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High Protein Diets Induce Autophagic Disruption in Macrophages of Atherosclerotic Lesions

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High-protein (HP) diets have long been touted as an effective weight-loss strategy. However, its long-term effects on cardiovascular disease have been inconclusive. Recent clinical and *in-vitro* studies have linked these diets to higher incidences of cardiovascular-related mortality and increased atherosclerotic lesion size. Atherosclerosis is a leading cause of cardiovascular disease, characterized by the accumulation of plaque along the arterial vasculature. The progression of lesions can increase the chances of acute cardiovascular events such as heart attack and stroke. There is mounting evidence that implicates the dysfunction of autophagy, a cellular degradative process that prevents accumulation of cytotoxic aggregates, with lesion progression. Taking this into account, the objective of this study was (1) to investigate the relationship between HP diets, autophagic dysfunction, and increasing lesion size and (2) to provide a mechanistic basis for HP-diet induced disruption of autophagy.

We conducted this investigation using a combination of *in-vivo* and *in-vitro* studies. Amino acid uptake by macrophages was analyzed using mass spectrometry. mRNA and protein levels were measured with quantitative PCR, Western Blot, and immunofluorescence techniques.

Our results suggest that protein-rich diets increase differential amino acid load into macrophages of atherosclerotic lesions. Two amino acids, leucine and glutamine, are found in high concentrations in lesional macrophages. Both stimulate independent biochemical pathways that aggravate autophagic disruption. Leucine inhibits autophagy through the induction of mammalian target of rapamycin complex 1 (mTORC1), while glutamine-mediated inhibition stymies the transcription rate of a key autophagic chaperone, p62/SQSTM1. These findings provide a mechanism to account for HP diets' proatherogenic qualities and highlight the crucial role autophagy plays in modulating atherosclerotic progression.