Visceral Adiposity Index as an Independent Marker of Subclinical Atherosclerosis in Individuals Prone to Diabetes Mellitus

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Aim: The visceral adiposity index (VAI) has been proposed as an estimate of visceral adipose tissue (VAT) mass and as an indicator of VAT dysfunction. Both parameters are associated with cardiometabolic risk, including insulin resistance. In this study, we investigated whether VAI is associated with subclinical atherosclerosis in subjects who were free of cardiovascular disease but were at risk of developing diabetes mellitus.

Methods: A total of 731 adults with a median age of 47 years old without diabetes mellitus were included in this cross-sectional study. The anthropometric data, blood pressure, and lipid profiles of 398 women and 333 men were measured. All subjects underwent an oral glucose tolerance test, and carotid intima-media thickness (cIMT) was evaluated by ultrasound. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR).

Results: VAI and HOMA-IR ($\beta_{st} = 0.44$, $p < 0.0001$), VAI and cIMT ($\beta_{st} = 0.17$, $p < 0.0001$), and HOMA-IR and cIMT ($\beta_{st} = 0.09$, $p = 0.0127$) were correlated with each other. After adjusting for cofounding variables, VAI is still correlated with HOMA-IR ($\beta_{st} = 0.42$, $p < 0.0001$). Furthermore, VAI ($\beta_{st} = 0.07$, $p = 0.0392$) but not HOMA-IR ($\beta_{st} = 0.03$, $p = 0.37$) was correlated with cIMT independently of other established cardiovascular risk factors.

Conclusion: The calculation of VAI may provide a better estimation of subclinical atherosclerosis than the calculation of HOMA-IR.

Key words: Carotid intima-media thickness, Visceral adiposity index, Insulin resistance, Diabetes mellitus, Metabolic syndrome

Abbreviations: Body mass index (BMI), cardiovascular disease (CVD), carotid intima-media thickness (cIMT), high density lipoprotein-cholesterol (HDL-cholesterol), high-sensitive C-reactive protein (hsCRP), insulin resistance (HOMA-IR), low density lipoprotein-cholesterol (LDL-cholesterol), visceral adipose tissue (VAT), visceral adiposity index (VAI), waist circumference (WC)
Methods

Participants and Study Design
In this cross-sectional analysis, data from the Tübingen intima–media thickness cohort for type 2 diabetes were analyzed. The methodology of the study has been described previously. Subjects had to be at least 18 years old, and individuals with a history of CVD, such as coronary heart disease or peripheral arterial disease, who have acute disease, or who are pregnant were not included in the study. Participation was allowed when at least one of the following criteria was fulfilled: a family history of type 2 diabetes mellitus, a BMI > 27 kg/m², previous diagnosis of impaired glucose tolerance, or current diagnosis of gestational diabetes. The participants underwent a 75 g oral glucose tolerance test to measure glucose and insulin. A high-resolution ultrasound of the carotid artery was performed to determine the cIMT. Referring to the calculation of VAI, subjects with serum triglycerides > 3.15 mmol/l and BMI ≥ 40 kg/m² were not included in the analyses. After the nature of the study was explained, all study subjects gave their written informed consent. The Ethics Committee of the University of Tübingen approved all protocols.

Anthropometric and Biochemical Data
Blood pressure was measured according to the Riva-Rocci method in sitting position on the upper arm. BMI was calculated using height and weight and is shown in kg/m². WC was performed undressed and was determined as described previously.

All blood samples were taken from the cubital vein, and each individual underwent a standardized 75 g oral glucose tolerance test after a 10-hour fasting period. We obtained plasma samples at 0, 30, 60, 90, and 120 minutes to determine plasma glucose and insulin levels. By using these samples, HOMA-IR was calculated according to the Homeostasis Model Assessment Test of insulin resistance. Glycated hemoglobin was measured by HPLC (Tosoh 2.2 HLC-723, Tokyo, Japan), and total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), and serum triglycerides were measured by the ADVIA 1650 Chemistry System (BAYER Health Care). Low-density lipoprotein cholesterol (LDL-cholesterol) and serum triglycerides were measured by the ADVIA 1650 Chemistry System. High-sensitivity C-reactive protein (hsCRP) was also measured by the ADVIA 1650 Chemistry System.

Determination of VAI
As proposed by Amato et al. when using anthropometric and biochemical data, VAI was calculated by separating the participants by gender:

death worldwide. The deposition of adipose tissue determines cardiometabolic risk and CVD-related death rather than the extent of obesity, which is mainly determined by body mass index (BMI). Different body fat compartments exist and may contribute to obesity-mediated metabolic disorders and CVD. Among these fat compartments, increased visceral adipose tissue (VAT) mass is strongly associated with insulin resistance, which itself is an important determinant of the inflammatory and atherothrombotic pathways. Increased liver fat content and increased VAT mass are among the strongest phenotypic determinants of subclinical atherosclerosis in subjects with prediabetes. The aforementioned types of adipose tissue have different biologies and functions. In particular, the accumulation of VAT appears to be more likely to contribute to CVD. Currently, VAT measurements are mostly performed by computed tomography or magnetic resonance tomography. However, these imaging techniques are unsuitable in the routine examination of the general population because of their temporal expenditure, lack of availability, and radiation hazard. By contrast, the waist circumference (WC) can be easily determined and is a widely used estimate of abdominal obesity. WC can be used to estimate not only VAT mass but also subcutaneous abdominal fat mass. Amato et al. developed the visceral adiposity index (VAI), which is considered a useful indicator of both VAT mass and VAT function. VAI is associated with cardiometabolic risk parameters, including insulin resistance, and is a simple mathematical model that includes anthropometric parameters (BMI and WC) and biochemical data (triglycerides and high-density lipoprotein cholesterol [HDL-cholesterol]).

The identification of individuals who are at increased cardiometabolic risk, particularly individuals prone to diabetes mellitus, is important in implementing preventive strategies early in the natural history of the cardiometabolic disease. VAI could serve as an interesting candidate for this purpose. Early alterations in vascular morphology can be assessed by the high-resolution B-mode ultrasound of the carotid intima–media thickness (cIMT), which is an accepted indicator of subclinical atherosclerosis. In the current study, we investigated the relative contributions of VAI and insulin resistance, which was estimated by the calculation of the homeostatic model assessment of insulin resistance (HOMA-IR), as determinants of subclinical atherosclerosis in middle-aged subjects who are free of CVD and diabetes.
By using high-resolution ultrasound with a linear ultrasound transducer (10–13 MHz; AU5 Harmonic, ESAOTE BIOMEDICA, Hallbergmoos, Germany), the intima–media thickness of the common carotid artery was measured. A trained physician performed ultrasound of the left and right common carotid arteries in B-mode according to the European Mannheim cIMT consensus\textsuperscript{32}. cIMT was assessed on the far wall of the artery approximately 10 mm proximal to the carotid bulb in supine position with the head slightly extended and turned 45° to the contralateral side of the scanning. Three measurements were performed on each side for reproducibility, and a mean of each side was calculated\textsuperscript{33, 34}. Finally, from the left and right means, one mean cIMT was determined by considering the known side differences\textsuperscript{35}.

**Statistical Analysis**

If not otherwise stated, normally distributed data are presented as means and standard deviations. Prior to linear regression analyses, we logarithmically transformed data that were not normally distributed (Shapiro–Wilk \(W\)-test) to approximate a normal distribution. The two-tailed two-sample \(t\)-test was performed to compare the groups. We performed multivariate linear regression analyses to adjust for covariates and to identify independent associations. Effect sizes were given as standardized beta coefficients (\(\beta_s\)). Furthermore, mul-
Table 1. Anthropometric data, metabolic characteristics including visceral adiposity index and carotid intima-media thickness of 731 study subjects

|                          | Total          | Women (n=398; 54.4%) | Men (n=333; 45.6%) | p value* |
|--------------------------|----------------|----------------------|-------------------|----------|
| Age (years)              | 46.0±12.9      | 45.6±12.5            | 46.6±13.2         | 0.42     |
| Body mass index (kg/m²)  | 27.0±4.3       | 26.8±4.8             | 27.2±3.7          | 0.06     |
| Waist circumference (cm) | 92.0±12.8      | 87.5±12.3            | 97.3±11.2         | <0.0001  |
| Systolic blood pressure (mmHg) | 133.4±21.5   | 129.5±22.3           | 138±19.6          | <0.0001  |
| Diastolic blood pressure (mmHg) | 77.2±11.6    | 75.6±11.8            | 79.1±11           | <0.0001  |
| Fasting blood glucose (mmol/l) | 5.0±0.5      | 5.0±0.5              | 5.0±0.5           | 0.21     |
| 2 hour post load glucose (mmol/l) | 5.6±1.7      | 5.8±1.7              | 5.4±1.6           | 0.0004   |
| Fasting insulin (pmol/l)  | 52.8±30.7      | 53.7±3              | 51.8±31.5         | 0.11     |
| 2 hour post load insulin (pmol/l) | 314.1±297.1 | 340±296.3            | 283.1±295.4       | <0.0001  |
| Homeostatic model assessment of insulin resistance | 2.0±1.3 | 2.0±1.2 | 2.0±1.3 | 0.21 |
| Glycated haemoglobin (%)  | 5.5±0.4        | 5.5±0.4              | 5.5±0.4           | 0.51     |
| Total cholesterol (mmol/l) | 5.3±1.0       | 5.3±0.9              | 5.3±1.0           | 0.97     |
| Triglycerides (mmol/l)    | 1.3±0.6        | 1.2±0.5              | 1.4±0.6           | <0.0001  |
| Low density lipoprotein-cholesterol (mmol/l) | 3.2±0.9 | 3.1±0.8 | 3.3±0.9 | 0.0016 |
| High density lipoprotein-cholesterol (mmol/l) | 1.5±0.4 | 1.7±0.4 | 1.4±0.3 | <0.0001 |
| High-sensitive C-reactive protein (mg/dl) | 0.2±0.2 | 0.2±0.2 | 0.2±0.2 | 0.0020 |
| Visceral adiposity index  | 1.5±0.9        | 1.5±0.9              | 1.5±0.8           | 0.94     |
| Carotid intima-media thickness (mm) | 0.56±0.12 | 0.54±0.12 | 0.58±0.13 | <0.0001 |

Data shown as mean ± standard deviation
*p = p-level for difference between women and men (two-sample t test)

Multivariate linear regression analysis was performed stepwise after a fivefold cross validation, and the results were given as k-fold $R^2$. All numerical variables were used as a continuous variable, and all t-tests were performed as two-tailed Student’s t-test. A p-value $< 0.05$ was considered statistically significant. JMP® 13.0 statistical software (SAS Institute, Cary, NC) was used for the analyses.

Results

Characteristics of the Participants

Data were collected from 2003 to 2006, including laboratory values and cIMT measurements, and a total of 844 individuals were examined. A total of 20 subjects were excluded from the study owing to incomplete data records. In 23 cases, prior unknown diabetes (glycated hemoglobin ≥6.5%, fasting blood glucose ≥7.0 mmol/l, or 2-hour postload glucose ≥11.1 mmol/l) was diagnosed and led to exclusion. A total of 70 participants were excluded owing to triglycerides ≥3.15 mmol/l or BMI ≥40 kg/m². Therefore, data from 731 study subjects were available for further analysis. Fig. 1 summarizes the individuals who were recruited and excluded. Table 1 shows the anthropometric data of these subjects, including cIMT and biochemical values, by gender.

The study population consisted of 398 women (54.4%) and 333 men (45.6%) and had a mean age of 46.0±12.9 years old (range: 18–69 years old). The mean BMI was 27.0±12.9 kg/m² (range: 15.8–39.3 kg/m²); this result showed that no difference existed between women and men (p=0.06). A total of 257 (77.7%) subjects had normal weight or were overweight (n=257 with a BMI 20.0–24.9 kg/m²; n=311 with a BMI 25.0–29.9 kg/m²). Obesity (BMI ≥30 kg/m²) was present in 163 (22.3%) participants. According to the criteria of the International Diabetes Federation, increased WC (>80 cm in women and >94 cm in men) was present in 289 (72.6%) women and 206 (61.9%) men. Men had significantly higher WC than women (97.3±11.2 vs. 87.5±12.3; p<0.0001). On the contrary, VAI did not differ between women and men (p=0.94) and amounted to a mean of 1.5±0.9 (range: 0.27–5.44). The mean cIMT was 0.56±0.12 mm (range: 0.28–1.05 mm), and men had significantly greater cIMT than women (p<0.0001). A total of 120 study subjects (14.9%) were smokers (55 [12.9%] women, 66 [17.4%] men).

The mean HOMA-IR was 2±1.3 (range: 0.2–9.9) with no gender difference (p=0.21), and 177 (24.2%) subjects had HOMA-IR >2.5. Laboratory values revealed a mean glycated hemoglobin of 5.5±0.4 (range 4.1%–6.4%), with 233 (31.9%) of the study...
the aforementioned variables were investigated in univariate and multivariate regression analyses. Age was the most strongly correlated variable with cIMT (Table 1). Furthermore, a positive correlation was found for cIMT with BMI, WC, blood pressure, blood glucose, glycated hemoglobin, triglycerides, hsCRP, VAI, and cholesterol (except HDL-cholesterol, which showed a negative correlation). No correlation could be detected between cIMT and fasting insulin or 2-hour postload insulin, but a positive correlation between cIMT and HOMA-IR was found. In multivariate regression analyses, only age, systolic blood pressure, and VAI were found to be independent determinants of cIMT (Table 4). We then performed another multivariate regression analysis with variables related to cIMT and included glycated hemoglobin instead of HOMA-IR in the statistical model. Only age, systolic blood pressure, and VAI were independent determinants of cIMT (Table 5). Both VAI and HOMA-IR were correlated with cIMT, and we demonstrated the collinearity between VAI and HOMA-IR in the previous section. To achieve a more precise analysis of covariates that influence cIMT, we performed a stepwise analysis with HOMA-IR, VAI, and glycated hemoglobin. After a fivefold cross validation, a correlation with cIMT could only be found for age (rank 1), systolic blood pressure (rank 2), and VAI (rank 3) (Table 6).

| Variable                                         | Homeostatic model assessment of insulin resistance | Carotid intima-media thickness |
|--------------------------------------------------|---------------------------------------------------|--------------------------------|
|                                                  | \( \beta \_st \) | \( p \text{ value} \) | \( \beta \_st \) | \( p \text{ value} \) |
| Age                                              | 0.03 | 0.49 | 0.67 | <0.0001 |
| Body mass index                                  | 0.51 | <0.0001 | 0.24 | <0.0001 |
| Waist circumference                              | 0.48 | <0.0001 | 0.34 | <0.0001 |
| Systolic blood pressure                          | 0.17 | <0.0001 | 0.28 | <0.0001 |
| Diastolic blood pressure                         | 0.20 | <0.0001 | 0.21 | <0.0001 |
| Fasting blood glucose                            | 0.46 | <0.0001 | 0.24 | <0.0001 |
| 2 hour post load glucose                         | 0.35 | <0.0001 | 0.15 | <0.0001 |
| Fasting insulin                                  | 0.98 | <0.0001 | 0.05 | 0.16 |
| 2 hour post load insulin                         | 0.64 | <0.0001 | 0.06 | 0.09 |
| Homeostatic model assessment of insulin resistance| –    | –     | 0.09 | 0.0127 |
| Glycated haemoglobin                             | 0.24 | <0.0001 | 0.31 | <0.0001 |
| Total cholesterol                                 | 0.02 | 0.63 | 0.22 | <0.0001 |
| Triglycerides                                    | 0.33 | <0.0001 | 0.17 | <0.0001 |
| Low density lipoprotein-cholesterol              | 0.07 | 0.05 | 0.24 | <0.0001 |
| High density lipoprotein-cholesterol             | –0.31 | <0.0001 | –0.1 | 0.0061 |
| High-sensitive C-reactive protein                 | 0.22 | <0.0001 | 0.1 | 0.0053 |
| Visceral adiposity index                         | 0.44 | <0.0001 | 0.17 | <0.0001 |
| Carotid intima-media thickness                   | 0.09 | 0.0127 | – | – |

Subjects having a glycated hemoglobin between 5.7%–6.4%. According to the criteria of the American Diabetes Association, 104 (14.2%) had impaired fasting glucose (5.6–6.9 mmol/l) and 82 (11.2%) had impaired glucose tolerance (7.8–11 mmol/l in a 2-hour post-load glucose). In summary, 297 (40.6%) participants had prediabetes and either had impaired fasting glucose, impaired glucose tolerance, or elevated glycated hemoglobin.

**Relationships of Anthropometric and Biochemical Parameters with HOMA-IR and cIMT**

HOMA-IR was correlated positively with BMI, and BMI showed the strongest correlation with HOMA-IR compared with WC, blood pressure, glycated hemoglobin, triglycerides, hsCRP, VAI, and cIMT, which were also associated positively with HOMA-IR (Table 2). After adjusting for other covariates including age, systolic and diastolic blood pressures, smoking, and hsCRP in a multivariate regression analysis (Table 3), VAI was found to be an independent determinant of HOMA-IR. hsCRP and smoking status were the only other independent (albeit weaker) determinants of HOMA-IR. LDL-cholesterol was included as a covariate in multivariate analysis despite a marginal lack of significance in univariate analysis.

Thereafter, the correlations between cIMT and
We performed analyses to test independence from gender and test the models in male/female subgroups. The addition of gender to each multiple linear regression model did not change the results (given in effect size $\beta_{st}$ and $p$-value of the variable VAI; the tables are not shown in the manuscript): independent of gender and other confounding variables the VAI was still correlated with 1) the HOMA-IR model ($\beta_{st}=0.42; p<0.0001$), 2) the HOMAR-IR influencing the cIMT model ($\beta_{st}=0.06; p=0.0466$), 3) the glycated hemoglobin influencing the cIMT model ($\beta_{st}=0.07; p=0.0112$).

We also performed further univariate and multivariate gender-specific analyses, as shown in the supplementary tables. In univariate analyses, VAI was correlated in both women and men, with HOMA-IR ($\beta_{st}=0.40; p<0.0001$ and $\beta_{st}=0.49; p<0.0001$) and cIMT ($\beta_{st}=0.20; p<0.0001$ and $\beta_{st}=0.14, p=0.0083$) (Table 2.1 in the Supplementary Tables). In multiple linear regression analysis fitted on HOMA-IR, VAI was an independent determinant of HOMA-IR in women and men (Table 3.1 in the Supplementary Tables).

In the multiple linear regression analysis of variables, including HOMA-IR fitted on cIMT and stratified by gender, VAI was no longer associated with cIMT in women ($p=0.35$) (Table 4.1 in the Supplementary Tables). In men, there was a trend for an association with cIMT, which barely missed statistical significance ($p=0.08$). Regarding gender-specific issues, we performed an additional analysis and found no interaction of VAI and gender on cIMT in multivariate linear regression analysis (Table 7 in the Supplementary Tables). In the multiple linear regression analyses of variables, including glycated hemoglobin fitted on cIMT and stratified by gender, VAI was not associated with cIMT in women ($p=0.17$), but an association was found in men ($\beta_{st}=0.08; p=0.0481$) (Table 5.1 in the Supplementary Tables). We again performed an additional analysis and found no interaction of VAI and gender on cIMT in multivariate linear regression analysis (Table 8 in the Supplementary Tables).

**Discussion**

In this cross-sectional study, which included non-diabetic individuals who were free of overt CVD but were at risk for developing diabetes mellitus, we found that HOMA-IR increased with VAT dysfunction, which

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**Table 3.** Multiple linear regression analysis of variables including visceral adiposity index influencing homeostatic model assessment of insulin resistance*

| Variable                               | Effect size ($\beta_{st}$) | Standard error | $p$ value |
|----------------------------------------|-----------------------------|---------------|-----------|
| Age                                    | $-0.07$                     | $0.06$        | $0.07$    |
| Systolic blood pressure                | $0.07$                      | $0.17$        | $0.16$    |
| Diastolic blood pressure               | $0.07$                      | $0.18$        | $0.13$    |
| Low density lipoprotein-cholesterol   | $-0.05$                     | $0.07$        | $0.18$    |
| High-sensitive C-reactive protein      | $0.12$                      | $0.02$        | $0.0006$  |
| Visceral adiposity index               | $0.42$                      | $0.03$        | $<0.0001$ |
| Smoking                                | $-0.08$                     | $0.03$        | $0.0176$  |

* = not adjusted for gender, BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)

**Table 4.** Multiple linear regression analysis of variables including homeostatic model assessment of insulin resistance influencing carotid intima-media thickness*

| Variable                               | Effect size ($\beta_{st}$) | Standard error | $p$ value |
|----------------------------------------|-----------------------------|---------------|-----------|
| Age                                    | $0.64$                      | $0.02$        | $<0.0001$ |
| Systolic blood pressure                | $0.13$                      | $0.05$        | $0.0010$  |
| Diastolic blood pressure               | $-0.06$                     | $0.06$        | $0.13$    |
| Low density lipoprotein-cholesterol   | $0.01$                      | $0.02$        | $0.72$    |
| High-sensitive C-reactive protein      | $0.04$                      | $0.01$        | $0.17$    |
| Visceral adiposity index               | $0.06$                      | $0.01$        | $0.0465$  |
| Homeostatic model assessment of insulin resistance | $0.03$                      | $0.01$        | $0.34$    |
| Smoking                                | $0.02$                      | $0.01$        | $0.47$    |

* = not adjusted for gender, BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)
Nevertheless, there are several risk calculators and surrogate indices such as BMI or WC, which are commonly used for the classification of adipose tissue content and dysfunction. Nevertheless, the aforementioned indices have limitations, and the accuracy of these indices remains controversial in routine clinical practice. BMI is an attempt to quantify the amount of total tissue mass. WC, which is an excellent marker of central localized obesity and is effective for predicting metabolic disease, is sensitive to height and weight. Furthermore, WC is not helpful in distinguishing between subcutaneous and visceral fat mass. Both BMI and WC are based on anthropometric measurements and present the amount of adipose tissue but do not reflect adipose tissue–derived metabolic disorders. In the present study, only age was associated with cIMT in a multivariate analysis that included both anthropometric and metabolic parameters. Consequently, more reliable indicators are necessary, and VAI takes into account the physical and metabolic parameters of particularly central localized obesity. In detail, the advantage of

was presented by increased VAI. Even after adjusting for other cardiovascular risk factors in multivariate analyses, VAI was independently related to HOMA-IR. However, by referring to subclinical atherosclerosis, our present study provides novel evidence that VAT dysfunction, which was estimated by VAI, is associated with cIMT. In line with the observation that VAI is associated with both the HOMA-IR and cIMT, these results emphasize the different effects of VAT accumulation and dysfunction in the development of cardiometabolic disorders.

To our knowledge, this study is the first study to investigate the relationship of VAI and HOMA-IR as independent determinants of subclinical atherosclerosis. Our results are consistent with other studies that demonstrated an association between VAT mass and HOMA-IR. Recently, an association between VAI and HOMA-IR was found even in subjects without central obesity; central obesity was determined by low WC. These data suggest that VAI could be a useful indicator of both VAT mass and dysfunction. Nevertheless, there are several risk calculators and surrogate indices such as BMI or WC, which are commonly used for the classification of adipose tissue content and dysfunction. Nevertheless, the aforementioned indices have limitations, and the accuracy of these indices remains controversial in routine clinical practice. BMI is an attempt to quantify the amount of total tissue mass. WC, which is an excellent marker of central localized obesity and is effective for predicting metabolic disease, is sensitive to height and weight. Furthermore, WC is not helpful in distinguishing between subcutaneous and visceral fat mass. Both BMI and WC are based on anthropometric measurements and present the amount of adipose tissue but do not reflect adipose tissue–derived metabolic disorders. In the present study, only age was associated with cIMT in a multivariate analysis that included both anthropometric and metabolic parameters. Consequently, more reliable indicators are necessary, and VAI takes into account the physical and metabolic parameters of particularly central localized obesity. In detail, the advantage of

| Table 5. Multiple linear regression analysis of variables including glycated haemoglobin influencing carotid intima-media thickness* |
|---------------------------------|-----------------|-----------------|-----------------|
| Variable                        | Effect size ($\beta_{\text{b}}$) | Standard error  | $p$ value       |
| Age                             | 0.62            | 0.02            | $<0.0001$       |
| Systolic blood pressure         | 0.13            | 0.05            | 0.0007          |
| Diastolic blood pressure        | -0.06           | 0.06            | 0.15            |
| Low density lipoprotein-cholesterol | 0.01           | 0.02            | 0.85            |
| High-sensitive C-reactive protein | 0.04           | 0.01            | 0.14            |
| Visceral adiposity index        | 0.07            | 0.01            | 0.0148          |
| Glycated haemoglobin            | 0.03            | 0.09            | 0.32            |
| Smoking                         | 0.02            | 0.01            | 0.53            |

* = not adjusted for gender, BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)

| Table 6. Variables influencing carotid intima-media thickness (stepwise analyses after fivefold cross validation)* |
|---------------------------------|-----------------|-----------------|-----------------|
| Rank   | Variable                        | k-fold $r^2$ | $p$ value       |
| 1      | Age                             | 0.44          | $<0.0001$       |
| 2      | Systolic blood pressure         | 0.45          | 0.0001          |
| 3      | Visceral adiposity index        | 0.45          | 0.0035          |
| 4      | High-sensitive C-reactive protein | 0.46        | 0.14            |
| 5      | Diastolic blood pressure        | 0.46          | 0.12            |
| 6      | Glycated haemoglobin            | 0.46          | 0.31            |
| 7      | Insulin resistance              | 0.46          | 0.50            |
| 8      | Smoking                         | 0.45          | 0.49            |
| 9      | Low density lipoprotein-cholesterol | 0.45      | 0.80            |

* = not adjusted for gender, BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)
gender-adjusted VAI may be explained by its close correlation with visceral adiposity. Given that VAT is known to be metabolically active regardless of the amount of adipose tissue, the combination of both anthropometric and metabolic parameters may be more advantageous in evaluating an individual’s cardiometabolic risk. Therefore, VAI, which is easy to calculate, is a surrogate marker of visceral adipose dysfunction and may reflect directly the proatherogenic processes leading to arteriosclerosis.

In respect to the associations between established cardiometabolic risk parameters and cIMT, increased age was repeatedly confirmed as an independent risk factor for early atherosclerosis and was most strongly associated with cIMT in our study\(^ {39, 40} \). Furthermore, systolic blood pressure was an independent risk factor for cIMT, which is in accordance with previously published data\(^ {40} \). VAI and HOMA-IR were associated with cIMT in our study, thus indicating that both variables may play a role in the development of atherosclerosis. Compared with HOMA-IR, VAI was strongly associated with cIMT. Even after adjusting for age and other cardiovascular risk factors, a higher VAI was independently associated with a higher cIMT. There was also an association between fasting glucose, 2-hour postload glucose, and glycated hemoglobin with cIMT; this result is in line with previous data showing a link between hyperglycemia and increased risk of atherosclerosis\(^ {42-44} \). In our subjects without diabetes, glycated hemoglobin showed a more pronounced relationship with cIMT than both fasting and 2-hour postload glucose levels. These results indicate that long-term hyperglycemia rather than acutely elevated glucose levels may contribute to the development of subclinical atherosclerosis. However, the association between glycated hemoglobin and cIMT was no longer present after adjusting for age, VAI, and other cardiovascular risk factors. In this statistical model, VAI was still associated with cIMT. This finding implied that VAT accumulation and dysfunction seems to have a stronger atherogenic potential than hyperglycemia.

VAT as an endocrine organ plays a key role in the development of both HOMA-IR and atherosclerosis by inflammatory atherothrombotic pathway\(^ {39, 45} \). VAT accumulation seems to have a more important role in the development of early atherosclerosis beyond total adipose body tissue owing to its secretion of more proinflammatory adipokines and nonesterified fatty acids, which are atherogenic\(^ {3, 46, 47} \). We found that the decrease of VAT mass is related to improved vascular function and an improvement of endothelial dysfunction in the narrow sense\(^ {48} \). Considering that adipose tissue and VAT is a source for proinflammatory cytokine expression and secretion, the association between VAT and cIMT may be due to an inflammatory process at the vascular wall, wherein VAT can be indirectly represented by VAI. HOMA-IR was associated with cIMT but was not an independent risk factor for subclinical atherosclerosis. However, a correlation was found for HOMA-IR with VAI in our participants, thus possibly displaying the interrelationship between altered adipose tissue function and insulin resistance in atherosclerosis due to insulin resistance\(^ {39, 49} \).

Another important finding of our study was the association between hsCRP levels and cIMT. The hsCRP level is supposed to be a good marker of subclinical inflammation of vascular structure\(^ {50} \). In the present study, the hsCRP level was associated with cIMT in the univariate analysis. However, it was not associated with cIMT after adjusting for confounding variables, including VAI. Other studies have confirmed that the hsCRP level can differ substantially in CVD and that there is no causal relationship between hsCRP and manifest macrovascular disease\(^ {51} \). Although there is evidence that chronic inflammation is related to CVD, most ischemic vascular diseases depend on conventional risk factors and other markers of chronic inflammation\(^ {51, 52} \). Therefore, hsCRP might not be a suitable biochemical marker in the early stage of atherosclerosis. Furthermore, other inflammatory markers, such as interleukin-6 or tumor necrosis factor alpha, may play a more important role.

The strength of our study is the availability of a well-characterized population with measurements of subclinical atherosclerosis, insulin, glucose, and parameters allowing the calculation of VAI. The latter appears to be a suitable index in routine clinical practice. Furthermore, the analysis was performed in individuals without diabetes and who were free of overt CVD. The limitation of this study is its cross-sectional design, which does not allow drawing conclusions about causal relationships. The correlation with cIMT was found for both VAI and HOMA-IR. However, in stepwise analysis, a correlation with cIMT could only be found for age, systolic blood pressure, and VAI. This additional analysis indicates that VAI may be a more reliable indicator of subclinical atherosclerosis than the calculation of HOMA-IR. Despite these results, we cannot exclude the influence of HOMA-IR on cIMT, in addition to VAI, owing to the collinearity between VAI and HOMA-IR. We demonstrated the association of VAI with cIMT in our study population. Additional analyses revealed that no significant interaction of gender and VAI existed on cIMT. However, in gender-stratified tests, which were probably affected by lower statistical power, only the male subgroup had significant or nearly significant associations with the outcome. We did not analyze the association between
VAI and manifest cardiovascular events, which would be an interesting issue and is one of the aims of a follow-up study of our individuals. In our study, we focused on a surrogate index that may classify individuals who were free of overt CVD but were at increased cardiometabolic risk and potentially needed an early appropriate treatment tailored to individual risk. To properly apply VAI, we excluded subjects with severe hypertriglyceridemia (>3.15 mmol/l) as mentioned above. Particularly, high values of triglycerides could affect the validity of VAI. Therefore, the use of the index in this study is not recommended. However, our data set does not allow a distinction between primary and secondary dyslipidemia. Therefore, we cannot exclude the possibility that individuals with primary dyslipidemia were present in our study. Furthermore, no data of medication and family history of CVD were recorded, thus potentially modifying the associations with cIMT. One limitation of our study is that the measurement of cIMT was limited to the wall approximately 10 mm proximal to the carotid bulb, and we did not examine more distal segments (i.e., the internal carotid artery) or plaque burden, which is known to be an important marker of advanced atherosclerosis.

In conclusion, we found that VAI was associated with cIMT in individuals who were free of CVD but were prone to diabetes mellitus. Therefore, VAI could be a simple and widely usable tool for estimating visceral fat mass and predicting cardiometabolic risk.

Author Contribution

All authors contributed to (1) the conception and design of the study and the acquisition, analysis, or interpretation of data; (2) the drafting of the article or the critical revision of the article for important intellectual content; and (3) the final approval of the version to be published. The authors have read and agreed to the editorial policies.

Declaration of Conflicting Interests

The authors have no conflicts of interest to declare.

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### Table 2.1. Univariate relationships of carotid intima-media thickness and homeostatic model assessment of insulin resistance with age, blood pressure and metabolic parameters separated by gender

| Variable                              | Homeostatic model assessment of insulin resistance | Carotid intima-media thickness |
|---------------------------------------|--------------------------------------------------|--------------------------------|
|                                      | Women \((n=398)\)                                 | Men \((n=333)\)                |
|                                      | \(\beta_{st}\) \(p\) value \(\beta_{st}\) \(p\) value | \(\beta_{st}\) \(p\) value \(\beta_{st}\) \(p\) value |
| Age                                   | \(0.04\) \(0.40\)                              | \(0.10\) \(0.08\)              | \(0.68\) \(<0.0001\) | \(0.66\) \(<0.0001\) |
| Body mass index                       | \(0.51\) \(<0.0001\)                          | \(0.54\) \(<0.0001\)           | \(0.26\) \(<0.0001\) | \(0.20\) \(<0.0002\) |
| Waist circumference                   | \(0.51\) \(<0.0001\)                          | \(0.57\) \(<0.0001\)           | \(0.34\) \(<0.0001\) | \(0.28\) \(<0.0001\) |
| Systolic blood pressure               | \(0.21\) \(<0.0001\)                          | \(0.16\) \(0.01\)              | \(0.29\) \(<0.0001\) | \(0.22\) \(<0.0001\) |
| Diastolic blood pressure              | \(0.25\) \(<0.0001\)                          | \(0.17\) \(0.06\)              | \(0.17\) \(0.0005\) | \(0.21\) \(<0.0002\) |
| Fasting blood glucose                 | \(0.41\) \(<0.0001\)                          | \(0.52\) \(<0.0001\)           | \(0.24\) \(<0.0001\) | \(0.23\) \(<0.0001\) |
| 2 hour post load glucose              | \(0.29\) \(<0.0001\)                          | \(0.40\) \(<0.0001\)           | \(0.14\) \(0.0039\) | \(0.20\) \(<0.0002\) |
| Fasting insulin                       | \(0.98\) \(<0.0001\)                          | \(0.98\) \(<0.0001\)           | \(0.04\) \(0.46\) | \(<0.02\) \(0.11\) |
| 2 hour post load insulin              | \(0.59\) \(<0.0001\)                          | \(0.70\) \(<0.0001\)           | \(0.05\) \(0.31\) | \(0.14\) \(0.0102\) |
| Homeostatic model assessment of insulin resistance | \(0.08\) \(0.10\) | \(0.12\) \(0.280\) | \(0.08\) \(0.10\) | \(0.12\) \(0.280\) | \(0.08\) \(0.10\) | \(0.12\) \(0.280\) |
| Glycated haemoglobin                  | \(0.28\) \(<0.0001\)                          | \(0.20\) \(0.0029\)            | \(0.34\) \(<0.0001\) | \(0.30\) \(<0.0001\) |
| Total cholesterol                     | \(0.02\) \(0.71\)                             | \(0.02\) \(0.76\)              | \(0.26\) \(<0.0001\) | \(0.18\) \(<0.0009\) |
| Triglycerides                         | \(0.30\) \(<0.0001\)                          | \(0.39\) \(<0.0001\)           | \(0.14\) \(0.0039\) | \(0.16\) \(<0.0030\) |
| Low density lipoprotein-cholesterol   | \(0.11\) \(0.0260\)                           | \(0.04\) \(0.44\)              | \(0.30\) \(<0.0001\) | \(0.14\) \(0.0085\) |
| High density lipoprotein-cholesterol  | \(-0.32\) \(<0.0001\)                         | \(-0.39\) \(<0.0001\)          | \(-0.11\) \(0.0286\) | \(0.03\) \(0.60\) |
| High-sensitive C-reactive protein     | \(0.29\) \(<0.0001\)                          | \(0.13\) \(0.01\)              | \(0.14\) \(0.0052\) | \(0.10\) \(0.07\) |
| Visceral adiposity index              | \(0.40\) \(<0.0001\)                          | \(0.49\) \(<0.0001\)           | \(0.20\) \(<0.0001\) | \(0.14\) \(0.0083\) |
| Carotid intima-media thickness        | \(0.08\) \(0.10\)                             | \(0.12\) \(0.0280\)            | \(-\) \(-\) \(-\) | \(-\) \(-\) \(-\) |

### Table 3.1. Multiple linear regression analysis of variables including visceral adiposity index influencing homeostatic model assessment of insulin resistance separated by gender

| Variable                              | Women \((n=398)\)                              | Men \((n=333)\)                |
|---------------------------------------|------------------------------------------------|--------------------------------|
|                                      | Effect size \(\beta_{st}\) \(p\) value \(\beta_{st}\) \(p\) value | Effect size \(\beta_{st}\) \(p\) value \(\beta_{st}\) \(p\) value |
| Age                                   | \(-0.17\) \(0.09\) \(0.0008\)                | \(0.03\) \(0.10\) \(0.56\)        |
| Systolic blood pressure               | \(0.10\) \(0.20\) \(0.11\)                  | \(0.07\) \(0.30\) \(0.31\)        |
| Diastolic blood pressure              | \(0.10\) \(0.22\) \(0.112\)                 | \(0.07\) \(0.31\) \(0.78\)        |
| Low density lipoprotein-cholesterol   | \(0.01\) \(0.09\) \(0.90\)                  | \(0.02\) \(0.11\) \(0.25\)        |
| High-sensitive C-reactive protein     | \(0.14\) \(0.02\) \(0.0028\)                | \(0.08\) \(0.03\) \(0.10\)        |
| Visceral adiposity index              | \(0.36\) \(0.05\) \(<0.0001\)                | \(0.48\) \(0.05\) \(<0.0001\)   |
| Smoking                               | \(-0.08\) \(0.04\) \(0.06\)                | \(-0.06\) \(0.04\) \(0.24\)      |

* *not adjusted for BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)*
Table 4.1. Multiple linear regression analysis of variables including homeostatic model assessment of insulin resistance influencing carotid intima-media thickness separated by gender

| Variable                                           | Women (n=398) | Men (n=333) |
|----------------------------------------------------|---------------|-------------|
|                                                    | Effect size (β<sub>st</sub>) | Standard error | p value | Effect size (β<sub>st</sub>) | Standard error | p value |
| Age                                                | 0.66          | 0.03        | <0.0001  | 0.65          | 0.03          | <0.0001  |
| Systolic blood pressure                            | 0.08          | 0.07        | 0.11     | 0.11          | 0.09          | 0.06     |
| Diastolic blood pressure                           | -0.05         | 0.07        | 0.30     | -0.08         | 0.10          | 0.18     |
| Low density lipoprotein-cholesterol                | 0.02          | 0.03        | 0.68     | -0.02         | 0.03          | 0.60     |
| High-sensitive C-reactive protein                  | 0.08          | 0.01        | 0.06     | 0.05          | 0.01          | 0.28     |
| Visceral adiposity index                           | 0.04          | 0.02        | 0.35     | 0.08          | 0.02          | 0.08     |
| Homeostatic model assessment of insulin resistance | 0.07          | 0.02        | 0.10     | 0.01          | 0.02          | 0.89     |
| Smoking                                            | 0.02          | 0.01        | 0.68     | 0.01          | 0.01          | 0.82     |

* not adjusted for BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)

Table 5.1. Multiple linear regression analysis of variables including glycated haemoglobin influencing carotid intima-media thickness separated by gender

| Variable                                           | Women (n=398) | Men (n=333) |
|----------------------------------------------------|---------------|-------------|
|                                                    | Effect size (β<sub>st</sub>) | Standard error | p value | Effect size (β<sub>st</sub>) | Standard error | p value |
| Age                                                | 0.63          | 0.03        | <0.001   | 0.64          | 0.03          | <0.0001  |
| Systolic blood pressure                            | 0.09          | 0.07        | 0.07     | 0.11          | 0.09          | 0.06     |
| Diastolic blood pressure                           | -0.05         | 0.07        | 0.36     | -0.08         | 0.09          | 0.18     |
| Low density lipoprotein-cholesterol                | 0.01          | 0.03        | 0.77     | -0.02         | 0.03          | 0.56     |
| High-sensitive C-reactive protein                  | 0.09          | 0.01        | 0.0305   | 0.05          | 0.01          | 0.28     |
| Visceral adiposity index                           | 0.06          | 0.02        | 0.17     | 0.08          | 0.02          | 0.0481   |
| Glycated haemoglobin                               | 0.04          | 0.12        | 0.41     | 0.03          | 0.15          | 0.47     |
| Smoking                                            | 0.01          | 0.01        | 0.77     | 0.01          | 0.01          | 0.86     |

* not adjusted for BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)
Table 7. Multiple linear regression analysis of variables including homeostatic model assessment of insulin resistance and interaction of VAI and gender influencing carotid intima-media thickness

| Variable                                      | Effect size ($\beta_{st}$) | Standard error | $p$ value   |
|-----------------------------------------------|-----------------------------|----------------|-------------|
| Age                                           | 0.64                        | 0.02           | $<0.0001$   |
| Systolic blood pressure                       | 0.10                        | 0.05           | 0.0016      |
| Diastolic blood pressure                      | $-0.07$                     | 0.06           | 0.09        |
| Low density lipoprotein-cholesterol           | $-0.01$                     | 0.02           | 0.96        |
| High-sensitive C-reactive protein             | 0.06                        | 0.01           | 0.0324      |
| Visceral adiposity index                      | 0.06                        | 0.01           | 0.0473      |
| Homeostatic model assessment of insulin resistance | 0.04                      | 0.01           | 0.22        |
| Smoking                                       | 0.01                        | 0.01           | 0.69        |
| Gender                                        | $-0.13$                     | 0.01           | $<0.0001$   |
| Gender-Visceral adiposity index (interaction term) | 0.01                      | 0.01           | 0.94        |

* = not adjusted for BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)

Table 8. Multiple linear regression analysis of variables including glycated haemoglobin and interaction of VAI and gender influencing carotid intima-media thickness

| Variable                                      | Effect size ($\beta_{st}$) | Standard error | $p$ value   |
|-----------------------------------------------|-----------------------------|----------------|-------------|
| Age                                           | 0.63                        | 0.02           | $<0.0001$   |
| Systolic blood pressure                       | 0.11                        | 0.05           | 0.0074      |
| Diastolic blood pressure                      | $-0.06$                     | 0.06           | 0.11        |
| Low density lipoprotein-cholesterol           | $-0.01$                     | 0.02           | 0.81        |
| High-sensitive C-reactive protein             | 0.07                        | 0.01           | 0.0218      |
| Visceral adiposity index                      | 0.07                        | 0.01           | 0.0119      |
| Glycated haemoglobin                          | 0.03                        | 0.09           | 0.28        |
| Smoking                                       | 0.01                        | 0.01           | 0.77        |
| Gender                                        | $-0.12$                     | 0.01           | $<0.0001$   |
| Gender-Visceral adiposity index (interaction term) | 0.01                      | 0.08           | 0.85        |

* = not adjusted for BMI, waist circumference, triglycerides and HDL-cholesterol (already included in visceral adiposity index)