Effects of Dietary Fish and Weight Reduction on Ambulatory Blood Pressure in Overweight Hypertensives

Danny Q. Bao, Trevor A. Mori, Valerie Burke, Ian B. Puddey, Lawrence J. Beilin

Abstract—Obesity is a major factor contributing to hypertension and increased risk of cardiovascular disease. Regular consumption of dietary fish and ω3 fatty acids of marine origin can lower blood pressure (BP) levels and reduce cardiovascular risk. This study examined the potential effects of combining dietary fish rich in ω3 fatty acids with a weight loss regimen in overweight hypertensive subjects, with ambulatory BP levels as the primary end point. Using a factorial design, 69 overweight medication-treated hypertensives were randomized to a daily fish meal (3.65 g ω3 fatty acids), weight reduction, the 2 regimens combined, or a control regimen for 16 weeks. Sixty-three subjects with a mean±SEM body mass index of 31.6±0.5 kg/m² completed the study. Weight fell by 5.6±0.8 kg with energy restriction. Dietary fish and weight loss had significant independent and additive effects on 24-hour ambulatory BP. Effects were greatest on awake systolic and diastolic BP (P<0.01); relative to control, awake pressures fell 6.0/3.0 mm Hg with dietary fish alone, 5.5/2.2 mm Hg with weight reduction alone, and 13.0/9.3 mm Hg with fish and weight loss combined. These results also remained significant after further adjustment for changes in urinary sodium, potassium, or the sodium/potassium ratio, as well as dietary macronutrients. Dietary fish also significantly reduced 24-hour (-3.1±1.4 bpm, P=0.036) and awake (-4.2±1.6 bpm, P=0.013) ambulatory heart rates. Weight reduction had a significant effect on sleeping heart rate only (-3.2±1.7 bpm, P=0.037). Combining a daily fish meal with a weight-reducing regimen led to additive effects on ambulatory BP and decreased heart rate. The effects were large, suggesting that cardiovascular risk and antihypertensive drug requirements are likely to be reduced substantially by combining dietary fish meals rich in ω3 fatty acids with weight-loss regimens in overweight medication-treated hypertensives. The reduction in heart rate seen with dietary fish suggests a cardio/autonomic component, as well as vascular effects, of increased consumption of ω3 fatty acid from fish. (Hypertension. 1998;32:710-717.)

Key Words: fish ■ ω3 fatty acids ■ weight control ■ blood pressure ■ obesity

Several randomized controlled trials have shown that fish oils may lower blood pressure (BP),1–4 although the effects have been most clear-cut in hypertensive subjects treated with relatively large doses of ω3 fatty acids.5–8 On the other hand, population studies suggest that regular consumption of even small amounts of fish may reduce the risk of coronary heart disease,9 an effect presumed to be due to actions of ω3 fatty acids on a variety of mechanisms underlying atherosclerosis.10 Obesity is a major factor contributing to hypertension, and weight loss reduces BP in overweight hypertensives.9 In addition, hypertension and obesity are both associated with impaired endothelial function.10,11 Because ω3 fatty acids improve endothelial dilator function and vascular reactivity,12,13 we hypothesized that combining weight reduction with daily fish meals rich in ω3 fatty acids would have additive effects on BP reduction. To investigate this hypothesis, we conducted a randomized controlled trial of the independent and combined effects of dietary fish intake and energy restriction on ambulatory BP levels in treated overweight hypertensives.

Study Population
Overweight nonsmoking men and postmenopausal women, aged 40 to 70 years, taking antihypertensive medication for at least 3 months were recruited from the general community by media advertising. Entry criteria included body mass index (BMI) >25 kg/m², clinic systolic blood pressure (SBP) >125 mm Hg and <180 mm Hg, diastolic blood pressure (DBP) <110 mm Hg (measured on 2 separate days using a Dinamap 1846 SX/P monitor), no lipid-lowering or anti-inflammatory drugs, and a usual consumption of not more than 1 fish meal and 175 g of ethanol per week. Sixty-nine of the 248 subjects screened satisfied the entry criteria. The study was approved by the ethics committee of the Royal Perth Hospital, and all subjects gave written consent. All procedures followed were in accordance with institutional guidelines.

Dietary Education and Intervention
During a 4-week familiarization period, subjects continued their usual diet and alcohol intake and, after collection of baseline measurements, were randomly assigned to 1 of 4 groups stratified by gender, age, and BMI. Maintenance of usual lifestyle was encouraged during the 16 weeks of intervention. Subjects were first randomized either to maintain their weight or to a weight-loss group.
The latter was given an individual dietary program to reduce energy intake by 2000 to 6500 kJ/d, aiming to achieve a 5- to 8-kg weight loss during the first 12 weeks followed by a further 4 weeks during which weight was stabilized. Within each of these study arms, subjects were further randomized to include a daily fish meal (~3.65 g/d of ω3 fatty acids) as part of their diet or to continue on the energy-restricted or weight-maintaining diet alone. Twelve weeks after the commencement of diets, all subjects were put on a weight-stabilizing diet for 4 weeks and continued on fish if they were in those groups.

At an initial interview with a dietitian, subjects were given written and verbal instructions on how to keep diet records, with food weighed or measured. Dietary intake was monitored by the same dietitian throughout the study, with completion of a monthly 3-day diet record (2 weekdays and 1 weekend day). After review of the initial diet records, volunteers allocated to the energy-restricted diet were instructed to reduce their fat intake to <30% of total energy by substituting low-fat alternatives for typical high-fat foods, increasing fruits and vegetables, and substituting complex carbohydrates such as whole-grain bread and cereals for refined carbohydrates. Because sodium restriction has been shown to result in a greater reduction of BP by fish oil, subjects in all groups were advised to avoid added salt, minimize high-salt foods, and use reduced-salt products. Volunteers who were not randomized to the energy-restricted diets were seen at 2-week intervals by the dietitian, who ensured that usual eating habits were maintained, with the only change being salt reduction. These same subjects were offered a weight-loss program on completion of the study. Participants taking fish followed diets similar to one of our previous studies and were instructed to eat 1 fish meal daily. A selection of previously analyzed fish from the same batch was supplied free of cost. This included Greenland turbot fillets (~200 g), canned sardines (~106 g), tuna (~102 g), and salmon (~54 g), providing approximately 3.5, 4.1, 3.2, and 3.8 g/d of ω3 fatty acids, respectively. Menus included all varieties of fish and provided an intake of ~3.65 g/d of ω3 fatty acids.

### Urinary Analyses, Lifestyle Assessment, and Anthropometry
Levels of 24-hour urinary sodium, potassium, calcium, and creatinine were measured at baseline and at weeks 4, 8, 12, and 16 of the intervention. Alcohol intake and physical activity were monitored every second week during the dietary intervention using 7-day retrospective diaries. All other measurements were made at baseline and at the end of the intervention. Weight was measured using an electronic scale while the subject was without shoes and wearing light clothing, and height was measured with a stadiometer.

### Ambulatory Blood Pressure Monitoring
Ambulatory BP monitoring (ABPM) over 24 hours at baseline and at the end of intervention was performed with the Accutracker II (Suntech model 104) fitted by a trained nurse. The recorder was preset to record BP and heart rate every 30 minutes during waking hours and hourly during sleep. BP records were not visible to the subjects. Volunteers completed a diary indicating their activity at the time of the ambulatory BP reading. When the Accutracker detected an error in BP measurement, volunteers were instructed to rectify the error or return to the department to have the recorder corrected. After readjustment of the recorder, a BP reading was initiated to check correct functioning. Readings associated with a test code and those with a difference of <20 mm Hg between SBP and DBP were excluded from analysis. All subjects were advised to maintain their usual antihypertensive medication throughout the intervention, unless they showed symptoms or SBP <90 mm Hg.

### Plasma and Fish Fatty Acids
Total ω3 fatty acids measured in plasma phospholipids included 20:5, 22:5, and 22:6, and ω6 fatty acids included 20:3, 20:4, and 22:4. Fish fats were determined by similar methods in homogenized flesh drained of oil (sardines) or brine (tuna and salmon).

### Statistical Analysis
Diet records were analyzed using Diet/1 Version 4 (Xyris, Brisbane, Australia) based on the Australian Food Composition Database (NUTTAB 1995A). Data were analyzed using SPSS or SAS software with general linear models (GLM) to assess main and interactive effects of fish and reduced-fat, energy-restricted diets. Significance levels were adjusted for multiple comparisons by the Bonferroni method. Values are mean±SEM.

#### TABLE 1. Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n=16)</th>
<th>Fish Diet (n=17)</th>
<th>Weight Loss (n=16)</th>
<th>Fish+Weight Loss (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>11/5</td>
<td>13/4</td>
<td>10/6</td>
<td>8/6</td>
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<tr>
<td>Age, y</td>
<td>54.5±1.5</td>
<td>53.7±1.7</td>
<td>55.1±1.9</td>
<td>53.1±1.9</td>
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<tr>
<td>BMI, kg/m²</td>
<td>32.0±1.2</td>
<td>32.3±1.1</td>
<td>31.3±0.8</td>
<td>30.9±1.1</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.91±0.02</td>
<td>0.93±0.02</td>
<td>0.90±0.02</td>
<td>0.90±0.02</td>
</tr>
<tr>
<td>Supine SBP, mm Hg*</td>
<td>135.9±2.9</td>
<td>132.1±2.9</td>
<td>137.6±4.1</td>
<td>132.1±2.9</td>
</tr>
<tr>
<td>Supine DBP, mm Hg*</td>
<td>75.4±1.9</td>
<td>75.2±1.7</td>
<td>78.3±2.3</td>
<td>74.9±1.8</td>
</tr>
<tr>
<td>Antihypertensive medication, n</td>
<td>11</td>
<td>9</td>
<td>10</td>
<td>11</td>
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<tr>
<td>ACE inhibitors</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>ß-Blockers</td>
<td>4</td>
<td>4</td>
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<td>5</td>
</tr>
<tr>
<td>Ca²⁺ channel blockers</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM.

*Average of 10 readings on 2 separate days in the clinic using a Dinamap 1846 SX/P monitor.
Energy-restricted diets resulted in a weight loss of 5.6 kg during the intervention because of low BP. Usual BP medication was maintained except for 1 subject in the weight-loss group and 1 in the fish-diet and weight-loss groups, and 1 in the combined fish-diet and weight-loss group. Those who withdrew were unable to maintain the schedule of laboratory visits. Baseline characteristics of the 4 groups confirmed that they were well matched (Table 1). Usual BP medication was maintained except for 1 subject in the weight-loss group and 1 in the fish+weight-loss group in whom medication was halved during the intervention because of low BP.

### Study Population
Of the 69 subjects randomized, 63 completed the study. There were 2 withdrawals in the control group, 1 in each of the fish-diet and weight-loss groups, and 1 in the combined fish-diet and weight-loss group. Those who withdrew were unable to maintain the schedule of laboratory visits. Baseline characteristics of the 4 groups confirmed that they were well matched (Table 1). Usual BP medication was maintained except for 1 subject in the weight-loss group and 1 in the fish+weight-loss group in whom medication was halved during the intervention because of low BP.

### Energy and Macronutrient Intake
Energy-restricted diets resulted in a weight loss of 5.6±0.8 kg \((p<0.0001)\) during the first 12 weeks of the intervention, with no further weight loss during the final 4 weeks of weight stabilization (Table 2 and Figure 1). There was no significant change in weight in the 2 groups who continued their usual energy intake (0.2±0.3 kg) (Table 2). Alcohol drinking and physical activity were unchanged during the intervention in all groups. Evidence of adherence to the fish diet in the 2 groups concerned was obtained from diet records and confirmed from plasma phospholipid fatty acid composition. There were no differences in nutrient intake between the groups at baseline (Table 3). At completion of the study, the 2 weight-loss groups showed significantly lower intake of energy \((p=0.001)\); percentage total fat \((p=0.001)\), saturated fat \((p=0.001)\), and monounsaturated fat \((p=0.007)\); and dietary sodium \((p=0.001)\) and potassium \((p=0.022)\). There was also a significant main effect of weight loss related to higher intake of protein \((p=0.028)\) and carbohydrate \((p=0.043)\). The fish diet was associated with a significantly increased intake of protein \((p=0.005)\) and polyunsaturated fat \((p=0.001)\) as a percentage of energy intake.

### Urinary Electrolytes
There was a nonsignificant reduction in urinary sodium and potassium excretion in the weight-loss groups, commensurate with lower dietary intake (Table 2). The sodium/potassium ratio was unchanged.

### Ambulatory Blood Pressure
The mean values for SBP and DBP at baseline and after intervention during the 24 hours of ABPM for each group are shown in Figure 2. Mean 24-hour, awake, and asleep ABPM by treatment group are shown in Table 4. There were significant additive effects of the diets on BP, with the greatest effects on awake pressures. With mean BP during waking hours as the dependent variable, there were significant additive effects of dietary fish and of weight reduction on SBP (fish: \(-6.8±2.6\) mm Hg, \(p=0.006\); weight: \(-6.2±2.6\) mm Hg, \(p=0.012\) and DBP (fish: \(-5.1±1.7\) mm Hg, \(p=0.001\); weight: \(-4.2±1.7\) mm Hg, \(p=0.003\) in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=16)</th>
<th>Fish Diet (n=17)</th>
<th>Weight Loss (n=16)</th>
<th>Fish+Weight Loss (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>91.5±4.0</td>
<td>100.6±4.7</td>
<td>91.6±4.0</td>
<td>89.2±4.2</td>
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<tr>
<td>Postintervention</td>
<td>91.4±4.1</td>
<td>101.1±4.9</td>
<td>86.4±3.5</td>
<td>83.3±4.3</td>
</tr>
<tr>
<td>Urinary Na+, mmol/24-h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>186.4±18.4</td>
<td>176.9±12.9</td>
<td>179.8±17.1</td>
<td>173.7±20.3</td>
</tr>
<tr>
<td>Postintervention</td>
<td>193.3±30.9</td>
<td>161.6±15.5</td>
<td>148.5±18.8</td>
<td>132.1±18.2</td>
</tr>
<tr>
<td>Urinary K+, mmol/24-h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>76.7±5.6</td>
<td>90.5±8.1</td>
<td>93.6±5.8</td>
<td>87.3±6.7</td>
</tr>
<tr>
<td>Postintervention</td>
<td>74.1±6.3</td>
<td>89.4±9.3</td>
<td>76.7±4.9</td>
<td>69.4±5.6</td>
</tr>
<tr>
<td>Urinary Na+/K+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.6±0.3</td>
<td>2.1±0.2</td>
<td>1.9±0.2</td>
<td>2.1±0.3</td>
</tr>
<tr>
<td>Postintervention</td>
<td>2.9±0.7</td>
<td>2.0±0.2</td>
<td>1.9±0.2</td>
<td>2.0±0.2</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. Baseline measures were compared by 1-way ANOVA and were not significantly different.

*Using GLM analysis, there was a significant main effect for weight loss \((p<0.0001)\) on postintervention body weight. There were no significant main effects or interactions for postintervention urinary sodium and potassium excretion after adjustment for age and baseline value.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Changes in weight during the 16-week intervention in the 4 groups.
GLM after adjustment for age, baseline weight, and baseline BP. Compared with the control group, mean awake SBP/DBP was $6.0\pm2.2/3.0\pm1.4$ mm Hg lower in the fish group, $5.5\pm2.9/2.2\pm1.3$ mm Hg in the weight-reduction group, and $13.0\pm2.4/9.3\pm1.4$ mm Hg in the fish+weight-reduction group after adjustment for age, baseline weight, and baseline value. Weight reduction led to a significant fall in 24-hour mean SBP ($-6.1\pm2.6$ mm Hg, $P=0.012$) and DBP ($-4.6\pm1.5$ mm Hg, $P=0.001$). There was a significant main effect of fish on 24-hour DBP ($-3.2\pm1.5$ mm Hg, $P=0.011$) but not SBP ($-3.5\pm2.5$ mm Hg, NS). The results were unaltered in models that adjusted for changes in urinary sodium, potassium, or the sodium/potassium ratio, as well as dietary macronutrients. Neither fish nor weight reduction independently had an effect on asleep BP (Table 4).

### Heart Rate

Hourly mean values for heart rate at baseline and postintervention during the 24 hours of ABPM for each group are shown in Figure 3. Mean 24-hour, awake, and asleep heart rates by treatment group are shown in Table 4. There were significant effects of dietary fish on 24-hour ($-3.1\pm1.4$ bpm, $P=0.036$) and awake ($-4.2\pm1.6$ bpm, $P=0.013$) ambulatory heart rates. Weight reduction had a significant effect on asleep heart rate only ($-3.2\pm1.7$ bpm, $P=0.037$). There were no significant interactions between weight loss and fish diets on ambulatory heart rate.
Discussion

The incorporation of a daily meal of fish rich in ω3 fatty acids into a reduced-fat, energy-restricted diet in obese treated hypertensive subjects resulted in additive effects on BP reduction. This dietary approach also conferred significant benefits relative to fish or weight loss alone in heart rate reduction. The effects on BP were most marked on awake pressures, with a fall of 13 mm Hg SBP and 9 mm Hg DBP compared with pressures in control subjects, which was over and above that already achieved by antihypertensive drug therapy. However, dietary fish alone also resulted in a significant reduction in ambulatory BP relative to control. Given the magnitude of the BP reduction with the diet combination, withdrawal of antihypertensive therapy may have been possible. However, for the purposes of this trial, volunteers’ family doctors were encouraged to continue usual antihypertensive therapy unless subjects showed symptoms or SBP < 90 mm Hg. Reduction in drug treatment because of low BP was needed in only 2 subjects, 1 in the weight-loss-only group and 1 receiving combination dietary treatment.

The patients for this study were selected so that the dietary fish intake would maximize any effect on the outcome variables. Analysis of diet records confirmed that these patients were not deficient in any of the macronutrients measured and their plasma fatty acid composition was not dissimilar to that of the general population in ω3 fatty acid content or other fatty acids. Furthermore, the consumption of fish in Australia approximates 1 or less fish meals per week. Therefore, these patients were not different in this respect from the general population in their dietary fish intake.

The antihypertensive effect of the fish diet was seen at the lower end of the range of ω3 fatty acid intake compared with doses previously shown to be effective. Possible reasons for this include the choice of obese hypertensives in whom the mechanisms of hypertension may be more amenable to antihypertensive effects of fish oil, improved statistical power due to the factorial design, and the use of ABPM. The use of fish as a vehicle for ω3 fatty acids rather than fish-oil extracts may have contributed to the effects seen, since fish contains a relatively higher proportion of docosahexaenoic acid (DHA) than eicosapentaenoic acid (EPA) compared with fish oils used in previous studies. Some animal studies suggest that DHA may be more potent in reducing BP than EPA, but the issue is unresolved in humans. The present finding with dietary fish is also in keeping with results of a recent population study showing substantially lower BP in Bantu fish eaters compared with nearby Bantu vegetarian villagers.

Constituents of fish other than ω3 fatty acids might also have contributed to the effects seen, since fish contains a relatively higher proportion of docosahexaenoic acid (DHA) than eicosapentaenoic acid (EPA) compared with fish oils used in previous studies. Some animal studies suggest that DHA may be more potent in reducing BP than EPA, but the issue is unresolved in humans. The present finding with dietary fish is also in keeping with results of a recent population study showing substantially lower BP in Bantu fish eaters compared with nearby Bantu vegetarian villagers.

Constituents of fish other than ω3 fatty acids might also have contributed to the BP reduction in this study. For example, the increase in protein intake in the combined fish-diet and weight-loss group may be pertinent, since recent epidemiological data suggest that increased dietary protein as a percentage of energy intake is associated with lower BP.
An antihypertensive effect of dietary protein has yet to be confirmed in randomized controlled trials but might be an additional mechanism accounting for the substantial BP fall in the group combining fish and weight loss. The modest reductions in 24-hour urinary sodium and potassium excretion were similar in both weight-loss groups, commensurate with the reduction in dietary intake, and could not explain the augmentation of BP reduction by the combination of fish and weight loss. Furthermore, the results were unaltered and remained significant after adjustment for changes in urinary sodium, potassium, or the sodium/potassium ratio, as well as dietary macronutrients.

The antihypertensive effect of ω3 fatty acids may depend on vascular effects, with improved endothelial vasodilator function, reduced reactivity of vascular smooth muscle of resistance vessels, and increased vascular compliance. Each of these mechanisms may be relevant to the pathophysiology of obesity-related hypertension. Reductions in heart function, reduced reactivity of vascular smooth muscle of resistance vessels, and increased vascular compliance. Each of these mechanisms may be relevant to the pathophysiology of obesity-related hypertension.
rate similar to those seen in the present study have been associated with consumption of fish oils or fish in humans, raising the likelihood of an autonomic/cardiac component to the antihypertensive effect. In addition, it is worth noting that in animal studies, ω-3 fatty acids are incorporated into myocardial cells and have potent antiarrhythmic effects.

A controlled trial demonstrating that fish or fish-oil diets reduced death rates from heart attack for 2 years after a first myocardial infarction, using doses of ω-3 fatty acids not dissimilar to those used here, lends further credence to a protective role for these compounds in patients at high risk of heart disease. Incorporating fish in the diet rather than fish-oil supplements offers the potential for a simultaneous reduction in saturated and total fat intake while maintaining an adequate intake of protein and other nutrients.

In summary, the present study has shown that incorporation of fish into a weight-reducing diet has additive effects in reducing ambulatory BP, as well as beneficial effects on heart rate, in overweight hypertensives taking antihypertensive medication. These effects, in conjunction with improvements in platelet function, plasma triglycerides, endothelial function, and inflammatory cell cytokines resulting from effects of ω-3 fatty acids in fish, are likely to substantially reduce the risk of atherothrombotic heart disease in these high-risk patients. The large changes in BP suggest potential additional benefits from reduced requirements for antihypertensive drugs.

Acknowledgments
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References


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