“Obesidad y aterosclerosis; principales factores de riesgo que desarrollan la Calcificación Cardiovascular”

ESCUELA SUPERIOR HUEJUTLA

LIC. MÉDICO CIRUJANO

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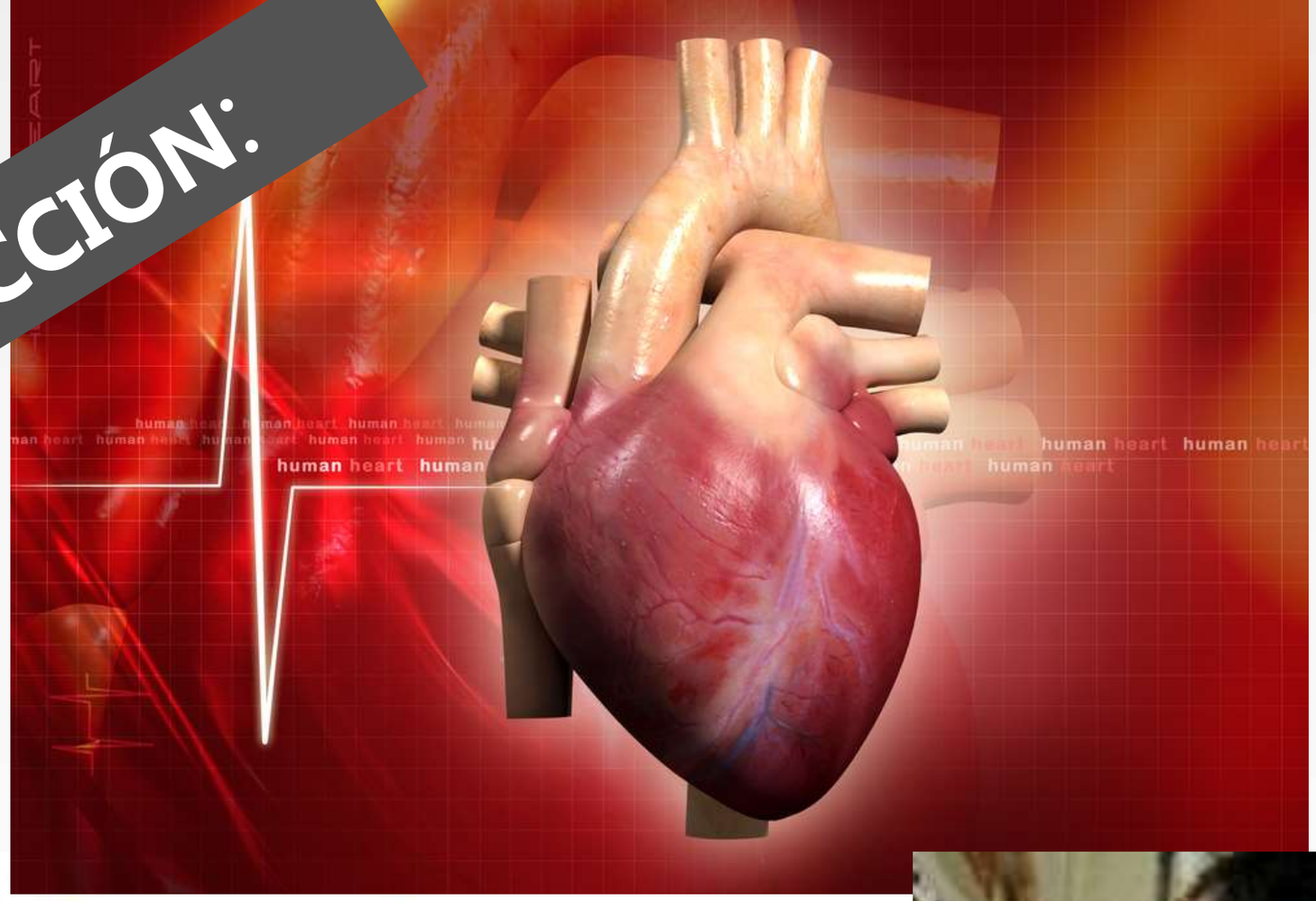
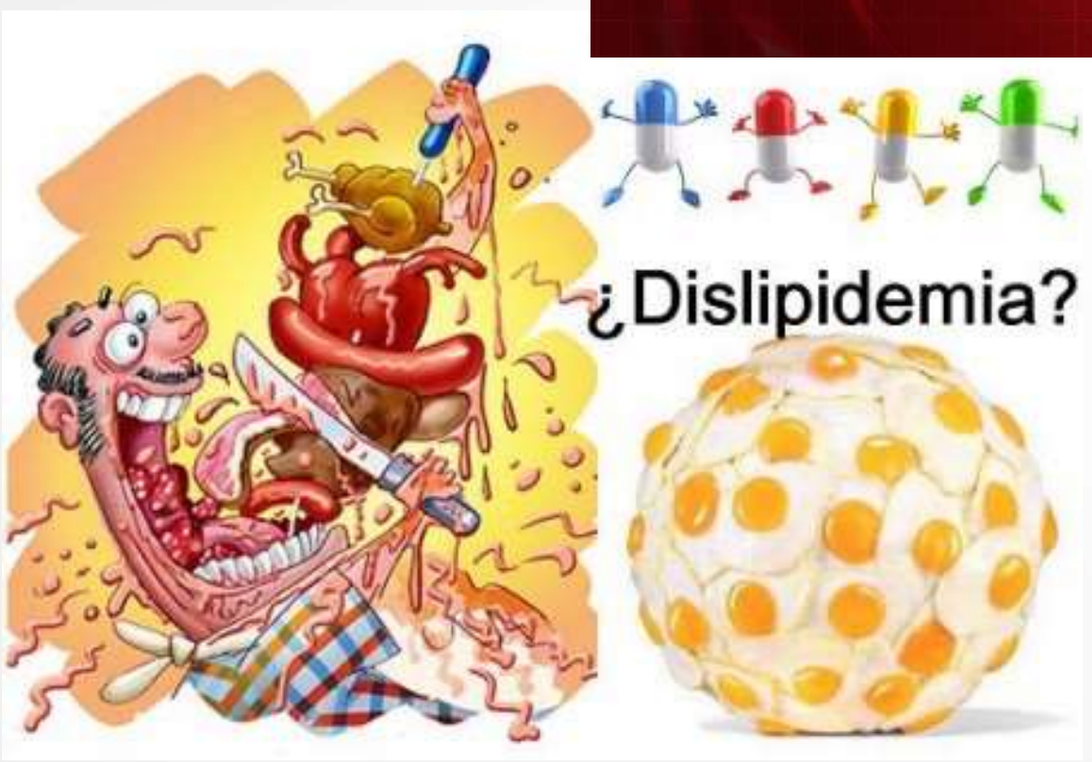
ABSTRACT:

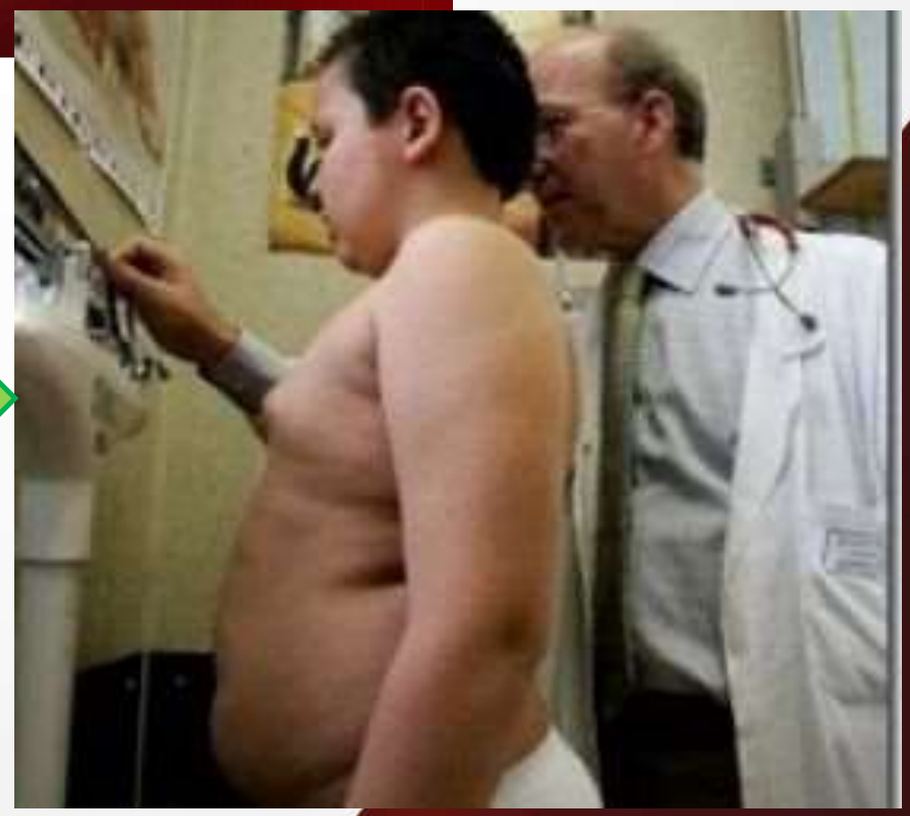
Cardiovascular calcification has been observed in the vasculature of the arteries for many decades, but recently, this phenomenon was seen simply as a passive consequence of aging. Nowadays, the accumulation of evidence points to a strictly regulated process, with competition between the inhibitory factors and the factors that promote mineralization. In spite of all these years of study, the mechanism of the moment in which the process of vascular protection is broken where the process of deregulation and the increase of the oxidative stress is promoted has not been clarified. Therefore, the process is developed inflammatory and degenerative vascular endothelium that occurs during cardiovascular calcification. In this review, we report the findings that have been published in recent years of the mechanism of cardiovascular calcification formation, promoted by the oxidative stress microenvironment and the ratio of the reduction of antioxidants during the process deregulation and development of this pathological process.

Key words: *Cardiovascular calcification, Oxidative stress, Reactive Oxygen Species, Osteopontin.*

INTRODUCCIÓN:







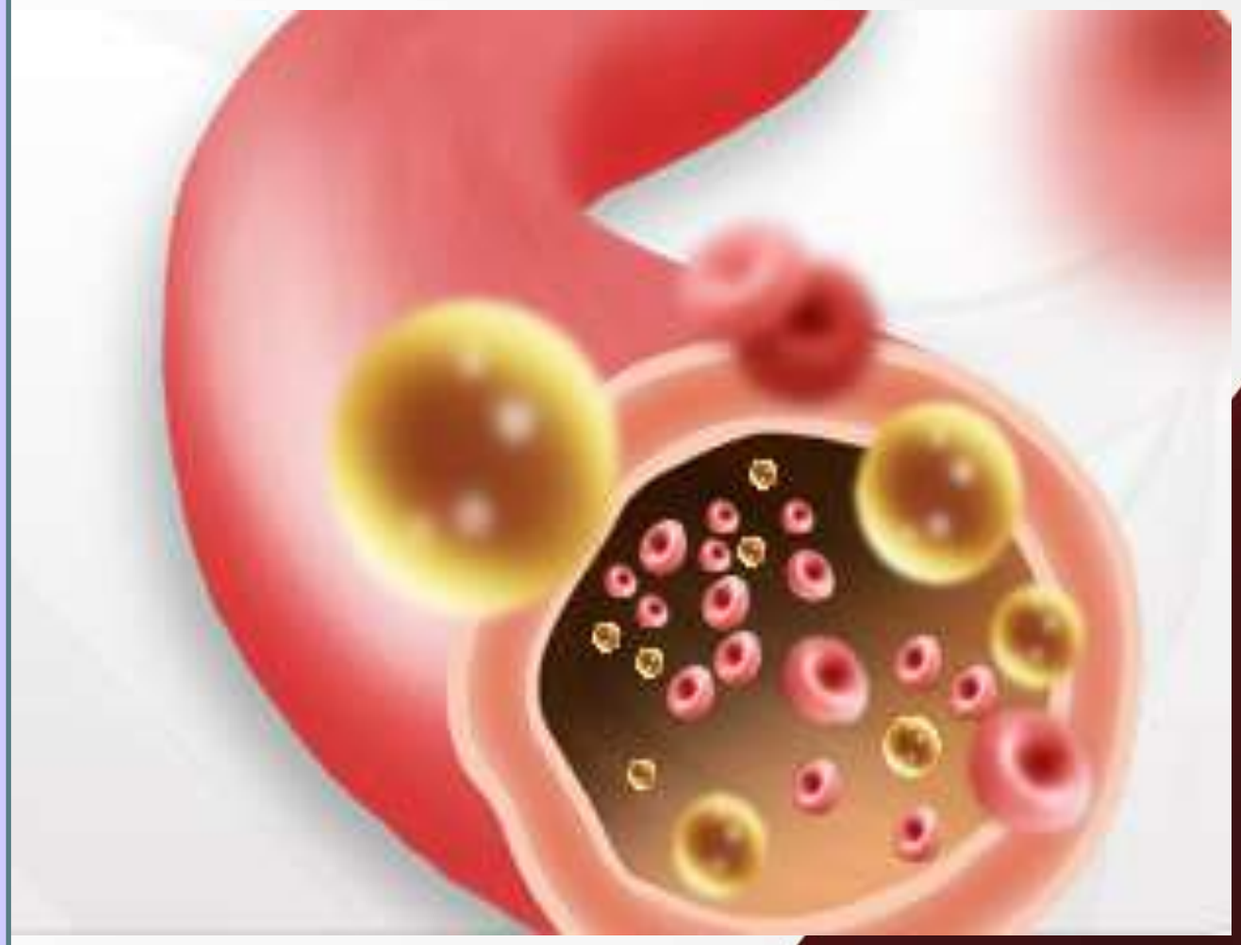
OBESIDAD → ATEROSCLEROSIS

Factores de riesgo:

- **LDL, HDL, triglicéridos, obesidad, hipertensión, tabaquismo, diabetes, insuficiencia renal y factores genéticos [Mc Gill et al., 1996].**

- **Niveles altos de estrés oxidativo VS Menor ingesta de sustancias antioxidantes, principales factores de riesgo para desarrollar aterosclerosis e insuficiencia cardiovascular [Zamora-González et al., 2015].**

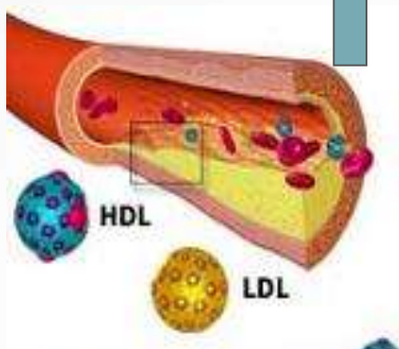
- **Osteopontina y otros biomarcadores, son importantes moléculas estudiadas para el control de riesgo y diagnóstico de la calcificación cardiovascular [Jiménez-Corona et al., 2008, 2010, 2012, presente].**

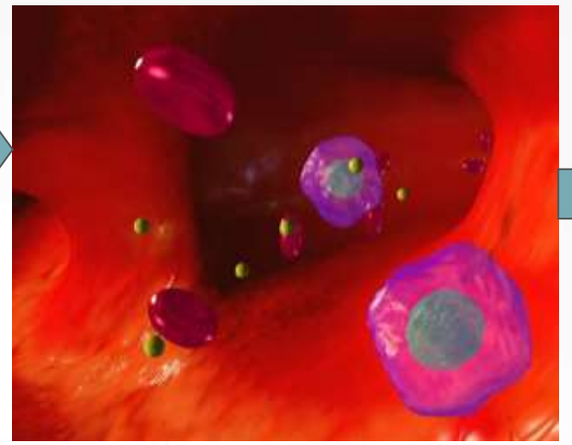


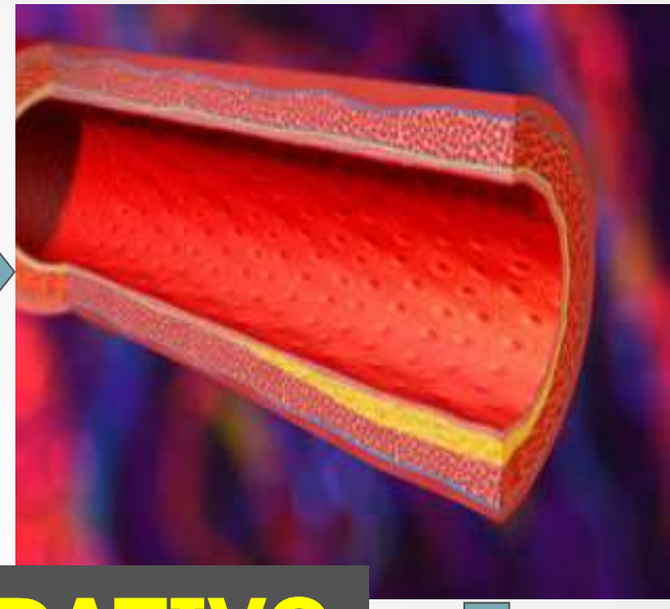
ATEROSCLEROSIS

- La aterosclerosis: se caracterizada por la presencia de una **placa de ateroma (PA).**

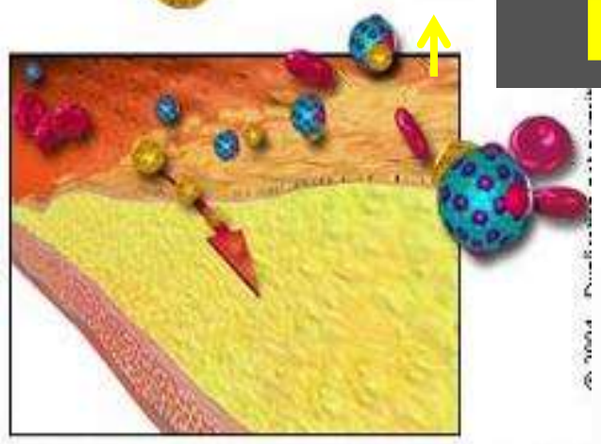
- PA: Constituida por **detritos celulares, trombos** y un depósito nodular de grasa, fundamentalmente de **LDLox** [Lehto et al., 1996].

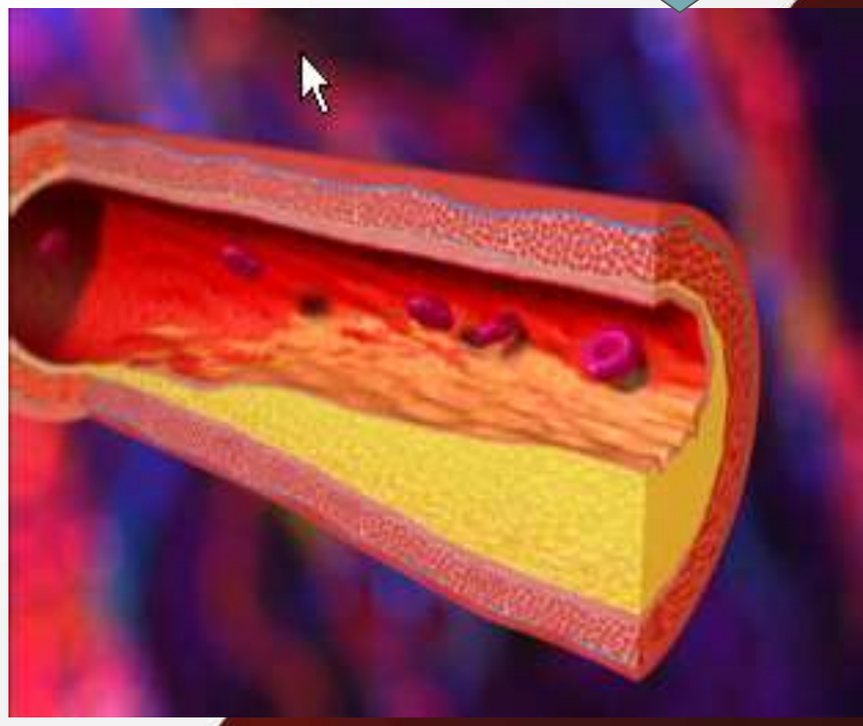




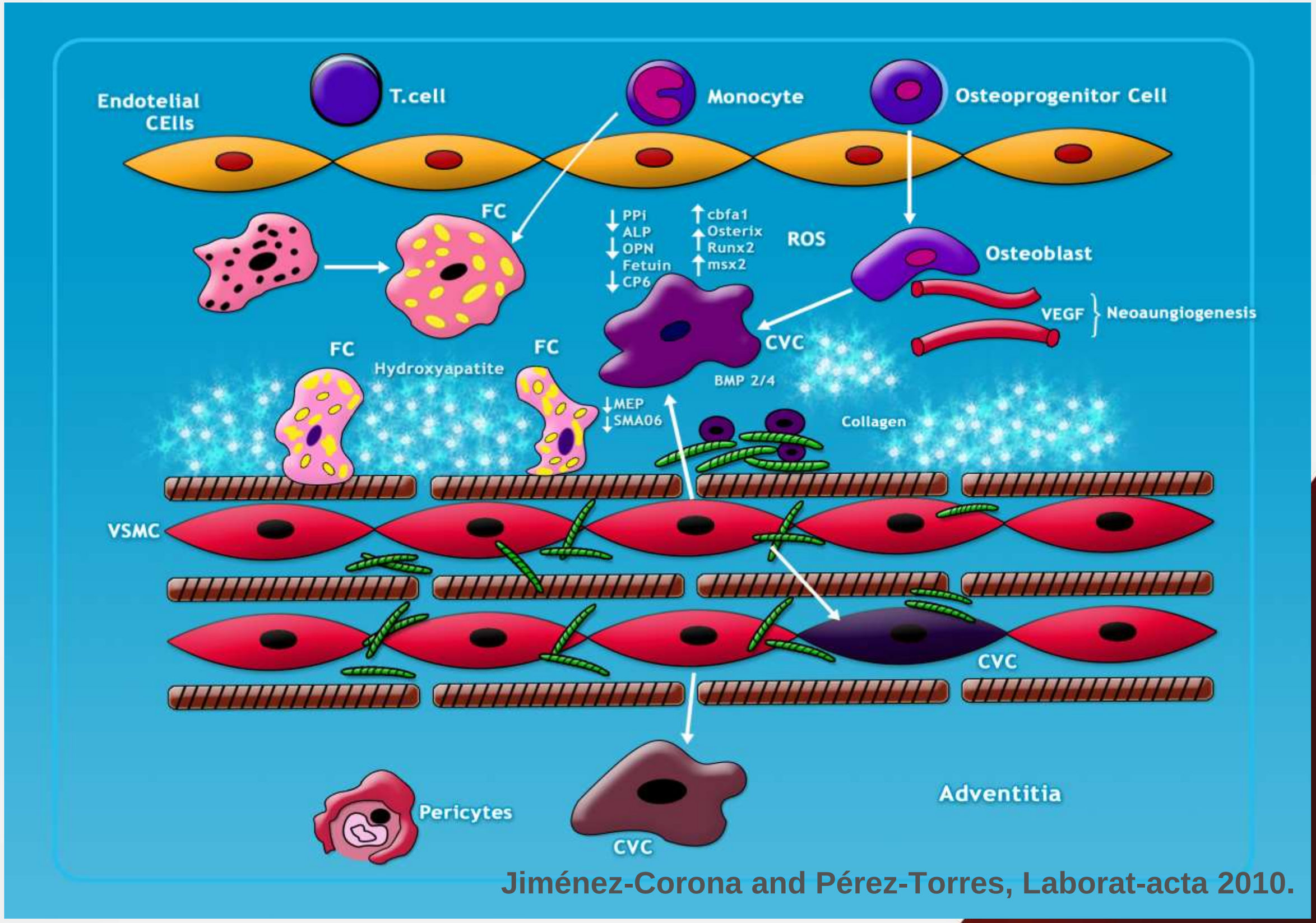


ESTRÉS OXIDATIVO





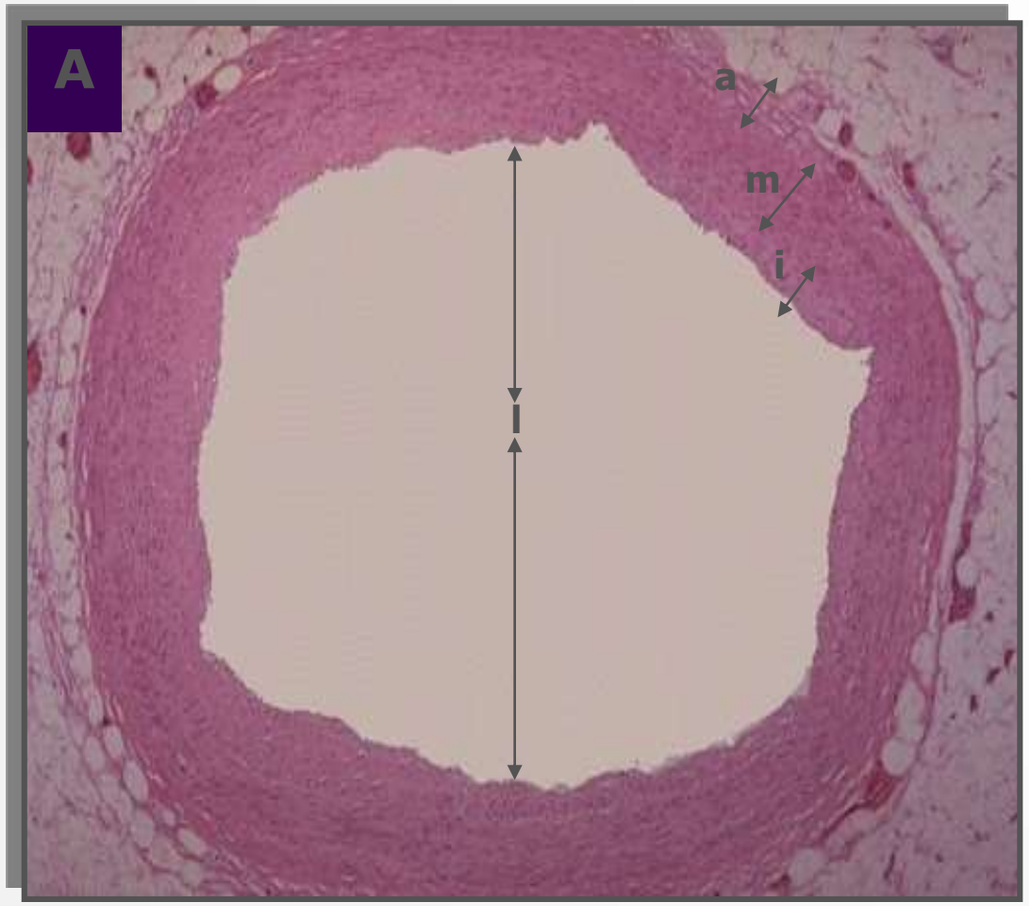
MECANISMO:



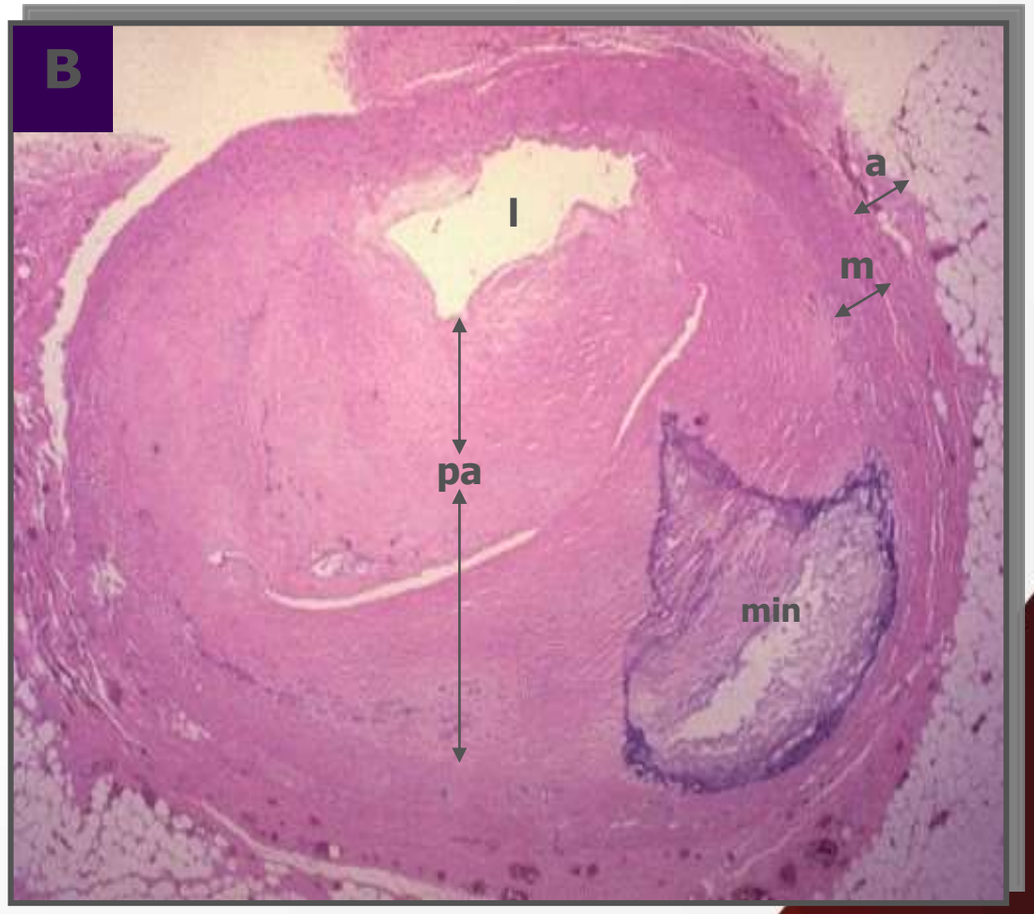
Jiménez-Corona and Pérez-Torres, Laborat-acta 2010.

Biomineralización cardiovascular (patológica).

Arteria normal



Arteria con placa aterosclerótica y mineralización



1. Circulación de los complejos nucleacionales

- Hiperfosfatemia
- Hipercalcemia

2. Inducción de la formación de hueso

Biomineralización cardiovascular

Observada:
En pacientes con aterosclerósis,
Diabetes mellitus y en pacientes
Con enfermedades crónicas renales.
[Wayhs R, 2002; London GM, 2003].

3. Muerte celular

4. Disminución de los inhibidores

OSTEOPONTINA

Osteopontina (OPN)

- **Glicoproteína fosforilada, rica en ácido siálico, 31 kDa (varía dependiendo del tejido de extracción).**

- **264 a 301 aminoácidos dependiendo de la especie.**

- **Extracelular y estructural del tejido óseo.**

- **Biosintetizada por: osteoblastos, osteocitos, odontoblastos, condrocitos, macrófagos, células de músculo liso (SMC), y células endoteliales (EC).**

OTRAS FUNCIONES:

- **Se asocia a la reparación de tejidos, fibrosis y calcificaciones distróficas** [Miyazaki Y, *et al.,* 1995, 760:334-341].

- **Participa en el crecimiento tumoral, en el desarrollo de cáncer y metástasis** [Shijubo N, *et al.,* 2000; 11:135-146; Zhang J, *et al.,* 2001; 171:215-222].

HIPÓTESIS

Algunas macromoléculas biológicas como la OPN, se encuentran interactuando con los cristales de HAP encontrados en forma de precipitados cardiovasculares, por lo tanto esta proteína podría estar implicada en los procesos de regulación en la biomineralización vascular, actuando como inhibidor o nucleador de estos cristales.

RESULTADOS:

CRYSTAL GROWTH & DESIGN
2008
VOL. 8, NO. 4
1335–1339

Effect of Osteopontin, Chondroitin Sulfates (B, C), and Human Serum Albumin on the Crystallization Behavior of Hydroxyapatite in Agarose and Silica Hydrogels

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ABSTRACT: This contribution describes the nucleation and crystal growth behavior of hydroxyapatite (HAP) crystals grown in agarose and silica hydrogels as well as their characterization via powder X-ray diffraction. The effect of several biological macromolecules such as osteopontin, chondroitin sulfates B and C, and human serum albumin (HSA) on crystal growth behavior of HAP is evaluated. From our results, osteopontin and chondroitin sulfates B and C inhibit the HAP crystal growth in agarose hydrogels. Nevertheless, employing silica hydrogels, only osteopontin inhibits the crystal growth of HAP. On the other hand, HSA does not show any effect on the formation of HAP crystals in both types of hydrogels.

- **En hidrogeles de agarosa y sílice se observó, que la Osteopontina es un potente inhibidor del crecimiento de cristales de Hidroxiapatita.**

ELSEVIER

Archives of Medical Research

Archives of Medical Research 43 (2012) 102–111

ORIGINAL ARTICLE

Osteopontin Upregulation in Atherogenesis Is Associated with Cellular Oxidative Stress Triggered by the Activation of Scavenger Receptors

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Background. Osteopontin (OPN) is a highly phosphorylated sialoprotein and a prominent component of mineralized extracellular matrices of bones and teeth. Although the structure of OPN has begun to be elucidated, the role of OPN overexpression in tissues distant from the bones and teeth remains poorly understood. In the present study, a rabbit model of hypercholesterolemia was employed to analyze the relationship between the vascular calcification process and OPN overexpression in the neointima of atherosclerotic plaques.

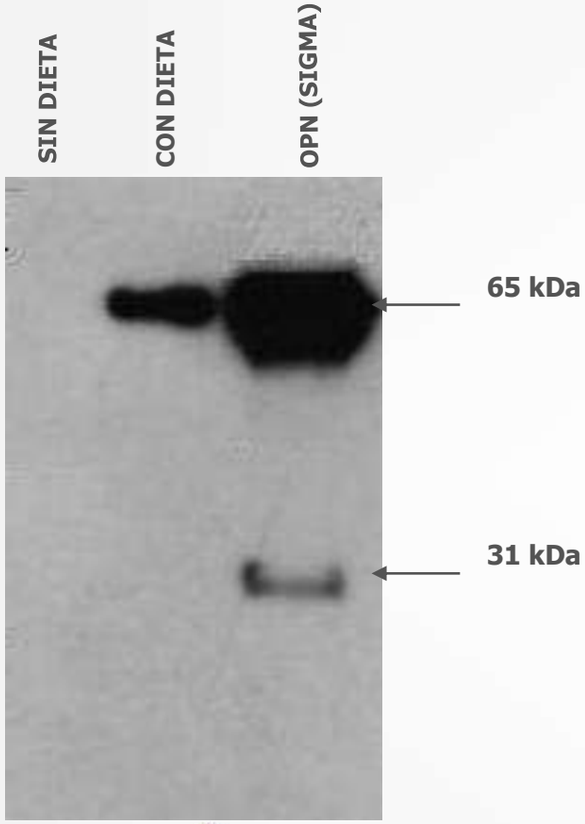
Methods. OPN identification in the aorta of experimental animals fed with a high cholesterol diet was carried out by immunohistochemical procedures and Western blot analysis of tissue homogenates. Transmission electron microscopy was employed to localize target-like extracellular structures of atherosclerotic aortas. The human cell line T/G HA-VSMC was employed in the establishment of a ROS generation model employing the internalization of OxLDL particles.

Results. Using immunohistochemical and Western blot analysis, OPN overexpression was detected in the aortas of rabbits fed a high-cholesterol diet. Results from the ultrastructural analysis of the rabbit neointima through transmission electron microscopy and from the detection of calcium phosphate precipitates by specific histochemical techniques, suggested that OPN may be functionally important as a regulator of vascular calcification. OPN was dramatically overexpressed by vascular smooth muscle cells in the presence of oxidized and acetylated LDL particles bound to scavenger receptors, thereby promoting cytosolic oxidative stress.

Conclusions. This study establishes the *in vivo* role of OPN in the intima of the aorta regulating calcium phosphate precipitate deposition in response to oxidative stress. © 2012 IMSS. Published by Elsevier Inc.

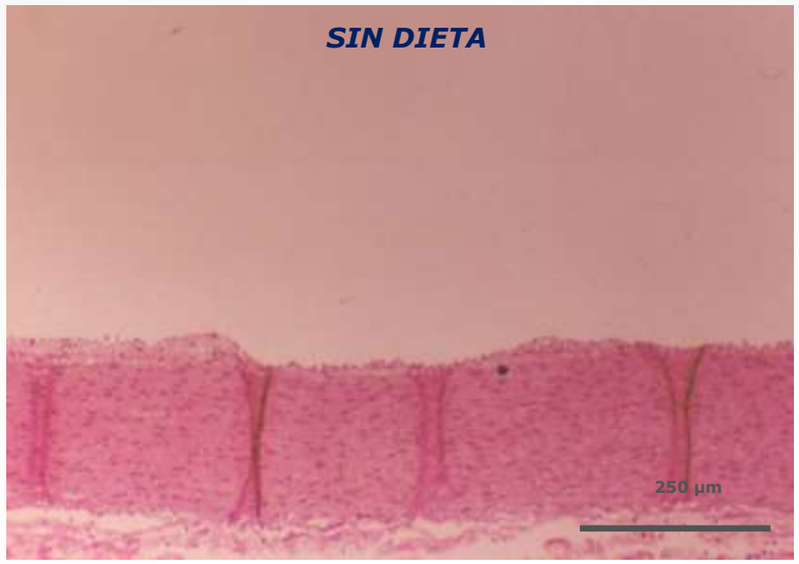
Key Words: Osteopontin, Vascular calcification, Atherosclerosis, Oxidized low-density lipoproteins, Scavenger receptor, Oxidative stress.

RESULTADOS (Parte *in vivo*):

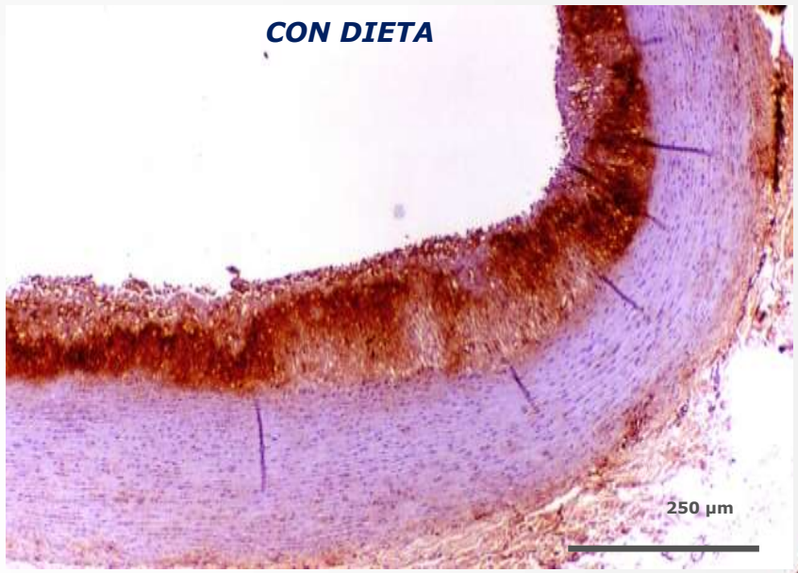


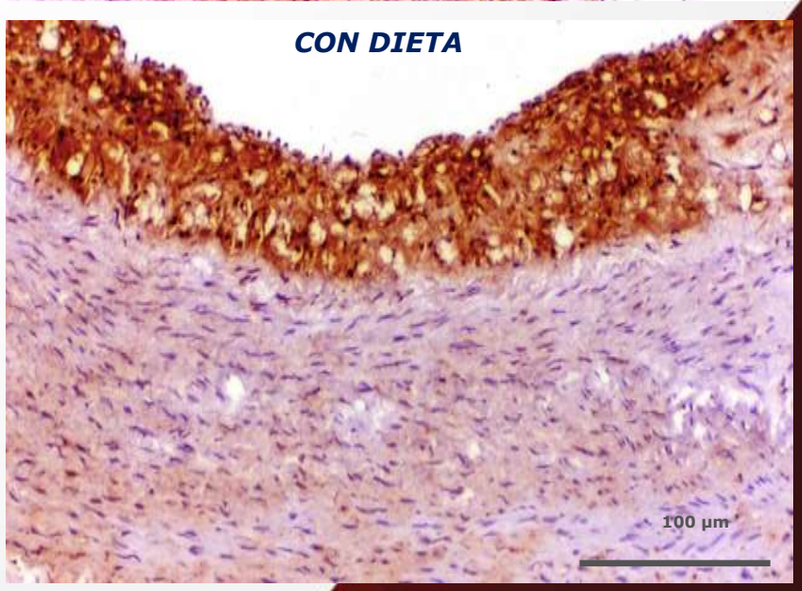
Inmunodetección de OPN por WB, del lisado celular de las aortas de conejos con y sin tratamiento

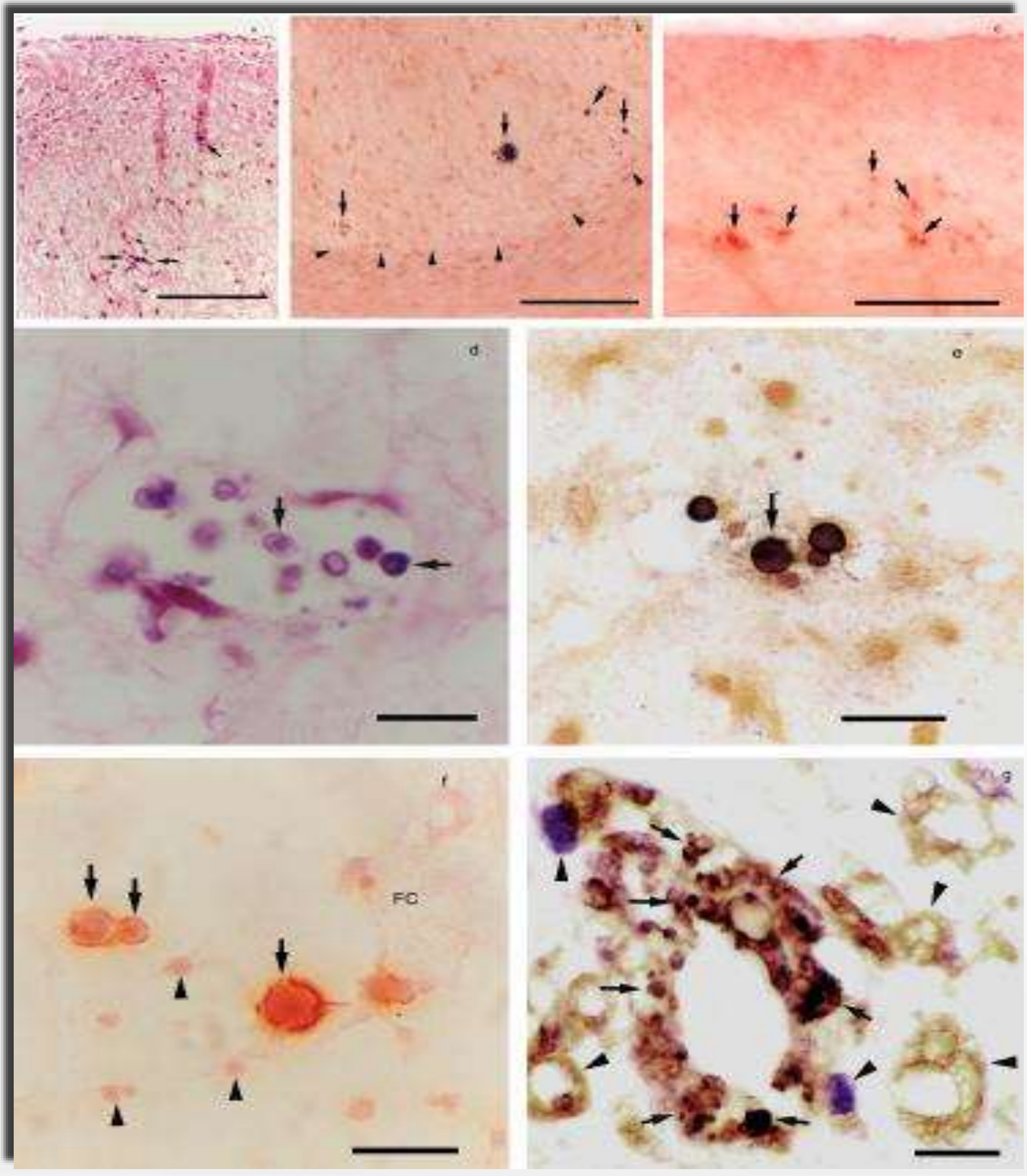
AORTAS DE CONEJO CONTROL



AORTAS DE CONEJOS HIPERCOLESTEROLEMICOS

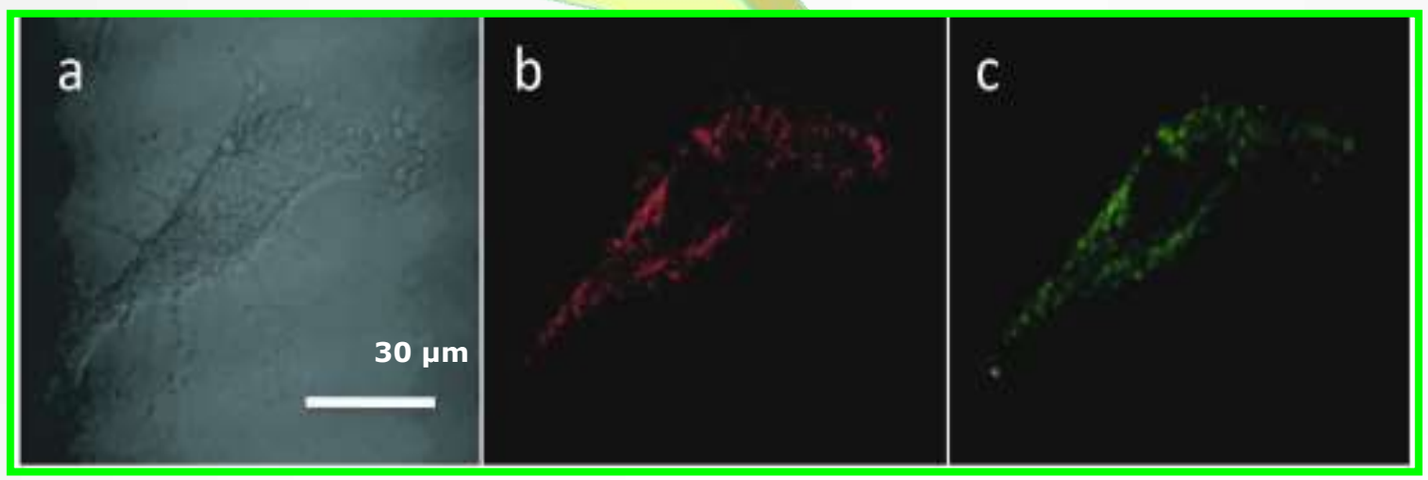






Detección de Calcio, en lesiones ateroscleróticas de aortas de conejos hipercolesterolemicos, por medio de **tinciones específicas (Von Kossa y Alizarina Roja.**

Sobreexpresión de OPN en VSMC asociada al estrés oxidativo



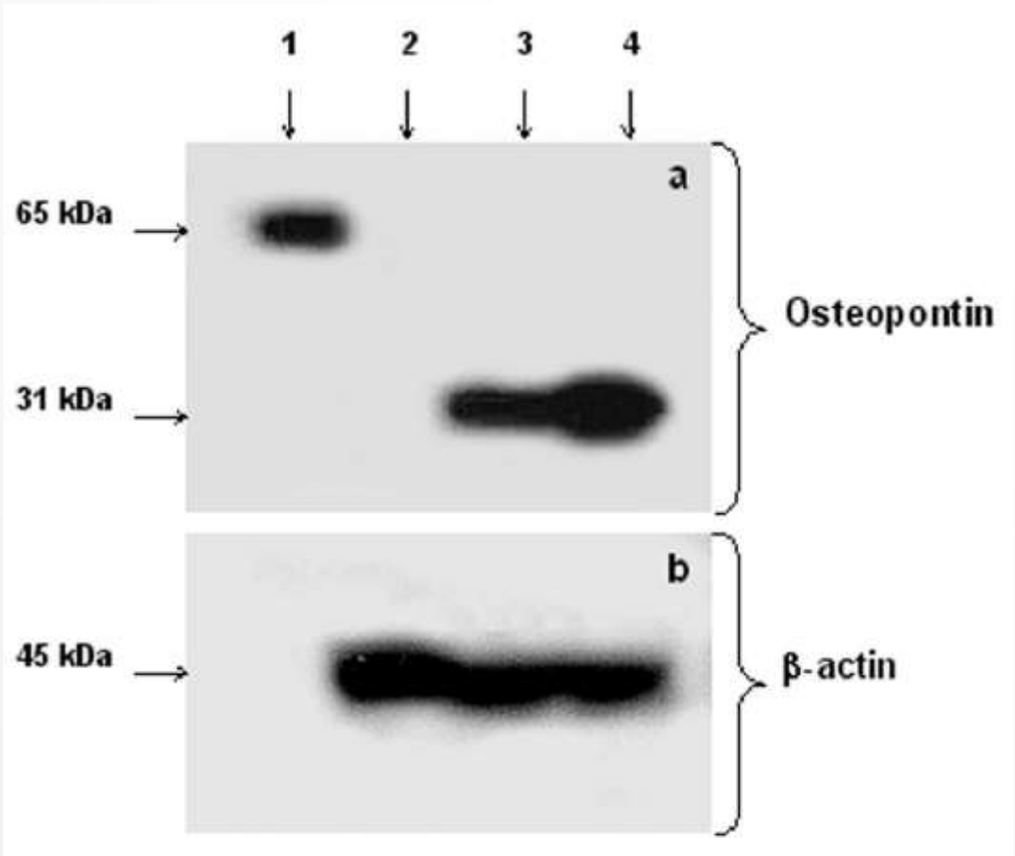
(a) Imagen de contraste de fase que muestra a T/G HA-CMLV.

(b) Internalización de LDLox.

(c) Marcaje de estrés oxidativo asociado a la generación de ROS.

* Excitación para 6 carboxi-H_2DCFA (448nm), y DiI (543nm).

* (DiI) 1,1′-dioctadecil-3,3,3′,3′-tetrametil-indocarbocianida



CONCLUSIONES:

- Se demostró en el estudio *In vitro* en hidrogeles de agarosa y sílice, que la osteopontina es un potente inhibidor del crecimiento de cristales de HAP.

- En el estudio *In vivo* se observó, que esta proteína se sobreexpresó en la neoíntima de las aortas de los conejos hipercolesterolémicos y se colocalizó en las células positivas a calcio, con las técnicas específicas correspondientes.

- Por lo tanto bajo estas condiciones, la OPN es un importante regulador en el proceso inflamatorio y una proteína clave en el proceso de inhibición en la biomineralización vascular.

- A su vez, se demostró que el estrés oxidativo intracelular promueve la sobreexpresión de la OPN en las VSMC, por lo cual la OPN actúa como un protector durante la aterosclerosis.

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