



Technical Literature

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The Los Angeles Atherosclerosis Study

Key Conclusions

- Serum lutein levels are inversely associated with arterial wall thickness in humans
- Lutein supplementation results in decreased arterial lesion size (-44%) and LDL oxidation (- 78%) in mice prone to CVD
- Lutein dose-dependently inhibits monocyte chemoattraction to oxidatively damaged arterial wall cells

A summary of: "Oxygenated Carotenoid Lutein and Progression of Early Atherosclerosis." The Los Angeles Atherosclerosis Study By: Dwyer J.H., M. Navab, K.M. Dwyer, K. Hassan, P. Sun, A. Shircore, S. Hama-Levy, G. Hough, X. Wang, T. Drake, C.N. Merz, A.M. Fogelman. (2001) *Circulation* 103(24): 2922-7.

Introduction

More lives are lost to cardiovascular disease (CVD) in the US than from any other single cause, making this a major public health concern (5). Researchers from the University of Southern California and University of California, Los Angeles, published a recent article in the journal *Circulation* describing the effect of lutein on the progression of atherosclerosis (4). The investigators performed three separate studies: a prospective epidemiology study, an animal intervention study, and an in vitro cell culture study. The results are summarized in Table 1.

Background

Cardiovascular disease or atherosclerosis is a progressive disease, resulting in occlusion of arteries due to repeated oxidation and accumulation of damaged cells and cell constituents along the arterial walls (10). Initiation of atherogenesis is caused by oxidation of low density lipoproteins (LDL) by free radicals and reactive oxygen species (ROS). This event damages the endothelial cells lining the arterial walls. The subsequent inflammatory response elicited by oxidatively damaged endothelial cells causes release of signaling, or adhesion molecules, which attract blood-clotting proteins and immune cells (monocytes) (Figure 1). The monocytes engulf the damaged cells in an attempt to destroy them. The build-up of monocytes and damaged cells, along with clotting proteins leads to the formation of fatty plaques, or lesions. This represents the atherogenic pathway and development of cardiovascular disease (1, 9).

Table 1. Summary of studies described by Dwyer et al. 2001

Study	Model	Objective	Outcome
Prospective epidemiology (observational)	Humans	Examine the relationship between serum lutein levels and arterial wall thickening over time	Arterial wall thickening was 80% higher in those individuals with the lowest vs. highest serum lutein level
Supplementation (intervention)	Mice	Determine the effect of lutein supplementation on:	Arterial lesion size was 44% smaller in lutein-supplemented mice vs. controls
		(1) arterial lesion size in mice prone to CVD (2) LDL oxidation in serum	LDL oxidation was 78% lower
<i>In vitro</i>	Human endothelial cells and monocytes	To assess the effect of lutein on the chemoattraction of monocytes to endothelial cells	Addition of lutein to the cell culture medium inhibited chemoattraction in a dose-dependent manner

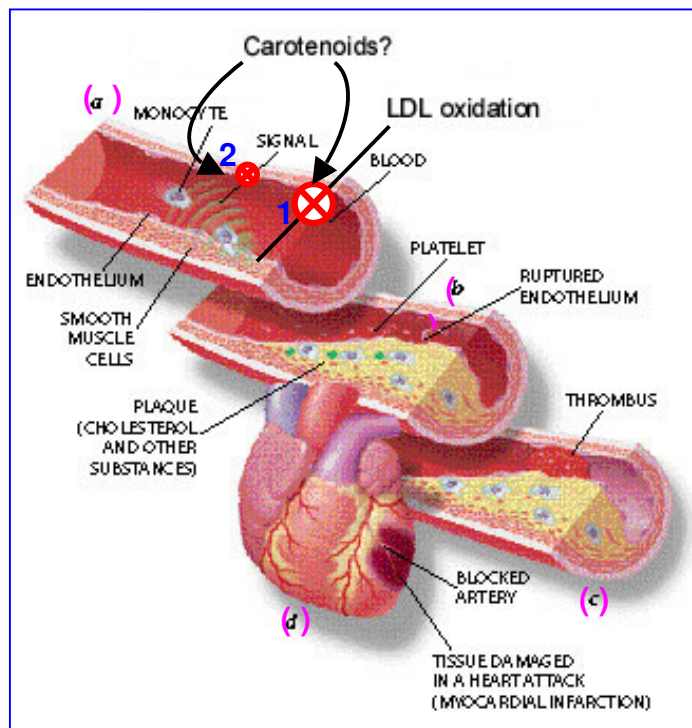


Figure 1.
Proposed atherosclerotic pathway.

LDL oxidation damages endothelial cells which release a signal that attracts monocytes (a). In an attempt to destroy the damaged cells the monocytes migrate into and under the endothelium where they amass cholesterol and other cellular debris. The endothelium then swells and ruptures, attracting clot-forming platelets (b). The platelets then aggregate forming a blood clot (c). The narrowed artery may cause chest pain (angina) or if completely obstructed, a heart attack (d). Antioxidants such as lutein are believed to act in the initial stages by preventing LDL oxidation and inhibiting the attraction of monocytes.

Van De Graaff, K. M. and I. S. Fox Concepts of Human Anatomy and Physiology. *Circulatory System*, WCB Publishers: 580-582

Some research suggests which in addition to acting as antioxidants, carotenoids such as lutein exert their beneficial effect by inhibiting the signaling from endothelial cells that attracts monocytes (Figure 1). Indeed, it has been shown that lutein, β -carotene, and lycopene all decrease the expression of adhesion molecules on the surface of interleukin-stimulated human aortic endothelial cells in culture (8).

Study Summary

In the study by Dwyer *et al.* investigators used three separate models to demonstrate the anti-atherogenic activity of lutein described above.

Study 1: Epidemiology

For the first model, an observational study, the serum levels of lutein and β -carotene were analyzed from 480 adults (225 women, 255 men) from the Los Angeles area. Subjects were then followed for approximately 18 months. The common carotid artery intima-media thickness (thickness of the arterial wall) was measured at the beginning and end of the study.

Results: Over the 18-month period, subjects with the highest serum lutein level (0.42 μ mole/L) had 80% less arterial wall thickening relative to those with the lowest serum lutein level (0.15 μ mole/L). No such relationship was observed with serum β -carotene.

Study 2: Mouse intervention

Mice genetically prone to developing CVD were fed a control or lutein-supplemented diet (0.2%) for 8 weeks. Serum obtained from the mice was incubated with LDL, and LDL oxidation measured. Mice were then sacrificed and atherosclerotic plaque, or lesion size, was measured.

Results: Mice on a lutein-supplemented diet had 44% smaller lesion size, and 78% less LDL oxidation, relative to those on a control diet.

Study 3. In vitro cell culture

Human aortic endothelial and smooth muscle cells were incubated with LDL in the presence and absence of increasing levels of lutein (0 – 100 nM) for up to 8 hours. Human monocytes were then added to the culture. Chemotaxis (attraction of monocytes) was measured.

Results: Attraction of monocytes to oxidatively damaged endothelial and smooth muscle cells was dose-dependently inhibited in cells incubated with lutein, with the inhibition of attraction up to eight-fold more than cells incubated with LDL alone.

Conclusion

In summary, Dwyer *et al.* showed that serum lutein levels are inversely associated with arterial wall thickness in humans. Lutein supplementation results in decreased lesion size and LDL oxidation in mice prone to CVD. Lutein may dose-dependently inhibit monocyte chemoattraction to oxidatively damaged arterial wall cells. This study represents both observational evidence in humans and direct evidence in animals and cell culture that lutein may reduce the risk of development of CVD by inhibiting the events that lead to atherosclerotic plaque formation and progression.

These results are consistent with those previously described in two prospective epidemiologic studies examining stroke incidence which have specifically included lutein in the analysis. Hirvonen *et al.* and Ascherio *et al.* both reported that lutein intake was inversely related to stroke risk (2, 6). These are also consistent with a report from Martin *et al.*, which showed that lutein inhibited the expression of adhesion molecules (compounds that attract monocytes) *in vitro* (8), and with studies that have shown marginal effects of lutein *ex vivo* (i.e., supplementation with carotenoids, and analysis of serum samples for LDL oxidation) (3, 4, 7). While this study and others suggest lutein may protect against the development of CVD, further research is needed to better define the role of lutein in CVD. Specifically, human intervention studies examining the effect of lutein supplementation on indices of CVD development and progression, must be forthcoming to assist in the determination of both safe and effective doses.

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