Association of Androgenetic Alopecia With Mortality From Diabetes Mellitus and Heart Disease

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Importance: Identifying predictors of mortality from diabetes mellitus (DM) and heart disease can help shape treatment strategies. Presence of androgenetic alopecia (AGA) might be such a predictor.

Objective: To determine whether the presence of AGA is associated with an elevated rate of mortality from DM and heart disease in both sexes after adjustment for potential confounders.

Design: A population-based prospective cohort study.

Setting: Community-based integrated screening in Taiwan.

Participants: A total of 7252 subjects aged 30 to 95 years participated in the baseline AGA survey using the Norwood and Ludwig classifications between April and June 2005. Baseline information on metabolic syndrome (MetS) and other possible risk factors was also collected. We then followed this cohort over time to ascertain death and cause of death until December 2010.

Interventions or Exposures: Application of Norwood and Ludwig ALA classifications to study population.

Main Outcomes and Measures: Deaths from DM and heart disease.

Results: Among the 7126 subjects (2429 men and 4697 women) who provided complete data, there were 70 deaths from DM and heart disease during the 57-month follow-up period. Subjects with moderate to severe AGA vs normal or mild AGA had a significantly higher risk of mortality from DM (adjusted hazard ratio [HR], 2.97; 95% CI, 1.26-7.01) (P=.01) and heart disease (adjusted HR, 2.28; 95% CI, 1.00-5.23) (P=.05) after adjusting for age, family history of DM or heart disease, and MetS.

Conclusions and Relevance: AGA is an independent predictor of mortality from DM and heart disease in both sexes. This finding may have significant implications for the identification of risk factors for DM and heart disease in patients with moderate or severe AGA, regardless of whether MetS is present.
dition, although Herrera et al\textsuperscript{13} used a modified Hamilton classification system, the validity of their AGA assessment is of concern because 12% of their subjects with a single bald area had encountered spontaneous regression without treatment, which is not supported by our current knowledge about AGA. In addition, the extent of baldness was not associated with any of the outcomes in their study. It seems to go against the concept of dose-response relationships, if the association between AGA and mortality from ischemic heart disease indeed existed.

It is worthwhile to further investigate the association between AGA and mortality from heart disease, including studies on subjects of both sexes. In addition, no study has yet focused on the association between AGA and mortality from DM. Because of the significant association between AGA and MetS, the association between AGA and mortality from DM cannot be overemphasized. Therefore, we conducted a community-based investigation of the association between AGA and mortality from DM and heart disease in subjects of both sexes.

**METHODS**

**STUDY SUBJECTS AND DESIGN**

The study protocol was approved by the ethics committee of the Bureau of Tainan County, and informed consent was obtained from all participants. Eligible subjects were residents of Tainan County, Taiwan, who were 30 years or older. Our study was part of a community-based integrated screening program that invited female residents 30 years or older and male residents 40 years or older to participate. The details of the screening program are described elsewhere.\textsuperscript{21} In brief, residents 30 years and older were invited to attend integrated mass screening for 5 major neoplastic diseases (breast cancer, colorectal cancer, cervical cancer, liver cancer, and oral cancer) and 3 non-neoplastic diseases (hypertension, DM, and hyperlipidemia), the majority of which have been supported by evidence-based medicine underpinning randomized clinical studies or large population-based observational studies from Western countries. A community-based survey of the prevalence of AGA was conducted between April and June 2005. A total of 7960 residents were selected from a Tainan County household registry and invited to participate in the survey.

A prospective cohort for evaluating the association between AGA and mortality from DM and heart disease was devised by defining 7126 respondents as a cohort and dividing the cohort into the 2 or 3 groups by the presence or severity of AGA, the main independent variable, together with other confounding factors at baseline. We then followed up with the entire cohort over time until the end of 2010 to ascertain the outcomes of deaths and causes of death by linking information obtained from the baseline survey with Taiwan mortality registry.

**CLASSIFICATION OF AGA**

Diagnosis of AGA was based on the pattern of hair loss in participants. Assessment of the degree of hair loss was performed by 37 independent public health nurses who had been trained by a dermatologist. To classify the degree of AGA for each subject, the Norwood classification, a standard classification system with good test-retest reliability, was used.\textsuperscript{21} Female pattern hair loss (not involving the frontal hairline) was separately assessed using the Ludwig classification system.\textsuperscript{23} To evaluate the reliability and validity of the hair status assessments, the assessments of the 37 nurses involved in the current study were evaluated using weighted \( k \) statistics to assess interobserver reliability. Validity was evaluated by comparing the results derived from the evaluations performed by the public nurses to those based on an evaluation by a specialist dermatologist.

Norwood type IV AGA represents the starting grade of severe frontotemporal AGA concurrent with vertex AGA. For additional analysis, we created 2 AGA categories: normal to mild AGA (equivalent to Norwood types I-III) and moderate to severe AGA (equivalent to Norwood types IV-VII). Then we assessed the associations of these groups with MetS and other potential risk factors. For female pattern hair loss, Ludwig types II and III were categorized as moderate to severe AGA, and normal and Ludwig type I hair loss were categorized as normal or mild AGA.

**MetS AND OTHER POSSIBLE RISK FACTORS**

In addition to the classification of AGA, we collected information on possible risk factors in face-to-face interviews. Anthropometric measurements, including waist circumference, were recorded. Blood pressure (BP) was measured twice with an interval of at least 5 minutes between readings.

To collect data on biochemical markers, a venous blood sample was taken after a 12-hour fast for measurement of blood glucose, triglycerides (TG), total cholesterol (CHO), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL).

Each subject completed a questionnaire regarding family history and diagnoses of chronic diseases (eg, hypertension, DM, cardiovascular disease), drug history (eg, use of antihypertensives, lipid-lowering drugs), exercise status, and smoking status (ie, never smoked, previous smoker, current smoker). "Smoking for 10 or more years" was defined as a regular, chronic smoker. Regular exercise was defined as "at least 30 min per session for at least five sessions per week.” Age was defined as the age at entry into the study.

**DEFINITION OF MetS**

The definition of MetS was based on criteria defined by the National Cholesterol Education Program Adult Treatment Panel III,\textsuperscript{24} which were modified to include the World Health Organization’s proposed waist circumference cutoff points for Asians.\textsuperscript{25} Subjects were required to fulfill 3 or more of the following criteria: (1) waist circumference greater than 90 cm for men and greater than 80 cm for women; (2) serum TG level of 150 mg/dL or higher; (3) HDL level lower than 40 mg/dL for men and lower than 50 mg/dL for women; (4) impaired fasting glucose level of 110 mg/dL or higher or DM; and (3) BP of 130/85 mm Hg or higher or treated hypertension. (To convert serum TG to millimoles per liter, multiply by 0.0113; to convert HDL to millimoles per liter, multiply by 0.0259; to convert impaired fasting glucose to millimoles per liter, multiply by 0.0555.)

**DEATH AND CAUSE OF DEATH**

Death and cause of death were identified by following up with this cohort until the end of 2010. Deaths from all causes, DM, heart disease, and other causes were analyzed. Causes of death were determined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10 using the following respective codes: DM, 230 and E14; hypertensive heart disease, 402 and I11; ischemic heart disease, 410-414 and 121 and 125; heart failure, 428 and 150; ill-
defined descriptions and complications of heart disease, 429 and 151; and cerebrovascular attacks (CVAs), 431-438 and 161, 163, and 169.

**STATISTICAL ANALYSIS**

Survival analysis was performed with survival time defined as the duration from the date of entry to the date of death. In the analysis of specific causes of death, individuals who died from other causes were treated as censored because the specific event would not have been observed in these subjects. Possible associated factors were analyzed using proportional hazards regression models to obtain hazard ratio (HR) estimates for the association between each factor and time to death. Factors with \( P \) values lower than 0.2 in univariate analyses were entered into multivariate analyses. In the evaluation of mortality from DM and heart disease, smoking, regular exercise, family history of DM, coronary heart disease, and hypertension were retained in the multivariate model because these factors were considered clinical factors that are strongly associated with DM and heart disease.

To evaluate the dose-response relationship between AGA and mortality, a proportional hazards regression model with 2 dummy variables was used to compare the HRs for the moderate group (L-I in the Ludwig classification and types III and IV in the Norwood classification) and severe group (types II and III in the Ludwig classification and types V, VI, and VII in the Norwood classification) with the baseline group (normal in the Ludwig classification and types I and II in the Norwood classification). To evaluate the trends in risk of mortality related to AGA, these 3 different groups were assigned ordinal variables of 1 to 3 and entered into the proportional hazards regression model.

The statistical analyses were carried out using SAS software, version 9.2 (SAS Institute Inc). All reported \( P \) values are 2-sided.

### RESULTS

**PARTICIPANTS**

The overall response rate was 91.1% (7252 of 7960). In men, the age-specific response rates were 91.8% (323 of 352), 93.0% (425 of 457), 93.3% (763 of 818), and 90.6% (960 of 1060) for participants aged 40 to 49, 50 to 59, 60 to 69, and 70 years or older, respectively. In women, the age-specific response rates were 92.1% (394 of 428), 91.4% (872 of 954), 91.5% (1021 of 1116), 91.9% (1141 of 1242), and 88.5% (1536 of 1753) for participants aged 30-39, 40-49, 50-59, 60-69, and 70 years or older, respectively. Among the 7252 participants, data for the 7126 subjects who provided complete data were analyzed. The 7126 subjects comprised 4697 women and 2429 men. The mean (SD) age of the women was 59.5 (13.7) years (range, 30-95 years). The mean (SD) age of the men was 65.0 years (range, 39-93 years). The fact that the response rates varied according to age suggested that adjusting for age in the association analysis was sine qua non.

### RELIABILITY AND VALIDITY

**FOR CLASSIFICATION OF AGA**

In the reliability and validity of the hair status assessments, the weighted \( \kappa \) statistic was 0.80 (95% CI, 0.79-0.81), which confirmed good interobserver reliability; the sensitivity was 93.5%, and the specificity was 97.3%, which revealed a good validity in the assessment.

### CAUSES OF MORTALITY

Among the 7126 subjects, there were 1558 subjects with mild AGA, 194 with moderate AGA, and 407 with severe AGA. Of the 7126, we ascertained 424 deaths, 218 women (4.64%) and 206 men (8.48%), during the 5-year follow-up period (average follow-up time, 55.7 months). Of the subjects 49 years or younger, only 5 died. The causes of death among subjects 50 years or older were categorized as DM and heart disease, CVA, cancer, and other causes. For all-cause mortality, the with the exception of the group consisting of women aged 50 to 69 years, for whom there were few data, a higher mortality rate from DM and heart disease was consistently noted in the moderate or severe AGA group compared with the normal or mild AGA group.

### ALL-CAUSE MORTALITY

Compared with normal or mild AGA, there was a significant association of moderate or severe AGA with all-cause mortality (HR, 2.11; 95% CI, 1.63-2.73) \( (P < .001) \) in univariate analysis. However, such an association was not statistically significant (HR, 1.11; 95% CI, 0.85-
1.47) (P = .45) after adjusting for age, sex, and other significant factors. Regarding the results on the severity of AGA, in a multivariate model, the severe group demonstrated a 1.23-fold higher risk of mortality (95% CI, 0.90-1.68), and the moderate group showed a 1.16-fold higher risk of mortality than the normal or mild AGA group (P = .25 for trend test). Therefore, there was a nonsignificant relationship between severity of AGA and all-cause mortality.

**MORTALITY FROM DM AND HEART DISEASE**

With regard to mortality from DM, coronary heart disease, hypertensive heart disease, and heart failure, subjects with moderate or severe AGA showed a 2.01-fold higher risk than the normal or mild AGA group (95% CI, 1.01-3.99) (P = .05) (**Table 2**). Cumulative mortality from DM or heart disease was significantly higher in the moderate to severe AGA group than in the normal or mild AGA group after adjusting for age, sex, and other significant factors. Age was significantly associated with mortality (HR, 1.12; 95% CI, 1.09-1.15) (P < .001). Patients who fulfilled the criteria for MetS demonstrated a higher risk of mortality from these diseases (HR, 2.01; 95% CI, 1.22-3.31) (P < .01). Among the components of MetS, TG level (HR, 1.74; 95% CI, 1.05-2.88) (P = .03) and fasting plasma glucose level (HR, 3.70; 95% CI, 2.25-6.06) (P < .001) were significantly associated with mortality. Findings of analyses of interactions between AGA and other factors were negative.

To evaluate the association between severity of AGA and mortality from DM and heart disease, the
subjects were categorized into 3 groups according to AGA status. In a multivariable model, the severe group demonstrated a 2.21-fold higher risk of mortality (95% CI, 1.00-4.07), and the moderate group showed a 1.02-fold higher risk of mortality compared with the normal or mild AGA group (P = .08 for trend test) (Table 2). Hence, there was a nonsignificant relationship between severity of AGA and mortality from DM and heart disease.

When death from DM (28 deaths) was evaluated separately, subjects with moderate to severe AGA had a significantly higher risk of mortality from DM (adjusted HR, 2.97; 95% CI, 1.26-7.01) (P = .01) after adjusting for age, family history of DM or heart disease, and presence of MetS (Table 3). When death from heart disease (42 deaths) was evaluated separately, subjects with moderate to severe AGA had a significantly higher risk of mortality from heart disease (adjusted HR, 2.28; 95% CI, 1.00-5.23) (P = .05) after adjusting for age, sex, and presence of MetS (Table 3).

**MORTALITY FROM CEREBROVASCULAR DISEASE AND CANCER**

Those with severe AGA had higher but not statistically significantly higher risk than those with normal or mild AGA (adjusted HR, 1.81; 95% CI, 0.67-4.85) (P = .24) after controlling for age, sex, the presence of MetS, and smoking status. Similarly, AGA did not show significant relationships with mortality from cancer (adjusted HR, 1.12; 95% CI, 0.68-1.84) (P = .65) after controlling for similar confounding factors.

**DISCUSSION**

Moderate or severe AGA was associated with a 2.01-fold higher risk of mortality from DM and heart disease compared with normal or mild AGA after adjusting for potential confounders. Although there was no dose-response relationship, unlike in previous reports, our results showed a significant relationship between AGA and mortality from DM and heart disease in both sexes. There were no significant relationships between AGA and cerebrovascular disease or cancer. When the associations between AGA and mortality from DM and heart disease were evaluated separately, the adjusted odds ratios (2.97 and 2.28, respectively) were significant.

Based on the results of this study, AGA could be considered a marker for other underlying risk factors for DM and heart disease but not a direct cause. We do not think that preventing or curing AGA will have any impact on risk of mortality from DM or heart disease. However, AGA could be used to identify susceptible individuals who might benefit from interventions focused on DM and heart disease risk factors such as smoking, cholesterol and blood glucose levels, and elevated BP. In other words, AGA can be considered an important indicator of increased risk of mortality from DM and heart disease.

In our group’s previous report, MetS was found to be associated with AGA after adjusting for established significant risk factors. It was also evident that fulfillment of a higher number of MetS criteria was associated with a greater risk of AGA. Therefore, rigorous investigation of components of MetS in patients with AGA is needed. In the present study, AGA was identified as an independent risk factor for mortality from DM and heart disease after adjusting for other potential factors, including MetS. Therefore, it should be emphasized that intervention and preventive strategies for DM and heart disease are important in AGA, regardless of the presence or absence of MetS.

There will be concerns about the effects of different treatments on the prognosis of DM and heart disease. Because our study subjects were recruited in a community setting and lived in the same area, the confounding effects of treatments on mortality should not differ between subjects with and without AGA. Therefore, the relationship between AGA and higher risk of mortality from DM and heart disease should not have been biased by the lack of adjustment for clinical treatments in the present study.

In conclusion, the present study revealed a significant relationship between AGA and mortality from DM and heart disease in both sexes. Based on our results, AGA can be considered a marker for other underlying risk factors for DM and heart disease. It could be used to identify susceptible individuals who might benefit from interventions targeting multiple DM and heart disease risk factors, such as smoking, cholesterol and blood glucose levels, and elevated BP. Androgenetic alopecia can be considered an important indicator of increased risk of mortality from DM and heart disease.

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REFERENCES


