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THE CENTER FOR RESTORATIVE
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INTRODUCTION 2

- Approximately 30% of humans carry one or both copies of the Apolipoprotein E 4 genotype (Apo E 4), the heterozygous Apo E 3/4, (25%), APO E 2/4 (2%), or the homozygous Apo E 4/4
- The Apo E 4 genotype is common to the great apes, but only humans can and do carry Apo E 2,3, and 4 alleles.

INTRODUCTION 3

- The presence of the Apo E 4 has been associated with increased susceptibility to accelerated atherosclerosis, decreased longevity, susceptibility to infectious diseases, and Alzheimer's disease, by changing the way lipoproteins interact with cell surface receptors and in regulating brain Amyloid Beta peptides in the brain.
- As such, I prefer the term "Fragility Gene"

INTRODUCTION 4

- Apo E 3/4 has a two fold increased association with the development of AD, while Apo E 4/4 may increase risks of AD 8-20 fold depending on the study

THE NIGERIAN CONUNDRUM

- Nigerians have the highest incidence of the Apo E 4 genotype of any studied population, yet their incidence of Alzheimer's Disease (AD) and other forms of dementia are extremely low.
- Age matched and Apo E matched African Americans from Indianapolis have significantly higher LDL and small particle LDL's than Nigerians, and significantly higher rates of AD

THE NIGERIAN CONNECTION

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- Despite the increased association of AD in African Americans with Apo E 4 versus Nigerians, elevated LDL-C had the highest association with AD, regardless of Apo E status

GREAT APES

- Great Apes carry Apo E 4, have levels of LDL-C that are extremely low, and even in captivity do not develop AD
- Perhaps the LDL connection is the “Missing Link” when carrying the ancestral Apo E 4

DIETARY STUDIES OF APO E

- **The Effect of Dietary Fat on LDL Size Is Influenced by Apolipoprotein E Genotype in Healthy Subjects¹**
- Juan Antonio Moreno, Francisco Pe´rez-Jime´nez, Carmen Mari´n, Purificacio´n Go´mez, Pablo Pe´rez-Marti´nez, Rafael Moreno, Cecilia Bellido, Francisco Fuentes, and Jose´ Lo´pez-Miranda²
- *Lipids and Atherosclerosis Research Unit, Hospital Universitario Reina Sofi´a, Co´rdoba, Spain*

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DIETARY STUDIES

- 86 subjects
- Crossover diets for a month each
- High saturated fat (Paleo Diet)
- High Carbohydrate, low fat (Ornish)
- High Olive Oil (MUFA) Mediterranean

DIETARY STUDIES

- LDL particle size was significantly higher (P 0.04) in subjects with the apoE 4/3 genotype compared with those with apoE 3/3 and apoE 3/2 in the basal state.
- The high sat fat diet increased LDL size in Apo E 4/3 subjects the most.
- After the CHO diet, a significant increase in LDL particle size (P 0.035) was noted with respect to the MUFA diet in apoE 4/3 subjects, whereas a significant decrease was observed in the apoE 3/3 individuals (P 0.043).

DIETARY STUDIES

- Thus, the hyper response of LDL-C concentrations associated with the E4 allele occurred only when the fat content in the diet varied.
- We observed that replacement of a CHO diet by a MUFA diet was associated with a significant decrease in LDL-C in apo E 3/4 subjects, and only apo E 3/4 subjects.
- J Nutr, Oct 1, 2004 Vol 134

Dietary Hypothesis

- Because of this, we have focused our attention upon keeping the small dense oxidizable particles of LDL as low as possible via a low animal fat, high MUFA, high soluble fiber and resistant starch diet.

DIETARY RULES FOR APO E 4

- Rule number 1: Limit animal fats
- Rule number 2: Cheese is not your friend!

Our studies over 15 years have found that dairy fats have the strongest correlation to the production of oxidized particles of LDL, and that removal or drastically limiting them improves oxidized LDL levels

Rule number 3: lowering triglycerides lowers oxidized LDL

DIETARY RULES FOR APO E 4

- We have found that limiting Triglyceride production by lessening sugars, fruits, and seeded vegetables also lowers small LDL production.
- Shellfish are emphasized as the animal protein of choice if desired, owing to our observed sdLDL lowering when these foods were added.

DIETARY RULES FOR APOE 4

- We further minimize the oxidization of small LDL particles using generous amounts of polyphenol rich Olive Oil as well as the polyphenols in Resveratrol, Grape Seed Extract, Turmeric, and Pomegranate Seed Oil and Extracts
- The only purpose of food is to get Olive Oil into your mouth!

OLIVE OIL AND NUTS PREVENT COGNITIVE IMPAIRMENT

- **Mediterranean Diet and Age-Related Cognitive Decline :A Randomized Clinical Trial**
- *JAMA Intern Med.* 2015;175(7):1094-1103.
doi:10.1001/jamainternmed.2015.1668
- Cinta Valls-Pedret, MSc^{1,2}; et al

OLIVE OIL AND NUTS

- Parallel-group randomized clinical trial of 447 cognitively healthy volunteers from Barcelona, Spain (233 women [52.1%]; mean age, 66.9 years), at high cardiovascular risk.
- Participants were randomly assigned to a Mediterranean diet supplemented with extra virgin olive oil (1 L/wk), a Mediterranean diet supplemented with mixed nuts (30 g/d), or a control diet (advice to reduce dietary fat).

OLIVE OIL AND NUTS

- 6 year follow-up, neuropsychological and memory tests at baseline and approx 5 year follow-up.
- All cognitive composites significantly ($P < .05$) *decreased from baseline in controls.*

OLIVE OIL AND NUTS

- Changes from baseline of the global cognition composite were 0.05 (−0.11 to 0.21; $P = .005$ vs controls) for the Mediterranean diet plus olive oil, −0.05 (−0.27 to 0.18) for the Mediterranean diet plus nuts, and −0.38 (−0.57 to −0.18) for the control diet

OLIVE OIL AND NUTS

- Respective changes from baseline of the frontal cognition composite were 0.23 Olive Oil (0.03 to 0.43; $P = .003$ vs controls), 0.03 Nuts (-0.25 to 0.31), and -0.33 low fat (-0.57 to -0.09)
- Changes from baseline of the global cognition composite were 0.05 (-0.11 to 0.21; $P = .005$ vs controls) for the Mediterranean diet plus olive oil, -0.05 (-0.27 to 0.18) for the Mediterranean diet plus nuts, and -0.38 (-0.57 to -0.18) for the control diet.

OLIVE OIL AND NUTS

- My advice to my Apo E 4 patients has always been that the only purpose of food is to get olive oil into your mouth!

FISH OIL AND MEMORY

- **Higher RBC EPA + DHA corresponds with larger total brain and hippocampal volumes WHIMS-MRI Study**
- [James V. Pottala, PhD, et al](#)
- Neurology. 2014 Feb 4; 82(5): 435–442.doi: [10.1212/WNL.0000000000000080](https://doi.org/10.1212/WNL.0000000000000080)

FISH OIL AND MEMORY

- At the time of enrollment in WHIMS, the subjects were 65 to 80 years of age and free of dementia. A further subset was recruited from 14 of the 39 US research centers to participate in the WHIMS Brain MRI Study.¹⁴ These women had an average age (range) of 78 years (71–88) at the time of MRI.
- A total of 1,111 women were followed for 8 years

FISH OIL AND MEMORY

- In fully adjusted models, a 1 SD greater RBC EPA + DHA (omega-3 index) level was correlated with 2.1 cm³ larger brain volume ($p = 0.048$). *DHA was marginally correlated ($p = 0.063$) with total brain volume while EPA was less so ($p = 0.11$).*
- A 1 SD greater omega-3 index correlated with greater hippocampal volume (50 mm³, $p = 0.036$). *Comparing the fourth quartile vs the first quartile of omega-3 index confirmed greater hippocampal volume (159 mm³, $p = 0.034$).*

SHELLFISH AND CHOLESTEROL

- Effects of shellfish consumption on lipoproteins in normolipidemic men. [Childs MT1, Dorsett CS, King IB, Ostrander JG, Yamanaka WK.](#)
- [Am J Clin Nutr. 1990 Jun;51\(6\):1020-7.](#)

SHELLFISH AND CHOLESTEROL

- Oyster, clam, crab, and mussel diets, low in cholesterol and high in n-3 fatty acids, lowered VLDL triglycerides, LDL and total cholesterol. Squid and shrimp diets, did not change the blood lipids. The ratio of LDL to HDL cholesterol was decreased on the oyster and mussel diets. Oyster, mussel, and squid diets increased HDL2 cholesterol. Cholesterol absorption was decreased on the oyster, clam, and mussel diets.

GRAPE SEED EXTRACT AND TRIGLYCERIDES

- **A Grape Seed Procyanidin Extract Ameliorates Fructose-Induced Hypertriglyceridemia in Rats via Enhanced Fecal Bile Acid and Cholesterol Excretion and Inhibition of Hepatic Lipogenesis.**[Downing LE1, Heidker RM1, Caiozzi GC1, Wong BS1, Rodriguez K1, Del Rey F1, Ricketts ML1.](#)
- [PLoS One. 2015 Oct 12;10\(10\):e0140267](#)

GRAPE SEED EXTRACT AND NAD AND SIRT1

- Sci Rep. 2016 Apr 22;6:24977. doi: 10.1038/srep24977.
- **Dietary proanthocyanidins boost hepatic NAD(+) metabolism and SIRT1 expression and activity in a dose-dependent manner in healthy rats.** **Aragonès G1, Suárez M1, Ardid-Ruiz A1, Vinaixa M2, Rodríguez MA3, Correig X2, Arola L1,3, Bladé C1**

TURMERIC AND NEURONS

- Biochem Biophys Res Commun. 2014 May 23;448(1):89-94. doi: 10.1016/j.bbrc.2014.04.066. Epub 2014 Apr 19.
- Activation of SIRT1 by curcumin blocks the neurotoxicity of amyloid- β 25-35 in rat cortical neurons. Sun Q1, Jia N1, Wang W1, Jin H1, Xu J1, Hu H2.

TURMERIC AND NEURONS

- Taken together, our results suggest that activation of SIRT1 is involved in the neuroprotective action of curcumin.
- We found that pretreatment of curcumin prevented the cultured cortical neurons from A β 25-35-induced cell toxicity. In addition, curcumin improved mitochondrial membrane potential ($\Delta\Psi_m$), decreased ROS generation and inhibited apoptotic cell death in A β 25-35 treated neurons.

DIETARY RULES APO E 4

- Unfortunately, the “Paleo Diet”, with its high animal fat and protein components, produces the exact opposite effect to what needs to happen in these people, a fact that we see repeated over and over in our previously naïve Apo E 4's.

RESULTS

- Using this protocol, we have successfully minimized the deleterious effects of this “Ancestral Gene” in thousands of patients followed for up to 15 years, with many Apo E 4/4’s successfully aging into their mid to late 80’s, and numerous Apo E 3/4’s now entering their 90’s.

ANTEDOTAL EVIDENCE

- Many patients arrive later in life to our Center and are found to carry the Apo E 4 genotype. Several have arrived thriving in their 80's.
- Most of these naïve Septo and Octogenerians have a lifetime history of eating greens and a dislike for animal products, but not a fondness for grains.

CONCLUSION FOR APO E 4

- EAT LIKE A NIGERIAN WHO LIVES IN GREECE OR ITALY!