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Visceral Adipose Tissue Dysfunction and Mortality among a Population-Based Sample of Males and Females

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Keywords

visceral fat; waist circumference; waist-hip ratio; population-based; hyperlipidemia

INTRODUCTION

Visceral adipose tissue (VAT) is one of the most deleterious fat deposits in the body, increasing the risk of developing cardiovascular disease [1], and certain types of cancer [2]. VAT is a complex endocrine organ that is associated with inflammation, insulin resistance, and immune function [2,3]. The accumulation of VAT often co-occurs with the dysregulation of lipid and liver metabolism, manifesting as elevated triglyceride and γ -glutamyl-transferase (GGT) concentrations, and depleted high density lipoprotein (HDL) cholesterol concentrations [2,3]. The Visceral Adiposity Index (VAI) and Fatty Liver Index (FLI) are composite measures derived from mathematical models that combine anthropometric [body mass index (BMI) and waist circumference (WC)] and biochemical variables (triglycerides, HDL cholesterol, GGT) to quantify adipose tissue distribution and function [4,5]. As aggregate measures of adipose tissue dysfunction, the VAI and FLI may have clinical utility in predicting cardiovascular events, cerebrovascular events, and hepatic steatosis [4,5]. However, the capacity for the VAI and FLI to predict all-cause and cause-specific mortality in a general population of adults has not been studied. We tested the hypothesis that the VAI and FLI would predict all-cause, cardiovascular-specific, and cancer-specific mortality among a large population-based sample of males and females living in the United States.

METHODS

Study Design and Participants

The Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III), was a stratified multistage study designed to provide health information on a nationally-

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CONFLICTS OF INTEREST

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representative sample of civilians living within the United States. Study participants included males and females age ≥ 18 years [6]. All participants provided written informed consent before completing any study-related activities.

Visceral Adiposity Index

The VAI was calculated as described by Amato *et al.* [4], using the following sex-specific equations:

$$\begin{aligned}\text{Males: VAI} &= \left(\frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})} \right) \times \left(\frac{\text{TG}}{1.03} \right) \times \left(\frac{1.31}{\text{HDL}} \right); \\ \text{Females: VAI} &= \left(\frac{\text{WC}}{36.58 + (1.89 \times \text{BMI})} \right) \times \left(\frac{\text{TG}}{0.81} \right) \times \left(\frac{1.52}{\text{HDL}} \right),\end{aligned}$$

where WC is expressed in centimeters, BMI in kg/m², and triglycerides (TG) and high density lipoprotein (HDL) cholesterol in mmol/L. A VAI of 1.0 depicts a non-obese person with a normal ratio between subcutaneous adipose tissue (SAT) and VAT and normal levels of triglyceride and HDL cholesterol. The VAI is correlated with VAT volume as quantified by magnetic resonance imaging ($r=0.744$; $P<0.001$), and insulin resistance ($r=-0.721$; $P<0.001$) in patients with cardiovascular and cerebrovascular risk factors [4].

Fatty Liver Index

The FLI was calculated as described by Bedogni *et al.* [5], using the following equation:

$$FLI = \frac{e^L}{(1+e^L)} \times 100$$

where $L = 0.953 \times \log_e(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{WC} - 15.745$, with TG measured in mmol/L, GGT in U/L, BMI in kg/m², and WC in cm. The FLI ranges from 0–100, with higher values indicating a greater likelihood of having hepatic steatosis [5]. The FLI is associated with abdominal fat mass ($r=0.662$; $P<0.001$) and insulin sensitivity ($r=-0.335$; $P<0.001$) in obese adults in the general population [7].

Mortality Outcome

Vital status and cause of death were identified using the National Death Index (NDI) database with follow-up through December 31, 2011. Cause of death was categorized using the International Classification of Diseases, 10th Edition (ICD-10). Cardiovascular-specific mortality was categorized using ICD-10 codes I00-I079. Cancer-specific mortality was categorized using ICD-10 codes C00-C97.

Covariates

Demographic information including date of birth and sex were self-reported using a standardized questionnaire. Height, body mass, and waist circumference were measured by study technicians. BMI was calculated as body mass divided by the square of height (kg/m²). Clinical characteristics including smoking history, the presence of comorbid health conditions including cancer, myocardial infarction, heart failure, and diabetes, and the use of

medications for cholesterol, hypertension, and diabetes were assessed using standardized questionnaires. Blood samples were collected and quantified using standardized laboratory procedures that have been previously described in detail [8]. The healthy eating index was calculated from a 24-hour food recall to form a score that ranges from 0 to 100 to quantify aspects of a healthy diet [9]. Bouts of walking in the past week were self-reported and included any bout of walking that was estimated to be 1 mile in duration, and of moderate or vigorous intensity. Sleeping difficulty was operationalized as a self-report of recent insomnia or trouble staying asleep.

Statistical Analysis

The primary outcome was all-cause mortality. The secondary outcomes were cardiovascular-specific and cancer-specific mortality. We fit Cox proportional hazards regression models to estimate the hazard ratio (HR) and 95% confidence interval (CI) of tertiles of VAI and FLI with mortality. We confirmed the assumption of proportional hazards by visual inspection of log-log plots. Sample weights were incorporated into all statistical analyses to account for nonresponse bias and multistage sampling probabilities.

RESULTS

Among 11,463 men and women, we observed 3,347 deaths during a median of 18.7 years of follow-up; 1,056 and 749 deaths occurred as a result of cardiovascular disease and cancer, respectively. The mean age of study participants was 44.0 ± 0.21 years and 51.8% were male (Supplementary Table 1). The mean BMI was 26.5 ± 0.08 kg/m², WC was 91.8 ± 0.21 cm, VAI was 2.3 ± 0.03 , and FLI was 41.9 ± 0.45 . The VAI and FLI were correlated ($r=0.48$; $P<0.0001$). Average tertiles of the VAI were: 0.81 ± 0.006 , 1.68 ± 0.008 ; and 4.65 ± 0.077 . Average tertiles of the FLI were 10.8 ± 0.18 , 42.9 ± 0.33 , and 84.2 ± 0.26 .

Visceral Adiposity Index and Mortality

Higher VAI was associated with an increased risk of all-cause (Figure 1A), cardiovascular-specific, and cancer-specific mortality. In multivariable-adjusted analyses that accounted for demographic, clinical, and behavioral characteristics, higher VAI was associated with an increased risk of all-cause ($P_{\text{trend}} < 0.0001$), cardiovascular-specific ($P_{\text{trend}} < 0.0001$), and cancer-specific mortality ($P_{\text{trend}} = 0.024$) (Table 1). Excluding participants with a history of cancer, myocardial infarction, heart failure, or diabetes did not substantively alter effect estimates.

Fatty Liver Index and Mortality

Higher FLI was associated with an increased risk of all-cause (Figure 1B), cardiovascular-specific, and cancer-specific mortality. In multivariable-adjusted analyses that accounted for demographic, clinical, and behavioral characteristics, higher FLI was associated with an increased risk of all-cause ($P_{\text{trend}} < 0.0001$), cardiovascular-specific ($P_{\text{trend}} < 0.0001$), and cancer-specific mortality ($P_{\text{trend}} = 0.003$) (Table 1). Excluding participants with a history of cancer, myocardial infarction, heart failure, or diabetes did not substantively alter effect estimates.

DISCUSSION

The principal finding of this study is that males and females with a higher VAI or FLI are more likely to die compared to those with a lower VAI or FLI in a large population-based cohort. Increasing tertiles of VAI or FLI were associated with a consistent increase in the risk of all-cause, cardiovascular-specific, and cancer-specific mortality. These data add to a growing literature that indicates that VAT dysfunction may have important implications for multiple health outcomes, including longevity.

An attractive characteristic of the VAI or FLI as potentially valuable metrics to quantify VAT dysfunction is the simultaneous integration of anthropometric measures (BMI and WC) and dynamic measures of lipid and liver metabolism [4,5]. VAT is a metabolically-active endocrine organ that is associated with circulating biomarkers, such as triglycerides, HDL cholesterol, and GGT [2,3]. The VAI and FLI also correlate with insulin resistance, which is often observed among adults with excess VAT [4,7], and is a risk factor for cardiovascular disease and cancer [10]. Therefore metrics such as the VAI or FLI which simultaneously integrate measures of VAT quantity (i.e., VAT volume or area) and quality (i.e., VAT metabolic activity) may be an important first step to globally characterize VAT dysfunction and help to differentiate patients with metabolically healthy obesity versus patients with metabolically unhealthy obesity [11]. Our findings that the VAI and FLI are independently associated with all-cause, cardiovascular-specific, and cancer-specific mortality underscore the importance of conducting future studies to confirm and expand upon the importance and utility of these metrics.

Calculating the VAI or FLI may help physicians identify patients in need of lifestyle counseling to promote the adoption of weight loss, exercise, and consumption of a healthy diet. Physical activity or exercise is an efficacious intervention to reduce the VAI and FLI [12]. Among 303 adults with type 2 diabetes, 12-months of twice-weekly aerobic and resistance exercise reduced the VAI by -0.28 [95% CI: -0.49 to -0.07 ; $P=0.005$] and the FLI by -6.19 [95% CI: -8.43 to -3.96 ; $P<0.001$] when compared to a usual care control group. The VAI and FLI declined in a dose-response fashion with increasing amounts of weekly exercise volume. These data are consistent with previous studies that exercise reduces VAT and improves metabolic abnormalities often observed with excess VAT [13]. These studies indicate that lifestyle behaviors, such as exercise, are important in the management of VAT dysfunction. These preliminary data warrant further investigation with the VAI, FLI, and clinical outcomes as potential study endpoints.

There are several strengths to this study. The population-based sampling framework of NHANES permitted our analyses to represent white males and females living in the United States. The sample size of our study was relatively large, and combined with a long period of follow-up allowed us to observe a large number of mortality events. This provided us with adequate statistical power to examine cardiovascular-specific and cancer-specific causes of death. We acknowledge that a weakness of this study is that despite adjustment for variables that are known or hypothesized to influence or confound the VAI or FLI and mortality relationship, we cannot exclude the possibility of residual confounding by unmeasured or unknown factors.

In conclusion, the VAI and FLI, quantified with widely utilized clinical variables, are associated with all-cause and cause-specific mortality among a large population of males and females living in the United States. The prognostic capacity of the VAI and FLI provide complementary tools to assess the deleterious health effects of dysfunctional body composition and metabolism. These results suggest the VAI and FLI may provide unique insight to VAT dysfunction as it relates to cardiovascular- and cancer-related mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Relationship between tertiles of A) the Visceral Adiposity Index and B) the Fatty Liver Index with All-Cause Mortality

Table 1
Associations between the Visceral Adiposity Index and Fatty Liver Index with Mortality Outcomes

Mortality Outcome	Hazard Ratio (95% Confidence Interval)					
	Visceral Adiposity Index			Fatty Liver Index		
	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 1 ^a	Model 2 ^b	Model 3 ^c
All-Cause						
Q1	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent
Q2	1.27 (1.11–1.46)	1.19 (1.03–1.37)	1.21 (1.02–1.43)	1.30 (1.14–1.50)	1.29 (1.12–1.48)	1.32 (1.12–1.56)
Q3	1.70 (1.49–1.94)	1.44 (1.25–1.66)	1.45 (1.23–1.71)	1.83 (1.59–2.10)	1.53 (1.32–1.79)	1.67 (1.39–2.01)
<i>P</i> for trend	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Cardiovascular-Specific						
Q1	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent
Q2	1.16 (0.90–1.49)	1.05 (0.81–1.35)	1.04 (0.76–1.42)	1.51 (1.17–1.95)	1.46 (1.12–1.91)	1.56 (1.15–2.19)
Q3	1.96 (1.53–2.51)	1.60 (1.24–2.07)	1.66 (1.21–2.28)	2.00 (1.54–2.60)	1.58 (1.18–2.11)	1.97 (1.36–2.84)
<i>P</i> for trend	<0.0001	<0.0001	0.001	<0.0001	0.003	<0.0001
Cancer-Specific						
Q1	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent	1.00—Referent
Q2	1.61 (1.21–2.15)	1.45 (1.08–1.94)	1.42 (1.01–1.99)	1.23 (0.93–1.61)	1.21 (0.91–1.60)	1.26 (0.91–1.75)
Q3	1.70 (1.28–2.25)	1.42 (1.06–1.90)	1.53 (1.09–2.13)	1.78 (1.34–2.36)	1.51 (1.12–2.04)	1.69 (1.19–2.38)
<i>P</i> for trend	<0.0001	0.024	0.014	<0.0001	0.006	0.003

^aModel 1 is adjusted for age and sex.

^bModel 2 is adjusted for age, sex, smoking status, healthy eating index, weekly bouts of walking, sleep difficulties, and use of medicine for blood pressure, cholesterol, or type 2 diabetes (including insulin).

^cModel 3 adjusted for the same covariates as model 2, but excludes participants with a history of cancer, myocardial infarction, heart failure, or diabetes at baseline.