Volume-4, Issue-5, May-2015 • ISSN No 2277 - 8160

Research Paper | Home Science

Synbiotic supplementation improves glycemic control and bio-marker for heart health in pre-hypertensive subjects with Type II Diabetes Mellitus- Randomized Control Trial.

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KEYWORDS : Type 2 Diabetes Mellitus, synbiotic, hs-CRP, pre-hypertension.

Introduction:
In the recent times, science based strategies have been established to prevent Cardiovascular disease (CVDs) using functional foods. Amongst these, the less explored foods include the probiotics, prebiotics and the synbiotics. Synbiotic have the potential to regulate hypertension, improve glycemic control and reduce the expression of inflammatory markers. Some of the mechanisms involved for these changes may be lowering of serum cholesterol, improved colonization of beneficial bacteria in the Gut, reduction in endotoxemia and increase in Gut hormone namely GLP1 and GIP. The global epidemic of CVDs can be reversed through modest investments in interventions. Probiotics, prebiotics and synbiotics are the new concepts that have been developed to modulate the target gastrointestinal micro flora balance. In addition to the probiotic approach of directly introducing live bacteria to the colon through dietary supplementation, another approach to increase the number of beneficial bacteria in the intestinal micro biota is through the use of prebiotics. Due to the potential synergy between probiotics and prebiotics, foods containing a combination of these ingredients are often referred to as synbiotics (Gibson & Roberfroid, 1995; Collins & Gibson, 1999). Interaction between the probiotic and the prebiotic in vivo might favour healthy environment in the Gut which can reverse some of the established parameters of CVD namely hs-CRP.

Objectives:
1. If there are significant associations between the glycemic and pre hypertension status with biomarker of heart health i.e. hs-CRP.
2. To determine the effect of synbiotic supplementation on hs-CRP, pre hypertension status and glycemia in type II diabetic subjects with pre-hypertension.

Methods:
The study was divided in to three phases:

Phase I: In this phase, pre hypertensive adults with type 2 NIDDM aged 35-55yrs were purposively selected from Sun Valley Hospital, Guwahati, Assam and baseline information was collected on their anthropometric profile, blood pressure, FBS, PP_2BS, HbA1c and hs-CRP.

Phase II: Intervention trials with synbiotic supplementation.

Based on their informed consent, 35 subjects fulfilling the inclusion and exclusion criteria were selected purposively and were randomly divided into Control (N=10) and Experimental groups (N=25). The experimental group was supplemented with 1gm of freeze dried synbiotic product (2 species of Lactobacillus and Bifidobacterium each, 1 species of Streptococcus, 1 species of yeast along with Fructooligosaccharide) daily to be taken along with meals for 45 days.

The inclusion criteria for selecting the patients were: pre hypertension (SBP-120-139mmHg; DBP-80-89mmHg), HbA1c between 7-9.5%, BMI between 18.5-<30. Subjects with BMI> 30, HbA1c >9.5%, those suffering from any disease like cancer, HIV, IBD, etc. or would have taken antibiotics in last two months, who have undergone surgery in last 6 months and those in need of dental treatment were excluded from the study. subjects having diabetes with hypertension under the age group of 35-55 years will be selected based on purposive sampling. The inclusion criteria for selecting the subjects will be: pre hypertension (SBP-120-139 mmHg; DBP-80-89 mmHg), stage-I hypertension (SBP-140-154mmHg; DBP-90-99 mmHg) and PP2BS ≥ 200 mg/dl, HbA1C between 7 – 9.5%, BMI between 18.5-<30. Subjects with BMI> 30, HbA1C >9.5%, those suffering from any other disease like cancer, HIV, IBD, etc. or would have taken antibiotics in last two months who have undergone surgery in the last 6 months and those in need of immediate dental treatment would be excluded from the study.

Phase III: Impact Evaluation of the synbiotic supplementation on parameters similar to baseline.

Blood samples were collected and B.P. was measured using standard methods after 45 days of intervention to check the parameters same as baseline data for both the groups.

Biochemical and bio-physiological Assay methods
Fasting blood glucose (FBS) and Post prandial blood glucose (PP2BS) were estimated using enzymatic reference method with hexokinase (Reinauer et al 2002). Glycated Hemoglobin (HbA_{1c}) was quantified assayed using IFFC and FDA approved automated dedicated high performance liquid chromatography (HPLC) method (IFFC 2002). hs-CRP- was estimated by using automatic chemistry analyzer **manufactured by Siemens and Model: Advia 2400.** Blood pressure measurements were taken by the physician using the standard method (Adams et al 2002; Thomas G et al 2005).

Results:
Baseline data of hs-CRP did not co-relate with the glycemic values, blood pressure as well as anthropometric data. No significant change in BMI was observed. Table: 1 shows that synbiotic supplementation significantly reduced the diastolic and systolic blood pressure by 7.7% and 6.24% respectively. Over all glycemic profile also showed statistically significant reductions in terms of FBS, PP_2BS and HbA1c by 14.8%, 4.67% and 7.49% respectively along with a reduction of 49% in hs-CRP. These values remained unchanged in the control group.

Table I: Impact of Synbiotic supplementation on hs-CRP, glycemic index and blood pressure.

Parameters	GROUPS	MEAN±SD	t stat	Paired two tail	% difference
hs-CRP	Control Pre	1.193 ± 0.335	0.14	0.89	0.25
	Control Post	1.196 ± 0.287			
	Exp Pre	1.23 ± 0.253	14.38	2.88***	48.78↓
	Exp Post	0.63 ± 0.252			
FBS	Control Pre	141.5 ± 17.56	3.61	0.005	4.24↑
	Control Post	147.5 ± 17.55			
	Exp Pre	154.12 ± 17.59	8.11	2.43***	4.67↓
	Exp Post	146.92 ± 16.51			
PP2BS	Control Pre	170.6 ± 15.19	3.36	0.008	2.63↑
	Control Post	175.1 ± 16.73			
	Exp Pre	176.2 ± 18.66	12.06	1.11***	7.49↓
	Exp Post	163 ± 16.91			
HbA1c	Control Pre	7.48 ± 0.407	1	0.34	0.13↑
	Control Post	7.47 ± 0.402			
	Exp Pre	7.7 ± 0.65	11.27	4.5***	14.8↓
	Exp Post	6.5 ± 0.50			
SYSTOLIC	Control Pre	134.2 ± 5.84	0.28	0.78	0.89↑
	Control Post	135 ± 7.81			
	Exp Pre	134.71 ± 4.84	14.62	1.95***	6.2↓
	Exp Post	126.37 ± 4.81			
DIASTOLIC	Control Pre	83.6 ± 4.78	2.13	0.06	5.2↑
	Control Post	88 ± 5.37			
	Exp Pre	85.58 ± 5.58	-10.04	7.04***	8.4↓
	Exp Post	78.2 ± 3.66			

*****p<0.001**

Discussion:

Elevation of hsCRP is associated with increased risk of type 2 diabetes development in patients with all levels of metabolic syndrome, type 1 and type 2 diabetes mellitus, hemoglobin A1c significantly correlates with hsCRP levels and future cardiovascular risk. Also, hsCRP levels increase with the stage of beta-cell dysfunction and insulin resistance (Pfützner A, Forst T., 2006). The present study also showed that the subjects selected had hs-CRP levels in the intermediate range. However, no significant co-relation was observed between the hs-CRP levels and the glycemic status. In contrast to this finding a study by Safiullah Amanullah et al. (2010) showed significantly higher values of hs-CRP in subjects with type 2 diabetes as compared to the non diabetics and a significant co-relation was also seen. This can be explained by the fact that both the study groups differed greatly in their ethnicity and race and probably took diets with different antioxidant levels which explains for intermediate hs-CRP values in Assamese diabetic subjects as compared to higher mean values of 4.8 in diabetic subjects from Jordon. In the present study supplementation of 1g of synbiotic for a period of 45 days to type 2 diabetic with pre-hypertensive adults brought about a significant reduction in glycemic, biophysical and inflammatory marker.

A combined review of studies conducted on similar lines revealed that the consumption of probiotics may help to reduce blood pressure (BP) by helping to regulate the hormone system that regulates blood pressure and fluid balance (Eleanor McDermid, 2014). Jia-Yi Dong et al, in the year 2013 studied the effect of probiotic fermented milk on BP by conducting a meta-analysis of randomised controlled trials. It suggested that probiotic fermented milk has BP-lowering effects in pre-hypertensive and hypertensive subjects (Consumption of probiotics can be part of a healthy lifestyle to help reduce high blood pressure). In the year 2014, Majid Mohamadshahi compared the effect of probiotic and conventional yogurt on inflammatory markers in patients with type 2 diabetes and suggested that probiotic yogurt may be used as an alternative prevention approach and treatment method to control diabetic complications. Another study conducted by Majed S Alokail in the year 2013 studied the effects of probiotics in patients with diabetes mellitus type 2: study protocol for a randomized, double-blind, placebo-controlled trial. It is expected that the probiotic product will induce beneficial changes in gut microbiota, reduce the systemic inflammatory state through altering systemic endotoxin levels and, as such, reduce the systemic inflammatory response observed in T2DM subjects.). When prebiotic supplementation was given to obese subjects, a significant increase was seen in GLP-1 which is known to positively affect the glycemic index (Sheth and Assudani, 2015). The present study also revealed a reduction of 48% in the hs-CRP values after supplementing the synbiotic product for 6 weeks. Similar findings are reported by Zatollah Asemi et al. (2013) where a reduction of 55% was observed after the period of 6 weeks of supplementation of synbiotic product to subjects with metabolic syndrome.

Conclusion: Daily intake of 1gm of synbiotic supplementation for 45 days improves glycemic control, reduces the levels of pro-inflammatory marker (hs-CRP) along with reduction in systolic and diastolic blood pressure.

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