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DAILY INTAKE OF FRUCTOLIGOSACCHARIDE REDUCES hs-CRP AND OTHER INFLAMMATORY MARKERS IN GRADE 1 SEDENTARY OBESE INDIVIDUALS RESIDING IN URBAN BARODA - A DOUBLE BLIND PLACEBO CONTROL TRIAL.

***Mini Sheth[1], Swati Parnami[1], Sania Quraishi[1], Jyoti Prakash[1], Anil Kumar[2], Manish Jain[2], Manoj Gote[2], Ashok Dubey[2]**

[1]Department of Food and Nutrition, Faculty of Family and Community Sciences, The Maharaja Sayajirao University of Baroda, Vadodara.
[2]Innovation Centre TATA Chemicals Ltd., Pune, Maharashtra.

***Corresponding Author: Dr. Mini Sheth**
Department of Food and Nutrition, Faculty of Family and Community Sciences, The Maharaja Sayajirao University of Baroda, Vadodara.

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ABSTRACT
Background: Obesity is not an immediate lethal disease in itself but is a significant risk factor associated with a range of serious non-communicable diseases probably due to its association with inflammation of tissues of certain vital organs. **Objective:** To study the putative role of Fructooligosaccharide in modulation of Gut microflora and thereby affect the levels of inflammatory markers in obese individuals. **Methodology:** Using a double blind placebo control study design, eighty two sedentary obese subjects in the age group of 20-50 years who voluntarily agreed to participate in the study were purposively selected and were equally divided into two groups who received 10 ml liquid FOS and 10 ml liquid sucrose solution respectively for a period of 30 days. Their serum inflammatory markers in terms of TNF α, Leptin, and IL-6 was determined using Metabolic Hormone Magnetic Bead Panel and hs-CRP was determined using nephelometry method. Assessment of hematological indices was based on the principle of cell counting and volumetric analysis and the fecal *bifidobacteria* counts were determined using selective medium under anaerobic conditions. **Results**: Supplementation of liquid FOS significantly reduced the hs-CRP levels by 17.24% with a non-significant reduction in the TNF α, IL6 and Leptin levels was observed by 4.94% and 2.90% respectively. **Conclusion**: Daily intake of 10g of liquid FOS helps in reducing the low grade inflammation especially in terms of hs CRP and improved *bifidobacteria* colonisation in sedentary obese individuals and can be used as an effective strategy to delay obesity related co-morbidities.

KEYWORDS: Fructooligosaccharide, *bifidobacteria*, Gut microflora.

INTRODUCTION
Obesity is one of the most neglected public health problem.[1] Once considered a problem only in high income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings.

Level of physical activity is also a contributing factor for obesity. Multiple cohort and cross-sectional studies have shown an association between obesity and inactivity.[2]

Since inflammation is believed to have a role in the pathogenesis of cardiovascular events, measurement of markers of inflammation has been proposed as a method to improve the prediction of the risk of these events**. hs-CRP** is an easily measured inflammatory biomarker. C-reactive protein (CRP) is pentameric protein found in the blood plasma, the levels of which rise in response to acute and chronic inflammatory conditions such as bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury and necrosis. Elevated serum levels of C-reactive protein (CRP) have been widely considered to be nonspecific but sensitive markers of the acute inflammatory response. **Leptin** is a protein produced by fatty tissue which is believed to regulate fat storage in the body.

Tumor necrosis factor (**TNF α**, **tumor necrosis factor alpha**, TNF α, cachexin, or cachectin) is a cell signaling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction. Researches on the pathophysiology of obesity have recently intensified, largely after the discovery of leptin. However, accumulating evidence suggests that the role of leptin is much broader than that of an antiobesity hormone; leptin also affects several neuroendocrine mechanisms and regulates multiple hypothalamic–pituitary axes. Leptin levels increase exponentially with

increasing fat mass. Leptin levels reflect not only the amount of fat stored but also energy imbalance; prolonged fasting substantially decreases leptin levels, whereas overfeeding greatly increases them. The composition of the diet-specifically, intake of macronutrients and hormonal factors also regulate leptin levels.[3]

Low-grade chronic inflammation is characterized by a two- to threefold increase in the systemic concentrations of cytokines such as TNF α, IL-6 and CRP. A predominant factor in this correlation is due to the autoimmune response triggered by adiposity, whereby immune cells may mistake fatty deposits for intruders. The body attacks fat similar to bacteria and fungi. When expanded fat cells leak or break open, macrophages mobilize to clean up and embed into the adipose tissue. Then macrophages release inflammatory chemicals, including TNF α and IL-6. TNF α's primary role is to regulate the immune cells and induce inflammation. White blood cells then assist by releasing more cytokines. This link between adiposity and inflammation has been shown to produce 10-35% of IL-6 in a resting individual, and this production increases with increasing adiposity.[4]

A review article examined 19 studies on the acute inflammatory response to exercise, 18 on cross-sectional comparisons of subjects by activity levels and 5 examining prospectively the effects of exercise training in the inflammatory process. Exercise produces a short term, inflammatory response, whereas both cross-sectional comparisons and longitudinal exercise training studies demonstrate a long term "anti-inflammatory" effect. This anti-inflammatory response may contribute to the beneficial effects of habitual physical activity[5]. β-2-1 fructans may have beneficial effects upon immune function, ability to combat infection, and inflammatory processes and conditions.[6] The hypothesis that gut microbiota influences weight gain was suggested recently. Animal and human data have suggested that the composition of gut micro flora may be an important mediator of risk of obesity and diabetes.[7]

Prebiotics, probiotics and synbiotic may have the potential to modify glycemic responses, lower plasma cholesterol and triglyceride levels, improve blood insulin sensitivity, and inflammatory biomarker. These properties makes prebiotic, probiotic and synbiotic attractive dietary target for the prevention of disease associated with obesity further leading to CVDs.[8,9,10, 11, 12]

METHODS AND MATERIALS

Selection of subjects

Eighty two obese sedentary subjects were purposively selected and enrolled in a randomized double blind placebo control trial based on the inclusion and exclusion criteria. The inclusion criteria were patients of either sex between age group 20-50 yrs, suffering from obesity with BMI >25 who are sedentary and willing to consume FOS supplement, and the exclusion criteria were patients suffering from Diabetes, Hypertension, CVD, Celiac disease, HIV, Cancer, Renal disorder and liver disorder, Infections and inflammatory disorders and hospitalization since last one month. Underweight subjects, highly active/sports people and subjects taking any supplements were also excluded from the study.

The subjects were randomly assigned using computer generated random tables to either placebo or experimental group (Anderson AF, 2008). Subjects were required to provide blood and fecal samples before and at the end of each intervention. Blood samples were collected for hs-CRP, TNF α, leptin and gut microbial counts in terms of fecal bifidobacteria. Anthropometric measurements were measured by the investigator before and after each intervention period. Subjects were advised not to alter their usual calorie intakes and were asked to document any unusual symptoms or side effects and to keep a diary of illness and medications. The subjects were followed up everyday using the compliance card and SMS reminders and were asked to report for side effects if any.

Trial monitoring plan

- Daily supplementation for 30 days and monitoring the daily supplement intake using a compliance card and daily SMS reminders was carried out.
- The supplements were provided in a wide mouth bottle for a period of 30 days along with 10 ml standard spoons and empty bottles were collected after 30 days.
- Subjects who consumed the supplement for at least 21 days were considered for analysis as studies have shown the effectiveness of FOS in minimum 21 days
- Spot observations were carried out to validate the compliance in 10% of the subjects.
- Subjects could withdraw from the study in case of any adverse effect observed during the intervention.

Study food and mode of intervention

The food grade Fructooligosaccharide FOS was procured from Tata Chemicals Pvt. Ltd. Mumbai, for the intervention trial in sedentary obese subjects. Group I and group II subjects were given packed airtight containers of 300 ml of FOS and 300 ml of sugar solution with a standard 10 ml spoon respectively (as shown in plate 4.8). Subjects were asked to take 10 ml FOS along with their meals or water daily for a period of 30 days and empty bottles were collected after 30 days. Subjects who consumed the supplement for atleast for 21 days were considered for analysis. Spot observations were carried out to validate the compliance in 10% of the subjects. A compliance card was given and daily SMS reminders were sent to monitor their regularity.

Airtight containers packed and coded for supplementation

Statutory clearances

The Medical Ethics committee of the Foods and Nutrition Department, The M.S. University of Baroda approved the study proposal and provided the Medical ethics approval number IECHR/2015/2. Written informed consent was obtained from the participants who agreed to give baseline information through questionnaire and give sample of blood for biochemical analysis.

Collection of baseline information

Administration of Interviewer based Questionnaires

The objective and benefits of the study were briefed to the subjects who met the inclusion criteria of the study, and were motivated and convinced to participate by providing an informed consent. Set of questions were administered on the subjects and baseline information was gathered on family history, medical history and personal habits and dietary practices.

Activity Pattern

Physical activity pattern of the subjects was determined using Global Physical Activity Questionnaire.[13] Information on physical activity pattern was collected from all the subjects. A checklist containing various types of activities along with the time spent to perform each activity was used to assess the activity pattern of the adults. The subjects with an activity of less than 600 MET minutes per week were classified as sedentary; those with activity level between 600-3000 MET minutes per week were classified as moderately active and above 3000 MET minutes per week were classified as vigorously active. For the present study, sedentary subjects were selected.

***Food Frequency Questionnaire** (FFQ)*

A list of foods rich in antioxidants and prebiotics and their frequency of consumption was prepared. The frequency of consumption of antioxidant and prebiotic rich foods was collected for daily, weekly, fortnightly, monthly, occasionally, seasonally and never and were scored as 6, 5, 4, 3, 2, 1, 0 respectively. A total score was then computed for each subject and used for further analysis. For the purpose of determining the frequency of consumption of specific food items, the data on food frequency was grouped into three groups. The foods that were consumed daily and weekly were considered as frequently consumed, the foods that were consumed fortnightly and monthly were considered as less frequently consumed and the foods which were taken on yearly basis were considered as rarely consumed foods.

Anthropometric Measurements

Weight

It is the most widely used and simplest reproducible anthropometric measurement. It indicates the body mass and is a composite of all body constituents like water, minerals, fat, protein, bone etc.[14]

Technique- A platform weighing scale to the nearest 100 g was used to measure weight. The subject was weighed in standard indoor clothing, bare feet and without leaning against or holding anything. Scale was 'zeroed' before taking any weight and was calibrated using standard weights after every third subject.

Height

It is a linear measurement made up of the sum of four components i.e. Legs, Pelvis, Spine and Skull.[15]

Technique- A spring- loaded non-stretchable tape was used to measure the height of the subjects. A convenient flat wall was identified at the clinic site for the measurement of height. The subject was made to stand barefoot with the arms hanging freely by the side. Heels of the feet were placed together with the medial (inner) border of the feet at an angle of 60 degrees. The scapula and the buttock were ensured to be in contact with the measuring wall. The head was held in the Frakfort plane (with the tragus of the ear and the lateral angle of the eye in a horizontal line). Height was recorded to the nearest 0.1 cm after the subject inhaled fully and maintained the erect position without altering the load on the heels. In this position, a mark was made on the wall and height was recorded with a measuring tape. Two consecutive measurements were taken.

Body Mass Index (BMI)

The BMI is a convenient and valid measure of adiposity.

It is computed as- $\text{BMI (kg/m2)} = \frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$

BMI Cut-offs

Category	BMI
Underweight	<18.5
Normal	18.5-22.9
Overweight	23-24.9
Obese grade I	25-29.9
Obese grade II	30-34.9
Obese grade III	≥ 35

(Asia Pacific Classification 2011).

Biochemical Evaluation and Assay methods

Random, venous blood sample was collected in clean, sterilized vacuum containers and allowed to stand at room temperature for 15 minutes. Serum was immediately separated and stored at -80^{0}C until analysis. The sample was then analysed for CBC, hs-CRP, TNF α, Interleukin 6 and leptin using standardized kits.

hs-CRP

hs-CRP was estimated using Nephelometry technology. This technology is popularly used for quantification of immunoglobulin concentration in the sera of patients. During reaction, antigen-antibody complexes are generated in solution which is then quantified with the aid of a light beam. The light when incident on the immune complex, is scattered, which is captured by lens fitted at right angles to the incident light. This scattered light is then measured to determine concentration of the analyte of interest. The analyzer which works under this principle is BN II [Siemens].

Determination of TNF α, Leptin and IL-6

TNF α, IL6 and Leptin were determined using HMHMAG-34K- MILLIPLEX MAP Metabolic Hormone Magnetic Bead Panel procured from Mehta Sales Chemie (Vadodara) manufactured by a USA based company millipore.

Enumeration of Bifidobacteria

Gut microflora with respect to Bifidobacteria was analysed in a sub sample of 20 using the standard technique by FAO/WHO, 1979, using selective media for *bifidobacteria* and gas packs procured from hi media laboratories, Mumbai, under anaerobic conditions.[15]

RESULTS

Most subjects under study were females who were highly educated, belonged to the age group of 20-35 years, led a sedentary life and were in grade I obesity category. More than half of the subjects consumed prebiotic and probiotic rich foods and antioxidant rich foods less frequently (table1).

The mean BMI of the subjects was 28.58 kg/m^2. The mean Leptin, TNF α, IL6 were all within the normal range. However, their mean hs-CRP level was 2.67 which was in the moderate risk category.

Table 1: Mean levels of anthropometric scores, PAL scores, frequency scores for intake of pebiotic and probiotic foods, inflammatory markers, bifidobacteria counts and hematology profile of obese subjects under study

Parameters	Obese sedentary (n=84)
Height (cms)	158.11±7.90
Weight (cms)	71.42±8.53
BMI (kg/m^2) Mean±SD	28.58±2.511
MET Minutes Mean±SD	213.80±201.00
Prebiotic and Probiotic rich foods (frequency intake scores) max=50	30.87±6.23
Antioxidant rich foods (frequency intake scores) max=71	44.57±9.40
hs-CRP (mg/l)	2.67±2.53
LEPTIN (pg/ml)	11359.06± 6783.14
TNF α (pg/ml)	7.94±11.00
IL6 (pg/ml)	18.97±13.90
Fecal Bifidobacteria $\log_{10}$ values (CFU/g)	5.71±0.38

As seen in Table 2, intervention with 10 ml of Liquid FOS daily for a period of 30 days to sedentary obese subjects brought about a significant reduction in the hs-CRP levels by 17.24% along with a significant rise in the Bifidobacteria counts by 4.94%. A non-significant reduction was seen in TNF α, Leptin and IL6 values.

Table 2: Effect of FOS supplementation to sedentary obese subjects on Inflammatory markers, Bifidobacteria counts and blood counts

Parameters		Control (N=41)	Experimental (N=41)	Student t
hs-CRP (mg/L)	Pre Post Paired t test % difference	3.07±2.80 2.93±2.73 0.198 NS *(p-0.845)* ↓4.56%	2.61±2.67 2.16±2.18 2.152* *(p-0.037)* ↓17.24%	0.00 NS *(p-0.979)* 1.328 NS *(p-0.252)*
TNFα (pg/mL)	Pre Post Paired t test % difference	6.75±3.23 7.74±5.99 0.797 NS *(p-0.433)* ↑14.66%	6.07±2.14 5.82±4.17 0.334 NS *(p-0.740)* ↓4.11%	2.524 NS *(p-0.117)* 2.657 NS *(p-0.108)*
Leptin (pg/mL)	Pre Post Paired t test % difference	10071.33±6315.46 13531.26±7928.92 2.747* *(p-0.011)* ↑34.35%	13146.90±6857.65 12385.35±8215.28 0.495 NS *(p-0.623)* ↓5.79%	0.103 NS *(p-0.750)* 0.000 NS *(p-0.999)*
IL 6 (pg/mL)	Pre Post Paired t test % difference	18.97±13.90 12.53±10.72 0.911 NS (*p* -0.404) ↓33.95	15.10±6.74 10.95±8.07 1.755 NS (p-0.154) ↓27.48	0.342 NS (0.734) 1.25 NS (0.224)
Bifidobacteria $\log_{10}$ (CFU/g)	Pre Post Paired t test % difference	5.89±0.39 5.65±0.29 0.877 NS *(p-0.430)* ↓4.07%	5.66±0.34 5.94±0.16 3.683** *(p-0.003)* ↑4.94%	0.054 NS *(p-0.818)* 1.428 NS *(p-0.248)*

DISCUSSION

The present study showed that obese subject had high serum hs CRP levels prior to supplementation. Adipose tissue functions as an endocrine organ with metabolic activities. Adipose tissue produces and releases a variety of inflammatory factors and adipokines, cytokines and chemokines, which have been implicated as active participants in the development of insulin resistance and cardiovascular disease.[17]

In the present study FOS supplementation led to significant reduction in the hs-CRP levels. Similar findings can be seen in the study conducted by Asemi Z et al in 2014 which showed that synbiotic supplementation for a period of 6 weeks to diabetic patients significantly reduced serum hs CRP levels as compared to the control group.[18] A study conducted by Sheth et al in diabetic subjects of Assam in 2015 showed 25% reduction in hs CRP levels when supplemented with 10ml liquid FOS for a period of 2 months.[19]

The possible mechanism for the significant reduction in inflammatory markers in FOS fed obese subjects could be attributed to protection of the GALT in presence of increased colonization of *bifidobacteria*. Two mechanisms have been understood in the pathophysiology of increased inflammatory markers in obesity. One mechanism is through the production of LPS in the gut and its leakage into systemic circulation causing a low grade inflammation of the vital organs of the body and the other is through the autoimmune response of the body to increased adiposity.

Several studies have shown increased colonisation of *bifidobacteria* and reduced colonisation of enteric pathogens in the gut with FOS supplementation in subjects.[10, 11, 12]

Studies have also shown reduced LPS levels that were significantly associated with BMI of the obese subjects.[20]

Another study conducted by Dehgan P et al in 2014, also showed that oligofructose-enriched inulin supplementation to obese diabetic women for a period of 8 weeks resulted in a significant decrease in the IL-6 and TNF α levels.[21] In the present study, TNFα levels decreased but the reduction was not significant. This could be because of lower grade of obesity in the subjects under study. Low-grade chronic inflammation characterized by a two- to threefold increase in the systemic concentrations of cytokines such as TNF α, IL-6 and CRP may be seen in subjects with high grades of obesity. A predominant factor in this correlation is due to the autoimmune response triggered by adiposity, whereby immune cells may mistake fatty deposits for intruders. The body attacks fat similar to bacteria and fungi. When expanded fat cells leak or break open, macrophages mobilize to clean up and get embedded into the adipose tissue, followed by release of inflammatory

chemicals, including TNF α and IL-6. TNF α whose primary role is to regulate the immune cells and induce inflammation. White blood cells then assist by releasing more cytokines. This link between adiposity and inflammation has been shown to produce 10-35% of IL-6 in a resting individual, and this production increases with increasing adiposity.[4]

Synbiotic therapy for inflammatory bowel diseases produces mixed results. OF-enriched in combination with Bifidobacterium longum improved markers of inflammation in patients with active ulcerative colitis, such as decreases in TNF α, IL-1a mRNA levels in mucosal tissue and decreased C-reactive protein levels in the blood.[22]

We can thus conclude that mild obesity (BMI -28) is a beginning of the onset of increase in the inflammatory markers such as TNF-α, IL6 and leptin, Hs CRP remains a more sensitive marker for low grade inflammation in the obese individuals and 10g liquid FOS supplementation to these subjects although lowered the four inflammatory markers, a significant reduction could be seen only in hs CRP marker. Hence daily intake of 10g of FOS can be recommended in obese individuals to lower the most sensitive inflammatory marker.

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