Bōndia

Meet the breakthrough synbiotic proving the future of bone health lives in the gut

Summary

Bone loss in menopause is a silent health crisis. Nearly half of women over 50 will suffer a low bone mass-related fracture, and fractures lead to more hospitalizations each year than breast cancer, heart attack, or stroke. Alarmingly, screening for bone mass starts far too late, leaving most women to accumulate bone loss without appropriate management. While healthcare providers often recommend dietary supplements and exercise to maintain bone mass, clinical evidence reveals that these solutions are not sufficient to preserve bone. In addition, pharmaceutical options for building bone in those most at risk carry rare but serious side effects that are unacceptable to many patients.

Bōndia, a synbiotic medical food composed of novel edible plant-derived probiotics plus prebiotic fibers, is designed to target inflammation in the gut that drives bone loss. In laboratory studies, Bōndia strengthened the gut epithelial barrier, decreased secretion of inflammatory cytokines by immune cells, and inhibited bone resorption by osteoclasts. Importantly, in a randomized, placebo-controlled clinical trial of 286 postmenopausal women, **Bōndia reduced mean bone loss by 84.5% in the femoral neck (n = 83) in women with low bone mass (osteopenia) and by 73.7% in the hip (n = 42) in women with elevated BMI after one year. Exploratory analysis also revealed that Bōndia administration reduced mean bone loss in the hip by 59.5% for women with ≥40% body fat, regardless of BMI.** Bōndia was safe, well tolerated, and significantly reduced severe gastrointestinal symptoms compared to placebo. This clinical evidence indicates that Bōndia is a safe and effective solution to proactively manage bone loss during and after menopause for groups of women most at risk. Moreover, these findings suggest that Bōndia may have benefits for additional groups of women and men with underlying inflammatory conditions.

Bone loss during and after menopause is an unseen health crisis

The sharp decrease in estrogen production that occurs in peri- and post-menopause leads to rapid loss of bone mineral density (BMD) throughout the body (**Fig 1**), rendering women susceptible to fractures[1]. Women over age 50 have an estimated 46.4% lifetime risk of suffering a bone mass

related fracture[2], and this risk increases steeply at lower bone density (**Fig 2**). Fragility fractures account for more hospitalizations than breast cancer, heart attack, or stroke[3]. Hip fractures carry a 5.75-fold increased risk of all-cause mortality in the first three months and substantially lessen the independence and quality of life of survivors[4]. Bone density screening by DXA for most women starts at age 65[5]. However, by this time, nearly 80% of women already have low bone density (osteopenia) or osteoporosis[6] (**Fig 3**). These observations indicate that most women are underserved by current approaches to managing bone health, and there is a clear need for early, proactive management of bone loss during and after the menopause transition.

FIGURE 1

Perimenopausal bone loss at lumbar spine and femoral neck in the Study of Women Across the Nation (SWAN) (adapted from Greendale et al., 2012[7]).

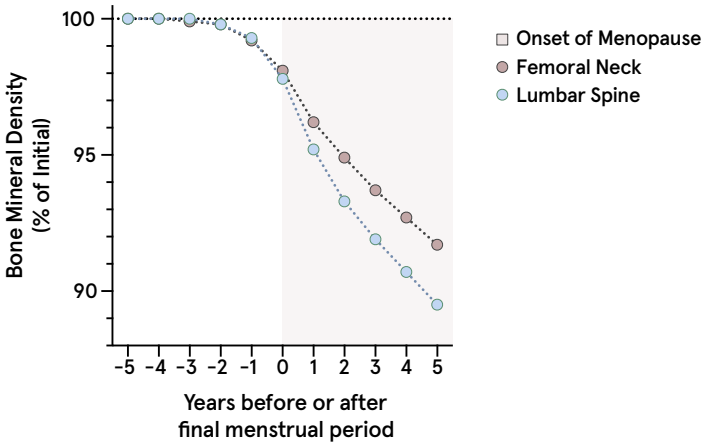


FIGURE 2

The relationship between hip BMD T-score and lifetime risk of hip fracture for women age 50 (reproduced from Reid and McClung 2024[6]).

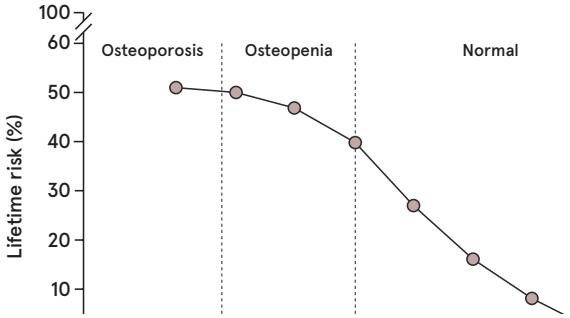
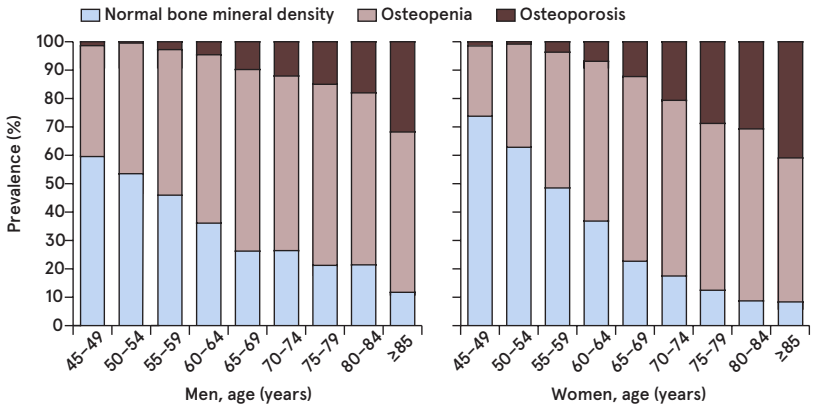


FIGURE 3

Prevalence of osteopenia and osteoporosis in men and women by age (reproduced from Reid and McClung 2024[6]).



Calcium supplements have shown modest benefit for bone density in large clinical trials, but the evidence regarding vitamin D3 and vitamin K2 is inconsistent, with meta-analyses of clinical studies finding no consistent benefit to BMD or fracture rates across randomized, controlled studies (Tang 2007; Liu 2020; Bolland 2018; Huang 2014). For these reasons, the United States Preventive Services Task Force does not recommend supplementation with vitamin D3 and/or calcium for the primary prevention of fractures in pre- or postmenopausal women[8]. A recent meta-analysis of 53 clinical studies found that exercise has benefits for BMD in the femoral neck and lumbar spine but no significant effects in hip[9]. Hormone therapy (HT) can also be used to manage perimenopausal bone loss, but many women do not tolerate or decline this option due to safety concerns. A recent survey found that only 10.5% of women experiencing menopausal symptoms have used HT[10]. These findings indicate that new, safe, and effective solutions are needed to proactively manage bone loss associated with menopause.

The gut–bone axis: connected through the immune system

The human gastrointestinal tract is home to the gut microbiome, a diverse community of microbes that plays crucial roles in nutrition, metabolism, and immunity[11,12]. Recent work has demonstrated that the gut microbiome also plays a pivotal role in bone loss following menopause. In conventionally raised female mice, sex steroid deficiency results in rapid loss of bone mass[13]. However, for mice born and maintained in sterile isolators absent any microbes, sex steroid deficiency leads to essentially no bone loss[13]. These findings provide compelling evidence for a "gut–bone axis" and suggest that the microbiome plays central role in postmenopausal bone loss.

The connection between the gut microbiome and bone turnover is thought to be mediated by inflammation[13]. Estrogen loss during menopause has effects on bone-resorbing osteoclasts mediated by immune signals, including tumor necrosis factor alpha (TNF-a), interleukin (IL)-1 Beta (IL-1b), and receptor activator of nuclear factor kB ligand (RANKL)[14–16]. Blockade of TNF-a or IL-1b has been shown to decrease bone resorption in postmenopausal women[17], and RANKL inhibition with denosumab is commonly used for decreasing bone resorption in patients with osteoporosis[18]. The efficacy of anti-inflammatory interventions underscore the importance of systemic inflammation as a driver of bone loss in menopause.

Immunity and inflammation are strongly influenced by the gut microbiome[12,19]. Probiotic microorganisms can regulate bone remodelling and protect against bone loss through several mechanisms, including (i) the production of anti-inflammatory short chain fatty acids (SCFA) that dampen inflammatory signalling, and (ii) enhanced gut barrier function that can reduce immune activation[20–22]. Together, these observations highlight an opportunity to identify novel, targeted microbial solutions to reduce inflammatory signalling and manage bone loss after menopause.

Bōndia–a groundbreaking synbiotic medical food for the dietary management of bone loss associated with osteopenia, menopause, weight, and age.

Sōlaria Biō was founded on the insight that the microbes (bacteria and fungi) naturally residing within fresh fruits and vegetables represent a diverse, untapped reservoir of functional potential for the dietary management of inflammation and associated conditions. Sōlaria Biō has built an industry-leading technology platform that combines (i) the world's largest library of fruit and vegetable-derived microbes and (ii) its formidable AI-based computational and discovery capabilities to unlock novel combinations of probiotic microbes and prebiotic fibers that function synergistically to reduce inflammation. Using this platform, Sōlaria Biō designed and built Bōndia, a synbiotic medical food for the dietary management of postmenopausal bone loss. Bōndia contains proprietary strains of *Lactiplantibacillus plantarum*, *Levilactobacillus brevis*, *Leuconostoc mesenteroides*, and *Pichia kudriavzevii*, isolated from edible plants, as well as oligofructose, organic blueberry powder, and algae-derived vitamin D3[23]. Bōndia's formulation was driven by computational prediction of synergistic functions that can modulate bone remodeling. For example, the specific combination of strains in Bōndia amplifies production of the short chain fatty acid, acetate, resulting in levels greater than the sum of each strain's individual output[23].

To evaluate the efficacy of Bōndia for managing postmenopausal bone loss, we conducted a randomized, double-blind, placebo-controlled trial, recently published in *Osteoporosis International*[24]. 286 women within 6 years of menopause were enrolled and randomized to receive either Bōndia synbiotic medical food (N = 144) or maltodextrin placebo (N = 142) twice daily for 1 year. Participants in both groups also received the recommended daily allowance of vitamin D3 (800 IU). Participants received DXA scans at the lumbar spine, hip, and femur at baseline, 6-months, and 12-months. This study revealed that Bōndia significantly reduced bone loss in groups of women most at risk, including those with low bone mass (osteopenia) and those with BMI ≥ 30. Women with osteopenia at baseline (defined as a T-score ≤ -1 at the total spine, N = 83) consuming Bōndia showed 84.5% reduced bone loss at the femoral neck at 12 months compared to women consuming placebo (**Fig 4A**). In addition, women with a BMI ≥ 30 (N = 42) randomized to receive Bōndia also showed 73.7% reduced bone loss at the total hip compared to women consuming placebo (**Fig 4B**). For both groups, similar trends were observed at all sites examined. Together, these groups of at-risk women represent nearly 70% of US women over the age of 50 (**Fig 4C**)[25].

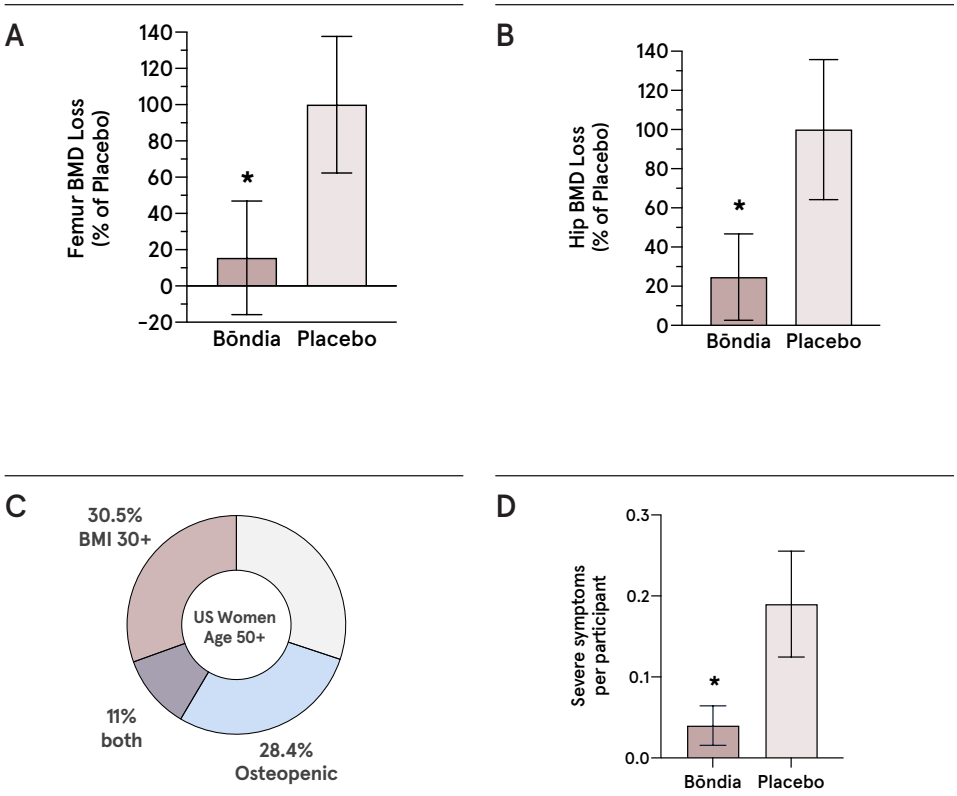
In this clinical study, Bōndia was safe and well tolerated, with no differences in adverse events observed between product and placebo groups[24]. Moreover, gastrointestinal tolerability questionnaires administered throughout the study revealed that administration of Bōndia reduced the number of severe gastrointestinal symptoms reported by study participants by 78.9% compared to placebo (**Fig 4D**), with severe GI symptoms reported

by 2.8% of participants in the Bōndia group compared to 9.4% of participants randomized to placebo. These results indicate that Bōndia preserved bone mass to a greater extent than vitamin D3 alone in groups of women at high risk and conferred meaningful improvements in gastrointestinal health.

FIGURE 4

Twice daily Bōndia for 12 months:
(**A**) *reduced femur bone loss by 84.5% for women with osteopenia at baseline*
(**B**) *reduced hip bone loss by 73.7% for women with BMI ≥ 30 at enrollment.*
(**C**) *70% of US women over age 50 have osteopenia or elevated BMI.*
(**D**) *Participants taking Bōndia in the clinical study reported 78.9% fewer severe gastrointestinal symptoms than those taking placebo.*

** Difference between groups showed statistical significance in Bōndia clinical study.*

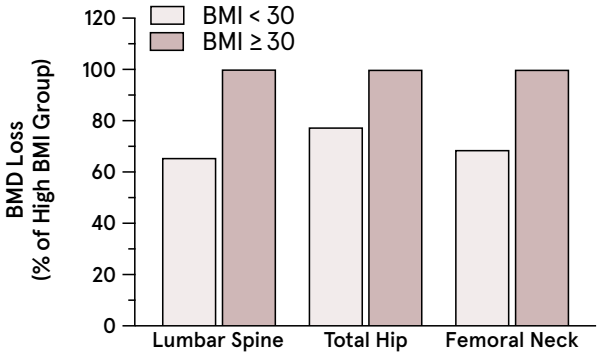


Challenging the dogma of how obesity impacts bone

The relationship between elevated BMI and bone health is controversial. It is commonly argued that high BMI is protective against osteoporosis and fracture due to increased mechanical loading on the skeleton[26]. Indeed, many clinical studies have reported an association between increased BMI and bone mineral density (BMD)[27], and in some cases, obesity has been linked to lower osteoporosis risk[28]. However, in the Bōndia clinical study, women with BMI ≥30 lost approximately 30% more bone mass than those who were not obese (**Fig 5**). The usefulness of BMI alone as a health metric is limited since it fails to distinguish between lean and fat mass, and recent research has demonstrated that body composition plays an important role in bone health. For instance, sarcopenic obesity, characterized by reduced muscle mass and strength in the context of excess adiposity, is associated with an increased risk of osteoporosis[29]. A large study of over 6,000 white and Chinese subjects reported a negative correlation between body fat percentage and bone mass[30], and a recent meta-analysis found that abdominal obesity is not protective against fractures in adults over age 40[31]. These findings support a more nuanced understanding of bone health wherein increased mechanical

FIGURE 5

Participants in the Bōndia clinical study with BMI ≥ 30 exhibited greater mean loss of bone mass than those with a healthy BMI.



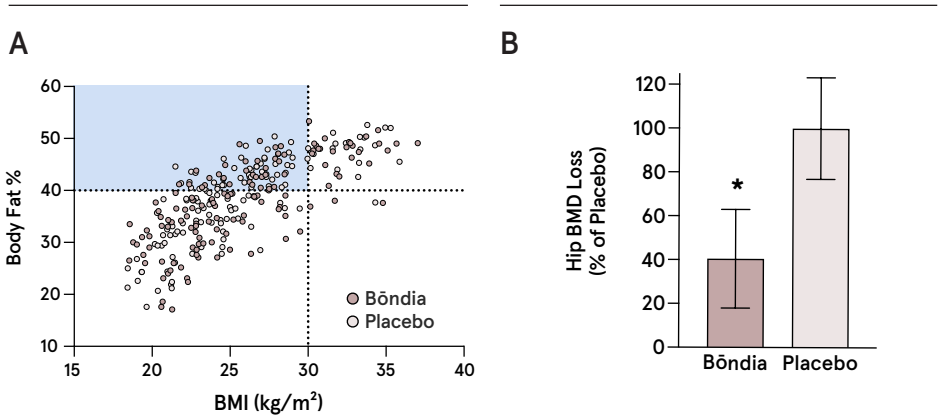
loading on the skeleton may be protective, but elevated levels of body fat are deleterious.

In the Bōndia clinical study, of all women recruited who exhibited ≥40% body fat (N = 128), 65.6% had a BMI under 30 (N = 84; **Fig 6A**)[24]. Closer examination of the data revealed that for all women with at least 40% body fat, Bōndia reduced bone loss at the total hip by 59.5% regardless of BMI (**Fig 6B**). These findings suggest that a substantial proportion of postmenopausal women exhibit elevated body fat but do not meet the BMI-based criterion for obesity and, further, that Bōndia may be protective against bone loss for these individuals.

FIGURE 6

(**A**) *Relationship between BMI and body fat percentage in the Bōndia study cohort. Each point represents a study participant. 65.6% of participants enrolled in the Bōndia study who exhibited 40% body fat or greater had a BMI under 30 (shaded region).*
(**B**) *Bōndia reduced bone loss at the hip for women with ≥40% body fat by 59.5%, independent of BMI.*

** Difference between groups showed statistical significance in Bōndia clinical study.*



There is substantial evidence that carrying excess body fat predisposes individuals to a chronic, systemic inflammatory state, driven by endocrine and pro-inflammatory mediators produced by adipose tissue[32]. For example, obesity is associated with increased expression of the inflammatory cytokines C-reactive protein (CRP), TNF-α, and interleukin(IL)-631. Additionally, visceral adipose tissue surrounding the internal organs has been reported to secrete high levels of TNF-α and IL-6. This chronic, systemic inflammation can drive increased osteoclast differentiation and function and, in turn, increase

bone loss and risk of fracture: a relationship coined "immunoporosis"[15,33,34]. Together, these observations suggest a mechanistic link between adiposity-driven inflammation, bone loss, and the synergistic anti-inflammatory properties of Bōndia.

Bōndia reduces bone loss through three interconnected anti-inflammatory mechanisms

We sought to investigate the mechanisms underlying Bondia's bone-sparing effects in postmenopausal women by examining its impacts on inflammation and bone resorption using in vitro gut models and ex vivo human immune cell assays.

First, to examine whether Bōndia affects barrier integrity, intestinal epithelial cell monolayers were established on semi-permeable membranes[35]. These monolayers were exposed to Bōndia at three concentrations, corresponding to ratios of the cells in Bōndia to epithelial cells of 36:1 (high), 12:1 (medium), or 2:1 (low), or to a media control (vehicle). The effect of Bōndia on intestinal barrier function was assessed by changes in electrical resistance across the monolayer at 0 and 24 h incubation. All tested Bōndia concentrations resulted in a significant increase in electrical resistance across the epithelial barrier. compared to the vehicle control (**Fig 7A**), suggesting improvement of barrier function.

We next explored how Bōndia may modulate systemic inflammation by treating human peripheral blood mononuclear cells (PBMCS) with increasing concentrations of the synbiotic[35]. Cryopreserved human PBMCS isolated from four peri- or postmenopausal female donors and three male donors were briefly treated with an inflammatory stimulus (lipopolysaccharide (LPS)), after which the LPS was removed and PBMCS were exposed to a media control (vehicle), or Bōndia at ratios of 10:1 or 1:1 (Bōndia cells:PBMCS). Bōndia administration significantly reduced secretion of the pro-inflammatory cytokines IL-6, IL-8, and CXCL1 in a concentration-dependent manner relative to the LPS-challenged vehicle control in both female and male PBMCS (**Fig 7B–D**).

Finally, to examine whether the interactions between Bōndia, the intestinal epithelium, and intestinal immune cells could modulate bone resorption, we used a co-culture model in which intestinal epithelial and immune cells were grown together with or without Bōndia administration, or a vehicle control[35]. Conditioned media from these cultures were then applied to cultures of primary human osteoclasts isolated from postmenopausal female donors and maintained on bone slices for 14 days. Administration of culture supernatant treated with Bōndia to osteoclasts significantly reduced production of CTX-1, a bone resorption marker, compared to untreated culture supernatant, indicating that administration of Bōndia to intestinal immune cell cultures was sufficient to suppress bone resorption in this model (**Fig 7E**). Notably, no significant effects were observed on osteoclast viability or differentiation.

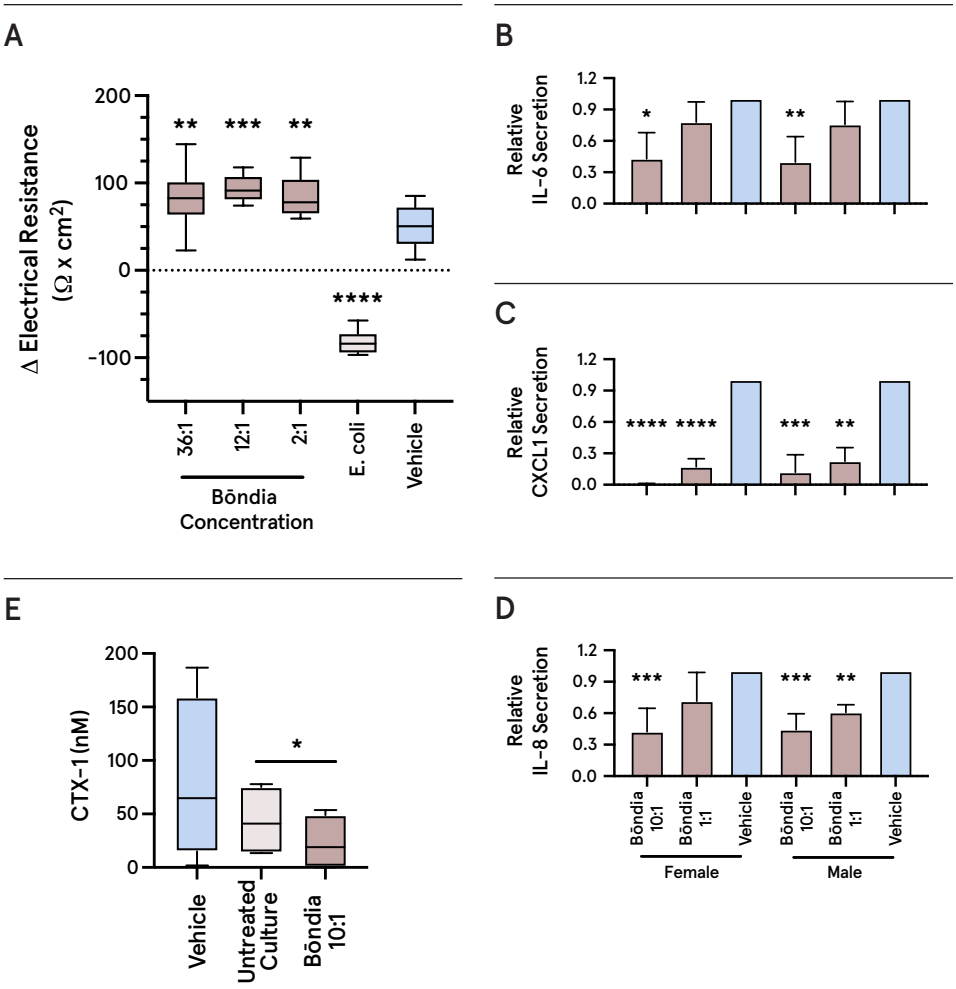
FIGURE 7

(**A**) *Bōndia increases barrier function (change in electrical resistance) of intestinal epithelial monolayers. Bōndia was administered at three concentrations, corresponding to ratios of the cells in Bōndia to epithelial cells of 36:1 (high), 12:1 (medium), or 2:1 (low), or to a media control (vehicle).*

(**B**-**D**) *Bōndia elicits robust, concentration-dependent reductions in secretion of inflammatory cytokines* (**B**) *Il-6,* (**C**) CXCL1, *and* (**D**) *Il-8 by human peripheral blood mononuclear cells (PBMCs) after inflammatory challenge. Bōndia was administered at ratios of 10:1 or 1:1 (Bondia cells:PBMCs).*

(**E**) *Bōndia-conditioned media reduces the resorptive activity of osteoclasts derived from human PBMCs, as measured by production of CTX-1, a bone resorption marker, compared to untreated culture supernatant. Bōndia was administered at a ratio of 10:1 (Bōndia cells:PBMCs).*

Significance by one-way ANOVA with Tukey's HSD:
** p<0.05,*
*** p<0.01,*
**** p<0.001,*
***** p<0.0001*



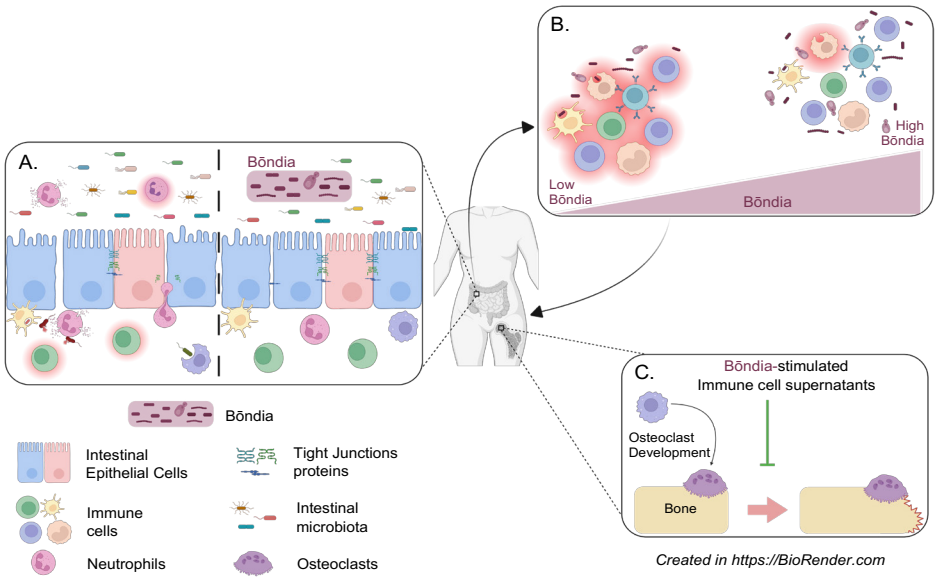
In summary, these studies indicate that Bōndia administration can improve intestinal barrier integrity, suppress immune cell cytokine secretion, and inhibit osteoclast activity (**Fig 8**)[35]. These observations are consistent with clinically observed reductions in severe gastrointestinal symptoms and bone resorption markers. Together, these findings suggest that Bōndia engages the gut–bone axis via complimentary barrier strengthening, immune-modulating, and antiresorptive pathways, supporting its role in maintaining skeletal health in groups of postmenopausal women most at risk for accelerated bone loss. In addition, the consistency observed in immune responses for PBMCs isolated from men and women to Bondia administration suggests that Bōndia has potential to benefit men as well as women.

Conclusions

Bone loss remains a silent crisis for women during and after the menopause transition, and there is a lack of safe and effective solutions to maintain bone during this period. Sōlaria Biō has developed Bōndia, a groundbreaking solution that contains seven ingredients sourced from edible plants: four unique probiotics derived from fresh fruits and vegetables,

FIGURE 8

Bōndia reduces bone loss via barrier improvement, inflammation reduction, and osteoclast inhibition.



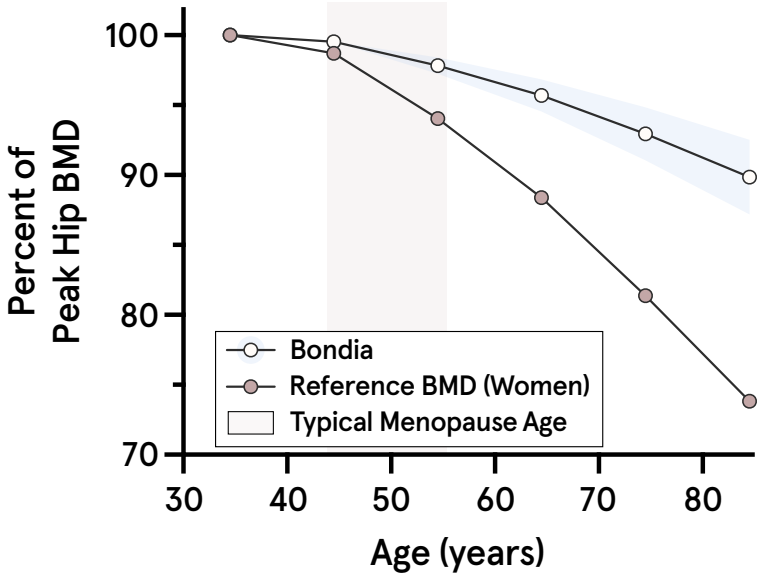
as well as oligofructose, organic blueberry powder, and vitamin D3. Our laboratory studies showed that Bōndia can influence inflammation and bone loss via three interconnected mechanisms: increasing gut barrier function, reducing inflammatory cytokine production by immune cells, and decreasing bone resorption by osteoclasts (**Fig 8**)[35]. In a large, double blind, placebo-controlled clinical trial, we demonstrated that Bōndia significantly reduced bone loss over one year in two groups of women most at risk for fracture: those with osteopenia and those with elevated BMI[24]. These groups represent 70% of women above the age of 50, suggesting that upwards of 45 million women in the US could benefit from this synbiotic medical food (**Fig 4C**)[25].

Our findings on the benefits of Bōndia in women with elevated BMI challenge the dogma that obesity is protective against bone loss. In this study, women with elevated BMI lost more bone mass than those with a healthy BMI (**Fig 5**). Moreover, Bōndia administration reduced bone loss in participants with elevated body fat, regardless of body weight (**Fig 6**)[24]. These results are consistent with the hypothesis that elevated fat mass can increase bone loss, possibly due to the inflammatory effects of this tissue. Together, these findings wwindicate that daily administration of Bōndia may help most women during the menopause transition to preserve bone mass before the development of osteoporosis or fracture. Finally, as bone loss is a continual process, these results suggest that the cumulative benefit of Bōndia over time could be highly clinically meaningful (**Fig 9**).

There is substantial evidence that carrying excess body fat predisposes individuals to a chronic, systemic inflammatory state, driven by endocrine and pro-inflammatory mediators produced by adipose tissue[32]. For example, obesity is associated with increased expression of the inflammatory cytokines C-reactive protein (CRP), TNF-α, and interleukin(IL)-631. Additionally, visceral adipose tissue surrounding the internal organs has been

FIGURE 9

Unmanaged bone loss in hip of women based on CDC reference values for a healthy control population[36] and projected benefit of Bōndia over the same period. The projected benefit represents the range of mean effect sizes observed in the Bōndia clinical study at the hip for participants with BMI ≥ 30 or osteopenia relative to unmanaged bone loss each year.



reported to secrete high levels of TNF-α and IL-6. This chronic, systemic inflammation can drive increased osteoclast differentiation and function and, in turn, increase bone loss and risk of fracture: a relationship coined "immunoporosis"[15,33,34]. Together, these observations suggest a mechanistic link between adiposity-driven inflammation, bone loss, and the synergistic anti-inflammatory properties of Bōndia.

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