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DEMONSTRATE THE DRUG DERIVED FROM OMEGA-3 FATTY ACIDS THERAPEUTIC EFFECT ON PATIENTS WITH OBESITY-ASSOCIATED OSTEOARTHRITIS.

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Abstract:

Objectives: *The aim of this study which is published in nature international journal of since on 23.01.2019 11 is to examine the role of macrophages in the progression of obesity-induced osteoarthritis which is mainly progress by synovial inflammation by using clodronate-loaded liposomes (CL) to locally deplete macrophages in the synovial joints.*

Methodology: *An evaluation of Rats where fed with a high-carbohydrate high-fat diet (HCHF) for 16 weeks which already showed: (a) significant increase in body weight 44.39 ± 2.82 g ($p < 0.05$). (B) Low-density lipoprotein (LDL), and triglyceride were markedly elevated. (C) Osteoarthritis -like changes in articular cartilage. By the D1 (RvD1), which is a unique family of pro-resolving lipid mediator derived from the omega-3 polyunsaturated fatty acid, the study hunt for determine whether RvD1 administration ameliorates obesity-induced osteoarthritis by resolving macrophage-mediated synovitis.*

Result: *shown marked potency in changing the pro-inflammatory behavior of the macrophages in obese mice models. Intra-articular treatment with in the knee joint from mice as follows: (a) decreases macrophages infiltration in synovium, (b) reduces the number of pro-inflammatory macrophages in synovium and (c) improves the severity of synovitis and cartilage degradation.*

Conclusion: *Results provide new evidence for the potential targeting of macrophages in the treatment of obesity-induced osteoarthritis.*

Key Words: *obesity-induced osteoarthritis, omega-3 polyunsaturated fatty acid, synovitis, cartilage degeneration, inflammatory macrophages.*

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INTRODUCTION:

Phenotype of osteoarthritis, which is associated with metabolic syndrome and obesity is definition of metabolic osteoarthritis 1. The pathophysiologic mechanism of obesity-associated osteoarthritis is permanent inflammation, resulting in cartilage loss, osteophyte formation and synovitis that lead to the development of osteoarthritis 2.

Resolvin D1 (RvD1), a pro-resolving lipid mediator, is derived from omega-3 docosahexaenoic acid during the resolution phase of inflammation, and displays potent anti-inflammatory and pro-resolving characteristics 4, 5.

These data suggest that novel therapies that target macrophage polarization may mitigate the development of obesity-induced osteoarthritis.

METHODOLOGY:

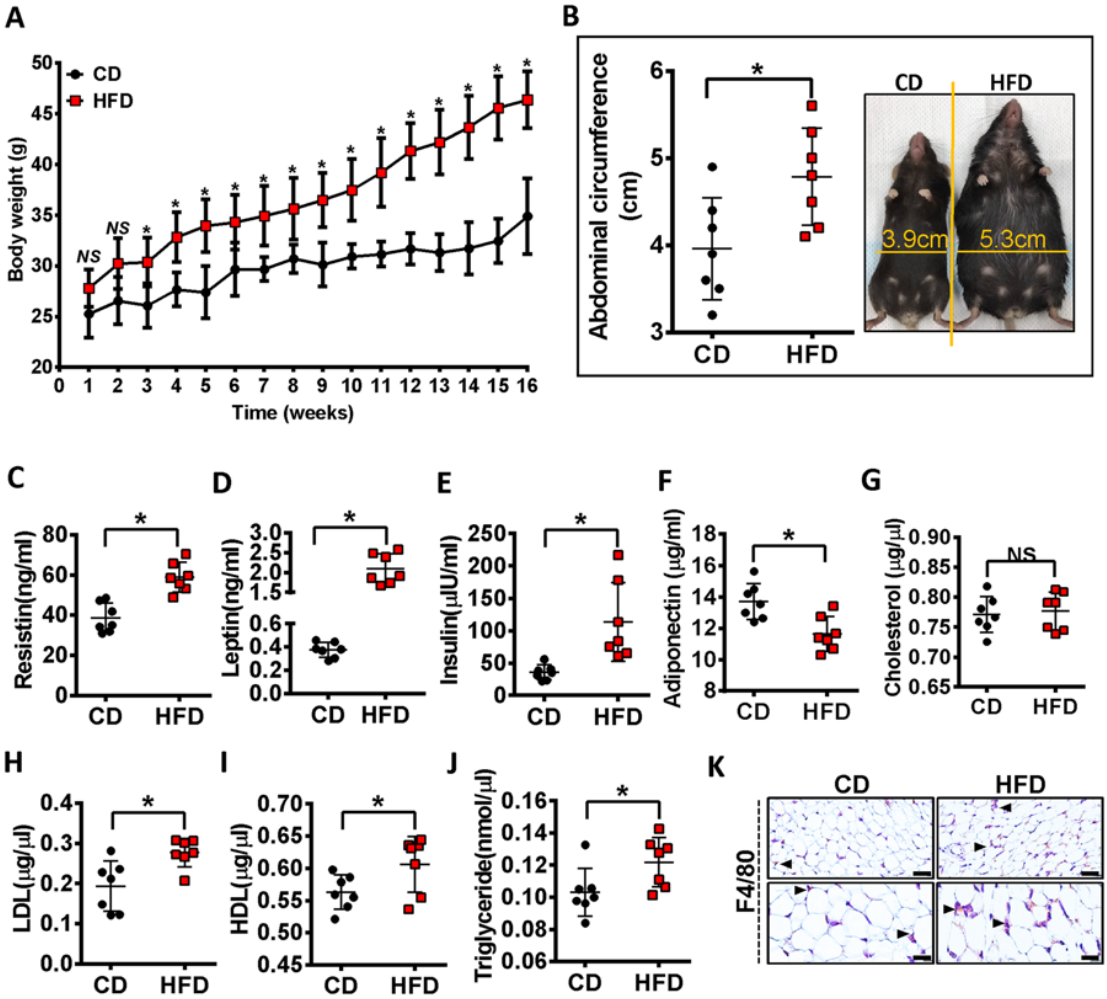
After 16 weeks of the High fat diet, mice showed a significant increase in body weight compared to mice fed the control diet , mice weighing 33.49 ± 2.28 g compared to High fat diet mice at 44.39 ± 2.82 g ($p < 0.05$) (Fig. 1A).

In line with body weight, High fat diet -fed mice had an increased abdominal circumference (Fig. 1B). High fat diet -fed mice showed increased serum resistin, leptin, insulin levels and decreased serum adiponectin level compared to control diet-fed mice (Fig. 1C–F). Furthermore, as shown in Fig. 1G–J, total cholesterol levels at 16 weeks were no different in High fat diet -fed mice compared with CD-fed mice, but low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride were markedly higher in HFD-fed mice. Overall these data demonstrate that a High fat diet leads to factors indicative of metabolic alteration.

Rats fed with a high-carbohydrate high-fat diet (HCHF) spontaneously developed osteoarthritis and macrophage infiltration in the joint synovium compared to control diet fed mice. In addition, the infiltrated macrophages showed a pro-inflammatory M1 phenotype in synovial tissue of knee joints 3. These data suggest that novel therapies that target macrophage polarization may mitigate the development of obesity-induced osteoarthritis.

Resolvins, which are produced upon interactions with neutrophils, platelets and macrophages in inflamed tissues, have been shown to be potent mediators of switching macrophages from a pro-inflammatory state (M1) to anti-inflammatory (M2) when tested in inflammatory diseases *in vivo* or *in vitro*5, 6, and 7. Considering the important role of macrophage polarisation in obesity-induced osteoarthritis, we tested the hypothesis that RvD1 may mitigate obesity-induced osteoarthritis progression by changing pro-inflammatory behavior of the macrophages.

Figure1



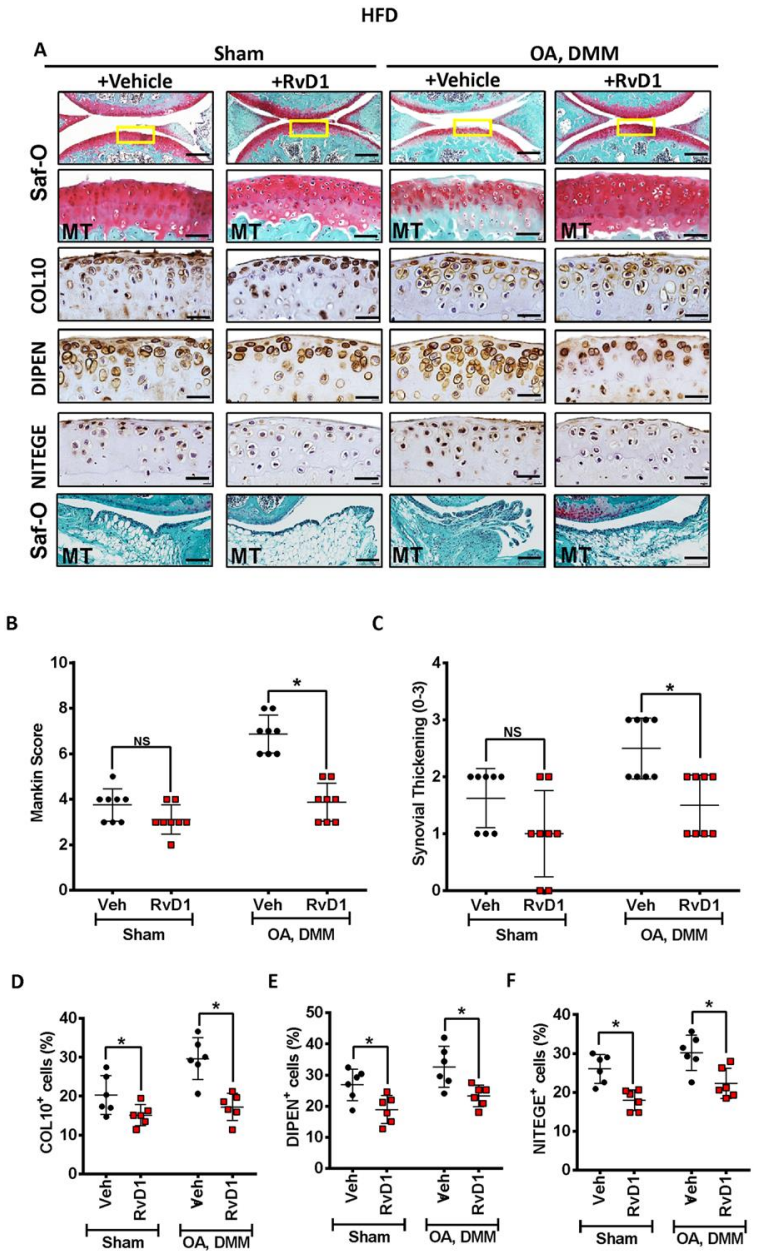
High-fat diet promotes weight gain and altered metabolic parameters. (**A**) Body weight of CD or HFD mice were monitored over 16 weeks. (**B**) Ventral view of the mice showing the changes in the total abdominal length caused by the two diets after 16 weeks. (**C**–**J**) Effect of HFD on metabolic parameters. Measurement of serum resistin (**C**), leptin (**D**), insulin (**E**), adiponectin (**F**), total cholesterol (**G**), LDL (**H**), HDL (**I**) and triglyceride (**J**). (**K**) Immunostained section of the infrapatellar fat pad (IFP) of mice fed a control or HFD diet.
Bar = 100 μm. Graphs represent mean ± SD (n = 7). **p* < 0.05. CD, control diet-fed mice; HFD, high fat diet-fed mice.

RESULTS:

In view of RvD1's protective actions in resolution of synovial inflammation, next we tested its effect on osteoarthritis cartilage severity under obese conditions. In response to RvD1 treatment, High-fat diet - osteoarthritis mice showed less evidence of cartilage degradation compared to untreated mice, such as proteoglycan loss and cartilage surface irregularities compared with the untreated osteoarthritis animals (Fig. 2a). The Mankin scores reiterated these observations with a lower score in both RvD1 treated High-fat diet - osteoarthritis mice (Fig. 2b). Histologic analysis of RvD1 treated High-fat diet - osteoarthritis mouse model showed significantly decreased synovial thickening compared with untreated group (Fig. 2ac). Immunohistochemical staining of cartilage specimens showed lower expression of COL10, DIPEN and NITEGE in both RvD1-treated animals

fed High-fat diet (Fig. 2a, d-f).

Figure2



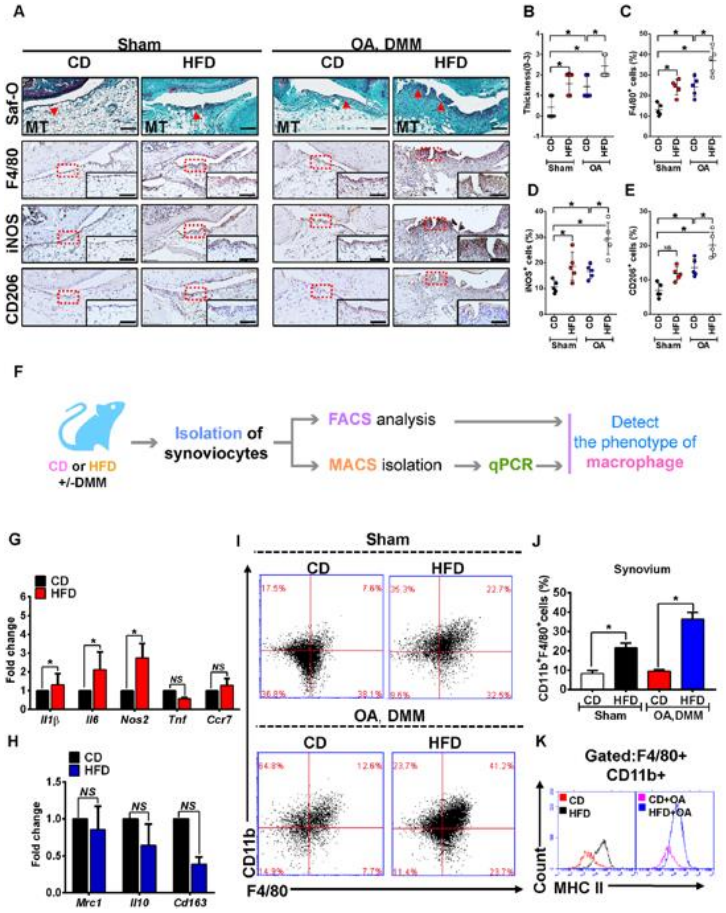
lower panels. Scale bars, 100 µm. Bottom panel: Similar sections were stained with COL10, DIPEN, and NITEGE to determine the effect of RvD1 on cartilage. Scale bars, 100 µm. Representative safranin-O image show treatment effects of RvD1 in the synovium of HFD-fed mice with surgically-OA. Scale bars, 10 µm. (**B**) Severity of articular

Resolvin D1 treatment reduces the severity of HFD in surgically induced OA. (**A**) Top panel: Representative Safranin O and fast green stained sagittal sections of sham or experimental OA knee regions in mice fed a HFD diet with or without RvD1 treatment. Scale bars, 100 µm. The inset boxes in upper re shown at higher resolution in

No effect on body weight were observed in RvD1 treated High-fat diet fed mice. Except for serum leptin, resistin and adiponectin levels were improved in High-fat diet -fed mice treated with RvD1 (Supplementary Fig. 3b-d). Intra-articular injection of RvD1 also led to an improvement in serum insulin level, although this was not significantly different compared to High-fat diet -fed mice (Supplementary Fig. 3e). Furthermore, serum triglyceride and total cholesterol levels were similar between RvD1 treated and untreated High-fat diet -fed mice (Supplementary Fig. 3f-g).

cartilage degradation was graded using Mankin scoring system. Graphs represent mean ± SD (n = 8). *$p < 0.05$. (**C**) Synovial inflammation was assessed using synovitis scoring based on degree of cell thickness in the synovial lining layer and cell density of the synovial stroma. Graphs represent mean ± SD (n = 8). *$p < 0.05$. (**D**–**F**)The percentage of COL10 (**D**), DIPEN (**E**), and NITEGE (**F**) -positive cells per knee section were counted. Graphs represent mean ± SD (n = 6). *$p < 0.05$. RvD1: resolvin D1; Veh: placebo (1% ethanol in saline). Saf-O: Safranin O and fast green staining; MT: medial tibia.

Figure 3



Inflamed synovium expresses a dominant M1 signature during the challenge of High-fat diet. (**A**)Top panel: Representative Safranin O and fast green stained sagittal sections of sham or experimental OA knee regions in mice fed a CD or HFD diet. Scale bars, 100 µm. Bottom panel: Similar sections were stained with F4/80, iNOS, and CD206 to determine the phenotype of synovial macrophage in activated synovium from CD- or HFD-fed mice. Scale bars, 100 µm. Insets are enlarged images of stained sections. (**B**) Synovial inflammation was assessed using synovitis scoring based on degree of cell thickness in the synovial lining layer and cell density of the synovial stroma.

Graphs represent mean ± SD (n = 7). *$p < 0.05$. (**C**–**E**)The percentage of F4/80 (**C**), iNOS (**D**), and CD206 (**E**) - positive cells per knee section were counted. Graphs represent mean ± SD (n = 5). *$p < 0.05$. (**F**) Schematic diagram showing the experimental procedure, from the isolation of synoviocytes from animals to analyse the phenotype of synovial macrophage in the synovium from multiple biopsies of CD- and HFD-fed mice. qPCR analysis of pro-inflammatory M1-like (**G**) or anti-inflammatory M2-like (H) genes in MACS isolated F4/80+ synovial macrophage from CD- or HFD-fed mice. (**I**–**J**) FACS analysis of synovial macrophage from CD- or HFD-fed mice. (**K**)Same biopsies were further stained with MHC II to analyse the population of M1 activated macrophage. Saf-O: Safranin O and fast green staining; MT: medial tibia.

DISCUSSION:

In this study, using relevant murine models of obesity and osteoarthritis, we show that (1) High-fat diet increases the rate of progression of osteoarthritis, (2) the metabolic effects of High-fat diet are driven in part by synovial infiltration of pro-inflammatory macrophages, (3) that depletion of macrophages using clodronate-liposomes may partially rescue the obesity-associated osteoarthritis, and (4) resolution of inflammation by RvD1 intervention can attenuate the effects of High-fat diet on osteoarthritis.

Moreover, a recent study showed that both local proliferation and migration of macrophages is responsible for adipose tissue macrophage infiltration during obesity development. Therefore, both local proliferation and migration of macrophages might contribute to synovial macrophage accumulation during development of obesity-associated .osteoarthritis

Interestingly, in our study, we observed that selective depletion of synovial macrophages induced cartilage damage, as indicated by increased expression of COL10, DIPEN and NITEGE in cartilage of CD mice, such observation was not detected in animals following liposome-only treatment. However, under the challenge of High-fat diet or High-fat diet - osteoarthritis, depletion of macrophages successfully decreased the severity of osteoarthritis. These results indicate that in the normal joint microenvironment homeostatic macrophages may have important phagocytic and reparative functions and depletion of these macrophages can have off-target effects; however in conditions such as those in obesity and osteoarthritis, prolonged macrophage responses are thought to exacerbate the injury by preventing the .resolution of inflammation

In conclusion, obesity induces an accumulation of pro-inflammatory macrophages in the synovium and fat pad tissues. The resulting resident macrophage population establishes a pro-inflammatory environment that enhances osteoarthritis development and pathology. Furthermore, RvD1 treatment reduces pro-inflammatory gene expression, increases anti-inflammatory gene expression, and ultimately induces M2 macrophage polarization to mitigate the effects of obesity-associated osteoarthritis development.

CONCLUSION:

In conclusion, obesity induces an accumulation of pro-inflammatory macrophages in the synovium and fat pad tissues. The resulting resident macrophage population establishes a pro-inflammatory environment that enhances osteoarthritis development and pathology. Furthermore, RvD1 treatment reduces pro-inflammatory gene expression, increases anti-inflammatory gene expression, and ultimately induces M2 macrophage polarization to mitigate the effects of obesity-associated osteoarthritis development.

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