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Editorial

Dietary fibers in osteoarthritis: What are the evidences?



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1. Introduction

Weight loss, obtained by the use of hypocaloric diet or by bariatric surgery, and physical activity are the 2 cornerstones of the non-pharmacological treatment of obese patients with knee OA [1]. Weight loss acts through a decrease of joint overloading and an improvement of metabolic-related inflammation (i.e. meta-inflammation) [2,3].

Beyond weight loss, new data have recently highlighted the beneficial effects of dietary fiber consumption on metabolism and low-grade inflammation in metabolic disorders through gut microbiota modification [4–7]. Indeed, short- and long-term dietary fibers intake lowers cholesterol levels, restore glucose tolerance and decreases the meta-inflammation. Since metabolic disturbances are closely linked to the development of OA [8], pre-clinical and observational recent data have investigated whether dietary fibers consumption could be a promising treatment modality in OA, especially in the setting of obesity.

2. Dietary fibers: definition and mechanisms of action

Dietary fibers are carbohydrate polymers mainly derived from plants. These edible carbohydrates show very heterogeneous origins and chemical compositions, but they are all resistant to digestion and to absorption in the human small intestine [9–11]. They subsequently pass relatively intact into the colon where they are fermented by the resident microbiota, leading to the production of short chain fatty acids (SCFAs) [12].

Butyrate, propionate and acetate, the main SCFAs produced by fermentation, are found in the large intestine but may also cross the intestinal barrier and pass into the bloodstream where they can act as signal molecules [11]. SCFAs may also enhance gut homeostasis and preserve the local integrity of the gut barrier by promoting the secretion of mucus and the repair of mucosal ulcerations [13,14].

Health effects of dietary fibers are mediated by SCFAs, which have shown immunomodulatory and anti-inflammatory

Table 1

Dietary fiber in principal food categories [19].

Food categories	Total dietary fiber (g/100 g)
Vegetables (excluding potatoes)	
Raw, steamed and baked vegetables	median 2.2
Soups	median 0.9
Fruit	
Fresh fruit	median 2.3
Processed fruit	median 1.3
Dried fruit	median 5.8
Nuts and seeds	median 4.2
Legumes	median 4.5
Potatoes and other starchy tubers	median 2.25
Leavened breads	
White flour	3–3.4
Whole flour	5.6–7.2
Oat porridge	median 1.74
Rice	
White	0.8– <1.1
Whole	median 3.4

properties, namely by activating the G Protein coupled Receptor 43 in neutrophils which is implicated in the inflammatory mediators and immune cell recruitment and by inhibiting histone deacetylases activity which is largely involved in the expression of inflammatory genes and the recruitment of monocytes. Furthermore, SCFAs were found to increase regulatory T cells response and immunoglobulin A secretion and to promote interleukin 18 production, which is implicated in epithelial integrity [14,15].

Dietary fibers have been shown to be protective against metabolic syndrome, cardiovascular disease and obesity [16]. Despite these effects are supported by robust data, dietary fibers intake is still below the fiber dietary guidelines [17]. The French Nutri-Net Santé study, a large population-based cohort study, estimated fibers intake in adults at 19 g/day [17]. In France, 2017 update of the ANSES (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail) guidelines established the optimal amount of daily fiber intake at 30 g [18]. This target is easily attainable by varying food sources (Table 1) and should be included in a global strategy to promote healthy dietary patterns [20].

3. Dietary fibers anti-inflammatory effects

In clinical studies, dietary fibers anti-inflammatory effects were reported in overweight and obese patients [21,22]. Consistent evidence showed that diet-induced obesity is associated with a chronic low-grade inflammation characterized by high serum

and tissue expression of pro-inflammatory factors such as tumor necrosis factor (TNF), interleukin 1 β (IL-1 β) and interleukin 6 [23]. Notably, lipopolysaccharide (LPS) which is released by gram-negative gut microbiota in the terminal ileum and colon has been identified to be the triggering factor of cytokine release as it was shown to activate the innate immune system cells [24]. Therefore, circulating LPS has been found in the bloodstream, resulting from intestinal absorption, in obese subjects [25]. This was mainly caused by high gut permeability, alteration of liver clearance and imbalance in gut microbiota [25,26].

Importantly, fiber supplementation in overweight and obese patients was associated with a reduction in LPS concentrations [21,22]. Dietary fiber benefits are likely driven by a shift of gut microbiota. This was demonstrated in experimental models where fiber supplementation was associated with a restoration of gut microbiota diversity [4] and a reduction of intestinal permeability [5]. Similar findings were reported in patients with type 2 diabetes [6]. In this study, fiber intake led to a decrease in LPS levels and a better glycemic control when compared with control diet. A possible protective role of dietary fibers on cardio vascular disease was also suggested in an experimental murine model [7]. Particularly, high fiber and acetate consumption were significantly associated with a reduced blood pressure, left ventricular hypertrophy and cardiac fibrosis. These beneficial effects have been attributed to a change in gut microbiota subsequent to fiber quantity intake.

Gut microbiota and its derived LPS are thought to play a determinant role in the pathophysiology of metabolic OA [26]. Therefore, an experimental study [27] has been recently conducted in a diet-induced obese rat model, showing a significant association between OA and microbial (*Lactobacillus* spp. and *Methanobrevibacter* spp.) abundance in the gut. Furthermore, serum LPS levels were significantly higher in obese rats than in controls suggesting a connection between gut microbiota, low-grade inflammation and cartilage loss. Based on these findings, dietary fibers possible protective effect on OA was particularly interesting to explore.

4. Dietary fibers in osteoarthritis: data from cohort studies

Dietary fibers intake was evaluated in knee OA in two large prospective cohorts. In both cohorts, fiber consumption was assessed at baseline by the Block Brief 2000 Food Frequency Questionnaire (FFQ), which estimates adequately dietary fiber intake (total fiber intake and fiber intake from the main food groups) [28].

The first study [29] was based on the findings of the Osteoarthritis Initiative (OAI), a prospective study conducted over an 8 years period including participants with or at risk of knee OA. In this multicenter cohort, 4,470 participants were assigned to 4 trajectory patterns according to knee pain status (no pain, mild pain, moderate pain and severe pain) as evaluated by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Total dietary fiber intake was found to be inversely associated with the risk of belonging to the moderate or severe pain groups ($P < 0.01$ for both groups). Similar findings were reported when the analysis was restricted to subjects with prevalent radiographic OA. Furthermore, being in the highest quartile for total fiber intake protected from belonging to the moderate and severe pain patterns when compared with the lowest quartile [Odds Ratio (OR) (95% confidence interval (CI)): 0.75 (0.61–0.93) and OR (95% CI): 0.56 (0.41–0.78) respectively]. However, these results were reported with no adjustment for body mass index (BMI) with subjects in the higher quartile having lower BMI than subjects in the lower quartile.

To ascertain these findings a second study [30] was conducted including participants from the OAI cohort ($n = 4051$) and from the Framingham Offspring (FO) cohort ($n = 971$). The latter cohort was designed to assess the inheritance of osteoarthritis and included the

adult children of the Framingham Study subjects. Incident symptomatic and incident radiographic osteoarthritis were followed during 4 years in the OAI cohort and determined after 9 years in the FO cohort. Overall, a significant dose-dependent inverse association was shown between belonging to the highest quartile for total fiber intake and the risk of incident symptomatic knee osteoarthritis when compared with the lowest quartile. While dietary fibers were found to be protective against symptomatic knee OA in the OAI cohort [OR_{Q4 vs. Q1} (95% CI): 0.70 (0.52;0.94)] and in the FO cohort [OR_{Q4 vs. Q1} (95% CI) = 0.39 (0.17;0.88)], they failed to show similar effect on incident radiographic OA.

As these are the only 2 observational cohort studies that evaluated fiber intake in symptomatic OA, such results need to be reproduced in other populations with other dietary patterns. In addition, determining a cut-off value of the amount of fiber required to show protection against OA is another key question that needs to be addressed. Last but not least, controlled interventional studies are needed to confirm fibers protective role in OA.

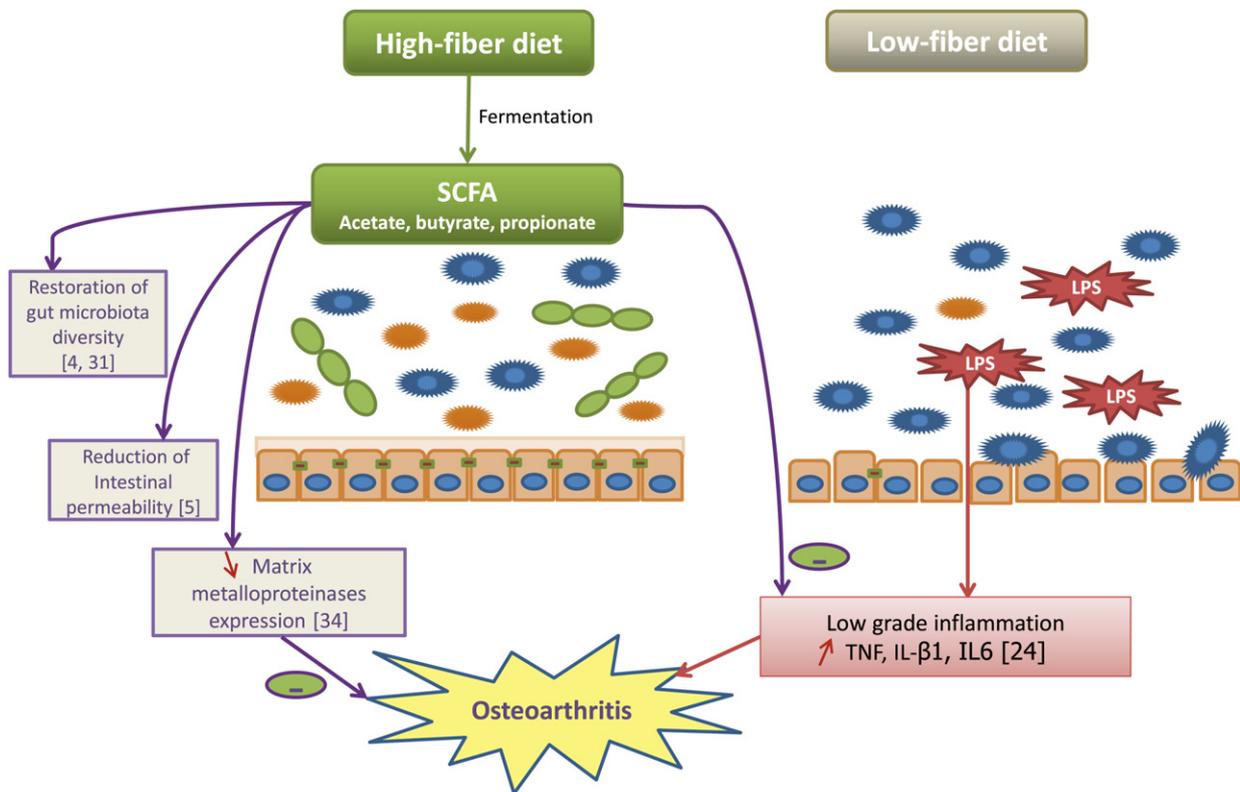
5. Dietary fibers in osteoarthritis: data from experimental studies

In order to investigate the potential protective role of dietary fibers in osteoarthritis, a recent experimental study was conducted [31]. Oligofructose, a dietary fiber with prebiotic characteristics [31], was assessed in mice with trauma-induced knee osteoarthritis secondary to destabilization of medial meniscus. Interestingly, in this model where mice had a diet-induced obesity, oligofructose supplementation inhibited the progression of obesity-induced OA in knee joints. In fact, oligofructose intake in obese mice favorably impacted on the synovial pro-inflammatory changes: both macrophage migration and Monocyte Chemoattractant Protein-1 levels, a chemokine implicated in the recruitment of inflammatory cells to joints [32], were significantly lower than in obese control mice. Moreover, systemic cytokine levels, in particular TNF, Macrophage Colony-Stimulating Factor (M-CSF), Macrophage Inflammatory Protein-1 β (MIP-1 β) and KC (the murine homolog of interleukin 8), were significantly reduced comparatively with obese controls. This resulted in a prevention of OA structural progression in histological analyses of the knees.

Since oligofructose did not affect body mass or body composition, these effects were likely driven by a shift in gut microbiome induced by oligofructose ingestion (i.e. *Bacteroidetes* and *Actinobacteria* increase, especially *Bifidobacterium pseudolongum* which belongs to *Actinobacteria*) [31,33]. Notably, oligofructose preventive effect was demonstrated in obese but not in lean mice. This emphasized that the main role of dietary fibers was to protect against obesity-induced inflammation at intestinal and systemic levels.

The beneficial effects of dietary fibers were recently suggested by another experimental investigation [34]. Sodium butyrate, a fermentation-derived SCFA, was shown to inhibit matrix metalloproteinases (MMP) expression and type II collagen degradation in human cultured chondrocytes. In this study, sodium butyrate reversed the induced IL-1 β up-regulation of MMP-1 MMP3 and MMP13, which are implicated in cartilage matrix degradation, and partially restored the expression of tissue inhibitors of metalloproteinase (TIMPs) TIMP-1 and TIMP-2.

In summary, there are emerging and converging data supporting a possible protective role of dietary fibers in OA. Dietary fibers intake is associated with a reduced risk of belonging to moderate and severe pain trajectories and to incident symptomatic knee osteoarthritis in observational studies. New data from an experimental study revealed that fiber intake prevented cartilage loss and inhibited the progression of obesity-induced osteoarthritis (Fig. 1). Since modulating gut microbiota through dietary fibers may



Abbreviations: SCFA:short chain fatty acids, LPS:lipopolysaccharides, TNF:tumor necrosis factor, IL-1β:interleukin 1β, IL6: interleukin6

Fig. 1. Dietary fibers may play a protective role in osteoarthritis by inducing a change in gut microbiota: Increase in *Bacteroidetes* and *Actinobacteria* levels and correction of *Bacteroidetes/Firmicutes* ratio.

Box 1: Research agenda.

Human prospective intervention studies to evaluate the short- and long-term dietary fiber intake on OA occurrence and (symptomatic and structural) progression.

To determine if there is a cut-off of dietary fiber intake to prevent OA or to limit OA progression.

To determine whether consumption of fibers coming from different food categories have the same or different effect on OA.

To determine the systemic anti-inflammatory role of dietary fiber intake in OA patients and its role on gut dysbiosis.

be a new treatment modality in OA, human intervention studies assessing the effects of fiber-enriched diet on OA symptoms and structural damage are needed to explore this promising interventional strategy (Box 1).

It remains true that fibers intake offers health benefits, especially by modifying metabolic profile and is recommended at a daily basis. Finally, there should be a greater awareness of the importance of promoting overall dietary quality as much as healthy lifestyle in combination with physical activity for a better metabolic health outcome, beyond the field of OA.

Disclosure of interest

The authors declare that they have no competing interest.

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