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More frequent olive oil intake is associated with reduced platelet activation in obesity

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Abstract

Background and Aims—Obesity is an independent risk factor for atherosclerotic cardiovascular disease (CVD), and platelet hyperactivation in obesity may contribute to this association. Olive oil consumption is associated with lower cardiovascular disease (CVD) risk in the general population. However, little is known for individuals with obesity. We investigated whether olive oil intake is associated with platelet activation in obesity.

Methods and Results—We assessed platelet activation (surface P-selectin expression) with and without thrombin exposure and diet composition in 63 patients with severe obesity.

Among 63 subjects with obesity, the mean age was 32.2±8.0 years and BMI 44.1±8.5 kg/m^2. Olive oil intake was stratified into <1 time/week (n=21), 1 – 3 times/week (n=18), ≥4 times/week (n=24). Strata did not differ by age, BMI or platelet count. Unstimulated P-selectin expression did not differ by olive oil consumption. Subjects with more frequent olive oil intake exhibited lower P-selectin expression on submaximal thrombin exposure.

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Author Contribution

S.H. conceived of the presented idea and directed the project. A.M. and R.Z. performed the experiments. R.Z. performed data analysis. K.M., E.L., S.V., M.J., and K.C. and J.B. assisted with data collection and analysis. R.Z. and S.H. wrote the manuscript in consultation with all authors. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Declaration of Interest

All authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Conclusions—More frequent olive oil intake is associated with reduced thrombin-induced platelet activation in obesity.

Keywords

Platelet activation; obesity; olive oil; P-Selectin; cardiovascular disease

Introduction

Mediterranean regions exhibit some of the lowest rates of atherosclerotic cardiovascular disease (CVD) in the world [1]. This has been partially attributed to the traditional Mediterranean diet, which is characterized by olive oil as the principal source of fat [1–3].

Other healthy lifestyle behaviors, including the maintenance of normal weight, are associated with lower CVD incidence and mortality [4,5]. Nearly ¼ of the worldwide CVD burden is attributable to obesity and more than 25% of European adults will be obese by 2025 [6]. We and others have shown that obesity is associated with increased platelet activity, a key mediator of atherothrombosis, which may account in part for the prothrombotic state and heightened risk associated with the condition [7,8].

Given the role of platelet activation in modulating inflammation and atherothrombosis in obesity and increasing prevalence of the disease, it is important to identify interventions that may reduce CV risk in high-risk individuals with obesity. Therefore, we sought to investigate whether olive oil intake is associated with reduced platelet activation in a cohort of individuals with obesity.

Methods & Materials

Prospective Study Design

Subjects were recruited from the Bellevue Hospital Center and NYU Langone Bariatric Surgery Clinics for an IRB-approved study. Non-diabetic, non-smoking individuals between 18 and 55 years of age otherwise meeting NIH criteria to undergo bariatric surgery (body mass index (BMI) ≥ 40kg/m^2, or ≥ 35kg/m^2 and at least one obesity-related comorbidity) were included [9]. Individuals on antiplatelet or anticoagulation medications, with NSAIDs use in the past 14 days, or on medications known to influence lipid levels were excluded.

Fasting blood samples were collected via a 19G needle at the initial preoperative visit. The first 2ml were discarded, the tourniquet removed, and the remaining blood was collected into tubes containing 3.2% (0.105M) sodium citrate as anticoagulant. Whole blood samples were exposed to thrombin at a submaximal concentration of 0.025U/mL (Instrumentation Laboratory, Bedford, MA) for five minutes or left untreated. Platelets were identified by staining with CD42b-APC (BD Biosciences) and platelet activation determined by platelet surface expression of P-selectin (FITC-conjugated anti-CD62P; BD Biosciences) on a C6 Plus flow cytometer (BD Accuri, San Jose, CA). A modified version of the National Cancer Institute Diet History Questionnaire II was used to estimate dietary composition at preoperative visits prior to dietary counseling.

Statistical analyses

Subjects were stratified by food intake frequency and platelet activation was compared using ANOVA, with post-hoc independent samples t-testing. P-values of <0.05 were set *a priori* as the criteria for statistical significance.

Results & Discussion

Among 63 subjects from the prospective study of platelet function in obesity, average age was 32.2±8.0 years and BMI 44.1±8.5 kg/m^2. Subjects were stratified into 3 groups by olive oil consumption frequency: ≤1 time/week, n=21; 1 – 3 times/week, n=18; ≥4 times/week, n=24. The groups did not differ by age, weight, BMI, waist and hip circumferences, platelet count or mean platelet volume (Table). There was no difference in consumption frequency of other cooking fats, including margarine, lard, butter and vegetable oils, among the olive oil groups. Platelet activity in the basal state did not differ significantly by olive oil consumption frequency. In contrast, subjects with more frequent olive oil intake demonstrated lower platelet activation to thrombin than those consuming olive oil ≤1 time/week (Figure 1). Notably, there were no associations between platelet activity (activated or non-activated) and consumption of fish, wine, nuts, red meat, eggs, butter or margarine.

In non-diabetic individuals with severe obesity, we found that more frequent olive oil consumption was associated with reduced inducible platelet activation. Interestingly, in the absence of diabetes as in our participants, obesity alone is not associated with increased platelet aggregation [10]. Additionally, there are no data supporting increased risk of arterial thrombosis, which is predominantly platelet aggregation mediated, in individuals with obesity, independent of other common comorbidities. These facts might initially prompt question of the clinical relevance of our findings. However, while platelet aggregation is not elevated in obesity, obesity is nonetheless associated with increased risk of developing CVD and adverse cardiovascular events [11,12] and platelet aggregation and activation are two distinct ways through which platelets contribute to CVD risk. Therefore, it is important to consider other potential roles of platelets in the pathophysiology of atherosclerotic disease beyond their canonical role in hemostasis and thrombosis.

Assessment of platelet activation as measured by surface markers such as P-selectin enables us to examine platelets' role as immune-modulating cells rather than purely as thrombotic agents. P-selectin is translocated to the platelet surface during activation and mediates platelet interactions with endothelial cells and immune cells [13]. As a direct marker of platelet activation, P-selectin is elevated in obesity and positively associates with carotid intimal medial thickness and atherosclerosis progression as well as other vascular risk factors [14]. Therefore, elevated P-selectin is thought to partly contribute to elevated CVD risk in obesity. We have previously shown that platelet P-selectin expression to thrombin is elevated in severe obesity and normalized after bariatric surgery [15,16].

Thrombin is a potent platelet agonist through proteinase-activated receptors (PARs). PAR activation in human platelets increases intracellular calcium, which in turn leads to a signaling cascade and P-selectin translocation from the α-granules to the platelet surface [11]. The similar unstimulated P-selectin expression across olive oil consumption groups

in our study suggests that olive oil intake does not influence basal P-selectin expression in circulating platelets, with the difference seen in thrombin-induced P-selectin expression indicative that the impact may be mediated through the aforementioned activation pathway.

Ed Nignpense et al. previously hypothesized that polyphenols could block receptor-agonist interactions, such as PAR1-thrombin binding, leading to downstream activation signaling inhibition, reduction of degranulation, and suppressed surface P-selectin translocation [17]. This proposed mechanism may explain the reduced thrombin-induced platelet P-selectin expression with hydroxytyrosol incubation seen in our study. Although prior *ex vivo* studies have used polyphenol concentrations that are much higher than physiologic levels, new biochemical methods under development will enable more sensitive quantification of plasma polyphenol concentrations and prompt *ex vivo* studies that can elucidate the underlying mechanism of the observed cardioprotective effect of more frequent olive oil consumption reported in our study [18,19].

Limitations

Our study has several limitations. The food frequency questionnaires used in the prospective study provide validated estimates, but not objective measures, of olive oil consumption in our sample, and the type of olive oil consumed was not reported.. Despite these limitations, our findings have clinical implications for CVD risk reduction in individuals with obesity.

In conclusion, the present study demonstrates that for individuals with obesity, more frequent olive oil intake may reduce CVD risk via suppression of inducible platelet P-selectin expression. Polyphenols may mediate this activity, although *ex vivo* studies are warranted to further elucidate the underlying mechanisms.

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Highlights

- Platelet hyperactivation may contribute to elevated CV risk in obesity
- More frequent olive oil intake is associated with lower induced platelet activation in obesity
- Olive oil consumption may reduce CVD risk in obesity by suppressing inducible platelet P-selectin expression

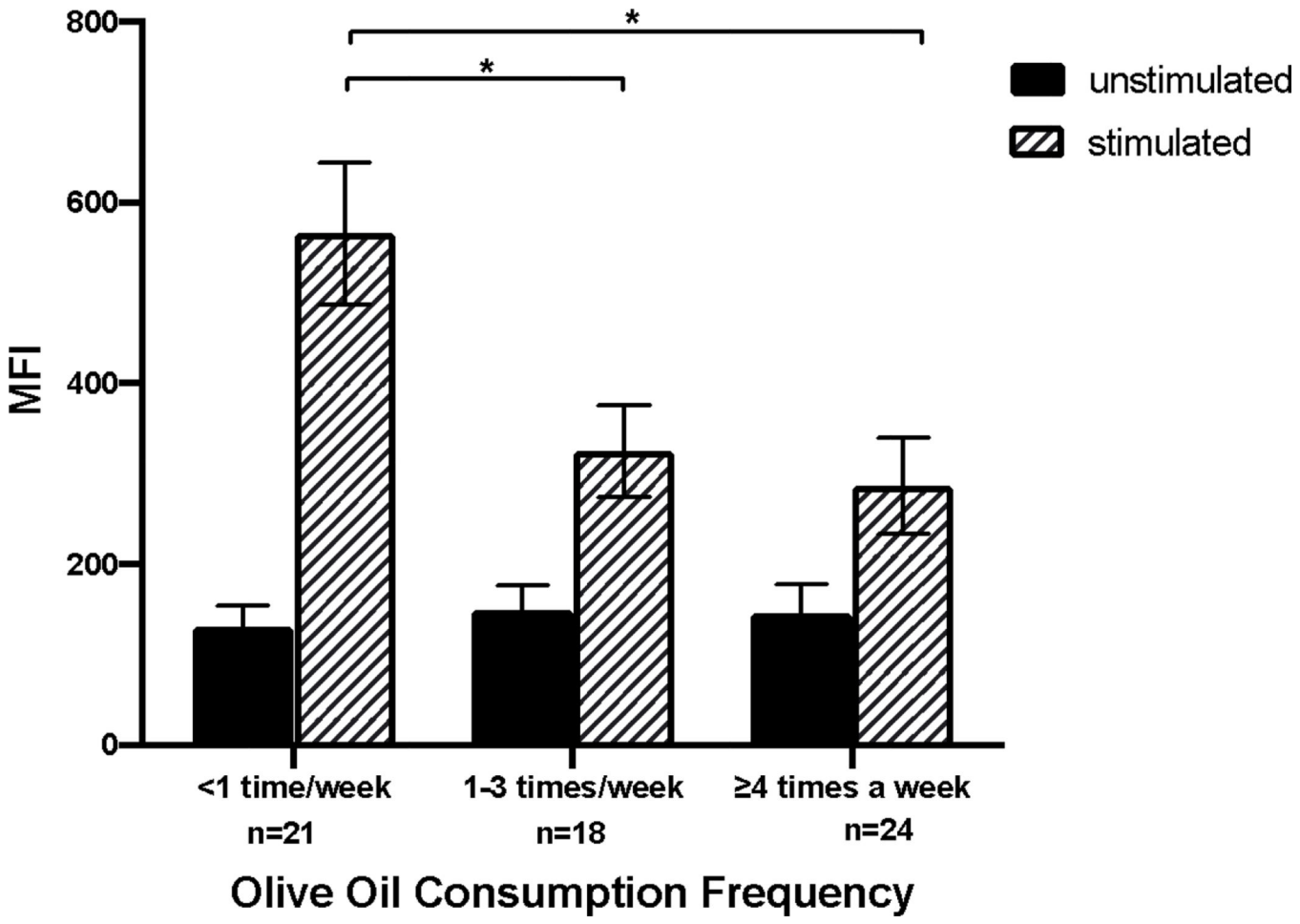

Figure 1.

Ex vivo unstimulated and thrombin-stimulated (0.025U/mL thrombin) platelet P-selectin expression. Bars represent mean ± SEM.

* indicates $p<0.05$ for post-hoc comparison with <1 time/week following ANOVA < 0.05

Table.

Baseline characteristics of subjects with obesity stratified by olive oil consumption frequency.

	Olive Oil Consumption		
	< 1 time/week (n=21)	**1–3 times/week (n=18)**	**≥ 4 times/week (n=24)**
Age (years)	29 ± 7	32 ± 8	32 ± 8
Sex (% female)	86%	89%	92%
Body weight (kg)	119 ± 20	119 ± 29	114 ± 20
Body mass index (kg/m^2)	43.8 ± 8.1	42.0 ± 9.9	42.0 ± 7.2
Waist circumference (cm)	118 ± 18	116 ± 20	117 ± 17
Hip circumference (cm)	124 ± 16	129 ± 20	126 ± 10
Blood pressure (mmHg)	124 ± 16 / 77 ± 11	124 ± 14 / 77 ± 13	121 ± 12 / 77 ± 10
Platelet Count (× 10^9/L)	266 ± 77	270 ± 83	268 ± 42
Mean Platelet Volume (fL)	10.4 ± 1.4	10.3 ± 1.3	9.7 ± 1.4