Original Article

Effect of Synbiotic Supplementation in Children with Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial

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Background: Nonalcoholic fatty liver disease (NAFLD) is one of the most common complication of obesity. Gut dysbiosis is implicated in the pathogenesis of NAFLD.

Objective: To investigate the effect of synbiotic supplementation in children with NAFLD.

Materials and Methods: This was a randomized, double-blind, placebo-controlled trial conducted during February to October 2016. All subjects had NAFLD defined by controlled attenuation parameter (CAP) value of greater than 225 dB/m without other causes of fatty liver. Participants received either a mixture of chicory inulin, *Lactobacillus acidophilus*, and *Bifidobacterium lactis* or placebo for 16 weeks. Body mass index (BMI), serum alanine transaminase (ALT), and liver stiffness measurement (LSM) with simultaneous CAP determination were assessed at baseline and after the completion of the intervention. Body mass index Z-score adjusted for age and sex was determined according to the 2007 WHO child growth references.

Results: There were 18 (78% male) and 19 (58% male) children in synbiotic and placebo groups. Children in intervention group had significantly greater mean age than those in placebo group (13.3±2.1 vs. 11.26±2.7 years, p = 0.02). There was no difference of baseline BMI Z-score, serum ALT, CAP, and LSM between the two groups. After the completion of the intervention, BMI Z-score significantly decreased in both groups. The reduction of CAP value tended to be significant in the placebo group (p = 0.047). The median (IQR) between-group difference in change from baseline for BMI Z-score, serum ALT, CAP, and LSM values were not statistically significant.

Conclusion: The present study is unable to demonstrate the beneficial effect of this particular synbiotic on BMI and hepatic derangement in children with NAFLD. The search for appropriate prebiotic type, dosage and strain of probiotic as well as the duration of treatment for pediatric NAFLD is still required.

Keywords: Children, NAFLD, Obesity, Prebiotic, Probiotic, Synbiotic

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The prevalence of childhood overweight and obesity has increased worldwide in the past two decades. A survey conducted in Thailand revealed the prevalence of overweight and obesity in 2011 among children aged 3 to 18 years was 7.6% and 9.0%, respectively(1). One of the most common complication of obesity is nonalcoholic fatty liver disease (NAFLD)(2). The NAFLD spectrums range from simple steatosis to nonalcoholic steatohepatitis (NASH), which can progress to advanced fibrosis and cirrhosis in 37% of patients(3).

The pathogenesis of NAFLD is complex and remains incompletely understood. It might be explained by the "multiple parallel hits hypothesis" which is the consequence of various insults performing together on genetically predisposed individuals to induce NAFLD(4). Fatty liver occurs by excessive ingestion of high fat diet, obese state, insulin resistance, resulting in free fatty acid accumulation in hepatocytes. In addition, the perturbation of the gut microbiota composition, so called gut dysbiosis, has been considered to have a role in NAFLD progression. It can increase hepatic steatosis through metabolic modulation specifically the production of short-chain fatty acids from bacterial fermentation of indigestible carbohydrates and proteins. Furthermore, gut dysbiosis results in dysregulation of gut endothelial barrier function that allows for the translocation of bacteria and its endotoxins, including lipopolysaccharide (LPS) into the hepatic portal circulation. LPS is one of the most prominent toll-like receptor (TLR)

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activators and can initiate the inflammatory cascade from Kupffer cells and inflammasome activation. These circumstances lead to NAFLD progression through increased hepatic inflammation and fibrosis[3,5,6].

Probiotics are living microorganisms that upon ingestion in specific numbers, exert health benefits beyond those of inherent basic nutrition[7]. Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating growth and/or activity of a number of colonic bacteria[8]. The food ingredients which meet the criteria of prebiotics at present consist of oligosaccharides including inulin as well as their derivatives. There have been a growing number of studies regarding the effect of prebiotic and probiotic on modulating the intestinal environment, decreasing the pathogenic bacteria, and improving intestinal barrier, which may lead to the reduction of hepatic inflammation and fibrogenesis[9,10].

Liver biopsy is considered as the gold standard to evaluate the presence and severity of hepatic steatosis. Nevertheless, it has many drawbacks, such as sampling error, cost, and risk of complications. A novel investigation named controlled attenuation parameter (CAP) evaluated with transient elastography has been developed to assess liver steatosis, simultaneously with liver stiffness measurement (LSM). There have been increasing number of studies regarding the role of CAP as a noninvasive investigation alternative to liver biopsy for the evaluation of liver fat content in subjects with liver disease[11].

The manipulation of the intestinal microbiota by probiotics, prebiotics or synbiotics might yield benefits for NAFLD patients in terms of ameliorating gut dysbiosis and hence attenuating liver abnormalities. The purpose of the present study was to investigate the effect of synbiotic supplementation on body mass index (BMI), serum alanine transaminase (ALT), liver steatosis and stiffness in children with NAFLD.

Materials and Methods

Subjects

Children aged 6 to 18 years participating in this randomized (blocked randomization), double-blind, placebo-controlled clinical trial (Clinical trial: TCTR20170128001, http://www.clinicaltrials.in.th) were recruited in King Chulalongkorn Memorial Hospital, during February to October 2016. Overweight and obesity were defined as BMI Z-score adjusted for child age and sex according to the 2007 WHO references of greater than 1 and 2, respectively. All subjects had NAFLD defined by CAP value of greater than 225 dB/m by Fibroscan® which is the optimal cut point to detect hepatic steatosis using liver biopsy as the gold standard from previous study in children[12]. Children with metabolic liver diseases, viral hepatitis, Wilson disease, autoimmune hepatitis, hepatotoxic drug exposure, and alcohol consumption were excluded. Subjects were instructed to avoid additional administration of prebiotic, probiotic, synbiotic and antibiotic during the follow-up period.

The study protocol was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB No. 530/58). Written informed consent was obtained from the participants' guardians.

Interventions

The investigating product was a powder mixture containing 2.24 gram of chicory inulin, 1.5×10^9 colony forming unit of *Lactobacillus acidophilus* and *Bifidobacterium lactis* in each sachet. The indistinguishable sachet of placebo contained maltodextrin. Both products were consumed one sachet daily for 16 weeks. All participants received the same advice regarding the appropriate dietary intake and physical activity.

Outcome measures

Body weight, height, BMI, serum ALT, and LSM with simultaneous CAP determination were determined at baseline and after completion of the intervention period. The primary study outcome measure was the change of liver steatosis evaluated by CAP. Secondary endpoints were treatment-related changes in BMI Z-score, serum ALT, and liver stiffness assessed by transient elastography.

Liver stiffness and CAP measurements

Liver stiffness and CAP measurements were performed by a trained study investigator (KS) who was certified by the manufacturer using the Fibroscan® (Echosens, Paris, France). The subjects were instructed to fast for 4 hours before the examination. All subjects had a thoracic perimeter >75 cm. The 3.5 MHz "M" or "XL" probe was used according to the manufacturer's specifications.

The reported liver stiffness result was the median value of 10 measurements performed between depths of 25 and 65 mm. Only results with 10 successful measurements, with a success rate >70% and interquartile range/median (IQR/median) liver stiffness ratio <30%, were recorded. The CAP value was the median of 10 measurements obtained simultaneously with the valid LSM.

Statistical analysis

Data were analyzed with SPSS (version 22.0; SPSS, Inc., Chicago, IL, USA). The differences between groups were tested for significance using the Student's t-test, Chi-square test, and Mann-Whitney U test. Wilcoxon signed-rank test was used for comparison within the same group. A *p*-value of less than 0.05 was considered statistically significant.

Results

There were 18 and 19 children in synbiotic and placebo groups. All subjects were obese except one child in intervention group who was overweight. Demographic data, BMI Z-score, serum ALT, and transient elastography features in all participants at entry into the study were shown in Table 1. Children in intervention group had significantly greater mean age than those in placebo group. Other baseline characteristics of the participants were comparable.

All participants completed the 16-week study with good adherence to therapy as documented by sachet count. No adverse effects were reported.

After the completion of the intervention, BMI Z-score significantly decreased in both groups (Figure 1). The reduction of CAP value tended to be significant in the placebo group ($p = 0.047$). Liver stiffness and serum ALT levels remained fairly steady in both groups during the study. The difference of outcome parameters at baseline and after 16 weeks of synbiotic or placebo treatment was listed in Table 2. The median (IQR) between-group difference in change from baseline for BMI Z-score, serum ALT, CAP, and LSM values were -0.0 (-0.1, -0.1), -1.7 (-19.4, 16.1) U/L, 5.7 (-22.8, 34.3) dB/m, and -0.6 (-1.8, 0.6) kPa, which were not statistically significant.

Table 1. Baseline characteristics of participating subjects

	Synbiotic group (n = 18)	Placebo group (n = 19)	*p*-value
Age (years)	13.3 (2.1)	11.3 (2.7)	0.02*
Gender			
Male	14 (77.8)	11 (57.9)	0.19
Female	4 (22.2)	8 (42.1)	
BMI Z-score	2.8 (0.9)	2.9 (0.6)	0.58
ALT (U/L)	50.0 (31.6)	53.4 (50.2)	0.81
CAP (dB/m)	311.4 (35.5)	314.2 (41.8)	0.83
LSM (kPa)	6.5 (4.7)	5.7 (1.8)	0.51

Values presented as mean (SD) and number (%)
BMI = body mass index; ALT = alanine transaminase; CAP = controlled attenuation parameter; LSM = liver stiffness measurement

Discussion

The prevalence of NAFLD in children and adolescents has been reported to be around 7.6% in the general population and up to 34.2% in obesity clinics[13]. Lifestyle intervention for weight loss is the fundamental treatment for pediatric obesity and NAFLD. This may be attained by dietary modification and/or physical activity. A recent systematic review in children aged 6 to 18 years with NAFLD demonstrated that lifestyle changes including aerobic exercise and dietary control resulted in improvements in BMI, transaminase levels and hepatic steatosis[14]. However, subjects participating in the present study showed significant improvement only in BMI Z-score after receiving advice about lifestyle changes regardless of intervention group assignment. This finding might be explained by weight loss of less than 5 to 10% during the follow-up period in most subjects.

Human intestine contains more than 2,000 species of microbiota which provide many benefits to the host, through a variety of physiological functions such as harvesting energy, strengthening gut integrity, protecting against

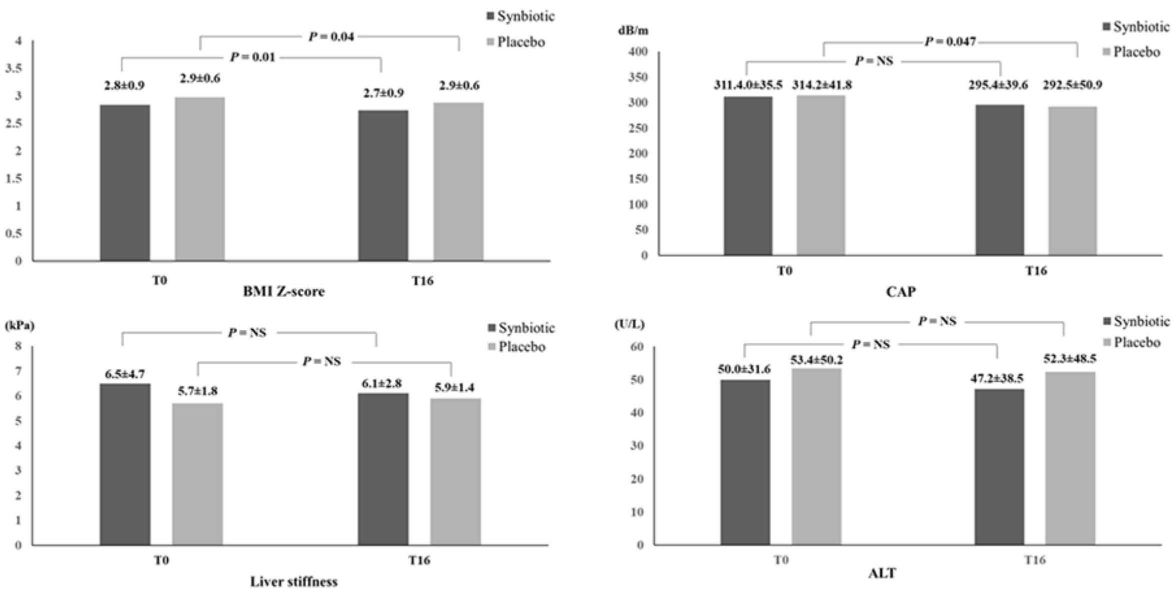

Figure 1. Effects of synbiotic supplementation on body mass index (BMI), controlled attenuation parameter (CAP), liver stiffness, and alanine transaminase (ALT) at baseline (T0) and after 16 weeks of synbiotic or placebo treatment (T16). Data expressed as mean ± SD

Table 2. The difference of body mass index Z-score, serum alanine transaminase, liver steatosis and stiffness values in the two groups of children with nonalcoholic fatty liver disease at baseline (T0) and after 16 weeks of synbiotic or placebo treatment (T16)

Parameter	Synbiotic group		Placebo group	
	T16 to T0	*p*-value	T16 to T0	*p*-value
BMI Z-score	-0.1 (-0.2, -0.0)	0.01*	-0.1 (-0.2, -0.0)	0.04*
ALT (U/L)	-2.8 (-12.5, 6.9)	0.62	-1.1 (-1.7,-0.5)	0.87
CAP (dB/m)	-16 (-36.3, 4.3)	0.12	-21.7 (-43.1, -0.4)	0.047*
LSM (kPa)	-0.4 (-1.4, 0.6)	0.43	0.24 (-0.5, 0.9)	0.49

Data expressed as median (interquartile range)
BMI = body mass index; ALT = alanine transaminase; CAP = controlled attenuation parameter; LSM = liver stiffness measurement

pathogens, and regulating host immunity[15]. Metagenomic analysis and 16s ribosomal RNA gene sequencing have shown that Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, Spirochaetes, and Verrucomicrobia are the predominant bacterial phylum in the intestine[16-18]. Evidences propose that gut dysbiosis lie beneath various diseases including obesity and fatty liver disease[16]. A number of studies have shown a reduced abundance of Bacteroidetes with a proportional increase in Firmicutes phylum in obese individuals[19-21]. Karlsson et al reported that increased Enterobacteriaceae in obese/overweight preschool children as well as the inverse correlation between *Bifidobacterium* and ALT level[22].

Therapeutic manipulation of intestinal microbial communities has the potential to ameliorate different gastrointestinal conditions including NAFLD. Probiotics alone or in combination with prebiotics have been demonstrated to yield beneficial effects on the treatment of NAFLD. A randomized controlled trial demonstrated that consuming VSL#3 (probiotic mixture-*Lactobacillus casei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus delbrueckii, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis,* and *Streptococcus salivarius*) can help diminish the accumulation of hepatic fat in patients with biopsy-proven NAFLD[23]. Aller et al reported that NAFLD patients treated with *Lactobacillus bulgaricus* and *Streptococcus thermophilus* for 3 months had significantly lower ALT activity at the end of treatment[24]. Vajro et al demonstrated that 8 weeks supplementation of *Lactobacillus rhamnosus* strain GG in obese children with NAFLD yielded a significantly decreased ALT level but no significant change in BMI Z-score and hepatic fat[25]. A recent meta-analysis on the efficacy of probiotics in patients with NAFLD revealed significant improvement of serum low density lipoprotein, ALT, and BMI in probiotic group[26].

There have been several studies demonstrating the benefit of synbiotic supplementation in addition to lifestyle change in adults with NAFLD. Malaguarnera et al reported that *Bifidobacterium longum* with fructo-oligosaccharides significantly improved serum AST level, hepatic steatosis, and the NASH activity index[27]. Another randomized controlled trial also showed that administration of 7 strains of probiotics with fructo-oligosaccharide was able to reduce inflammatory markers including C-reactive protein (CRP), nuclear factor-kappa B, tumor necrotic factor-α, decrease serum ALT level, and fibrosis score as determined by transient elastography[28]. A recent meta-analysis showed that probiotic/synbiotic use improved transaminase levels as well as reduced CRP and liver fibrosis score in NAFLD patients[29]. The data regarding synbiotic treatment of pediatric NAFLD is scarce. A trial without a placebo group demonstrated that synbiotic (*Bifidobacterium lactis*, *Lactobacillus acidophilus*, and *Lactobacillus casei*, and chicory inulin) supplementation for 4 months in addition to lifestyle changes decreased BMI Z-score, liver enzymes, and inflammatory markers as well as improved fatty liver documented by ultrasound in around two-third of children with NAFLD[30].

The present study failed to demonstrate a beneficial effect of synbiotic treatment in obese children with NAFLD. There are several reasons contributing to this negative result. The efficacy of the treatment depends on the strain, dosage, and duration of probiotic treatment. This particular synbiotic might not be effective in the treatment of NAFLD. The other drawbacks include short-term treatment and limited number of subjects which may not be sufficient to demonstrate the efficacy of the treatment. The present study utilized noninvasive tests comprising serum ALT, CAP, and LSM for outcome measurement which might not be sensitive or accurate enough to evaluate hepatic derangement. It is impractical to perform liver biopsy routinely in order to evaluate fatty liver disease in children without signs of chronic liver disease due to its invasiveness.

Conclusion

The present study is unable to demonstrate the beneficial effect of this particular synbiotic on BMI and hepatic derangement in children with NAFLD. Novel synbiotic or probiotic therapy based on NAFLD/NASH specific microbial composition together with the search for the appropriate treatment duration represents a promising future direction.

What is already known on this topic?

Gut dysbiosis plays a role on the development and progression of NAFLD. Oral administration of probiotic or synbiotic in addition to lifestyle modification has been proposed as an effective treatment of NAFLD.

What this study adds?

The present study adds more data regarding the efficacy of synbiotic supplementation in children with NAFLD. Nevertheless this particular synbiotic fails to demonstrate the beneficial effect on BMI and the hepatic derangement evaluated by serum ALT and transient elastography.

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Conflicts of interest

The authors declare no conflict of interest.

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ผลของการเสริมซินไบโอติกในเด็กที่มีภาวะตับคั่งไขมัน: การวิจัยเชิงทดลองแบบสุ่มชนิดมีกลุ่มควบคุม

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ภูมิหลัง: ภาวะตับคั่งไขมันเป็นหนึ่งในภาวะแทรกซ้อนที่พบได้บ่อยที่สุดในเด็กอ้วน การเสียสมดุลของจุลินทรีย์ในลำไส้มีบทบาทต่อพยาธิกำเนิดของภาวะตับคั่งไขมัน

วัตถุประสงค์: เพื่อศึกษาผลของการเสริมซินไบโอติกในเด็กที่มีภาวะตับคั่งไขมัน

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาเชิงทดลองแบบสุ่มชนิดมีกลุ่มควบคุมแบบปกปิดสองทางระหว่างเดือนกุมภาพันธ์ถึงเดือนตุลาคม พ.ศ. 2559 โดยศึกษาในเด็กที่มีภาวะตับคั่งไขมัน ซึ่งวินิจฉัยจากการตรวจพบมีค่า controlled attenuation parameter (CAP) มากกว่า 225 เดซิเบล/เมตร โดยไม่มีโรคตับอื่น ๆ เด็กกลุ่มแรกได้รับซินไบโอติกที่ประกอบด้วย chicory inulin, *Lactobacillus acidophilus* และ *Bifidobacterium lactis* ส่วนกลุ่มที่สองได้รับยาหลอก เป็นระยะเวลา 16 สัปดาห์ ทำการเปรียบเทียบค่าดัชนีมวลกาย ค่า alanine transaminase (ALT) รวมทั้ง liver stiffness measurement (LSM) และ CAP ก่อนเริ่มการศึกษาและเมื่อสิ้นสุดการศึกษา ค่าดัชนีมวลกาย Z-score ปรับตามอายุและเพศอ้างอิงตามมาตรฐานการเจริญเติบโตขององค์การอนามัยโลก พ.ศ. 2550

ผลการศึกษา: มีผู้เข้าร่วมการศึกษา 37 ราย โดยแบ่งเป็นกลุ่มที่ได้รับซินไบโอติก 18 ราย (เพศชายร้อยละ 78) และกลุ่มที่ได้ยาหลอก 19 ราย (เพศชายร้อยละ 58) เด็กในกลุ่มที่ได้รับซินไบโอติกมีอายุเฉลี่ยมากกว่ากลุ่มที่ได้ยาหลอก (13.3±2.1 เทียบกับ 11.3±2.7 ปี, ค่าพีเท่ากับ 0.02) แต่ค่าดัชนีมวลกาย, ALT, LSM และ CAP ก่อนเริ่มการศึกษาของทั้งสองกลุ่มนั้นไม่แตกต่างกัน เมื่อสิ้นสุดการศึกษาค่าดัชนีมวลกายของทั้งสองกลุ่มลดลงอย่างมีนัยสำคัญ ค่า CAP มีแนวโน้มลดลงในกลุ่มที่ได้ยาหลอก (ค่าพีเท่ากับ 0.047) แต่เมื่อเปรียบเทียบการเปลี่ยนแปลงของค่าดัชนีมวลกาย ค่า ALT, CAP และ LSM ของทั้งสองกลุ่มกลับพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ

สรุป: การศึกษานี้ไม่สามารถแสดงให้เห็นถึงประโยชน์ของซินไบโอติกในแง่ของการลดดัชนีมวลกายและความผิดปกติของตับในเด็กที่มีภาวะตับคั่งไขมัน ยังต้องมีการศึกษาเกี่ยวกับชนิดของพรีไบโอติก ปริมาณ และสายพันธุ์ของโพรไบโอติก รวมทั้งระยะเวลาที่เหมาะสมของการรักษาภาวะตับคั่งไขมันในเด็กต่อไป