Differential Effects of Body Adiposity and Serum Lipids on Right and Left Carotid Artery Lesions

To the Editor:

I read with interest the article by De Michele et al in the December issue of Stroke. The authors acknowledged that the association between obesity and atherosclerotic disease is controversial. However, their study demonstrated a graded and independent association between general and abdominal obesity reflected by high body mass index (BMI) and waist-hip ratio (WHR) and carotid artery wall thickening in a population of middle-aged women.

A review of their results in the light of ongoing work in our laboratory revealed a rather complex interaction of carotid plaque, body adiposity, and serum lipoprotein levels. Ninety consecutive patients aged 56.2 ±14 years (60 male and 30 female) were studied. All were right-handed. Color-flow Doppler and B-mode ultrasound of the carotid were performed to determine the percentage stenosis in the internal carotid artery. BMI was calculated as weight divided by height squared (kg/m²); WHR was calculated as waist divided by hip.

Lipid profile was determined using the enzymatic method. Analysis of 3D surface plots of data obtained from results of piecewise linear regression (using ICA percentage stenosis as dependent variable, independent variables were in one analysis BMI and WHR, and in another LDL and HDL) with breakpoint set at 70% stenosis. All analysis was performed with statistical software package (Statistica for Macintosh, StatSoft, Tulsa, Okla).

Mild to moderate RICA (≤70%) stenosis correlated positively with BMI (P=0.00001) and negatively with WHR (P=0.00006) (see Figure 1A), severe RICA (>70%) stenosis correlated positively with both BMI (P=0.016) and WHR (P=0.0002), R=0.82, accounting for variance in 65% of cases. Mild to moderate LICA (≤70%) stenosis did not with BMI (P>0.05), but correlated positively with WHR (P=0.0009), (see Figure 1B), severe LICA (>70%) stenosis correlated positively with both BMI (P=0.000001) and WHR (P=0.01); R=0.79, and accounting for variance in 62% of cases.

Mild to moderate percentage RICA stenosis correlated positively with LDL levels (P=0.0001) and negatively with HDL levels (P<0.0001), severe LICA (>70%) stenosis correlated negatively with LDL (P<0.00001); R=0.81, and accounting for 65% of cases (Figure 1C). Conversely, mild to moderate LICA (<70%) stenosis correlated positively with both LDL levels (P<0.000001) and HDL levels (P<0.000001) (Figure 1D); severe LICA (>70%) stenosis correlated negatively with LDL (P=0.00045), but not with HDL (P=0.05); R=0.8, and accounting for variance in 65% of cases.

The results suggest that general body adiposity (high BMI) influences accumulation of plaque in the RICA at all levels of severity, but only accentuated an already severe plaque in the LICA associated with abdominal adiposity. Conversely, abdominal body adiposity (high WHR) facilitates accumulation of plaque in the LICA but accentuated an already severe plaque in the RICA due to general body adiposity. LDL levels facilitate the formation of carotid plaques in both RICA and LICA. Conversely, HDL reduces the formation of carotid artery plaque only in the RICA but accentuated LICA plaque formation.

The reason for these complex interactions is not known and could only be open to different interpretations at this time. One likely factor is that of anatomic asymmetry of both carotid systems. The left common carotid artery (CCA) takes its origin directly from the aortic arch, while the right CCA branches off from the brachiocephalic artery (BCA). There may be indications that LICA plaque formation is related to atheromatous process in the trunk and lower part of the body and the mechanisms of plaque formation differ from right. These mechanisms may involve active transport rather than the biochemical regulations implicated in right plaque formation. For example, the fact the HDL levels did not reduce LICA plaque but rather increased with plaque size may indicate that HDL cholesterol was actively incorporated in left plaque formation. This could only be possible if there was active transport to the site of lesion bypassing the regulatory mechanisms. What plausible mechanisms could be involved in plaque propagation from the lower part of the body into the left carotid system but not the right? The anatomic location of the left CCA at a critical point in the aortic arch curvature with a unique flow geometry involving helical flow pattern, bound-

A 3-dimensional surface plot of results of piecewise regression analysis. Relationships between carotid stenosis and obesity (top) and serum lipids (bottom) are illustrated.
ary conditions, secondary flow, and reflections from aorto-iliac bifurcation\(^8\) might serve as a clue. The plausible rise in blood column of low-specific-gravity fatty globules from areas of the abdominal aorta into the aortic arch outer curvature and propagation into left CCA due to secondary flow phenomenon are all clues that require further investigation. Another important issue raised by these findings is whether 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, which lower lipid levels, will have a considerable impact on LICA plaque size as would be expected for RICA, considering a plausible difference in mechanisms of formation. Elucidation of these issues could have far-reaching pharmacological and clinical implications for stroke prevention.

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**Response**

We appreciate Dr Njemanze’s comment on our article\(^1\) evaluating the relationship between intima-media thickness of the common carotid arteries, as assessed by high resolution B-mode ultrasound, and estimates of adiposity in middle-aged women. In that patient series, the author found side-related differences in the relationship between severity of carotid atherosclerosis, as evaluated by color-flow Doppler and B-mode imaging, and cardiovascular risk factors, including body mass index and waist-to-hip ratio (an estimate of abdominal adiposity). A previous report shows side-related differences in intima-media thickness of carotid arteries in primary hypertensive patients.\(^2\)

To evaluate the possibility of side-related influences on the relationship between overweight or obesity and carotid intima-media thickness, we performed a separate analysis for the right and left common carotid artery in our cohort of free-living middle-aged women. No side-related differences were detected in the mean values of common carotid intima-media thickness (right common carotid artery, 0.98±0.01; left common carotid artery, 0.97±0.01 [mean±SE]). The results of further multivariate regression analyses are reported in the Table. The multivariate analyses evaluating intima-media thickness in relation to estimates of adiposity and taking into account the influence of age, blood pressure, and traditional risk factors (cigarette smoking, serum cholesterol) demonstrated the same results for both sides.

There are reasons for the different outcome of our study as evaluated comparatively with that of Dr Njemanze. One reason is the different number and sex distribution of the individuals who underwent ultrasound examination (310 women in our study, 60 men and 30 women in Dr Njemanze’s series). A second reason was the different clinical condition: healthy women in our population-based cohort, patients with overt cardiovascular disease in most cases (61%) in the other study. A third reason is the different methodology and site of examination. We measured intima-media thickness of the common carotid artery by quantitative B-mode imaging; Dr Njemanze used an estimate of percentage lumen stenosis of the internal carotid artery. We have demonstrated significant differences in the risk factors pattern between different, even contiguous, sites in the extracranial carotid arteries.\(^3\) A final reason was the difference in the statistical analyses that we applied on the whole cohort, whereas our colleagues from Nigeria focused on patient subgroups with different severity of carotid stenosis.

In conclusion, the 2 surveys are quite different studies of different statistical power, but both indicate a relevant role of increased adiposity in relation to the presence and severity of carotid atherosclerosis.

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| Relationship Between Estimates of Adiposity and Right and Left Common Carotid Intima-Media Thickness as Determined by Multiple Regression Analyses |
|----------------------------------------------|----------------|----------------|----------------|
|                                             | RCCA-IMT β (SE) | RCCA-IMT P   | LCCA-IMT β (SE) | LCCA-IMT P |
| **Model 1**                                 |                |                |                |
| Age, y                                      | 0.008 (0.001)  | 0.0001         | 0.009 (0.001)  | 0.0001     |
| Systolic BP, mm Hg                          | 0.001 (0.001)  | 0.017          | 0.0008 (0.0001)| 0.04       |
| BMI, kg/m\(^2\)                             | 0.007 (0.002)  | 0.003          | 0.012 (0.005)  | 0.02       |
| R\(^2\)                                     | 22%            | 24%            |
| **Model 2**                                 |                |                |                |
| Age, y                                      | 0.007 (0.001)  | 0.0001         | 0.009 (0.001)  | 0.0001     |
| Systolic BP, mm Hg                          | 0.001 (0.001)  | 0.011          | 0.0009 (0.0001)| 0.05       |
| WHR                                         | 0.46 (0.16)    | 0.005          | 0.30 (0.16)    | 0.02       |
| R\(^2\)                                     | 22%            | 25%            |

The following variables did not enter the regression models: LDL cholesterol, triglycerides, diastolic blood pressure, cigarette smoking, and insulin. β (SE) indicates regression coefficient (standard error), R\(^2\), the coefficient of determination, represents the percentage of the variation in the dependent variable explained by the independent variables in the model. RCCA IMT indicates right common carotid intima-media thickness; LCCA IMT, left common carotid intima-media thickness; BP, blood pressure; BMI, body mass index; WHR, waist/hip ratio.
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