

## EFFECT OF NATURO FRUIT BARS ON BLOOD GLUCOSE LEVELS IN PATIENTS WITH TYPE-II DIABETES MELLITUS

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### ABSTRACT

The effect of Naturo Fruit Bars in altering metabolic parameters in type-2 diabetes was tested in a randomized open-label clinical trial on healthy volunteers and type-2 diabetics. To determine the safety of the fruit bars, 13 healthy volunteers and 10 type-2 diabetics were administered with 2, 3, 4 fruit bars on day 0, 7 and 14 and blood glucose levels were determined at time 'zero' and two hours after consumption. In the efficacy study 18 type-2 diabetics consumed two bars of apple flavor without added sugar per day for 12 weeks. Blood glucose, insulin, hemoglobin A1C, lipid profile and adiposity were determined on day zero and at the end of study. Results of the safety study indicated that consumption of 2, 3 or 4 fruit bars did not elevate blood glucose levels in both healthy and type-2 diabetes subjects. Consumption of two bars per day for 12 weeks in type-2 diabetics did not increase the blood glucose levels. The levels of cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and Body Mass Index did not alter. Consumption of Naturo fruit bars did not increase the blood glucose levels and thus can be used as a substitute for healthy food in type-2 diabetics without any undesirable effects.

**Keywords:** Naturo Fruit Bar, post-prandial blood glucose, lipid profile, insulin, HbA1C

## INTRODUCTION

Diabetes mellitus is a metabolic disorder and its prevalence is an important global health problem (King *et al.*, 1998). In 1985 an estimated 30 million people world-wide had diabetes, and in 2010, there were 285 million cases. This number is projected to increase to about 439 million by 2030 (Shaw *et al.*, 2010). The prevalence of diabetes is higher in developed countries than in developing countries, but the incidence of diabetes in developing countries is likely to increase at a higher rate (Mohan V *et al.*, 2010). Increased urbanization, economic development and job related sedentary habits in developing countries are likely the contributory factors for the expected rise in the cases of diabetes (Wasir JS and Misra A, 2004).

In recent years, several nutritional supplements specifically designed for diabetic patients have been commercialized, which are unlikely to increase the post-prandial blood glucose levels compared to glucose or high glycemic foods (Fix *et al.*, 2000). Liquid nutritional supplements (*e.g.* Glucerna) have been shown to reduce the post-prandial blood glucose levels in diabetes patients (Gonza'lez-Ortiz M *et al.*, 2000). Many snacks/bars are available as nutritional supplements for diabetic subjects, but their effect on blood glucose levels, insulin secretion and glycated hemoglobin (HbA1C) and lipid profile in diabetes has not been examined systematically. The aim of the present study was to investigate the effect of chronic administration of Naturo fruit bars (manufactured by Naturo Food and Fruit products Private Ltd, Bangalore, India) on metabolic parameters in patients with type-2 Diabetes mellitus. Earlier we determined the Glycemic Index (GI) value of Naturo fruit bar (apple flavor) and found it to be 38.50 [Reddy KK *et al.*, 2009]. There are very limited supplements available in India to cater to the needs of the increasing number of diabetes

population, who are concerned and selective in taking appropriate snacks. It is anticipated that NFB are likely to serve as a healthy food choice for diabetic population in India.

## MATERIALS AND METHODS

### Investigational Product

Naturo fruit bars (Photo slide 1) were prepared from fresh fruits by a unique process without any artificial additives and available in different flavors (Apple, Mango, Pineapple and Guava) containing with or without added sugars. The present study is focused on the Naturo Fruit bar, apple flavor without added sugars. Nutritional information of the Naturo fruit bar (apple flavor): Serving size: one fruit bar (20 g): calories (65.48 KCal), protein (0.35 g), carbohydrate (15.73 g), sugar (13.48 g), total fat (0.15 g), saturated fat (0.0004 g), dietary fiber (1.55 g), sodium (10 mg), potassium (120.92 mg), calcium (0.21 mg), Iron (0.91 mg), vitamin C (2.4 mg) and vitamin A (43.51 IU). In view of low carbohydrate, fat and sugar content, but enriched with fiber and protein, the NFB can be considered as a substitute for healthy food in type-2 diabetic patients.

### Study design

A randomized open-label, clinical trial was carried out on normal healthy volunteers and type-2 diabetic patients at Sugan Life Sciences Pvt Ltd, Tirupati, India. The protocol for the study was adhered to Good Clinical Practice (GCP) guidelines and followed the recommendations of the World Medical Association Declaration of Helsinki. The study protocol was approved by an Independent Ethics Committee (IEC) of Snehil Hospitals, Bombay, India. Informed Consent Form (ICF) was obtained from all healthy volunteers and diabetes patients and all subjects were closely monitored and recorded for any adverse events throughout the study.

### Photo Slide 1: Displaying the market available Naturo Fruit Bars



#### Subject selection parameters

The clinical trial was initiated to assess the safety in healthy volunteers and diabetic patients followed by efficacy study in diabetic subjects only. In safety study, dose escalation and the safety of the NFB was determined in 13 adult healthy volunteers and 10 adult type-2 diabetes subjects. In efficacy study, NFB was administered for 12 weeks in 18 type 2 diabetics to monitor the levels of blood glucose, insulin, HbA1C and lipid profile. There were no drop-outs in the present study.

The age range of the subjects in the present study is 30–70 years. Both healthy volunteers and type-2 diabetes subjects were non-obese ( $BMI < 25 \text{ kg/m}^2$ ), non-smoking and non-alcoholic. All the healthy volunteers were in good health, as determined by medical history and physical examination; no history of hypertension, hepatic and renal disease, coronary artery disease, and or type-1 or 2 Diabetes mellitus was reported. The inclusion criteria for diabetic subjects were those taking standard medication of Oral Hypoglycemic Agents (OHA) advised by the physician for the past three months, whose fasting blood glucose levels are maintained in the range of 100–120 mg/dL and otherwise normal in other clinical and laboratory parameters. The exclusion criteria: Diabetic patients currently under treatment for heart disease, cancer, post-surgery patients, tuberculosis and other chronic diseases, subjects who are bedridden for chronic diseases for prolonged time and kidney diseases, users of drugs which exert

intoxication and pregnant women. The duration of diabetes in the study subjects was between 3–7 years. During the study period the subjects were given clear instructions by the physician not to deviate from their regular drug intake, diet regime and physical exercise. Throughout the study, principal investigator and clinical research coordinator have monitored the subjects at regular intervals for any events.

Weight and height were recorded with the subjects wearing light clothing without shoes. Height was measured and rounded off to the nearest centimeter, with the subjects standing in erect posture. Body Mass Index (BMI) was calculated as weight in kg divided by the height in meter square. Waist girth was measured at the level of umbilicus with person breathing silently and hip measured as standing inter-trochanteric girth according to the method specified by Weiner and Lourie (Weiner JS and Lourie JA *et al.*, 1981). Waist Hip Ratio (WHR) was calculated from the circumferences of waist and hip. Systolic and diastolic pressures were considered in Korotkoff phase I and V respectively as specified by Rose *et al.*, (Rose GA *et al.*, 1982). Diabetic subjects were requested to withdraw drug intake prior to blood sample collection. Fasting (11h) venous blood collected from the patients was allowed to clot for 30 min at room temperature and then centrifuged. The resulting plasma was separated into two aliquots. The first aliquot was used for the measurement of glucose, total cholesterol, high-density lipoproteins (HDL), triglycerides and HbA1C. Low-density lipoprotein cholesterol was calculated

according to the Friedwald *et al.*, (1982) formula (total cholesterol- HDLC/5 + TG). The second aliquot was frozen at  $-20^{\circ}\text{C}$  and processed within 30 days for the estimation of insulin by radioimmunoassay method with an intra- and inter-assay coefficient of variation of  $<4.4$  and  $6.9\%$  respectively. Blood glucose was determined by the glucose-oxidase method with an intra- and inter-assay coefficient of variation of  $<1\%$ . Serum lipid levels (total cholesterol, HDL cholesterol and triglycerides) and HbA1C were measured by enzymatic methods with an intra- and inter-assay coefficient of variation of  $<3\%$ . The HDL cholesterol was estimated after selective precipitation of non-HDL fractions.

In the safety study, all the subjects consumed an iso-caloric diet (69 Kcal, 15 g of carbohydrate, 1.2 g of protein, 0.2 g of total fat) through the personal substitution by the investigators on scheduled visit to the clinic (day 0, 7 and day 14). After the withdrawal of first blood sample, an iso-calorie diet was provided to all the subjects apart from Naturo fruit bars. Subjects were provided with 2, 3, 4 Naturo fruit bars on day 0, 7, 14 respectively (one time supplementation) and allowed to consume the bars in the clinic itself after taking the breakfast, under the supervision of the physician. To ascertain the safety of the NFB we conducted dose escalation study of fruit bars initially in the healthy volunteers followed by the type-II diabetes subjects. After the intake of fruit bars the subjects stayed in the clinic and were under the supervision of the physician and the blood was withdrawn after two hours of consumption of NFB. In addition these volunteers did not report any adverse effects after completion of the short-term study. Blood samples were drawn (fasting) and after two hours upon consumption of Naturo fruit bars for the estimation of glucose levels. In the efficacy study, 18 adult type-2 diabetes patients were recruited and instructed to consume two NFB / day for 12 weeks. The protocol adopted for efficacy study is same as in safety study. In the diabetes patients (safety study), post-prandial blood sugar levels (Table-2) were reduced after the consumption of two Naturo

fruit bars. But the consumption of three and four bars moderately elevated the post-prandial blood sugar. This allowed us to select two fruit bars for efficacy study. Fasting and post-prandial blood glucose levels were monitored weekly. On day 'zero' and on 12th week, fasting and post-prandial blood glucose, lipid profile (Cholesterol, HDL-Cholesterol, and Triglycerides), HbA1C and insulin levels were determined. Blood pressure, pulse rate, overall and abdominal obesity were recorded.

### Analysis

Statistical analysis was performed using the statistical package (SPSS) version 16.0. Sample size was calculated using a clinical trial formula as described (Jayeseelan L and Rao PSS, 1989). Utilizing a standard deviation of 0.7, a sample size of 18 subjects was chosen to detect the effect with 80% power and a two-sided significance level of 5% was adopted. Initially the data was subjected to normality distribution. In descriptive statistics, results were expressed as mean  $\pm$  SD unless otherwise specified. One-way analysis of variance (ANOVA) and student's 't' test was applied where necessary.

### RESULTS

The demographic and metabolic variables for the safety study are shown in table-1 for healthy volunteers and diabetes patients. As shown in table-1 no significant difference was observed in the overall obesity between healthy volunteers compared to type-2 diabetic patients, however, a significant difference was observed in abdominal obesity ( $p < 0.05$ ). Mean systolic blood pressure was higher in diabetes patients ( $118.45 \pm 6.82$  vs  $113.11 \pm 10.28$ ). Mean total cholesterol ( $163.70 \pm 27.93$  vs  $181.03 \pm 23.49$ ) and LDL cholesterol ( $101.45 \pm 28.67$  vs  $117.23 \pm 20.92$ ) were lower in diabetic patients when compared to healthy volunteers with no change in triglycerides and HDL cholesterol and there were no adverse events throughout the study. These results indicate that all the subjects, both healthy volunteers and diabetes patients, have similar overall metabolic profiles.

**Table.1 Demographic and metabolic profile of the study subjects (data as Mean  $\pm$  SD)**

Characteristic value	Healthy volunteers (N=13)	Type-II Diabetics (N=10)
Age (years)	37.28 $\pm$ 7.16	45.80 $\pm$ 5.27
Body Mass Index (Kg)	20.85 $\pm$ 2.30	20.92 $\pm$ 2.60
Waist Hip Ratio (WHR)	0.848 $\pm$ 0.06	0.890 $\pm$ 0.04*
Systolic blood pressure	113.11 $\pm$ 10.28	118.45 $\pm$ 6.82
Diastolic blood pressure	78.03 $\pm$ 5.67	78.95 $\pm$ 5.23
Pulse rate	69.97 $\pm$ 4.91	70.80 $\pm$ 4.66
Total cholesterol	181.03 $\pm$ 23.49	163.70 $\pm$ 27.93
HDL cholesterol	41.58 $\pm$ 5.68	42.50 $\pm$ 4.77
LDL cholesterol	117.23 $\pm$ 20.92	101.45 $\pm$ 28.67
Triglycerides	119.76 $\pm$ 38.93	126.95 $\pm$ 44.26

\*p&lt;0.05

Changes in the post-prandial blood glucose levels upon the consumption of NFB in both healthy and diabetic subjects were shown in table-2. These results show that consumption of two NFB decreased the post-prandial blood glucose ( $P < 0.0001$ ) in diabetic subjects. Further, administration of 3 and 4 NFB bars moderately elevated the post-prandial glucose; however this elevation did not increase the base-line post-prandial glucose levels in diabetic subjects. In healthy volunteers the consumption of two NFB decreased the blood

glucose. Subsequent administration of 3 and 4 fruit bars showed an elevation from the base line glucose levels with some fluctuations in healthy volunteers. Overall, the F-values indicate that the fluctuation in post-prandial blood glucose levels from the base line values is significant in both healthy and diabetic subjects. Because two fruit bars were preferred by a majority of the subjects, this dose was chosen for the efficacy study (12-week) in type-2 diabetes patients.

**Table.2 Mean values of fasting and post-prandial blood glucose levels in healthy and diabetic subjects (data as Mean  $\pm$  S.D)**

	Healthy Volunteers (N=13)	Type II Diabetes (N=10)
Fasting	74.0 $\pm$ 10.6	117.2 $\pm$ 8.5
Postprandial (2hrs) after test glucose:	96.3 $\pm$ 14.2*	145.1 $\pm$ 9.1*
2 NFBs	91.9 $\pm$ 13.0*	126.1 $\pm$ 9.0
3 NFBs	95.3 $\pm$ 11.3*	129.0 $\pm$ 7.4
4 NFBs	99.0 $\pm$ 14.3*	131.6 $\pm$ 6.4*

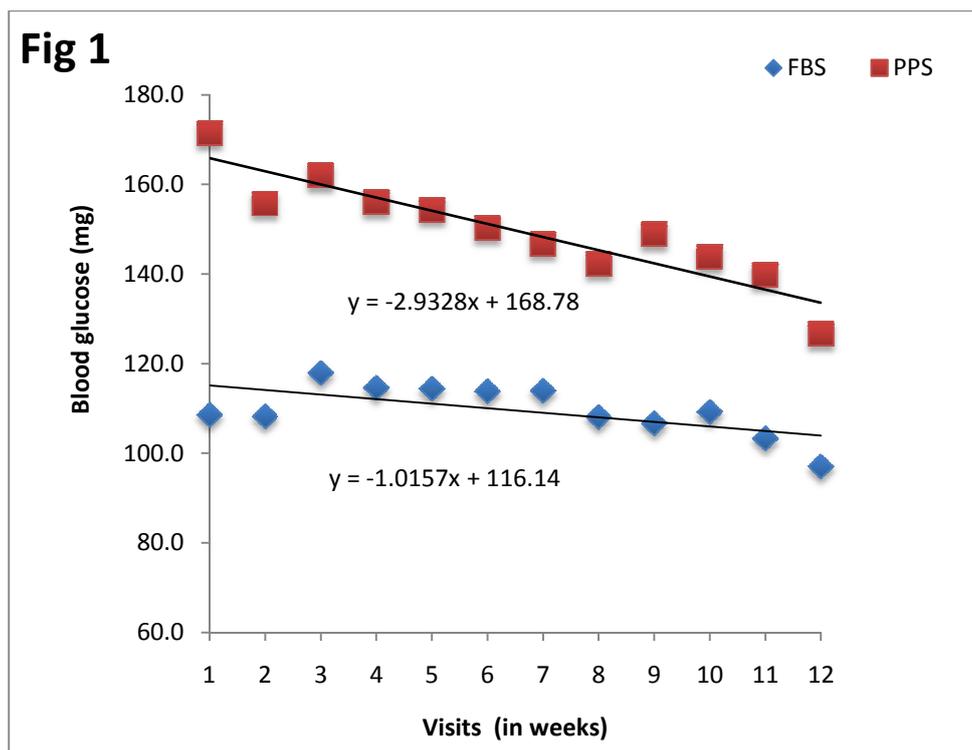
\*F value for post-prandial blood glucose in healthy subjects=7.60;  $P < 0.05$ \*F value for post-prandial blood glucose in diabetic subjects=15.44;  $p < 0.05$

Mean differences for overall and abdominal obesity as well as on blood pressure did not show significant variation between day ‘zero’ and at the end of the 12-week study. Significant ( $p < 0.05$ ) reduction in fasting blood glucose levels from day ‘zero’ to 12 weeks was observed in type-2 diabetes patients. There was a decrease in HbA1C ( $p < 0.11$ ) and an increase in insulin levels between day ‘zero’ and towards the end of the study ( $p < 0.08$ ). The extremities in mean difference (95 % CI) with altered S.E failed to show significant difference for HbA1C and insulin between day ‘zero’ and at the end of the study. Similarly, there was no significant changes in lipid profile (Cholesterol, HDL-cholesterol, LDL-cholesterol and

triglycerides) in the subjects following the consumption of two fruit bars for 12 weeks.

Alterations in blood glucose levels in type-2 diabetes subjects upon consumption of two NFB for twelve weeks are shown in Fig.1. A gradual decrease in both fasting and post-prandial blood glucose levels was observed in diabetic patients upon consumption of NFB. Overall these results indicate that the window between the fasting and post-prandial glucose levels decreased from day ‘zero’ to 12th week ( $p < 0.05$ ). In order to attain the linear growth rate for both fasting blood sugar (FBS) and post-prandial (PPBS) a regression line is fitted and observed that the rate of decrease for FBS is  $-0.7$  and for PPBS it is  $-2.0$ .

**Figure 1: Alterations in blood glucose levels in type-2 diabetes patients administered with Naturo Fruit Bars for twelve weeks**



Changes in the levels of fasting and post-prandial blood glucose levels in type-2 diabetes patients administered with two Naturo fruit bars for a period of 12 weeks. Each point in the graph represents mean values observed on every week. One-way analysis of variance was applied to find out the changes in fasting blood glucose (F-value = 2.252;  $P < 0.01$ ) and post-prandial blood glucose (F-value = 4.109;  $P < 0.001$ ). The regression equation is specified for FBS and PPBS separately. Linear Growth Rate  $\{(\hat{X}/\bar{X}) * 100\}$  for FBS =  $-0.7$  and for PPBS =  $-2.0$

## DISCUSSION

Since prevalence of type-2 diabetes mellitus is increasing, offering nutritional supplements that improve glycemic control without any adverse effects is critical in the long-term management of diabetes patients. In the present study, the safety of NFB consumption in type-2 diabetes patients was evaluated in a well-controlled clinical trial. No adverse events were recorded throughout the study.

The results presented in the safety study demonstrate that, consumption of two/three/four NFB did not increase the post-prandial blood glucose levels in healthy volunteers and diabetes subjects. Based on the results of the safety study, an efficacy study over a period of 12 weeks (two fruit bars/day) was performed. The objective of this study was to determine whether consumption of NFB for longer periods of time has any effect on blood glucose levels and metabolic profile in type-2 diabetes patients. In addition, this study allowed us to monitor for any adverse effects and changes in key biochemical parameters.

The results of the long-term study demonstrate that consumption of two NFB everyday over a period of 12 weeks did not increase the blood glucose levels and has no adverse effects in type-2 Diabetes mellitus patients. Interestingly, NFB produced a significant decrease in both fasting and post-prandial blood glucose levels after 12 weeks of consumption compared to day 'zero' (Fig.1). These results are in agreement with earlier studies by González-Ortiz *et al.*, 2006, that nutritional supplements containing carbohydrates of low glycemic value has decreased the post-prandial blood glucose. In our earlier studies the GI value of NFB (apple flavor) was found to be 38.50 (Reddy KK *et al.*, 2009). Peters *et al.*, 1992 showed that Glucerna (70 g carbohydrates/L) in type-1 diabetes patients produced a decrease in basal glucose in comparison with Enrich and Ensure HN supplements, which contain 146 and 141 g of carbohydrates/L respectively. Similarly, Tsai *et al.*, 1987 in their study shown that the

supplementation of 10 g of soy polysaccharides (low GI value) showed a diminished post-prandial glucose with no change in insulin in type-2 diabetes patients. The carbohydrate content of the Naturo fruit bar (15.73 g) was relatively lower when compared to HN supplements, which could be a key determinant in altering post-prandial glucose levels.

A study (Jayagopal *et al.*, 2002) showed that nutritional supplementation of soy protein (containing 132 mg/day isoflavones) reduced post-prandial glucose in post-menopausal women with type-2 diabetes. Similar to this study we also observed decreased post-prandial blood glucose in diabetic patients consuming Naturo fruit bars for 12 weeks. However, we observed no significant decrease in HbA1C levels. Future studies with large population size may explain the significance of this observation.

Previous studies of González-Ortiz *et al.*, (2006) using Glucerna-SR showed that administration of 75 g of glucose decreased the blood glucose and insulin concentration in addition to the total insulin secretion with an increment in the insulin sensitivity in healthy volunteers. The results from our study are in agreement with the above studies, in that a 12-week supplementation of a Naturo fruit bar (containing 15.73 g of carbohydrate, 65.48 calories and 1.55 g of dietary fiber) reduced the fasting and post-prandial blood glucose levels ( $p < 0.05$ ). Nutritional supplementation with 28 % dietary fiber has been shown to reduce total cholesterol and LDL levels (Brown L *et al.*, 1999). In the present study, supplementation of NFB did not affect blood lipids (Cholesterol, HDL cholesterol, LDL cholesterol and Triglycerides) and obesity in type-2 diabetes patients. It is possible that intake of NFB for longer-term (more than 12 weeks) may have some influence on insulin and HbA1C.

## CONCLUSION

In conclusion, the study demonstrates that consumption of NFB (Apple flavor without added sugar) does not increase blood glucose

levels and may have beneficial effects and may be used as a substitute for healthy food in type-2 diabetes patients without any side-effects. We hope that studies like this on indigenously developed products would offer high benefit to the increasing number of diabetes patients (~40 million) in India.

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