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Abstract

Cigarette smoke induces oxidative stress with subsequent polyunsaturated fatty acids (PUFAs) peroxidation. Low concentrations of omega-3 PUFAs can affect neurotransmission, resulting in hypofunctioning of the mesocortical systems associated with reward and dependence mechanisms and thus may increase cigarette craving, hampering smoking cessation efforts. PUFA deficiency, in particular eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3), has also been linked to reduced psychological health and ability to cope with stress. Although stress is well linked to smoking urges and behavior, no research to date has examined the effects of PUFA supplementation on tobacco craving. In this double-blind, randomized, placebo-controlled pilot study, performed in regular cigarette smokers ($n=48$), administration of 2710 mg EPA/day and 2040 mg DHA/day for one month was accompanied by a significant decrease in reported daily smoking and in tobacco craving following cigarette cue exposure. Craving did not return to baseline values in the month that followed treatment discontinuation. This is the first study demonstrating that omega-3 PUFA supplementation reduces tobacco craving in regular smokers, compared to placebo treatment. Thus, omega-3 PUFAs may be of benefit in managing tobacco consumption. Further studies are needed on larger samples to explore the possible therapeutic implications for heavy cigarette smokers.

Keywords

Omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, craving, smoking, tobacco

Introduction

Chronic exposure to smoke-derived toxicants is the primary cause of progressive pulmonary and immune dysfunctions, as well as carcinogenesis (Centers for Disease Control and Prevention (US) et al., 2010). Cigarette smoke also induces oxidative stress with subsequent polyunsaturated fatty acids (PUFAs) peroxidation. PUFA levels, in particular eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3) levels, are different in the plasma of smokers than in the plasma of nonsmokers; smoking influences the processes related to metabolism and bioavailability of serum levels of omega-3 PUFAs (e.g. a higher percentage of EPA is utilized for 22:5 n-3 synthesis), implying a reduced brain tissue percentage due to the imbalanced turnover caused by oxidative stress (Pawlosky et al., 2007; Simon et al., 1996). Low concentrations of omega-3 PUFAs disrupt neural membrane integrity and fluidity affecting neurotransmission (Yehuda et al., 1999). Specifically, omega-3 PUFA deficiency results in hypofunctioning of dopamine mesocorticolimbic pathways (Zimmer et al., 2002), that are associated with reward and dependence (Ahmad et al., 2008) and thus may increase craving response to cigarette-cues or other stressors, hampering smoking cessation efforts (Zaparołi and Galduróz, 2012).

A growing body of evidence now suggests that omega-3 PUFA status and metabolism are involved in individual reactivity and sensitivity to psychosocial stress. DHA and EPA deficiency facilitates excessive stress responses such as hypothalamus-pituitary-adrenal (HPA) hyperactivity (Hibbeln et al., 2004),

hostility, and anger (Hamazaki and Hamazaki, 2008). In contrast, PUFA supplementation inhibits stress-elicited adrenal activation (Bradbury et al., 2004), activates brain serotonin metabolism, and improves stress-coping behavior potential in the cerebral limbic system (Takeuchi et al., 2003).

DHA and EPA are essential fatty acids that cannot be readily synthesized by the human body. Therefore, brain function is critically dependent on the intake of omega-3 PUFAs (Innis, 2008). Accordingly, PUFA supplementation reduces symptoms of depression, anger, and aggressiveness in substance abusers and normal adults ingesting 1.5–2 g DHA/day (Buydens-Branchey and Branchey, 2008; Hamazaki and Hamazaki, 2008; Lin and Su, 2007), as well as improving mood in ADHD children (Yehuda et al., 2011). The few clinical investigations that have tested the effect of PUFAs on anxiety support their apparent anxiolytic effect (Matsuoka et al., 2010; Ross, 2009). Yehuda et al. (2005) have investigated the effects of PUFAs on test anxiety and observed a decrease in cortisol levels and an improvement in associated variables such as appetite, mood, and concentration.

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Table 1. Demographics and baseline smoking measures for the full sample and by group.^a

	All participants (<i>n</i> =48)	Omega-3 PUFAs (<i>n</i> =25)	Placebo (<i>n</i> =23)	Statistics
Age (years)	29.1±6.7	29.6±6.4	28.7±7.0	<i>t</i> (46)=0.47, <i>p</i> =0.64
Gender (male)	16(33%)	7(28%)	9(39%)	$\chi^2(1)=0.41$, <i>p</i> =0.54
Level of education (years)	12.9±1.4	12.7±1.2	13.2±1.5	<i>t</i> (46)=1.38, <i>p</i> =0.17
Marital status				
Presently married	17(35.4%)	7 (28%)	10 (43.5%)	
Single	26(54.2%)	16 (64%)	3 (13%)	
Divorced/separated	5(10.4%)	2 (8%)	10 (43.5%)	$\chi^2(2)=2.1$, <i>p</i> =0.36
Age at beginning of regular smoking (years)	17.7±3.1	17.0±2.7	18.3±3.5	<i>t</i> (46)=1.43, <i>p</i> =0.16
Number of cigarettes smoked daily	13.9±4.3	14.3±4.4	13.5±4.3	<i>t</i> (46)=0.60, <i>p</i> =0.55
FTND ^b	5.8±1.1	5.76±1.1	5.8±1.0	<i>t</i> (46)=0.22, <i>p</i> =0.83

PUFA: polyunsaturated fatty acid.

^aValues are means±standard deviation or *n*(%). Comparisons between the PUFA and placebo groups were made with two-tailed Student's *t*-test or chi-square tests with Yates' continuity correction, as appropriate.

^bFagerström test for nicotine dependence (Heatherton et al., 1991).

Recently, Barbadoro et al. (2013) found that DHA and EPA supplementation reduced distress symptoms and basal cortisol secretion in abstinent alcoholics.

Studies using omega-3 or fish oil as supplementation to treat smokers' stress-reaction are very rare. One study has linked DHA supplementation to improvements in psychological health and coping with stress in smokers after only one month of administration (Nitta et al., 2007). However, effectiveness in alleviating psychosocial stress in smokers that is likely to be attributable to DHA was tested on only seven subjects, who consumed a reduced dosage of lipids (1.2 g/day) as well as antioxidant vitamins and minerals in an open trial, with no control group (Nitta et al., 2007).

Although smokers have imbalanced omega-3 levels that predispose them to stress vulnerability/hyperactivity, and stress is well linked to smoking urges and behavior (McKee et al., 2011), no research to date has examined omega-3 PUFA effects on cigarette craving. Stress significantly increases HPA axis reactivity, negative emotion, and physiologic reactivity. In tobacco-dependent smokers, smoking abstinence and cigarette cue exposure produce a significantly enhanced craving state that is marked by increased stress, anxiety, and other negative emotions; systolic blood pressure responses; and behavioral distress responses. Smokers are also less able to resist smoking, smoke more intensely, and perceive greater satisfaction and reward from smoking when stressed (McKee et al., 2011). Exposure to stress and to drug cues both result in significant increases in craving and subjective anxiety, pulse rate, systolic blood pressure, adrenocorticotrophic-hormone, cortisol, prolactin and norepinephrine as compared to the response to neutral cues (Sinha et al., 2003). A considerable overlap exists in neural circuits involved in processing stress and drug cues, with altered activity in the corticostriatal limbic circuitry underlying both affective and reward processing associated with stress-induced and drug cue-induced craving states and an increased susceptibility to relapse (Sinha et al., 2007).

Therefore, the purpose of this study was to assess the effects on tobacco craving of DHA and EPA as a new supplement in regular cigarette smokers not interested in quitting. No previous randomized double-blind controlled study has been conducted to

evaluate these effects. We hypothesized that dietary supplementation of omega-3 PUFA in regular cigarette smokers would decrease both cigarette daily consumption (by reducing general cigarette craving) and cue-induced cigarette craving, compared to placebo treatment.

Methods and materials

Participants (*n*=48) were recruited through local fliers and were eligible to enroll if they were 18–45 years old, smoked >10 cigarettes per day (CPD) for the past 12 months, were free from significant medical or neurological conditions, and did not meet criteria for any DSM IV Axis I disorders other than nicotine dependence. Participants were excluded if they had used chronic medications or food supplements in the past three months, were currently attempting to quit smoking, or were pregnant. The study was approved by the Helsinki Committee, Hillel-Yaffe Hospital, Hedera, Israel and has been registered at www.clinicaltrials.gov (identifier NCT01284660). Written informed consent was obtained from all participants after a complete description of the study.

Participants were Caucasian, smoked an average of 13.9 CPD, and reported moderate levels of nicotine dependence. See Table 1 for demographics and smoking variables both for the full sample and by group. There were no significant baseline differences by treatment condition, nor were there significant differences in the dietary frequency of fish intake or total unsaturated fatty acids in the 24-hour dietary recall and three-day dietary records of participants in both groups (all *ps*>0.05).

The study design was a one-month, double-blind, randomized, placebo-controlled, parallel group, fixed-dose omega-3 pilot trial with a one month follow-up. Smokers were not asked to stop smoking at any point. Forty-eight regular smokers were randomized 1:1 into two groups, either to PUFA (index group; *n*=25) or placebo (control group; *n*=23). Subjective craving was reported on three occasions (day 0: baseline; day 30; and day 60: follow-up). See the flowchart in Figure 1 for an overview. Each PUFA capsule contained 542 mg of EPA and 408 mg of DHA (Omega 950 as Ethyl Esters, Solgar, New Jersey, USA; Solgar, Israel). The placebo capsules contained mineral and soybean oil

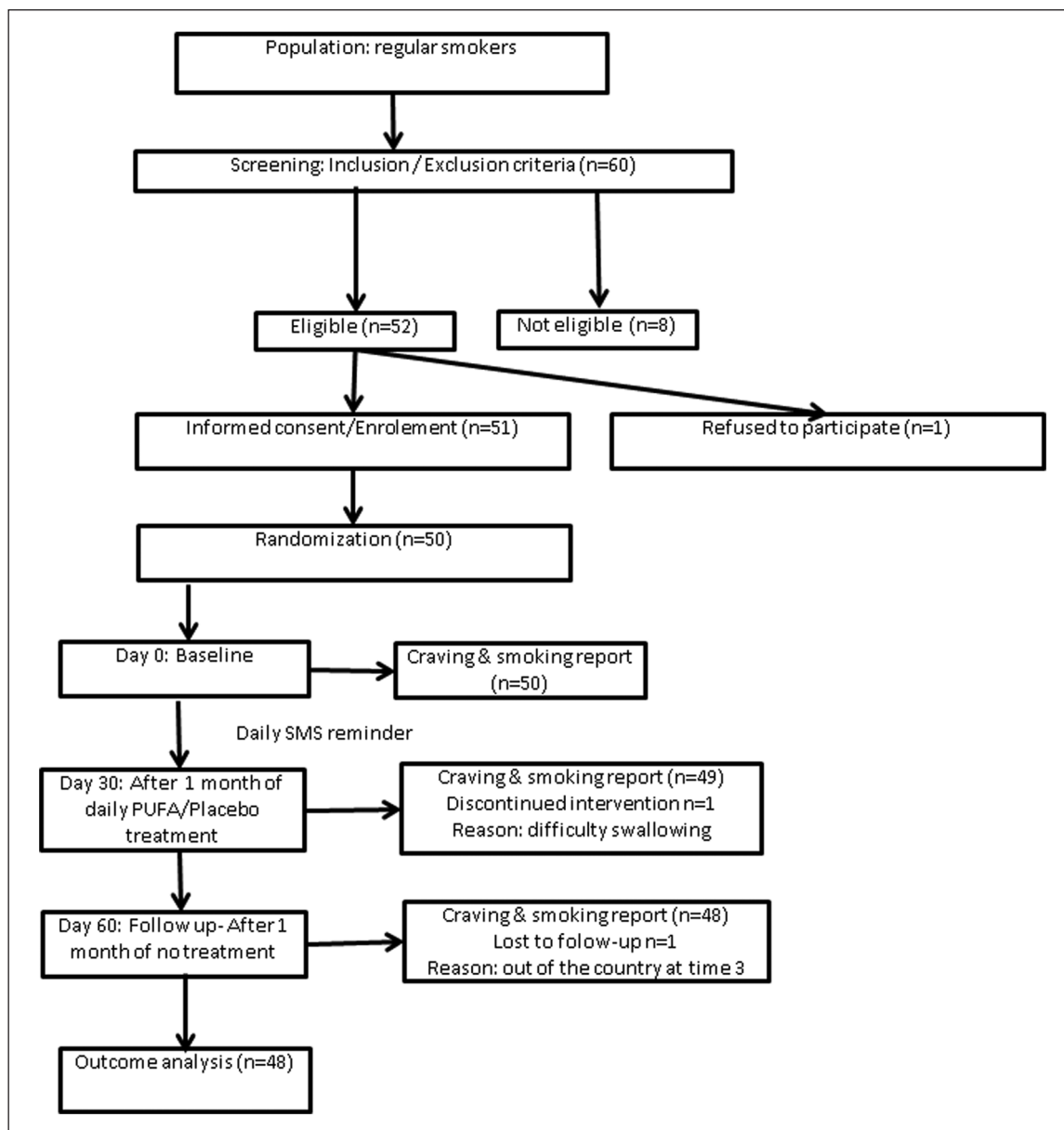


Figure 1. Flow chart diagram, mapping study participants and procedures. PUFA: polyunsaturated fatty acid.

(Solgar, New Jersey, USA). All capsules contained vitamin E (2.75 IU) as an antioxidant, were isocaloric (14 kcal per capsule) and were given in identical bottles. Participants were advised to take five capsules/day for a period of 30 days (Antypa et al., 2009; Nitta et al., 2007). Those taking the active substances were thus given 2710 mg EPA/day and 2040 mg DHA/day (Abeywardena and Patten, 2011; Browning et al., 2007; Moertl et al., 2011). The PUFA and placebo capsules were well-tolerated, and no adverse effects were reported. Participants in both groups reported minimal aftertaste or fish taste and smell while debriefed at follow-up. The blinding procedure was successful, as there were no differences between the groups in terms of expectancy ($\chi^2(2)=3.6$, $p>0.05$). Six out of 25 participants who were randomized to the PUFA group and seven participants in the placebo group correctly guessed their group allocation. Five

participants in each group guessed wrongly, and 25 participants had no idea about treatment assignment.

Participants were considered compliant if 5% or less of the initial number of capsules was left in the containers (Buydens-Branchey and Branchey, 2008). To increase treatment adherence, all participants received daily short message service (SMS) reminders on their cell phones and were asked to reply after the capsules had been taken (Strandbygaard et al., 2010). Adherence to the supplementation protocol was excellent in both groups. On average over 94% of capsules being apparently consumed and there was no difference between the two groups ($t(46)=0.5$; $p>0.05$; placebo: mean (M)=4.8, standard deviation (SD)=2.6; PUFA: $M=5.4$, $SD=2.5$).

Each participant was examined at three points—at baseline, after 30 days of treatment, and after 30 days of follow-up. Standard

demographic and baseline smoking measures were obtained at baseline. At baseline, one month of the treatment protocol, and follow-up (two months) participants completed the Tobacco Craving Questionnaire-Short Form (TCQ-SF) (Heishman et al., 2008). Participants were asked to smoke before coming to the lab and refrained from smoking for two hours under the supervision of the experimenter. Before assessing their current levels of tobacco craving, stress was manipulated via cue exposure (McClernon et al., 2007): participants were asked to view 14 full 14-inch screen pictures depicting photographic cigarette-related cues (e.g. hands holding lit cigarettes, smoking-related objects and people smoking cigarettes). Cues were presented for 3 s in random order, each picture was presented twice. Target cues ($n=7$) were pictures of animals. Participants were asked to press a button whenever they saw a target. Total presentation time took about 1.5 min, depending on individual reaction times.

The total craving score represents emotionality (anticipation of relief from withdrawal symptoms or negative mood), expectancy (anticipation of positive outcomes from smoking), compulsivity (lack of control over tobacco use), and purposefulness (intention and planning to smoke for positive outcomes).

Statistical analysis

Results are shown as the $M(\pm SD)$. Statistical analyses were performed using SPSS statistical software version 20.0 for Windows. The effect of PUFA treatment was examined by mixed-measures analysis of variance (ANOVA) with time as a repeated factor, treatment (placebo or omega-3 PUFAs) as an independent factor, and reported craving as a dependent measure. Baseline characteristics were compared using the χ^2 test for qualitative variables and nonpaired t -test for quantitative variables. The difference is considered statistically significant if $p < 0.05$.

Results

A comparison between the placebo and PUFA groups failed to show a significant difference in cigarette craving at the baseline ($t(46)=0.51, p=0.61$). Data were analyzed using a 2 (treatment: PUFA, placebo) \times 3 (time: baseline, after one month; follow-up) mixed measures ANOVA, which revealed a significant treatment by time interaction ($F(2, 92)=8.73, p < 0.01$, Wilks' $\Lambda=0.75, \eta_p^2=0.16$). Analysis of this effect indicated that PUFAs significantly lowered tobacco craving after one month of treatment ($M=45.5, SD=6.5$) when compared to baseline ($M=61.2, SD=11.6, t(24)=6.1, p < 0.001$). Although craving rose significantly at follow-up ($M=51.4, SD=7.2, t(24)=-3.41, p < 0.01$), participants who received PUFAs still reported lower craving levels at follow-up when compared to baseline ($t(24)=3.51, p < 0.01$).

Conversely, the placebo failed ($ps > 0.05$) to change cigarette craving significantly—similar craving levels were reported in the placebo group before ($M=59.4, SD=12.9$) and after treatment ($M=56.3, SD=9.9$) and at follow-up ($M=56.5, SD=10.8$).

Figure 2 shows the differences in reported craving levels between the two groups before, after one month of treatment, and at follow-up.

A significant main effect of time (before treatment, after one month, at follow-up) on cigarette craving was also found ($F(2, 92)=19.9, p < 0.001$, Wilks' $\Lambda=0.59, \eta_p^2=0.30$). Prior to treatment, participants reported the highest levels of craving ($M=60.3,$

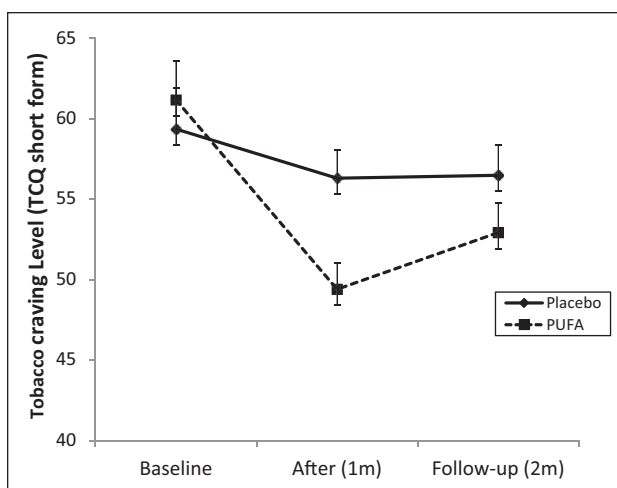


Figure 2. Tobacco craving level (mean (M) \pm standard error (SE)) of regular cigarette smokers at baseline, after one-month of daily administration of omega-3 polyunsaturated fatty acids (PUFAs) or placebo, and after one month (m) follow-up. Items were rated on a Likert-type scale from 1 (strongly disagree) to 7 (strongly agree). Score for each participant was obtained by summing the 12 items, yielding a score ranging from 12–84. TCQ: Tobacco Craving Questionnaire.

$SD=12.1$) as opposed to craving levels after one month of treatment or at follow-up ($M=50.7, SD=9.8; M=53.8, SD=9.3$, respectively). A significant main effect of treatment ($n=3$ PUFA, placebo) on cigarette craving was found ($F(2, 92)=4.16, p < 0.05, \eta_p^2=0.08$). Smokers treated with PUFAs reported lower craving levels ($M=52.68, SD=5.2$) than those treated with the placebo ($M=57.38, SD=10.2$).

A second mixed measure ANOVA failed to reveal a significant interaction of treatment \times time effect on CPD ($F(2, 92)=2.82, p=0.065$, Wilks' $\Lambda=0.85, \eta_p^2=0.06$). However, specific comparisons show that PUFAs significantly lowered CPD after one month of treatment ($M=12.7, SD=3.4$) when compared to the baseline ($M=14.3, SD=4.4, t(24)=3.01, p < 0.01$), a reduction of 11.2% in reported daily consumption. The placebo failed ($p > 0.05$) to change CPD significantly (Baseline: $M=13.5, SD=4.3$; one month: $M=13.3, SD=4.1$; 1.5% not significant change).

Discussion

This double-blind, randomized, placebo-controlled pilot study performed in regular cigarette smokers showed that a daily administration of omega-3 PUFAs EPA and DHA for one month was accompanied by a significant decrease in the number of daily cigarettes smoked and in reported tobacco craving in response to cue exposure. Craving did not return to baseline values in the month that followed treatment discontinuation.

Nicotine activation of nicotinic acetylcholine receptors (nAChrs) in the ventral tegmental area (VTA) cause dopamine (DA) release in the nucleus accumbens (NAc) and project to reward-related brain areas such as the prefrontal cortex, amygdala, and hippocampus. The constant elevation of DA levels in the mesolimbic DA system is associated with reward processing and

dependence development. Linked with relapse and continued nicotine consumption (Di Chiara, 2000), decreased DA activity of this brain reward system could initiate tobacco craving and other negative symptoms of withdrawal common when smoking ceases.

Low concentrations of omega-3 PUFAs affect DA neurotransmission, resulting in hypofunctioning of the mesocortical systems associated with reward and dependence (Ahmad et al., 2008). Hypofunctioning of the mesocortical systems, in its turn, may contribute to elevated craving response and hamper smoking cessation efforts (Zapardi and Galduróz, 2012). Likewise, McNamara et al. (2008) reported that omega-3 deficient mice showed increased sensitization to amphetamine, which was related to selective changes in the mesolimbic DA pathway, due to the incorporation of DHA and EPA into membrane phospholipids. It is assumed that the re-establishment of PUFA levels in the current study reduced tobacco craving following cigarette cue exposure by affecting DA transmission compromised by smoking-induced lipid peroxidation. It is also possible that the PUFA supplementation improved psychosocial stress coping, thus enabling smoking reduction (Bradbury et al., 2004).

The finding that PUFAs reduced cigarette craving and consumption in non-abstinent smokers suggests that PUFA supplementation may be of benefit in helping smokers manage consumption before quitting. As most available pharmacological smoking reduction and cessation treatments are associated with side effects and low efficacy (Zaniewska et al., 2009), the development of new strategies and treatments is necessary. Omega-3 PUFA supplements, which are both inexpensive and well tolerated, could be considered as treatment adjuncts for smokers interested in more easily managing smoking urges and possibly behavior. Cigarette smoking is detrimental to health and also contributes to cardiovascular disease (CVD) via alterations in the lipid profile. The role of omega-3 PUFAs in CVD has been the subject of a recent debate (Kromhout et al., 2012), but the effects of PUFAs on cigarette craving in smokers remained unknown until the current study.

However, this effect was only investigated in smokers who reported moderate levels of nicotine dependence and were followed for a short period of time, and was not validated by assessment of serum PUFA bioavailability or metabolism rate; the study also needs to be replicated with larger samples. Future studies should examine if PUFA supplementation affects smoking behavior and its relation to subjective stress via PUFA serum bioavailability and metabolism and should attempt to determine the neural mechanisms that may have played a role in the decreased craving observed in this study.

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Conflict of interest

The author declares that there is no conflict of interest.

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