
Acute Effects of Oats and Vitamin E on Endothelial Responses to Ingested Fat

David L. Katz, MD, MPH, Haq Nawaz, MD, MPH, Josette Boukhalil, MD, Vanessa Giannamore, CVT, Wendy Chan, MPH, Ramin Ahmadi, MD, MPH, Philip M. Sarrel, MD

Objective: To assess the effects of oats and vitamin E on endothelial function following a high-fat meal in healthy adults as measured by brachial artery reactivity studies (BARS).

Methods: A total of 25 men and 25 women (N=50) were recruited from a community population to participate in this randomized, crossover study. All subjects were free of known vascular disease, and female subjects were postmenopausal. Subjects underwent BARS before and after a high-fat meal (50 gm fat) on three occasions 1 week apart, one each with vitamin E 800 IU, oatmeal containing 3 gm β -glucan, or a comparable bowl of wheat cereal serving as a placebo, in random sequence. The ultrasonographer was blinded to treatment status.

Results: Endothelial function, as measured by brachial artery peak flow during one minute of post-occlusive hyperemia, declined significantly from baseline when the high-fat meal was consumed with the wheat cereal (-13.4% ; $p=0.02$). There was no difference in brachial artery flow change before and after a high-fat meal with oats ($+0.37\%$; $p=0.77$) or a high-fat meal with vitamin E ($+1.87\%$; $p=0.42$). No significant differences in flow-mediated vasodilation before and after the high-fat meal were detected among the three supplements.

Conclusions: Endothelial dysfunction induced by acute fat ingestion in healthy adults is apparently prevented by concomitant ingestion of oats or vitamin E, but not wheat. Nutrient distribution and meal composition may have important implications for cardiovascular health.

Medical Subject Headings (MeSH): brachial artery, blood flow velocity, cereals, dietary fiber, oats, vascular endothelium, vasodilation (Am J Prev Med 2001;20(2):124-129)
© 2001 American Journal of Preventive Medicine

Introduction

Endothelial function refers to arterial vasomotor responses mediated predominantly by the release of nitric oxide (vasodilating) and endothelin (vasoconstricting) from the vascular endothelium.¹ Endothelial dysfunction refers to the propensity of vessels to constrict and impede flow in response to stimuli that should lead to dilatation and flow augmentation.² Endothelial function testing relies on the induction of hyperemic flow to stimulate nitric oxide release.³ Due to the strong correspondence between peripheral and coronary endothelial responses, testing of the brachial artery using high-resolution ultrasound before and after occlusion and post-occlusive hyperemia has become the standard assessment method.⁴

Endothelial dysfunction has been shown to predict higher cardiovascular event rates,⁵ to be associated with anatomically overt coronary artery disease (CAD),⁶ to correlate strongly with both coronary disease and its risk factors,⁷⁻¹² and to reverse in response to risk modification efforts.¹³⁻¹⁵ While a definitive association between endothelial function and clinical events awaits the results of a multi-center trial now underway, endothelial dysfunction has increasingly been viewed as an indicator of coronary risk,⁶ and its amelioration as an indicator of risk reduction.^{13,15}

Endothelial dysfunction has been demonstrated following the ingestion of a high-fat meal in healthy subjects.¹² Acute fat ingestion has long been associated with an acute increase in coronary event rates in susceptible individuals.¹⁶⁻¹⁸ Endothelial dysfunction may be a marker of, or even the mechanism of, acute coronary vulnerability; endothelial responses to foods may be an important determinant of coronary risk.^{12,19}

Although the recently published HOPE trial failed to show a beneficial effect of vitamin E supplementation on cardiovascular events,²⁰ there is evidence to support

From the Yale Prevention Research Center (Katz, Nawaz, Boukhalil, Giannamore, Chan, Ahmadi, Sarrel), Derby; and Yale University School of Medicine (Katz, Nawaz, Sarrel), New Haven, Connecticut

Address correspondence and reprint requests to: David L. Katz, MD, MPH, Yale Prevention Research Center, 130 Division Street, Derby, CT 06418. E-mail: katzdl@pol.net.

a role for vitamin E supplementation in the prevention of endothelial dysfunction induced by a high-fat meal.¹² While soluble fibers, including β -glucan, pectin, guar, gums, and psyllium mucilloid have been associated with reduced risk of coronary heart disease,²¹⁻²³ their effect on endothelial function has not been reported. We conducted a controlled, randomized, double-blinded, crossover trial of whole oats on endothelial function following acute fat ingestion in healthy adult subjects. Vitamin E, previously shown to prevent fat-induced endothelial dysfunction,¹² was used as an index by which to gauge the effects of oats on vascular reactivity (positive control). Whole rolled wheat cereal containing predominantly insoluble fiber was used as the placebo.

Methods

Subjects

A total of 50 healthy adult subjects (25 women and 25 men) were recruited from the Lower Naugatuck Valley, Connecticut, community through advertisements in local newspapers and posters at frequented sites, to participate in a study of vascular endothelial responses to ingested fat. Sample size was determined by calculating the number of subjects required to test the study hypothesis with 80% power, given variance and outcome effects from prior published studies, and to accommodate an attrition rate of 15%. Inclusion criteria follow: (1) age >35 for men; postmenopausal and amenorrheic for at least 1 year for women; (2) nonsmoking; (3) no known CAD or other vascular disease; (4) no vasoactive medication use; (5) no daily prescription medication use; (6) no regular use of vitamin E supplement or fiber supplements. Different age criteria were applied to men and women to ensure that subjects would be selected from gender groups most likely to be at risk for subclinical atherosclerosis. Exclusion criteria, limited to optimize external validity, were failure to meet inclusion criteria or anticipated inability to complete the study protocol for any reason. Equal numbers of male and female subjects were recruited by closing the study to either gender once that gender represented half of the required sample size.

Those subjects who responded to advertisement were screened over the telephone to assess eligibility. Subjects who met initial screening criteria were scheduled for a screening examination and laboratory testing. During the screening visit, all subjects underwent height, weight, and blood pressure measurements by resident physicians in the integrated Internal Medicine/Preventive Medicine Residency at Griffin Hospital in Derby, CT. Participating physicians were trained by the core research team, and employed identical measurement methods. Blood pressure was measured at rest after 5 minutes and again after ten minutes, then averaged. Weight was measured in a hospital gown and bare feet. Weight measurements were used to calculate each subject's body mass index (BMI, calculated as a ratio of weight in kg to height in m²). Laboratory testing included measures of random total cholesterol, high-density lipoprotein (HDL) cholesterol, and total plasma homocysteine.

A total of 106 subjects responded to study advertisements.

Table 1. Nutrient composition of study cereals

Nutrient	Quaker oatmeal (per 60 gm)	Rolled whole wheat (per 60 gm)
Fat (gm)	3	1
Saturated	0.5	0
Polyunsaturated	1	0
Monounsaturated	1	0
Carbohydrates (gm)	27	30
Dietary fiber	4	4
Soluble fiber	2	1
Insoluble fiber	2	3
Sugars	1	0
Others	—	—
Proteins (gm)	5	5

Fifty subjects were determined to be ineligible by telephone screening and four declined to participate, resulting in a final sample of 52 subjects. The first 50 subjects were entered into the trial in the order of enrollment. One subject dropped out after completing her second scan. To organize brachial artery reactivity studies (BARS), subjects were divided into eight groups based on availability. Each group was then randomly assigned, by use of a random number table, to a treatment sequence consisting of oats, wheat, and α -tocopherol.

All subjects provided informed consent before randomization. Participants were compensated monetarily for their time at the end of the study.

Protocol

The study was approved by the institutional review board of Griffin Hospital. Each group of subjects presented once each week on 3 consecutive weeks for vascular reactivity testing. On each occasion, a baseline vascular reactivity study was performed in the morning following an overnight fast. Immediately after baseline testing, each subject received the high-fat meal and the assigned test food/nutrient over a 15-minute period. The high-fat meal consisted of a milk shake made with ice cream, cream of coconut, and pasteurized eggs, and provided a standard load of 50 gm of predominantly saturated fat (68% of calories) with the following distribution of ingredients: 163 gm Haagen Daaz vanilla ice cream; 72 gm cream of coconut; and 22 gm pasteurized egg product.²⁴ The test shake, providing 662 total kilocalories, was eaten together with a bowl of oatmeal providing 3 gm of β -glucan on one occasion; with a comparable bowl of whole rolled wheat cereal on another occasion; and with a capsule providing 800 IU α -tocopherol on a third occasion. The oat cereal consisted of 60 gm of rolled oats and the wheat cereal consisted of 60 gm of whole rolled wheat. The nutrition composition of each cereal is provided in Table 1. Vascular reactivity testing was repeated exactly 3 hours postprandially for each subject on each of the three occasions.

Vascular Reactivity Testing

Vascular reactivity testing consisted of pre- and post-prandial BARS. The BARS methodology employed is comparable to that reported by other labs.^{4,8,12,25,26} Subjects were required

Table 2. Clinical characteristics of study population by gender

Variable	Mean±SD (range)	
	Men (N=25)	Women (N=25)
Age (years)	51.7±11.4 (35–75)	61.6±7.2 (47–75)
Total cholesterol (mg/dL)	191.3±28.6 (142–255)	213.5±33.2 (165–319)
Total plasma homocysteine (μmol/L)	7.0±1.89 (3.0–11.0)	7.3±2.04 (5–13)
Weight (kg)	94.1±28.2 (55.9–181.8)	69.5±12.2 (52.7–102.3)
Body mass index ^a	30.3±10.7 (19.3–75.7)	26.4±5.4 (17.8–44.03)
Baseline diameter ^b (cm)	0.52±0.09 (0.33–0.78)	0.42±0.08 (0.27–0.61)
Baseline flow (mL/sec) ^b	21.0±10.01 (7.0–77.0)	15.4±6.5 (4.1–34.7)
HDL cholesterol (mg/dL)	42.5±16.75 (26.0–113.0)	55.4±16.5 (28.0–88.0)
Blood pressure—baseline scan (mm Hg)	129/80	136/80
Blood pressure—repeat scan (mm Hg)	127/77	130/78

^aBody mass index = weight in kg/height in m²

^bAcute phase baselines averaged over three scans

HDL, high-density lipoprotein

to lie at rest for at least 10 minutes before scanning was initiated. The diameter of the brachial artery was measured from two-dimensional ultrasound images using a high resolution, 10 MHz, vascular ultrasound transducer (Hewlett Packard; Sonos 5500; L7540 linear transducer). Arterial flow velocity was measured by means of a pulsed Doppler signal at a 70° angle to the vessel, with the range gate in the center of the artery. Flow was determined by multiplying the arterial cross-sectional area (πr^2) by the Doppler flow velocity. The arterial diameter was measured at a fixed distance from an anatomical marker, such as a bifurcation, with ultrasonic calipers. One cardiac cycle was analyzed for each scan at three different sites and the measurements were averaged. Measurements were taken from the anterior to the posterior “m” line in diastole. The brachial artery was imaged at a location 3–7 cm above the antecubital crease. The placement of the transducer was marked to assure that pre- and post-prandial measurements were taken from the same vascular segment.

Images were obtained in a longitudinal view with optimizing attempts, using depth and gain, to locate maximal vessel diameter and to delineate the blood vessel walls optimally. The transmit (focus) zone was set to the depth of the near wall because of difficulty in differentiating the near from the far wall “m” line (the interface between media and adventitia).⁸ Images were recorded on videotape for evaluation and analysis subsequent to the examination. Measures of vessel diameter and flow velocity were generated by a dedicated vascular ultrasonographer blinded to subject treatment status. Velocity measures were generated automatically, while diameter measures were obtained by videotape review. A random collection of 30 scans was provided to the ultrasonographer for a blinded second reading. The resultant coefficient of intraobserver consistency was .95.

Flow was occluded by placing a blood pressure cuff on the forearm distal to the transducer and inflating it to 40 mm Hg above the systolic blood pressure. The cuff remained inflated for 5 minutes. Repeat scans were obtained 30 seconds before cuff deflation, and 15, 30, 45, 60, 90, 120, 150, and 180 seconds postdeflation. At each scanning interval, both cross-sectional vessel diameter and flow velocity were recorded.

Data Analysis

All data were entered and stored by a dedicated data manager using Microsoft Excel 97. Data were manually checked for entry errors; comparison to intake forms was performed to ensure accuracy. Three key measures of flow and diameter were used for the analysis: (1) peak flow and diameter after cuff deflation within the first minute of the scan, (2) flow and diameter at 1 minute after cuff deflation, and (3) average flow and diameter over 1 minute following cuff deflation (calculated by taking the average of the readings at 15, 30, 45, and 60 seconds post-cuff deflation).

SAS (version 6.12) was used to perform all statistical analyses; data were imported to SAS from Excel. The three preprandial scan results for each subject were averaged to provide a stable measure of baseline endothelial function.

Two-way, repeated-measures ANOVA tests were performed on the data with treatment and time as the main effects to compare flow-mediated dilation and brachial artery hyperemic flow after each of the three high-fat meals plus treatments while accounting for time differences (pre- and post-prandial periods). Paired *t*-tests were performed to compare pre- and post-prandial vascular responses within treatments. Within-treatment effects were calculated as the magnitude of the hyperemic response, and the difference between the postprandial response and preprandial, or baseline, response. A Cochran Mantel–Haenszel test was used to assess the proportion of subjects with positive or constant hyperemic flow versus negative hyperemic flow across treatments. The association of baseline characteristics (body mass index, total cholesterol levels, total plasma homocysteine levels, age, gender, HDL-cholesterol levels, systolic blood pressure and diastolic blood pressure) with endothelial function were assessed with partial correlations. A two-tailed *p* value of <0.05 was considered significant.

Results

Subjects ranged in age from 35 to 76, with a mean age of 56. Demographic and baseline data are provided in Table 2. One female subject dropped out before her

Table 3. Hyperemic flow change before and after a high-fat meal with oats, wheat, or vitamin E

Flow measurement (mL/min)	Pre-prandial	Post-prandial	Post- and pre-prandial phase hyperemic flow difference		
			Difference ^a (% change) ^b	95% CI	SD
Hyperemic flow using:					
Oats + high-fat meal			—	—	—
Baseline	19.12±8.03 ^c	19.27±8.00	—	—	—
Peak flow (<i>n</i> =49) ^d	12.56±11.20	12.64±10.34	+0.44 (0.37%)	(-2.62, 3.50)	+/-10.65
Flow at 60s (<i>n</i> =49)	2.62±4.90	3.40±5.10	-0.23 (-1.27%)	(-1.75, 1.29)	+/-5.29
Avg. flow over 60s (<i>n</i> =49)	5.89±5.49	6.37±5.85	-0.02 (-1.31%)	(-1.75, 1.71)	+/-6.02
Hyperemic flow using:					
Wheat + high-fat meal			—	—	—
Baseline	17.95±11.00	19.25±9.44	—	—	—
Peak flow (<i>n</i> =49)	11.00±7.62	9.45±7.41	-2.76 (-13.44%) ^f	(-5.08, -0.44)	+/-8.08
Flow at 60s (<i>n</i> =49)	4.38±5.09	2.81±5.34 ^e	-0.79 (-3.52%)	(-2.25, 0.67)	+/-5.09
Avg. flow over 60s (<i>n</i> =48)	6.36±5.25	4.95±5.55	-1.44 (-7.14%)	(-3.06, 0.19)	+/-5.60
Hyperemic flow using:					
α-tocopherol + high-fat meal			—	—	—
Baseline	17.51±7.19	19.72±9.43	—	—	—
Peak flow (<i>n</i> =48)	13.15±6.77	13.70±13.02	+1.47 (1.87%)	(-2.18, 5.11)	+/-12.56
Flow at 60s (<i>n</i> =47)	3.94±4.40	3.89±7.23	+0.36 (0.44%)	(-1.52, 2.24)	+/-6.41
Avg. flow over 60s (<i>n</i> =47)	6.97±4.67	7.15±8.45	+0.92 (2.20%)	(-1.32, 3.16)	+/-7.61

^aPostprandial (hyperemic flow in absolute terms) – preprandial (hyperemic flow in absolute terms).

Postprandial (% hyperemic flow) – preprandial (% hyperemic flow).

^cMean hyperemic flow in absolute terms ± SD.

^dData are missing for some measurements due to subject dropout and the inability to detect brachial artery flow at certain time points for some subjects during brachial artery scanning.

^e*p* < 0.05 compared to high-fat meal with oats.

^f*p* < 0.05 compared to preprandial phase hyperemic flow.

third scan, but the subject's available brachial artery reactivity data were included in the final analysis.

As illustrated in Table 3, there was a difference in postprandial hyperemic flow at 60 sec between the oat and wheat supplements (*p*<0.05). There were no differences in postprandial hyperemic flow between oats and vitamin E or between wheat and vitamin E. Within-treatment comparisons indicated that hyperemic flow decreased after a high-fat meal with wheat cereal compared to baseline (absolute difference, -2.76 [% change, -13.44%], *p*<0.02). There was no difference in hyperemic flow before and after a high-fat meal accompanied by oats or vitamin E. No differences were detected in brachial artery vasodilation among the three high-fat meals with treatments (Table 4).

The absolute differences in brachial artery vasodilation and hyperemic flow did not differ by gender. A ratio measure of brachial artery vasodilation over hyperemic flow did not reveal any differences among the high-fat meals plus treatments. An analysis of the proportion of subjects with positive or constant hyperemic flow versus negative hyperemic flow across treatments revealed that positive or no change in hyperemic flow occurred in 49% of subjects with vitamin E, 38% of subjects with oats, and 34% of subjects with wheat; these proportions did not differ statistically. Partial correlations indicated that baseline variables (BMI, total cholesterol, total plasma homocysteine level, age, gender, HDL cholesterol, systolic blood pressure, and diastolic blood pressure) were not associated with the observed endothelial responses.

Discussion

This is the first report of the effects of cereal grains on endothelial function, as well as replication of previously reported findings with vitamin E.¹² The results suggest that whole oats and vitamin E oppose the endothelial dysfunction induced by acute fat ingestion. The wheat cereal used as a placebo had no apparent effect on the previously reported endothelial dysfunction seen after acute fat ingestion in healthy subjects.

Endothelial dysfunction is thought to result from either depletion of endothelial-derived nitric oxide, or interference with its actions.²⁷ Postprandial conditions conducive to endothelial dysfunction include insulin release,¹¹ the generation of triglyceride-rich lipoprotein particles,²⁸ and the generation of oxygen-free radicals.²⁹ The role of oxidation has been considered particularly important, and both fat- and water-soluble antioxidants have demonstrated beneficial effects.^{12,30}

Dietary fiber has been associated with decreased risk of coronary disease,^{21–23,31} and soluble fiber, specifically, has been reported to decrease coronary heart disease risk through effects on total and LDL cholesterol.^{32–35} Properties of soluble fiber support the hypothesis that it should improve postprandial endothelial responses. Soluble fiber attenuates postprandial elevations in both glucose and insulin, as well as triglycerides, especially in diabetics.^{21,31,36} The effects of β-glucan in oats on endothelial function reported here are consistent with this body of literature.

While the effects of oats on endothelial function may

Table 4. Flow-mediated vasodilation before and after a high-fat meal with oats, wheat, or vitamin E

Diameter measurement (cm)	Pre-prandial	Post-prandial	Post- and pre-prandial phase diameter difference		
			Difference ^a (% change) ^b	95% confidence interval	SD
Flow-mediated vasodilation using: Oats + high-fat meal					
Baseline	0.477±0.084 ^c	0.465±0.092	—	—	—
Peak diameter (<i>n</i> =49) ^d	0.480±0.087	0.476±0.092	+0.005 (1.10%)	(-0.005, 0.014)	+/-0.03
Diameter at 60s (<i>n</i> =49)	0.476±0.087	0.475±0.093	+0.009 (1.93%)	(-0.001, 0.018)	+/-0.033
Avg. diameter over 60s (<i>n</i> =49)	0.472±0.088	0.469±0.091	+0.005 (1.20%)	(-0.003, 0.014)	+/-0.029
Flow-mediated vasodilation using: Wheat + high-fat meal					
Baseline	0.469±0.111	0.470±0.107	—	—	—
Peak diameter (<i>n</i> =49)	0.474±0.107	0.481±0.104	+0.003 (0.83%)	(-0.001, 0.008)	+/-0.016
Diameter at 60s (<i>n</i> =49)	0.467±0.105	0.474±0.102	+0.002 (0.66%)	(-0.004, 0.009)	+/-0.026
Avg. diameter over 60s (<i>n</i> =48)	0.462±0.108	0.468±0.103	+0.001 (0.30%)	(-0.004, 0.006)	+/-0.02
Flow-mediated vasodilation using: α-tocopherol + high-fat meal					
Baseline	0.476±0.093	0.472±0.088	—	—	—
Peak diameter (<i>n</i> =48)	0.480±0.092	0.481±0.087	+0.006 (1.25%)	(-0.000, 0.012)	+/-0.02
Diameter at 60s (<i>n</i> =47)	0.475±0.091	0.473±0.092	+0.004 (0.54%)	(-0.002, 0.009)	+/-0.02
Avg. diameter over 60s (<i>n</i> =47)	0.473±0.092	0.470 ± 0.089	+0.003 (0.61%)	(-0.002, 0.009)	+/-0.02

^aPostprandial (flow-mediated vasodilation in absolute terms) – preprandial (flow-mediated vasodilation in absolute terms).

^bPostprandial (% flow-mediated vasodilation) – preprandial (% flow-mediated vasodilation).

^cMean flow-mediated vasodilation in absolute terms ± SD.

^dData are missing for some measurements due to subject dropout and the inability to detect flow-mediated vasodilation at certain time points for some subjects during brachial artery scanning.

be solely attributable to the β-glucan content, phytoestrogens and fat-soluble antioxidants found in oats constitute another possible explanation for our results. Both estrogen³⁷ and antioxidants^{12,30} have been shown to improve endothelial function. Wheat also contains a weak phytoestrogen, enterolactone^{38–40} and fat-soluble antioxidants.^{40,38} In this trial, oats and vitamin E were administered separately so that previously reported findings with vitamin E could be replicated, providing an index by which to gauge the effects of oats. In a trial now beginning, we will use a factorial design, administering oats and vitamin E both separately and in combination, to determine if their benefits overlap, or are additive.

Measures of endothelial function in resistance vessels such as the brachial artery include both flow and diameter changes.²⁸ While we were able to demonstrate a significant treatment effect with regard to flow, differences in diameter did not reach significance. Several technical limitations of the study likely account for this. Two recent studies^{4,25} reported greater changes in brachial artery diameter when the occlusive cuff is placed around the upper arm rather than the forearm. For technical ease, and consistent with previous investigations,^{41,42} we placed the cuff around the forearm. In addition, greater image clarity is achieved with higher resolution vascular probes than the model used in this

study. Greater image resolution increases the capacity to measure diameter change.

Finally, the temporal correspondence between diameter measures and the cardiac cycle in our study differs from that used by other labs, due to our efforts to obtain sequential measures of both diameter and flow. This protocol enhanced our ability to track changes in flow, but limited our ability to measure diameter changes. The magnitude of treatment effects was further reduced by conducting this initial study in healthy subjects without appreciable risk factors for vascular disease. Finally, the wheat cereal used may have been an imperfect placebo, as it has a soluble fiber content approximately half that of the oat cereal.

Consistent with previous studies,^{11,28} we have shown that acute fat ingestion compromises endothelial function in healthy adults. Presumably, this effect is at least as great in higher-risk populations, although this remains to be shown. If so, there may be patient populations, such as those with hyperlipidemia or diabetes, in whom postprandial endothelial dysfunction is of clinical importance. In this context, the confirmation of benefits of vitamin E, and demonstration of benefits with oats, provide preliminary evidence that acute cardiac risk may be raised or lowered by acute nutrient effects, and the composition of individual meals.

Uncertain at this time are the effects of sustained dietary supplements on endothelial function. In contrast to the acute effects reported here and previously, Simon et al.⁴³ recently reported no effects of 10 weeks of supplementation with vitamin E in healthy subjects. Also of interest, and presently unknown, are the effects of habitual diet on endothelial function, and the effects of nutrients on endothelial function in high-risk groups.

In conclusion, the degradation of endothelial function seen in healthy adults following acute fat ingestion is apparently mitigated by concomitant ingestion of vitamin E or oats. The true clinical significance of these findings awaits further study.

We gratefully acknowledge the clerical assistance of Jennifer Ballard, and the support of Anastasia Timpko and the staff of the Griffin Hospital Resource Center/Library. Funding for this study was provided by the Quaker Oats Company, which also provided the cereals used in this study.

References

- Luscher T, Barton M. Biology of the endothelium. *Clin Cardiol* 1997;20:3-10.
- Rubanyi G, Romero D, Vanhouette P. Flow-induced release of endothelium-derived relaxing factor. *Am J Physiol* 1986;250:1115-9.
- Hutcheson I, Griffith T. Central role of intracellular calcium stores in acute flow- and agonist-evoked endothelial nitric oxide release. *Br J Pharmacol* 1997;122:117-25.
- Corretti M, Plotnick G, Vogel R. Technical aspects of evaluating brachial artery vasodilatation using high frequency ultrasound. *Am J Physiol* 1995;268:1397-404.
- Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;101:1899-906.
- Neunteufl T, Katzschlager R, Hassan A, et al. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. *Atherosclerosis* 1997;129:111-8.
- Celermajer D, Adams M, Clarkson P, et al. Passive smoking and impaired endothelium-dependent arterial dilation in healthy young adults. *New Eng J Med* 1996;334:150-4.
- Celermajer DS, Sorensen SK, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;340:1111-5.
- Panza J, Quyyumi A, Brush JE Jr, Epstein S. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *New Eng J Med* 1990;323:22-7.
- Creager MA, Cook JP, Mendelsohn ME, et al. Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. *J Clin Invest* 1990;86:228-34.
- McVeigh G, Brennan G, Johnston G, et al. Impaired endothelium-dependent and independent vasodilation in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1992;35:771-6.
- Plotnick GD, Corretti M, Vogel RA. Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal. *JAMA* 1997;278:1682-6.
- O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-coenzyme and reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997;95:1126-31.
- Treasure CB, Klein JL, Weintraub WS, et al. Beneficial effects of cholesterol-lowering therapy on the endothelium in patients with coronary artery disease. *New Eng J Med* 1995;332:481-7.
- Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *New Eng J Med* 1995;332:488-93.
- Kuo P, Joyner C. Angina pectoris induced by fat ingestion in patients with coronary artery disease. *JAMA* 1955;158:1008-13.
- Cohn J. Postprandial lipemia: emerging evidence for atherogenicity of remnant lipoproteins. *Can J Cardiol* 1998;14(suppl B):18B-27B.
- Ulbricht T, Southgate D. Coronary heart disease: seven dietary factors. *Lancet* 1991;338:985-92.
- Quinn M, Parthasarathy S, Fong L, Steinberg D. Oxidatively modified low-density lipoproteins: a potential role in recruitment and retention of monocyte/macrophages during atherogenesis. *Proc Natl Acad USA* 1987;84:2995-8.
- Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study investigators. *N Engl J Med* 2000;342:154-60.
- Rimm E, Ascherio A, Giovannucci E, Spiegelman D, Stampfer M, Willett W. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* 1996;275:447-51.
- Pietinen P, Rimm E, Korhonen P, et al. Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation* 1996;94:2720-7.
- Wolk A, Manson J, Stampfer M, et al. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA* 1999;281:1998-2004.
- Tangney C, Hafner J, McQuiston B, Domas A, Rosenson R. Postprandial changes in plasma and serum viscosity and plasma lipids and lipoproteins after an acute test meal. *Am J Clin Nutr* 1997;65:36-40.
- Mannion T, Vita J Jr, Keaney JF, Jr, Benjamin E, Hunter L, Polak J. Non-invasive assessment of brachial artery endothelial vasomotor function: the effect of cuff position on level of discomfort and vasomotor responses. *Vasc Med* 1998;3:263-7.
- Sorensen KE, Celermajer DS, Spiegelhalter KJ, et al. Non-invasive measurement of human endothelium-dependent arterial responses: accuracy and reproducibility. *Br Heart J* 1995;74:247-53.
- Joannides R, Haefeli W, Linder L, et al. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. *Circulation* 1995;91:1314-9.
- Vogel R, Corretti M, Plotnick G. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol* 1997;79:350-4.
- Celermajer D. Endothelial dysfunction: does it matter? Is it reversible? *J Am Coll Cardiol* 1997;30:325-33.
- Gokce N Jr, Gokce N, Keaney JF Jr, et al. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1999;99:3234-40.
- Farrell P. Vitamin E. In: Shils ME, Young VR, eds. *Modern nutrition in health and disease*, 7th ed. Philadelphia, PA: Lea and Febiger, 1988:340-53.
- Brown L, Rosner B, Willett W, Sacks F. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr* 1999;69(1):30-42.
- Glore S, Treeck DV, Knehans A, et al. Soluble fiber and serum lipids: a literature review. *J Am Diet Assoc* 1994;94:425-36.
- Sprecher D, Harris B, Goldberg A, et al. Efficacy of psyllium in reducing serum cholesterol levels in hypercholesterolemic patients on high- or low-fat diets. *Ann Int Med* 1993;119:545-54.
- Jenkins D, Wolever T, Rao A, et al. Effect on blood lipids of very high intakes of fiber in diets low in saturated fat and cholesterol. *N Eng J Med* 1993;329:21-6.
- Guevin N, Jacques H, Nadeau A, Galibois I. Postprandial glucose, insulin, and lipid responses to four meals containing unpurified dietary fiber in non-insulin-dependent diabetes mellitus (NIDDM), hypertriglyceridemic subjects. *J Am Coll Nutr* 1996;15:389-96.
- Gilligan D, Badar D, Panza J, Quyyumi AA, Cannon RO III. Acute vascular effects of estrogen in postmenopausal women. *Circulation* 1994;90:786-91.
- Murkies A, Lombard C, Strauss B, Wilcox G, Burger H, Morton M. Dietary flour supplementation decreases post-menopausal hot flashes: effect of soy and wheat. *Maturitas* 1995;21:189-95.
- Shoff S, Newcomb P, Mares-Perlman J, et al. Usual consumption of plant foods containing phytoestrogens and sex hormone levels in postmenopausal women in Wisconsin. *Nutr Cancer* 1998;30:207-12.
- Thompson L. Antioxidants and hormone-mediated health benefits of whole grains. *Crit Rev Food Sci Nutr* 1994;34:473-97.
- Lieberman E, Gerhard M, Uehata A. Estrogen improves endothelium-dependent, flow-mediated vasodilatation in postmenopausal women. *Ann Intern Med* 1994;121:936-41.
- Celermajer D, Sorensen K, Georgakopoulos D. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilatation in healthy young adults. *Circulation* 1993;Nov:88.
- Simons L, Konigsmark MV, Simons J, Stocker R, Celermajer D. Vitamin E ingestion does not improve arterial endothelial dysfunction in older adults. *Atherosclerosis* 1999;143:193-9.