

# Microbiome and Weight Management Research Review

## Utilizing Targeted Probiotic *Bifidobacterium animalis* ssp. *lactis* B420

### THE OBESITY EPIDEMIC

According to a recent analysis of data from the National Health and Nutrition Examination Survey (NHANES), 35% of men and 40.4% of women in the US are obese (defined as BMI  $\geq$  30), and this trend has continued to increase over the past decade particularly among women and adolescents.<sup>1,2</sup> Obesity is an established driver of many conditions including certain cancers, sleep apnea, osteoarthritis, cardiovascular disease, and diabetes,<sup>3</sup> and obesity management continues to be a major healthcare challenge worldwide.

**Adiposity-Based Chronic Disease** The American Association of Clinical Endocrinologists and American College of Endocrinology conceptualize obesity as an Adiposity-Based Chronic Disease (ABCD). The term ABCD addresses the chronic nature and pathophysiological basis of obesity more precisely than the traditional definition by assessment of BMI.<sup>4</sup>

The quantity and distribution of body fat (adipose tissues) have significant physiological impacts in adiposity-based complications. For example, intra-abdominal (visceral) adiposity, but not subcutaneous adiposity in the extremities, is linked to metabolic dysfunction and poses a greater overall risk to metabolic health.<sup>5</sup> Higher waist-to-hip ratio, waist-to-height ratio, and waist circumference are indicators of increased proportion of abdominal adipose tissues, and therefore are better predictors of cardio-metabolic risks than BMI.<sup>6-8</sup>

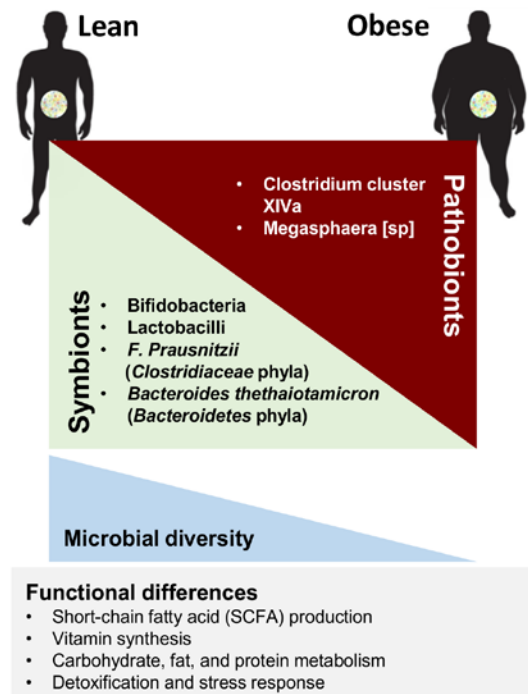
Even a modest reduction of 3-10% of total body weight is sufficient to have a clinically measurable benefit for diabetes prevention, symptoms of osteoarthritis, dyslipidemia, hyperglycemia, and hypertension.<sup>9</sup> While achieving weight loss is a challenge, it is maintaining weight loss over time that is often more difficult. In one large population study, the odds of achieving a 5% weight loss within one year for individuals with Class I Obesity (BMI 30-34.9 kg/m<sup>2</sup>) were 1 in 12 men and 1 in 10 women.<sup>10</sup> In another population-based survey in the US, only 1 in 6 overweight and obese adults reported ever having maintained weight loss of at least 10% for one year.<sup>11</sup> An additional consideration is that weight regain occurs over time. For example, the Helsinki Health Study reported that approximately 30% of the population had a steady weight gain of at least 5 kg (11 lb) during a 5-7 year follow-up period.<sup>12</sup>

### MICROBIOME AND OBESITY

Energy balance and body weight regulation are complex and involve many factors that affect energy intake, expenditure, or storage.<sup>13</sup> Increasing evidence is now pointing to a crucial factor linking energy balance and obesity: **the microbiome**. The Human Microbiome Project has shown that the intestinal microbiome—a complex ecosystem colonized by more than 100 trillion microorganisms co-evolving with the host—contains rich communication networks between the intestine and other organ systems (e.g., gut-brain, gut-liver, gut-adipose axes) and plays a central role in host metabolism and overall health.<sup>14</sup>

**Dysbiosis**—an imbalance within the microbiome—is now recognized to have wide clinical impacts, with links established to a diverse set of adverse health conditions including obesity.

Genomic content and diversity in the microbiome have been shown to be different in obese individuals as compared with lean individuals. Lower microbial diversity is associated with obesity and fat mass variables, particularly the visceral fat mass,<sup>15</sup> and lower gene count is associated with more marked weight gain over time.<sup>16</sup> Differences in community structure have been identified, such as a reduction in *Bifidobacterium animalis* and *Bifidobacterium* genus overall and in *Faecalibacterium prausnitzii* and *Clostridiaceae* family, as well as an increase in *Megasphaera* (Figure 1).<sup>17</sup>



**Figure 1.** Differences in the microbiome between lean and obese population. Obesity-associated dysbiosis exhibits a decrease in symbionts (health-promoting microorganisms) and an increase in pathobionts (pathogenic microorganisms). There is also a decrease in microbial diversity and bacterial gene counts as well as changes in functions.<sup>16-19</sup>

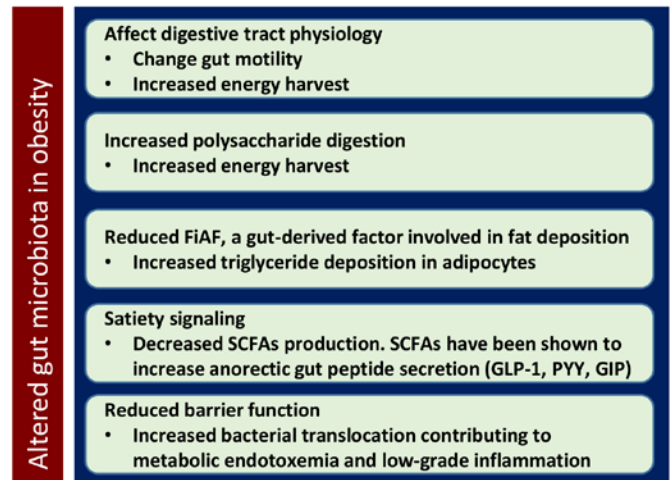
**Increased Energy Harvest and Storage** Research has demonstrated that changes in the microbiome in obese individuals affect carbohydrate, lipid, and amino acid metabolism, leading to increases in energy harvest (i.e., more efficient extraction and absorption of macronutrients from the host's diet) and fat storage (**Figure 2**).<sup>15,19,20</sup> For example, transplanting the gut microbiota from obese mice to gnotobiotic (germ-free) mice leads to increased energy harvesting, and in turn increased hepatic lipogenesis and stimulation of both hepatic lipoprotein lipase (LPL) and sterol regulatory element-binding proteins (SREBPs).<sup>21</sup> The microbiome can influence fat deposition by modulating release of intestinally derived signals that influences digestion of fat as well as uptake of fatty acids by adipocytes.<sup>22</sup> Similarly, transplanting fecal microbiome from the obese humans into germ-free mice leads to increased total body and fat mass and obesity-associated metabolic abnormalities in these animals.<sup>19</sup> On the other hand, germ-free mice colonized with fecal microbiome from lean humans did not have the same unfavorable response.<sup>19</sup>

**Satiety Signaling** Gut microbes can metabolize dietary fibers and prebiotics, which are indigestible to humans, to short-chain fatty acids (SCFAs). SCFAs not only have a role in glucose and lipid metabolism, gut integrity, and immune function, they are also involved in appetite regulation.<sup>23</sup> Increased SCFAs have been shown to trigger the expression and secretion of anorectic gut peptide such as glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and glucose-dependent insulinotropic polypeptide (GIP).<sup>24-26</sup> It has been observed that a Western-style, high-fat, high-sugar diet is linked to dysbiosis and a significantly decreased concentration of SCFA (**Figure 2**).<sup>27</sup>

**Metabolic Endotoxemia and Metabolic Bacteremia** Dietary patterns can significantly affect the microbiome. For example, diets high in fat and low in fiber can lead to dysbiosis, increased intestinal permeability, and the initiation of a low-grade inflammation via two phenomena: metabolic endotoxemia and metabolic bacteremia (**Figure 2**).<sup>28,29</sup>

Metabolic endotoxemia indicates an increased plasma concentration of lipopolysaccharides (LPS), components that are found on the membrane of Gram-negative bacteria. Increased gut permeability allows LPS to cross the gut mucosal membrane and enter into the circulation. Metabolic bacteremia describes the translocation of bacteria from the intestine into the mesenteric adipose tissue and the blood as a result of increased intestinal permeability.<sup>5</sup> The presence of these bacteria and LPS in adipose tissue triggers inflammation, leading to the development of insulin resistance and other

metabolic abnormalities.<sup>28</sup> Experimental research has demonstrated that long-term exposure of LPS in circulation led to increased caloric intake and body mass.<sup>28,30</sup> The positive correlation between endotoxemia and higher energy intake has been seen in humans as well.<sup>31</sup>



**Figure 2.** Interactions between the host and the microbiome in obesity.<sup>18,25,26</sup>

## PROBIOTICS FOR WEIGHT MANAGEMENT

Probiotics are live microorganisms which, when administered in adequate amounts, alter the microbiota of the host and may confer mostly beneficial health effects on the host.<sup>32</sup> Numerous studies have demonstrated various favorable effects of probiotics such as improving overall gastrointestinal (GI) health, modulating the immune system, and reducing antibiotic-associated diarrhea, just to name a few (please refer to MET1872: Probiotics Research Review).

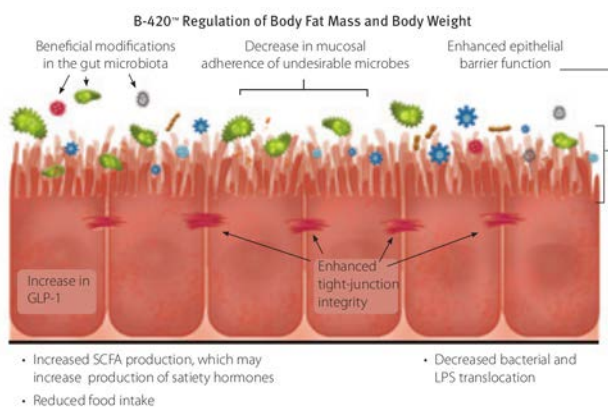
A growing body of literature is also supporting the use of probiotics in the management of body weight. However, as stated by the World Health Organization (WHO), not all probiotics are the same. The health benefits of probiotics are genus, species, and strain specific, and probiotics should be chosen based on the desired health benefits.<sup>33</sup>

***Bifidobacterium animalis ssp. lactis B420*** (acronym: B420) is a naturally occurring probiotic strain originally isolated from dairy products. Increasing preclinical evidence supports the use of B420 for overall GI health, cardiometabolic endpoints, and body weight regulation. Clinical evidence now supports the use of B420 for body weight and body fat mass regulation.

**Beneficial Properties of B420 in Experimental Studies** The genome characterization of B420 was published in 2012.<sup>34</sup> Experimental research indicated that:

1. B420 increased tight junction integrity of gut epithelial cells and therefore protected gut epithelial cells from the harmful effects of pathogenic microbes.<sup>35</sup>
2. B420 protected against NSAID-induced GI side effects in a rat model by reducing an NSAID-induced increase in stomach permeability.<sup>36</sup>
3. B420 reduced mucosal dysbiosis, bacterial translocation, expression of major pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , PAI-1, and IL-6) in various tissues, and improved glucose metabolism in mice fed a high-fat diet (HFD).<sup>29</sup>
4. In HFD-fed mice, B420 (in combination with the prebiotic polydextrose) modulated gut microbiota and improved glucose intolerance. Further, the combination prevented the impairment of intestinal immunity (as indicated by loss of Th17 and Treg cells in the small intestine) due to metabolic abnormalities induced by HFD.<sup>37</sup>
5. In a mouse model of diabetes, B420 enhanced concentrations of ileum GLP-1, a protein involved in both insulin secretion and satiety signaling.<sup>38</sup>

The proposed mechanisms of action of B420 are summarized in the graph below:<sup>29,35,36,38-40</sup>



**B420 and Adiposity in Experimental Studies** There have been studies investigating the effect of B420 co-administered with HFD in murine models. For example:

1. In an obese mouse model, increases in body weight and fat mass in mice fed with HFD for 12 weeks were significantly reduced if the mice were co-administered B420.<sup>40</sup>
2. In a diabetes mouse model, mice receiving both HFD and B420 had decreased fat mass compared with mice receiving only HFD.<sup>40</sup> B420 also improved glucose metabolism in this mouse model.

**B420 and Adiposity in Human Clinical Trial** A randomized, double-blind, clinical study was conducted to examine the

impact of B420 in adiposity-related outcomes.<sup>39</sup> Healthy adults with overweight or obesity (BMI 28-34.9; waist-to-hip ratio  $\geq$  0.88 for men and  $\geq$  0.83 for women) with normal glucose and insulin concentrations at baseline were randomized to 10 billion CFUs/day B420 (n=55) or placebo (n=57) for six months (there were additional intervention groups in this trial, but information from those groups was beyond the scope of this report and is thus excluded). The following results were based on the post-hoc factorial analysis of participants who completed the six-month study.

**Fat mass:** The placebo group had increases in fat mass over the six-month period, whereas the B420 group showed blunted rises in fat mass (**Table 1**). For instance, there was an average 3.1% increase in total body fat mass in the placebo group but only 0.1% increase in the B420 group.<sup>39</sup>

**Table 1.** Changes in body fat mass in different regions.

| Percent change (over 6 months) | Placebo (mean $\pm$ SD) | B420 (mean $\pm$ SD) | P value* |
|--------------------------------|-------------------------|----------------------|----------|
| Total body fat mass            | 3.1% $\pm$ 5.6%         | 0.1% $\pm$ 7.0%      | 0.002    |
| Trunk fat mass                 | 5.0% $\pm$ 6.7%         | -0.4% $\pm$ 8.5%     | 0.0002   |
| Android fat mass               | 5.2% $\pm$ 11.0%        | -0.4% $\pm$ 9.0%     | 0.004    |
| Gynoid fat mass                | 2.9% $\pm$ 7.2%         | 1.3% $\pm$ 8.0%      | 0.064    |

\*post-hoc factorial analysis of changes B420 vs. placebo

**Waist circumference (WC):** Compared with placebo, participants supplemented with B420 had a lower WC by 2.4% (approximately 1 inch, or 2.4 cm) over the six-month period.

**Energy intake:** Analysis of participants' five-day food diaries showed that B420 group reduced energy intake by ~300 kcal/day compared with placebo over the six-month period.

**Short-chain fatty acids (SCFAs):** A significant increase in SCFAs, including propionic acid, butyric acid, and valeric acid, was seen in stool samples from the B420 group compared with the placebo group. As SCFAs are produced by the microbial activity, the change in fecal SCFAs is suggestive of alterations in the microbiome occurring with B420 supplementation.

**Table 2.** Changes in fecal SCFAs.

| Change over 6 months ( $\mu$ M/g) | Placebo (mean $\pm$ SD) | B420 (mean $\pm$ SD) | P value* |
|-----------------------------------|-------------------------|----------------------|----------|
| Propionic acid                    | -1.91 $\pm$ 4.1         | +0.92 $\pm$ 5.8      | 0.025    |
| Butyric acid                      | -1.33 $\pm$ 6.2         | +1.35 $\pm$ 13       | 0.0497   |
| Valeric acid                      | -0.31 $\pm$ 0.9         | +0.26 $\pm$ 1.4      | 0.046    |
| Total                             | -10.0 $\pm$ 23          | +4.6 $\pm$ 41        | 0.049    |

\*post-hoc factorial analysis of changes B420 vs. placebo

**Zonulin and hsCRP:** There was a trend towards a decrease ( $p=0.06-0.07$ ) in levels of circulating zonulin (a biomarker of intestinal permeability<sup>41</sup>) and high-sensitivity C-reactive protein (hs-CRP; a biomarker of inflammation) in the B420 group compared with the placebo group over the six-month period.

## CONCLUSION

Over the past decade a strong link between the microbiome and obesity points to the potential for interventions targeting the microbiome for more effective weight management. The probiotic strain B420 has been shown clinically to improve body weight and body fat regulation and may be particularly beneficial for long-term body weight and fat maintenance. The microbiome is one important factor involved in the complex regulation of body weight and fat maintenance, and targeted interventions represent another tool that may be integrated into a diet and lifestyle management program to improve patient outcomes.

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