Workshop on Focus su sicurezza d´uso e nutrizionale degli alimenti.
Alimentazione e Nutrizione. Istituto Superiore de Sanitá

Rome, November 21-22, 2005

Bioavailability and Antioxidant Effects of Olive Oil Phenolic Compounds in Humans

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Background

The benefits of olive oil consumption are becoming increasingly recognized.

So far, most of the protective effect of olive oil, within the context of the Mediterranean diet has been attributed to its high MUFA content.

Recently, the FDA permitted a claim on olive oil labels concerning the benefits on the risk of coronary heart disease (CHD) of eating about 2 tablespoons (23 grams) of olive oil daily, due to the monounsaturated fat (MUFA) in olive oil .

However, if the effect of olive oil can be attributed solely to is MUFA content, any type of olive oil, rapeseed/canola oil, or MUFA-enriched fat would provide the same health benefits

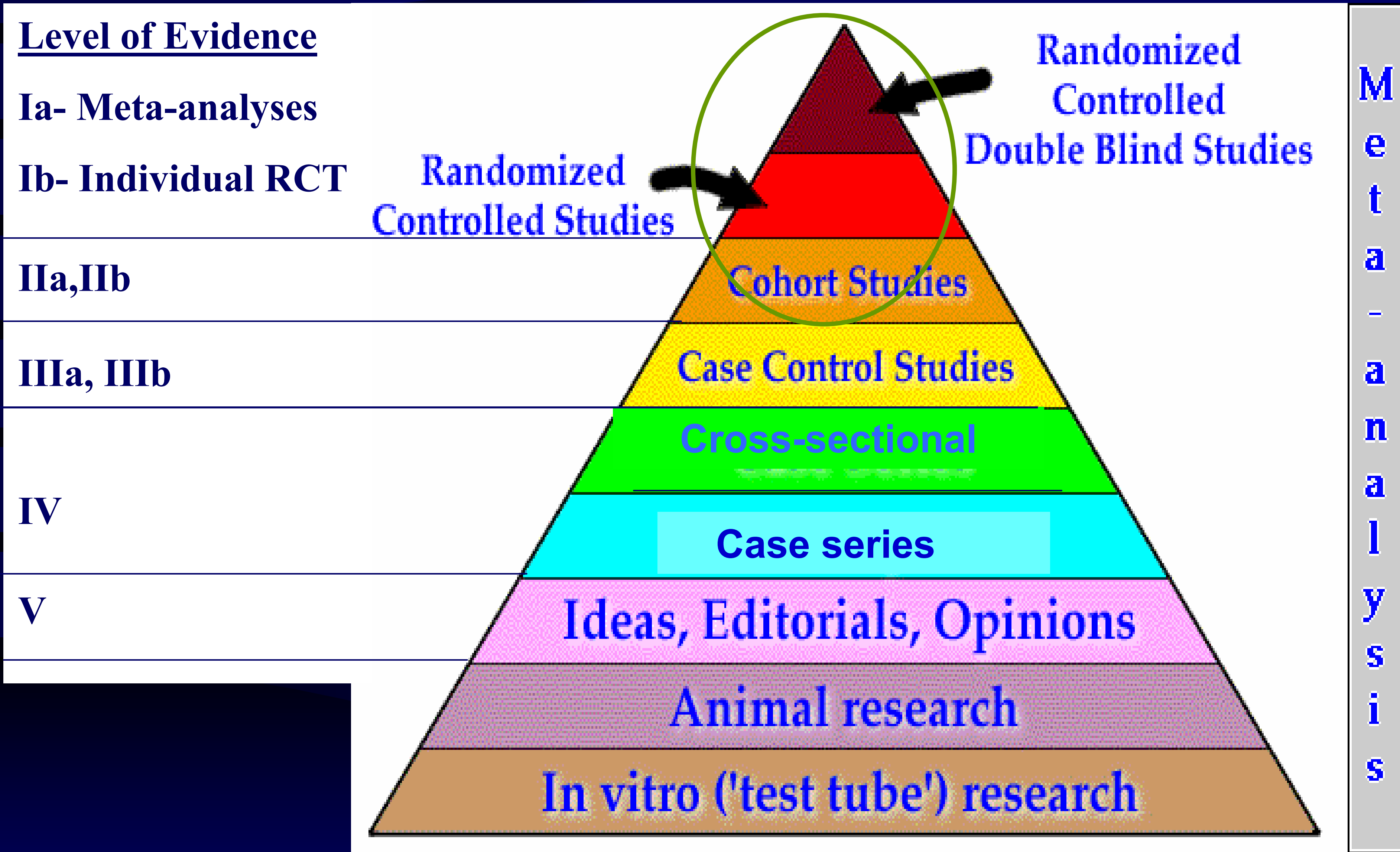
Background

Olive Oil Components

- Major components: Fatty acids
  - Saturated (8-14%)
  - Monounsaturated (oleic acid 55-83%)
  - Poliunsaturated (4-20%)

- Minor components:
  - Squalene, Sterols, triterpenes
  - Vitamin E, Beta-carotene
  - Phenolic compounds (tyrosol, hydroxytyrosol, oleuropeine, lignanes..)

Thus, Public Health implications are involved in order to specifically recommend olive oil, and which type of olive oil, as individualized eating strategies for CHD prevention.



Canadian Task Force on the Periodic Health Examination. J Clin Epidemiol 1990; 43:891-905; U.S. Preventive Task Force. Williams and Wilkins 1989; The Swedish Council of Technology Assessment in Health and Care., 1993; Agència d´Avaluació de Tecnologia Mèdica de Catalunya. Med Clin (Barc) 1995:105:740-743.

Background

Olive oil phenolic compounds are the most well studied olive oil minor components and have been a subject of great interest in the last years.

In experimental studies, olive oil phenolics have shown strong antioxidant properties.

In animal models, olive oil phenolics delayed the progression of the atherosclerosis, and retained their antioxidant properties "in vivo".

Results of the studies performed in humans on the antioxidant effects of olive oil phenolic compounds are, however, controversial.

Antioxidant effect of olive oil phenolic compounds in randomized, crossover, controlled studies in healthy volunteers (HV) until 2001

Subjects (n) (sex)	Intervention	Int. period	Washout period	Baseline adjust.	Compliance markers	Markers	Effects	Reference
HV (10) (men)	Virgin olive oil vs oleic acid-rich sunflower oil [a]	3 weeks	1 week with usual diet	No	No	In vitro LDL resistance to oxidation	**Only Dienes decreased**	Nicolaiew et al. (1998)
HV (14) (10 women and 4 men)	Virgin vs refined olive oil (50 g/day) (raw?)	4 weeks	4 weeks[b]	No	No	In vitro LDL resistance to oxidation	**None**	Bonanome et al (2000)
HV (46) (32 women and 17 men)	High-phenol vs Low-phenol (69 g/d) (raw and with baked products)	3 weeks	2 weeks without olives and olive oil	No	No	In vitro LDL resistance to oxidation MDA, FRAP Lipid peroxides Protein carbonyl	**None** (all markers)	Vissiers et al. (2001)
HV (25) (14 women and 11 men)	High-phenol vs Low-phenol olive oil (70 g/d, raw)	3 weeks	2 weeks without olives and olive oil	No	No	Idem previous study	**None** (all markers)	Moschandreas et al. (2001)

Vissiers MN, Zock PL, Katan MB. Eur J Clin Nutr 2004;58:955-65.

[a]Added to meals, quantity not defined. Only percentage of MUFA (21%) in diet available. [b] Characteristics of the washout period not defined.

Desired characteristics in nutritional intervention studies on the antioxidant capacity of olive oil minor components from olive oil

- Dietary control of washout and intervention periods, mainly the fat ingested.
- Sensitivity of oxidation biomarkers (i.e. Circulating oxidized LDL[1], F_2-isoprostanes[2], GSH-Px[3].....)
- Adjustment for baseline of each intervention period
- Biomarkers of compliance

Are olive oil phenolic compounds bioavailable in humans from real-life doses of natural olive oil?

Dose-dependent absorption of Tyrosol and Hydroxytyrosol in humans from olive oil

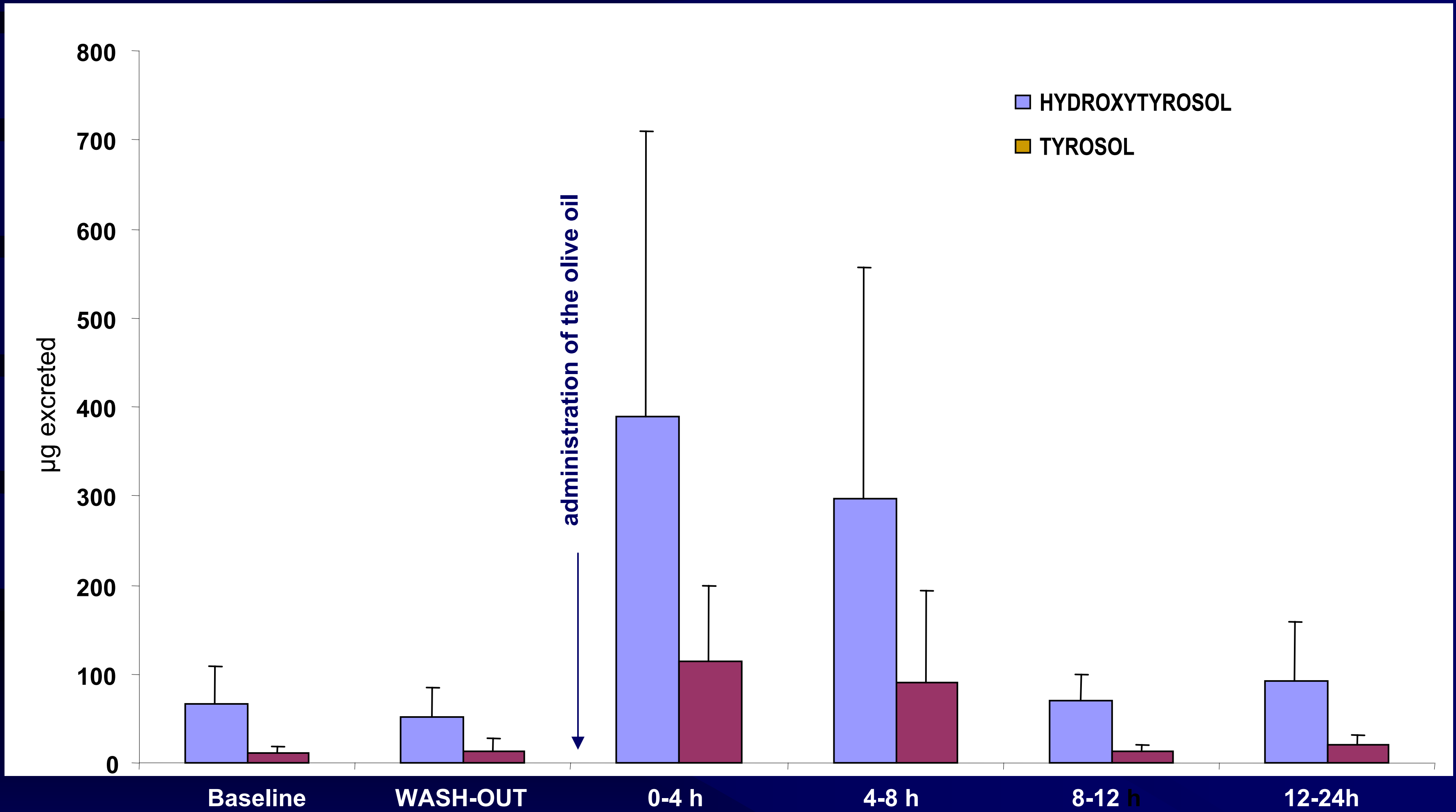
Visioli F, Galli C, Bornet F, et al. FEBS Letters 2000;468 :159-160

[1] T oshima S, et al. Arterioscler Thromb Vasc Biol 2000; 20: 2243-7. 1; Liu ML, Arterioscler Thromb Vasc Biol. 2004;24:1492-7.

[2] Schwedhelm E et al. Circulation 2004;109:843-8.

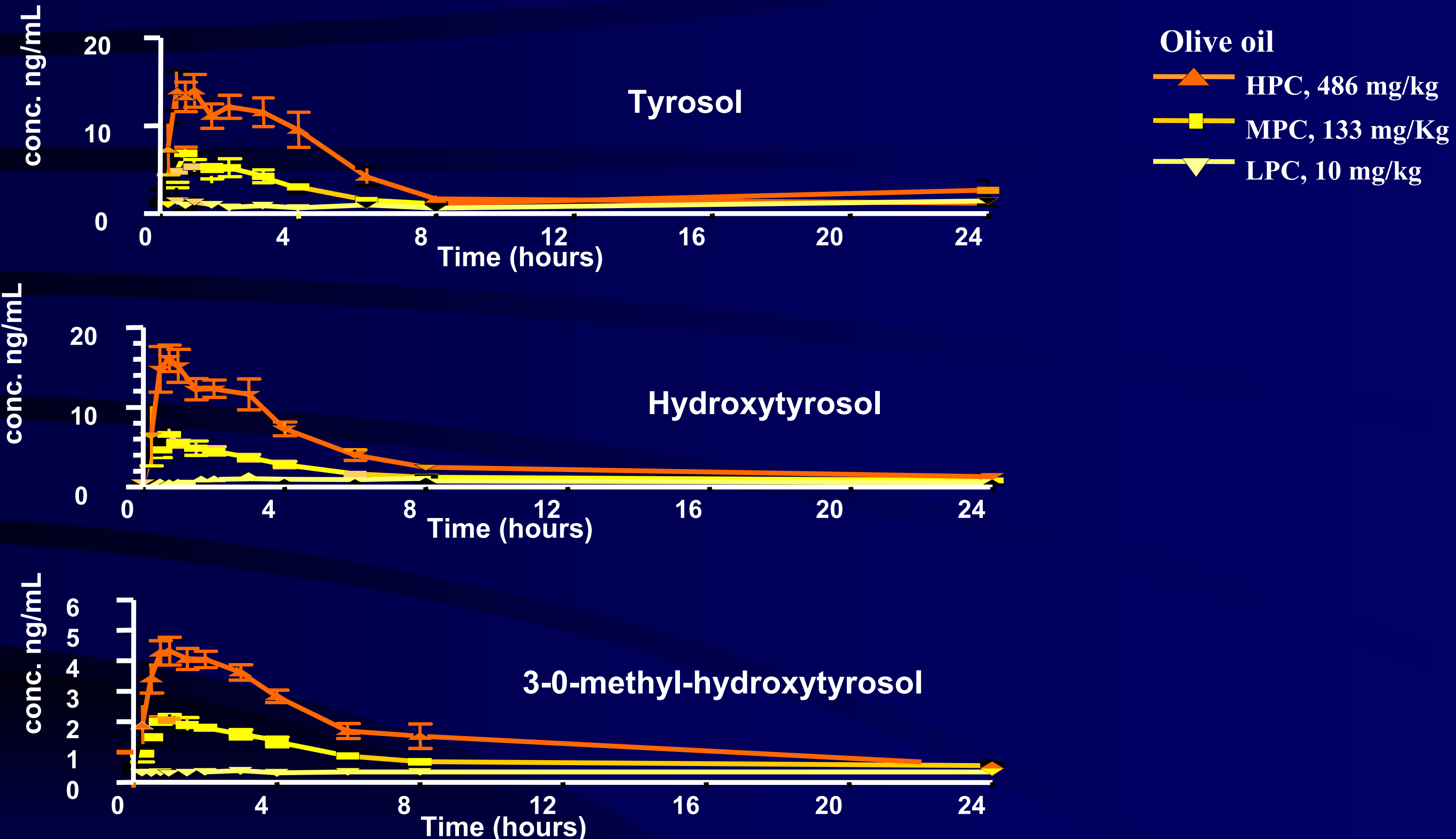
[3] Blankenberg S et al. New Engl J Med 2003; 349:1605-13

Bioavailability of tyrosol and hydroxytyrosol, from 50 mL virgin olive oil ingestion,(251 ppm) in humans after urine acidic treatment



Miró-Casas et al. Anal Biochem 2001; 294:63-72

Plasma Concentration vs Time curves for phenolic compounds in the 3 treatments (dose 25 mL) (n=12)



Free forms of these phenolic compounds were not detected in plasma

Weinbrenner et al. J Nutr 2004

Plasma pharmacokinetic parameters for HT and 3-O-methyl-HT

	C_{max} (µg/L)	t_{max} (h)	$t_{½}$ (h)	AUC_{0-8h}
Acidic hydrolysis				
HT	25.83 (12.96)	0.58 (0.26)	3.12 (1.5)	72 (26)
3-O-methyl-HT	3.94 (2.13)	0.88 (0.54)	2.96 (0.9)	12 (4)
Enzymatic hydrolysis				
HT	17.09 (6.84)	0.54 (0.21)	3.01 (1.1)	47 (12)
3-O-methyl-HT	3.02 (1.53)	0.82 (0.53)	2.37 (1.3)	10 (2.9)

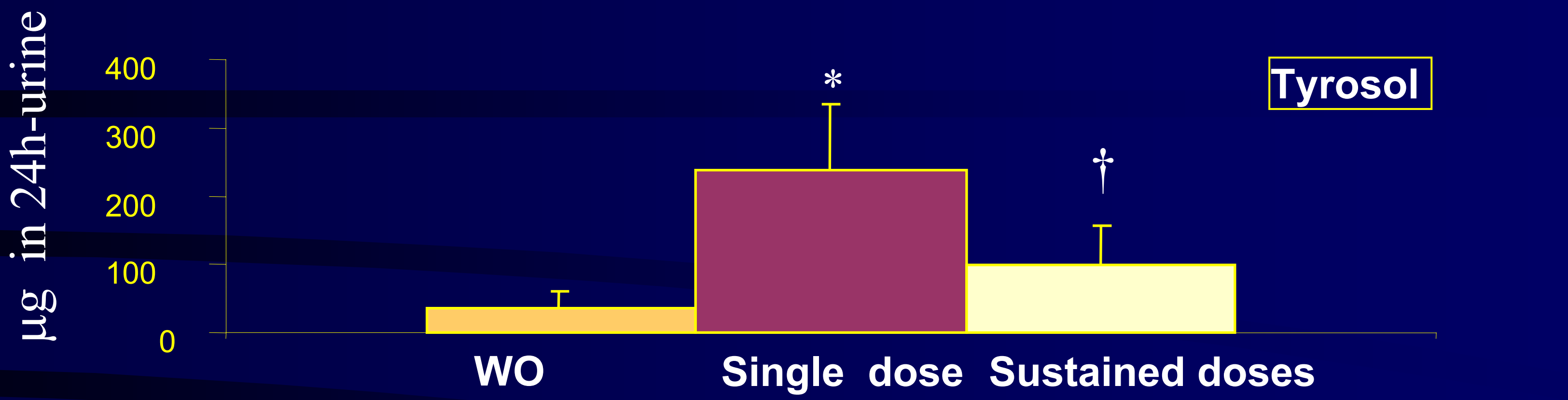
HT was present in plasma as around 65% as glucuronate and 35% in other conjugated forms

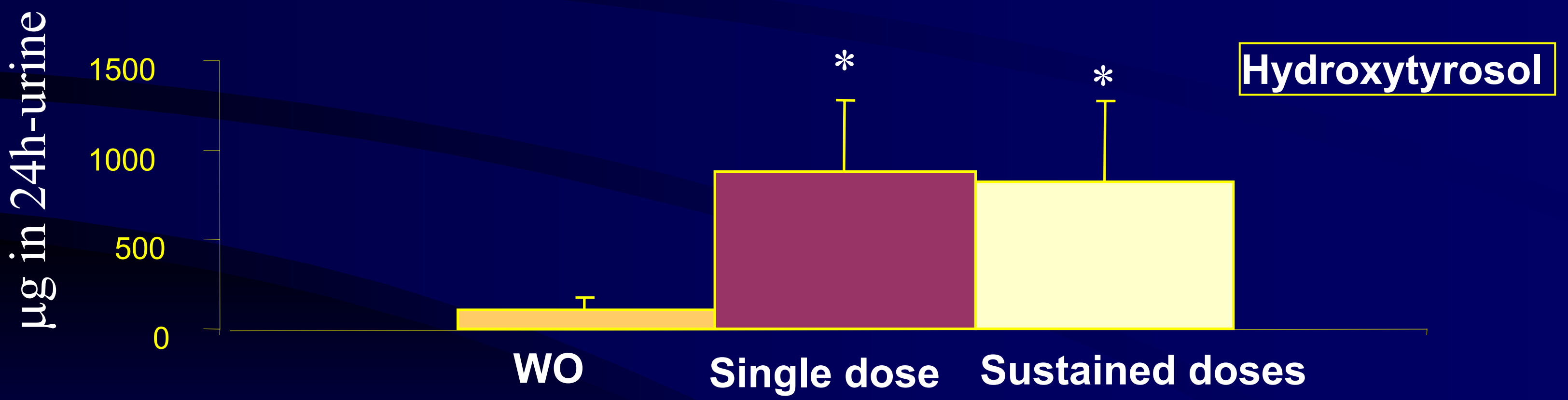
The short half-life supports the concept that the benefits of virgin olive oil consumption would be associated to daily sustained doses of olive oil

Are olive oil phenolic compounds accumulable from daily doses of olive oil?

Could tyrosol and hydroxytyrosol in plasma or urine be biomarkers of olive oil consumption?

Levels of Tyrosol and Hydroxytyrosol in 24-h urine after a single dose (50 ml) and sustained (1 week, 25ml/day) doses of virgin olive oil (250 mg/Kg) (n =16)

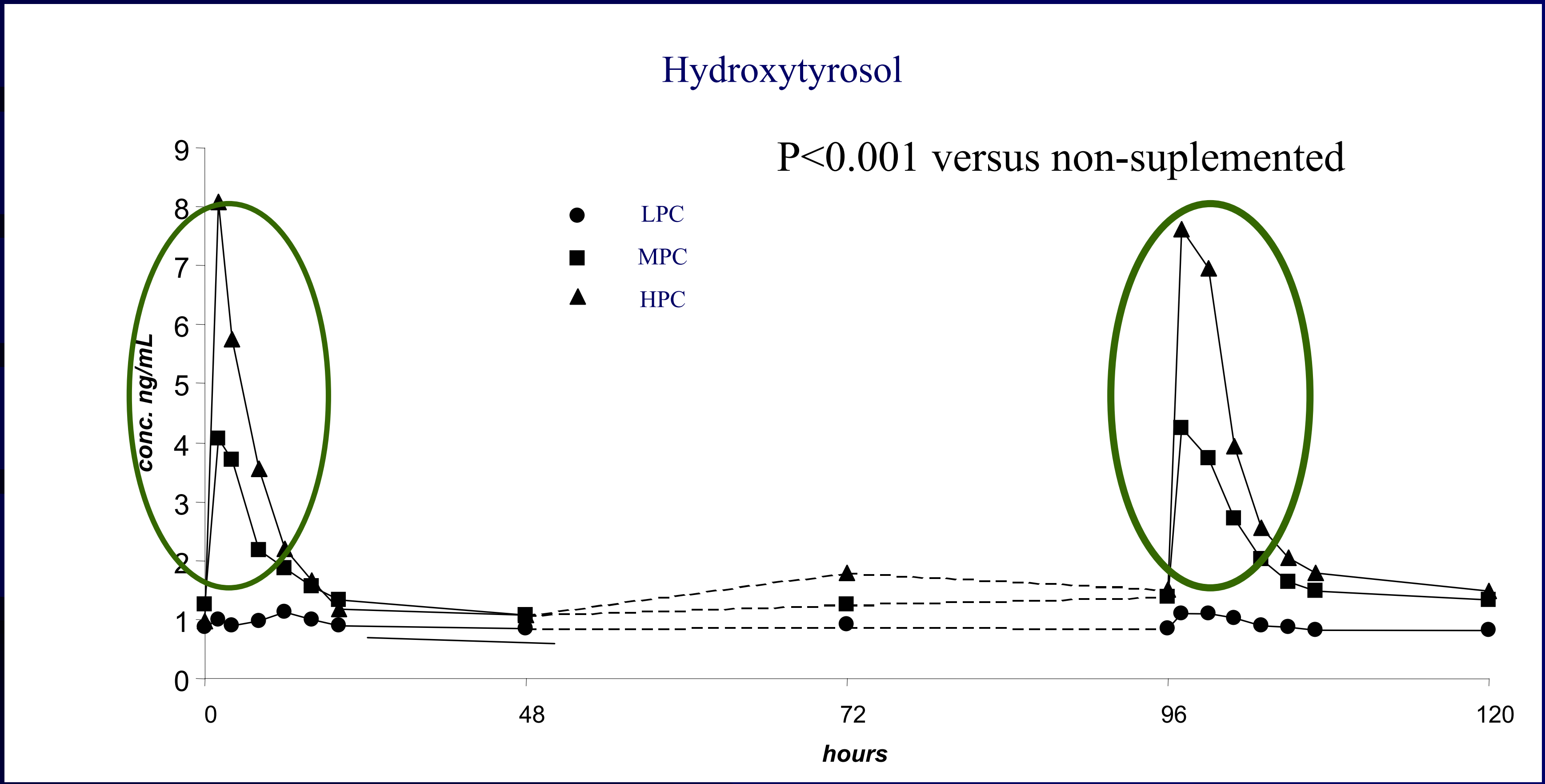




* P < 0.005, † P < 0.025

Miró-Casas et al. Eur J Clin Nutr 2003;57:186-90

Levels of Hydroxytyrosol in plasma after a single dose (25 mL) of olive oils



Non-supplemented

25mL/day of olive oils among meals

Supplemented

•Tyrosol and Hydroxytyrosol are absorbed from moderate, real-life doses, of olive oil present in the market , in a dose-dependent manner with the phenolic content of the olive oil administered.

•No threshold exists for tyrosol and hydroxytyrosol absorption in humans from olive oil.

•Around 98% of tyrosol and hydroxytyrosol were present in plasma and urine in conjugated forms, mainly glucuronoconjugates; suggesting an extensive first pass intestinal/enterohepatic metabolism of the ingested phenolic compounds.

•Results suggest that the possible biological activity of tyrosol and hydroxytyrosol is linked to their biological metabolites rather than to the primary compounds present in the vegetal forms.

Sustained consumption of virgin olive oil lead to an increase of the pool of tyrosol and hydroxytyrosol in the body

Antioxidant effect of olive oil phenolic compounds in humans

ANTIOXIDANT EFFECTS OF OLIVE-OIL PHENOLIC CONTENT IN A DOUBLE-BLIND RANDOMIZED CONTROLLED CLINICAL TRIAL

Participants

32 volunteers from a religious community, aged 23 to 91 years.

Inclusion criteria

Healthy non-smoking voluntary men

Exclusion criteria

- Intake of any drug with established antioxidant properties
- High physical activity practice (>3000 kcal/day)
- Diabetes, coeliac or other intestinal diseases
- Any disease or condition that would impair compliance.

Dietary habits assessment

- Daily food records from religious centre kitchen.
- Participants were requested to avoid high intakes of foods containing high levels of phenolic compounds
- Daily management by trained personal during the 15 weeks of the study

Marrugat J et al,. EJN 2004

Placebo-controlled, double-blind, cross-over, randomised clinical trial.

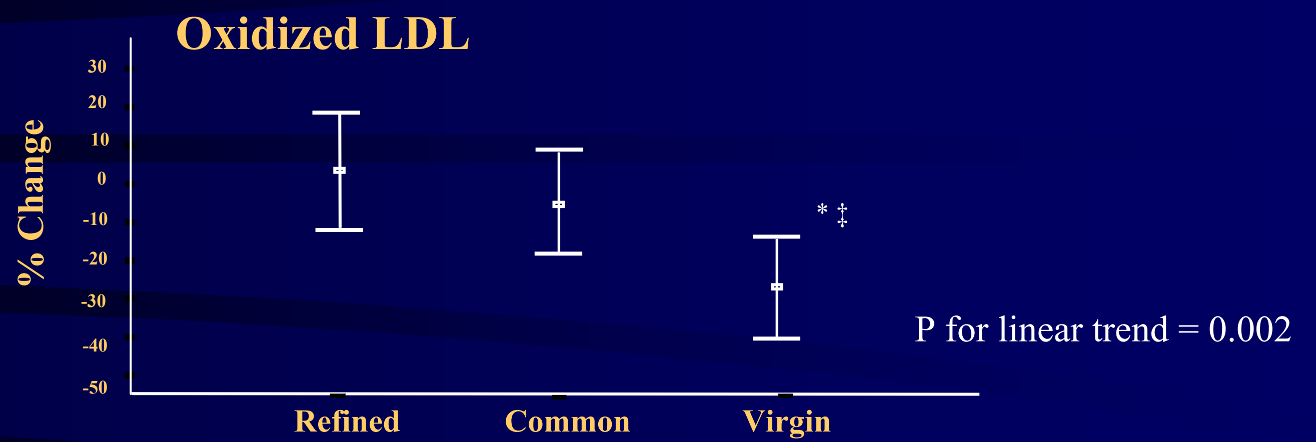
Order 1	wo	Virgin	wo	Common	wo	Refined
Order 2	wo	Common	wo	Refined	wo	Virgin
Order 3	wo	Refined	wo	Virgin	wo	Common

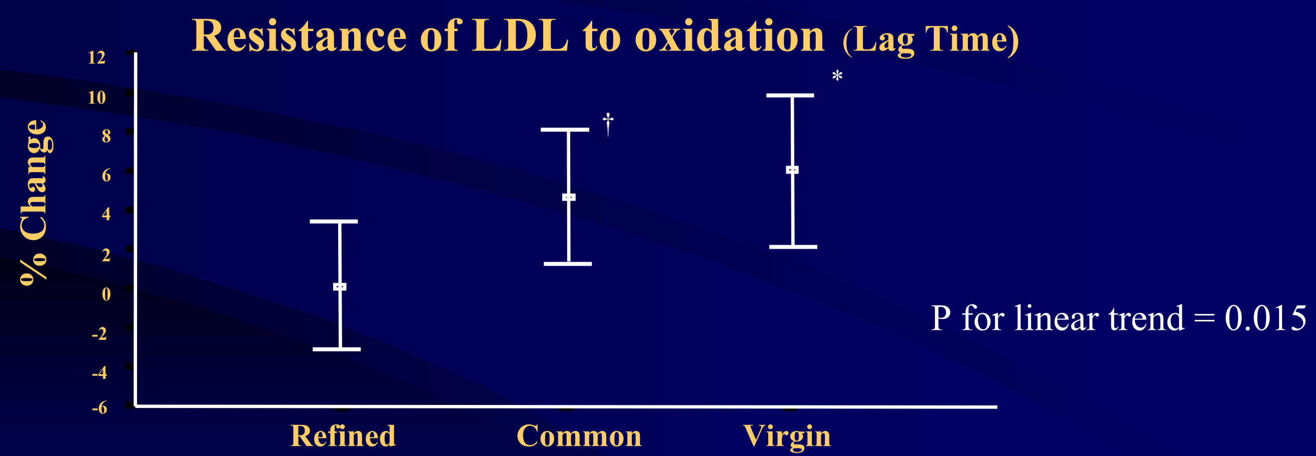
Phenolic content: Refined: 0mg/Kg; Common: 68 mg/Kg; Virgin: 150 mg/Kg

Intervention period: 3weeks, 25 ml/day. Refined olive oil was supplied for cooking purposes

WO: wash-out period (2 weeks) with refined olive oil for raw and cooking purposes (supplied for the community)

% of change in oxidative stress biomarkers after each intervention period



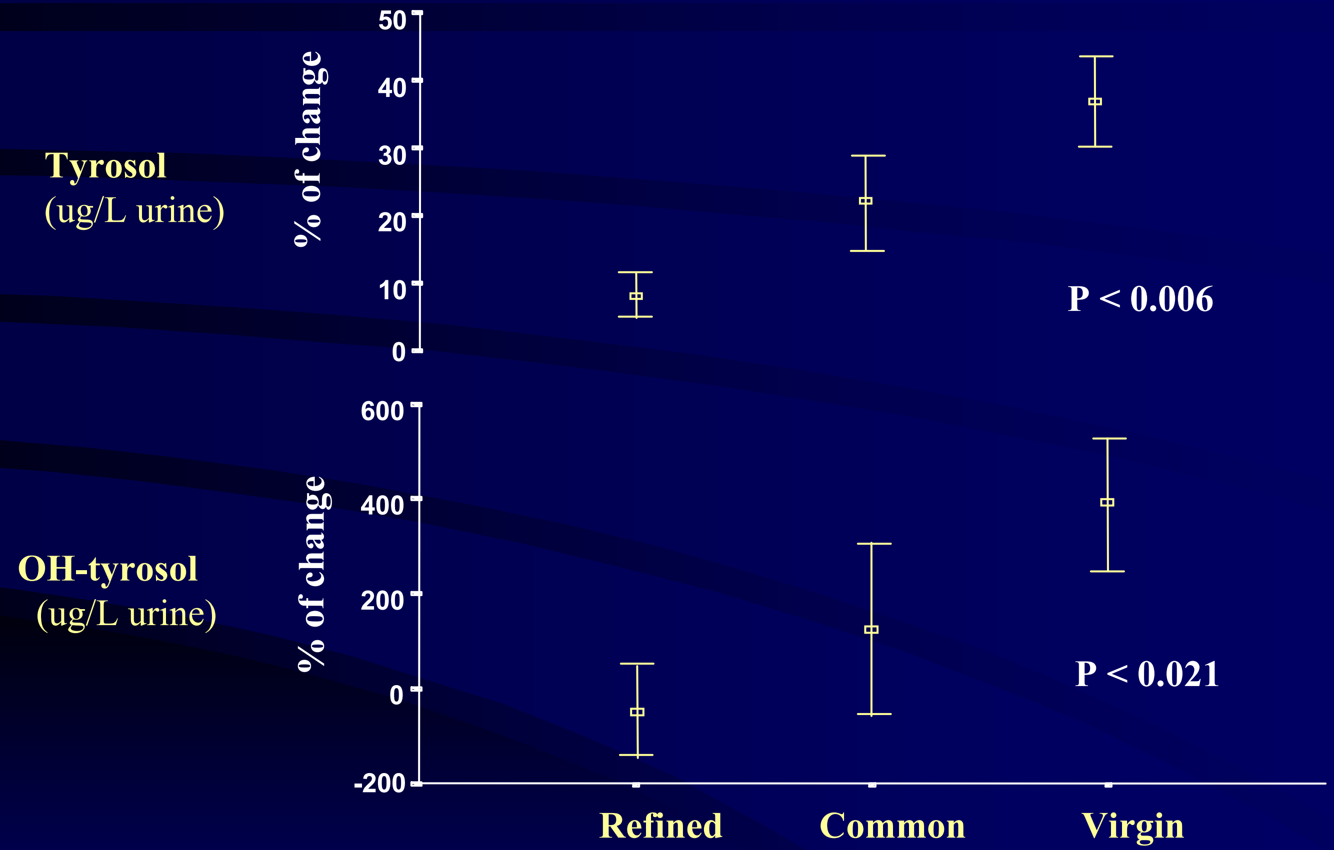


No significative differences were obtained in lipid peroxides and antibodies against oxidized LDL

Marrugat et al. Eur J Nutr. 2004

RESULTS

Order-adjusted changes in tyrosol and OH-tyrosol in each olive oil administration periods (n = 32, mean, SE)



Marrugat J, et al. Eur J Nutr. 2004

Participants: 12 healthy men aged 18-26 years

Two latin squares of 3 x 3 for six treatments were used to randomize olive oil administration to participants.

	1	2	3	4	5	6	7
Order 1	wo	LPC	wo	MPC	wo	HPC	
Order 2	wo	MPC	wo	HPC	wo	LPC	
Order 3	wo	HPC	wo	LPC	wo	LPC	
Order 4	wo	LPC	wo	HPC	wo	MPC	
Order 5	wo	MPC	wo	LPC	wo	HPC	
Order 6	wo	HPC	wo	MPC	wo	LPC	

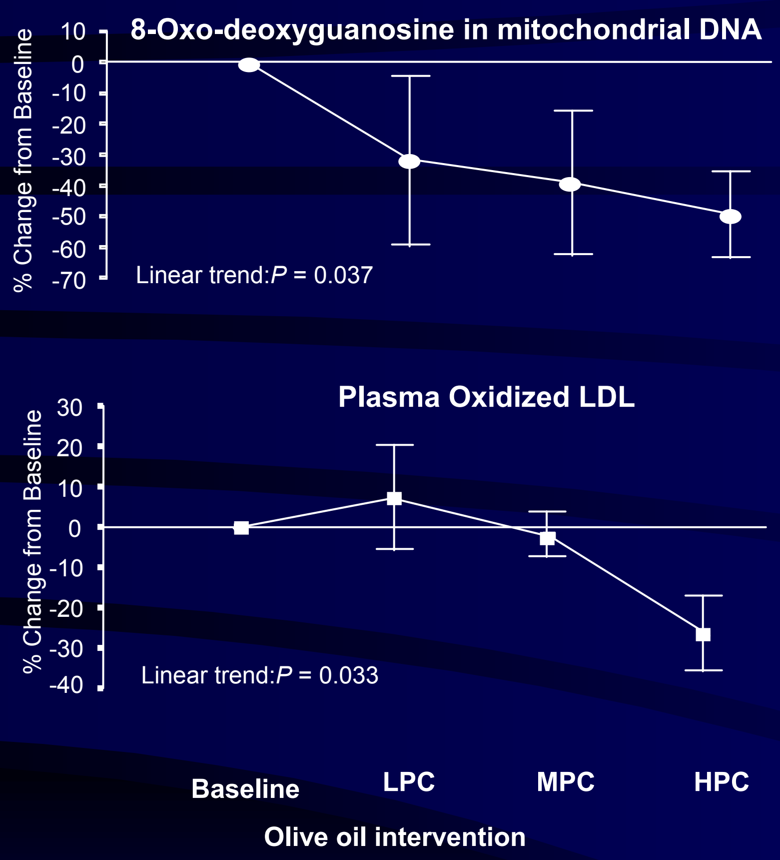
LPC: low phenolic content, 10 mg/Kg; MPC: medium phenolic content, 133 mg/Kg; HPC: high phenolic content, 486 mg/Kg, olive oils.

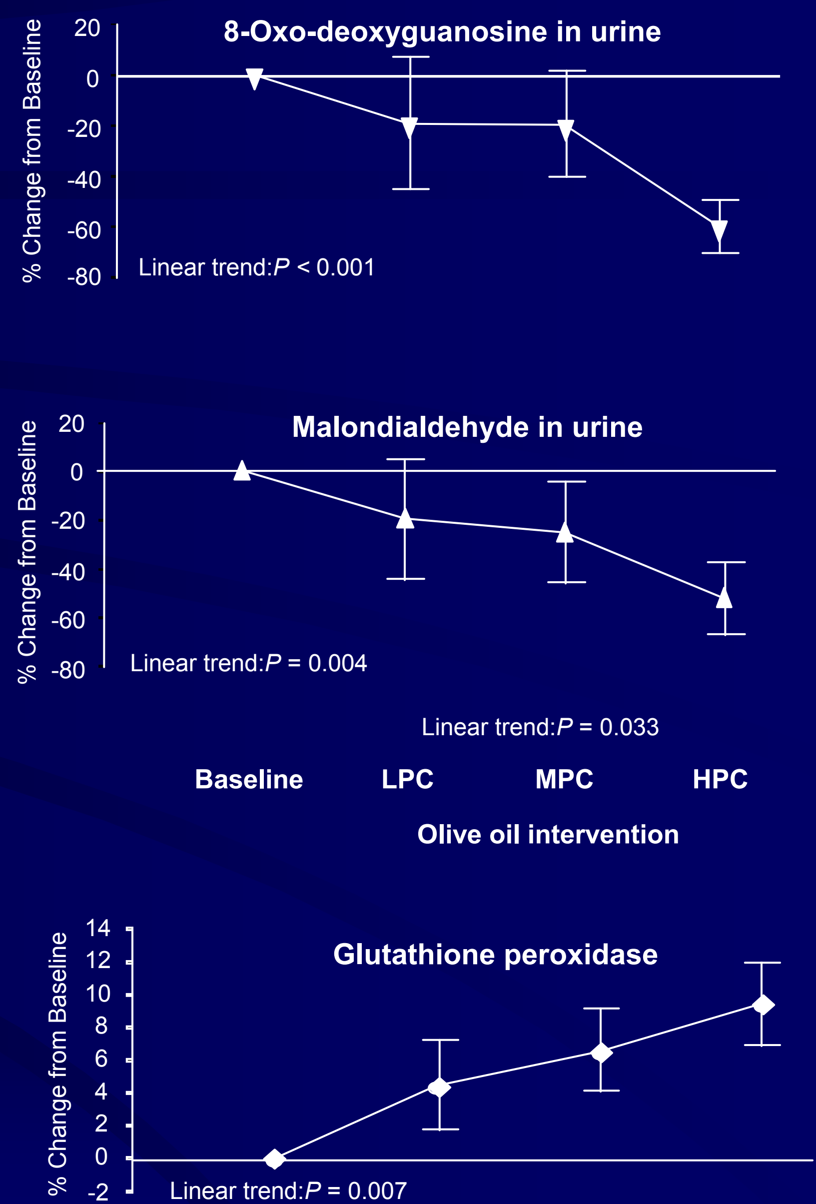
Intervention period: 4 days, 25 mL/day. LPC olive oil for cooking purposes. Very low-antioxidant diet

Washout period: 10 days: Days 1-7 with Low antioxidant diet, Days 8-10 with very low antioxidant diet. LPC olive oil for cooking and raw purposes (supply for the family)

Weinbrenner et al. J Nutr 2004

Changes in oxidative stress markers after 4 days of 25 mL/day consumption of olive oils with high (HPC, 486 mg/Kg), medium (133 mg/Kg), and low (10 mg/Kg) phenolic content

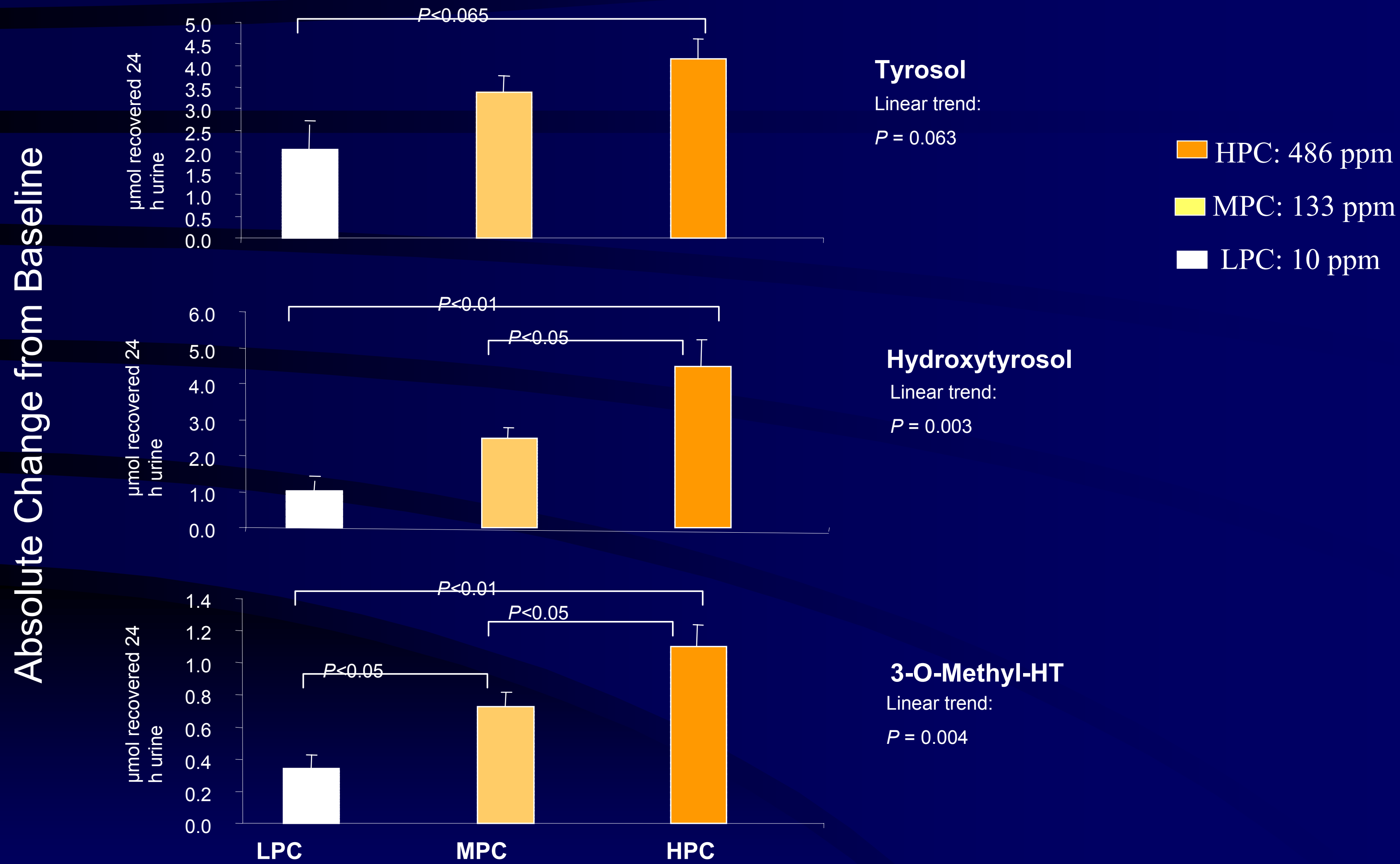




No differences were observed in F_2-isoprostanes

Weinbrenner T, et al. J Nutr 2004

Changes in T, HT and MHT in urine after 4 days of sustained consumption of olive oil (25 mL/day)



Weinbrenner T, et al. J Nutr 2004

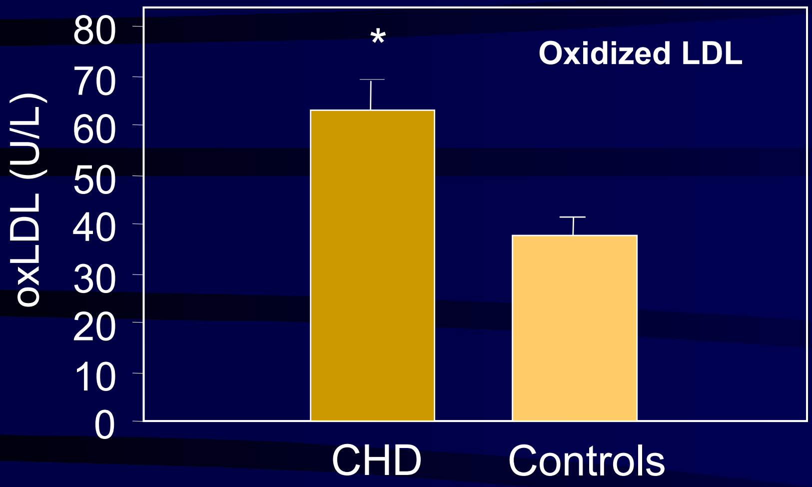
Antioxidant effect of olive oil phenolic compounds in randomized, crossover, controlled studies in NON healthy individuals

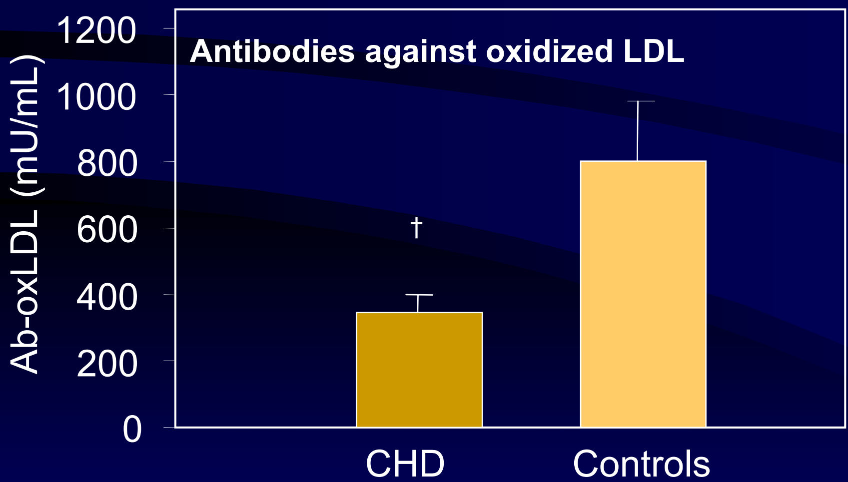
Subjects (n) (sex)	Intervention	Int period	Washout period	Baseline adjust.	Compliance markers	Markers	Effects	Reference
Peripheral vascular disease (24, men)	Virgin vs refined for all purposes	3 mo	3 mo usual diet	No	No	LPO in LDL Macrophage plasma oxidized LDL uptake	Decrease with olive oil phenol (all markers)	Ramírez-Tortosa et al (1999)
Hyperlipemic Patients (22) (12 men and 10 women)	Virgin vs refined (raw) (40 mL/day)	7 w	4 w usual diet	Yes	No	Plasma total antioxidant capacity F2-isoprostanes	Increase with olive oil phenols None	Visioli et al (2005)

Masella R, et al. Effects of dietary virgin olive oil phenols on low density lipoprotein oxidation in hyperlipidemic patients. Lipids. 2001;1195-202.

Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomised, crossover, controlled, clinical trial

Oxidative status in patiens with stable CHD





* p < 0.001, † p < 0.05

Weinbrenner T, et al. Atherosclerosis 2003; 168; 99-106

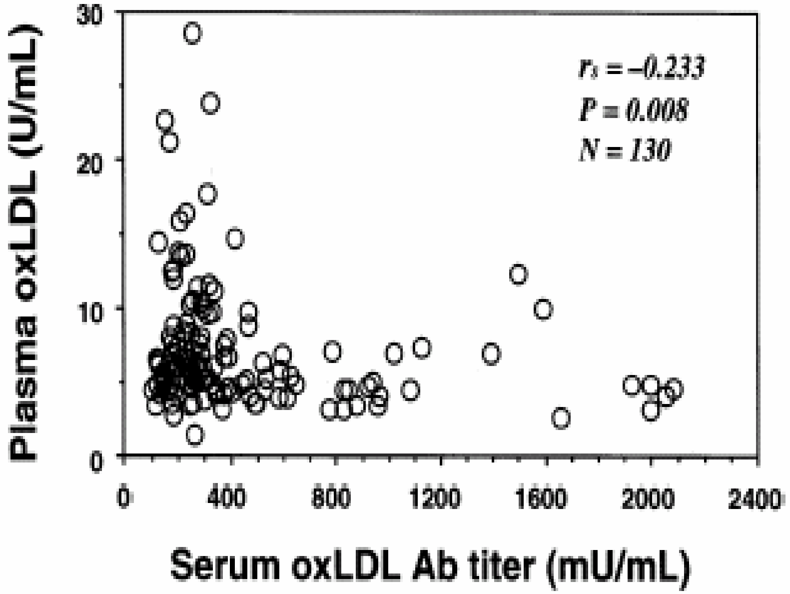


Fig. 2. Correlation between serum anti-oxidized LDL antibody titer and plasma oxidized LDL level. Correlation was evaluated by Spearman's rank correlation test. Abbreviations; oxLDL, oxidized low density lipoprotein; oxLDL Ab, anti-oxidized low density lipoprotein antibody; r_s, Spearman's correlation coefficient; P, level of significance.

Soji T et al. Atherosclerosis 2000;38; 171-177

Oxidative status markers in stable CHD patients after refined and virgin olive oil administration [mean (SD)]

n=40	Post refined olive oil (14.7 mg/Kg)	Post virgin olive oil (161 mg/Kg)	Mean difference between interventions (95% CI)	P for intervention (olive oil) effect	P for period (time) effect	P for interventi on-period effect
Oxidized LDL (µmol/L)	58.66 (23.05)	54.01 (19.89)	-4.66 (-7.08; -2.23)	< 0.001	0.941	0.705
Antibodies against oxidized LDL*	230 (122 - 495)	246 (140 - 487)	9.18 (-27.79; 9.42)	0.323	0.208	0.762
Lipid peroxides (µmol/L)	1.47 (1.23)	1.23 (0.72)	-0.24 (-0.40; -0.09)	0.003	0.563	0.205
Glutathione Peroxidase (U/L)	7308 (711)	7668 (854)	412 (35.98; 788)	0.033	0.346	0.258
Total antioxidant status (mmol/L)	0.92 (0.12)	0.91 (0.11)	-0.01 (-0.03; 0.01)	0.301	0.715	0.172
Tyrosol (µg/L urine) *	23.68 (9.38 – 53.3)	77.5 (74.8 – 81.0)	32.67 (3.18 – 62.16)	0.031	<0.000	0.459
Hydroxytyrosol (µg/L urine) *	87.2 (74.1 – 156)	484 (439 – 531)	374 (310 – 438)	< 0.001	<0.001	0.478
O-methylhydroxytyrosol (µg/L urine) *	10.00 (2.93 – 17.00)	43.18 (31.3 – 63.9)	33.50 (4.67 – 62.32)	0.024	<0.000	0.651

Adjusted by age, order of olive oil intervention and baseline vlues. * Median, 25-75 percentile

Fitó M, et al. Atherosclerosis (in press)

Consensus reports

International Conference of Olive Oil and Health. Jaen, Spain October 2004

IOOC Workshop on State of the Art, Nutrition and Health. Madrid, Spain, March 2005

Olive oil phenolic compounds are bioavailable in humans in a dose-dependent manner with the phenolic content of the olive oil administered

Data regarding the benefits of olive oil phenolic compounds in humans from real-life daily doses of olive oil are still controversial

The protective effects on lipid oxidation in these trials being better displayed in oxidative stress conditions

In general the best results obtained on lipid oxidation were displayed in those markers directly associated with LDL oxidation.

Carefully controlled studies in appropriate populations, or with a large sample size, are required to definitively establish in which conditions phenolics from olive oil can exert their most benefitial effect controlling oxidative stress

Eur J Clin Invest 2005;35:421-424

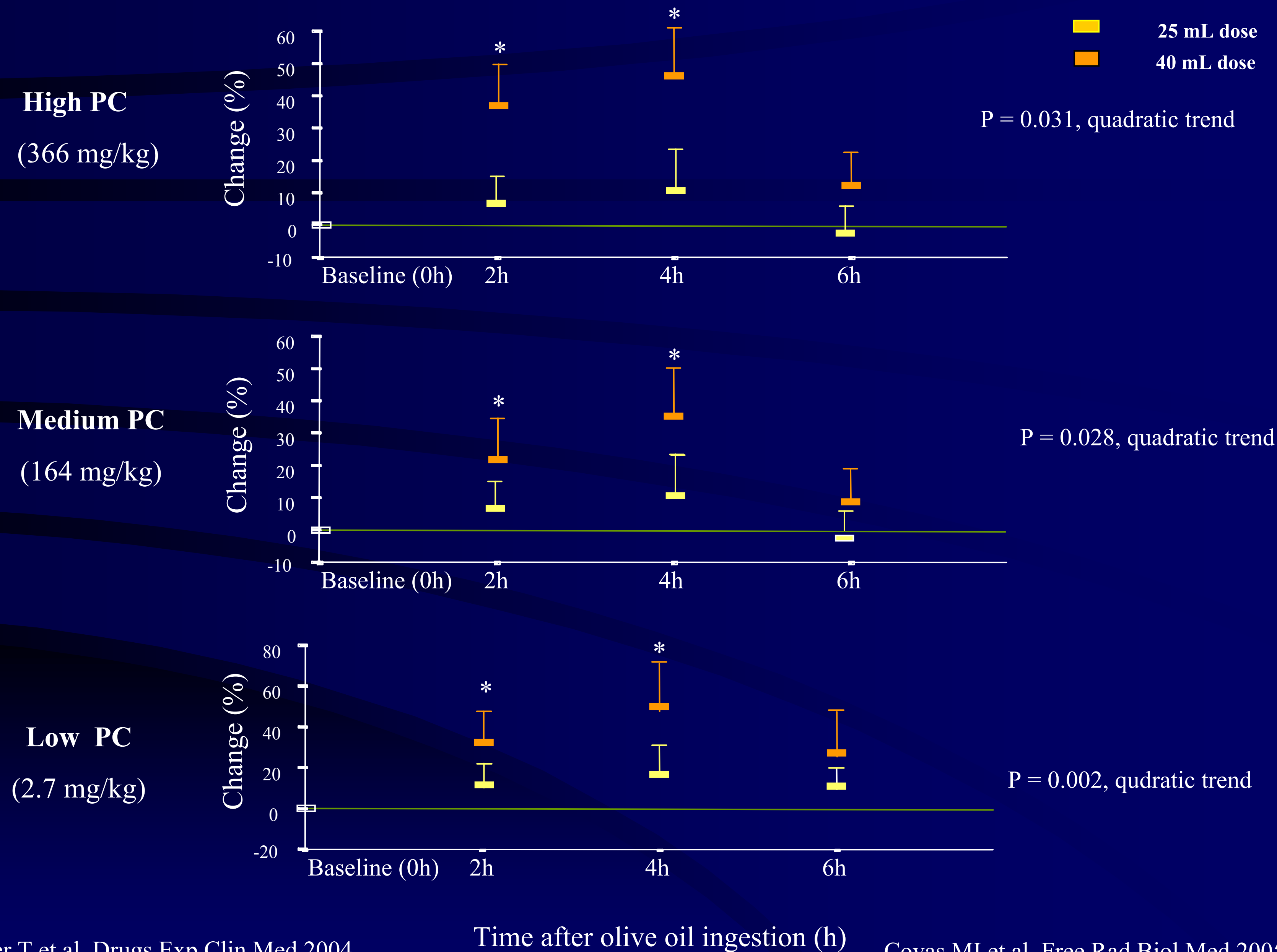
The effects of olive oil phenolics on oxidative markers in humans are more likely to be displayed in oxidative stress conditions

(i.e: males,males submitted to a very strict antioxidant diet, hyperlipidaemic, peripheral vascular disease, or CHD patients)

This can be explained by the fact that the balance of proxidant and antioxidant reactions is well regulated in the body.

Due to this, an intervention with an antioxidant-rich compound without any oxidative stress involved may exert only a marginal effect.

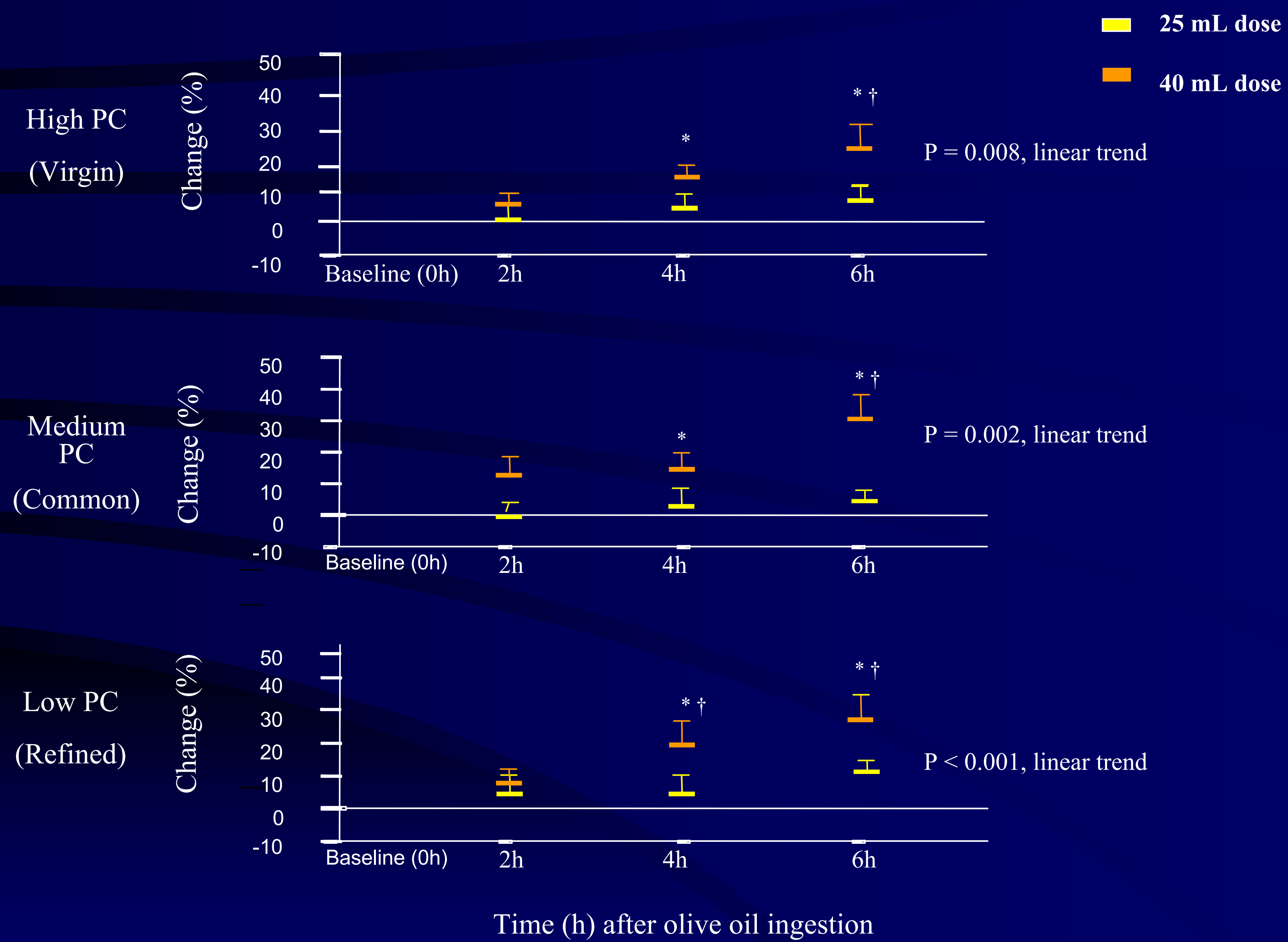
Postprandial changes in Triglycerides after olive oil ingestion



Weinbrenner T et al. Drugs Exp Clin Med 2004

Covas MI et al. Free Rad Biol Med 2005 (in press)

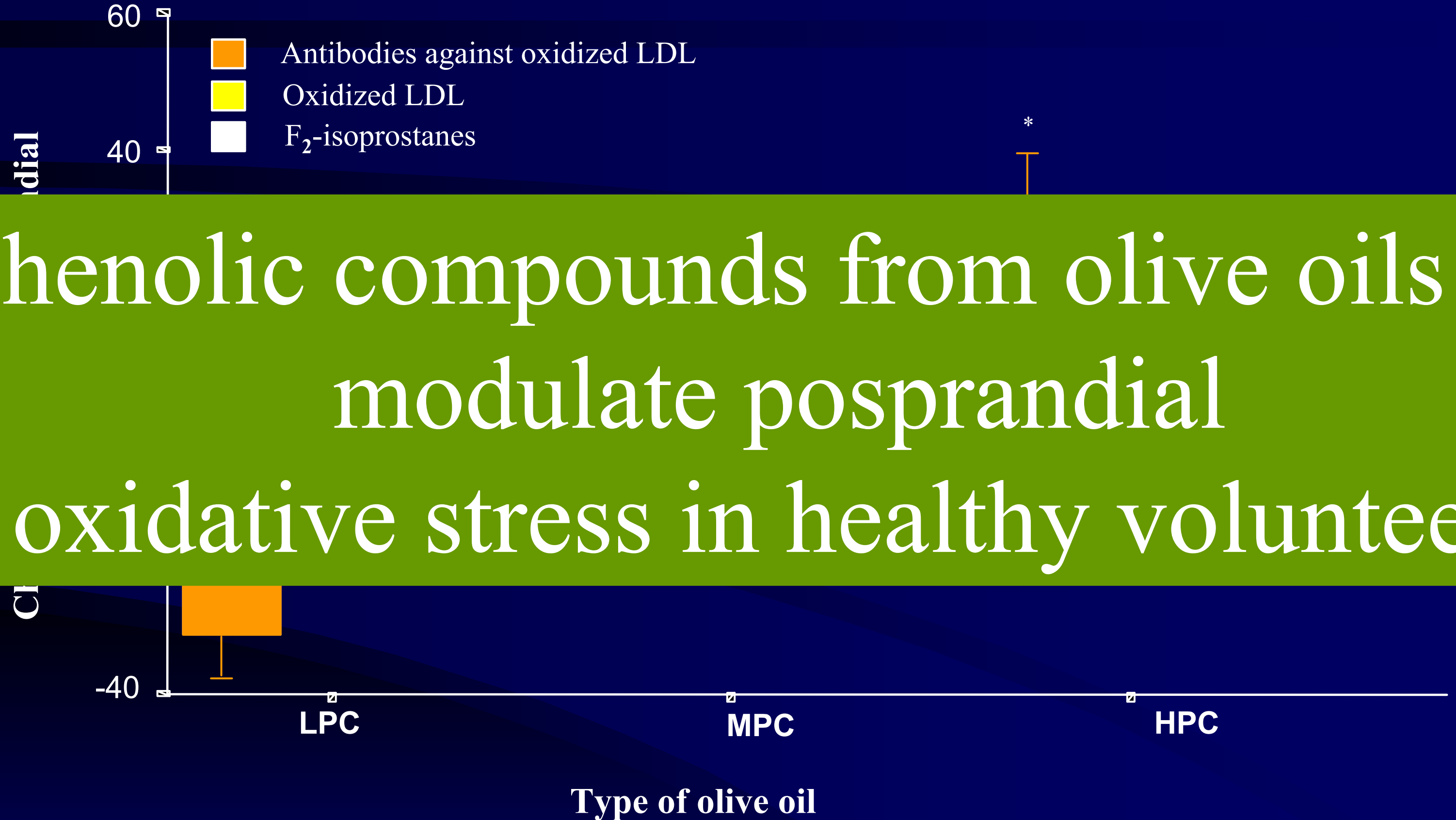
Postprandial changes in isoprostanes after olive oil ingestion



Weinbrenner T et al. Drugs Exp Clin Med 2004

Covas MI et al. Free Rad Biol Med 2005 (in press)

Changes in oxidative stress markers at 4 h after ingestion of 40 mL olive oil with low (LPC), medium (MPC), and high (HPC) phenolic content



Phenolic compounds from olive oils can modulate posprandial oxidative stress in healthy volunteers

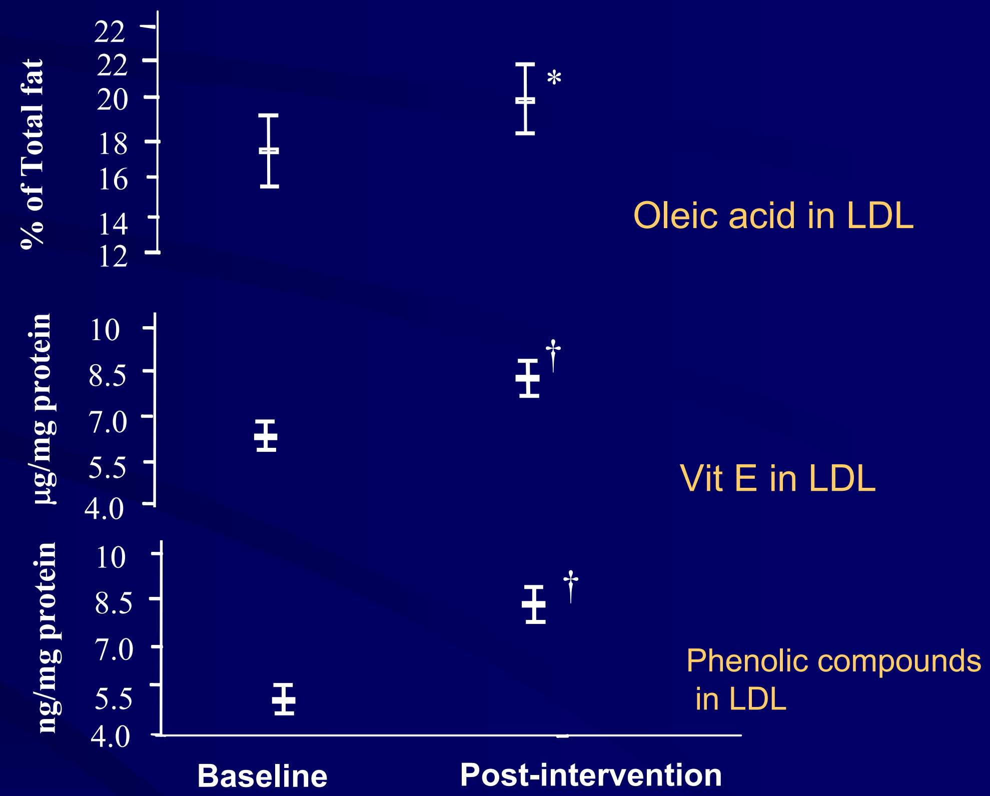
* $P < 0.05$ for linear trend. GLMM adjusted by individual level of test subjects and olive oil administration order .

Covas MI et al. Free Rad Biol Med 2005 (in press)

In general the best results obtained on lipid oxidation were displayed in those markers directly associated with LDL oxidation.

The fact that the ingestion of phenolic compounds from olive oil promote an increase in the antioxidant LDL phenolic content could account for this fact.

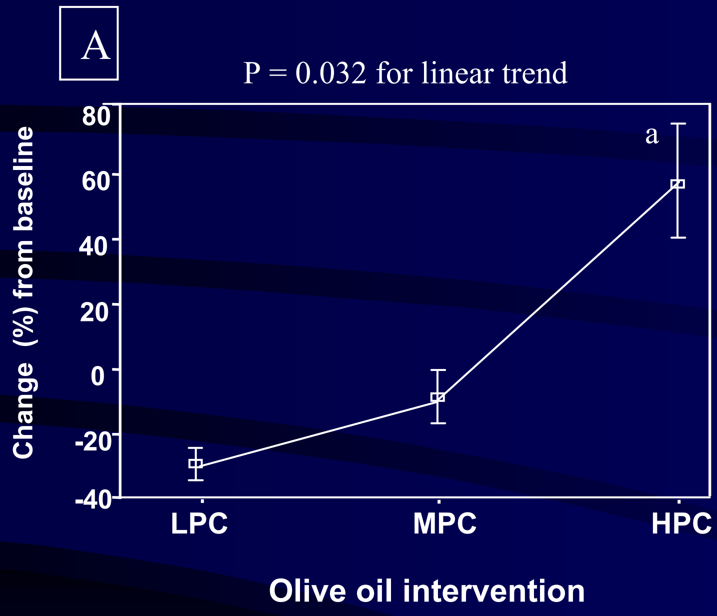
Levels of oleic acid and antioxidants in LDL after sustained (1 week, 25ml/day) doses of virgin olive oil

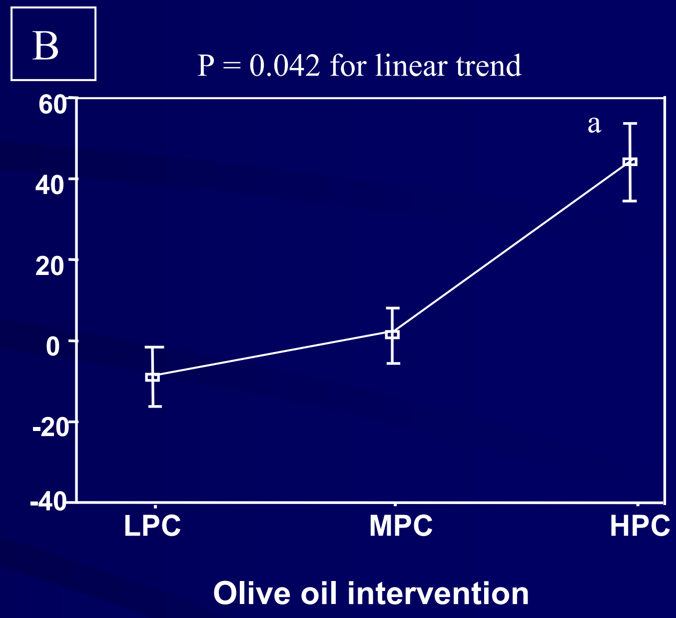


Gimeno et al. Eur J Clin Nutr 2002; 56:114-120

Changes in the total phenolic content of the LDL

at 1h (A), and after 4 days (B) of 25 mL/day consumption of olive oils with high (HPC, 360 mg/Kg), medium (164 mg/Kg), and low (2.7 mg/Kg) phenolic content

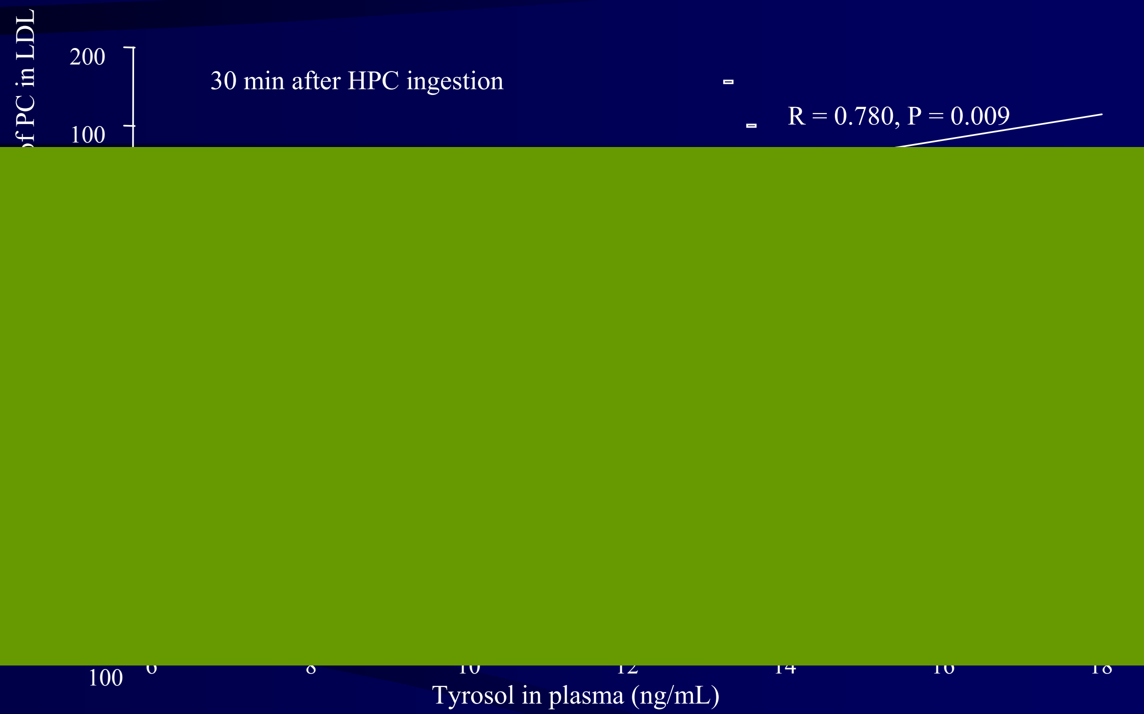


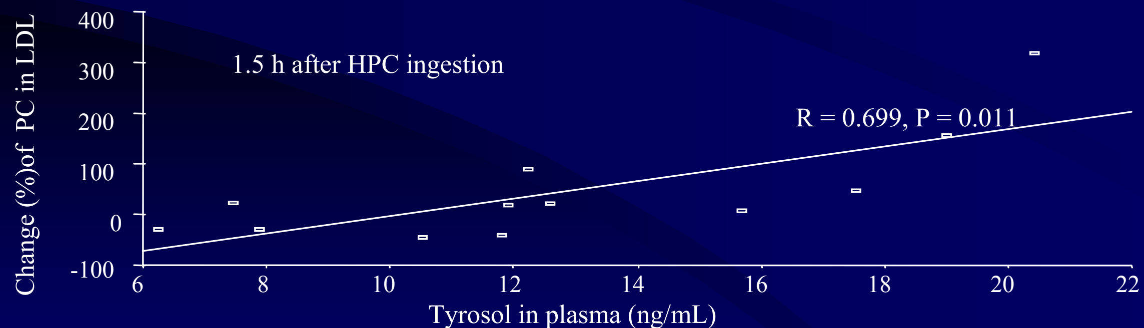


[a] P< 0.05 versus LPC

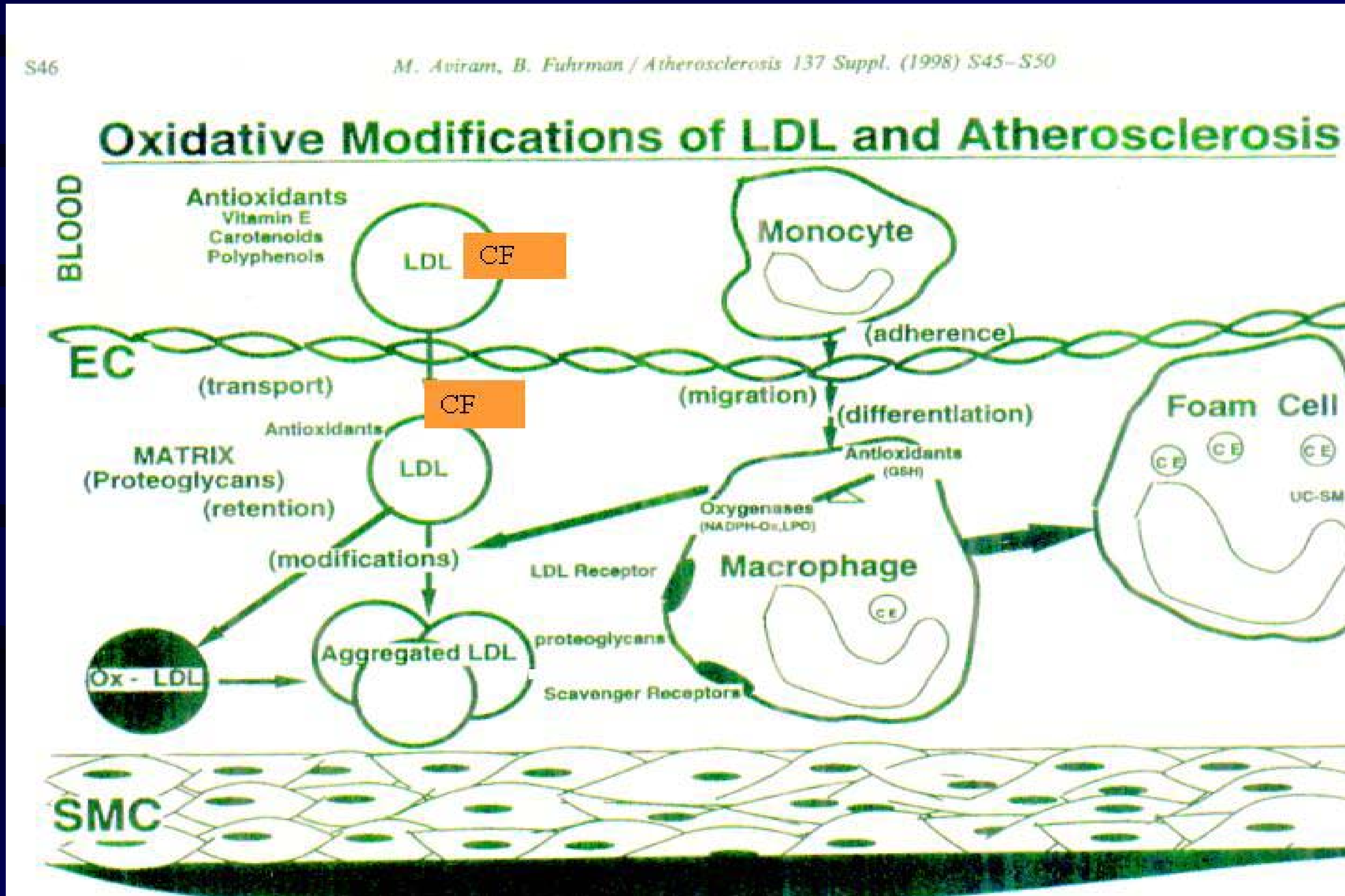
Covas MI et al. Free Rad Biol Med 2005 (in press)

Relationship between changes in the Total Phenolic Content (PC) of the LDL and plasma hydroxytyrosol and tyrosol levels after high phenolic content olive oil (HPC, 360 mg/Kg) ingestion





Covas MI et al. Free Rad Biol Med 2005 (in press)


S46
M. Aviram, B. Fuhrman / Atherosclerosis 137 Suppl. (1998) S45–S50
Oxidative Modifications of LDL and Atherosclerosis
BLOOD
Antioxidants
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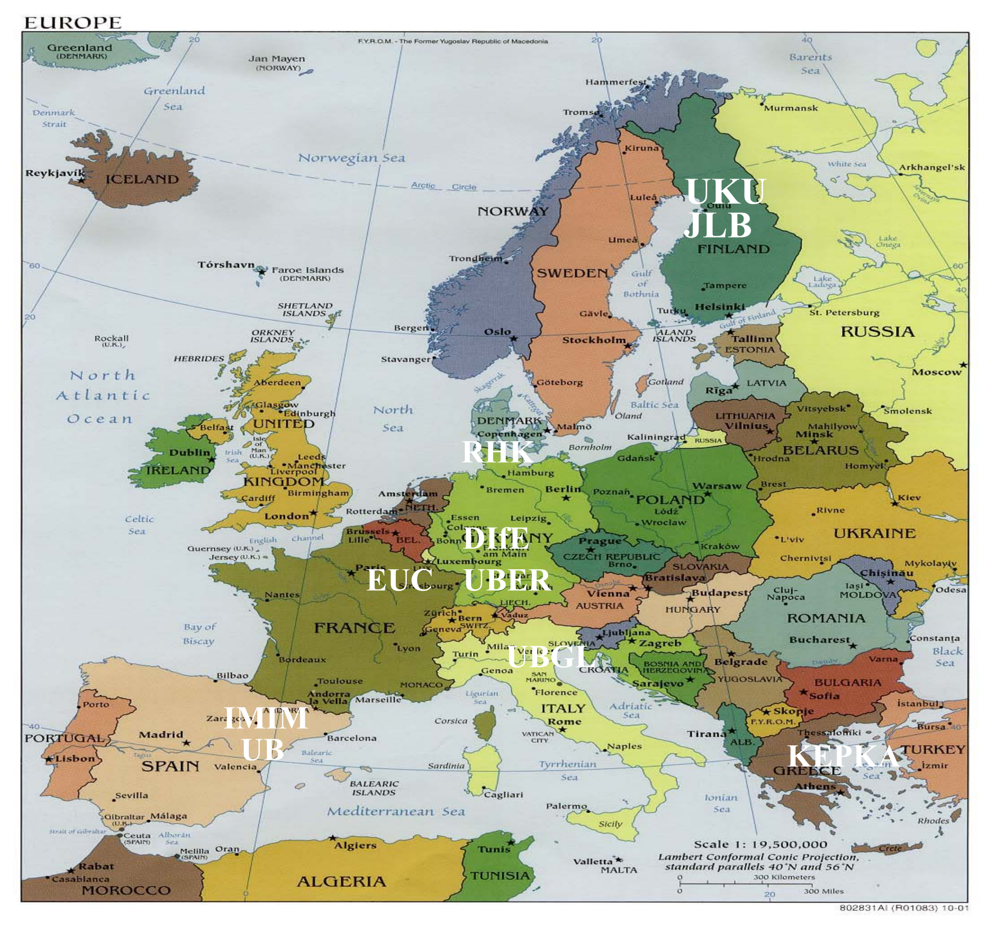
Carotenoids
Polyphenols
LDL
CF
Monocyte
(adherence)
EC
(transport)
CF
(migration)
(differentiation)
Foam Cell
Antioxidants
MATRIX
(Proteoglycans)
(retention)
LDL
Antioxidants
(GSH)
Oxygenases
(NADPH-Ox,LPO)
UC-SM
(modifications)
LDL Receptor
Macrophage
proteoglycans
Aggregated LDL
Ox - LDL
Scavenger Receptors
SMC

Comments

Carefully controlled studies in appropriate populations, or with a large sample size, are required to definitively establish in which conditions phenolics from olive oil can exert their most benefitial effect controlling oxidative stress

The results of the EUROLIVE study *(The effect of olive oil consumption on oxidative damage in European populations),* an European study performed in 200 individuals from 6 Centres of 5 European countries will contribute to clarify the antioxidant effect of olive oil phenolic compounds in healthy individuals



IMIM

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Oxidative status markers in stable CHD patients after refined and virgin olive oil administration [mean (SD)]

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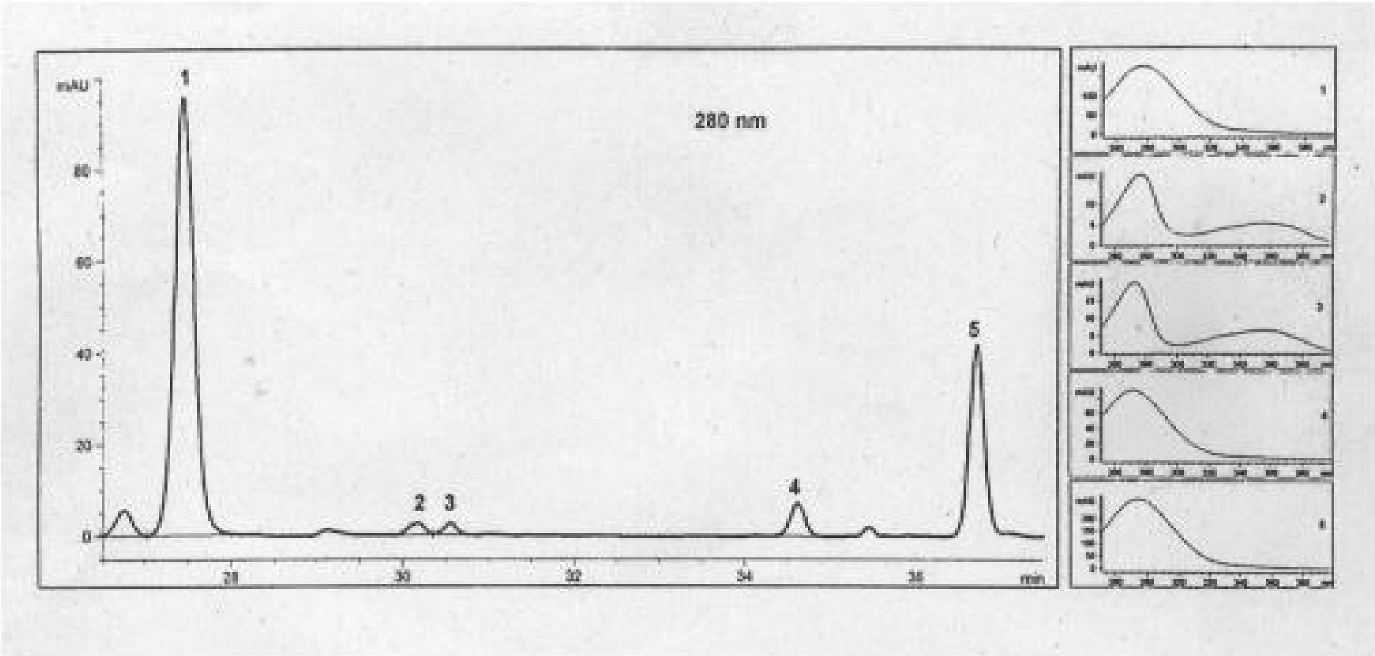
Glutathione Peroxidase (U/L)	7308 (711)	7668 (854)	412 (35.98; 788)	0.033	0.346	0.258
Total antioxidant status (mmol/L)	0.92 (0.12)	0.91 (0.11)	-0.01 (-0.03; 0.01)	0.301	0.715	0.172
Tyrosol (µg/L urine) *	23.68 (9.38 – 53.3)	77.5 (74.8 – 81.0)	32.67 (3.18 – 62.16)	0.031	<0.000	0.459
Hydroxytyrosol (µg/L urine) *	87.2 (74.1 – 156)	484 (439 – 531)	374 (310 – 438)	< 0.001	<0.001	0.478
O-methylhydroxytyrosol (µg/L urine) *	10.00 (2.93 – 17.00)	43.18 (31.3 – 63.9)	33.50 (4.67 – 62.32)	0.024	<0.000	0.651

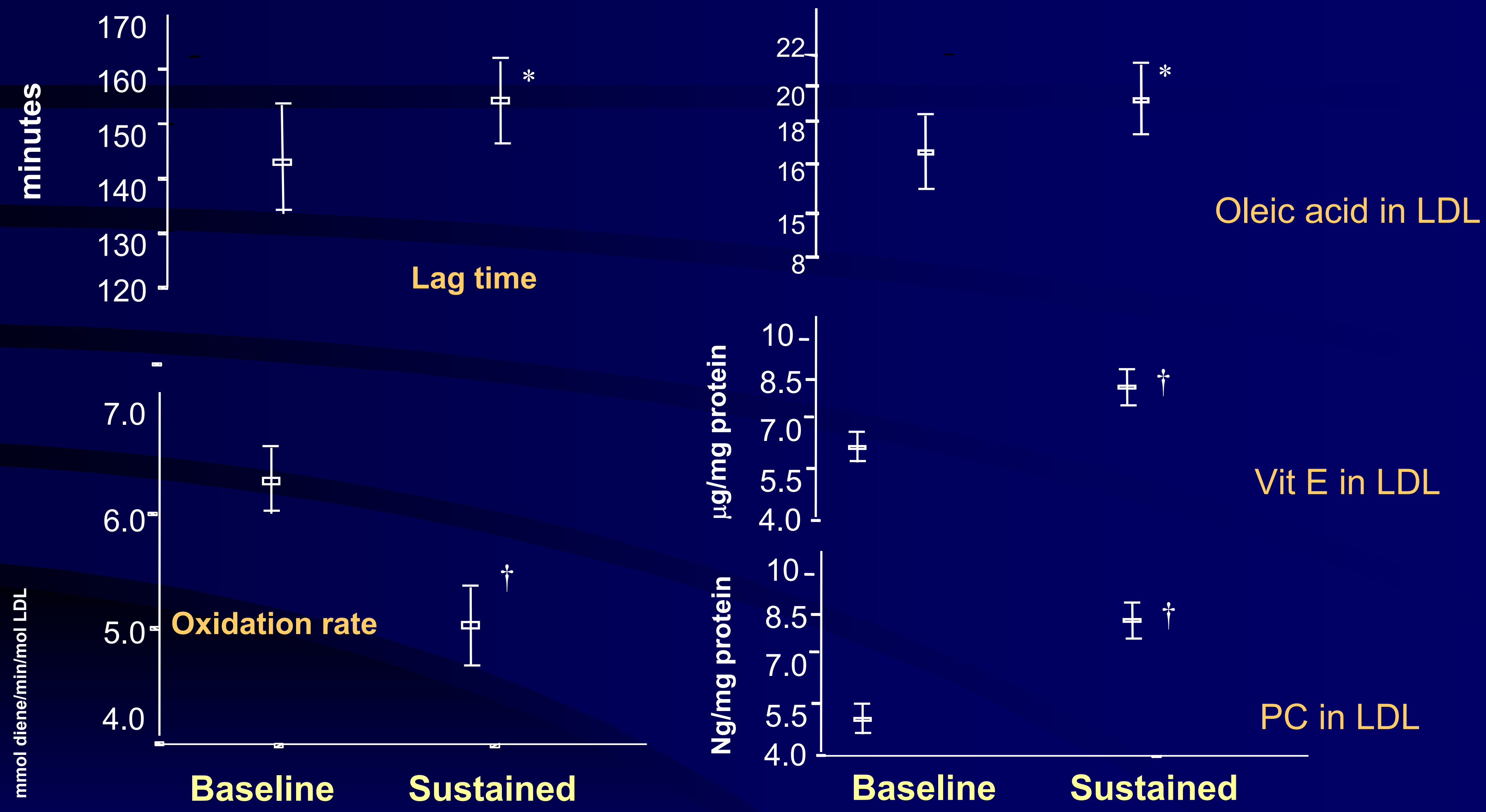
Adjusted by age, order of olive oil intervention and baseline vlues. * Median, 25-75 percentile

Fitó M, et al. Atherosclerosis (in press)



Lamuela-Raventós MR et al. Clin Chem 1999;45:1870-2

LDL oxidation and levels of oleic acid and antioxidants in LDL after sustained (1 week, 25ml/day) doses of virgin olive oil



Gimeno et al. Eur J Clin Nutr 2002; 56:114-120

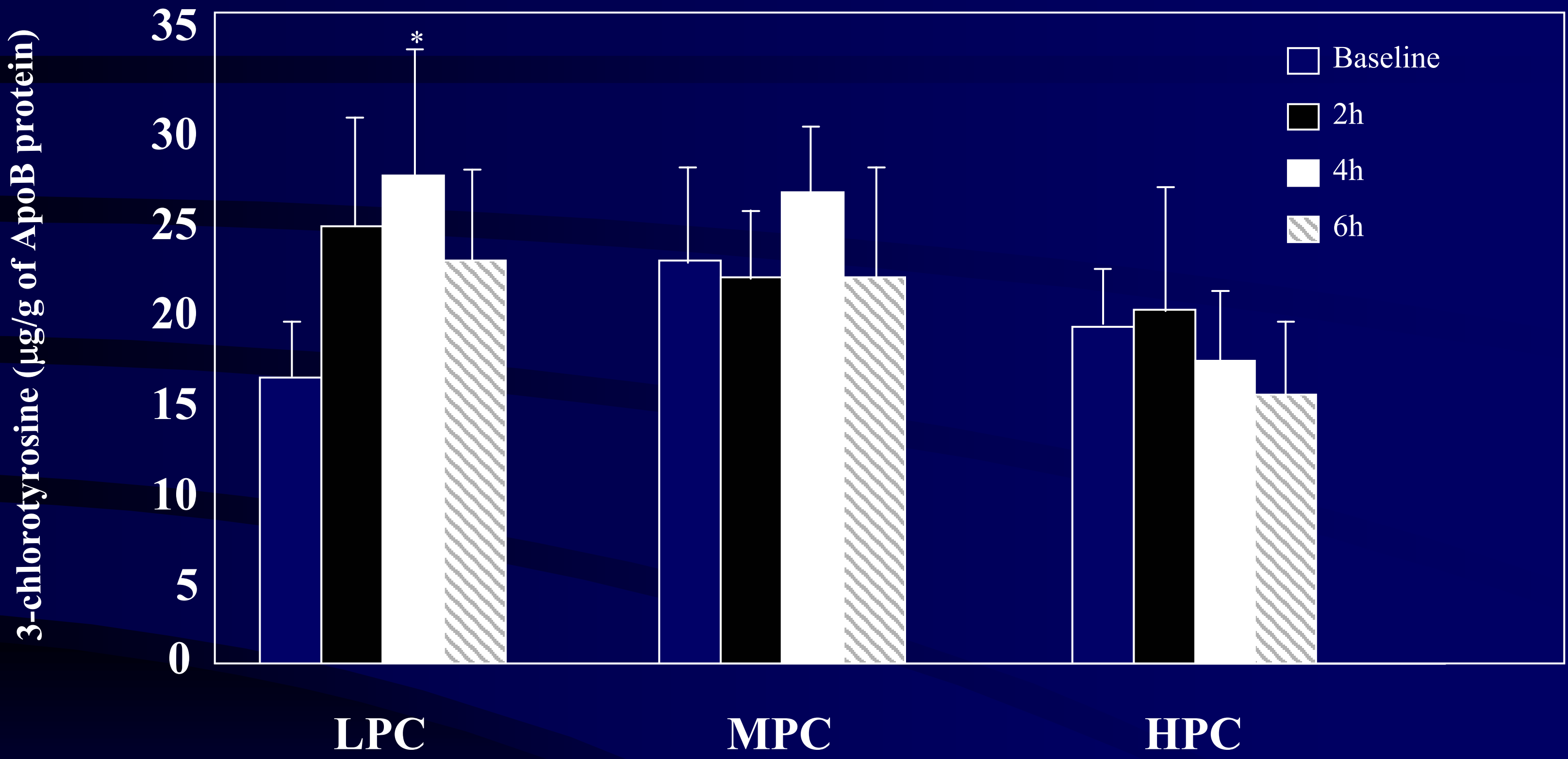
Compliance markers in stable CHD patients after refined and virgin olive oil administration [mean (SD)]

n=40	Post refined olive oil (14.7 mg/Kg)	Post virgin olive oil (161 mg/Kg)	Mean difference between interventions (95% CI)	P for intervention (olive oil) effect	P for period (time) effect	P for intervention-period effect
Tyrosol (µg/L urine) *	23.68 (9.38 – 53.3)	77.5 (74.8 – 81.0)	32.67 (3.18 – 62.16)	0.031	<0.001	0.459
Hydroxytyrosol (µg/L urine) *	87.2 (74.1 – 156)	484 (439 – 531)	374 (310 – 438)	< 0.001	<0.001	0.478
O-methylhydroxytyrosol (µg/L urine) *	10.00 (2.93 – 17.00)	43.18 (31.3 – 63.9)	33.50 (4.67 – 62.32)	0.024	<0.000	0.651

Adjusted by age, order of olive oil intervention and baseline vlues. * Median, 25-75 percentile

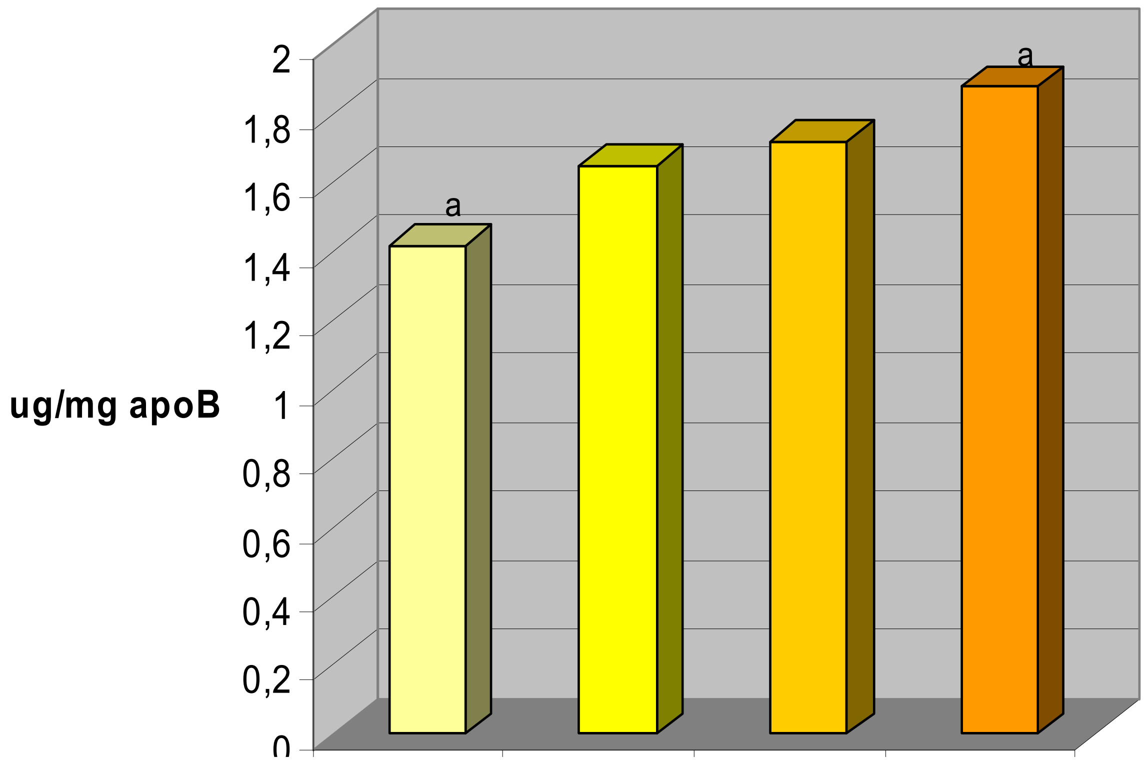
Fitó M, et al. Atherosclerosis (in press)

Changes in 3-chlorotyrosine in VLDL+LDL at baseline (0h) and at 2, 4, and 6 h after ingestion of olive oils with low (LPC), medium (MPC), and high (HPC) phenolic content



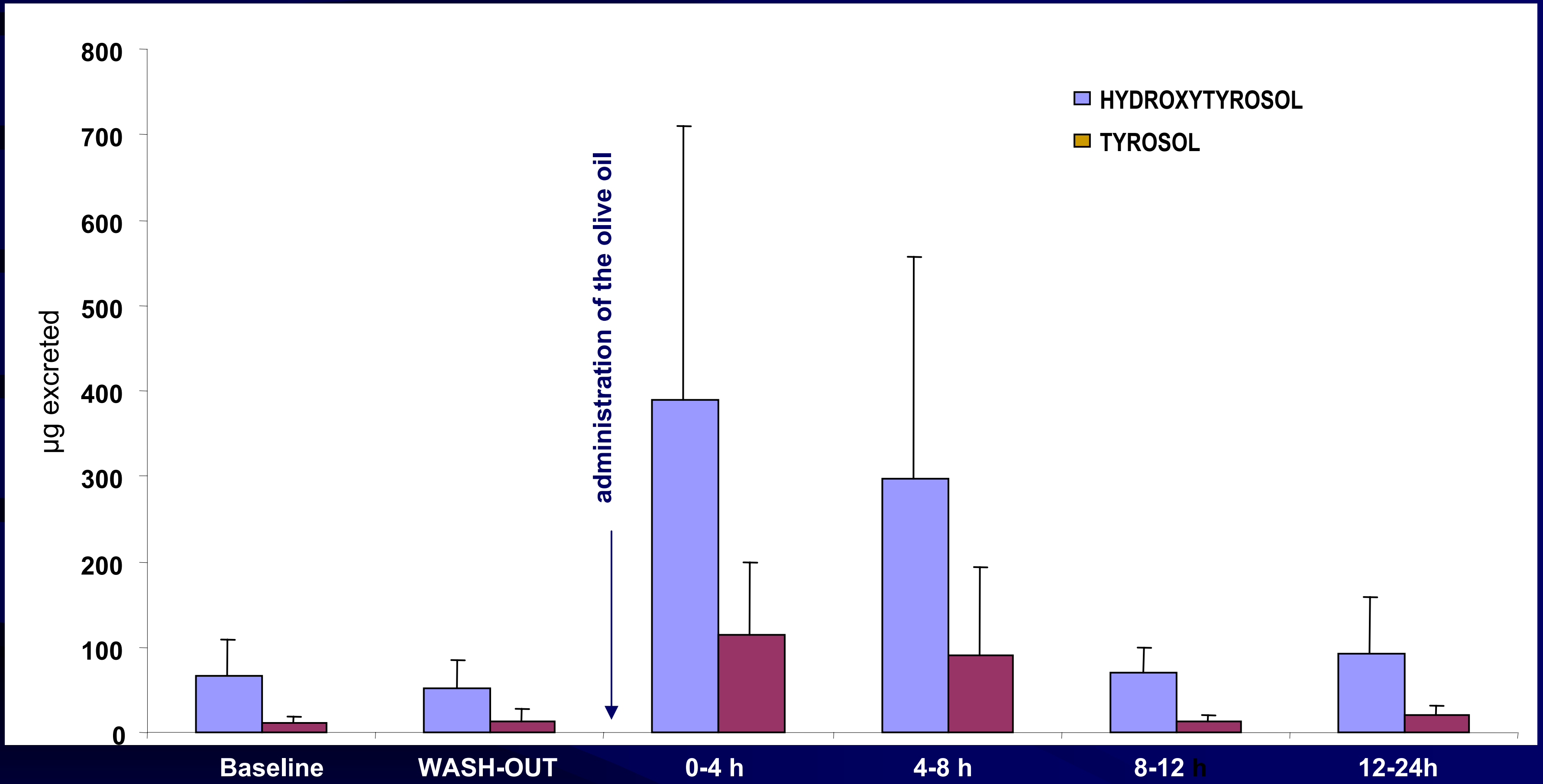
Covas MI et al. Free Rad Biol Med 2005 (in press)

Total phenolic content in LDL at the begining of the study and after each intervention period



[a] $P<0.05$

Bioavailability of tyrosol and hydroxytyrosol, from 50 mL virgin olive oil ingestion,(251 ppm) in humans after urine acidic treatment



Miró-Casas et al. Anal Biochem 2001; 294:63-72

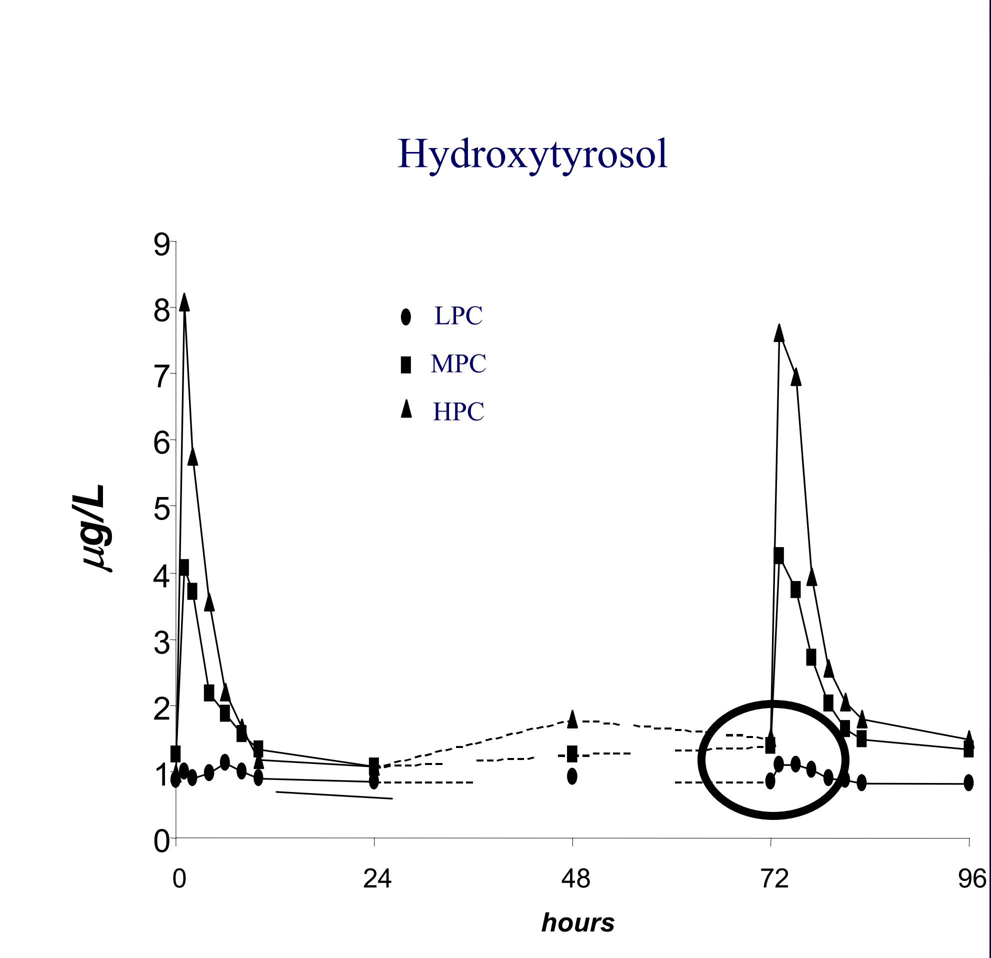
Oxidative status markers in stable CHD patients after refined and virgin olive oil administration [mean (SD)]

n=40	Post refined olive oil (14.7 mg/Kg)	Post virgin olive oil (161 mg/Kg)	Mean difference between interventions (95% CI)	P for intervention (olive oil) effect	P for period (time) effect	P for intervention-period effect
Oxidized LDL (µmol/L)	58.66 (23.05)	54.01 (19.89)	-4.66 (-7.08; -2.23)	< 0.001	0.941	0.705
Antibodies against oxidized LDL*	230 (122 - 495)	246 (140 - 487)	9.18 (-27.79; 9.42)	0.323	0.208	0.762
Lipid peroxides (µmol/L)	1.47 (1.23)	1.23 (0.72)	-0.24 (-0.40; -0.09)	0.003	0.563	0.205
Glutathione Peroxidase (U/L)	7308 (711)	7668 (854)	412 (35.98; 788)	0.033	0.346	0.258
Total antioxidant status (mmol/L)	0.92 (0.12)	0.91 (0.11)	-0.01 (-0.03; 0.01)	0.301	0.715	0.172

Adjusted by age, order of olive oil intervention and baseline vlues. * Median, 25-75 percentile

Fitó M, et al. Atherosclerosis 2005

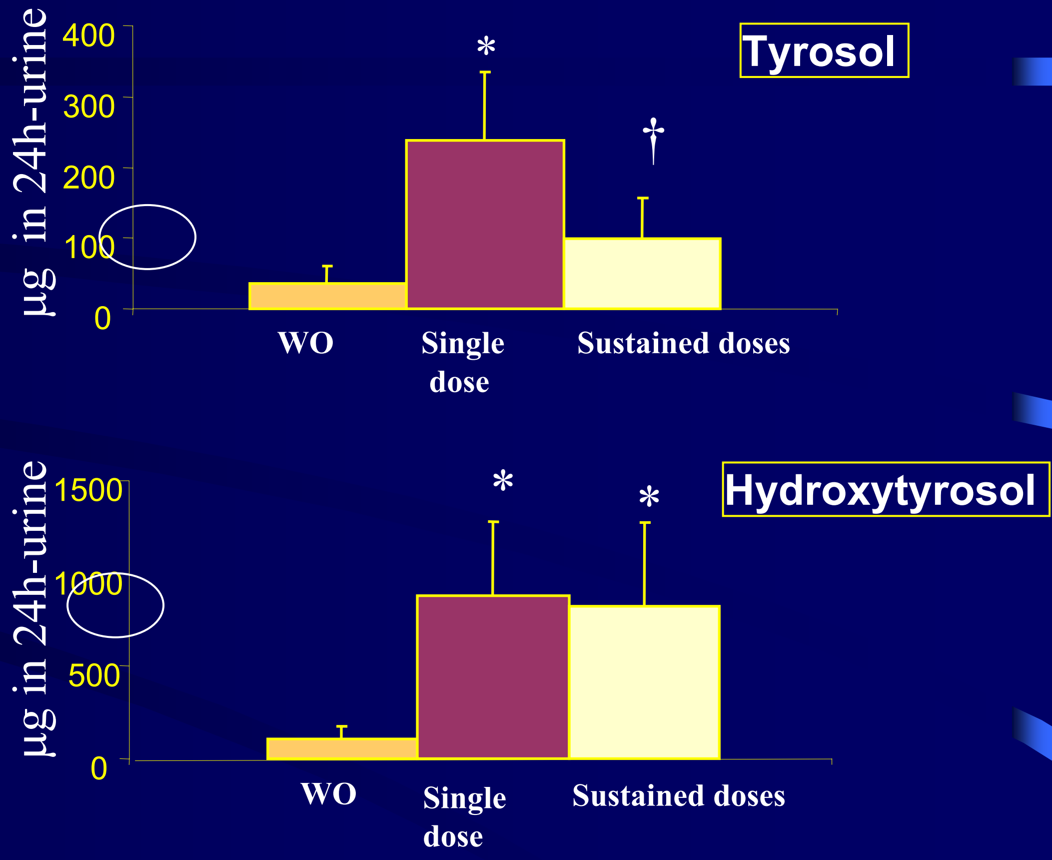
Levels of Tyrosol and Hydroxytyrosol in 24-h urine after a single dose (50 ml) and sustained (1 week, 25ml/day) doses of virgin olive oil (250 mg/kg)



Non-supplemented

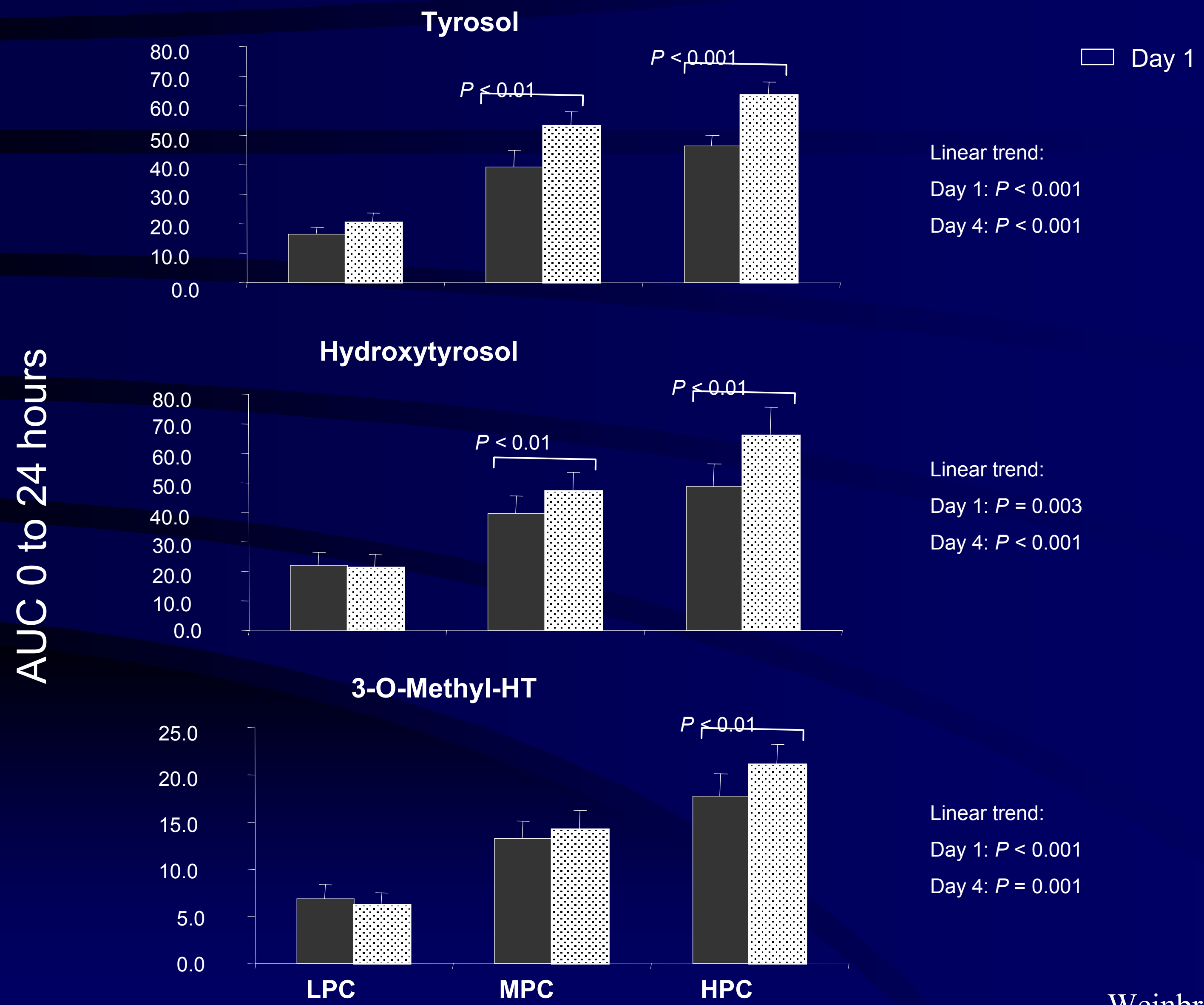
Supplemented

Weinbrenner T et al. J Nutr 2004;



Miró-Casas et al. Eur J Clin Nutr 2003;57:186-90

Plasma AUC for T, HT and MHT after a single dose (25 mL, day 1) and after 4 days of sustained olive oil consumption (25 mL day)



HPC: 486 ppm

MPC: 133 ppm

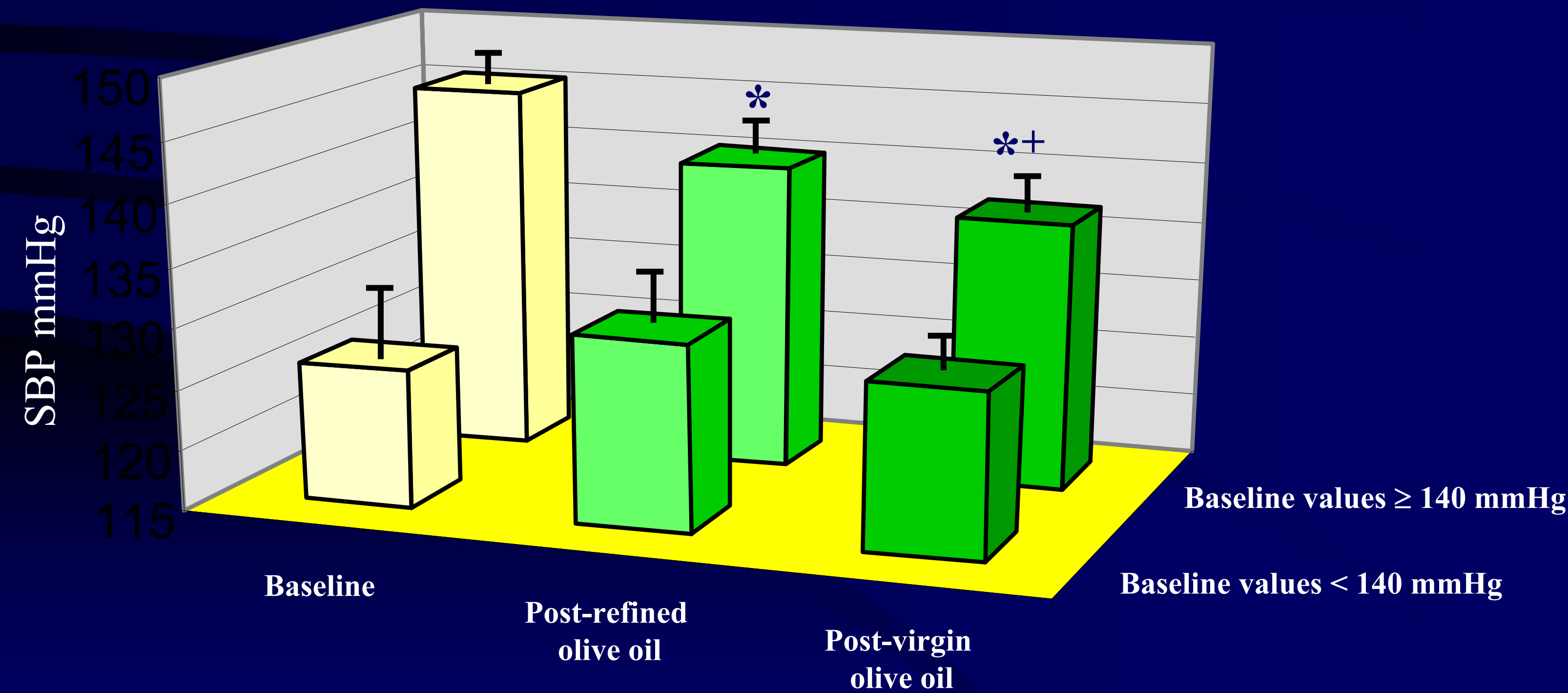
LPC: 10 ppm

Weinbrenner et al. J Nutr 2004

Changes in SBP after olive oil treatments in hypertensive stable CHD patients

n=19	Post refined olive oil (14.67 mg/Kg)	Post virgin olive oil (161 mg/Kg)	Mean difference between interventions (95% confidence interval)	P for intervention (olive oil) effect	P for period (time) effect	P for intervention-period effect
Systolic blood pressure (mmHg)	135.2 (6.58)	132.6 (5.6)	-2.53 (-3.78; -1.27)	0.001	0.799	0.340

Changes in SBP after olive oil treatments according to SBP baseline values in stable CHD patients after olive oil interventions



Fitó M, et al. Atherosclerosis 2005