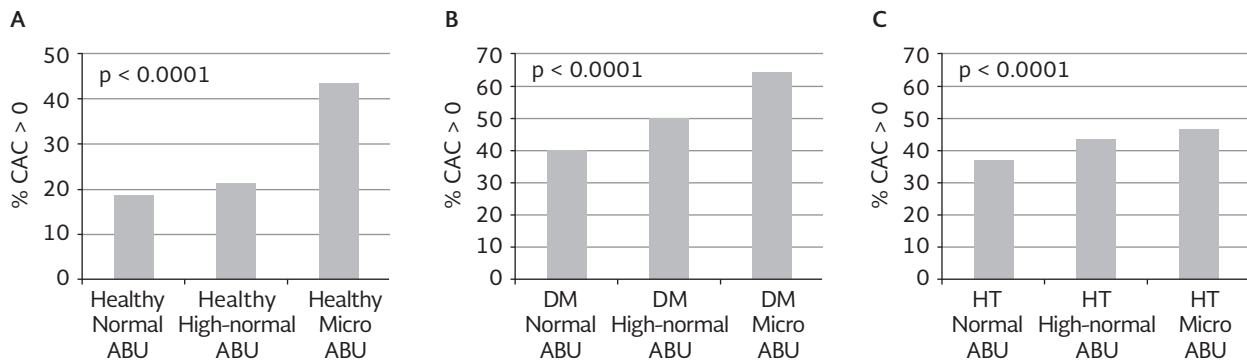
Table 1. Clinical and biochemical characteristics of study population stratified by albuminuria concentration

|                                                  | Normal<br>n = 1176<br>(80%) | Normal-high<br>n = 143<br>(9.7%) | Microalbuminuria<br>n = 137<br>(9.3%) | Macroalbuminuria<br>n = 16<br>(1%) | p*       |
|--------------------------------------------------|-----------------------------|----------------------------------|---------------------------------------|------------------------------------|----------|
| Age (years)                                      | 52.6 ± 9.2                  | 55.7 ± 9.6                       | 55.5 ± 10.0                           | 57.9 ± 9.0                         | < 0.0001 |
| Men (%)                                          | 46.1                        | 55.9                             | 70.8                                  | 75.0                               | < 0.0001 |
| BMI (kg/m <sup>2</sup> )                         | 28.3 ± 4.3                  | 29.5 ± 4.5                       | 29.4 ± 4.9                            | 28.3 ± 3.5                         | < 0.01   |
| Waist (cm)                                       | 94.1 ± 11.3                 | 98.5 ± 11.5                      | 98.3 ± 12.5                           | 97.4 ± 9.5                         | < 0.0001 |
| SAF (cm <sup>2</sup> )                           | 296 ± 112                   | 306 ± 116                        | 282 ± 118                             | 256 ± 99                           | 0.182    |
| VAF (cm <sup>2</sup> )                           | 151 ± 61                    | 181 ± 67                         | 179 ± 71                              | 186 ± 78                           | < 0.0001 |
| SBP (mmHg)                                       | 115 ± 15                    | 125 ± 21                         | 130 ± 22                              | 134 ± 19                           | < 0.0001 |
| DBP (mmHg)                                       | 71 ± 8                      | 75 ± 11                          | 78 ± 12                               | 77 ± 7                             | < 0.0001 |
| HT (%)                                           | 20.9                        | 39.9                             | 41.6                                  | 50.5                               | < 0.0001 |
| DM (%)                                           | 8.3                         | 23.8                             | 35.0                                  | 75.0                               | < 0.0001 |
| Smoking (%)                                      | 21.9                        | 22.4                             | 23.5                                  | 31.3                               | 0.814    |
| LDL-C (mg/dl)                                    | 119 ± 31                    | 120 ± 35                         | 111 ± 31                              | 111 ± 38                           | < 0.05   |
| HDL-C (mg/dl)                                    | 47 ± 13                     | 45 ± 13                          | 43 ± 12                               | 44 ± 8                             | < 0.05   |
| TG (mg/dl)                                       | 144 (108-197)               | 162 (121-208)                    | 167 (120-230)                         | 183 (139-187)                      | < 0.0001 |
| UA (mg/dl)                                       | 5.6 ± 1.5                   | 5.6 ± 1.6                        | 6.0 ± 1.6                             | 5.7 ± 1.7                          | < 0.05   |
| GF <sub>MDRD</sub> (ml/min/1.73 m <sup>2</sup> ) | 90 ± 20                     | 97 ± 26                          | 91 ± 19                               | 86 ± 25                            | < 0.05   |
| Agatston (HU)                                    | 24 ± 137                    | 34 ± 115                         | 86 ± 259                              | 189 ± 601                          | < 0.0001 |
| CAC > 0 (%)                                      | 23.7                        | 33.8                             | 51.5                                  | 31.3                               | < 0.001  |

\*ANOVA.

BMI: body mass index; CAC: coronary artery calcium; DBP: diastolic blood pressure; DM: diabetes; GF<sub>MDRD</sub>: glomerular filtration rate; HDL-C: High-density lipoprotein cholesterol; HT: hypertension; LDL-C: low-density lipoprotein cholesterol; SAF: subcutaneous abdominal fat; SBP: systolic blood pressure; TG: triglycerides; UA: uric acid; VAF: visceral abdominal fat.

Figure 1. Proportion of subjects with subclinical atherosclerosis (CAC > 0) in: **A.** Healthy subjects (without hypertension or diabetes mellitus) **B.** Subjects with diabetes mellitus, **C.** Subjects with hypertension without diabetes mellitus, by albuminuria concentration. chi-square.



## DISCUSSION

The results of this investigation demonstrate that the prevalence of MA in patients without diabetes or arterial hypertension is 5.4%, while this prevalence increased to 12.0, 25.0, and 11.6%, for HT, diabetic, and obese subjects, respectively. Our most important

finding was identified in the logistic regression analysis, adjusted for CAC confounding factors, including renal function. This analysis showed that even normal-high levels of albuminuria, and not MA exclusively, may be associated with subclinical coronary atherosclerosis, defined as CAC > 0. Despite their expected higher cardiovascular risk, the finding of a

Table 2. Odds ratios (95% CI) for coronary artery calcification (&gt; 0) by albuminuria concentration in healthy, diabetic, and hypertensive subjects

|                   | Normal albuminuria | Normal-high albuminuria | Microalbuminuria | p*      |
|-------------------|--------------------|-------------------------|------------------|---------|
| Healthy           | Referent           | 0.7 (0.4-1.5)           | 2.9 (1.5-5.8)    | < 0.05  |
| Diabetes mellitus | Referent           | 1.8 (1.09-3.1)          | 2.6 (1.5-4.6)    | < 0.001 |
| Hypertension      | Referent           | 1.4 (0.9-2.4)           | 1.4 (0.7-2.6)    | 0.319   |

\*Logistic regression analysis adjusted for age, sex, visceral abdominal fat, uric acid, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, glomerular filtration rate, and treatment with angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers.

lower prevalence of CAC in the participants with macroalbuminuria may be explained by the much smaller number of subjects in this subgroup, thus potentially biasing this observation toward the null.

Differences in renal albumin excretion have been reported between Hispanic and Caucasian subjects<sup>10</sup>. Some studies have documented that MA is approximately twice as common in Hispanic populations of Mexican origin<sup>16,21</sup>. Our results are not consistent with these observations. The prevalence of MA in our healthy population was 5.4%, close to the 6% detected in the Framingham study performed on Caucasians with similar clinical characteristics<sup>6</sup>. On the other hand, previous data showed MA in ~30% of patients with type 1 or 2 DM<sup>22</sup>, which agrees with our finding of MA in a quarter of the DM patients in this investigation.

Obesity is a condition with an important role in the development of MA. Epidemiologic studies have found an independent association between increased BMI and MA<sup>23</sup>. It has been suggested that excess visceral abdominal fat and the accompanying insulin resistance result in a state of oxidative stress and endothelial dysfunction that leads to MA<sup>24</sup>. In the PREVEND study, the prevalence of MA was 29.3% in obesity, while in normal-weight subjects it was 9.5%<sup>23</sup>. In the present study, the prevalence was 13.7 and 7.5%, respectively.

Despite the fact that several studies have not found a significant relationship between MA and CAD<sup>25,26</sup>, many investigations have reported an independent association between these two conditions. Gerstein, et al.<sup>27</sup> identified a relationship between MA and the presence of stroke, myocardial infarction, and cardiovascular mortality in patients with and without diabetes. Other population-based studies have demonstrated an association of MA with a higher incidence of

coronary events, as well as an elevated risk of cardiovascular morbidity and mortality<sup>4,28,29</sup>. Furthermore, normal-high concentrations of urinary albumin have been reported to be independently and strongly associated with coronary disease<sup>5</sup>, even in individuals without DM or HT<sup>6</sup>. Conversely, some<sup>30,31</sup> but not all intervention studies<sup>32</sup> have observed that the incidence of cardiovascular events is reduced as albuminuria levels are decreased. Altogether, these findings show that the presence of MA may be associated with higher risk of cardiovascular events and mortality in high-risk patients, as well as those without DM or HT.

Microalbuminuria has also been shown to be associated with subclinical atherosclerosis, defined by the presence of CAC<sup>10</sup>. In the multi-ethnic study of atherosclerosis (MESA) carried out in 6,814 adults, with an average age of 62.7 years and with no clinical manifestations of cardiovascular disease, participants with MA and normal-high levels of albuminuria exhibited a higher frequency of elevated CAC scores<sup>10</sup>. In a more recent, cross-sectional study that included 1,318 asymptomatic subjects, without DM or HT, high CAC values of 100-400 and even > 400 Agatston units were significantly more common in subjects with MA<sup>33</sup>. Moreover, previous studies examined the influence of MA in the progression of coronary calcification. Subjects with MA were shown to have a higher degree of CAC progression even after adjusting for basal CAC and other confounding factors, in type 1<sup>34</sup> and 2<sup>35</sup> DM patients without clinical cardiovascular disease, followed during four years. The association between MA and the development and progression of atherosclerosis was also investigated in MESA<sup>36</sup>. The authors found a significantly higher risk in the incidence and progression of CAC in participants with MA. The results of the present study performed in a Mexican-Mestizo population



are consistent with the findings of previous studies<sup>5,10</sup> when demonstrating that normal-high levels of albuminuria, as well as MA, may be associated with subclinical coronary atherosclerosis, defined by the presence of CAC. These results were found even after adjusting for age, gender, visceral abdominal fat, uric acid, LDL-C, HDL-C, and GFR. This association was identified in apparently healthy subjects, as well as in patients with arterial hypertension and DM. Since the GEA study is currently in the follow-up stage, the effect of MA on the progression of atherosclerosis, as well as cardiovascular morbidity and mortality, may be established in the future.

The mechanisms that take part in the association between MA and CAD are not well known. Some factors that associate MA with atherogenesis, such as low-grade systemic inflammation<sup>37</sup> and endothelial dysfunction<sup>38</sup>, have been identified. In addition, some authors have suggested that albuminuria may be a sign of endothelial dysfunction that affects the vascular beds in the brain, eyes, heart, and kidneys<sup>39</sup>. Furthermore, they have suggested that MA may represent the renal manifestation of microvascular disease<sup>40</sup> produced by a variety of hemodynamic, metabolic, and inflammatory processes. In the early stages of these conditions, microvascular alterations and MA are reversible by controlling the processes from which they originate. However, in later stages, the movement of albumin towards the arterial wall may result in an inflammatory response, accumulation of lipids, and development of atherosclerosis<sup>41</sup>. The results of the present and previous studies<sup>10,33</sup> are consistent with the hypothesis that MA and normal-high levels of albuminuria reflect glomerular endothelial dysfunction. Therefore, albuminuria may be an important marker for the presence of coronary atherosclerosis and future cardiovascular events, even in individuals without diabetes or hypertension<sup>6</sup>.

## Limitations

The authors of the present study recognize that the study has several limitations. First, as is the case with every cross-sectional study, our results cannot establish a cause-effect relationship. Second, albumin was quantified from a single urine sample. Previous studies have suggested that urinary albumin levels may have important, intra-individual variability<sup>42</sup>. Nevertheless, measuring the albumin/creatinine relationship from a single,

random urine sample has been recommended because it is a simple procedure and the results often closely correlate with those obtained after collecting urine for 24 hours<sup>43</sup>. Third, the subjects of the GEA study were volunteers and therefore may not fully or correctly represent the general population. However, due to the unlikelihood that the studied population knew their coronary vascular bed score, we expect the risk relationship to be similar to one obtained from a random sample.

The results obtained in the present study allow us to identify the prevalence of microalbuminuria in the Mexican-Mestizo population. They also confirm that normal-high levels of urinary albumin and the presence of MA are associated with subclinical coronary atherosclerosis in arterial hypertension and DM patients, as well as in healthy subjects. The ongoing monitoring of the GEA study's subjects will allow us to identify the usefulness of MA in the prediction of cardiovascular events in the studied population.

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