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FRI0374 PLASMA LEVELS OF 14-3-3 PROTEIN, S100A8/S100A9-PROTEIN, INTERLEUKIN-6, INTERLEUKIN-18, INTERLEUKIN-4, INTERLEUKIN-17, INTERLEUKIN-1Β AND TUMOR NECROSIS FACTOR-A IN CHRONIC NON-BACTERIAL OSTEOMYEILITIS AND NON-SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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Background: Chronic non-bacterial osteomyelitis (CNO) is an immune-mediated disease associated with cytokine dysbalance.

Objectives: The aim of our study was to evaluate the cytokines levels in CNO and compare to juvenile idiopathic arthritis (JIA) – disease with immune-mediated mechanism.

Methods: The diagnosis of CNO made with criteria, proposed by Jansson (2007, 2009), after the exclusion of other causes of bone disease [1]. We included 42 patients with NBO, 28 patients with non-systemic juvenile idiopathic arthritis (JIA). We evaluated plasma levels of 14-3-3 protein, S100A8/S100A9-protein, interleukine-6 (IL-6), interleukine-18 (IL-18), interleukine-4 (IL-4), interleukine-17 (IL-17), interleukine-1β (IL-1 β) and tumor necrosis factor-α (TNFα) in 2 groups by the ELISA. Statistical analysis was carried out with Statistica 10.0 software. We utilized descriptive statistics (Me; IQR), Mann-Whitney tests.

Results: We have found differences in the proinflammatory biomarkers between CNO, JIA. Patients with NBO had lower levels of studied cytokines, exclude14-3-3-protein, S100A8/S100A9 and interleukin-6 compare to JIA patients (table 1).

Table 1. Comparison the cytokine levels between CNO, JIA N

Parameter	NBO (n=42)	JIA (n=28)	p
Hemoglobin, g/l	112 (104; 124)	120 (114.5; 126.0)	0.02
WBC x 10^9/l	7.9 (7.0; 10.5)	8.0 (6.7; 10.0)	0.86
PLT x 10^9/l	347 (259; 408)	336.5 (274.0; 390.5)	0.98
ESR. mm/h	25.0 (9.0; 46.0)	8.5 (2.5; 13.0)	0.013
CRP, mg/l	6.1 (0.6; 2.4)	1.8 (0.4; 11.9)	0.027
14-3-3, ng/ml	21.4 (18.5; 27.1)	19.9 (18.0; 27.8)	0.77
S100A8/S100A9, ng/ml	5.9 (5.2; 6.5)	5.9 (5.0; 6.2)	0.76
IL-6, ng/ml	126,2 (112.8; 137.5)	132.4 (117.4; 142.9)	0.16
IL-18, ng/ml	270.1 (200.1; 316.1)	388.3 (373.9; 405.1)	0.0000001
IL-4, ng/ml	15.3 (11.5; 18.2)	18.7 (16.2; 20.2)	0.003
IL-17, ng/ml	83.1 (71.1; 97.3)	99.2 (87.3; 115.8)	0.003
IL-1b, ng/ml	47.4 (42.0; 51.3)	70.8 (65.3; 73.6)	0.0000001
TNFa, ng/ml	19.4 (17.8; 21.3)	23.1 (20.2; 25.9)	0.0006

Conclusion: Patients with CNO had less proinflammatory activity then JIA patients, besides IL-6 and S100A8/S100A9. Further investigations required for finding new more precise biomarkers and finding possible molecular targets for treatment.

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[1] Jansson AF, et al. Clinical score for nonbacterial osteitis in children and adults. Arthritis Rheum. 2009;60(4):1152-9.

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FRI0375 VISFATIN EFFECTS ON MSCS DURING OD VIA DIFFERENTIAL REGULATION OF LNCRNA H19 AND MICRO RNA 675-3P

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Background: Long non-coding (lnc-)RNA are regulatory molecules transcribed from DNA similar to mRNA and interact directly with DNA, RNA and proteins. Some lncRNAs have been shown to contain micro (mi-)RNAs in their sequence that can be released by splicing and lead to active miRNA molecules, e.g. lncRNA H19 includes two miRNAs 675-3p and -5p in its sequence.

Adipose tissue derived factors (adipokines) are involved in inflammation processes and osteoarthritis (OA) development. The proinflammatory adipokine visfatin has been shown to alter osteogenic differentiation (OD) of pluripotent mesenchymal stem cells (MSCs) and reduces elastic fiber expression, increases matrix mineralization and proinflammatory cytokine and chemokine production [(1)].

Objectives: We evaluated a novel effect of visfatin on lncRNA H19 in MSCs during OD. The goal was to explore the kinetics of the visfatin effect during OD with regard to H19 regulation and to investigate H19 downstream mechanisms leading to the observed altered MSC differentiation and osteoblast activity.

Methods: MSCs isolated from OA hip or knee bone (phMSC) and commercially obtained healthy human (h-)MSCs were differentiated towards osteoblasts with/without visfatin, resistin, leptin, TNF and Wnt/TGFβ1 pathway inhibitors. Supernatants were collected at days 2, 7, 9, 14 and 21 of OD, cell lysates at day 2, 7, 9, 14 and matrix mineralization assays conducted at day 21. H19 and miRNA expression was evaluated by real-time PCR after mi-/RNA isolation. IL-6 was analyzed by ELISA.

Results: H19 was continuously upregulated in unstimulated controls as expected during OD but also when stimulated with other adipokines. In contrast, stimulation with visfatin significantly decreased H19 (day 2 to 14 of OD, hip-phMSCs: p = 0.0097, knee-phMSCs: p=0.0075, h-MSC: p = 0.044). Visfatin increased matrix mineralization and IL-6 production as expected (hMSC: p = 0.03, phMSC: p = 0.013) [(1)]. TNF stimulation during OD did not lead to a downregulation of H19 nor increased matrix mineralization, thus showing that the effects were visfatin-dependent. H19s endogenous miRNA 675-5p was changed in parallel with H19, increased during control OD and significantly down-regulated by visfatin (e.g. day 14 p = 0.015). However, H19s endogenous miRNA 675-3p was inversely regulated, downregulated during control OD while visfatin stimulation attenuated this effect (e.g. day 14 p = 0.025). Altered Wnt-signaling and involvement of the TGFβ1 pathway could not be observed.

Conclusion: H19 is upregulated during OD and may therefore play a regulatory role in the process of osteogenesis. Visfatin stimulation of MSCs during OD showed pro-inflammatory effects, increased matrix mineralization while reducing elastic fiber production [(1)]. These effects were associated with a downregulation of H19, a specific visfatin effect not triggered by other adipokines or TNF. The H19 sequence includes two endogenous micro-RNAs 675-3p and 5p. We demonstrated miRNA 675-5p to be regulated in parallel to H19, whereas miRNA 675-3p was inversely regulated and increased continuously upon visfatin stimulation. Based on these results, we hypothesize that visfatin provides a specific stimulus for the splicing of miRNA 675-3p from H19, in turn leading to H19 reduction. miRNA 675-3p thus represents an effector mechanism of visfatin that contributes to the observed functional effects in differentiating MSCs.

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[1] Tsiklauri, L. *et al.* Visfatin alters the cytokine and matrix-degrading enzyme profile during osteogenic and adipogenic MSC differentiation. *Osteoarthr. Cartil.* **26**, 1225–1235 (2018).

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FRI0376 EFFECT OF CARBAMYLATED LOW-DENSITY LIPOPROTEINS ON BONE CELLS HOMEOSTASIS

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Background: Carbamylation is a post-translational modification occurring under several conditions such as uremia, smoking and chronic inflammation as in rheumatoid arthritis (RA). Low-density lipoproteins (LDL) represent a target of carbamylation. Carbamylated-LDL (cLDL) have an increased inflammatory and atherogenic potential. Growing evidence supports an influence of modified lipids on bone cells homeostasis. However, the role of cLDL on bone cells physiology is still unknown.

Objectives: Considering the rate of carbamylation and the role of anti-carbamylated proteins antibodies as markers of erosive disease in RA, the purpose of this study is to investigate the effect of cLDL on bone homeostasis.

Methods: *In-vitro* carbamylation of LDL was performed as previously described by Ok et al. (Kidney Int. 2005). Briefly, native LDL (nLDL) were treated with potassium cyanate (KOCN) for 4 hours, followed by excessive dialysis for 36 hours to remove KOCN. Both osteoclasts (OCs) and osteoblasts (OBLs) were treated at baseline with 20 µg/ml, 100 µg/ml and 200 µg/ml of cLDL or nLDL. To induce osteoclast differentiation, CD14+ monocytes were isolated from peripheral blood of healthy donors by magnetic microbeads separation and then cultured on a 96-wells plate in DMEM media supplemented with RANKL and M-CSF. After 10 days cells were fixed, stained for tartrate-resistant acid phosphatase (TRAP), a marker of OC differentiation, and counted. OBLs were isolated from bone specimens of 3 patients who had undergone to knee or hip arthroplasty for osteoarthritis and treated for 5 days with different concentrations of cLDL and nLDL. OBLs were fixed and stained for alkaline phosphatase positive activity (ALP), a marker of osteogenic differentiation. Total RNA was extracted from cell lysates. Copies of single-stranded complementary DNA (cDNA) were synthesized and analyzed by real-time PCR to evaluate RANKL and Osteoprotegerin (OPG) mRNA expression levels.

Results: In OCLs culture, cLDL significantly decreased the number of OC compared to untreated cells (200 µg/ml p=0,0015) and nLDL treated cells (200 µg/ml p= 0,011; 20 µg/ml p= 0,0014) (Fig 1). Moreover, treatment with cLDL induced an increase of not terminally differentiated OCs, reduced dimensions of OCs, less intense TRAP staining and vacuolization (Fig 2). In OBLs culture, cLDL (20, 100 µg/ml) significantly reduced the ALP activity of OBLs compared with untreated cells (p<0.05) (Fig 3). nLDL did not affect the ALP expression. Treatment with cLDL stimulated RANKL mRNA expression in osteoblasts increasing the RANKL/OPG ratio (Fig 4).

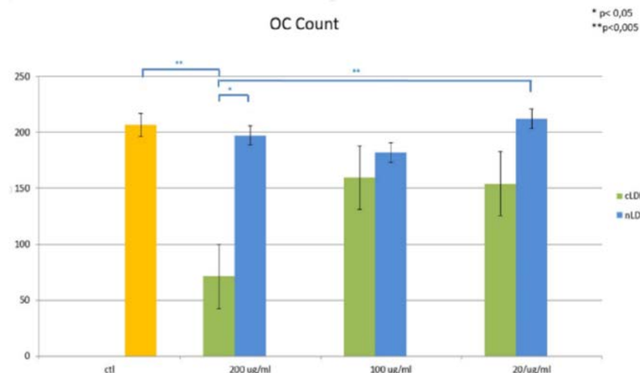

Fig 1.

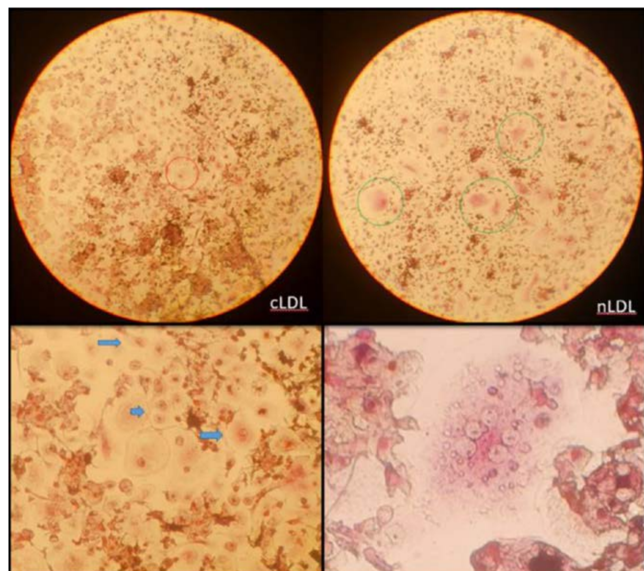

Fig 2.

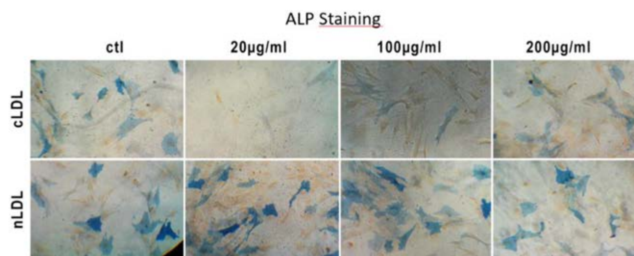

Fig 3.

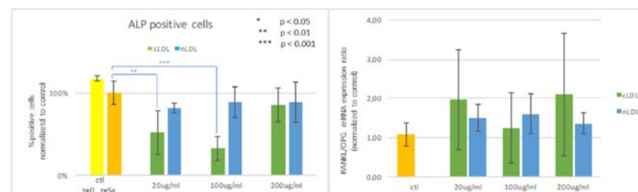

Fig 4.

Conclusion: cLDL induce a significant depression of OC and OBL differentiation. Moreover, cLDL increase RANKL expression in OBL, unbalancing bone tissue turnover towards bone resorption. Accordingly, cLDL could be implicated in the bone loss characterizing several conditions associated to an increased carbamylation, such as RA

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FRI0377 BARIATRIC SURGERY: EFFECTS ON BONE METABOLISM

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Background: There are few data about variations in bone metabolism associated with weight loss in obese patients undergoing bariatric surgery.

Objectives: To assess the influence on the bone metabolism of bariatric surgery in morbidly obese patients.

Methods: Longitudinal pre-post study with analytical components. All morbidly obese patients undergoing bariatric surgery were, prior to this, referred to Rheumatology Department. In all cases, the baseline characteristics of the patients were collected and a complete bone metabolic analytical study and bone densitometry (BMD) were requested. This same study was repeated one year later, with a window period of ± 3 months. Statistical analysis was performed with the SPSS 20.0 software.

Results: Of the 91 patients included in the study and who underwent baseline BMD and analytical tests prior to surgery, only follow-up data of 27 patients could be collected at the time of the present data analysis. Within this sample, the median age was 54 years (AIQ 11), with 6 men and 21 women (11 premenopausal, 10 postmenopausal). Prior to surgery, median body mass index (BMI) was 39.2 (AIQ4.43) and median vitamin D (25OHD) level was 22 (AIQ 16). High values of PTH were detected in two patients. Regarding baseline BMD, 78% had normal values and 22% had values in the range of osteopenia.

After surgery, all patients presented a significant weight loss, being the median loss in BMI per year 9.8 Kg/m^2 (AIQ 3.8) as absolute value, and 25% (AIQ 8.12) as a percentage value. This weight loss was accompanied by a significant BMD worsening that was evident in all locations: lumbar spine (median -6.97%, AIQ 6.3), total hip (median -6.4%, AIQ 7.7) and femoral neck (median -3.57 %, AIQ 8); so that an additional 22% of patients changed to osteopenia values. All this despite a significant increase in 25OHD levels in all cases (35.7%; AIQ 52.3). No clinical or morphometric fractures were collected. Despite the parallel

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