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Is there any place for resistant starch, as alimentary prebiotic, for patients with type 2 diabetes?

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Highlights

- Resistant Starch type II can decrease glycated hemoglobin in patients with type 2 diabetes
- Resistant Starch type II can reduce serum levels of TNF-α in patients with type 2 diabetes
- Resistant Starch type II can improve lipid profile in patients with type 2 diabetes

Abstract

Objective: The aim of the present study was to determine effects of Resistant Starch (RS2) on metabolic parameters and inflammation in women with type 2 diabetes (T2DM).

Methods: In this randomized controlled clinical trial, 60 females with T2DM were divided into intervention (n=28) and placebo groups (n=32). They received 10g/d RS2 or placebo for 8 weeks, respectively. Fasting blood sugar (FBS), glycated hemoglobin (HbA1c), lipid profile, high-sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were measured at baseline and at the end of the trial. Paired *t* test, unpaired *t*-test and ANCOVA were used to compare the quantitative variables. The data were analyzed using SPSS software version 13.0.

Results: RS2 decreased HbA1c (-0.3%, -3.2%), TNF-α (-3.4 pg/mL, -18.8%), triglyceride (-33.4 mg/dL, -15.4%), and it increased HDL-c (+9.4 mg/dL, +24.6%) significantly compared with the placebo group ($p<0.05$). Changes in FBS, total cholesterol, low-density lipoprotein, hs-CRP and IL-6 were not significant in the RS2 group compared with the control group. RS2 can improve glycemic status, inflammatory markers and lipid profile in women with T2DM.

Conclusions: Although findings of the present study indicated positive effects of RS2 on inflammation and metabolic parameters, more studies are needed to confirm efficacy of RS2 as an adjunct therapy in diabetes.

Key words: Inflammation, Lipid profile, Resistant starch, Type 2 diabetes.

Introduction

Inflammation is one of the main mechanisms in the development of diabetes mellitus (T2DM). Increased proinflammatory factors, including Interleukin-6 (IL-6), Tumor necrosis factor-alpha (TNF-α) and high-sensitivity C-reactive protein (hs-CRP), play important roles in beta cell dysfunction and insulin resistance. Moreover, inflammation is a linkage between T2DM and other metabolic dysfunctions such as lipid disorders and increased oxidative stress which trigger diabetes complications [1]. Recently, the roles of intestinal microbiota in inflammation and metabolic dysfunction have attracted a great deal of attention [2].

Resistant Starch (RS) is a kind of starch which escapes digestion in the stomach and small intestine. RS is fermented and utilized by the microbiota in the large intestine [3]. RS is classified into five subtypes (RS1-RS5) [4]. RS2, also known as high-amylose maize starch, is uncooked starch that has a B- or C-type polymorph [5]. High-amylose maize starch (Hi-Maize) is the best-characterized type of RS. It is naturally found in raw potato, green banana, some legumes and high amylose starches. RS2 passes undigested to the large intestine where it can be used as a substrate for microbial fermentation [6]. Colonic fermentation results in raising some bacterial growth including Lactobacilli bacteria and Bifidobacteriaceae family which have anti-inflammatory properties [6,7]. Short chain fatty acids (SCFAs) such as butyrate, propionate and acetate are other productsof fermentation. Butyrate is the main SCFA which is produced from RS fermentation and it acts as an anti-inflammatory factor. Moreover, RS can produce more butyrate compared with other prebiotics [7- 9]. Due to its aforementioned characteristics, RS can be considered as a prebiotic [2].

Fiber intake among Iranian subjects with diabetes mellitus is lower (16.7 g/d) than the recommended fiber intake for patients with diabetes (20-35 g/d) [10]. It seems that RS can be

proposed as a dietary fiber supplement with prebiotic properties for T2DM. There are limited studies with diverse results on the effects of resistant starch on biochemical parameters [11-14]. Nilson et al indicated that supplementation with barley-kernel bread reduced IL-6 level in healthy individuals [15]. Conversely, Johnson et al reported that RS2 did not change inflammatory markers in patients with metabolic syndrome [12]. Mitra et al indicated that consumption of rice containing RS2 in patients with T2DM decreased fasting glucose level after 3 months [16]. Conversely, based on Penn et al. study 12 g/d High-maize™ 260 did not change FBS and insulin in subjects at risk of diabetes after 14 weeks [17]. Due to the limited number of studies and their inconsistent results, it is difficult to make conclusions about the effects of RS2 on inflammation and metabolic parameters. Therefore, the aim of the present study was to determine the effects of supplementation with RS2 on glucose levels, lipid concentrations and inflammatory parameters in women with T2DM.

Materials and Methods

Patients

In this triple-blind randomized controlled clinical trial, volunteer women with T2DM (n=60; aged 30-65 yrs) were recruited from Iran Diabetes Society and Endocrinology Clinics in Tabriz University of Medical Sciences. They were collected from December 2011 through February 2012. Inclusion criteria were as follow: having T2DM (fasting blood sugar≥126 mg/dL) for more than six months, taking common anti-diabetic medications, and having Body Mass Index (BMI) ≥25 kg/m^2. Patients were excluded if they had history of gastrointestinal, cardiovascular, renal, thyroid, liver, or pancreatic diseases; if they were pregnant, smokers, lactating, consuming prebiotics/ probiotics products (two weeks prior to the intervention and during the intervention), and taking antibiotics, antacids, alcohol, anti-diarrheal, anti-inflammatory, lipid-lowering or laxatives drugs; and if they had typical fiber intake of >30g/d. At the beginning of

the study, general characteristic including age, medication history, and diabetes duration (in years) were collected, using a questionnaire. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences and written informed consent was obtained from each patient. The present study was registered on Iranian registry of clinical trial website (IRCT201110293253N4).

Experimental design

The patients were randomly divided into two groups using a block randomization procedure, based on BMI and age. In every permuted block of patients, four subjects were allocated to each of the two groups. The allocation sequence was randomly generated by random allocation software (RAS). The intervention group received 10 g/day RS2 (Hi-maize 260, National Starch LLC.) and the placebo group received similar amount (10g/day) of maltodextrin as placebo (Jiujiang Hurirong Trade CO., LTD, China) for 8 weeks. Based on the company's report, Hi-maize 260 contains about 60% resistant starch type II.

Both maltodextrin and RS2 were provided for patients in similar opaque packages and they had a similar taste and appearance. Supplements were divided into two packages of 5 g. They were consumed during breakfast and dinner suspended in a cup of water. Supplements were divided among patients based on allocation codes after randomization. Patients received half of the packages at the beginning and the remainder in the middle of the study. To maintain blinding, the allocation and coding of the packages were performed by an investigator who had no clinical involvement in the study while the investigators and statistician remained blind until the end of analysis. In order to minimize the patients' withdrawal and ensure their consumption of the supplements, they received a phone call every week. Throughout the study, the patients were asked to have their usual physical activity and diet. All the collected data were coded for analysis.

The sample size was calculated based on the primary outcome (change in TNF-α), obtained from a pilot study on five subjects. A minimum sample size of 24 was determined for each group by Pocock's formula [18] with a confidence level of 95% and a power of 0.80. To cover an anticipated dropout of 30%, the sample size was increased to 32 per group.

Body weight and dietary intake assessment

Anthropometric indices including body weight and height as well as dietary intake were evaluated at baseline and at the end of the study as explained in the previous study [19].

Biochemical measurements

At baseline and at the end of the study, after an overnight fasting, 10 mL venous blood samples were collected and transferred into two Vacutainer tubes, one of which contained ethylenediamine tetraacetic acid for the measurement of HbA1c while theotherwas used for measurement of fasting blood sugar (FBS), inflammatory biomarkers (hs-CRP, TNF-α IL-6) and lipid profile (total cholesterol (TC), triglyceride (TG) and high-density lipoprotein (HDL-c)). The serum samples were separated from whole blood by centrifugation at 1048G for 10 minutes (Beckman Avanti J-25; Beckman Coulter, Brea, CA) at room temperature. FBS, HbA1c and lipid profile were analyzed on the day of sampling and the remaining serum was stored at -70°C. FBS concentration was measured by the enzymatic method using an autoanalyzer (Abbot Model Aclyon 300, USA) with a kit from Pars-Azmone (Tehran, Iran). HbA1c was determined in whole blood using an automated high-performance liquid chromatography analyzer with commercially available kits (Bio-Rad D-10 Q1Laboratories, Schiltigheim, France). Serum hs-CRP concentration was determined using an immunoturbidimetric assay (Pars Azmoon Co., Tehran, Iran). IL-6 and TNF-α levels were determined using an ELISA kit (Bioscience, San Diego, California).

The levels of serum TC, HDL-c and TG were measured by enzymatic colorimetric methods with a kit (Cholesterol CHOD-PAP and Triglycerides GPO-PAP; Pars-Azmone, IRI) on an automatic analyzer (Abbott, model Alcyon 300,USA). Serum Low-density lipoprotein (LDL-c) was calculated according to the Friedwald equation.

Statistical analysis

The data were analyzed using SPSS software version 13.0. The results were expressed as mean (SD). The normality of the distribution of data was evaluated by the one-sample Kolmogorov-Smirnov test. Unpaired *t* tests (for baseline measurements) and ANCOVA were used to compare quantitative variables after intervention. Paired *t* test was used for comparing the quantitative data at the beginning and at the end of the trial in each group. The hs-CRP analysis was performed after log transformation. The effects of medications used in the two groups were compared using the Mann-Whitney *U* test. Analysis of covariance adjusting for baseline measurements of the primary outcome was used to identify any differences between the two groups after intervention. For calculating the percentage of mean changes of markers, at the beginning and at the end of the study, mean changes of markers from baseline were calculated in each group by [(8 weeks values-baseline values) / baseline values)] × 100. A significant value of $p<0.05$ was considered significant.

Results

Of the 64 patients, 60 completed the trial (n=28 intervention group; n=32 control group; Fig 1). Table 1 shows the baseline characteristics of the patients in the two groups. Initial characteristics were similar at baseline in both groups. The comparisons between the two groups showed that there were no significant differences in anthropometric indices including BMI, waist circumference, hip circumference, waist to hip circumference (Table1) and dietary

intake of macronutrients at the begging and at the end of the study (Table 2). Thus, the effects of the mentioned confounders were controlled. Furthermore, at the begging of study, there were no significant differences in systolic blood pressure and diastolic blood pressure. At the end of the study, we observed significant differences in systolic blood pressure (131.9 (17.3) to 122.4 (11.2)), while diastolic blood pressure remind unchanged. Also, all of the parameters remained unchanged in the maltodextrin group.

Effect of RS2 supplementation on glucose levels and lipid profile

Glycemic status and lipid profile did not differ between the two groups at baseline (Table 3). At the end of the study, there was a significant decrease in HbA1c (-0.3 %, -3.6%), triglyceride (-33.4 mg/dL, -15.4%), and a significant increase in HDL-c (+9.4 mg/dL, +24.6%) compared with the maltodextrin group ($p<0.05$, analysis of covariance adjusted for hs-CRP and baseline values). Reductions in FBS (-7.8 mg/dL, -4.6 %), TC (-20.1 mg/dL, -1.0%) and LDL-c (-17.7 mg/dL, -1.48%) were not significant in the RS2 group compared with the maltodextrin group ($p>0.05$, analysis of covariance adjusted for hs-CRP and baseline values). There was a significant decrease in FBS and a significant increase in HDL-c concentrations in the RS2 group compared with the baseline ($p<0.05$, paired *t* test), while in maltodextrin group they remained unchanged.

Effects of RS2 supplementation on inflammatory parameters

Comparison of the two groups indicated that there were no significant differences in inflammatory markers at baseline (with the exception ofhs-CRP) (Table 4). After 8 weeks, a significant decrease in TNF-α (-3.4 pg/mL, -18.9) was observed in the RS2 group compared with the maltodextrin group (analysis of covariance for baseline values). Reduction in levels of hs-CRP (-4.6ng/mL,-35.9%) and IL-6 (-1.4 pg/mL,-22.6%) was not significant. The

inflammatory biomarkers including IL-6 and TNF-α levels decreased in the RS2 group compared with the baseline (paired *t* test), whilst in the maltodextrin group they remained unchanged.

Discussions

It was previously reported that prebiotics are able to modulate metabolic disorders such as blood glucose homeostasis, lipid profile, oxidative stress and inflammation [19-22]. In this study, we showed that 10g/day RS2 decreased HbA1c, TNF-α and increased HDL-c levels after 8 weeks. Bodinham et al reported that supplementation with 40 g/day RS2 decreased TNF-α levels but had no effects on IL-6 in patients with type 2 diabetes after 12 weeks [23]. Also supplementation with barley-kernel bread (31% of bread)reduced IL-6 levels in healthy individuals [14]. Conversely, Johnson et al reported that 40 g/d type II RS did not change inflammatory markers (IL-6, C-reactive protein and hs-CRP) after 12 weeks in patients with metabolic syndrome [12]. Differences in the dietary intake (RS, macronutrient, total fiber), dose and type of RS**,** basal inflammatory/anti-inflammatory status, duration of intervention, ethnicity and genotype may result in the contrary results. Mechanisms for the effects of RS2 on inflammation are not yet clear. Some potential mechanisms include (1) changes in intestinal microbiota, (2) a reduction in insulin resistance (3) rise in HDL-c concentrations and (4) an increase in SCFAs production. RS can produce SCFAs in two pathways: directly (RS fermentation) or indirectly (increasing colonic butyrate-producing microbiota such as Lachnospiraceae and Ruminococcaceae). Butyrate can control macrophage activity and expression of NF-κB that is a main inflammatory and immune response. Also it can raise the expression of cytokine signaling 3 suppressor (SOCS 3), secretion of IL-10, reduce the expression of pyrogenic factors (e.g., Myeloperoxidase) and IL-12 level [24]. Prebiotics such as RS can decrease inflammatory status via increased mucosal thickness and reduced intestinal

permeability. Moreover, RS can reduce inflammatory parameters via increasing Bifidobacteria and decreasing negative gram bacteria [6]. In the present study, RS decreased some inflammatory markers in patients with T2DM. Changes in intestinal microbiota population contribute to insulin homeostasis and directly influence insulin sensitivity. The modulation in insulin level can improve Kupffer cell functions which decreases inflammatory biomarkers. In this study, reduction in insulin resistance (data were presented in another study) may lead to reduction in inflammatory biomarkers. Moreover, HDL-c plays anti-inflammatory role and is an important factor involved in the elimination of inflammatory factors [25]. In this study, increased level of HDL-c may have led to reduction in inflammatory markers.

Based onthe present results, RS2 decreased HbA1C and increased HDL-c concentrations after 8 weeks. Previous studies indicated contrary results for effects of different types of RS on glycemic status and lipid profile in healthy subjects and T2DM patients [12, 17, 26]. In a study by Maki et al, consumption of 15 and 30 g/d RS2 did not change FBS in overweight and obese men and only an increase ininsulin sensitivity was observed after 4 weeks [13]. Castillo et al reported that consumption of native banana starch supplementation (24 g/d) as a rich source of RS2 for 4 weeks did not affect lipid profile, HbA1c and FBS and insulin resistance in obese T2DM patients [26]. The diversity in results may be due to differences in diet composition, total dietary fiber intake, dietary RS content, source of RS, dose and type of RS supplementation, and the pathologic state of the subjects. Possible mechanisms of RS on glycemic status and lipid profile are as follows: RS can affect the basal expression levels of transcription factors involved in lipogenesis (SREBP-1c) and fatty acid oxidation (PPARα) [27]. Also, RS may improve glycemic status by delaying gastric emptying, slowing the entrance of glucose into the bloodstream, decreasing inpostprandial glucose concentrations, hepatic-muscle glucose transport,causing inflammation and increasing levels of SCFAs [19]. Additionally, through several mechanisms SCFAs can involve in modulation of glycemic

status such as effects on ileocolonic brake, contraction of the ileum and shortened emptying pathway, production of methylmalonyl-CoA and succinyl-CoA, inhibition of gluconeogenesis by pyruvate carboxylase, and reduction inhepatic glucose output via effects on G protein-coupled receptors (GPR)-41 and GPR-43 [21]. Moreover, butyrate can indirectly decrease insulin resistance and glucose levels [28]. In our study, an improvement in glycemic status may be due to reduction in TNF-α levels.

The present study had some limitations including small sample size, fairly short duration of its intervention, as well as no assessment of serum short-chain fatty acids, serum FFA among other inflammatory and anti-inflammatory biomarkers. We also did not evaluate gut and fecal microbial composition.

Conclusions: Supplementation with resistant starch type II can improve inflammatory markers, lipid profile and HbA1c in women with type 2 diabetes. Subjects with type 2 diabetes particularly who intake less than dietary fiber recommendation (14g fiber/ 1000 kcal) are encouraged to consume dietary fiber sources especially prebiotics to improve metabolic factors and prevent from diabetes complications. Due to potential benefits of prebiotic such as RS2, it can be recommended as an adjunct therapy in type 2 diabetes. However, more studies are needed to confirm efficacy of RS on metabolic profile and inflammatory status in subjects with type 2 diabetes.

Conflict of interest: Authors declare no conflict of interest.

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Fig1: Flow chart of the study

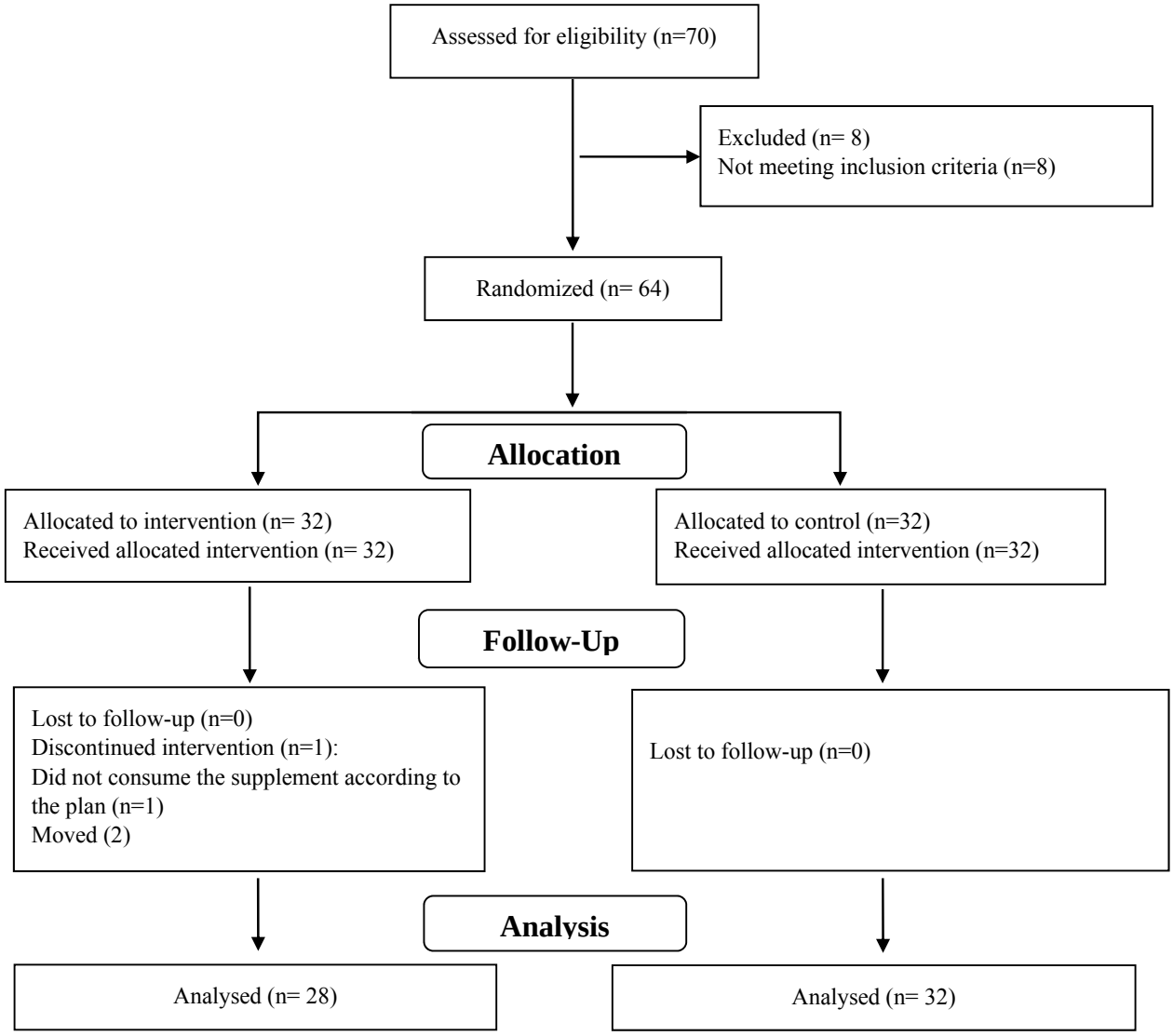

Table 1- Baseline characteristics and dietary intakes of the study participants.

Variables	Maltodextrin group (*n*=32)	Resistant starch group (RS2) (*n*=28)
Age(y) (range)	49.6 (8.4) (34-60)	49.5 (8.0) (33-65)
Menopausal status (n (%))		
Pre- menopausal	9 (36)	8 (28.5)
Post- menopausal	16 (64)	20 (71.5)
Diabetes duration (y)	5.2(4.4)	7.5(5.9)
Weight (kg)	71.8 (3.5)	74.2 (4.3)
Height (cm)	152.6 (6.4)	153.3 (5.2)
Body mass index (kg/m^2)	30.8 (5.2)	31.5 (4.5)
Waist circumference (cm)	99.8 (4.6)	100.5 (10.5)
Hip circumference (cm)	105.9 (13.9)	108.6 (10.7)
Waist to hip circumference (cm)	0.94 (0.07)	0.92 (0.06)
Systolic Blood Pressure (mmHg)	131.8 (15.1)	131.9 (17.3)
Diastolic Blood Pressure (mmHg)	85.6 (7.8)	86.6 (11.5)
Metformin, 500 mg (tablets/d)	2.6 (1.1)	2.8 (1.1)
Glibenclamide, 5 mg (tablets/d)	1.7 (1.2)	2.3 (1.4)

Data are presented as mean (SD), with the exception of menopausal status, which is presented as number (percent).

Table 2- Dietary intakes of patients at baseline and at the end of the study

Variables	Period	Maltodextrin group (*n*=32)	Resistant starch group (RS2) (*n*=28)
Energy (kcal/day)	Initial	1796.2(235.9)	1539.0 (405.6)
	End	1625.3 (331.0)	1500.0 (326.5)
Carbohydrate (g/day)	Initial	194.7 (62.7)	211.4 (74.6)
	End	221.4 (35.3)	211.6 (46.7)
Carbohydrate (%)	Initial	46.7 (6.1)	50.8 (17.9)
	End	54.4 (4.0)	50.9 (11.3)
Protein (g/day)	Initial	51.9 (12.5)	50.9 (12.4)
	End	54.3 (14.6)	51.7 (14.9)
Protein (%)	Initial	13.2 (2.6)	13.1 (3.2)
	End	13.6 (2.0)	13.3 (3.8)
Total fat (g/day)	Initial	53.2 (14.5)	52.1 (18.4)
	End	51.8 (14.9)	57.9 (18.4)
Total fat (%)	Initial	32.9 (4.9)	30.0 (10.9)
	End	31.2 (4.7)	34.5 (10.9)
Dietary fiber (g/day)	Initial	11.6 (3.4)	12.3 (5.0)
	End	14.2 (3.9)	13.7 (4.1)

Data are presented as mean (SD)

Table 3— Changes in glycemic status and lipid profile of patients at baseline and the end of the study.

Variable	Period	Maltodextrin group (n=32)	Resistant starch (RS2) group (n=28)	MD†(95%CI‡) between groups
FPG (mg/dL)	Initial	157.8 (28.6)	170.5 (45.9)	12.7 (- 8. 1 to 33.5)
	End	156.1 (14.2)	151.9 (36.3)	7.8 (-26.5 to 6.9)[#]
	MD†(95% CI‡) within groups	-1.7 (-6.5 to 3.3)	-18.6 (-33.9 to -6.7) [a]	
HbA1c (%)	Initial	8.2 (1.0)	7.9 (1.1)	-0.3 (-0.7 to 0.4)
	End	8.3 (1.0)	7.7 (1.1) [b]	-0.3 (-0.8 to -0.1)[#]
	MD(95% CI) within groups	0.1 (-0.1 to 0.4)	-0.2 (-0.5 to 0.5)	
TG (mg/dL)	Initial	198.5 (63.7)	162.6 (99.3)	-35.9 (-81.2 to 9.40)
	End	216.7 (59.8)	146.5 (63.70)[b]	-33.4 (-56.7 to -10.1) [#]
	MD(95% CI) within groups	21.2 (-9. 8 to 9.4)	-16.1 (10.8 to -27.1)	
TC (mg/dL)	Initial	193.1 (40.0)	188.3 (44.1)	-4.8 (-27.1 to 17.6)
	End	203.1 (45.6)	181.5 (39.1)	-20.1 (-34.7 to 19.1) [#]
	MD(95% CI) within groups	10.2 (-3.2 to 13.6)	-6.8 (-15.9 to 7.5)	
HDL-c (mg/dL)	Initial	38.7 (4.5)	37.3 (10.1)	-1.4 (-6.0 to 3.3)
	End	38.2 (7.1)	45.2 (9.5)[a,b]	9.4 (3.4 to 15.5)[#]
	MD(95% CI) within groups	-0.5 (-1.1 to 4.2)	7.9 (10.8 to 5.0)	
LDL-c (mg/dL)	Initial	111.3 (40.9)	113.6 (41.3)	2.3 (-20.6 to 25.2)
	End	119.1 (41.2)	101.7 (40.8)	-17.7 (-34.4 to 18.9)[#]
	MD(95% CI) within groups	7.8 (-15.5 to 16.9)	-11.9-22.6 to 14.8)	

FPG= Fasting plasma glucose, HbA1c= Glycated hemoglobinA1c, TG= triglyceride, TC= total cholesterol, HDL-c= HDL cholesterol, LDL-c= LDL cholesterol.MD†, mean difference. CI‡, confidence interval. Values are presented as mean (SD). [a]$P<0.05$, paired t test and [b]$P<0.05$ analysis of covariance adjusted for hs-CRP and baselines values. [#] Adjusted for hs-CRP and baselines values with analysis of covariance.

Table 4—Changes in inflammatory biomarkers of patients at baseline and the end of the study.

Variables	Period	Maltodextrin group (n=32)	Resistant starch (RS2) group (n=28)	MD†(95%CI‡) between groups
hs-CRP* (ng/mL)	Initial	12.5 (7.4)	5.5 (2.7)	-7.0 (-10. 5 to 3.5)
	End	12.8 (7.1)	4.9 (2.6)	-4.6 (-3.4 to 1.7) [#]
	MD†(95% CI‡) within groups	0.3 (-0.1 to 1.0)	-0.6 (-2.0 to -0.9)	
TNF-α (pg/mL)	Initial	17.4 (3.9)	17.3 (4.1)	-0.1 (-2.1 to 1.1)
	End	18.1 (3.9)	15.4 (4. 5) [a, b]	-3.4 (-5.2 to -1.3) [#]
	MD(95% CI) within groups	0.7 (-0.2to 1.50)	-1.9 (-3.0 to -1.0)	
IL-6 (pg/mL)	Initial	5.9 (2.1)	5.6 (2.7)	0.3 (-2.5 to 2.4)
	End	6.2 (1.6)	4.8 (1.7) [a]	-1.4 (-2.8 to-0. 1) [#]
	MD(95% CI) within groups	0.3 (-0.2 to 0.8)	-0.8 (-1.2 to -0.1)	

hs-CRP= high-sensitive C reactive protein, IL-6= interleukin-6, TNF-α= tumor necrosis factor-alpha. MD†, mean difference.CI‡, confidence interval. Values are presented as mean (SD). *use log transformation. [a]$P<0.05$, paired t test [b]$P<0.05$ analysis of covariance adjusted for baselines values. [#]Adjusted for baselines values with analysis of covariance.