**Serum Vascular Adhesion Protein-1 Predicts 10-Year Cardiovascular and Cancer Mortality in Individuals With Type 2 Diabetes**

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**OBJECTIVE**—Vascular adhesion protein-1 (VAP-1) participates in inflammation and catalyzes the breakdown of amines to produce aldehyde, hydrogen peroxide, and ammonia. Serum VAP-1 correlates positively with both acute hyperglycemia and diabetes. We conducted a cohort study to evaluate whether serum VAP-1 predicts 10-year survival in type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS**—Between July 1996 and June 2003, we enrolled 661 type 2 diabetic subjects at National Taiwan University Hospital. Serum VAP-1 in the samples obtained at enrollment was measured by time-resolved immunofluorometric assay. The vital status of all subjects was ascertained by linking their data with computerized death certificates in Taiwan.

**RESULTS**—The medium follow-up period was 10.4 years. Subjects with serum VAP-1 in the highest tertile had a hazard ratio (HR) of 2.19 (95% CI 1.17–4.11) for all-cause mortality adjusted for age, sex, smoking, history of cardiovascular disease, obesity, hypertension, hemoglobin A1c, diabetes duration, total cholesterol, use of statins, abnormal ankle-brachial index, estimated glomerular filtration rate (eGFR), and proteinuria. The adjusted HRs for logarithmically transformed serum VAP-1 were 5.83 (95% CI 1.17–28.97) for cardiovascular mortality, 6.32 (95% CI 1.25–32.00) for mortality from cardiovascular and diabetic causes, and 17.24 (95% CI 4.57–65.07) for cancer mortality. There were four variables, including age, serum VAP-1, proteinuria, and eGFR, which could enhance mortality prediction significantly.

**CONCLUSIONS**—Serum VAP-1 can predict 10-year all-cause mortality, cardiovascular mortality, and cancer mortality independently in type 2 diabetic subjects. Serum VAP-1 is a novel biomarker that improves risk prediction over and above established risk factors. *Diabetes 60:993–999, 2011*

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Recently, we have shown that serum VAP-1 is elevated in acute and chronic hyperglycemia and in patients with diabetes (13). We also found that serum VAP-1 is associated positively with albuminuria and is elevated in subjects with chronic kidney disease (12); both are risk factors for atherosclerosis. We have also noted that the change in serum VAP-1 after glucose challenge was correlated with systemic oxidative stress, AGEs, and carotid intima-media thickness, which is an index for atherosclerosis (14). Our results indicated that serum VAP-1 may be a good predictor for cardiovascular mortality. Therefore, we explored this issue in subjects with type 2 diabetes in this prospective cohort study.

**RESULTS**

We included 661 subjects with type 2 diabetes (327 men and 334 women), with mean age 61.9 ± 9.8 years and a medium follow-up period of 10.4 (interquartile range, 7.0–11.4) years. The correlation coefficients between serum VAP-1 and fasting plasma glucose, postprandial plasma glucose, and HbA1c were 0.20, 0.27, and 0.32, respectively (all \( P < 0.0001 \)).

During follow-up, 160 subjects died, including 59 (36.9%) from malignancy, 30 (18.8%) from diabetes, 27 (16.9%) from cardiovascular diseases, 12 (7.5%) from kidney diseases, nine (5.6%) from infectious diseases, eight (5.0%) from gastrointestinal or liver diseases, five (3.1%) from traumatic injuries, and others. At baseline, these subjects were older, had longer duration of diabetes, higher HbA1c, and lower estimated GFR (Table 1). A higher percentage of these subjects had a smoking habit, history of cardiovascular disease, hypertension, proteinuria, and abnormal ABI. Their serum VAP-1 levels were higher, and more subjects had serum VAP-1 in the highest tertile.

People with serum VAP-1 in the highest tertile were older, had higher mortality, longer duration of diabetes, higher fasting plasma glucose, higher postprandial plasma glucose, higher HbA1c, and lower estimated GFR (Table 2). There was a higher percentage of women and subjects with proteinuria and fewer smokers in this tertile.

Kaplan-Meier survival curves showed that during 10.4 years of follow-up, subjects with serum VAP-1 in the highest tertile had a lower rate of survival than subjects in the other tertiles (Fig. 1). In Table 3, the HRs of all-cause mortality are shown to be significantly higher in subjects with serum VAP-1 in the highest tertile, after adjusting for age, sex, smoking, history of cardiovascular disease, BMI category, hypertension, HbA1c, diabetes duration, total cholesterol, use of statins, abnormal ABI, estimated GFR, and/or proteinuria in different models. Serum VAP-1 significantly predicted all-cause mortality in different subgroups divided by age (at 65 years), sex, smoking status, history of cardiovascular disease, BMI category (at 24 and 27 kg/m²), hypertension, HbA1c (at 7.4%), diabetes duration (at 9 years), plasma total cholesterol (at 200 mg/dL), use of statins, ABI category, estimated GFR (at 77 mL/min per 1.73 m²), and proteinuria, adjusted for age, sex, smoking, history of cardiovascular disease, BMI category, hypertension, HbA1c, diabetes duration, total cholesterol, statins, and ABI, apart from the stratification variable. Further adjustment for estimated GFR and proteinuria showed similar results, except in overweight subjects, those without hypertension, and in subjects with plasma total cholesterol greater than 200 mg/dL (all \( P < 0.05–0.10 \)).

The results of disease-specific mortality are shown in Table 4. Serum VAP-1 predicted 10-year cardiovascular mortality independent of age, sex, smoking, and history of cardiovascular disease. There were very few subjects whose underlying cause of death was diabetes. According to the rules defined by the World Health Organization (20), diabetes is likely to be selected as the underlying cause of death in subjects who die directly from cardiovascular diseases. Therefore, we analyzed predictors for cardiovascular
or diabetes-related mortality. As shown in models 2 and 3, serum VAP-1 significantly predicted cardiovascular and diabetes-related mortality adjusted for history of cardiovascular disease, age, sex, smoking, BMI category, hypertension, HbA1c, diabetes duration, total cholesterol, use of statins, and/or estimated GFR. Fifty-nine subjects died of cancer, including colon cancer (n = 26), hepatobiliary cancer (n = 13), lymphoma or leukemia (n = 5), lung cancer (n = 4), urinary tract cancer (n = 4), and others (n = 7). Of interest, serum VAP-1 predicted cancer-related mortality independently (model 4). More specifically, serum VAP-1 independently predicted colon cancer-related mortality (HR 12.19 for logarithmically transformed serum VAP-1, 95% CI 1.77–67.97, P < 0.001). Table 5 shows the incremental predictive ability of different variables for all-cause mortality. Using serum VAP-1 alone can distinguish 63% of all pairs of subjects (one died and one survived), with an area under the ROC curve (AUC) of 0.64. In model 1, the increment in concordance statistics and AUC were 0.11 and 0.12 for serum VAP-1 and 0.01 and 0.01 for history of cardiovascular disease, respectively. In model 2, only serum VAP-1, age, and smoking increased the concordance statistics, whereas serum VAP-1, age, smoking, BMI category, hypertension, HbA1c, diabetes duration, total cholesterol, use of statins, and abnormal ABI increased the AUC. In model 3, only four variables increased the concordance statistics, including serum VAP-1, age, estimated GFR, and proteinuria. Smoking increased the AUC in model 3.

**DISCUSSION**

In this study, we found that serum VAP-1 can independently predict 10-year all-cause mortality, cardiovascular mortality, and cancer-related mortality in subjects with type 2 diabetes and in most subgroups. The improved predictive ability of serum VAP-1 was comparable with that of age, smoking, serum creatinine, and proteinuria.

Recently, inflammation has been found to be an important cause of atherosclerosis (3). Circulating leukocytes, especially monocytes, are recruited to blood vessels, where they transmigrate and are activated. Various chemokines, cytokines, and enzymes are secreted, which may modify low-density lipoprotein, propagate inflammation, and result in atherosclerosis. Endothelial VAP-1 can participate in inflammation by binding granulocytes, lymphocytes, and monocytes, with the aid of SSAO activity (2). In subjects with acute myocardial infarction, VAP-1 can mediate

| TABLE 1 Baseline characteristics of survivors and nonsurvivors with type 2 diabetes |
|---------------------------------|------------------|------------------|------------------|
|                                | Alive            | Dead             | P                |
| N (%)                          | 501 (75.8)       | 160 (24.2)       | <0.0001          |
| Age (years)                    | 60.2 ± 9.3       | 67.4 ± 9.1       | 0.7              |
| Men (%)                        | 246 (49.1)       | 81 (50.6)        | 0.022            |
| Smoking (%)                    | 79 (15.8)        | 34 (21.3)        | 0.03             |
| History of cardiovascular disease (%) | 50 (10.0) | 26 (16.3) | 0.6             |
| SBP (mmHg)                     | 134 ± 16         | 137 ± 18         | 0.065            |
| DBP (mmHg)                     | 79 ± 9           | 79 ± 10          | 0.6              |
| Hypertension (%)               | 152 (30.3)       | 70 (43.8)        | 0.002            |
| Hypertension (%)               | 285 (56.9)       | 113 (70.6)       | 0.002            |
| Duration of diabetes (years)   | 7.0 (3.0–14.0)   | 12.0 (7.0–18.0)  | <0.0001          |
| Fasting plasma glucose, mmol/L (mg/dL) | 8.27 ± 2.55 (149 ± 46) | 8.44 ± 2.55 (152 ± 46) | 0.6 |
| Postprandial plasma glucose, mmol/L (mg/dL) | 11.82 ± 4.11 (213 ± 74) | 12.71 ± 4.39 (229 ± 79) | 0.054 |
| HbA1c (%)                      | 7.6 ± 1.4        | 7.9 ± 1.5        | 0.036            |
| Total cholesterol, mmol/L (mg/dL) | 5.20 ± 0.96 (201 ± 37) | 5.22 ± 1.22 (202 ± 47) | 0.7 |
| Statins (%)                    | 19 (3.8)         | 6 (3.8)          | 1.0              |
| Triglycerides, mmol/L (mg/dL)  | 1.52 (1.06–2.17) | 1.51 (1.10–2.34) | 0.2              |
| BMI (kg/m²)                    | 24.65 ± 3.27     | 24.54 ± 3.25     | 0.7              |
| ≥24–47 (%)                     | 165 (32.9)       | 44 (27.5)        | 0.3              |
| Creatinine, µmol/L (mg/dL)     | 80 (71–88) 0.9 (0.8–1.0) | 97 (71–123) 1.0 (0.8–1.4) | <0.0001 |
| Estimated GFR (mL/min per 1.73 m²) | 81 (22) | 63 (24) | <0.0001 |
| Proteinuria (%)                | 50 (10.0)        | 61 (38.1)        | <0.001           |
| ABI <0.9 or >1.3 (%)           | 29 (5.8)         | 24 (15)          | <0.001           |
| Serum VAP-1 (ng/mL)            | 681 (581–799)    | 786 (636–967)    | <0.0001          |
| By tertile                     |                   |                  | <0.001           |
| Middle, 630–780 (%)            | 176 (35.1)       | 39 (24.3)        |                  |
| Highest, ≥780 (%)              | 140 (27.9)       | 82 (51.2)        |                  |

Means ± SD or medians (interquartile ranges) are shown. DBP, diastolic blood pressure; SBP, systolic blood pressure.
leukocyte binding to endothelia in the infarcted areas (21). Because serum VAP-1 originates from various tissues, it may serve as a measure of systemic inflammation. On the other hand, serum VAP-1 retains its SSAO activity (6). End products of SSAO can modify various proteins and generate AGEs (4). Moreover, end products of SSAO can also propagate inflammation by upregulating the expression and facilitating the release of selectins in endothelium (22). Both functions of SSAO end products contribute to the development of atherosclerosis. Therefore, because

### TABLE 2
Baseline characteristics by serum VAP-1 tertile in people with type 2 diabetes

| Serum VAP-1 tertile (ng/mL) | <630       | 630–780    | ≥780       | P       |
|----------------------------|------------|------------|------------|---------|
| N                          | 224        | 215        | 222        |         |
| Survivors (%)              | 185 (82.3) | 176 (81.9) | 140 (63.1) | <0.001  |
| Age (years)                | 60.1 ± 9.6 | 61.8 ± 9.5 | 63.7 ± 9.9 | 0.0005  |
| Men (%)                    | 132 (58.9) | 102 (47.4) | 93 (41.9)  | 0.001   |
| Smoking (%)                | 48 (21.4)  | 35 (16.3)  | 30 (13.5)  | 0.079   |
| History of cardiovascular disease (%) | 31 (13.8) | 18 (8.4)   | 27 (12.2)  | 0.2     |
| SBP (mmHg)                 | 134 ± 16   | 134 ± 14   | 135 ± 19   | 0.9     |
| DBP (mmHg)                 | 79 ± 9     | 78 ± 9     | 79 ± 9     | 0.6     |
| Hypertension (%)           | 68 (30.4)  | 74 (34.4)  | 80 (36.0)  | 0.4     |
| Hypertension (%)           | 133 (59.4) | 130 (60.5) | 135 (60.8) | 0.9     |
| Duration of diabetes (years) | 5.0 (2.0–12.0) | 9.0 (4.0–13.0) | 11.0 (6.0–18.0) | <0.0001 |
| Fasting plasma glucose (mmol/L, mg/dL) | 7.71 ± 2.00 (139 ± 36) | 8.27 ± 2.39* (149 ± 43) | 8.99 ± 3.05† (162 ± 55) | <0.0001 |
| Postprandial plasma glucose (mmol/L, mg/dL) | 11.21 ± 3.55 (202 ± 64) | 11.60 ± 3.50 (209 ± 63) | 13.32 ± 5.00† (240 ± 90) | <0.0001 |
| HbA1c (%)                  | 7.1 ± 1.2  | 7.8 ± 1.3* | 8.2 ± 1.6† | <0.0001 |
| Total cholesterol (mmol/L, mg/dL) | 5.09 ± 1.01 (197 ± 39) | 5.30 ± 0.98 (205 ± 38) | 5.22 ± 1.11 (202 ± 43) | 0.14     |
| Statins (%)                | 4 (1.8)    | 13 (6.0)   | 8 (3.6)    | 0.065   |
| Triglyceride (mmol/L, mg/dL) | 1.52 (1.13–2.25) | 1.63 (1.16–2.22) | 1.45 (0.99–2.11) | 0.4     |
| BMI (kg/m²)                | 24.65 ± 3.00 | 24.79 ± 3.22 | 24.43 ± 3.55 | 0.5     |
| 24–47 (%)                  | 74 (33.0)  | 71 (33.3)  | 64 (28.8)  | 0.6     |
| ≥27 (%)                    | 42 (18.8)  | 51 (23.7)  | 50 (22.5)  |         |
| Creatinine (μmol/L, mg/dL) | 80 (71–97) 0.9 (0.8–1.1) | 80 (71–88) 0.9 (0.8–1.0) | 80 (71–115) 0.9 (0.8–1.3) | 0.005   |
| Estimated GFR (mL/min per 1.73 m²) | 82 (23)    | 79 (22)    | 71 (25)†   | 0.0001  |
| Proteinuria (%)            | 23 (10.6)  | 26 (12.4)  | 62 (28.2)*† | <0.001  |
| ABI <0.9 or >1.3 (%)       | 14 (6.3)   | 17 (7.9)   | 22 (9.9)   | 0.4     |

Means ± SD or medians (interquartile ranges) are shown. *P < 0.05 vs. first tertile (serum VAP-1 < 630 ng/mL); †P < 0.05 vs. second tertile (serum VAP-1 630–780 ng/mL).

FIG. 1. Kaplan-Meier survival curves by tertile of serum VAP-1 levels. P = 0.0001 among subgroups by tertile. Blue line, subjects with serum VAP-1 in the first tertile; green line, subjects with serum VAP-1 in the second tertile; red line, subjects with serum VAP-1 in the third tertile.
TABLE 3
HRs (95% CI) of 10-year all-cause mortality in people with type 2 diabetes

| VAP-1 tertile (ng/mL) | 1                      | 2                      | 3                      | 4                      |
|----------------------|------------------------|------------------------|------------------------|------------------------|
| <630                 | 1.00                   | 1.00                   | 1.00                   | 1.00                   |
| 630–780              | 0.96 (0.61–1.52)        | 0.86 (0.54–1.38)        | 0.87 (0.54–1.39)        | 0.89 (0.45–1.77)        |
| ≥780                 | 2.03* (1.37–3.02)       | 1.94† (1.25–3.00)       | 2.00† (1.29–3.09)       | 2.19† (1.17–4.11)       |
| P for trend          | <0.001                 | 0.003                  | 0.002                  | 0.008                  |
| Age (years)          | 1.07* (1.05–1.09)       | 1.07* (1.05–1.09)       | 1.07* (1.05–1.09)       | 1.06* (1.03–1.09)       |
| Female sex           | 0.93 (0.67–1.30)        | 0.91 (0.64–1.28)        | 0.91 (0.64–1.28)        | 0.93 (0.59–1.48)        |
| Smoking              | 1.89† (1.26–2.85)       | 1.95† (1.29–2.95)       | 1.88† (1.24–2.85)       | 2.25† (1.34–3.79)       |
| History of cardiovascular disease | 1.49 (0.95–2.31) | 1.48 (0.95–2.30) | 1.30 (0.76–2.23) |

BMI (kg/m²)

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| <24 | 1.00 | 1.00 | 1.00 |
| 24–27 | 0.86 (0.59–1.26) | 0.86 (0.59–1.26) | 0.60 (0.36–1.02) |
| ≥27 | 1.35 (0.90–2.01) | 1.35 (0.90–2.01) | 0.95 (0.56–1.60) |
| P for trend | 0.2 | 0.2 | 0.5 |

Hypertension

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| 124 | 1.33 (0.94–1.90) | 1.30 (0.91–1.85) | 1.16 (0.72–1.87) |

HbA1c (%)

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| 1.09* (1.04–1.14) | 1.11* (1.06–1.16) | 1.11* (1.06–1.16) | 1.04* (1.00–1.08) |

Diabetes duration (years)

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| 1.00 (0.98–1.02) | 1.00 (0.98–1.02) | 0.99 (0.96–1.01) |

Total cholesterol (mg/dL)

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| 1.00 (1.00–1.00) | 1.00 (1.00–1.00) | 1.00 (0.99–1.01) |

Statins

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| 0.88 (0.38–2.04) | 0.82 (0.35–1.91) | 0.71 (0.28–1.84) |

Proteinuria

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| 2.38† (1.44–3.92) |

Note: P < 0.001; †P < 0.01; ¥P < 0.05; §P = 0.060.

Subjects with diabetes are associated with an increased risk of the development of and mortality associated with various cancers, including colorectal cancer (24), hepatocellular carcinoma (25), and others. Hyperinsulinemia, increased bioavailability of insulin-like growth factors-1, and hypoadiponectinemia may be part of the causes of oncogenesis and tumor progression in patients with diabetes (26,27). Surprisingly, we found that serum VAP-1 predicted cancer-related mortality in subjects with type 2 diabetes. Because serum VAP-1 was higher in subjects with diabetes (13), VAP-1/SSAO may serve as a link between diabetes and cancer. Studies in a knock-out mice model indicated that VAP-1 may play a role in angiogenesis, recruitment of myeloid cells, and the growth of melanoma and lymphoma.

TABLE 4
HRs (95% CI) of 10-year disease-specific mortality in people with type 2 diabetes

|                      | Cardiovascular | Diabetes | Cardiovascular + diabetes | Cancer |
|----------------------|----------------|----------|---------------------------|--------|
| Ln VAP-1 (ng/mL)     | 5.83‡ (1.17–28.97) | 9.71† (2.02–46.67) | 6.32‡ (1.25–32.00) | 17.24* (4.57–65.07) |
| History of cardiovascular disease | 1.43 (0.49–4.21) | 1.64 (0.61–4.40) | 1.97 (0.80–4.86) |
| Age (years)          | 1.09* (1.04–1.14) | 1.11* (1.06–1.16) | 1.11* (1.06–1.16) | 1.04* (1.00–1.08) |
| Female sex           | 1.34 (0.59–3.05) | 0.81 (0.37–1.80) | 0.90 (0.41–1.97) | 0.81 (0.41–1.61) |
| Smoking              | 1.14 (0.32–4.02) | 3.92† (1.62–9.50) | 4.05† (1.74–9.45) | 2.41† (1.05–5.55) |
| BMI (kg/m²)          |                |            |                           |        |
| <24                  | 1.00           | 1.00      | 1.00                       |        |
| 24–27                | 1.00 (0.41–2.42) | 0.72 (0.31–1.69) | 0.88 (0.39–1.95) |
| ≥27                  | 2.48† (1.00–6.13) | 1.71 (0.67–4.31) | 1.23 (0.56–2.71) |
| P for trend          | 0.088          | 0.5       | 0.7                        |        |
| Hypertension         | 0.78 (0.38–1.60) |
| HbA1c (%)            | 1.31‡ (1.06–1.64) |
| Diabetes duration (years) | 0.99 (0.95–1.03) |
| Total cholesterol (mg/dL) | 1.00 (0.99–1.01) |
| Statins              | 0.93 (0.20–4.32) |
| Estimated GFR (mL/min per 1.73 m²) | 1.00 (0.98–1.02) | 0.98‡ (0.97–0.997) |

Cause of death: cardiovascular (27 [16.9% of total death]), diabetes (30 [18.8%]), cardiovascular + diabetes (57 [35.6%]), and cancer (59 [36.9%]). ¥P < 0.001; †P < 0.01; ¥P < 0.05.
TABLE 5
The concordance statistics and AUC without indicated variables in models predicting 10-year all-cause mortality for people with type 2 diabetes

| Variable deleted from models | Model 1 |          | Model 2 |          | Model 3 |          |
|-----------------------------|---------|----------|---------|----------|---------|----------|
|                             | Concordance statistics | AUC (0.60–0.70) | Concordance statistics | AUC (0.73–0.82) | Concordance statistics | AUC (0.79–0.88) |
| Full model                  | 0.64    | 0.65     | 0.73    | 0.78     | 0.78    | 0.84     |
| Ln serum VAP-1 (ng/mL)      | 0.53 (0.11) | 0.53 (0.12) | 0.71 (0.02) | 0.75 (0.03) | 0.75 (0.03) | 0.82 (0.02) |
| History of cardiovascular disease | 0.63 (0.01) | 0.64 (0.01) | 0.73 (0)   | 0.78 (0)   | 0.78 (0)   | 0.84 (0)   |
| Age (years)                 | 0.68 (0.05) | 0.72 (0.06) | 0.76 (0.02) | 0.82 (0.02) | 0.78 (0)   | 0.84 (0)   |
| Female sex                  | 0.73 (0)   | 0.78 (0)   | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| Smoking                     | 0.72 (0.01) | 0.76 (0.02) | 0.78 (0)   | 0.84 (0.01) | 0.78 (0)   | 0.84 (0)   |
| BMI category (kg/m²)        | 0.73 (0)   | 0.77 (0.01) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| Hypertension                | 0.73 (0)   | 0.77 (0.01) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| HbA1c (%)                   | 0.73 (0)   | 0.77 (0.01) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| Diabetes duration (years)   | 0.73 (0)   | 0.77 (0.01) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| Total cholesterol (mg/dL)   | 0.73 (0)   | 0.77 (0.01) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| Statins                     | 0.73 (0)   | 0.77 (0.01) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| ABI <0.9 or >1.3            | 0.73 (0)   | 0.77 (0.01) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| Estimated GFR (mL/min per 1.73 m²) | 0.77 (0.01) | 0.81 (0.03) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |
| Proteinuria                 | 0.76 (0.02) | 0.82 (0.02) | 0.78 (0)   | 0.84 (0)   | 0.78 (0)   | 0.84 (0)   |

Model 1, Ln serum VAP-1 and history of cardiovascular disease; model 2, Ln serum VAP-1, history of cardiovascular disease, age, sex, smoking, BMI category, hypertension, HbA1c, diabetes duration, total cholesterol, statins, and ABI; model 3, model 2 plus estimated GFR, and proteinuria. Differences of concordance statistics or area under the ROC between reduced and full models are shown in parentheses.

(28). Colorectal cancer patients have been shown to have higher serum VAP-1 than healthy subjects (29). Serum SSAO activity has been correlated with the angiogenic vascular endothelial growth factor in subjects with lung cancer (30). Serum SSAO activity has also been shown to be higher in prostate cancer subjects with bone metastases than subjects without metastases (31). Taken together, these data strongly support our observations and suggest a role for VAP-1/SSAO in cancer growth and metastasis. However, VAP-1 may participate in tumor surveillance. VAP-1 has been shown to mediate the adhesion of tumor-infiltrating lymphocytes to head and neck squamous cell carcinoma and hepatocellular carcinoma and to kill cancer cells (32,33). Subjects with advanced colorectal cancer have been shown to have low serum VAP-1 (29). In human melanoma, a higher expression of VAP-1 in intratumoral microvessels was associated with better five-year survival, although there was only borderline statistical significance and the results were not adjusted for other confounders, such as the presence of metastasis or not (34). To sum up, although VAP-1/SSAO may have opposing roles in cancer development and progression, our results favored the hypothesis that there was a positive effect of VAP-1 on angiogenesis and metastases in subjects with type 2 diabetes. Whether there is any tumor-specific effect of VAP-1 on tumor surveillance remains to be further investigated.

The strength of this study is in the 100% follow-up rate after 10 years, with accurate records of the vital status of a homogenous population of Han Chinese. In addition, the highly sensitive time-resolved immunofluorometric assay for measuring serum VAP-1 enabled us to differentiate subtle differences in circulating VAP-1 concentrations. However, our study had some limitations. First, serum VAP-1 was measured only once at baseline, which may limit the value of serum VAP-1 over time for the prediction of outcomes. Second, generalization of the findings to other populations may be limited because all the subjects in the current study were Han Chinese. Third, determination of proteinuria by reflectance colorimetry is relatively insensitive and may not accurately detect kidney dysfunction.

In conclusion, we showed for the first time that serum VAP-1 can independently predict 10-year all-cause mortality, cardiovascular mortality, and cancer-related mortality in subjects with type 2 diabetes. Our results showed that serum VAP-1 is a novel biomarker and improves risk prediction over and above the established risk factors for cardiovascular and cancer mortality in subjects with type 2 diabetes. Our data also indicated the potential of using VAP-1/SSAO inhibitors or antibodies, which are currently being tested for their ability to treat autoimmune diseases and to treat or prevent cardiovascular diseases and cancer in high-risk individuals with type 2 diabetes.

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REFERENCES

1. Salmi M, Jalkanen S. A 90-kilodalton endothelial cell molecule mediating lymphocyte binding in humans. Science 1992;257:1407–1409.

2. Merinen M, Irjala H, Salmi M, Jalkanola J, Hamininen A, Jalkanen S. Vascular adhesion protein-1 is involved in both acute and chronic inflammation in the mouse. Am J Pathol 2005;166:793–800.

3. Mazzzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. Lancet 2008;371:1800–1809.

4. Yu PH, Wright S, Fan EH, Lun ZR, Gubines-Harboner D. Physiological and pathological implications of semicarbazide-sensitive amine oxidase. Biochim Biophys Acta 2003;1647:193–199.

5. Stolen CM, Madanat R, Marti L, et al. Semicarbazide sensitive amine oxidase overexpression has dual consequences: insulin mimicry and diabetes-like complications. FASEB J 2004;18:702–704.

6. Salmi M, Stolen C, Jousilaiti P, et al. Insulin-regulated increase of soluble vascular adhesion protein-1 in diabetes. Am J Pathol 2002;161:2255–2262.

7. Stolen CM, Yegutkin GG, Kurkiijarvi R, Bono P, Alitalo K, Jalkanen S. Origins of serum semicarbazide-sensitive amine oxidase. Circ Res 2004;95:50–57.

8. Gökturek C, Nilsson J, Nordquist J, et al. Overexpression of semicarbazide-sensitive amine oxidase in smooth muscle cells leads to an abnormal structure of the aortic elastic laminas. Am J Pathol 2003;163:1921–1928.

9. Kurkiijarvi R, Yegutkin GG, Gunson BK, Jalkanen S, Salmi M, Adamus DH. Circulating soluble vascular adhesion protein 1 accounts for the increased serum monoamine oxidase activity in chronic liver disease. Gastroenterology 2000;119:1096–1103.

10. Abella A, Garcia-Vicente S, Viguere N, et al. Adipocytes release a soluble form of VAP-1/SSAO by a metalloproteinase-dependent process and in a regulated manner. Diabetologia 2004;47:429–438.

11. Garcia-Vicente S, Abella A, Viguere N, et al. The release of soluble VAP-1/SSAO by 3T3-L1 adipocytes is stimulated by isoproterenol and low concentrations of TNFalpha. J Physiol Biochem 2005;61:395–401.

12. Lin MS, Li HY, Wei JN, et al. Serum vascular adhesion protein-1 is higher in subjects with early stages of chronic kidney disease. Clin Biochem 2008;41:1362–1367.

13. Li HY, Wei JN, Li MS, et al. Serum vascular adhesion protein-1 is increased in acute and chronic hyperglycemia. Clin Chim Acta 2009;404:149–153.

14. Li HY, Lin MS, Wei JN, et al. Change of serum vascular adhesion protein-1 after glucose loading correlates to carotid intima-media thickness in non-diabetic subjects. Clin Chim Acta 2009;403:97–101.

15. Jiang YD, Chuang LM, Wu HP, Tai TY, Lin BJ. Role of an outpatient clinic in screening chronic complications of diabetes: a model for diabetes managed care. J Formos Med Assoc 1998;97:521–527.

16. Levey AS, Greene T, Kusek J, Beck GJ, Group MS. A simplified equation to predict glomerular filtration rate from serum creatinine (Abstract). J Am Soc Nephrol 2000;11:828A.

17. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3335–3341.

18. Yang HJ, Lu SN, Liaw YF, et al.; Taiwan Community-Based Cancer Screening Project Group. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–174.

19. Boomstra F, Bhaagoe UM, van der Houwen AM, van den Meiracker AH. Plasma semicarbazide-sensitive amine oxidase in human (patho)physiology. Biochim Biophys Acta 2003;1647:46–54.

20. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. Geneva, World Health Organization, 1993.

21. Jaakola K, Jalkanen S, Kaunismäki K, et al. Vascular adhesion protein-1, intercellular adhesion molecule-1 and P-selectin mediate leukocyte binding to ischemic heart in humans. J Am Coll Cardioil 2000;36:122–129.

22. Jalkanen S, Karikoski M, Mercier N, et al. The oxidase activity of vascular adhesion protein-1 (VAP-1) induces endothelial E- and P-selectins and leukocyte binding. Blood 2007;110:1864–1870.

23. Boomstra F, de Kam PJ, Tjeerdmsa G, van den Meiracker AH, van Veldhuisen DJ. Plasma semicarbazide-sensitive amine oxidase (SSAO) is an independent prognostic marker for mortality in chronic heart failure. Eur Heart J 2000;21:1859–1863.

24. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97:1679–1687.

25. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4:360–380.

26. Barb D, Williams CJ, Neuwirth AK, Mantzoros CS. Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. Am J Clin Nutr 2007;86:858S–866.

27. Pollak MN. Insulin, insulin-like growth factors, insulin resistance, and neoplasia. Am J Clin Nutr 2007;86:820S–821S.

28. Marttila-Ichihara F, Auvinen K, Elima K, Jalkanen S, Salmi M. Vascular adhesindependent protein-1 enhances tumor growth by supporting recruitment of Gr1-CD11b+ myeloid cells into tumors. Cancer Res 2009;69:7875–7883.

29. Toyama Y, Miki C, Inoue Y, Kawamoto A, Kusunoki M. Circulating form of vascular adhesion protein-1 mediates binding of immunotherapeutic effector cells to tumor endothelium. J Immunol 2001;166:6937–6943.

30. Ekblom J, Grönvall J, Lennernäs B, Nilsson S, Garpenstrand H, Oreland L. Circulating form of human vascular adhesion protein-1 (VAP-1): decreased serum levels in patients with skeletal metastases of prostate cancer. Med Oncol 2004;21:241–250.

31. Ekblom J, Grönvall J, Lennernäs B, Nilsson S, Garpenstrand H, Oreland L. Elevated activity of semicarbazide-sensitive amine oxidase in blood from patients with skeletal metastases of prostate cancer. Clin Sci (Lond) 1999;97:111–115.

32. Arlt J, Salmi M, Alalen K, Grénman R, Jalkanen S. Vascular adhesion protein-1 mediates binding of immunotherapeutic effector cells to tumor endothelium. J Immunol 2001;166:6937–6943.

33. Yoong KF, McNab G, Hubscher SG, Adams DH. Vascular adhesion protein-1 enhances tumor growth by supporting recruitment of Gr1-CD11b+ myeloid cells into tumors. Cancer Res 2009;69:7875–7883.

34. Forster-Horváth C, Döme B, Paku S, et al. Vascular adhesion protein-1 mediates binding of immunotherapeutic effector cells to tumor endothelium in human hepatocellular carcinoma. J Immunol 1998;160:3978–3988.

35. Forster-Horváth C, Döme B, Paku S, et al. Loss of vascular adhesion protein-1 expression in intratumoral microvessels of human skin melanoma. Melanoma Res 2004;14:135–140.