Fish Oil Improves Arterial Compliance in Non-Insulin-Dependent Diabetes Mellitus

Gary E. McVeigh, Geraldine M. Brennan, Jay N. Cohn, Stanley M. Finkelstein, Randal J. Hayes, George D. Johnston

Abstract
In a double-blind, placebo-controlled study we investigated the effects of dietary fish oil supplementation on arterial wall characteristics in 20 patients with non-insulin-dependent diabetes mellitus. Estimates reflecting compliance values in the large arteries and more peripheral vasculature, as measured by pulse-contour analysis, improved significantly after 6 weeks of fish oil therapy compared with values recorded at baseline and after 6 weeks' administration of olive oil. The large-artery compliance estimate increased from 1.50 (confidence interval [CI], 1.31 to 1.69) mL/mm Hg at baseline to 1.68 (CI, 1.52 to 1.84) mL/mm Hg after fish oil administration (P<.01). The oscillatory compliance value increased from 0.015 (CI, 0.011 to 0.019) mL/mm Hg at baseline to 0.022 (CI, 0.016 to 0.028) mL/mm Hg after fish oil ingestion (P<.05). No changes occurred in arterial blood pressure, cardiac output, stroke volume, or systemic vascular resistance with either intervention. The improved compliance estimates with fish oil ingestion occurred without altering fasting blood glucose and cholesterol concentrations. These results support the hypothesis that fish oils alter vascular reactivity and favorably influence arterial wall characteristics in patients with non-insulin-dependent diabetes mellitus. These direct vascular effects, expressed at the level of the vessel wall, may contribute to the cardioprotective actions of fish oil in humans. (Arterioscler Thromb. 1994;14:1425-1429.)

Key Words • fish oil • compliance • resistance • hemodynamics

The metabolic abnormalities associated with diabetes mellitus produce structural and functional changes in the arterial vasculature that account for the increased cardiovascular morbidity found in diabetic subjects. The accelerated atherosclerotic vascular disease in large arteries has been partially attributed to the excess of conventional cardiovascular risk factors in the diabetic population. The development of microangiopathy involves concentric hyaline thickening of arteriolar walls, capillary basement membrane thickening, nonenzymatic glycosylation of tissue proteins, and abnormalities of the endothelial cells.

Diet rich in fish oils appear to be associated with a low incidence of atherosclerosis and acute thrombotic complications due to atherosclerosis. Because fish oils favorably influence many of the mechanisms involved in atherogenesis, they are attractive candidates for therapy in diabetic subjects. Recent evidence also supports a role for a direct action of fish oils on the microvasculature in diabetes that may delay complications attributable to microvascular disease.

The widespread changes in arterial wall properties that occur with diabetes modify the ventricular-vascular interaction and alter the shape of the pressure-pulse contour. Changes in waveform morphology that occur with disease and with pharmacologic interventions can be quantified by pulse-contour analysis and reflect alterations in the compliance characteristics of the arterial system. Such changes in arterial compliance may provide an index of early vascular damage that predisposes affected individuals to the development of major vascular disease. Fish oil therapy can influence vascular tone and reactivity and alter the functional properties of the systemic circulation, and changes in vascular tone influence the compliance characteristics of the arterial blood vessels. We therefore investigated the effects of dietary fish oil administration on arterial compliance estimates in patients with non-insulin-dependent diabetes mellitus (NIDDM) by using the pulse-contour analysis technique.

Methods

Subjects
Sixteen male and four female patients with NIDDM were recruited from diabetic clinics in the Belfast area. The patients' ages ranged from 45 to 61 years, and diabetic control was achieved with diet alone or diet plus sulfonylurea, biguanide preparations, or both. The mean fasting blood glucose was 9.9 mmol/L (range, 5.4 to 15.7), and mean glycated hemoglobin was 9.7% (range, 6.3% to 12.9%). The known duration of diabetes was 5.2 years (range, 9 months to 16 years). Subjects were excluded if there was a history of cerebrovascular disease, ischemic heart disease, hypertension (blood pressure > 150/90 mm Hg), or significant renal impairment (creatinine clearance < 30 mL/min) or if they were taking cardiovascular drugs. No subjects took fish oil supplements before the study.

Patients entered a double-blind, placebo-controlled crossover study with randomized allocation of treatments consisting of three 6-week phases. During the first 6 weeks the patients randomly received either 10 capsules per day of fish oil
Compliance with the medication was assessed by capsule counts and by measurement of platelet membrane fatty acid composition by gas chromatography. Venous blood was drawn from each subject after a 30-minute supine rest during the baseline study and on completion of the active treatment phases for estimation of fasting glucose, platelet membrane fatty acids, total cholesterol, and total triglyceride concentrations. Samples for lipid profiles were collected in EDTA tubes and measured by ultracentrifugation. All participants gave written informed consent for all procedures. This study was approved by the Ethics Committee of the Queen’s University of Belfast.

Procedures

Investigations were performed between 8 and 9 AM in a quiet, temperature-controlled laboratory with the subjects lying supine. Participants fasted for 14 hours before the study, during which time alcohol, caffeine, and smoking were prohibited. Under local anesthesia (lidocaine 1%) and sterile conditions, a 20-gauge polyethylene catheter (Vygon Leader Cath) was inserted into the left brachial artery. The catheter was connected to a Bell and Howell pressure transducer with 24-inch fluid-filled pressure tubing. The transducer was aligned with an amplifier on an Electron Physics physiological recorder for the recording of arterial blood pressure. The catheter-transducer-amplifier system introduced minimal disturbance to the recorded signal. All subjects rested for 30 minutes after catheter placement to establish a stable baseline before data collection. Saline (0.9%) was infused into the brachial artery at a rate of 0.3 mL/min in the control period.

A commercial pulse-wave Doppler flow-meter system (Quantascope, Vital Science) based on the attenuated compensation volume-flow meter principle was used to measure cardiac output.18 The Quantascope uses a 2-MHz two-element annular-array transducer. The system automatically chooses the appropriate aperture settings (amplitude and phase), which allow wide and narrow ultrasound beams to be generated. The probe was positioned in the suprasternal notch of patients lying in the supine position to insonate the ascending aorta, and cardiac waveforms were averaged on a beat-to-beat basis. Cardiac output, stroke volume, and flow acceleration were computed from the averaged waveforms. Measurements of cardiac output were obtained immediately after vascular compliance recordings.

Beat Marking and Waveform Analysis

Brachial arterial waveforms were recorded for 30 seconds for each subject in the supine position. The pressure-transducer-amplifier system was connected directly to a specially designed board (kindly provided by Hypertension Diagnostics, Inc) placed in an IBM personal computer. The pulse-wave data were collected, digitized at 200 samples per second, and stored in computer memory. The data were automatically displayed on the computer screen for visual analysis to confirm that recorded waveforms were uniform and showed no artifacts. The most consistent (by visual inspection) 10 consecutive marked points was checked for accuracy of the beat-marking procedure. The passive, transient response of the arterial system to the stroke volume produced during systole, which occurs after aortic valve closure, is determined by analyzing the diastolic portion of the pressure-pulse waveform. Pulse-contour analysis segments the diastolic interval into an exponential decay curve that reflects the compliance characteristics predominantly of the larger arteries and an oscillatory dicrotic wave that results from peripheral pulse-wave reflections and a damped resonance occurring in the arterial tree. The first term in the third-order equation (A2e−A3t) fits to the exponential decay; the second term (A4e−A5t cos(A6t+A7)) represents a decaying sinusoid that fits to the oscillatory dicrotic wave.

FIG 1. The passive and transient response of the arterial system to the stroke volume produced during systole, which occurs after aortic valve closure, is determined by analyzing the diastolic portion of the pressure-pulse waveform. Pulse-contour analysis segments the diastolic interval into an exponential decay curve that reflects the compliance characteristics predominantly of the larger arteries and an oscillatory dicrotic wave that results from peripheral pulse-wave reflections and a damped resonance occurring in the arterial tree. The first term in the third-order equation (A2e−A3t) fits to the exponential decay; the second term (A4e−A5t cos(A6t+A7)) represents a decaying sinusoid that fits to the oscillatory dicrotic wave.

Statistical Analysis

ANOVA was used to compare changes from baseline in hemodynamic impedance parameters and metabolic variables for each treatment and to compare differences between treatment results. Results are expressed as means with a 95% confidence interval (CI).

Results

Adherence to the prescribed regimens was confirmed by capsule counts and by measurement of platelet membrane fatty acid composition. Incorporation of eicosapentaenoic acid and docosahexaenoic acid into platelet membranes occurred at the expense of arachidonic acid (Fig 2). Assessment of platelet lipid fractions showed an increase in the percent membrane constituent of eicosapentaenoic acid after fish oil administration (2.9; CI, 2.2 to 3.6) compared with values recorded at baseline (1.2; CI, 0.2 to 2.2) and after olive oil administration (1.1; CI, 0.8 to 1.4) (P<.001 for both). The membrane percentage constituent of docosahexaenoic acid also increased significantly after fish oil administration.

Neither intervention significantly altered heart rate, arterial blood pressure, cardiac output, or stroke volume compared with baseline values (Table 1). Metabolic parameters are outlined in Table 2. Compared with baseline values, fish oil ingestion increased fasting glucose levels from 10.2 (CI, 8.9 to 11.4) to 11.4 (CI, 9.7 to 12.6).
to 13.3) mmol/L (P=.07). Baseline levels of total cholesterol (5.3 [CI, 4.9 to 5.7] mmol/L) were unchanged by either intervention. A reduction in fasting triglyceride values occurred with fish oil ingestion compared with baseline values (1.8 [CI, 1.4 to 2.2] versus 1.4 [CI, 1.1 to 1.8] mmol/L; P=.08).

No differences were recorded in the model parameters reflecting the steepness of the exponential decay (A2) and damping of the diastolic oscillation (A4) when baseline values were compared with those recorded after olive oil administration. In contrast, fish oil ingestion significantly decreased values for A2 and A4 compared with estimates obtained at baseline and after olive oil administration. This was reflected in the improved large-artery (C2) and oscillatory (C4) compliance estimates (Table 3). C2 increased from 1.50 (CI, 1.31 to 1.69) mL/mm Hg at baseline and 1.52 (CI, 1.35 to 1.69) mL/mm Hg after olive oil administration to 1.68 (CI, 1.52 to 1.84) mL/mm Hg after fish oil administration (P<.01). C4 increased from 0.015 (CI, 0.011 to 0.019) mL/mm Hg at baseline to 0.022 (CI, 0.016 to 0.028) mL/mm Hg after fish oil ingestion (P<.05). The increase in C4 after fish oil administration compared with values recorded after olive oil ingestion were nonsignificant (P=.08). No changes occurred in systemic vascular resistance values during the study.

### Discussion

The cardioprotective actions of fish oil have largely been attributed to its antiplatelet activity and effects on lipoprotein metabolism. The direct vascular actions of fish oils expressed at the level of the vessel wall after incorporation into the phospholipids of cell membranes may also contribute to their vascular protective effects. Dietary supplementation with fish oil improved the large-artery and oscillatory compliance estimates compared with responses recorded at baseline and after olive oil administration in patients with NIDDM. In contrast, neither intervention influenced the systemic vascular resistance compared with baseline values.

The diastolic pulse contour is composed of an exponential decay and a superimposed oscillatory dicrotic wave found in the proximal portion of the waveform. The pulse-contour analysis technique segments diastole into two components, identifying the exponential decay as a function of large-artery compliance and the dicrotic wave as a measure of oscillations in the arterial system that reflect altered compliance characteristics of the more peripheral vasculature. From the earliest measurements of accurate arterial pressure waveforms, the presence of diastolic fluctuations were believed to represent the effects of peripheral wave reflections producing a form of damped resonance superimposed on the basic shape of the pressure waveform. Pressure-pulse waveform reflections arise primarily from discontinuities in the caliber of or elastic properties along vessels in the arterial system, with the major reflections residing in the high-resistance arterioles. Studies in populations from Japan that used pulse-wave velocity as a measure of arterial stiffness in large-artery segments have shown that subjects who regularly consumed fish had a lower pulse-wave velocity and more distensible vasculature than subjects whose diets were virtually devoid of fish. Improved arterial wall characteristics have also been described in fish-

### Table 1. Hemodynamic Variables at Baseline and After 6 Weeks of Olive Oil and Fish Oil Ingestion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (Systolic BP, mm Hg)</th>
<th>Olive Oil (Systolic BP, mm Hg)</th>
<th>Fish Oil (Systolic BP, mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>108 (100-116)</td>
<td>107 (100-117)</td>
<td>103 (96-110)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>71 (67-75)</td>
<td>70 (66-74)</td>
<td>68 (65-71)</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>83 (78-88)</td>
<td>82 (76-88)</td>
<td>79 (75-83)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71 (60-82)</td>
<td>71 (61-81)</td>
<td>70 (60-80)</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6.0 (5.2-6.8)</td>
<td>5.9 (5.2-6.6)</td>
<td>5.9 (5.3-6.5)</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>92 (85-99)</td>
<td>89 (80-98)</td>
<td>91 (84-98)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values expressed are mean (95% confidence interval). P=NS for all comparisons.

### Table 2. Metabolic Parameters at Baseline and After 6 Weeks of Olive Oil and Fish Oil Ingestion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Olive Oil</th>
<th>Fish Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>10.2 (8.9-11.4)</td>
<td>11.0 (9.3-12.7)</td>
<td>11.4 (9.7-13.3)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.3 (4.9-5.7)</td>
<td>5.3 (4.9-5.7)</td>
<td>5.3 (4.9-5.7)</td>
</tr>
<tr>
<td>Total triglycerides</td>
<td>1.8 (1.4-2.2)</td>
<td>1.6 (1.4-1.9)</td>
<td>1.4 (1.1-1.8)</td>
</tr>
</tbody>
</table>

Values are given as millimoles per liter and are mean (95% confidence interval). There were no significant differences.
eating compared with non–fish-eating patients with NIDDM. Fish consumption may favorably improve arterial stiffness by retarding the progression of atherosclerosis. However, atherosclerosis is a patchy disease and probably plays a relatively minor role in decreasing arterial compliance, which suggests that direct vascular actions of polyunsaturated fatty acids may be of greater importance in influencing arterial wall characteristics.

Fish oils may influence vascular reactivity through effects on the endothelium, by altering the production of substances by other cells that affect endothelial cell function or by directly altering the activity of the smooth muscle cell. Dietary marine oil supplementation suppresses forearm vasoconstrictor responses to the local infusion of angiotensin II and norepinephrine, and fish oil supplementation in patients with NIDDM augments stimulated and basal release of nitric oxide from the vascular endothelium.

In experimental models of atherosclerosis and hypertension, fish oil therapy improves endothelium-dependent relaxation in large arteries. Simon et al report that administration of the exogenous nitric oxide donor nitroglycerin alters vascular tone and improves arterial compliance without significantly lowering the mean arterial pressure. Coupled with the known effects of fish oils on prostaglandin metabolism, these data suggest that polyunsaturated fatty acids exert direct vascular actions that influence arterial function by altering the production, release, or breakdown of vasoactive substances from blood vessel walls. Such actions probably account for the improved compliance characteristics observed in this study, as the short-term prescription of fish oils would be unlikely to influence the structural properties of the arterial vasculature. Although a trend for a decrease in plasma triglyceride levels was apparent, the improved compliance estimates occurred without significantly altering cholesterol or triglyceride concentrations, suggesting that possible vascular protective actions of fish oils may be dissociated from their effects on lipid metabolism.

A major problem in assessing the direct effects of pharmacological agents on arterial compliance has been that the administration of vasoactive drugs often alters blood pressure in addition to influencing vascular tone and reactivity. This alteration in blood pressure makes it difficult to know whether a change in compliance in response to vasoactive compounds directly reflects an alteration in vessel wall properties or occurs as a consequence of the change in blood pressure. In this study, fish oil administration improved the compliance characteristics of the arterial vasculature independent of effects on cardiac output and resistance to blood flow. That changes in arterial compliance with fish oil ingestion occurred without alteration in systemic resistance supports the observations of others in diabetic patients and suggests that the ability of a vessel to respond to a pressure load is more sensitive than its basal caliber in identifying abnormal structure and tone. Pulse-contour analysis could therefore prove to be a useful technique to follow disease progression in patients and monitor the effects of drug interventions on the arterial vasculature, especially as technological advances now permit the recording of high-quality waveforms noninvasively.

In conclusion, short-term dietary supplementation with fish oils improved the compliance characteristics of the arterial circulation in patients with NIDDM. Improving arterial wall characteristics may represent an additional mechanism whereby fish oils exert their cardioprotective action in humans.

Acknowledgments

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References

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