Oral Hydrolyzed Type 2 Collagen Protects Against the OA of Obesity and Mitigates Obese Gut Microbiome Dysbiosis

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Introduction

- While there are no disease modifying therapies to treat OA, numerous nutraceuticals, including glucosamine, chondroitin sulfate, and various undenatured collagen formulations, are purported to have joint protective properties. The mechanism of action of these agents is unknown.
- It has recently been discovered that dysbiosis of the gut microbiome leads to various systemic disease states, with increases in pro-inflammatory microbial species considered pathogenic, particularly in obesity.
- Here we evaluate the ability of orally consumed hydrolyzed type 2 collagen (hCol2) to be protective in the OA of obesity, and examine their potential action as prebiotics that could be associated with reduced inflammation and effects in degenerating joints.

Methods

- C57BL/6 mice were fed chow or HFD for 12 weeks, at which point they were provided a daily oral hCol2 supplement. After 2 weeks on supplement, early development of OA was induced by DMM surgery.
- Fecal samples were collected before initiation of supplementation and at 3 weeks post-DMM. 16S rRNA sequencing was performed on fecal extracts to analyze the gut microbiome.
- Three weeks post-DMM joint tissues were harvested and analyzed via standard tissue-based methods including histomorphometric analysis of cartilage structure.

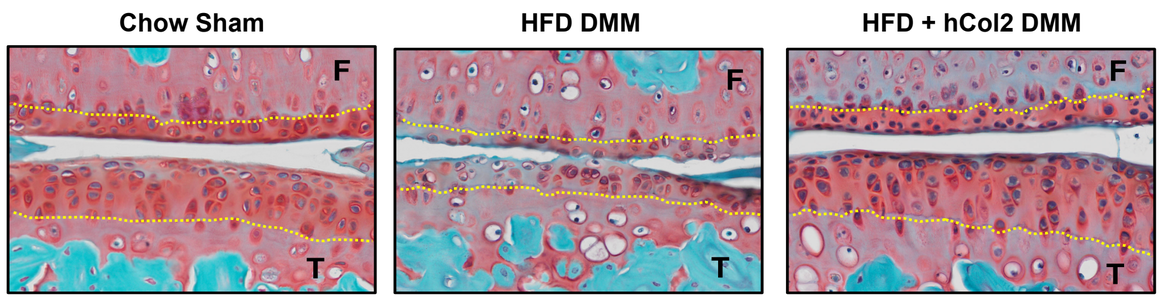

Figure 1

- **hCol2 protects against trauma-induced OA in Obese mice.** Mice fed chow or 3 months of the high fat diet (HFD) were supplemented daily with hCol2 (or vehicle) for 2 weeks prior to administration of DMM injury (or sham surgery). Knee joints were harvested 3 weeks later. Safranin O-stained sagittal sections from chow-fed sham control mice, HFD-fed obese mice that were DMM injured, and HFD-fed obese hCol2-supplemented mice that were DMM injured are depicted (dotted lines denote tidemarks, F=femur, T=tibia).

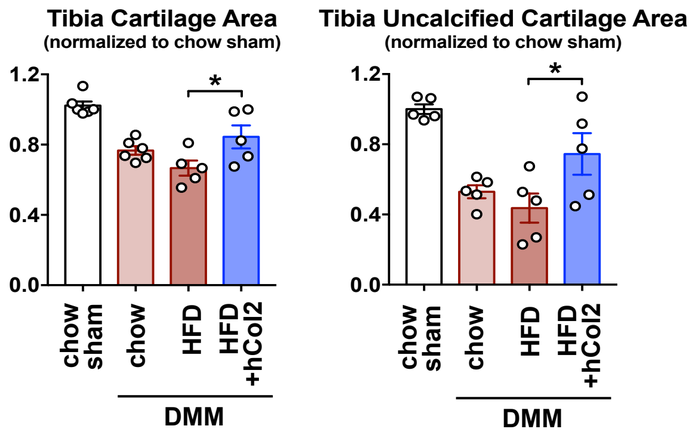

Figure 2

- **hCol2 preserves articular cartilage following trauma-induced OA in Obese mice.** Histology samples like those depicted in Results 1 wew subjected to histomorphometric analysis. Histomorphometric evaluation of tibial cartilage area and uncalcified tibial cartilage area permitted statistical analysis (*p<0.05, one way ANOVA with a Tukey's Multiple Comparison test, N=5).

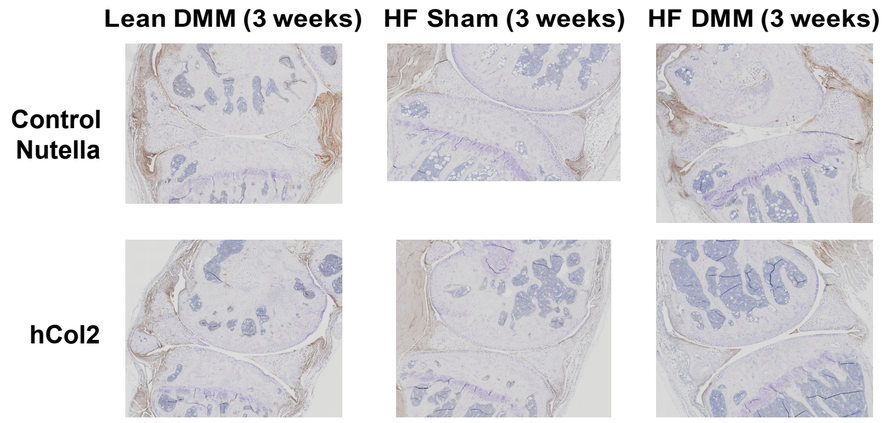

Figure 3

- **hCol2 protects against trauma-induced knee inflammation in Obese mice.** hCol2 supplementation is associated with reduced synovial TNF expression in chow-fed (Lean) and obese mice (HF) 3 weeks following traumatic injury. Brown stain is synovial membranes denotes areas with TNF-positivity.

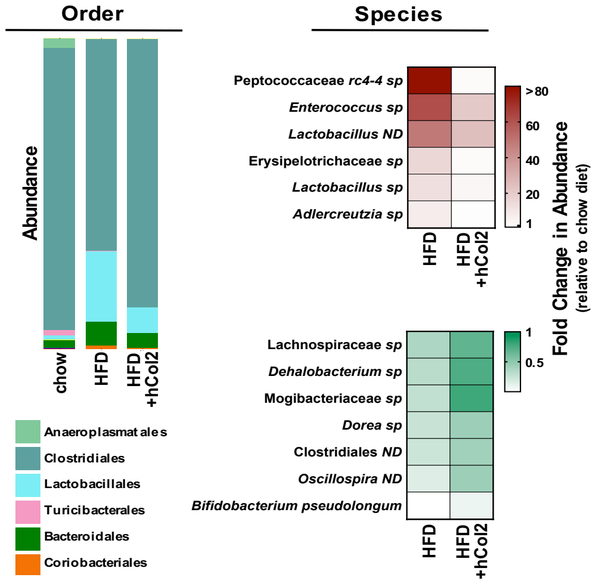

Figure 4

- **hCol2 protects corrects obesity-related dysbiosis of the gut microbiome.** Mice fed chow or 3 months of the high fat diet (HFD) were supplemented daily with hCol2 (or vehicle) for 2 weeks prior to administration of DMM injury (or sham surgery). rDNA extracted from fecal samples collected at euthanasia revealed the average relative abundance of microbes from key taxonomic orders, and species level analysis identified a subset of bacterial populations that were altered in HFD-induced obesity and were corrected by supplementation with hCol2.

Discussion

- Here we report that dietary supplementation with a novel hCol2 formulation is joint protective in the context of obesity-accelerated PTOA. A parallel a set of effects occur in the gut microbiome, where hCol2 substantially converts the obese microbial profile to that seen in chow-fed mice, with significant suppression of key pro-inflammatory populations that we have previously implicated as pathogenic in the OA of obesity, including Peptococcaceae *rc4-4 sp*. Complimenting this is hCol2-induced expansion of various Actinobacteria, key among them *Bifidobacterium Pseudolongum*, that have been extensively reported in the literature to reduce various obesity-related systemic issues, including inflammation and type 2 diabetes. Given the debate about how nutraceuticals impact the joint and reduce symptoms in OA, we propose the novel concept that hCol2 and agents like it influence joint degeneration indirectly through an alteration in the gut microbiome, begging deeper study of cause and effect in this context.