Obesity, Fat Metabolism and Cardiovascular Disease

By John W. Gofman, M.D., Ph.D., and Hardin B. Jones, Ph.D.

Lipoproteins of the Sf 12–100 class, representing only about 10 to 15 per cent of the serum cholesterol, are strongly associated with atherosclerosis. The major independent contributions to this association are from the Sf 12–20 lipoproteins and the Sf 35–100 lipoproteins. The Sf 20–35 lipoproteins are primarily associated by virtue of their intercorrelation with the other classes. Obesity is moderately associated with the Sf 35–100 and definitely, but to a lesser degree, with the Sf 12–20. The association of obesity with total serum cholesterol is so low as to obscure the stronger association with the Sf 35–100 lipoproteins. The relationship of the Sf 12–100 lipoproteins with obesity may be adequate to explain the major share, if not all, of the association of obesity with atherosclerosis. The control of obesity should therefore be a prime consideration in the management of atherosclerosis and its complications.

The clinical association of obesity with the occurrence of cardiovascular disease has been extensively reported and is quite generally accepted. Yet the exact mechanism by which obesity facilitates the development of vascular disease has remained obscure, except for speculation on the possible physical burden of the excess adipose tissue. Atherosclerosis is the underlying basis for the major fraction of degenerative vascular disease. In several previous reports concerning serum lipid transport via lipoproteins, we have established that certain special classes of lipoproteins are closely associated with the development of human atherosclerosis. It was of obvious interest to determine whether obesity is significantly related to the serum levels of atherosclerosis-associated lipoproteins, and whether any such relationship might explain the role of obesity in atherosclerosis. The data of this report show that such a relationship of obesity with certain classes of lipoproteins does exist and may adequately explain the excessive atherosclerosis associated with the obese state.

Recently we have reported that two major classes of lipoproteins, the Sf 12–20 class and the Sf 20–100 class, provide essentially the entire contribution of serum lipids to atherosclerosis. In toto, the cholesterol of these two classes represents only approximately 10 to 15 per cent of the total serum cholesterol. The remaining 85 to 90 per cent of the serum cholesterol is not significantly associated with atherosclerosis.* Neutral fat is a prominent structural component of the Sf 20–100 class of lipoproteins, whereas it is low in the Sf 12–20 class. Cholesterol and cholesterol esters are more prominent constituents of the Sf 12–20 class than of the Sf 20–100 class. Of the two classes of lipoproteins, the Sf 12–20 class is more stable in level, being unaffected acutely by food intake. The Sf 20–100 class, especially the lipoproteins from Sf 35 to Sf 100, are more labile in level, showing appreciable increases with the ingestion of fat. However, in individuals with a moderate or severe degree of the lipid metabolic error previously described, the Sf 20–100 class of lipoproteins is more stable in concentration and is present at moderate or high levels even in the postabsorptive state. In spite of the individual

*The Sf 8–10 and Sf 10–12 lipoproteins are associated with atherosclerosis. However, they are very closely related to the Sf 12–20 lipoproteins, so that generally no change in ranking occurs if they are not measured. If the Sf 8–12 lipoproteins are included, the remaining unassociated cholesterol is closer to 80 or 85 per cent.
variability in serum $S_f \ 20-100$ level, it has been possible to demonstrate unequivocally the independent association of this class of lipoproteins with atherosclerosis to a degree essentially equivalent to that of the $S_f \ 12-20$ class of lipoproteins.

Earlier crude inspection of the data indicated that there was no marked relationship between estimated obesity and the serum $S_f \ 12-20$ lipoprotein level. In this study we have been able to make a precise evaluation of the relationship within the limits of the collected data for both the $S_f \ 12-20$ and $S_f \ 20-100$ lipoproteins with obesity. The group considered consists of 241 normal men 41 to 50 years of age in whom height, weight, serum $S_f \ 12-20$ and $S_f \ 20-100$ lipoproteins, and total serum cholesterol were measured. As an estimation of obesity subjects were rated in pounds above and below the normal values from the height-weight data of Armstrong. Lipoprotein analysis by the ultracentrifugal method and serum cholesterol analysis were made on aliquots of the same serum sample. A summary of the quantitative relationships found is given in table 1.

It is evident from the data of table 1 that there is definitely a significant positive correlation between serum $S_f \ 35-100$ lipoprotein level and estimated obesity. This is the strongest relationship with estimated obesity observed in these data. The over-all $S_f \ 12-100$ lipoprotein level correlates positively with estimated obesity nearly as well. However, a significant, but much weaker, relationship is seen between serum $S_f \ 12-20$ level and estimated obesity.

There is a trend in the same direction in the relationship of total serum cholesterol with obesity, but quantitatively this relationship is of only borderline significance. It is to be noted that the measurement of total serum cholesterol alone would obscure the much stronger relationship of the $S_f \ 35-100$ lipoprotein level with estimated obesity. The data are expressed in a practical way below, assuming rectilinear regression between the various levels measured and estimated obesity.

<table>
<thead>
<tr>
<th></th>
<th>No. of Cases</th>
<th>$S_f \ 12-20$</th>
<th>$S_f \ 35-100$</th>
<th>$S_f \ 12-100$</th>
<th>Total Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above Normal Wt.</td>
<td>199</td>
<td>47.6 ± 2.03*</td>
<td>68.3 ± 3.1</td>
<td>147.8 ± 6.0</td>
<td>264 ± 3.6</td>
</tr>
<tr>
<td>Below Normal Wt.</td>
<td>42</td>
<td>36.3 ± 2.9</td>
<td>43.1 ± 6.6</td>
<td>102.2 ± 9.6</td>
<td>245 ± 8.8</td>
</tr>
<tr>
<td>Probability that difference is not significant</td>
<td></td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>~0.05</td>
</tr>
<tr>
<td>Standard deviation for entire group.</td>
<td>241</td>
<td>27.4</td>
<td>44.4</td>
<td>82.6</td>
<td>52.7</td>
</tr>
<tr>
<td>Inter correlation with obesity ($r$)†</td>
<td>241</td>
<td>0.14 ± .065†</td>
<td>0.28 ± 0.065</td>
<td>0.27 ± 0.065</td>
<td>0.065 ± 0.065</td>
</tr>
<tr>
<td>Probability that correlation is not significant</td>
<td></td>
<td>&lt;.02</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>~0.10</td>
</tr>
</tbody>
</table>

* Values are given as the mean plus or minus the standard error of the mean, which is calculated from the equation

$$
\sigma_{se} = \frac{\text{standard deviation of distribution}}{\sqrt{N-1}}
$$

† $r$ is the Pearson product-moment correlation coefficient.

‡ The standard error is that used in null-hypothesis testing for the significance of a correlation coefficient.

Thus

$$
\sigma_{se} = \frac{1}{\sqrt{N-1}}
$$

While these observations bear out the earlier impression of the very low correlation of
the Sf 12–20 level with estimated obesity, the slight relationship is a significant one and has bearing upon atherogenicity. The much higher relationship of the Sf 35–100 molecules with estimated obesity has real implications for atherosclerosis. Crudely, obesity accounts for approximately 8 per cent of the relationship of the Sf 35–100 lipoproteins with atherosclerosis, a relationship previously demonstrated to be a reasonably high one. Since obesity was estimated here by height-weight relationships (at best a crude approximation to its assessment), and since there are biologic and technical variations in the estimate of the Sf 35–100 level, it is highly probable that the over-all Sf 35–100–obesity relationship is of the order of twice the measured one. This might then indicate that about 15 to 20 per cent (or more) of the relationship of the Sf 35–100 lipoproteins with atherosclerosis is accounted for by obesity. Further, since the relationship of Sf 35–100 level with obesity is only of moderate degree, we may infer that for some patients obesity is contributing far more than the estimated 15 to 20 per cent, whereas for others it contributes much less. The relationship of obesity with the other atherosclerosis-associated lipoproteins, the Sf 12–20 class, while of lesser degree than that for the Sf 35–100 class, is still appreciable and hence is of real importance for at least a segment of the population.

There are several possible explanations for the association of elevation of Sf 35–100 lipoproteins with obesity. In previous work we have actually observed an acute rise in level of such molecules in the first several hours following a high fat meal. Thus the obese individual, who commonly ingests excessive quantities of dietary fat, may have part of his elevation through either the dietary fat excess itself or a slowed removal of dietary fats from the blood to tissues. Neither of these is exclusive of the possibility that there is at steady state a greater re-entry of fats from tissue depots into this part of the blood lipid transport mechanism as a feature of fat metabolism of the obese state itself as compared with the nonobese.

Significance of the Sf 35–100– and Sf 12–20–Obesity Relationship in Atherosclerotic Cardiovascular Disease

The clinical vascular consequences of atherosclerosis, such as coronary occlusion, are, in a general way, dependent upon the degree of atherosclerosis and atherosclerotic activity. Inasmuch as a large fraction of the "normal" population shows moderate to severe atherosclerosis, we may anticipate that small increases in degree of atherosclerosis or atherosclerotic activity may be all-important in determining whether atherosclerosis will remain silent or will result in a frank clinical manifestation. The relationship of obesity to the Sf 35–100 lipoproteins especially (and its lesser relationship to the Sf 20–35 and Sf 12–20 lipoproteins) is of sufficient degree to account for a small, but definite, part of the association of these lipoproteins with atherosclerosis. Observations made in patients before and after reduction in weight have shown definite lowering of the Sf 35–100 lipoprotein levels in many subsequent to weight reduction. To what extent this is due to lowered dietary fat ingestion rather than to the reduction in weight itself in a specific case can not now be definitely answered.

The possibilities of lessening the clinical hazards incident to atherosclerosis through the control of obesity are of promise, and provide a sound rationale for the already clinically-established practise of advising weight reduction in the obese. While every patient will not respond, a certain proportion may be anticipated to show large responses in their lipoprotein levels, and hence, in all likelihood, in their atherosclerotic potentialities.

Summary

1. Of the two classes of serum lipoproteins which are strongly associated with atherosclerosis, the Sf 35–100 class is moderately related to obesity, whereas the Sf 12–20 class shows a much lesser, yet significant, relationship to obesity.

2. The positive correlation of atherosclerosis-associated Sf 35–100 and Sf 12–20 lipoproteins
with obesity provides part of the basis, and possibly the largest part, of the relationship of obesity with atheromatous vascular disease. This subtle relationship is almost entirely obscured by the total serum cholesterol measurement.

3. The control of obesity, as a prophylactic and therapeutic measure in atherosclerosis, already a part of clinical practice, derives support from the finding of the association of certain lipoprotein classes with obesity.

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