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Associations of medium and long chain omega-3 polyunsaturated fatty acids with blood pressure in Hispanic and non-Hispanic smokers and nonsmokers

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Summary

Epidemiology studies and clinical trials have shown that omega-3 polyunsaturated fatty acids (n-3 PUFAs) are inversely associated with blood pressure. We sought to determine the influence of cigarette smoking and Hispanic ethnicity on this association. Age- and sex-matched smokers and nonsmokers (n=98) 19–50 years old lacking cardiovascular disease were recruited. Systolic and diastolic blood pressure (SBP, DBP), heart rate, HbA1c, lipids, BMI, and RBC fatty acids were measured. The omega-3 index (percent eicosapentaenoic and docosahexaenoic acid, EPA+DHA, in RBCs) was significantly lower in smokers (Smokers: $3.19 \pm 0.86\%$; Nonsmokers, $3.88 \pm 1.05\%$, $p=0.001$) and Hispanics (Hispanic $3.32 \pm 0.93\%$; Non-Hispanic, $3.82 \pm 1.03\%$, $p=0.006$). DHA exhibited a significant inverse association with BP in both smokers and nonsmokers, while alpha-linolenic acid (ALA) exhibited a significant positive association with BP only in smokers. Multiple regression analyses showed that BMI, DHA, smoking status, and smoking status*ALA interaction significantly predicted SBP ($p<0.0001$, $R^2=0.44$) and DBP ($p<0.0001$, $R^2=0.33$), while ethnicity had no effect. The observed lower BP when DHA levels are high suggests a possible protective role of DHA on BP in normotensive smokers and nonsmokers. Additionally, the observed higher BP when ALA levels are high only in smokers suggests that ALA may influence the BP-lowering effects of chronic smoking.

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Author's contributions

The author contributions were as follows: MKW and JRA conceived the study; KRZ, AS, MS, and MTW-W contributed to data acquisition; MKW and BHB conducted the statistical analyses, prepared the tables and figures, and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest
None.

Keywords

Omega-3 index; blood pressure; docosahexaenoic acid; alpha-linolenic acid; Hispanic; cigarette smoking

1. Introduction

Meta-analyses of randomized, placebo-controlled trials consistently have found that treatment with long chain omega-3 polyunsaturated fatty acids (LC n-3 PUFAs), eicosapentaenoic acid (EPA, 20:5n3) and docosahexaenoic acid (DHA, 22:6n3), significantly reduces both systolic and diastolic blood pressure (SBP, DBP) in hypertensive individuals [1–4]. Further, two recent meta-analyses show that EPA+DHA supplementation also significantly reduces SBP and DBP in normotensive individuals [5, 6]. These results are consistent with epidemiology studies showing that blood levels of LC n-3 PUFAs are significantly and inversely associated with SBP and DBP [7].

The relationship between the medium chain n-3 PUFA, alpha-linolenic acid (ALA, 18:3n3), and BP is not as well established. Two recent meta-analyses of randomized, placebo-controlled trials using supplementation with flaxseed products, which are highly enriched in ALA, found slight but significant reductions in both SBP and DBP [8, 9], while one epidemiology study failed to find a significant association between ALA and BP in normotensive individuals [7]. These data may suggest that typical dietary intake of ALA may not influence BP levels, while supplementation may slightly reduce BP.

Dietary intake of fatty fish and consumption of dietary fish oil supplements are the primary determinants of blood levels of LC n-3 PUFAs, often reported as the omega-3 index (EPA +DHA expressed as a percentage of total fatty acids in RBCs). However, diet and dietary supplements account for only ~50% of the variability in LC n-3 PUFA status [10, 11]. Two cross sectional studies found that age and female sex were positively associated with the omega-3 index, while triglycerides and smoking were inversely associated [10, 12]. One study demonstrated that smoking resulted in the largest proportional decrease in EPA and DHA, compared to all other clinical correlates measured [12]. Smoking may also influence the levels of ALA, although this relationship remains less well defined. Finally, ethnicity is also a determinant of the omega-3 index. It has been shown that Hispanics living in the U.S. having significantly lower levels of LC n-3 PUFAs, compared to whites, blacks, and Chinese [13].

Given that smoking and ethnicity are determinants of n-3 PUFA levels, the objectives of this study were to determine the degree to which smoking and Hispanic ethnicity were associated with the percentage of n-3 PUFAs in RBCs, and influenced the association between n-3 PUFAs and BP in normotensive individuals.

2. Patients and Methods

2.1 Study subjects

We recruited male and female cigarette smokers and nonsmokers between 19–50 years of age living in the Albuquerque, NM area (n=98). Smokers were defined as having smoked > 0.5 cigarette packs/day for at least the past year, while nonsmokers were defined as having smoked < 50 cigarettes in their lifetime and none in the past year. We excluded subjects that were pregnant, or that self-reported hypertension, elevated cholesterol, diabetes mellitus, chronic kidney disease, ischemic heart disease, stroke, or heart failure. We recruited individuals of all ethnicities for this study and the ethnic distribution of study participants reflected the ethnic distribution of Bernalillo County, New Mexico. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the University of New Mexico Institutional Review Board (HRRC: 15-033). Written informed consent was obtained from all subjects.

2.2 Assessment of clinical characteristics

Each subject's height and weight were measured, and body mass index (BMI) calculated. SBP and DBP were measured according to American Heart Association guidelines [14], and resting heart rate was recorded. Whole blood SST samples were drawn to measure HbA1c, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG), using a point-of-care instrument, and serum and urine cotinine by ELISA (limit of detection = 0.5 ng/ml, Calbiotech, Spring Valley, CA). Whole blood EDTA samples were collected for analysis of n-3 PUFAs from packed RBCs (OmegaQuant, Sioux Falls, SD).

2.3 Statistical Methods

The data analyses for this paper were generated using SAS software, Version 9.4 and SigmaPlot Version 13. Smokers and nonsmokers were age- and sex-matched. Demographic and clinical characteristics were compared between smokers and nonsmokers using t-tests, except for ethnicity where values were compared by Chi-square analysis. When data were not normally distributed, analysis was conducted on log10 transformed values. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) were compared between smokers and nonsmokers, and between Hispanics and non-Hispanics using t-tests and when data were not normally distributed, analyses were conducted on log10 transformed values. Bivariate linear regressions were used to determine the association of EPA, DPA, DHA and ALA with SBP and DBP. Multiple regression analysis was conducted using the general linear model (GLM) to determine the degree to which smoking and ethnicity predicted the omega-3 index. Additionally, multiple regressions using the GLM were used to determine the degree to which BMI, smoking status, DHA, and ALA were able to predict levels of SBP and DBP. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of study subjects

The characteristics of individuals enrolled in this study are shown in Table 1. Smokers had significantly lower SBP and DBP, compared to nonsmokers. As expected, serum and urine cotinine were significantly higher in smokers, compared to nonsmokers. No other significant differences between groups were identified. Individuals of Hispanic ethnicity made up 45% of study participants and the percentage did not differ between smokers and nonsmokers.

3.2. Effect of smoking and Hispanic ethnicity on omega-3 index

When comparing levels of n-3 PUFAs between smokers and nonsmokers, smokers exhibited significantly lower levels of the medium chain n-3 PUFA ALA, and the LC n-3 PUFA DHA (Table 2). Additionally, the omega-3 index (EPA+DHA) and the sum of all n-3 PUFAs were significantly lower in smokers, compared to nonsmokers. When comparing the levels of n-3 PUFAs between Hispanics and non-Hispanics, individuals of Hispanic ethnicity exhibited significantly lower levels of two LC n-3 PUFAs, EPA and DHA, and this was reflected by a significantly lower omega-3 index and sum of all n-3 PUFAs (Table 3). The degree to which the omega-3 index was predicted by smoking and ethnicity was investigated using multiple regression analysis. These results showed that both smoking and Hispanic ethnicity were significantly and independently associated with a lower omega-3 index $F(2, 82)=8.93$, $p<0.001$, $R^2=0.18$ (Fig. 1, Table 4).

3.3. Association of medium and long chain n-3 PUFAs with SBP and DBP in smokers and nonsmokers

Linear regression analyses were used to assess the degree of association between ALA, EPA, DPA and DHA with SBP and DBP in smokers and nonsmokers, separately. There was no association between EPA and BP in either group (data not shown). In contrast, DHA was significantly and inversely associated with SBP and DBP in both smokers and nonsmokers (Fig. 2). Notably, the intercepts of the regression lines were lower for smokers than nonsmokers, but the slopes of the lines were the same for the two groups. The biggest difference between smokers and nonsmokers, however, was the association of ALA with SBP and DBP. Although there was no direct effect of ALA on BP, we found that there was an interaction between ALA and smoking status. While ALA showed no association with SBP or DBP in nonsmokers, there was a statistically significantly positive association with SBP and DBP in smokers (Fig. 3). None of these relationships were influenced by ethnicity.

Multiple regression analyses using GLM were then used to develop an overall model to predict SBP and DBP. We found that BMI, smoking status, DHA, and the interaction between smoking status and ALA were significantly able to predict levels of SBP, $F(5, 87) = 13.73$, $p<0.0001$, $R^2=0.44$ (Table 5), and DBP, $F(5, 87)=8.62$, $p<0.0001$, $R^2=0.33$ (Table 6). There were no significant interaction effects for smoking status and BMI or smoking status and DHA. There was not a significant main effect for ALA.

4. Discussion

The results of this study demonstrate for the first time that the inverse relationship between DHA and BP, observed in studies composed solely or mostly of nonsmokers, is observed in smokers. Further this occurs despite smokers having a significantly lower omega-3 index and significantly lower SBP and DBP than nonsmokers. More intriguing, however, is the novel observation that the medium chain n-3 PUFA ALA exhibits a significant positive relationship with BP but only in smokers. Finally, with our predictors BMI, smoking status, DHA, and the ALA*smoking status interaction, our models are able to explain 44% of the variance in SBP and 33% of the variance in DBP.

Although dietary intake of fish or LC n-3 PUFA supplements are the primary determinants of blood levels of LC n-3 PUFAs, non-dietary factors significantly contribute to the variability in n-3 PUFA status [10–12, 15]. Consistent with these observations we found that both smoking and Hispanic ethnicity are independently associated with lower blood levels of LC n-3 PUFAs. The importance of assessing n-3 PUFA status by measuring blood levels is further supported by a meta-analysis of prospective cohort studies investigating the association between n-3 PUFAs and incident hypertension [16]. This analysis found that neither fish consumption nor dietary LC n-3 PUFA intake is associated with the incidence of hypertension, but in contrast circulating blood levels of LC n-3 PUFAs are significantly inversely associated with the incidence of hypertension.

Blood levels of LC n-3 PUFAs are also associated with BP in normotensive subjects. A recent study reported a significant inverse association between blood levels of the LC n-3 PUFA DHA, and SBP and DBP in normotensive individuals, but no association of blood levels of the medium chain n-3 PUFA ALA with BP [7]. However, this study did not investigate the influence of smoking on these associations. Our results extend the knowledge from this previous study to show that there is a significant inverse association between DHA and SBP and DBP in both smokers and nonsmokers. While the slopes of the DHA-BP regression lines are similar for smokers and nonsmokers, the intercept of the DHA-BP regression line for smokers is shifted downward since smokers have significantly lower BP than nonsmokers. One mechanism by which LC n-3 PUFAs, such as DHA, may reduce BP is by improving flow-mediated dilation. [17–19]. Flow-mediated dilation is the arterial response to increases in shear stress that is mediated, in part, by nitric oxide. LC n-3 PUFAs may improve flow-mediated dilation by enhancing nitric oxide production and reducing vascular oxidative stress and inflammation [20].

In addition, our results also reveal a significant positive association between blood ALA levels and SBP and DBP in smokers, but not in nonsmokers. Thus, smokers with higher levels of ALA exhibit higher SBP and DBP. Notably, the higher levels of ALA in smokers are not associated with hypertension (SBP $\geq$ 140 and/or DBP $\geq$ 90 mmHg, definition at the time of enrollment), but rather with SBP and DBP values that are similar to nonsmokers. The reason underlying the this positive association of ALA with BP only in smokers is not known. It has been shown that both ALA and smoking are associated with lower BP. Dietary supplementation with ALA-enriched foods is associated with slight decreases in SBP and DBP [8, 9], while multiple studies, including a recent meta-analysis, show that cigarette

smoking is associated with significantly lower SBP and DBP, compared to nonsmokers [21–23]. However, our results suggest that there is a unique interaction of ALA and smoking in BP regulation.

There are some limitations to our study. First, the cross-sectional design captures information at only one point in time and is unable to reveal cause-and-effect relationships. Further, the sample size is small, and the overall average and range of the omega-3 index (omega-3 index: mean, 3.57%; range, 1.76–7.37%) is low, compared to other geographical regions, potentially making it difficult to identify associations. Despite these limitations we were able to develop a model in which BMI, smoking status, DHA, and ALA*smoking interaction significantly predict a substantial portion of the variance in SBP and DBP.

5. Conclusions

In conclusion our results suggest that the blood levels of n-3 PUFAs may serve as a biomarker that can integrate the influence of non-dietary factors on n-3 PUFA status, such as smoking and ethnicity. Additionally, the observed lower BP when DHA levels are high suggests a possible protective role of DHA on BP in both normotensive smokers and nonsmokers. Finally, the observed higher BP when ALA levels are high only in smokers suggests that ALA may influence the BP-lowering effects associated with chronic smoking.

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Highlights

- The omega-3 index is significantly lower in smokers and Hispanics
- Docosahexaenoic acid is significantly and inversely associated with blood pressure in smokers and nonsmokers
- Alpha-linolenic acid is significantly and positively associated with blood pressure only in smokers

Figure 1. Effect of smoking (A) and Hispanic ethnicity (B) on the omega-3 index. Multiple regression analysis using the GLM demonstrated that both smoking and Hispanic ethnicity were associated with a significantly lower omega-3 index.

Figure 2.

Linear regression of percent docosahexaenoic acid (DHA) in RBCs with systolic blood pressure (SBP) (A) and diastolic blood pressure (DPB) (B) in smokers and nonsmokers. Open circles and dash line represent data points and regression line, respectively, for nonsmokers. Solid circles and solid line present data points and regression line, respectively, for smokers. (A) Nonsmoker regression line, $p < 0.001$ (slope, -6.78 ± 1.85 ; intercept, 142.29 ± 6.57). Smoker regression line, $p < 0.001$ (slope, -6.26 ± 2.13 ; intercept, 129.46 ± 6.20).

(B) Nonsmoker regression line, $p<0.001$ (slope, -3.72 ± 1.38 ; intercept, 90.62 ± 4.89). Smoker regression line, $p<0.001$ (slope, -4.12 ± 1.85 ; intercept, 84.72 ± 5.38).

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Figure 3.

Linear regression of percent alpha-linolenic acid (ALA) in RBCs versus systolic blood pressure (SBP) (A) and diastolic blood pressure (DPB) (B) in smokers and nonsmokers. Open circles and dash line represent data points and regression line, respectively, for nonsmokers. Solid circles and solid line present data points and regression line, respectively, for smokers. (A) Nonsmoker regression line, $p=0.260$ (slope, -40.69 ± 35.68 ; intercept, 126.96 ± 7.18). Smoker regression line, $p<0.001$ (slope, 138.45 ± 36.75 ; intercept, 88.84 ± 6.37). (B) Nonsmoker regression line, $p=0.621$ (slope, -12.68 ± 25.43 ; intercept, 80.33 ± 5.12). Smoker regression line, $p<0.001$ (slope, 88.75 ± 32.70 ; intercept, 58.35 ± 5.67).

Table 1.

Demographic and clinical characteristics of age- and sex-matched cigarette smokers and nonsmokers.

Characteristic	Smoker (n=49)	Nonsmoke (n=49)	p-value ^a
Age (years)	36 ± 9 ^b	33 ± 9	0.224
Female Sex	26 (53%)	26 (53%)	1.000
Ethnicity			0.727
Hispanic	20	24	
Non-Hispanic	24	20	
NR ^c	5	5	
BMI (kg/m ²)	25.1 ± 4.7	27.7 ± 6.7	0.095
SBP (mmHg)	112 ± 12	119 ± 13	0.007
DBP (mmHg)	73 ± 10	78 ± 9	0.013
Heart rate (bpm)	71 ± 11	67 ± 11	0.095
Total cholesterol (mg/dL)	163 ± 34	177 ± 30	0.073
LDL-C (mg/dL)	91 ± 31	101 ± 34	0.113
HDL-C (mg/dL)	52 ± 12	51 ± 12	0.604
Triglycerides (mg/dL)	104 ± 52	124 ± 86	0.505
HbA1c (%)	5.3 ± 0.4	5.5 ± 1.0	0.081
Serum cotinine (ng/mL)	166 ± 102	0.5 ± 1.3	<0.001
Urine cotinine (ng/ml)	3,712 ± 4,102	5.7 ± 17.6	<0.001

^aValues were compared between smokers and nonsmokers, using a t-test, except for ethnicity where values were compared by Chi-square analysis. When data were not normally distributed, analysis was conducted on log10 transformed values. $p < 0.05$ was considered statistically significant.

^bData are expressed as mean ± SD.

^cNR, not reported.

Table 2.

Percentage of omega-3 polyunsaturated fatty acids (n-3 PUFAs) in RBCs from cigarette smokers and nonsmokers.

Fatty Acid	Smokers (n=46)	Nonsmokers (n=47)	p-value ^a
n-3 Polyunsaturated Fatty Acids			
C18:3n3 (α-Linolenic, ALA)	0.17 ± 0.04 ^b	0.19 ± 0.04	0.013
C20:5n3 (Eicosapentaenoic, EPA)	0.39 ± 0.12	0.44 ± 0.18	0.073
C22:5n3 (Docosapentaenoic, DPA)	2.41 ± 0.32	2.28 ± 0.42	0.108
C22:6n3 (Docosahexaenoic, DHA)	2.80 ± 0.81	3.43 ± 0.95	<0.001
Omega-3 Index (EPA+DHA)	3.19 ± 0.86	3.88 ± 1.05	<0.001
Σn-3 PUFAs	5.76 ± 0.98	6.35 ± 1.09	0.008

^aValues were compared between smokers and nonsmokers, using a t-test. When data were not normally distributed, analysis was conducted on log10 transformed data. $p < 0.05$ was considered statistically significant.

^bData are expressed as mean ± SD.

Table 3.

Percentage of omega-3 polyunsaturated fatty acids (n-3 PUFAs) in RBCs from individuals of Hispanic and non-Hispanic ethnicity.

Fatty Acid	Hispanic (n=43)	Non-Hispanic (n=42)	p-value ^a
n-3 Polyunsaturated Fatty Acids			
C18:3n3 (α-Linolenic, ALA)	0.19 ± 0.05 ^b	0.18 ± 0.05	0.692
C20:5n3 (Eicosapentaenoic, EPA)	0.39 ± 0.10	0.46 ± 0.19	0.027
C22:5n3 (Docosapentaenoic, DPA)	2.29 ± 0.41	2.38 ± 0.34	0.277
C22:6n3 (Docosahexaenoic, DHA)	2.93 ± 0.89	3.36 ± 0.92	0.032
Omega-3 Index (EPA+DHA)	3.32 ± 0.93	3.82 ± 1.03	0.021
Σn-3 PUFAs	5.80 ± 0.88	6.38 ± 1.13	0.009

^aValues were compared between individuals of Hispanic and non-Hispanic ethnicity, using a t-test. When data were not normally distributed, analysis was conducted on log10 transformed data. $p < 0.05$ was considered statistically significant.

^bData are expressed as mean ± SD.

Table 4.

Multiple regression coefficients for smoking status and Hispanic ethnicity to predict the omega-3 index.

Variable	Estimate (Standard Error)	p-value
Intercept	4.20 (0.18)	<0.0001
Smoking status	−0.69 (0.20)	0.001
Hispanic Ethnicity	−0.57 (0.20)	0.0056

GLM: $F(2, 82)=8.93$, $p<0.001$, $R^2=0.18$

Table 5.

Multiple regression coefficients to predict systolic blood pressure (SBP) in smokers and nonsmokers.

Variable	Estimate (Standard Error)	p-Value
Intercept	132.29 (9.83)	< 0.0001
BMI	0.59 (0.19)	0.0026
Smoking status	−37.74 (8.47)	< 0.0001
DHA	−6.07 (1.25)	< 0.0001
ALA	−46.40 (28.07)	0.1019
Smoking*ALA interaction	163.91 (44.71)	0.0004

GLM: $F(5, 87) = 13.73$, $p < 0.0001$, $R^2 = 0.44$

Table 6.

Multiple regression coefficients to predict diastolic blood pressure (DBP) in smokers and nonsmokers.

Variable	Estimate (Standard Error)	p-value
Intercept	76.38 (8.18)	< 0.0001
BMI	0.55 (0.16)	0.0008
Smoking status	-19.69 (7.05)	0.0064
DHA	-3.28 (1.04)	0.0021
ALA	-13.48 (23.36)	0.5654
Smoking*ALA interaction	85.53 (37.22)	0.0239

GLM: $F(5, 87)=8.62$, $p<0.0001$, $R^2=0.33$