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Prebiotics, Probiotics and Synbiotic for Bone Health

Bolaji Lilian Ilesanmi-Oyelere and Marlena Cathorina Kruger

Abstract

Prebiotics, probiotics and synbiotics has been shown to enhance calcium absorption, gut and bone health. Probiotics are also known to ferment prebiotics to produce the fermentative substrates such as short chain fatty acids (SCFAs), mainly acetate, butyrate and propionate with the help of beneficial micro-organisms in the gut. The expression of these SCFAs has been associated with the inhibition of osteoclast differentiation and bone resorption both *in vitro* and *in vivo*. In this review, we discuss the benefits of SCFAs and ways in which prebiotics and probiotics affect bone health by the reduction of inflammation in the gut and the bone.

Keywords: prebiotic, probiotic, synbiotic, gut microbiota, bone metabolism

1. Introduction

Prebiotics and probiotics have been proven to confer multiple health benefits to animals and humans alike when consumed either singly or in combination. Consumption of prebiotics and probiotics modulates the gut microbiota and the colonization of the gastrointestinal tract which is now known as the second gene pool of the human body. Evidence shows the health benefits of synbiotic intake in many aspects of human health including metabolic functions, gastrointestinal diseases, and bone health. Some of these documented evidence-based benefits include their immunomodulatory effect [1], improvement of diarrhea, lactose metabolism, digestive health and metabolic syndrome [2], antidiabetic and hypocholesterolemic [3], anticarcinogenic [4] and hypotensive attributes/features [5]. In a short review that we conducted, the importance of prebiotics, probiotics and synbiotics was expressed to be important across human lifespan from childhood to adulthood and the elderly [6].

2. The significance of prebiotics and probiotics

Probiotics in the presence of prebiotics undergo different biochemical pathways/ messenger systems to inhibit pathogens and boost the immunity of the host, these includes

- a. Presence of probiotics in the gut leads to competition for nutrients with pathogens which can then lead to starvation and reduction of these unwanted bacteria.

- b. Probiotics tend to compete for space via the adhesion effect to the mucosal lining by directly decreasing the adhesion of the pathogens and their toxins; this has been confirmed by in vitro studies demonstrating that probiotics possess lectin-like adhesion properties capable of binding carbohydrates from the receptors of glycoconjugate of epithelial cell surface [7] which blocks pathogen binding to the epithelial cell surface. Some probiotic strains of the *Lactobacillus* genus have shown some features and ability to bind to the enterocyte surface in vitro [8].
- c. Probiotics are responsible for the synthesis of bacteriocins such as lantibiotics (class I) and class II bacteriocins by the probiotics, and this mainly by lactic acid bacteria (LAB) can help prevent the growth, colonization, and establishment of pathogens in the gut environments. These bacteriocins present a better activity on the pathogens than antibiotics due to their narrow-spectrum activity on foreign unwanted bacteria. Bacteriocins from Gram-positive bacteria are composed of membrane peptides capable of targeting and causing apoptosis of the cell membrane; however, most antibiotics inhibit enzymes and biosynthesis pathway in cells such as DNA, RNA, protein and cell-wall synthesis [9].

Probiotic microorganisms may also be able to produce enzymes, such as lipase, esterase, and co-enzymes A, Q, NAD, and NADP [10]. Likewise, some of the by-products of probiotics' metabolism may exhibit antibiotic properties and these include bacitracin, lactacin and acidophilin [11].

- d. The bio-metabolization of prebiotics into lactate and short chain fatty acids (SCFAs) such as acetate, mainly produced by *Bifidobacteria*, *Lactobacilli* and *Akkermansia muciniphilia* through fermentation by probiotics has significant beneficial role to the health. Acetate is the most abundant in the human colon. Butyrate is produced by *Faecalibacterium prausnitzii*, *Eubacterium rectale* and *Roseburia* spp. and mainly by *Lachnospiraceae* and *Ruminococcaceae* and propionate which is produced by *Propionibacteria*, *Firmicutes*, *Lachnospiraceae* and *Bacteroidetes* [12]. The release of these SCFAs by the prebiotic fermentation reduces the intestinal pH level and also reduces the production of putrefactive compounds such as ammonia, phenol, as well as indole and branched-chain fatty acids (BCFAs) [13]. SCFA synthesis are mainly by anaerobic saccharolytic fermentation of carbohydrates that have not been digested or absorbed in the small intestine. Acetate is metabolized in the muscles, kidney, brain and heart, butyrate acts mainly in the colon while propionate and butyrate are cleared by the liver. SCFAs may also regulate fat and glucose metabolism as reported in rat adipocytes [14]. In chronic inflammatory diseases such as IBD, it has been shown that fecal butyrate levels are significantly reduced while high levels of lactic acid are observed [15].

The production of butyrate is mainly from complex carbohydrates through the pyruvate and acetyl-coenzyme A (CoA) pathway; however, it can also be produced from amino acids via the glutarate, 4-aminobutyrate and lysine pathways in the gut [13]. Butyrate acts epigenetically as histone deacetylase (HDAC) inhibitors and the research into HDAC may be capable of providing cancer chemoprevention and therapies [16]. There are different functions of butyrate in the colon; it is the main source of energy for colonocytes. Furthermore, butyrate has been documented to inhibit proinflammatory cytokines such as tumor necrosis α (TNF- α) in monocytes [17], interferon- α (IFN- α) and IL-2 in rat mesenteric lymph nodes [18], chemokine CXCL-8 (IL-8) in Caco-2 cells [19].

- e. Intake of prebiotics and probiotics has been linked to the development of immunomodulatory capacity by decreasing inflammation, antibody response and phagocytosis. Probiotics may be involved in the prevention of cytokine-induced epithelial damage. *Lactobacillus rhamnosus* GG (LGG) promoted the survival and enrichment of epithelial cells by the activation of antiapoptotic and inhibition of proapoptotic pathways [20].
- f. Probiotic and prebiotic intake results in the improvement of the epithelial barrier integrity by the secretion of mucin [21] and defensins [22] including antimicrobial proteins (AMPs). Probiotics enhance the mucosal integrity also by inducing cytoprotective substance production by enterocytes such as heat shock proteins [23]. In an in vitro study, *Bifidobacterium infantis* enhanced the intestinal mucosal barrier (T84 human epithelial cells) [24]. Similarly, *Lactobacillus plantarum* is responsible for acting on the tight junctions via increasing the expression of occludins and *zonula occludens* proteins [25].
- g. Prebiotics and probiotics are capable of the stimulation and production of antioxidant-related enzymes, systemic hormones, and neurochemicals such as serotonin, gamma-aminobutyric acid (GABA) and cortisol, as well as production of bile salt hydrolase. Consumption of probiotics and prebiotics has also been reported to be able to reduce cholesterol levels. Prebiotic fibers increased levels of satiety hormones (glucagon-like peptide-1, proglucagon and peptide YY mRNA) and decreased levels of ghrelin O-acyltransferase mRNA in rats [26]. Furthermore, prebiotic fermentation in the gut likewise improved satiogenic and incretin gut peptide production, thereby increasing the plasma glucagon-like peptide 1 and peptide YY concentrations in humans [27].
- h. Prebiotics and probiotics are responsible for the synthesis of antigens via production of anti-inflammatory cytokine such as IL-10 which inhibits the T-helper cells (1, 2, 7 and 17) and transforming growth factor- β responsible for the production of immunoglobulin A [28].

The concept and use of prebiotics has been argued to be more important when compared to probiotics due to the vulnerability and susceptibility of probiotics to environmental stresses, manufacturing process (such as heat) and endangered conditions during storage [29].

3. Prebiotics and human health

Glenn Gibson and Marcel Roberfroid launched the prebiotic concept in 1995 as 'a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health' [30]. This definition has however been modified several times, but the initial main features have been retained. Prebiotics tend to stimulate the growth of the gut bacteria endogenously. The pH of the gut environment plays a major role in determining bacterial interspecies competition outcome.

Food sources of prebiotics consist of edible plants such as fruits, vegetables, cereal component which provides the body with carbohydrate. Specific potential sources are artichokes, tomatoes, bananas, asparagus, garlic, berries, kiwi fruit, onions, chicory, green leafy vegetables, legumes as well as linseed, barley, oats, and wheat.

Even though various molecules can be prebiotics, the great majority are dietary fibers which are oligosaccharides such as inulin (mainly from chicory), GOS (obtained from lactose using β -galactosidase), Fructooligosaccharides (FOS) (from chicory by partial enzymatic hydrolysis), soybean oligosaccharides (SOS), and xylooligosaccharides (XOS). Inulin, GOS and FOS have been widely studied. The list of prebiotics also includes compounds such as resistant starches, arabinoxylan, pectin, whole grains as well as non-carbohydrate complex such as polyphenols [13]. Absence of dietary fiber in the colon causes anaerobic bacteria to obtain their energy from protein fermentation, and this metabolism leads to the production of potentially toxic and carcinogenic compounds such as ammoniac and phenolic compounds [31]. In contrast, carbohydrate fermentation (for example dietary fiber) will produce non-toxic SCFAs which can serve as fuel for the epithelial cells. The production of volatile fatty acids, including, SCFAs and BCFAs, play a role in energy homeostasis maintenance as well as in the regulation of functionality in peripheral tissues [32]. Prebiotics are also mainly active in the large intestine/colon.

Different strains of bacterial genus or species would prefer different substrates for fermentation in the colon. Generally, the strains of *Bifidobacterium* and *Lactobacillus* genera have been reported to prefer fructans as substrate, as opposed to glucose while other bacteria such as *Clostridia* and *Bacteroides* have been reported to thrive on fructans [33, 34].

The use of prebiotics has been shown to be efficient and effective against a few human health disorders such as Type 2 diabetes mellitus and inflammatory bowel diseases which has been termed the “Western” chronic diseases and colorectal cancer. This is accomplished by the modulation of the intestinal gut microbiota which confer a protective, metabolic, and trophic benefits to the host [13].

4. Probiotics and human health

The history of probiotics spans back to the 20th century when Mechnikoff (1907) revealed the virtues associated with the consumption of fermented dairy products, he hypothesized that the aging process resulted from the putrefaction of the large intestine. Almost simultaneously, another scientist Tissier indicated that the main component of the gut flora of breast-fed infants were bifidobacterial [35]. Even earlier, biblical recommendations have pointed out yoghurt as important/significant for the treatment of some ailments [36]. Furthermore, the indication has been that probiotics is more beneficial when consumed with food as opposed to supplement due to the available nutrient and energy sources. Probiotics are mainly active in the small and large intestine.

Organizations such as FAO, WHO and the European Food Safety Authority have indicated probiotic strains must meet both safety and effectiveness criteria for their selection process. The regulations require that safety and absence of risks is paramount for human and animal health. The human probiotic products usually belong to the *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus* and *Enterococcus* genus. In addition, there are some Gram-positive bacteria of genus *Bacillus* and some yeast of *Saccharomyces* genus which are also used as probiotics.

Probiotic use has been postulated to be potent against human disorders such as inflammatory enteral diseases such as Crohn's disease, colitis, and non-specific ileitis. Intake of probiotics has also been assessed by various studies as capable of treating lactose intolerance, irritable bowel syndrome [37] and in the prevention of peptic ulcers and colorectal cancer [38]. Beneficial effects of probiotics have been observed in the process of digestion, food allergies treatment [39], dental caries [40], and candidoses [41]. The beneficial effects of probiotics observed by the host

through augmentation of the epithelial wall, intestinal mucosal and competitive elimination of pathogens has been reported to aid inflammatory bowel disease (determined by cytokine-induced harm to the epithelial cell walls). Probiotics is capable of repressing gut inflammation via the downregulation of Toll-like Receptors' expression, the prevention of TNF- α entrance into the mononuclear cell in blood and the suppression of enterocyte's NF- κ B (Nuclear Factor kappa-light-chain-enhancer of activated B cells) signaling pathway [42].

5. Synbiotics and human health

Synbiotics are a combination of prebiotics and probiotics. The consumption and intake of the combination of prebiotics and probiotics has been reported to stimulate, modulate, and alter the gut microbiota by lowering the colonic secretion of pro-inflammatory and immunoregulatory cytokines such as TNF- α , IL-1 β and IL-6. Synbiotics can be used to help improve the beneficial microbes as well as increase the number of specific beneficial strains in the gastrointestinal tract [11].

Immunomodulatory effects of prebiotics and probiotics on human health.

One of the putative ways by which prebiotics and probiotics affect the health is altering the immune system. There are two categories of the immune system: either the innate immunity or the adaptive immune system. The immune system is responsible for protecting the host against pathogens. The type of effective immune response which recognizes and mounts reactions to eliminate the pathogen is determined by the site and type of pathogen present. Prebiotics and probiotics modulate the gut immune system thereby also having effects on bone health.

Further studies are needed to investigate the benefits of synbiotics on bone health both in human and animal model.

6. Probiotics and bone health

Bone loss/osteoporosis is a major health problem that is associated with the imbalance between bone formation and bone resorption; often resulting in osteoporotic fractures. In addition, the estimation is that one in two women and one in four men over the age of 50 years will break a bone due to osteoporosis in their life time [43]. Postmenopausal osteoporosis is largely attributed to estrogen deficiency in women age 50 years and above due to ablation of the ovarian function which stimulates bone resorption resulting in bone loss. Risk factors leading to bone diseases include internal (genetic and aging) and external modifiable factors (e.g., diet, exercise, environment, medication etc). In osteoporosis treatment, different approaches have been used but lately due to the safety, low adverse effect and lack of major side effects, probiotics and prebiotics have been introduced. Treatment of bone diseases including osteoporosis and fracture has been mainly through hormone replacement therapy (HRT) as well as others such as bisphosphonates and more recently low-dose parathyroid hormone. However, there are side effects reported with this such as tumorigenesis, mood swings, fluid retention and bleeding as well as low compliance of daily injections [44].

7. The role probiotics in inflammatory homeostasis

Probiotics may aid the modulation of the hosts' inflammatory status by reducing the cytokine secretion levels. The downregulation of proinflammatory cytokines

such as IL-6 [45] and TNF- α [46, 47] by probiotics has been reported on several occasions. Studies have shown that some peptides such as p40 and p75 secreted by *Lactobacillus rhamnosus* GG (LGG) may prevent cytokine-induced apoptosis, increase heat-shock proteins, and could lead to the activation of mitogen-activated protein kinase (MAPK) [48]. Furthermore, TNF (as well as IL-1 and RANKL) has been described as the major physiological inducer of NF-kappa B, one of the transcription factors responsible for the regulation of normal cell functions and the development of inflammatory osteolysis [49].

The role of the intestinal microbiota has been implicated in influencing bone health. A way by which the intestinal tract aids bone is by the regulation of the absorption of minerals such as calcium, phosphorus, and magnesium. This can also be accomplished by endocrine and gut-derived factors such as incretins and serotoninins which may influence bone remodeling. Evidence from using germ-free mice indicated the effect of the intestinal microbiome on bone physiology. These studies observed higher bone mass in germ-free mice as compared to the conventional mice. In addition, a decrease in the number of osteoclasts per bone surface and a reduction in CD4⁺ T cells and osteoclasts precursors were observed in the bone marrow of the mice [50].

The RANKL/RANK/OPG pathway is one of the mechanisms that influence bone turnover/remodeling. Osteoclast's formation and activities are controlled by the RANKL/RANK pathway. They are also an essential pathological process of the bone remodeling. Concomitantly, OPG (decoy receptor of RANKL) acts as a bone protector by binding to RANKL and preventing further resorption [42]. Probiotics (beneficial microbes) have been postulated to reduce inflammation [51] and increase OPG expression in bone [52].

8. Studies emphasizing the importance of probiotics for bone health

8.1 Animal studies

Studies have shown that various strains of *Lactobacillus* [52–54] and *Bifidobacterium* [55, 56] possess the ability to prevent and restore estrogen deficiency-related bone loss in animal models. However, not many studies have been conducted in humans. The study by Ohlsson et al. showed that C-terminal telopeptides (resorption markers) levels were not increased in probiotic treated mice as compared to the vehicle treated mice. Furthermore, there was a reduction in expression of two proinflammatory cytokines (TNF- α and IL-1 β), and an increase in the expression of OPG in the cortical bone of ovariectomised mice [52].

Lactobacillus reuteri ATCC PTA 6475 has been used in two animal studies to modulate bone outcomes. Findings from the first study showed increase in femoral trabecular BV/TV, BMD, BMC, trabecular number, spacing, and thickness as well as suppression of the basal TNF- α mRNA expression in the ileum and jejunum in 14-week-old C57Bl/6 J male mice [51]. Meanwhile, the second study showed similar positive bone effects in Ovx Balb/c mice when treated with *Lactobacillus reuteri* for four weeks and changes in the gut microbiota composition was observed revealing an increase in *Clostridiales* and a decrease in *Bacteroidales* in the ileum and jejunum [57]. Furthermore, a study by Collins et al. showed that supplementation with *Lactobacillus reuteri* 6475 could influence inflammatory status and bone formation after the inflammatory state of female mice were mildly induced. This was achieved via a dorsal surgical incision (DSI) and then administration of the probiotic. The findings indicated that the probiotic supplementation increased bone density, the DSI-treated female mice showed higher trabecular number and mineral apposition

rate when compared to the non-treated mice. Although *L. reuteri* treatment had no effect on CD4⁺ T cell numbers, it led to a decrease in IL-1 β and TGF β expression in the non-surgery cohort [58].

Probiotics are known to aid mineral absorption for the purpose of bone health maintenance. A study showed that supplementation of growing rats with *L. rhamnosus* HN001 enhanced calcium and magnesium absorption [59]. In addition, rats treated with yoghurt with a mix of *Lactobacillus casei*, *L. reuteri* and *L. gas-seri* presented higher calcium absorption which resulted in an increased BMC in comparison to the control as well as production of SCFAs [60].

Narva et al. demonstrated the effect a bioactive peptide (valylprolyl-proline) and *Lactobacillus helveticus* LBK-16H fermented milk on bone loss in ovariectomized rats. Their findings showed that *L. helveticus* fermented milk decreased bone turnover and increased BMD in growing rats [61], ovariectomised rats [62] and increased serum calcium while reduced serum PTH was observed in postmenopausal women [63].

Studies have also shown that supplementation with *Bifidobacterium longum*-fermented broccoli suppressed TRAP-positive osteoclast differentiation on the alveolar bone surface in rats [64]. Similarly, administration of yacon flour as prebiotics with *B. longum* as probiotics resulted in significant retention of minerals (such as Ca, Mg and P) in bones of Wistar rats [56]. *B. longum* also increased the BMD of ovariectomised rats by increasing the expression of Sparc and Bmp-2 genes [55].

In a study, male senescence-accelerated mice prone to developing osteoporosis with aging were orally administered heat-killed and living (viable) *Lactococcus lactis* subsp. *cremoris* H61 (strain H61). The protective effect of the heat-killed bacterium included reduction in loss of bone density, reduction in incidence of skin ulcer and reduction in hair loss of the aged SAMP6 [65]. On the other hand, reduction of bone density loss was not observed for the administration of the viable bacterium which may suggest the role of membrane-bound protein, inactivated microbial cells or cell fractions from the cellular death, that is, paraprobiotic and/or postbiotic effect.

The growth of bone as an extra-intestinal organ is suppressed by undernutrition in children. The study by Schwarzer et al. indicated that *L. plantarum* promoted juvenile growth in a strain-dependent manner using mono-colonized mouse model [66]. Supplementation with the bacterium increased the levels of insulin growth factor (IGF-1) and IGF-1 binding protein-3 (IGFBP- 3), the endocrine determinants of somatic growth to wild type levels [66].

Furthermore, the effects of probiotics have also been reported in dysbiosis-induced bone loss observed in the periodontal model [67, 68], Type-1 diabetes-induced bone loss [69] and IBD-induced bone loss [70, 71].

8.2 Human studies

A human study conducted in Denmark evaluated the combined effects of bioavailable isoflavones and probiotics on bone health and estrogen metabolism using a randomized controlled trial in postmenopausal women. Their findings showed that administration red clover extract (isoflavones) and probiotic attenuated BMD at the lumbar spine and femoral neck, reduced plasma concentrations of C-terminal telopeptide of type I collagen (CTX-1) as well as increased the urinary 2-hydroxyestrone (2-OH) to 16 α -hydroxyestrone (16 α -OH) ratio (the equol producer status) [72].

The use of probiotics however needs to be administered with caution since although the potential beneficial effect in the treatment of inflammatory and auto-immune gastrointestinal diseases for the modulation of immune response is well recognized, individuals with weaker immune systems may still be at risk of

viable bacterial cells; in which case the administration the use of killed/inactivated bacteria might be more beneficial [73].

9. Prebiotics and bone health

Prebiotics are non-digestible short-chain carbohydrates also known as oligosaccharides (and maybe polysaccharides) which selectively improves the function and activities of specific types of beneficial microbes. The chemical compounds are neither hydrolyzed by the human digestive system nor absorbed in the upper gastrointestinal tract. Prebiotics have been termed 'colonic foods' due to the ability of these types of foods to move through the colon serving as a substrate to endogenous bacteria while benefitting the host by providing energy and essential nutrients [74].

9.1 Animal studies

Some varieties of benefits have been attributed to the consumption of prebiotics. These include the ability of prebiotics to increase the absorption of minerals such as calcium, magnesium, and phosphorus [75–78] as well as iron [79] as reported quite recently. The absorption of these minerals has consequently been observed to improve bone mineralization and density [80], trabecular structure and increase equal production [81] which is known to reduce bone loss.

9.2 Human studies

FOS supplementation has been administered to both Korean [82] and Chinese [83] postmenopausal women to investigate its effect in the prevention of osteoporosis, modulation of bone biomarkers and mineral absorption. Their findings indicate that there is potential for prebiotics to play a pivotal role in the above mentioned. The study by van den Heuvel et al. reported the benefit of intake of both GOS and inulin in increasing calcium absorption in postmenopausal women [84] and oligofructose stimulating calcium absorption in adolescents [85]. Intake of oligofructose-enriched inulin resulted in improved mineral absorption and impacted the bone turnover markers in postmenopausal women [86]. Other studies also looked into the effect of prebiotics in infants as was recorded with GOS, polydextrose [87] and inulin [88]. Some of these studies have also been conducted in animal models as has been shown in a recent review [89].

10. Other clinical benefits of prebiotics

Due to the effect of the change in metabolism from protein fermentation causing the release of ammonia that leads to an increase in pH to more carbohydrate fermentation resulting in the release of acids, a reduction in the intestinal pH is observed. Low intestinal pH tends to increase bowel movement while protecting against pathogens. Diseases such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and Crohn's diseases are characterized by high pH levels [90]. Prebiotics are therefore able to reduce the symptoms and severity of these diseases. In addition, they are able to restore intestinal bacterial imbalance created by antibiotics, diarrhea, stress and sometimes medication and drugs intake [74].

Prebiotics are also known to help relief constipation. Most carbohydrates are able to increase water retention of the intestine and the acids' production thereby increasing intestinal motility [91]. Furthermore, prebiotics have been used as

bioactive functional foods to modulate blood lipid levels [92] and it also been effective in weight loss and metabolic syndrome [93]. The anti-carcinogenic effects of both prebiotics and probiotics have been reported in the inhibition of aberrant crypt foci (ACF) which is a biomarker of colon cancer [94–96].

Recently, prebiotic food and *Bifidobacterium* spp. have been reported to improve bone resorption and reduce serum TRACP-5b levels of Japanese female athletes [97]. Application of the combination of probiotic and prebiotic has been reported to confer a synergistical effect on the host due to the combined benefits of the two. This has been backed with the study by Scholz-Ahrens et al. which showed that probiotics supports the growth of other habitual microbiota strains and prebiotics chain length impacts the composition colonic, caecal, and fecal microflora. The combined administration of oligofructose and *Lactobacillus acidophilus* reduced the pH in the intestinal segments including the caecum, stimulated the colonic absorption as is indicated by increase in the colon weight [98].

11. Conclusion

The study of the effect of synbiotics on gut microbiota and bone health profile is now growing rapidly. Probiotic strains have differing genotype and phenotype and may therefore show different metabolic and immunological functions. The mechanisms however still need further investigation to look into the effect of synbiotics on the gut for the regulation of bone metabolism via the process of mineral absorption, the immune, endocrine system. Further studies are needed to elucidate the importance and mechanisms by which prebiotics and probiotics modulates the microbiota-gut-bone axis in order to get the full benefit of the long-term safety and efficacy of consumption of these functional bioactive products.

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