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Short-Time Infusion of Fish Oil-Based Lipid Emulsions, Approved for Parenteral Nutrition, Reduces Monocyte Proliferative Cytokine Generation and Adhesive Interaction with Endothelium in Humans

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Potential impact of ω-3 fatty acids, as contained in fish oil, on immunological function has been suggested because observations of reduced inflammatory diseases in Greenland Inuit were published. A fish oil-based lipid emulsion has recently been approved for parenteral nutrition in many countries. We investigated the influence of a short infusion course of fish oil-based (ω-3) vs conventional (ω-6) lipid emulsion on monocyte function. In a randomized design, twelve healthy volunteers received ω-3 or ω-6 lipid infusion for 48 h, with cross-over repetition of the infusion course after 3 mo. Fatty acid profiles, monocyte cytokine release and adhesive monocyte-endothelium interaction were investigated. Resultant ω-6 lipid emulsion increased plasma-free fatty acids including arachidonic acid, whereas the ω-3/ω-6 fatty acid ratio in monocyte membranes remained largely unchanged. It also caused a tendency toward enhanced monocyte proinflammatory cytokine release and adhesive monocyte-endothelium interaction. In contrast, ω-3 lipid emulsion significantly increased the ω-3/ω-6 fatty acid ratio in the plasma-free fatty acid fraction and in monocyte membrane lipid pool, markedly suppressing monocyte generation of TNF-α, IL-1, IL-6, and IL-8 in response to endotoxin. In addition, it also significantly inhibited both monocyte-endothelium adhesion and transendothelial monocyte migration, although monocyte surface expression of relevant adhesive molecules (CD11b, CD18, CD49 days, CCR2) was unchanged. Although isocoloric, ω-3 and ω-6 lipid emulsions exert differential impact on immunological processes in humans. In addition to its nutritional value, fish oil-based ω-3 lipid emulsion significantly suppresses monocyte proinflammatory cytokine generation and features of monocyte recruitment. The Journal of Immunology, 2003, 171: 4837–4843.
In the present study, we performed short-term lipid infusions in healthy volunteers, comparing the impact of standard ω-6 lipid-based emulsions to fish oil-derived ω-3 lipid-based emulsions in a cross-over design. In addition to analysis of plasma and membrane fatty acids, we focused on relevant monocyte characteristics, as these cells are intimately involved in various inflammatory sequelae (15). Indeed, monocytes release both pro- and anti-inflammatory substances, and these cells are intimately involved in various inflammatory diseases. In essence, we found that infusing an ω-3 based lipid emulsion for two 12-h periods within a 48-h window exerts a major impact on monocyte cytokine release and in vivo analyzed monocyte-endothelial interaction. Compared with preinfusion baseline and to infusion of conventional ω-6 lipid emulsions, proinflammatory cytokine generation was markedly inhibited and endothelial adhesion and transendothelial migration were significantly reduced. These findings provide proof of the concept that i.v. administered ω-3 lipids, which are approved for parenteral nutrition in many countries, rapidly interfere with monocyte-related immunological and proinflammatory functions.

Materials and Methods
Study design
The study was approved by the University Ethics Committee, and written informed consent was obtained from each volunteer. Twelve volunteers were recruited and blood was drawn by venipuncture at 8 am of the first day. Via an antecubital venous access, a heparin infusion with 10,000 U/day was started for 48 h. Volunteers were then randomized to receive either 350 ml of 10% Omegaven or 10% Lipoven on both day 1 and day 2 (composition of lipid emulsions is detailed in Ref. 13). Each infusion was started at 4 pm and lasted for 12 h. Four hours after completion of the second lipid infusion (8 am on the third day), blood was drawn by antecubital venipuncture. After 12 wk, the volunteers underwent the same 3-day course with the alternate lipid emulsion infused. Both volunteers and investigators performing the laboratory investigations were blinded for the nature of lipid emulsion used in each course.

Volunteer selection
The volunteers were ≥18 years of age, did not smoke, and were not vegetarians. They did not take fish oil capsules or any comparable nutritional supplementation. They were evaluated as to be completely healthy after a complete history, an ECG, normal routine laboratory including differential blood count, coagulation parameters, electrolytes, liver and pancreas enzymes, renal parameters, creatinine kinase, lipid status, urine test, and physical examination performed by physicians not related to our facilities. We did not accept volunteers with a history or current episode of metabolic disorder (especially diabetes or lipid disorder), gastrointestinal, pulmonary, cardiovascular, hematological, allergic, rheumatological, or immunological disease. The volunteers did not take medications for at least 6 wk before the start of the infusions. Twelve volunteers were included, six were male and six female. The median age was 32.5 years (range 19 to 42 years), the body mass index was 22.1 ± 0.8 kg/m², mean ± SEM.

Preparation of endothelial cells
Endothelial cells were obtained from human umbilical veins according to the method described by Jaffe et al. (16).

Monocyte isolation
Human monocytes were isolated by centrifugation on Ficoll-Hypaque density gradient centrifugation, followed by counterflow centrifugation elutriation using a Beckman JE-5.0 rotor (Beckman Instruments, Fullerton, CA). Monocyte purity (89–91%) was confirmed by light scatter (FACScan; BD Biosciences, Heidelberg, Germany). Cell viability, as assessed by trypan blue exclusion, ranged above 96% throughout, and LDH release was consistently below 3%.

Monocyte adhesion and rolling assay
Monocyte adhesion and rolling was determined as previously described (17) using a parallel plate flow chamber according to Lawrence and Springer (18). Confluent endothelial monolayers were preincubated with TNF-α (1 ng/ml) overnight.

Transmigration assay
Monocyte transmigration was measured in a static trans-well system as described (19) with HUVEC sham-incubated (control) or preincubated with TNF-α (1 ng/ml) overnight. In addition, monocyte chemotactic peptide (MCP)-1 (100 ng/ml) or buffer (control) was added into the lower compartment of the trans-well. Transmigrated monocytes were quantified microscopically using a counting chamber and a sample from the lower compartment (20).

Immunofluorescence analysis
EDTA-anticoagulated blood was subjected to immunofluorescence staining by incubation of samples with appropriately diluted FITC-labeled anti-CD14 mAb, and either PE-labeled anti-CD11b (Mac-2) mAb or anti-CD18 marker or anti-CD49d (very late antigen (VLA)-4) mAb or anti-CCR2 mAb (R&D Systems, Wiesbaden, Germany) for 30 min at ambient temperature. Combined lysis of RBC and fixation of stained leukocyte populations for flow cytometric analysis was performed using FACS lysing solution (BD Biosciences), followed by one washing step using PBS (pH 7.4). Analysis of CCR5 expression was done by incubation of blood samples with FITC-labeled anti-CCR5 mAb (R&D Systems) and PE-labeled anti-CD14 mAb. All mAbs were purchased from BD Biosciences, unless otherwise stated.

Flow cytometry
Dual-color flow cytometric analysis of stained leukocyte populations was performed using a FACSscan station (BD Biosciences). Processing of data was performed using CellQuest software.

Culture and stimulation of monocytes
Monocytes (5 × 10⁶ in a 24-well tissue culture plate) were cultivated in 400 µl RPMI 1640 medium containing 1% heat-inactivated autologous serum, antibiotics (penicillin 100 U/ml, streptomycin 100 µg/ml) and 2 mmol/l glucose. Cells were stimulated with 0 ng/ml (vehicle control), 1 ng/ml, or 10 ng/ml LPS from Salmonella typhimurium for 24 h at 37°C, 5% CO₂. Measurement of cytokines was performed using commercially available ELISA kits.

Statistical analysis
Data are given as the mean ± SEM and Student’s t test for paired samples with Bonferroni correction for multiple comparisons was used to test for differences between the pre- and postinfusion values within each infusion group and between the corresponding intergroup values; a p value <0.05 was considered to indicate statistical significance.

Results
Clinical course
All volunteers received two complete courses of ω-3 and ω-6 lipid infusion in a randomized fashion. During the infusion period, no adverse events occurred. Both infusions were well tolerated, no overt bleedings were recorded and the volunteers did not report problems concerning the infusion site.

Immunofluorescence analysis
Monocytes were examined for changes in expression of adhesion molecules CD11b (Mac-2), CD18, CD49d (VLA-4), and CCR2 and CCR5 before and after the infusion period. No significant changes were detected comparing preinfusion to postinfusion
FIGURE 1. Impact of ω-3 vs ω-6 lipid infusion on monocyte rolling, adhesion, and transmigration on human endothelial monolayer. Monocytes originated from volunteers receiving either ω-3 or ω-6 lipid infusion (pre- and postinfusion blood sampling). Rolling (A) and adhesion (B) were investigated on TNF-α-activated HUVEC under laminar flow conditions, and number of cells fulfilling criteria of rolling per high power field (hpf) is given. Transmigration (C) was investigated in TNF-α-activated HUVEC, with additional presence of MCP-1 in the lower compartment of the trans-well system. A sample of the buffer with transmigrated monocytes was transferred to a counting chamber and number of cells per high power field is given. Error bars represent mean ± SEM (n = 12 experiments each); *, p < 0.05 for comparison between pre- and postinfusion values.
values within one infusion group. In addition, no significant difference was found between infusion groups.

**Rolling of monocytes on HUVEC**

Neither lipid infusion had an effect on rolling of monocytes using control HUVEC. In contrast, using TNF-α-activated HUVEC, we observed that an enhanced percentage of monocytes isolated from volunteers with ω-6 lipid infusion showed features of rolling. The number of rolling monocytes per high power field increased strikingly from 32.9 ± 7.9 before to 60.8 ± 12.8 after ω-6 lipid infusion (p < 0.05). In contrast, after ω-3 lipid infusion the number of rolling monocytes was reduced from 40.3 ± 7.4 to 28.9 ± 5.7 per high power field (Fig. 1).

**Adhesion of monocytes to HUVEC**

Adhesion of monocytes to endothelial cells was tested after incubation of HUVEC for 16 h with TNF-α or sham incubation (control cells). Without preadministration of TNF-α, no effect of either lipid infusion on monocyte adhesion was detectable. In contrast, when TNF-α-activated HUVEC was used, the pre- and postinfusion values of the ω-3 group differed markedly: the number of adhering monocytes was reduced by ~40% from 132.2 ± 17.4 to 79.6 ± 6.4 per high power field (p < 0.05, Fig. 1). No influence of the ω-6 lipid infusion on the number of adhering monocytes was found.

**Transmigration of monocytes through HUVEC**

Transmigration of monocytes was examined using control and TNF-α-activated endothelial monolayers. In addition, MCP-1 was used as chemotactic stimulus in the lower compartment of a transwell system. No influence of either lipid infusion on transmigration was found when examining control HUVEC in the absence of TNF-α or MCP-1. MCP-1 increased the transmigration rate through the endothelial monolayer. ω-6 lipid infusion had no effect on the MCP-1 driven transmigration, whereas the ω-3 lipid infusion led to a 28% reduction of migrating monocytes (p < 0.05). The same pattern of reduction was found when TNF-α-activated HUVEC with or without addition of MCP-1 were examined: infusion of ω-6 lipids did not change the number of transmigrating monocytes, whereas ω-3 lipids reduced migration of monocytes by ~30–40% (p < 0.05, Fig. 1).

**Cytokines**

Cytokines were measured following 24-h culture of monocytes in the absence of LPS (control), in the presence of 1 ng/ml LPS, or 10 ng/ml LPS. Both lipid infusions had no effect on any cytokine release measured in the absence of LPS. Lipid infusion with ω-3 caused a 28% and 29% reduction in TNF-α release after incubation with 1 and 10 ng/ml LPS, respectively (p < 0.05; Fig. 2). No significant effect of the ω-6 lipid infusion on LPS-induced TNF-α release was found. Similarly, ω-6 lipid infusion had no effect on LPS-stimulated IL-1 secretion, but ω-3 lipid infusion reduced the LPS- provoked IL-1 generation by 30–45%. LPS-induced secretion of IL-6 and IL-8 was even increased by ω-6 lipid infusion, but this finding was not significant due to the scattering of data. After ω-3 infusion, the generation of these cytokines was reduced: secretion of IL-6 was decreased by ~20%, and generation of IL-8 was reduced by up to 46% (p < 0.05, Fig. 2). No significant influence of either lipid infusion was found on LPS-activated IL-10 secretion.

**Free fatty acids**

Free fatty acids were measured before institution and 4 h after cessation of lipid infusions. In both groups, all free fatty acids were elevated after the infusion period, with the sum of free fatty acids rising from 496.8 ± 35.5 to 1519.5 ± 253.5 μmol/l and from 471.7 ± 70.8 to 1350.1 ± 113.6 μmol/l in the ω-6 and in the ω-3 group, respectively (p < 0.05 each). Free arachidonic acid rose markedly in both groups, with mean values approaching 100 μmol/l (p < 0.05 each). The ω-3 fatty acids EPA and DHA were strikingly increased in the ω-3 infusion group to 63.1 ± 8.6 μmol/l and 97.4 ± 12.5 μmol/l. The summed concentrations of both fatty acids then surpassed the concentration of arachidonic acid by nearly 60%. Accordingly, the arachidonic acid/EPA plus DHA quotient was nearly reversed from ~1:0.5 after ω-6 lipid infusion, but approached 0:6:1 after ω-3 lipid infusion.

**Monocyte fatty acid membrane composition**

The monocyte membrane composition of fatty acids was determined before and after the infusion period. No significant influence of lipid infusions on the relative molecular amount of arachidonic acid was detectable. The percentage of arachidonic acid among all membrane fatty acids was 16.7 ± 0.8 before and 16.3 ± 0.7 after ω-6 lipid infusion. In good comparison, the percentage of arachidonic acid contents determined before and after ω-3 lipid infusion were 17.5 ± 0.5 and 16.8 ± 0.8 M_r. In contrast, the percentage of membrane EPA and DHA increased markedly after ω-3 lipid infusion. The percentage of baseline EPA content was ~0.2–0.3 M_r in both groups, did not change after ω-6 lipid infusion, and was increased to 1.9 ± 0.2 M_r after the ω-3 lipid infusion (p < 0.01). Similarly, baseline DHA content percentage (~2.4–2.5 M_r) was not altered by ω-6 lipid infusion, but rose to 3.8 ± 0.3 M_r after ω-3 lipid infusion (p < 0.05). Baseline arachidonic acid/EPA plus DHA ratio in the monocyte membrane lipids was ~6:1 and changed to ~3:1 after ω-3 lipid infusion.

**Influence of gender on rolling and IL-8 generation**

In a posthoc analysis, influence of gender on rolling and production of IL-8 in isolated monocytes was tested. After ω-6 lipid infusion, an increased number of monocytes on TNF-α-activated HUVEC displayed features of rolling (Fig. 1, p < 0.05), which was found in both the male and female subgroup (p < 0.05 for each comparison). Number of rolling monocytes was reduced after ω-3 lipid infusion (Fig. 1). The male subgroup reached a level of significance (p < 0.05), whereas the female subgroup did not differ significantly. IL-8 synthesis was increased after ω-6 lipid infusion when comparing all volunteers (Fig. 2), but neither subgroup differed significantly. A reduction in IL-8 generation after infusion of ω-3 lipids was detected in all volunteers (Fig. 2, p < 0.05), as well as in both subgroups (p < 0.05 for each comparison).

**Discussion**

In the present study, a distinctive differential impact of ω-3 vs ω-6 lipid infusion on key monocyte features was noted after an infusion period of only 48 h in healthy volunteers. The conventional ω-6 based lipid emulsion increased plasma free fatty acids including arachidonic acid, did not alter the ω-3/ω-6 fatty acid ratio in monocyte membranes, caused a tendency toward enhanced monocyte proinflammatory cytokine release, and increased monocyte rolling. In contrast, ω-3-based lipid emulsion significantly increased the ω-3/ω-6 fatty acid ratio in the plasma free fatty acid fraction and in the monocyte membrane lipid pool, markedly suppressed the monocyte proinflammatory cytokine generation, and inhibited both monocyte-endothelium adhesion and transendothelial monocyte migration.

After initiation of fish oil-based lipid infusion, a rapid increase in free EPA and DHA levels was noted, reversing the arachidonic
acid/EPA plus DHA quotient in this compartment from ω-6 predominance to ω-3 predominance within 48 h. The prompt appearance of free ω-3 fatty acids indicates rapid hydrolysis of the EPA- and DHA-containing triglycerides. This is consistent with the notion that synthetic lipid aggregates activate endothelial lipoprotein lipases, including translocation of the enzyme from its cellular binding sites into the vascular compartment. Activation and translocation result in an increase in plasma free fatty acids due to escape from local cellular uptake mechanisms (21, 22). Kinetics and extent of plasma ω-3 lipid increase thus exceed corresponding alterations in response to conventional dietary fish oil uptake by order of magnitude (23, 24). Interestingly, some increase in arachidonic acid was also noted in response to ω-3 lipid infusion. It remains enigmatic whether this increase results from cleavage of arachidonic acid from the fish oil-based lipid emulsion (which contains ~1.5% arachidonic acid as triglyceride), or whether arachidonic acid is secondarily released from endogenous arachidonic acid-containing lipid pools due to substitution by EPA and/or DHA. In fact, a significant increase of the ω-3/ω-6 fatty acid ratio in the monocyte membrane lipid pool was noted. However, within the given infusion time the changes were not as dramatic as in the plasma free fatty acid fraction.

Endotoxin-induced secretion of proinflammatory cytokines TNF-α, IL-6, and IL-8 was significantly reduced after ω-3 lipid infusion, with some additional tendency of decreased IL-1 formation. In contrast, increased formation of IL-6 and IL-8 was found after ω-6 lipid infusion. Reduced generation of TNF-α after long-term dietary intake of fish-oil capsules was first described by Endres et al. (25) and later confirmed (26). The underlying mechanisms are, however, not yet resolved. The membrane ω-3 fatty acid enrichment may have an inhibitory effect on phospholipolytic activities (phospholipase A2, phospholipase C). This may affect downstream signaling events such as generation of second messenger molecules inositol-phosphates and diacylglycerol, with subsequent impact on calcium fluxes and activation of kinases such as protein kinase C (6, 27–29). Recent studies from our group using ω-3 fatty acid-incubated endothelial cells showed rapid incorporation of EPA and DHA into the sn-2 position of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol pool including its PAF precursor subclasses. Moreover, decreased PAF formation was noted under these conditions (30, 31). In addition, at the transcriptional level, the NFκB has been described as activated by arachidonic acid, but not by EPA (32), and DHA was reported to prevent TNF-α-mediated activation of NFκB (10). Furthermore, generation of EPA-derived eicosanoids such as leukotriene B4 and thromboxane A2 has been demonstrated under ω-3 lipid infusion (33), and these mediators possess markedly reduced

FIGURE 2. Impact of ω-3 vs ω-6 lipid infusion on monocyte cytokine release. Monocytes originated from volunteers receiving either ω-3 or ω-6 lipid infusion (pre- and postinfusion blood sampling). Cytokine release into the supernatant was provoked by the presence of 10 ng/ml LPS within a 24-h incubation period. Data are given for TNF-α (A) and IL-8 (B), and error bars represent mean ± SEM (n = 12 experiments each); *, p < 0.05 for comparison between pre- and postinfusion values.
inflammatory capacities as compared with arachidonic acid-de-
derived leukotriene B4 and thromboxane A2 (34). Such a shift might
interfere with eicosanoid-dependent autoamplification loops, as
described for regulation of TNF-α synthesis by thromboxane A2 (35).

Monocytes spontaneously adhere to endothelial cell monolayers
under static conditions. However, substantial monocyte-endothe-

tial adhesion under flow, as assessed in the present investigation
for more correct mimicry of the in vivo situation, demands pre-
ceding cytokine stimulation of the endothelial cells. E-selectin–L-
selectin, ICAM-1–β2-integrin, and VCAM-1–VLA-4 interactions
were shown to represent predominant adhesive forces under these
conditions (36–42). TNF-α pretreatment of HUVEC according to
our protocol was previously shown to enhance endothelial
ICAM-1 and VCAM-1 expression (31). It was thus tempting to
speculate that the marked reduction of endothelial adhesion and
transendothelial migration of monocytes harvested after ω-3 lipid
infusion might be due to down-regulation of complementary
monocyte adhesion molecules under this lipid infusion regimen.
However, we could not detect any change in expression of mono-
cyte surface proteins CD11b (Mac-2), CD18 and CD49d (VLA-4),
as well as the CCR2. This contrasts the finding of reduced levels
of CD11a, CD18, and CD44 on lymphocytes after a fish-oil diet in
rats (43). In addition, it differs from the observation that supple-
mentation of the diet of healthy volunteers with 3 g fish oil per day
for 3 wk resulted in a significant reduction in the expression of
ICAM-1 and CD11a on both freshly prepared and IFN-stimulated
peripheral blood monocytes (44). The reasons underlying these
differences and the mechanisms responsible for reduced monocyte-
endothelial adhesive interaction in our study with short-term ω-3
lipid infusion remain unresolved. We cannot rule out that a change
in monocyte selectin expression may be the causative factor for
reduced adhesion rate under laminar flow conditions. However,
using a static assay, we noted a corresponding reduction of mono-
cyte transmigration after ω-3 lipid infusion, and selectins are not
assumed to play a key role in this late phase of the recruitment
process. As we did not examine expression of adhesion proteins
after confrontation with a chemotactic stimulus we may not ex-
clude that recruitment of adhesion molecules to the surface or a
change in avidity of β2-integrins under this condition is respon-
sible for the reduced adhesive features after infusion of ω-3 lipids.
Moreover, studies of Lewis et al. and Zimmerman and coworkers
(45–47) strongly suggested that endothelial PAF and the leukocyte
PAF receptor contribute to adhesive interactions between endo-
thelial cells and monocytes, followed by a juxtacrine activation of
the adherent mononuclear cells. Alterations in this complex interactive
loop might therefore be considered as underlying mechanisms for
the ω-3 lipid effect.

In a posthoc analysis, we examined the impact of gender on lipid
infusions. Previous reports showed that androgens are responsible
for immunodepression. Female sex steroids prevent androgen-in-
duced suppression of immune responses in experimental models
and influence course of disease in severe sepsis and trauma (48, 49).
Regarding our data, no significant gender difference could be
revealed. This may be due to the study design, which was not
primarily focused on this point. Examination of data lead to the
formation of four smaller subgroups (n = 6 each) and scattering of
the data.

From the present assessment we only can speculate on the du-
ration of the effects. We tested cytokine generation and adhesive
features of isolated monocytes shortly after the end of the infusion
period. Changes in plasma free fatty acids are short-lived as they
are subjected to modulation by the type of lipid infusion used, e.g.,
in an intensive care environment (50). This may be advantageous
given that the immune status of a patient suffering from sepsis or
the adult respiratory distress syndrome may change from a hyper-
inflammatory status to a hypoinflammatory state (51), thereby per-
mitting the clinician to adapt nutrition to the “immunologic needs”
of a patient. On the other hand, isolated monocytes were examined
ex vivo, and results of cytokine generation and adhesive features are
obtained in the absence of free fatty acids. The observed change in membrane fatty acid composition may be responsible for
these characteristics. The effect on membrane composition is more
durable than plasma fatty acid levels and persists up to 10 days
after the end of the infusion period (50).

These findings provide proof of concept that i.v. administered
ω-3 lipids, which are approved for parenteral nutrition in many
countries, rapidly interfere with monocyte related immuno-
logical and proinflammatory functions. Our study was planned as an
explorative examination, and only limited details of mechanisms may
be deduced. However, changes in membrane lipid distribution may
impact lipid dependent signal transduction (lipid signaling) with
respect to the generation of phosphatidylinositol phosphates, diac-
 glycerol, release of intracellular calcium, and activation of de-
pendent protein kinases. The precise mechanisms are currently be-
ing examined, but this was beyond the scope of the present study.

Impact of ω-3 fatty acids on immunological functions was sus-
pected from the first reports on reduced incidence of psoriasis,
asthma, and type I diabetes in Inuit subjects (48). Clinical studies
with fish-oil capsules have shown an immune-modulating effect in
inflammatory bowel disease, rheumatoid arthritis, and transplan-
tation (6, 7). Moreover, so-called “tailored” enteral nutrition with
diets including EPA was suggested to reduce morbidity and mor-
tality in intensive care medicine (3, 4). The present study extends
these observations in demonstrating, in a cross-over design in
healthy volunteers, that a short-time (48 h) infusion period with
ω-3 lipids suffices to achieve significant suppression of monocyte
proinflammatory cytokine generation and monocyte-endothelium
adhesive interaction including transmigration. This observation is
of interest because the fish oil-based lipid emulsion employed in
this investigation is approved for parenteral nutrition in many
countries. The findings of this study suggest that, in addition to
fulfilling nutritional functions, i.e. ω-3 lipid infusion has strong
impact on monocyte-related immunological functions and inflam-
matory processes in humans.

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