ADIPOSE TISSUE AND OSTEOARTHRITIS

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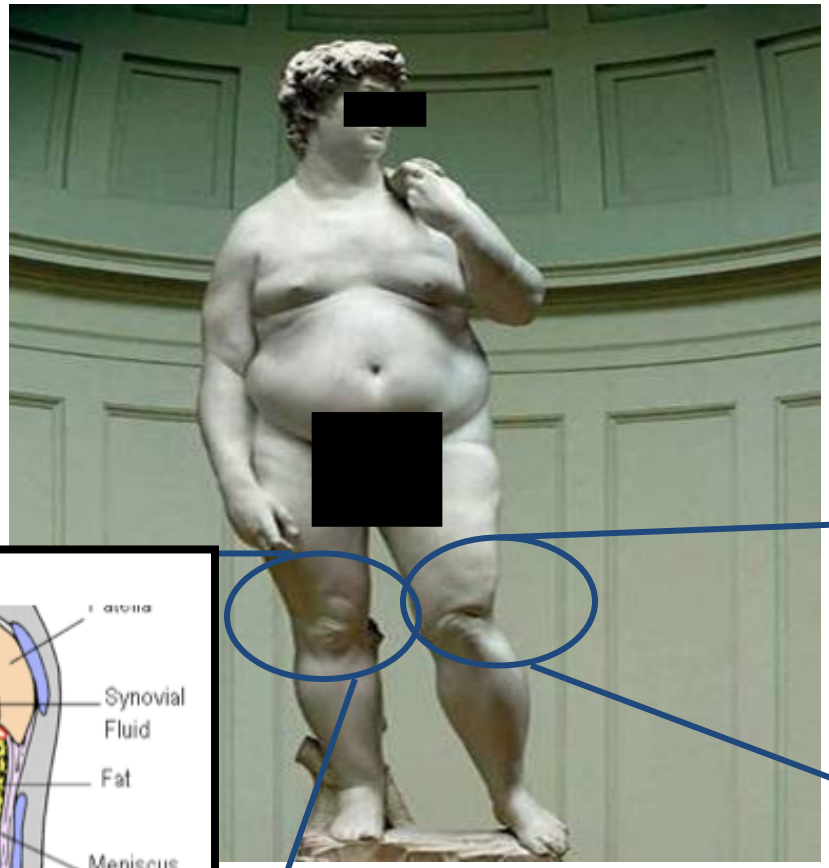
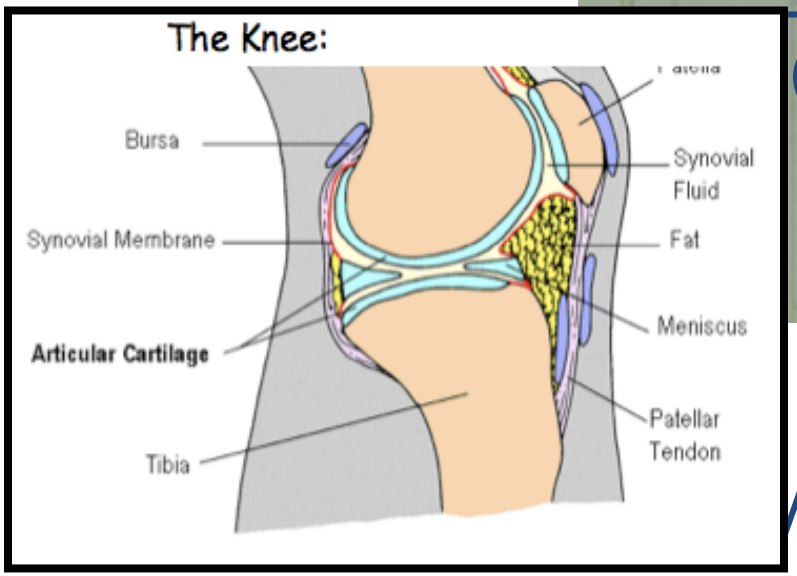
DISCLOSURES

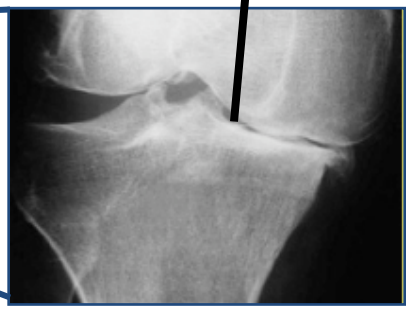
- Fidia Farmaceutici Spa
- Blue Srl
- Medical Net
- Dynamicom srl
- Eli Lilly
- Janssen

MICHELANGELO'S DAVID: THE LATE YEARS

Diagnosis:
OSTEOARTHRITIS



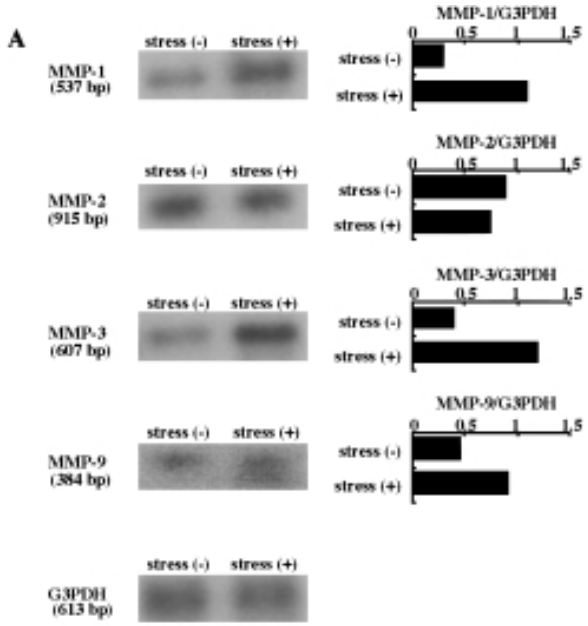




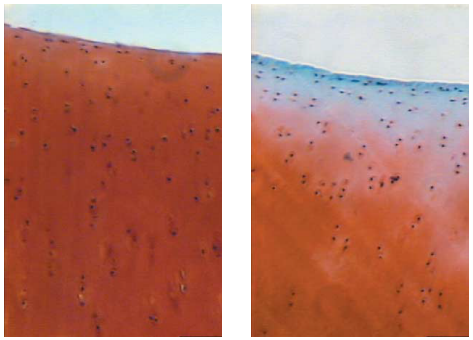
MODIFIABLE RISK FACTOR

By courtesy of MB Goldring

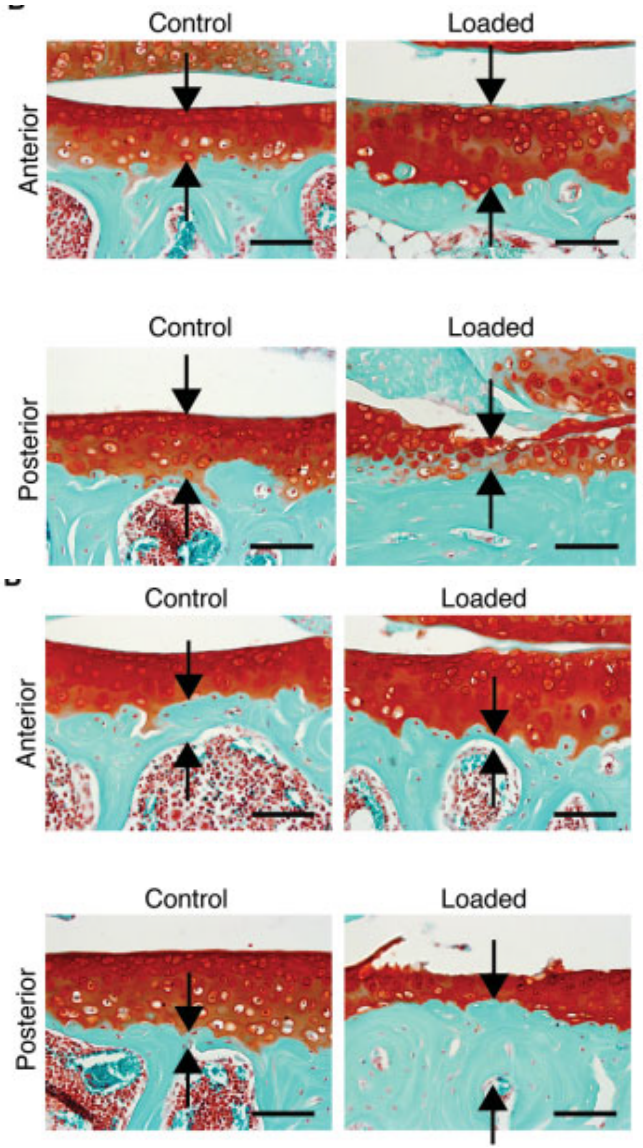
OBESITY: ALTERED LOADING



Honda K, Eur J Biol 2000.



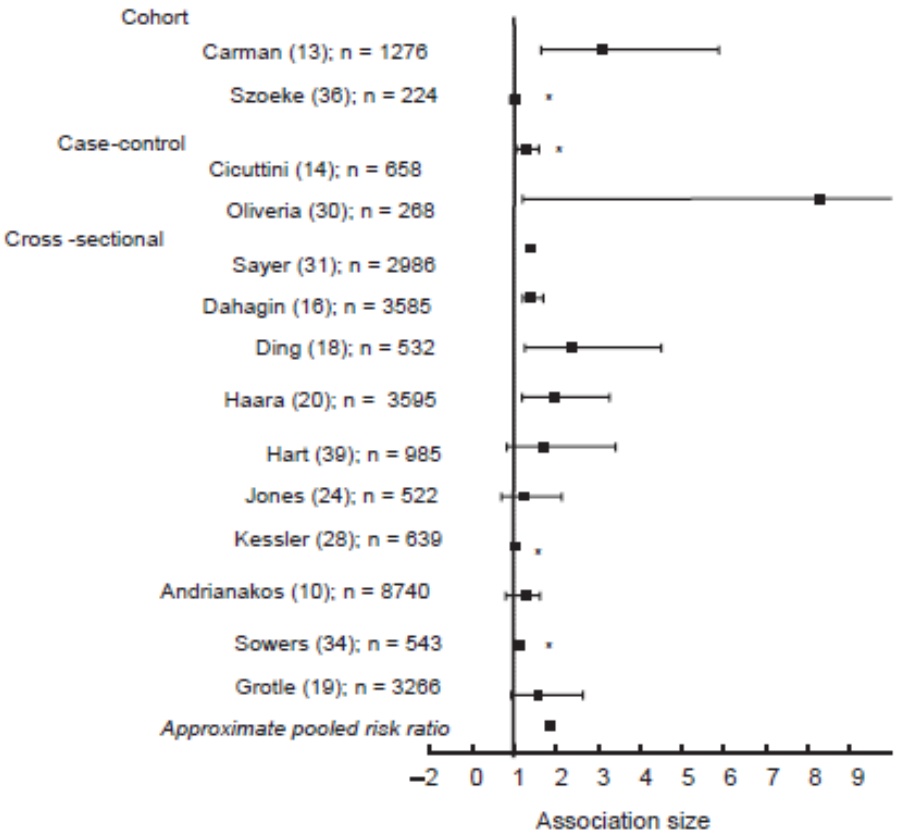
Lin PM, Osteoarthritis Cartilage 2004



Ko FC, Goldring MB, Arthritis Rheum 2013.

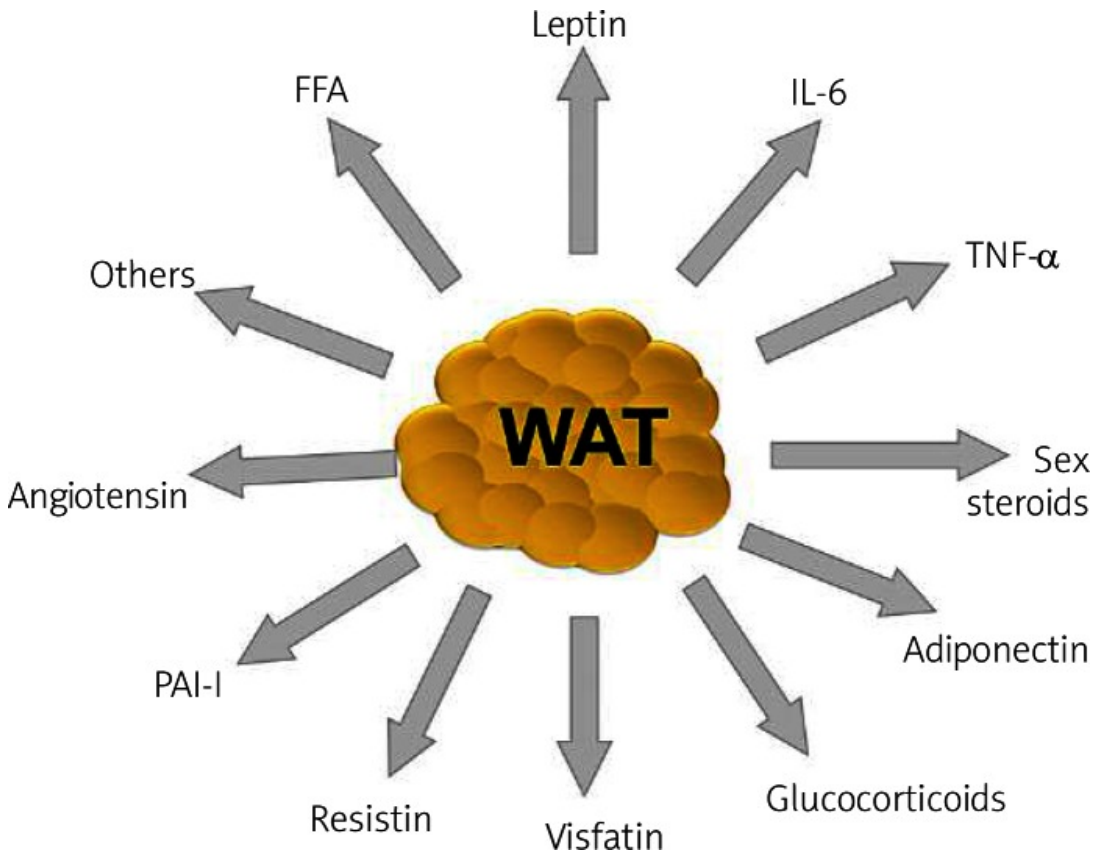
Association between weight or body mass index and hand osteoarthritis: a systematic review

Erlangga Yusuf,[1] Rob G Nelissen,[2] Andreea Ioan-Facsinay,[1] Vedrana Stojanovic-Susulic,[3] Jeroen DeGroot,[4] Gerjo van Osch,[5] Saskia Middeldorp,[6] Tom W J Huizinga,[1] Margreet Kloppenburg[1]



Yusuf E, Ann Rheum Dis. 2010

ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

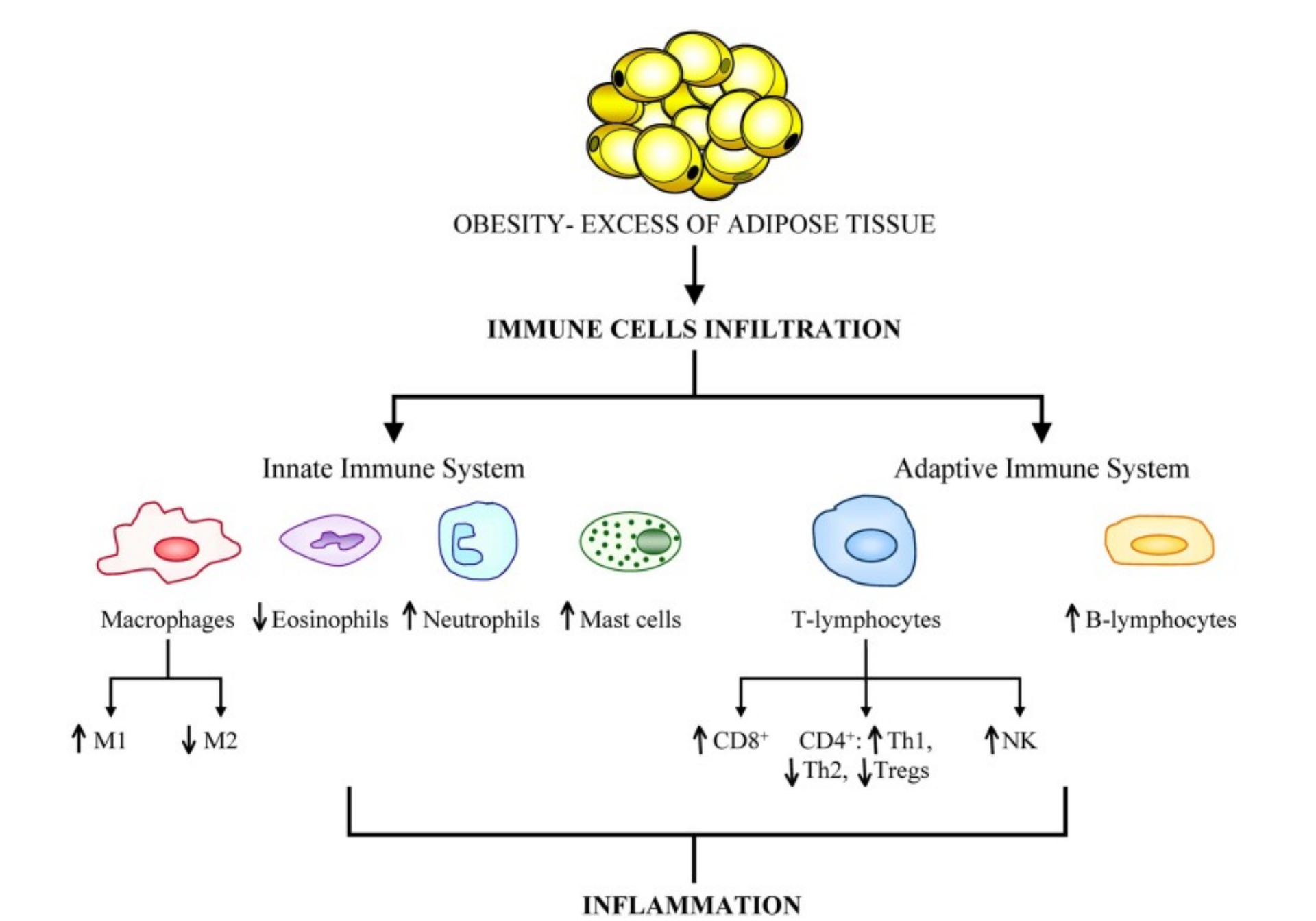


LOW GRADE INFLAMMATION

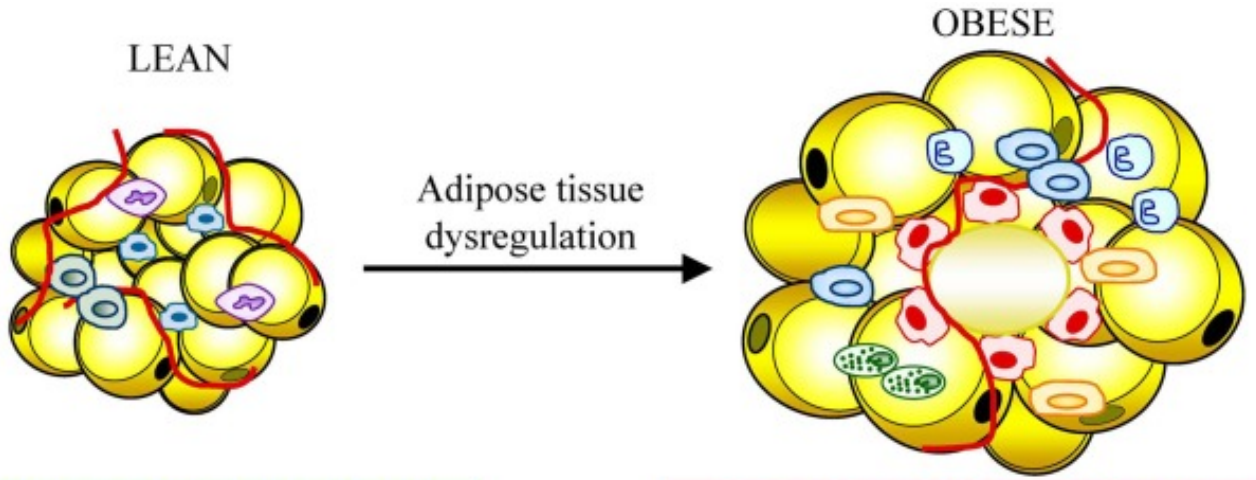
Coelho M, Arch Med Sci 2013

Osteoarthritis is not a “non-inflammatory” form of arthritis

- Signs of inflammation are common
- Synovitis is common in early and late OA *(Benito 2005, Pearle 2007)*
- Synovitis is related with OA symptoms and progression
- Synovial inflammation is a factor that contributes to dysregulation of chondrocyte function, favoring an imbalance between the catabolic and anabolic activities of chondrocyte in remodeling the cartilage ECM *(Loeser 2006)*



Catalan V, Front Physiol 2013



ANTI-INFLAMMATORY PROFILE:
IL-4, IL-10, IL-13

Normal metabolic function

Normal vascularization

Immune cells: M2 macrophages, eosinophils and Tregs

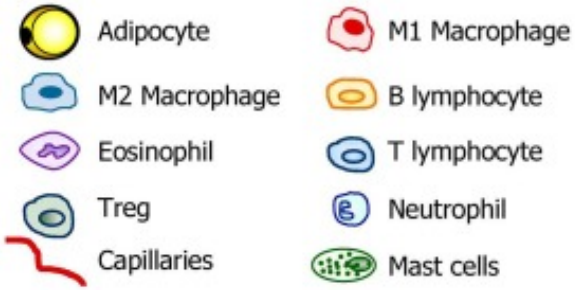
PRO-INFLAMMATORY PROFILE:
IFNγ, TNF-α, MCP-1, IL-6, IL-1β

Metabolic dysfunction

Severe hypoxia

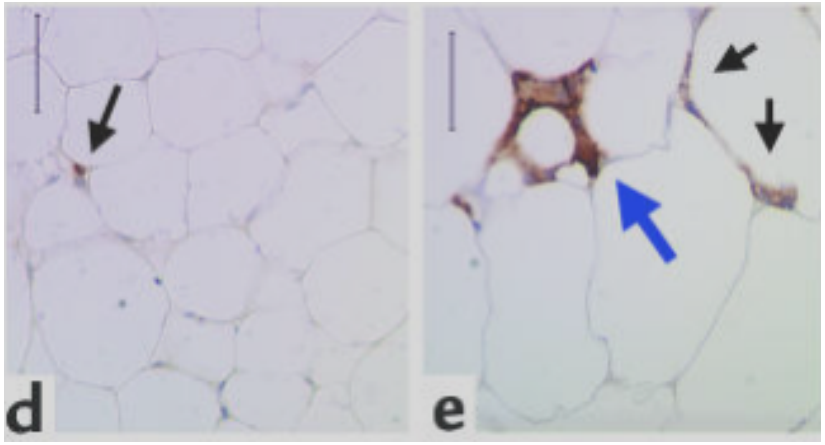
Adipocyte necrosis

Immune cells: M1 macrophages (crown-like structures), $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes, B lymphocytes and mast cells

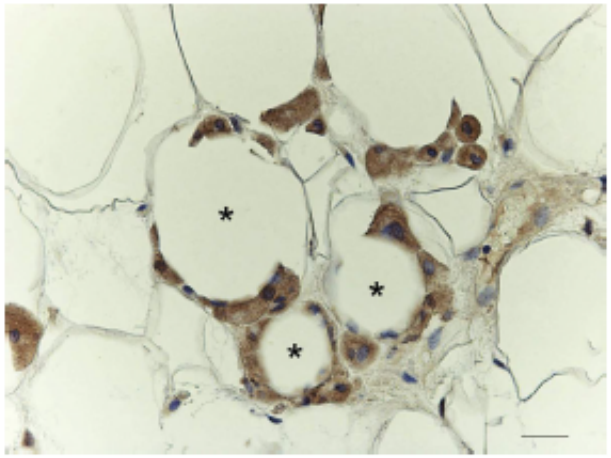


Catalan V, Front Physiol 2013

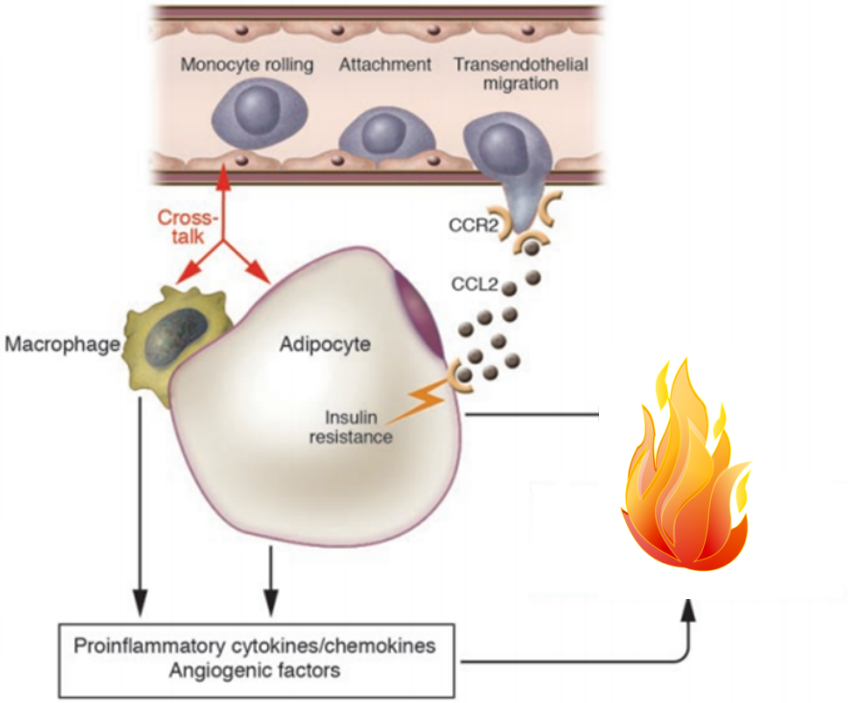
Inflamed fat: what starts the fire?



Weisberg SP, J Clin Invest 2003



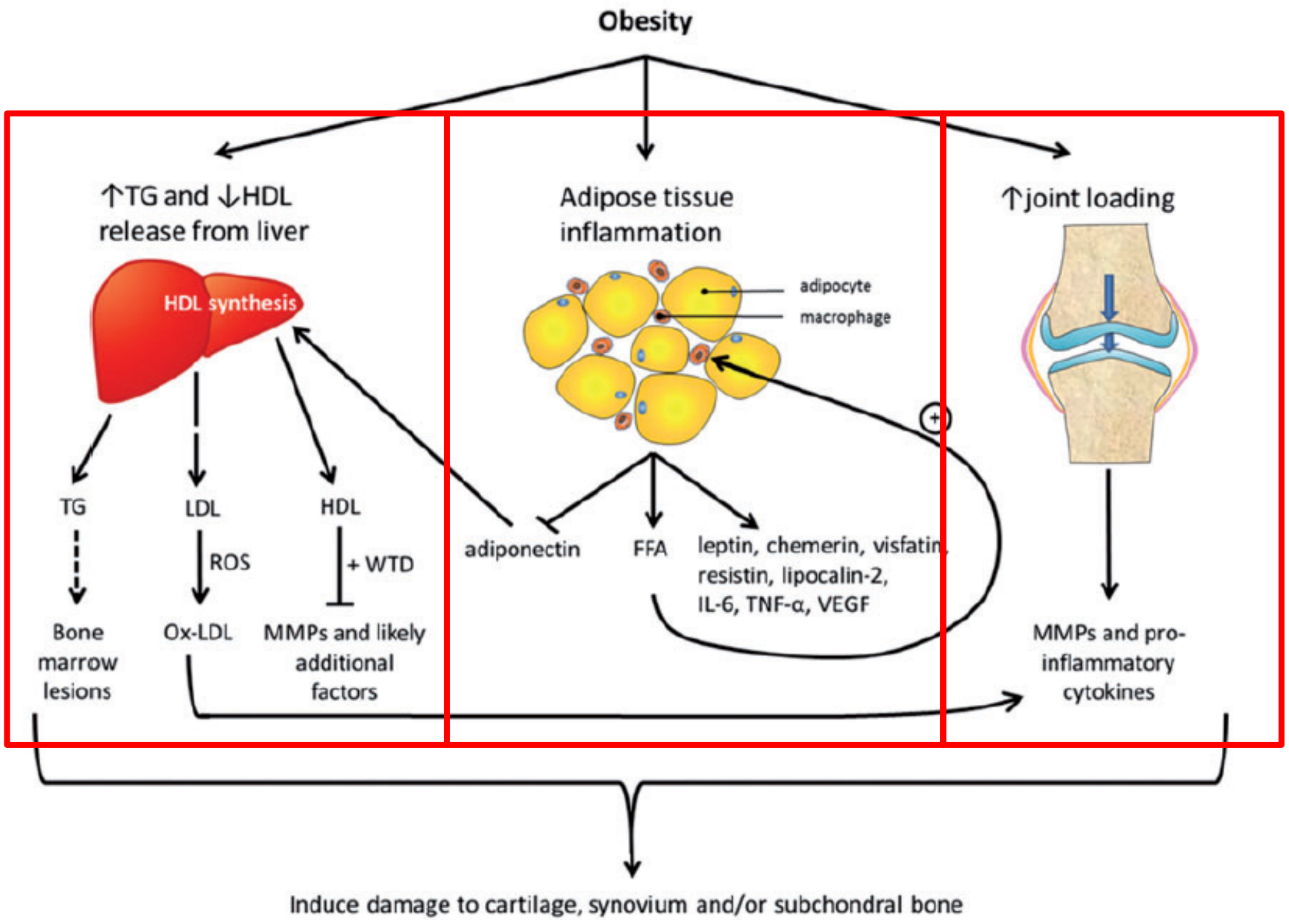
Cinti S, Am J Physiol Endocrinol Metab 2009



Neels J, The Journal of Clinical Investigation 2006

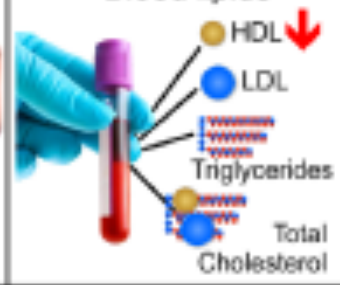
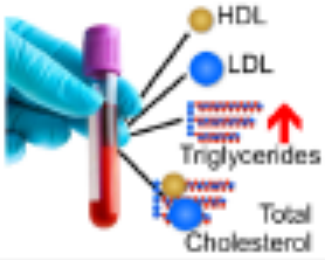
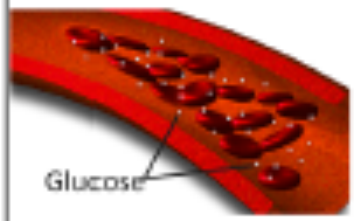
Mediator	Expression in obesity	Association with OA severity, positive/negative	Effect on: Subchondral bone	Synovium	Cartilage
Leptin	Increased [96, 97]	Positive [97]	Reduced subchondral bone thickness in leptin-deficient mice [106] Subchondral bone thickness is associated with OA susceptibility in guinea pigs [25]	Increased IL-6 [107] and IL-8 [108] expression in synovial fibroblasts	Leptin levels positively correlate with cartilage destruction [97] Leptin IA injection in rats: Anabolic effects reported: increased proteoglycan synthesis [97] Catabolic effects reported: increased ECM-degrading enzymes and proteoglycan depletion [109, 110]
Adiponectin	Decreased [98]	Negative [111]	No effects reported	Increased IL-6 [112, 113] and PGE2 production and synergy with IL-1β on IL-6, IL-8 and PGE2 expression in synovial fibroblasts [114]	Cartilage-destructive, by increased NOS2 expression and increased release of IL-6, MMP-3, MMP-9 and MCP-1 [115] At high dose: cartilage-protective, namely by increased TIMP-2 and decreased IL-1β-induced MMP-13 expression [116]
Resistin	Increased [99, 100]	Positive [117] or no significant association [118, 119].	No effects reported	Increased IL-6 and TNF-α mRNA expression in synoviocytes [120] Synovitis upon IA resistin injection in mouse knee joints [120]	Increased expression of pro-inflammatory cytokines, chemokines and MMPs [120–122] Decreased collagen type II and aggrecan expression in articular chondrocytes [122] Decreased proteoglycan synthesis in cartilage explants [121] Cartilage degradation upon IA resistin injection in mouse knee joints [120]
Visfatin	Increased [101]	Positive [123]	Increased IL-6, IL-8 and MCP-1 expression and production in primary osteoblasts from subchondral bone [124] Increased radiological (subchondral) bone erosion in mice with CIA [125]	Inreased MMP-3, IL-8 and MCP-1 expression in human fibroblasts [125] Similar upregulation in RA synovial fibroblasts, although many more pro-inflammatory mediators were upregulated, e.g. increased IL-6 production [126] Increased synovitis in mice with CIA [125]	Increased cartilage degradation in mice with CIA [125] *In articular chondrocytes:* increased PGE2, MMP-3, MMP-13 release [126, 127] increased ADAMTS-4 and ADAMTS-5 expression [127] decreased aggrecan synthesis [127]

Thijssen, Rheumatology 2015



Thijssen, Rheumatology 2015

METABOLIC SYNDROME (MetS)

Large Waistline	Low Blood HDL Cholesterol	High Blood Triglycerides	High Fasting Blood Sugar	High Blood Pressure
>102 cm >88 cm 	<40 mg/dL <50 mg/dL Blood lipids 	≥150 mg/dL or medication Blood lipids 	≥100 mg/dL or medication 	≥130/85 mm Hg or medication 
96.6%	61.1%	84.0%	50.7%	49.0%
88.0%	57.5%	86.6%	57.4%	47.8%

Ronald J, Journal of Orthopaedic Research Month 2016

OA AND METABOLIC SYNDROME (MetS)

- MetS is an independent risk factor for OA *(Barenbaum 2009)*
- 59% of OA patients had MetS compared to 23% in the general population *(Puenpatum 2009)*
- Obese patients with MetS have an increased risk of incidence and severity of knee OA *(Hoeven TA 2013)*
- The presence of MetS is also associated with hand OA *(Tomi A-L 2016, Visser AW 2015)*
- The accumulation of MetS components is associated with OA incidence and severity, and with TKR, independently of BMI *(Yoshimura N 2012, Monira Hussain S 2014)*

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 61, No. 10, October 15, 2009, pp 1328–1336
DOI 10.1002/art.24739

Knee Osteoarthritis in Obese Women With Cardiometabolic Clustering

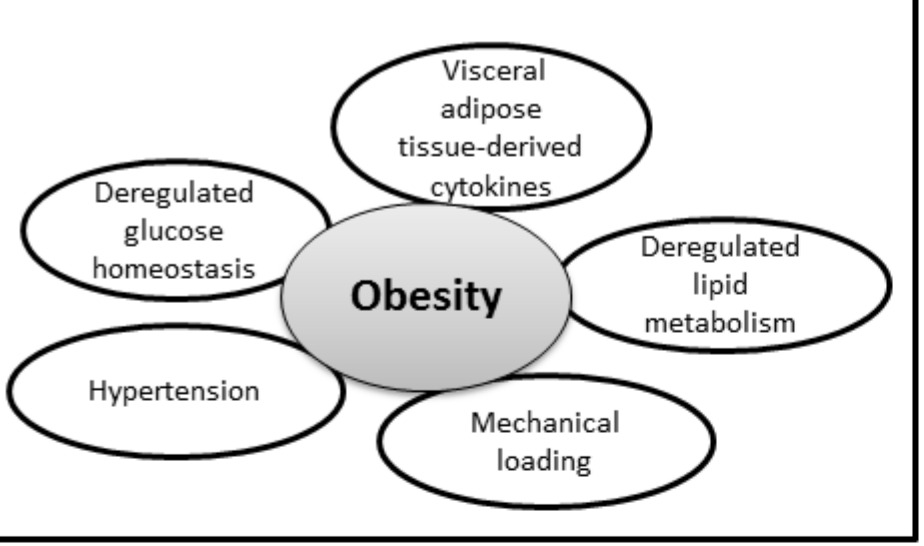
MARYFRAN SOWERS, CARRIE A. KARVONEN-GUTIERREZ, RIANN PALMIERI-SMITH, JON A. JACOBSON, YEBIN JIANG, AND JAMES A. ASHTON-MILLER

Objective. **To assess the role of obesity and metabolic dysfunctionality with knee osteoarthritis (OA), knee joint pain, and physical functioning performance, adjusted for joint space width (JSW) asymmetry.**

Methods. **Knee OA was defined as a Kellgren/Lawrence score ≥2 on weight-bearing radiographs. Obesity was defined as a body mass index ≥30 kg/m^2. Cardiometabolic clustering classification was based on having ≥2 of the following factors: low levels of high-density lipoprotein cholesterol; elevated levels of low-density lipoprotein cholesterol, triglycerides, blood pressure, C-reactive protein, waist:hip ratio, or glucose; or diabetes mellitus. The difference between lateral and medial knee JSW was used to determine joint space asymmetry.**

Results. **In a sample of women (n = 482, mean age 47 years), prevalences of knee OA and persistent knee pain were 11% and 30%, respectively. The knee OA prevalence in nonobese women without cardiometabolic clustering was 4.7%, compared with 12.8% in obese women without cardiometabolic clustering and 23.2% in obese women with cardiometabolic clustering. Nonobese women without cardiometabolic clustering were less likely to perceive themselves as limited compared with women in all other obesity/cardiometabolic groups ($P < 0.05$). Similar associations were seen with knee pain and physical functioning measures. The inclusion of a joint space asymmetry measure was associated with knee OA but not with knee pain or physical functioning.**

Conclusion. **Knee OA was twice as frequent in obese women with cardiometabolic clustering compared with those without, even when considering age and joint asymmetry. Obesity/cardiometabolic clustering was also associated with persistent knee pain and impaired physical functioning.**

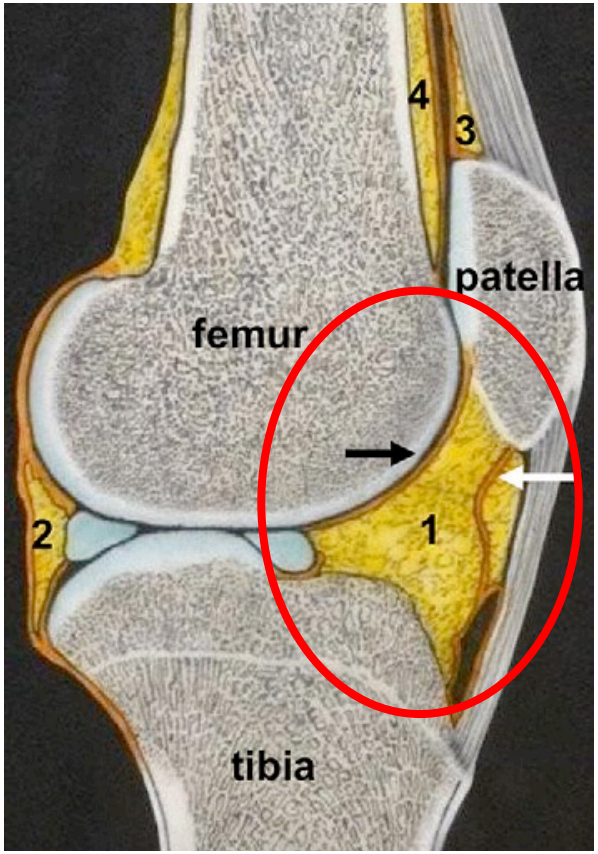


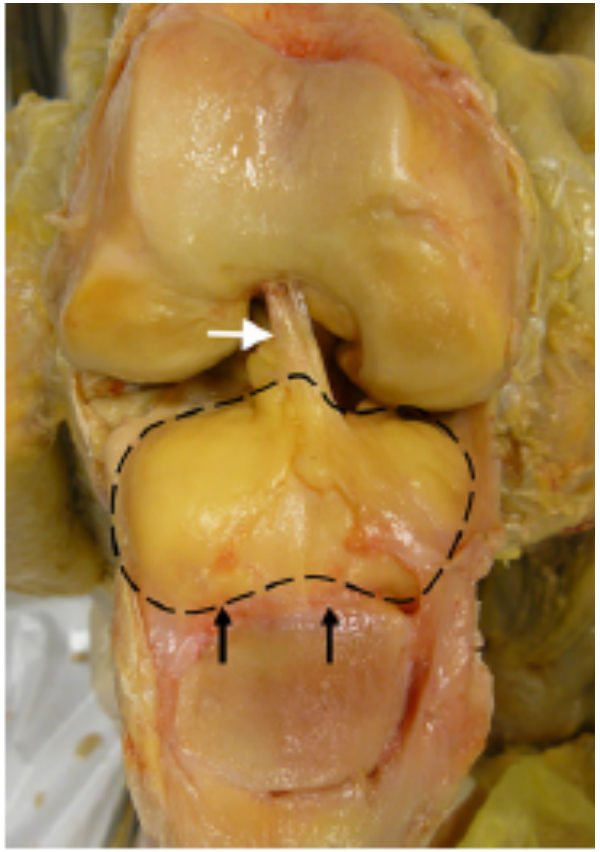
- **Inflammation**
(cytokines, adipokines, oxidative stress)
- **Catabolic enzyme production**

Knee joint damage

Belluzzi E et al. submitted

INFRAPATELLAR FAT PAD (IFP)





- Intracapsular and extrasynovial
- Innerved and vascularized

- Distribution of lubricant
- Biomechanical function

S. Clockaerts yz. Osteoarthritis Cartilage 2010

PLOS ONE

RESEARCH ARTICLE

Influence of the Infrapatellar Fat Pad Resection during Total Knee Arthroplasty: A Systematic Review and Meta-Analysis

Chenyi Ye[1‡], Wei Zhang[1‡], Weigang Wu[1‡], Mingyuan Xu[2], Nwofor Samuel Nonso[1], Rongxin He[1]*

Study or Subgroup	IPFP-R Events	IPFP-R Total	IPFP-P Events	IPFP-P Total	Weight	Odds Ratio M-H, Random, 95% CI
Maculé, 2005	28	34	26	34	41.4%	1.44 [0.44, 4.70]
Pinsornsak, 2014	4	45	3	45	25.0%	1.37 [0.29, 6.48]
Tanaka, 2003	12	54	3	53	33.6%	4.76 [1.26, 18.00]
Total (95% CI)		**133**		**132**	**100.0%**	**2.12 [0.95, 4.73]**
Total events	44		32			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 2.16$, $df = 2$ ($P = 0.34$); $I^2 = 7\%$

Test for overall effect: $Z = 1.84$ ($P = 0.07$)

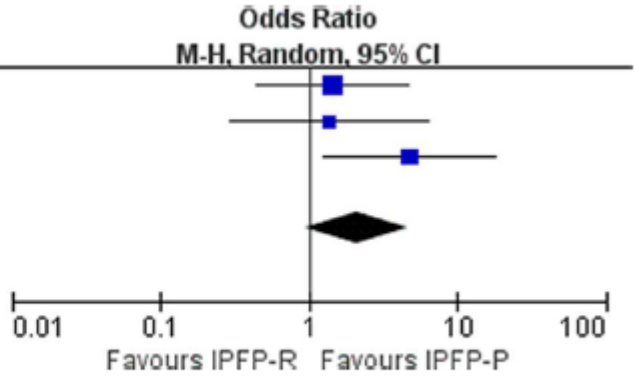


Fig 2. Forest plot shows that IPFP resection trended to increase the incidence of anterior knee pain within 2 months postoperatively comparing with the IPFP preservation group.

REVIEW

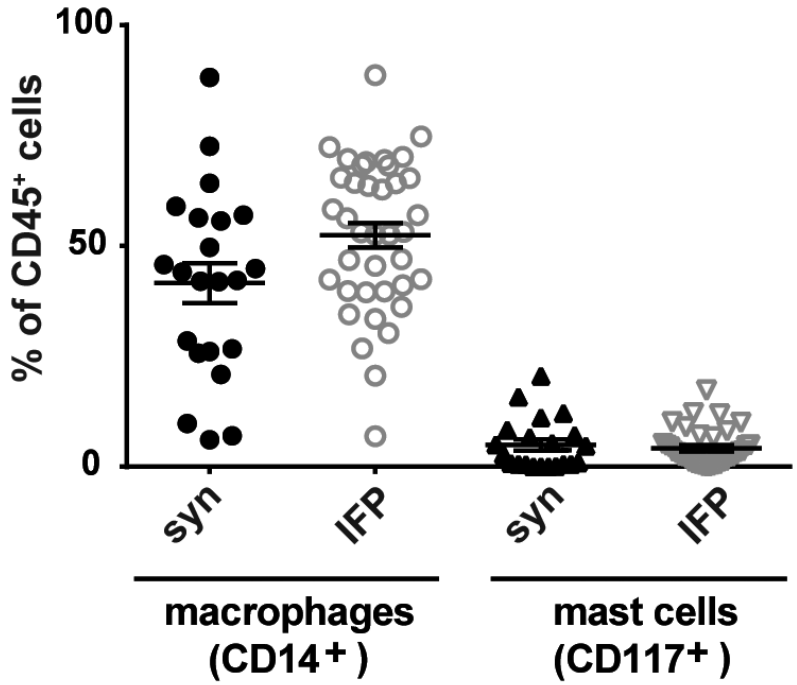
An emerging player in knee osteoarthritis: the infrapatellar fat pad

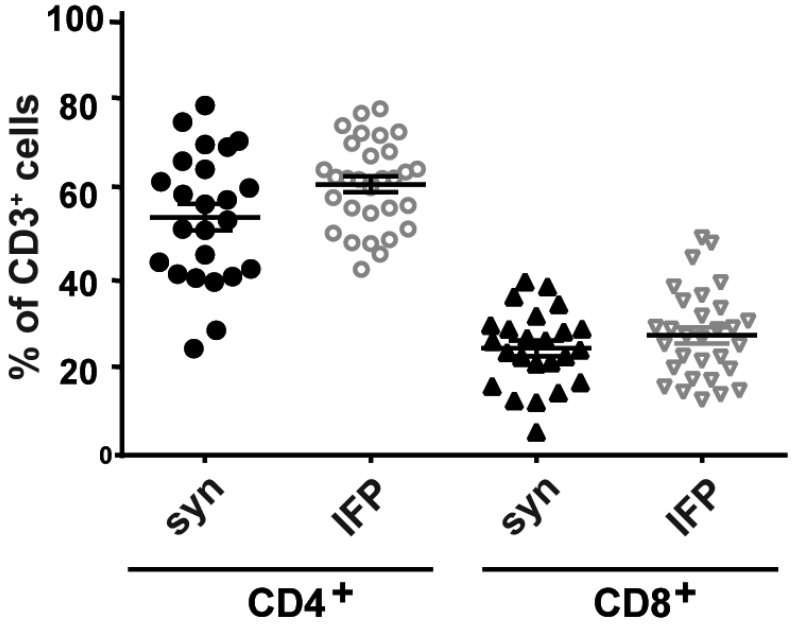
Ioan-Facsinay A, Arthritis Res Ther. 2013

- The cytokine production/expression of IFP has been investigated only in few studies.
- Homogenates of IFP tissue obtained from patients undergoing surgery displayed detectable levels of b-FGF, IL-6, VEGF, TNF-α *(Ushiyama 2003).*
- Increased levels of IL-6 and IL-6 soluble receptor have been detected in IFP of obese OA patients compared to controls *(Distel 2006).*
- Decreased expression levels of leptin were found in IFP of obese OA patients compared to subcutaneous adipose tissue (AT). Leptin secretion in IFP was decreased by 40% of that observed in subcutaneous AT, and adiponectin secretion in IFP was increased by 70% of that observed in subcutaneous AT (Distel *2006).*

Inflammatory Cells in Patients with Endstage Knee Osteoarthritis: A Comparison between the Synovium and the Infrapatellar Fat Pad

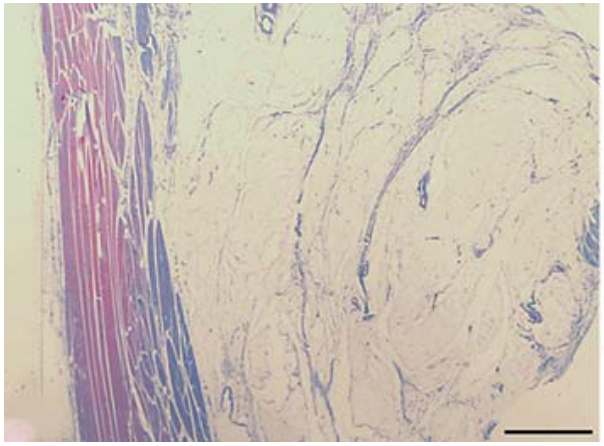
Inge R. Klein-Wieringa, Badelog J.E. de Lange-Brokaar, Erlangga Yusuf, Stefan N. Andersen, Joanneke C. Kwekkeboom, Herman M. Kroon, Gerjo J.V.M. van Osch, Anne-Marie Zuurmond, Vedrana Stojanovic-Susulic, Rob G.H.H. Nelissen, René E.M. Toes, Margreet Kloppenburg, and Andreea Ioan-Facsinay





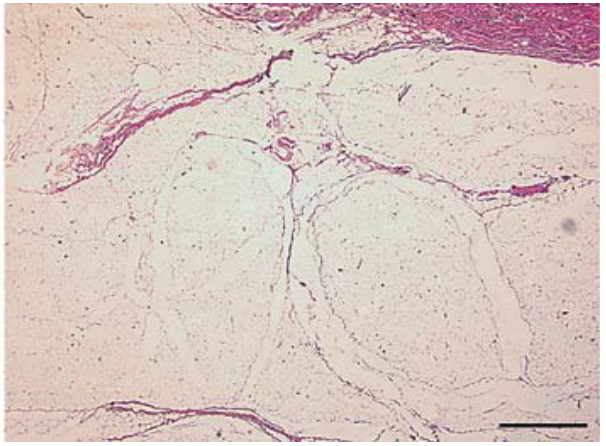
Klein-Wieringa IR, The Journal of Rheumatology 2016

IFP



SUBCUTANEOUS

ABDOMEN



Macchi V, Cells Tissues Organs. 2016

MATERIALS AND METHODS

VS

CADAVERS OF THE DONATION PROGRAM "BODY TO SCIENCE" OF PADOVA UNIVERSITY

VS

SUBCUTANEOUS ADIPOSE TISSUE OF THE KNEE OF THE SAME PATIENTS

Favero et al. submitted

MATERIALS AND METHODS

HISTOLOGY

SYNOVIAL MEMBRANE
Mononuclear cell infiltration (0-3)
Synovial hyperplasia (0-2)
Vascularization (0-2)
Fibrosis (0-2)
Mucoid change (0-4)
Detritus (0-2)

Scanzello CR, Arthritis Rheum. 2011

IFP
Mononuclear cell infiltration (0-2)
Vascularization (numbers)
Adipose lobules dimension
Thickness of interlobular septa

Favero et al. submitted

Favero et al. submitted

RESULTS

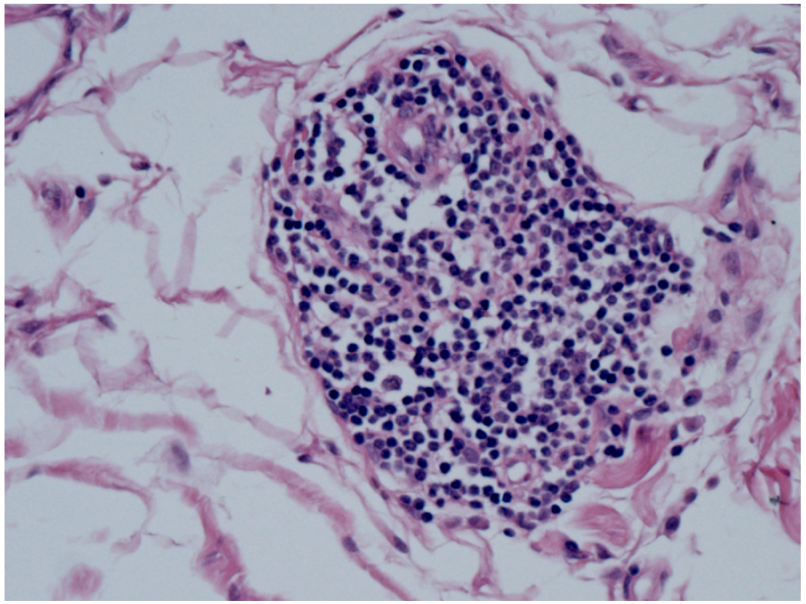
PATIENT CHARACTERISTICS

	OA PATIENTS	CONTROLS	P
Number of patients	28	8	
Sex (female), number (%)	21 (75)	4 (50)	0.047*
Age, mean (SD), years	68.9 (7.8)	81.8 (4.9)	<0.0001*
BMI, mean (SD), Kg/m²	30.5 (5.0)	21.8 (2.3)	0.0002*
Comorbidities -Hypertension, number (%) -Diabetes, number (%) -Hypercholesterolemia, number (%)	17 (68%) 3 (12%) 8 (32%)	6 (60%) 3 (30%) 3 (30%)	0.382 0.073 0.468

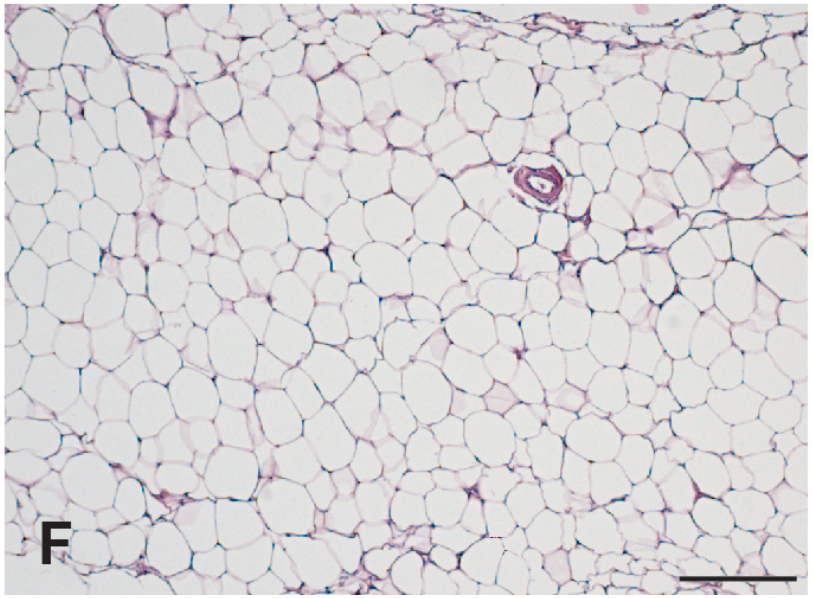
Favero et al. submitted

RESULTS

OA



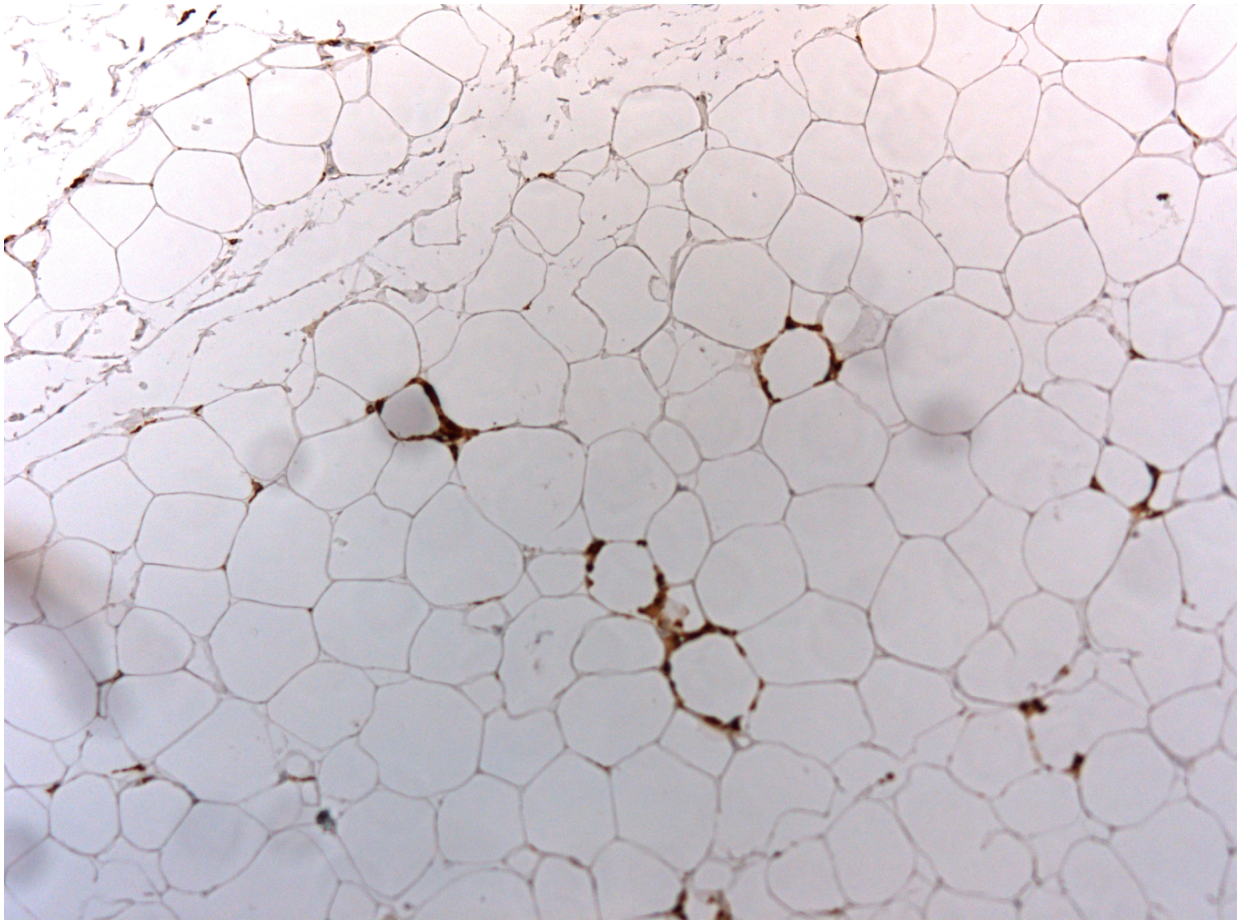
CONTROLS



IFP HISTOPATHOLOGIC GRADING	OA PATIENTS	CONTROLS	P
Mononuclear cell Infiltration, number (%)			0.001*
Grade 0	5 (18.5%)	8 (100%)	
Grade 1	8 (29.6%)	0 (0%)	
Grade 2	14 (51.9%)	0 (0%)	

Favero et al. submitted

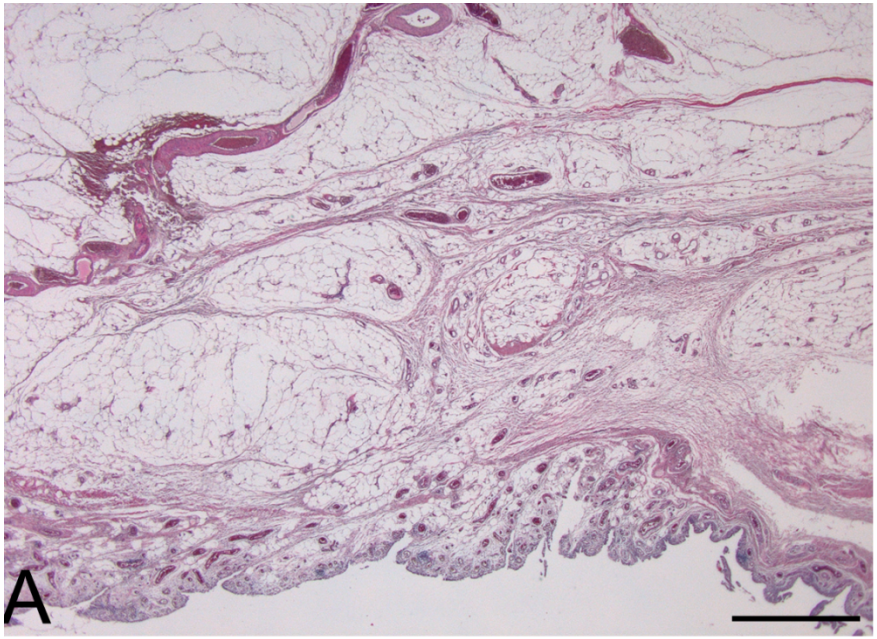
CD28+ IMMUNOHISTOCHEMISTERY



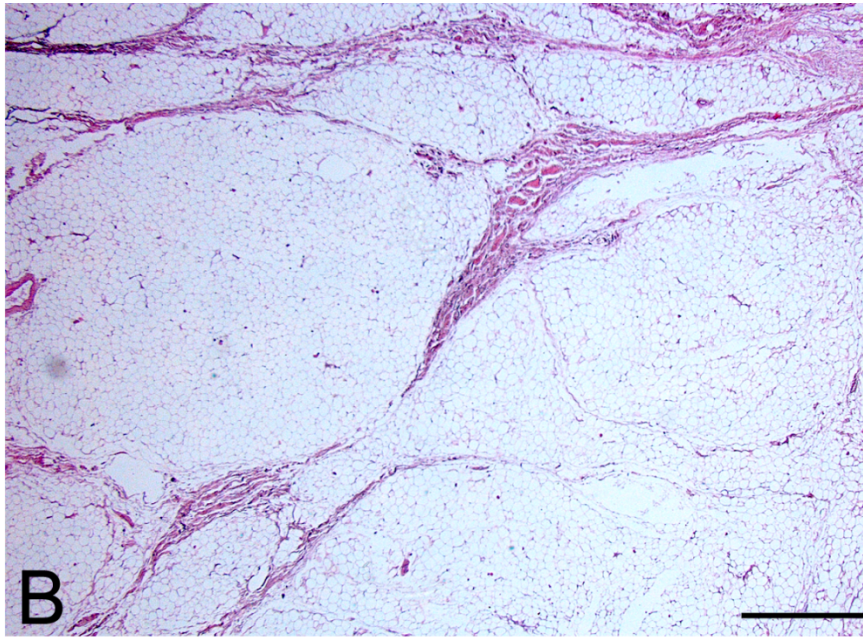
Macchi V. et al. unpublished

RESULTS

OA



CONTROLS

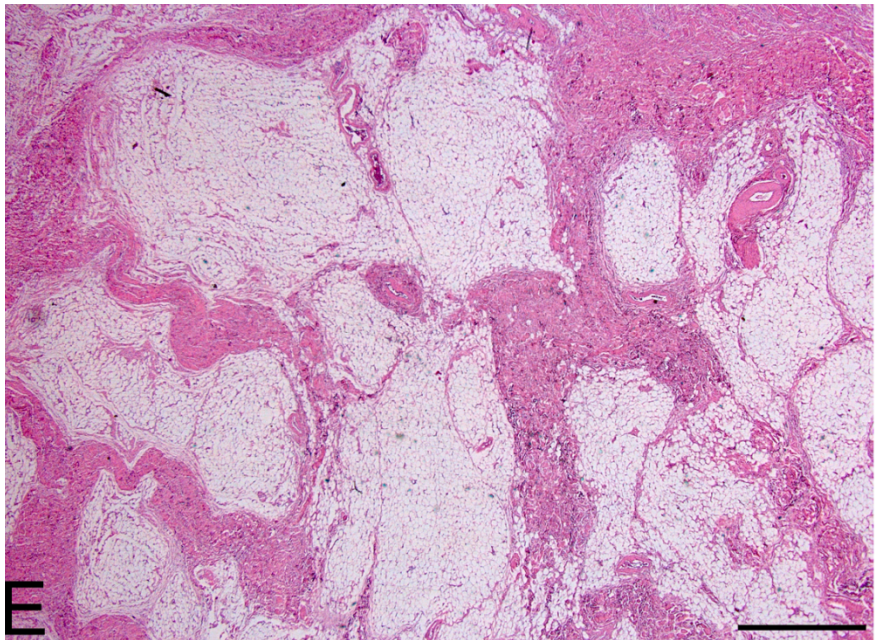


IFP HISTOPATHOLOGIC GRADING	OA PATIENTS	CONTROLS	P
Vascularity, mean (SD), number	34.91 (16.26)	11.81 (4.25)	<0.0001*

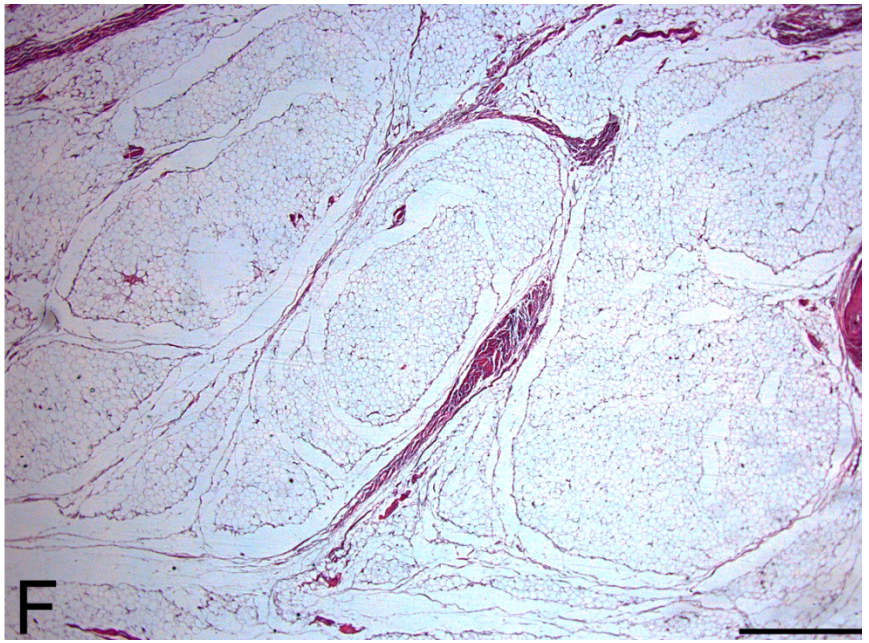
Favero et al. submitted

RESULTS

OA

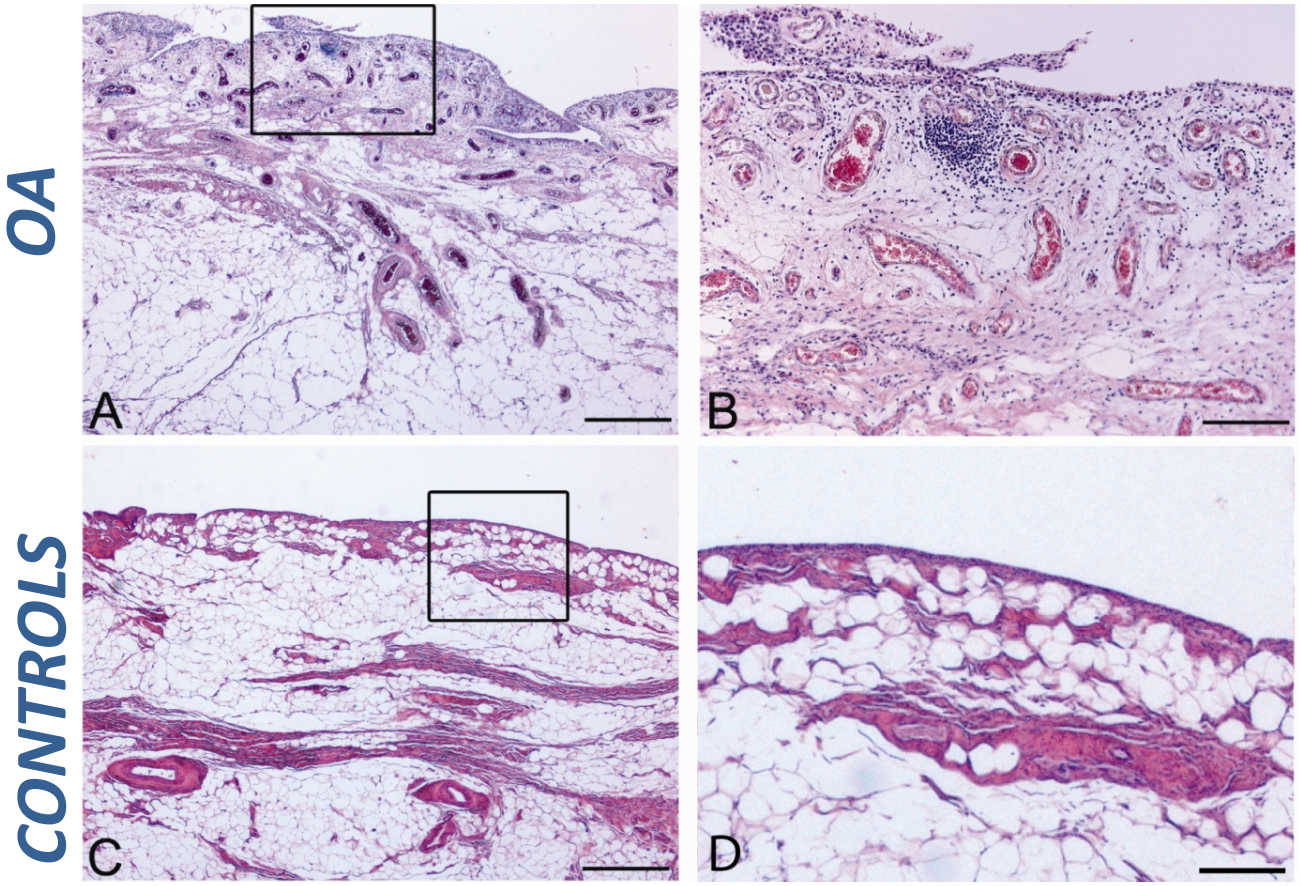


CONTROLS



IFP HISTOPATHOLOGIC GRADING	OA PATIENTS	CONTROLS	P
Thickness of the interlobular septa, mean (SD), mm	0.30 (0.08)	0.23 (0.03)	0.004 *
Diameter of adipose lobuli, mean (SD), mm	1.09 (0.42)	1.15 (0.11)	0.141

Favero et al. submitted



SYNOVIAL MEMBRANE	OA PATIENTS	CONTROLS	P
Lymphocytic infiltration (0-3)	2.5 (1-3)	0 (0-1)	<0.001*
Synovial hyperplasia (0-2)	2 (1-2)	0 (0-0)	0.001*
Vascularization (0-2)	0 (0-2)	0 (0-0)	<0.001*
Fibrosis (0-2)	1 (0-2)	0 (0-1)	0.002*

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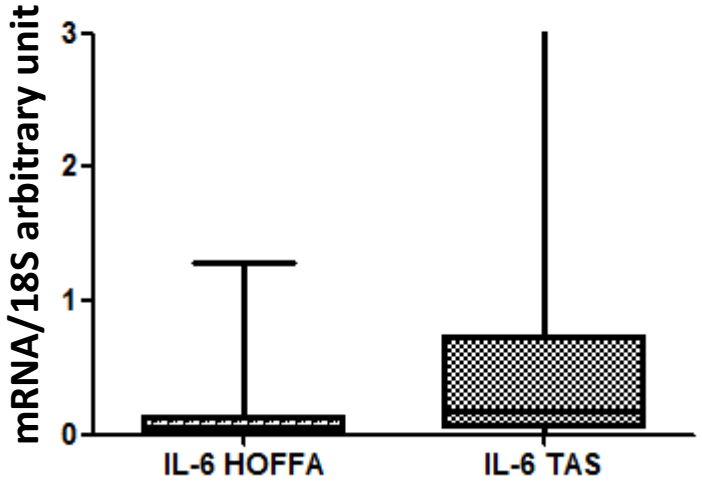
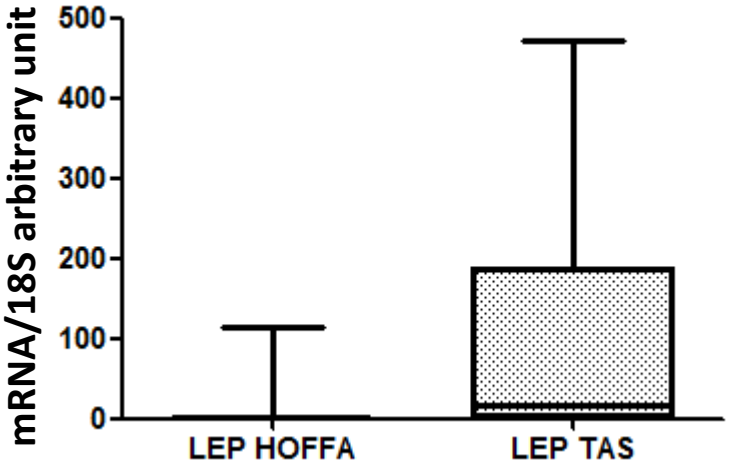
RESULTS: *gene expression*

	IFP	SAT	P
IL-6	0,2 (0,3)	0,8 (1,8)	0,02*
ADIPONECTINA	1,0 (0,9)	1,8 (1,2)	0,05
MCP-1	3,5 (3,0)	4,2 (3,3)	0,96
LEPTINA	5,4 (22,1)	108,6 (151,2)	<0,01*
TNF-α	0,6 (0,4)	1,0 (0,8)	0,1
PPAR-ϒ	2,6 (3,9)	2,3 (1,4)	0,36
FABP	6,7 (12,2)	1,3 (0,7)	0,81

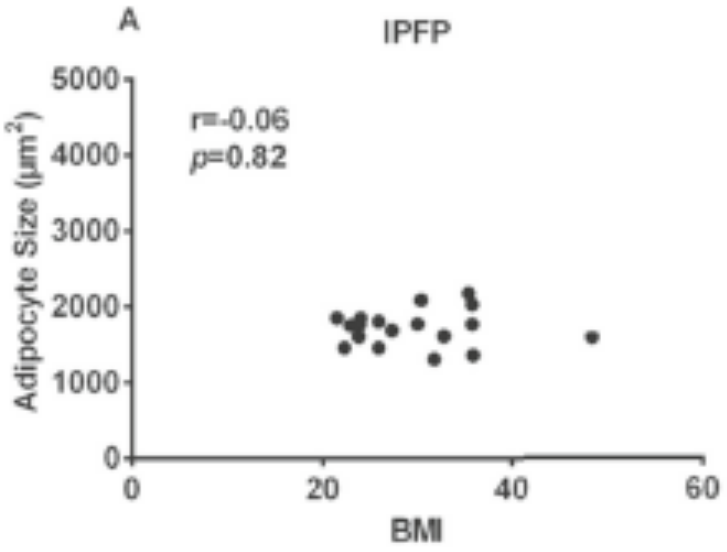


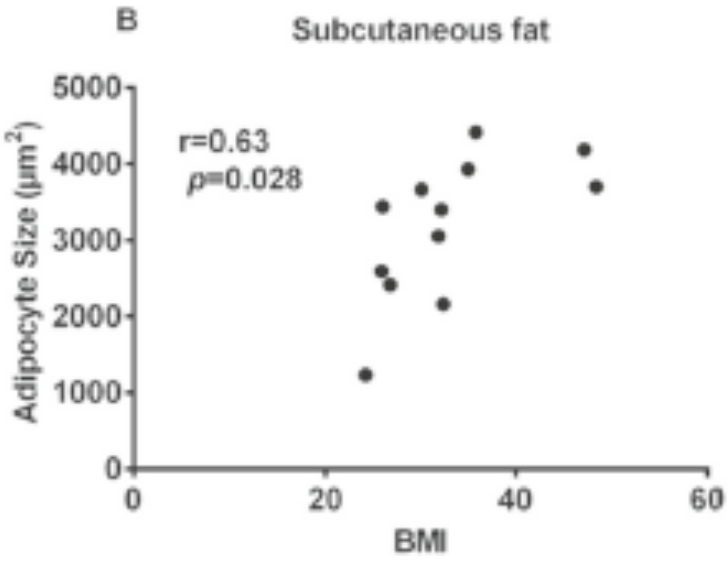


Favero et al. unpublished

STUDY LIMITATION

- Age and BMI of the OA group were significantly different compared to controls.





Garcia J, Osteoarthritis and Cartilage; 2016

Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score)

D.J. Hunter †*, A. Guermazi ‡, G.H. Lo §||, A.J. Grainger ¶, P.G. Conaghan #, R.M. Boudreau ††, F.W. Roemer ‡‡‡

Osteoarthritis and Cartilage

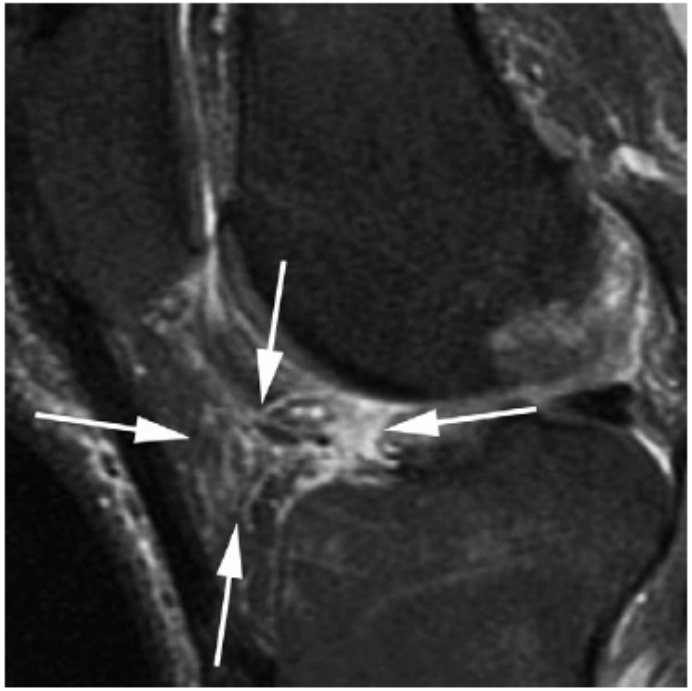
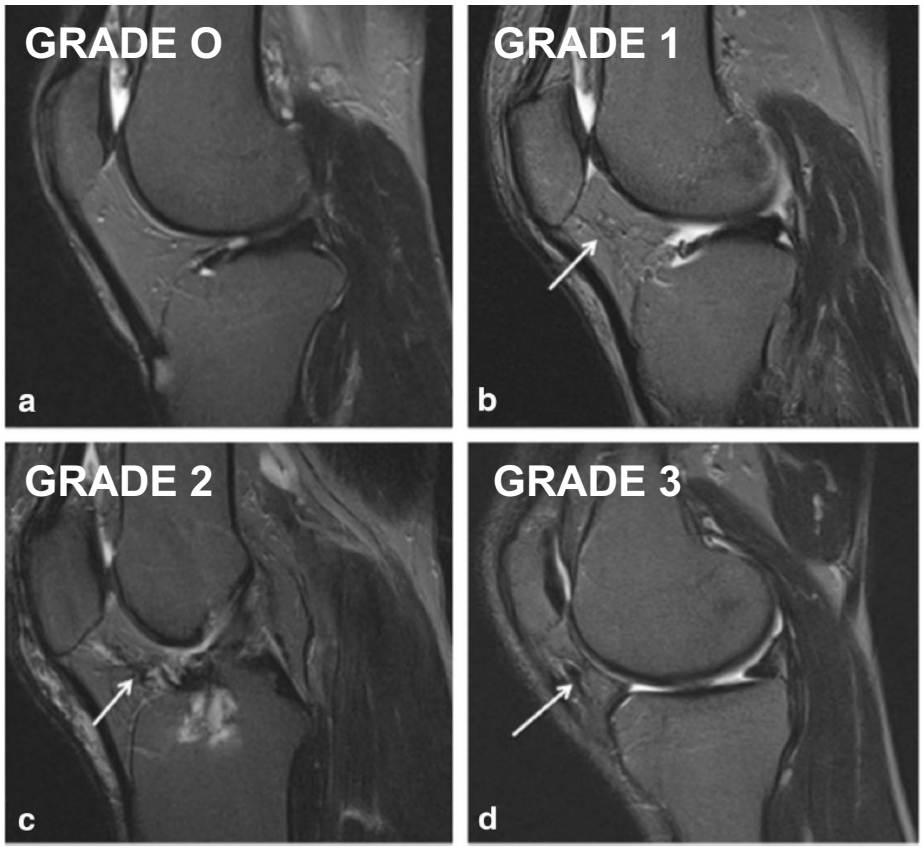
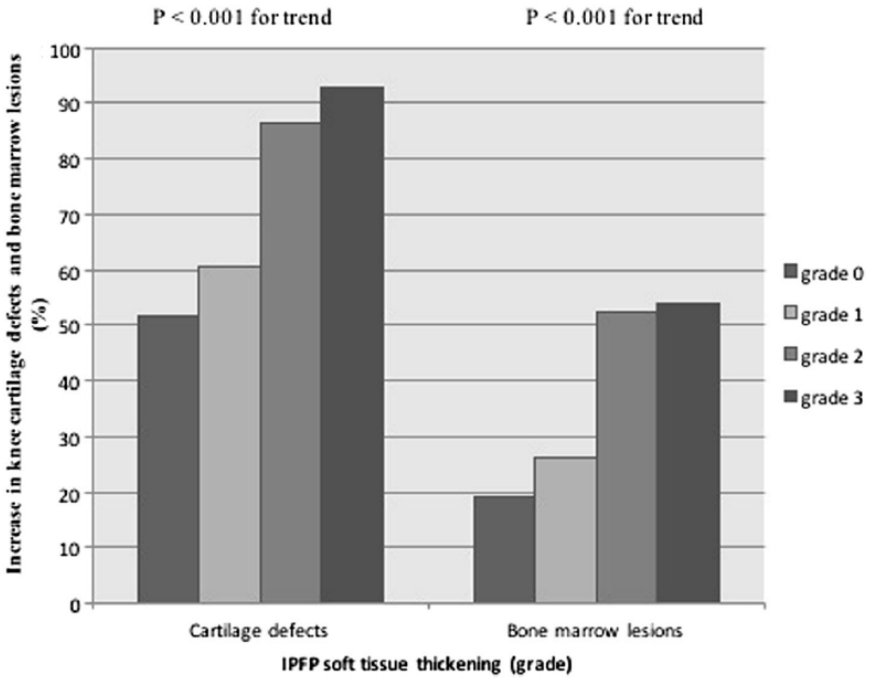


Fig. 8. Hoffa-synovitis. Sagittal T2w image shows grade 2 hyperintense signal changes in Hoffa's fat pad consistent with Hoffa-synovitis.

Hyperintense signal of IFP on saggital T2 weighted images is associated with knee symptoms and structural changes *(Roemer 2009, Hill CL 2007, Han 2016)*

Hypointense signals in the infrapatellar fat pad assessed by magnetic resonance imaging are associated with knee symptoms and structure in older adults: a cohort study





Han; Arthritis Research Therapy 2016

CONCLUSIONS

- Obesity is a risk factor for osteoarthritis development related to low-grade systemic inflammation other than joint overloading.
- Metabolic syndrome is an indipendent risk factor for osteoarthritis and accumulation of MetS components is associated with OA incidence, OA severity and TKR
- Infrapatellar fat pad seems to have a role in the pathogenesis of osteoarthritis producing adipocytokines.
- Infrapatellar fat pad and adjacent synovial membrane of OA patients showed increased mononuclear cell infiltration, vascularization and fibrosis compared to controls.

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Original Investigation

Change in Pain and Physical Function Following Bariatric Surgery for Severe Obesity

Wendy C. King, PhD; Jia-Yuh Chen, MS; Steven H. Belle, PhD; Anita P. Courcoulas, MD, MPH; Gregory F. Dakin, MD; Katherine A. Elder, PhD; David R. Flum, MD, MPH; Marcelo W. Hinojosa, MD; James E. Mitchell, MD; Walter J. Pories, MD; Bruce M. Wolfe, MD; Susan Z. Yanovski, MD

IMPORTANCE The variability and durability of improvements in pain and physical function following Roux-en-Y gastric bypass (RYGB) or laparoscopic adjustable gastric banding (LAGB) are not well described.

OBJECTIVES To report changes in pain and physical function in the first 3 years following bariatric surgery, and to identify factors associated with improvement.

DESIGN, SETTING, AND PARTICIPANTS The Longitudinal Assessment of Bariatric Surgery-2 is an observational cohort study at 10 US hospitals. Adults with severe obesity undergoing bariatric surgery were recruited between February 2005 and February 2009. Research assessments were conducted prior to surgery and annually thereafter. Three-year follow-up through October 2012 is reported.

EXPOSURES Bariatric surgery as clinical care.

MAIN OUTCOMES AND MEASURES Primary outcomes were clinically meaningful presurgery to postsurgery improvements in pain and function using scores from the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (ie, improvement of ≥5 points on the norm-based score [range, 0-100]) and 400-meter walk time (ie, improvement of ≥24 seconds) using established thresholds. The secondary outcome was clinically meaningful improvement using the Western Ontario McMaster Osteoarthritis Index (ie, improvement of ≥9.7 pain points and ≥9.3 function points on the transformed score [range, 0-100]).

RESULTS Of 2458 participants, 2221 completed baseline and follow-up assessments (1743 [78.5%] were women; median age was 47 years; median body mass index [BMI] was 45.9; 70.4% underwent RYGB; 25.0% underwent LAGB). At year 1, clinically meaningful improvements were shown in 57.6% (95% CI, 55.3%-59.9%) of participants for bodily pain, 76.5% (95% CI, 74.6%-78.5%) for physical function, and 59.5% (95% CI, 56.4%-62.7%) for walk time. Additionally, among participants with severe knee or disability (633), or hip pain or disability (500) at baseline, approximately three-fourths experienced joint-specific improvements in knee pain (77.1% [95% CI, 73.5%-80.7%]) and in hip function (79.2% [95% CI, 75.3%-83.1%]). Between year 1 and year 3, rates of improvement significantly decreased to 48.6% (95% CI, 46.0%-51.1%) for bodily pain and to 70.2% (95% CI, 67.8%-72.5%) for physical function, but improvement rates for walk time, knee and hip pain, and knee and hip function did not (*P* for all ≥.05). Younger age, male sex, higher income, lower BMI, and fewer depressive symptoms presurgery; no diabetes and no venous edema with ulcerations postsurgery (either no history or remission); and presurgery-to-postsurgery reductions in weight and depressive symptoms were associated with presurgery-to-postsurgery improvements in multiple outcomes at years 1, 2, and 3.