REDUCTION OF INSULIN RESISTANCE AND PLASMA GLUCOSE LEVEL BY SALSALATE TREATMENT IN PERSONS WITH PREDIABETES

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ABSTRACT

Objective: To evaluate the effect of salsalate as an antiinflammatory agent on insulin resistance and glycemic control in persons with prediabetes.

Methods: In this double-blind, placebo-controlled clinical trial, 66 persons who had prediabetes on the basis of the American Diabetes Association criteria were enrolled. They were randomly assigned to receive salsalate (3 g daily) or placebo for 12 weeks. Fasting plasma glucose (FPG) and insulin, glucose 2 hours after oral administration of 75 g of glucose, hemoglobin A_{1c}, lipid profile, homeostasis model assessment of insulin resistance (HOMA-IR), and homeostasis model assessment of beta-cell function were determined before and after treatment.

Results: Salsalate treatment reduced the FPG level from 5.86 ± 0.07 mmol/L to 5.20 ± 0.11 mmol/L and HOMA-IR from 4.2 ± 0.9 to 3.8 ± 0.3 (P = .01 for both changes). Homeostasis model assessment of beta-cell function increased in the salsalate-treatment group from 139.8 ± 11.0 to 189.4 ± 24.6 (P = .01). At the end of the study, FPG, HOMA-IR, and insulin levels were significantly different between salsalate and placebo groups (5.20 ± 0.11 mmol/L versus 5.53 ± 0.10 mmol/L, 3.8 ± 0.3 versus 4.4 ± 0.9, and 16.1 ± 1.9 μIU/mL versus 18.2 ± 2 μIU/mL, respectively; P<.05 for all). There were no persistent complications after salsalate therapy.

Conclusion: Treatment with salsalate can reduce insulin resistance and the FPG level in subjects with prediabetes. Determination of the long-term safety and efficacy of the use of salsalate necessitates further investigation. **(Endocr Pract. 2012;18:826-833)**

Abbreviations:
A1C = hemoglobin A_{1c}; **BMI** = body mass index; **FPG** = fasting plasma glucose; **HOMA-B** = homeostasis model assessment of beta-cell function; **HOMA-IR** = homeostasis model assessment of insulin resistance; **IFG** = impaired fasting glucose; **IGT** = impaired glucose tolerance; **LDL** = low-density lipoprotein; **NF-κβ** = nuclear factor-κβ; **T2DM** = type 2 diabetes mellitus

INTRODUCTION

The number of patients with prediabetes is increasing worldwide. By the year 2030, the number is expected to increase to 472 million people (1). Prediabetes is associated with increased mortality and morbidity. The available data recommend frequent screening for the diagnosis and possibly early intervention for prediabetes, including changes in lifestyle as well as appropriate pharmacologic treatment if necessary (2).

The progression of prediabetes to type 2 diabetes mellitus (T2DM) results from multiple defects, including resistance to actions of insulin to stimulate glucose transport as well as inadequate secretion of insulin for the specific metabolic state (3).

Mechanisms underlying increased insulin resistance and decreased insulin secretion capacity remain under intense study. A possible link between inflammation and insulin resistance (and perhaps insulin secretion)

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was proposed many years ago (4). Recent data confirm the importance of subclinical inflammation mediated by activation of a serine-threonine kinase cascade—the IκB kinase beta (IKK-β)/nuclear factor-κβ (NF-κβ) pathway—and secreted cytokines as an important contributor to altered insulin action (5). This proposal has led to the investigation of the effects of antiinflammatory agents on glucose homeostasis in patients with T2DM (6).

Salicylates inhibit the activation of NF-κβ and thereby reduce the subacute inflammatory state that is associated with T2DM (6-8). Previous studies have shown that salsalate (a nonacetylated and better tolerated form of salicylic acid) can lower hemoglobin A_{1c} (A1C) levels and improve glycemia in T2DM (9-13). Data on the potential effects of salsalate in reducing insulin resistance and improving glucose homeostasis in the prediabetic state, however, are limited.

This study tested the hypothesis that therapy with salsalate in persons with prediabetes increases their insulin sensitivity, stimulates basal insulin secretion, and thus improves glucose-insulin homeostasis. The study enrolled subjects with prediabetes who also had a first-degree relative with T2DM. Such persons are known to be predisposed to development of T2DM during the subsequent years (3).

PATIENTS AND METHODS

Study Subjects

This was a double-blind, placebo-controlled clinical trial. All study participants had a first-degree relative with T2DM and were recruited from members enrolled in a diabetes prevention project. Participants were 40 to 70 years old, and all had prediabetes according to the American Diabetes Association criteria—namely, impaired fasting glucose (IFG) (fasting plasma glucose [FPG], 5.6 to 6.9 mmol/L) or impaired glucose tolerance (IGT) (2-hour plasma glucose level of 7.8 to 11.0 mmol/L after oral administration of a 75-g glucose load) (or both) (14). Patients with T2DM were excluded. Other exclusion criteria included a history of renal or hepatic dysfunction, cardiovascular disease, a malignant lesion, acute gastritis or gastrointestinal bleeding, psychologic disorders, asthma, tinnitus, and central nervous system disorders. Persons with drug or alcohol abuse or those with aspirin allergy were also excluded from the study, as were pregnant women.

From a total of 230 persons evaluated for eligibility, 110 did not meet the criteria, and the remaining 120 subjects with prediabetes were invited to participate in the study (see the Consolidated Standards of Reporting Trials [CONSORT] diagram in Figure 1). After written informed consent was obtained, an explanatory session was conducted that was focused on diabetes and prediabetes, possible effects and side effects of salsalate, and the project protocol. Sixty-six persons agreed to participate in the study. Participants were randomly assigned to receive salsalate (3 g daily in 2 divided doses, orally administered) or placebo for 12 weeks. Salsalate was supplied by Caraco Pharmaceutical Laboratories (Detroit, Michigan), and placebo was from Alborz Darou Pharmaceutical Company (Tehran, Iran).

Laboratory Tests and Procedures

At baseline, FPG, 2-hour plasma glucose, A1C, insulin, cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, triglycerides, and renal and liver function were measured in all enrolled study subjects. Blood samples were also obtained for these measurements at the end of the study, except for FPG, which was measured monthly during the 12-week follow-up period. Baseline participant characteristics, including height, weight (measured in light clothing and bare feet with use of a Seca scale), and body mass index (BMI), calculated as the weight divided by the square of the height (kg/m^2), were measured. Waist circumference was measured according to a standardized method (15). Blood pressure was measured twice with the patient in the seated position after at least 15 minutes of rest, with a 5-minute interval between the 2 measurements, and with the sphygmomanometer being placed at the level of the heart.

Study participants were instructed to ingest an unrestricted regular diet (containing more than 150 g of carbohydrate daily) and to avoid heavy physical activity for at least 3 days before undergoing laboratory tests. After an overnight fasting period of 10 hours, a standard 75-g oral glucose tolerance test was performed. Plasma glucose and blood lipids were measured by an autoanalyzer (Liasys, Rome, Italy). A1C was measured by a chromatographic-spectrophotometric method (BioSystems SA, Barcelona, Spain). LDL cholesterol was calculated by using the Friedewald formula (16). Insulin was measured by an immunoradiometric assay method (DiaSource Europe SA, Nivelles, Belgium). Homeostasis model assessment of insulin resistance (HOMA-IR), an indirect measure of insulin resistance, was calculated as the product of FPG (mmol/L) and insulin (μIU/mL) divided by 22.5. Homeostasis model assessment of beta-cell function (HOMA-B), an indirect estimate of beta-cell function, was calculated (17) as fasting insulin (μIU/mL) × 20/[FPG (mmol/L) – 3.5].

Statistical Analysis

Statistical analysis was performed by using SPSS software version 13 (SPSS, Inc., Chicago, Illinois). Normality of distribution of the data was assessed with a Kolmogorov-Smirnov test. Because all the descriptive data had a normal distribution, they are expressed as means ± standard error. Unpaired (salsalate versus placebo) and paired (before versus after treatment) Student *t* tests were used. *P* values <.05 were considered statistically significant. Analysis of variance was used to determine whether the changes in plasma glucose levels were the direct effect of salsalate after

adjustment for age, BMI, baseline insulin, 2-hour plasma glucose, and FPG.

The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran. The study was registered in the Iranian Registry of Clinical Trials (IRCT138709011465N1).

RESULTS

Baseline characteristics of the study participants with prediabetes are summarized in Table 1. In this cohort of 66 persons, 29 had isolated IFG, 15 had IGT alone, and 22 met both criteria. On average, they had a BMI of approximately 30.3 kg/m^2, approximate FPG and 2-hour plasma glucose levels of 5.9 mmol/L and 7.5 mmol/L, respectively, and an A1C of 5.3%; there were no significant differences between those randomized to receive placebo versus salsalate treatment.

Placebo Versus Salsalate Group Changes

Fifty-four participants (28 in the placebo group and 26 in the salsalate group) from the original study cohort of

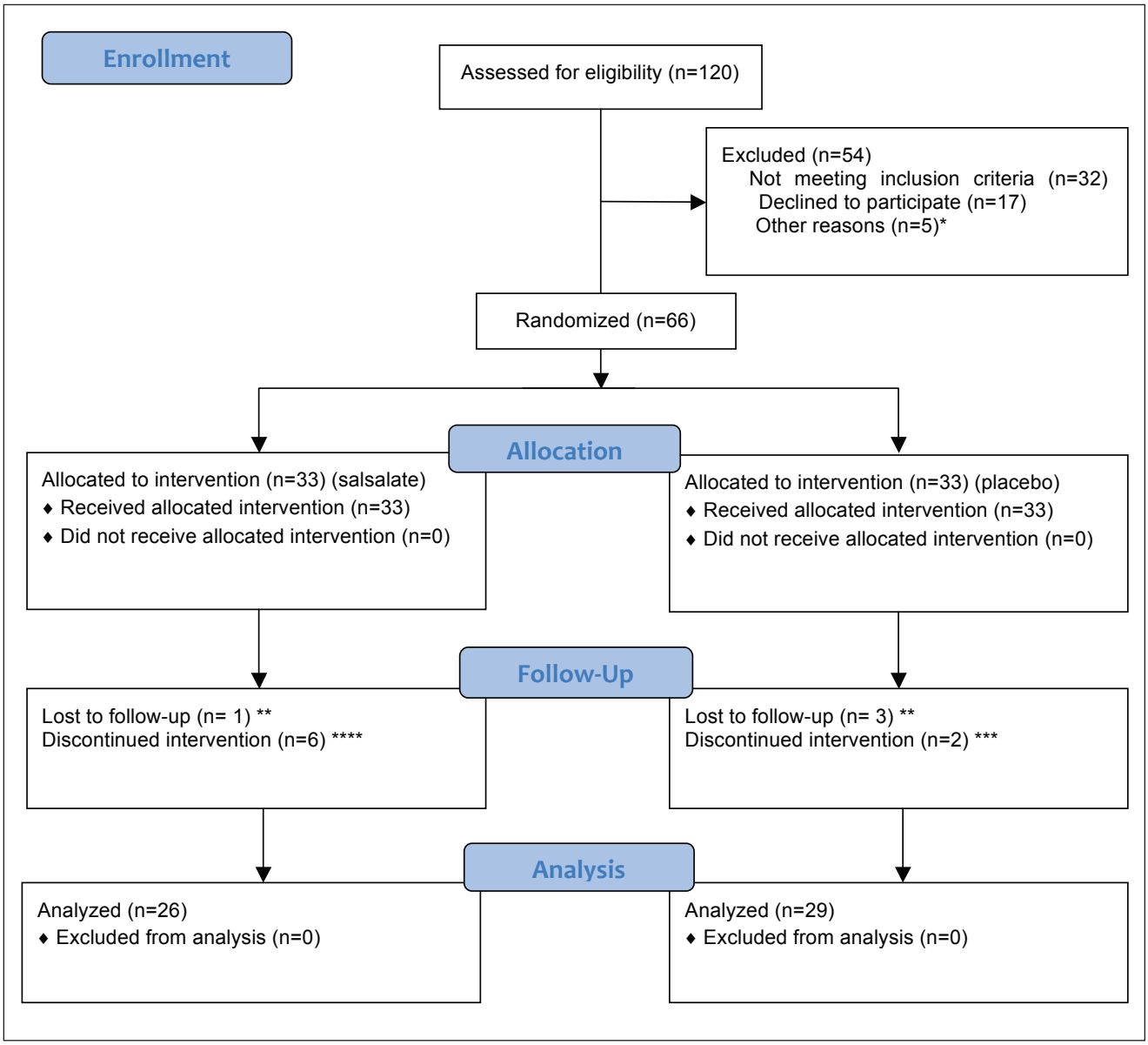

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram, showing disposition of study subjects. *Women who could not begin the study because of some family problems. **Subjects living outside the city who could not undergo the laboratory tests when scheduled. ***Subjects with mild gastrointestinal upset who refused to continue the study. ****Two participants who did not tolerate salsalate because of tinnitus and dizziness, 3 who had macular rash, and 1 who was withdrawn from the study because of severe gastrointestinal upset, including nausea, vomiting, and flatulence.

Table 1
Baseline Characteristics of Study Participants at Enrollment[a]

Variable	Salsalate (n = 33)	Placebo (n = 33)	*P* value
Age (y)	47.5 ± 0.8	48.3 ± 0.9	NS
Waist (cm)	95.5 ± 1.9	90.9 ± 1.6	NS
Body mass index (kg/m^2)	30.6 ± 0.6	29.8 ± 0.7	NS
Blood pressure (mm Hg)			
Systolic	124.5 ± 2.5	121.1 ± 2.4	NS
Diastolic	80.9 ± 1.9	79.5 ± 1.7	NS
Plasma glucose (mmol/L)			
Fasting	5.9 ± 0.07	5.9 ± 0.06	NS
2-hour	7.1 ± 0.22	7.8 ± 0.25	NS
Insulin (μIU/mL)	18.9 ± 1.7	17.6 ±1.6	NS
Homeostasis model assessment			
Of insulin resistance[b]	4.9 ± 0.2	4.6 ± 0.5	NS
Of beta-cell function[c]	157.5 ± 10.6	146.6 ± 12.1	NS
Hemoglobin A_{1c} (%)	5.3 ± 0.13	5.3 ± 0.16	NS
Triglycerides (mmol/L)	1.53 ± 0.10	1.67 ± 0.11	NS
Cholesterol (mmol/L)			
Total	3.9 ± 0.58	4.2 ± 0.10	NS
Low-density lipoprotein	2.41 ± 0.06	2.64 ± 0.09	NS
High-density lipoprotein	0.97 ± 0.02	0.94 ± 0.03	NS

Abbreviation: NS = no significant difference.
[a] Values are means ± standard error.
[b] mmol/L/μIU/mL.
[c] μIU/mL/mmol/L.

66 completed the 12-week protocol. Baseline characteristics of the subjects in the placebo and salsalate groups who completed the study did not differ significantly from each other (Table 2) or from the larger group at baseline (shown in Table 1). There was no significant change in BMI during the study. After 12 weeks, FPG levels were 5.20 ± 0.11 mmol/L and 5.53 ± 0.10 mmol/L in the salsalate-treated subjects in comparison with the placebo-treated subjects, respectively (P = .04). Insulin levels were less in the salsalate group than in the placebo group at the end of the study (P = .001); HOMA-IR was also lower in the salsalate group than in the placebo group after 12 weeks of salsalate treatment (P = .02), as shown in Table 2.

Within-Group Changes, Before Versus After Salsalate Therapy

Likewise, within groups, the FPG level decreased from 5.86 ± 0.07 mmol/L to 5.20 ± 0.11 mmol/L, and HOMA-IR decreased from 4.2 ± 0.9 to 3.8 ± 0.3 after 12 weeks of treatment with salsalate (P = .01 for both changes). FPG decreased from 5.80 ± 0.07 mmol/L to 5.53 ± 0.10 mmol/L (P = .06) in the placebo group; however, comparison of changes from baseline showed that FPG levels decreased in the salsalate-treated arm more than in the placebo arm of the study (P = .03). HOMA-B, an indicator of beta-cell function, increased in the salsalate-treatment group from 139.8 ± 11.0 to 189.4 ± 24.6 (P = .01), whereas fasting insulin levels did not change significantly. There were no significant changes in any of the foregoing variables in the placebo group.

The mean FPG levels in the placebo- and salsalate-treatment groups during the course of the 12-week intervention period are shown in Figure 2. Plasma glucose levels declined significantly by the fourth week of salsalate therapy and remained significantly lower thereafter. In contrast, the slight reduction of plasma glucose concentrations in the placebo group was not significant. We also compared the effect of salsalate therapy in participants with IFG and IGT, separately. Treatment with salsalate decreased FPG levels in study participants with IFG more than in those

with IGT, but the difference was not statistically significant. Systolic blood pressure decreased after treatment with salsalate (P = .01) but did not change significantly in the placebo group. Salsalate treatment did not change diastolic blood pressure, A1C, 2-hour plasma glucose, total cholesterol, or triglyceride levels significantly. The LDL level increased in the salsalate-treated group from 2.38 ± 0.09 mmol/L to 2.64 ± 0.08 mmol/L (P = .01); the reason for this unexpected change is not apparent. There was no significant change of LDL concentration in the placebo group.

We found no significant difference in response to salsalate therapy based on age or sex. Treatment with salsalate appeared to decrease the FPG level independent of fasting plasma insulin, HOMA-IR, and HOMA-B at baseline.

Safety and Tolerability

Results of liver function tests and serum creatinine did not change with salsalate therapy. Two study participants could not tolerate the salsalate treatment because of tinnitus and dizziness and were withdrawn from the study. Most study subjects in the salsalate group and some in the placebo group (18 and 6, respectively) had transient gastrointestinal upset. One person treated with salsalate developed severe nausea and did not continue the protocol. Three additional participants in the salsalate-treated group were withdrawn from the study because of development of a rash (with one requiring orally administered corticosteroid therapy for the macular rash). There were no lasting complications after salsalate therapy.

DISCUSSION

In the current study, we examined whether treatment with salsalate would have a positive effect on glucose homeostasis in obese persons with prediabetes and a family history of T2DM in a first-degree relative. Use of 3 g of salsalate daily for 12 weeks in a double-blind,

Table 2
Variables Before and After the 12 Weeks of Intervention in Participants Who Completed the Study[a]

	Salsalate (n = 26)			Placebo (n = 28)		
Variable	Before	After	*P* value	Before	After	*P* value
Age (y)	48.3 ± 0.7	48.3 ± 0.7	.2	50.0 ± 1.3	50.0 ± 1.3	.2
Waist (cm)	94.0 ± 1.2	93.9 ± 1.5	.3	91.1 ± 1.2	92.2 ± 1.5	.2
Body mass index (kg/m^2)	30.6 ± 0.6	30.7 ± 0.5	.4	29.8 ± 0.5	30.0 ± 0.7	.2
Blood pressure (mm Hg)						
Systolic	122.9 ± 2.0	112.7 ± 3.6	.01	122.7 ± 1.8	124.6 ± 2.6	.4
Diastolic	79.6 ± 1.4	80.2 ± 1.6	.5	81.5 ± 1.5	76.8 ± 1.4	.1
Plasma glucose (mmol/L)						
Fasting	5.86 ± 0.07	5.20 ± 0.11[b]	.01	5.80 ± 0.07	5.53 ± 0.10[b]	.06
2-hour	7.90 ± 0.25	8.53 ± 0.49	.1	7.62 ± 0.28	8.53 ± 0.49	.2
Insulin (μIU/mL)	16.5 ± 1.8	16.1 ± 1.9[b]	.1	17.8 ± 1.9	18.2 ± 2[b]	.2
Homeostasis model assessment						
Of insulin resistance[c]	4.2 ± 0.9	3.8 ± 0.3[b]	.01	4.5 ± 0.8	4.4 ± 0.9[b]	.1
Of beta-cell function[d]	139.8 ± 11.0	189.4 ± 24.6	.01	154.7 ± 14.4	180.2 ± 18.9	.2
Hemoglobin A_{1c} (%)	5.3 ± 0.1	5.1 ± 0.1	.10	5.5 ± 0.1	4.9 ± 0.1	.16
Triglycerides (mmol/L)	1.57 ± 0.13	1.53 ± 0.20	.7	1.83 ± 0.21	1.69 ± 0.11	.4
Cholesterol (mmol/L)						
Total	3.93 ± 0.10	4.14 ± 0.10	.09	4.32 ± 0.17	4.09 ± 0.16	.1
Low-density lipoprotein	2.38 ± 0.09	2.64 ± 0.08	.01	2.65 ± 0.13	2.43 ± 0.14	.1
High-density lipoprotein	0.94 ± 0.03	0.91 ± 0.02	.3	0.97 ± 0.06	0.94 ± 0.04	.3

[a] Values are means ± standard error.
[b] P<.05 (between salsalate and placebo groups; comparison at study end).
[c] mmol/L/μIU/mL.
[d] μIU/mL/mmol/L.

placebo-controlled study resulted in an 11% decrease in FPG level, which was significantly different in comparison with placebo.

The number of persons with T2DM and the burden of its complications are projected to increase dramatically worldwide (1). It is highly desirable and necessary to introduce novel interventions that will help impede the development of T2DM or at least delay its onset. One such approach is control of subclinical inflammation that is frequently present in subjects with prediabetes and appears to have a contributory role in the development of T2DM. The available data indicate that NF-κβ has an important role in inflammation (18-20). After its activation and translocation into the cell nucleus, NF-κβ stimulates the transcription of cytokines and inflammatory markers, which lead to insulin resistance. Indeed, a few studies have documented a reduction in inflammation, insulin resistance, and FPG levels in persons with prediabetes (21). In a double-blind study performed in obese nondiabetic adults, salsalate reduced FPG by 13% (22). Both in that study and in our current study, insulin levels were unchanged. Using HOMA-IR as an indicator of insulin resistance, we found its value significantly decreased by 10% in the salsalate-treated group, a result that is similar to that found in other studies (23). Not all studies, however, have reported a reduction in HOMA-IR with use of salsalate therapy (22). In our current study, we also noted that beta-cell function, estimated by HOMA-B, improved in the salsalate-treated group. In a previous 12-week study that used salsalate versus placebo in a group of patients with newly diagnosed T2DM, we also found an increase in HOMA-B in the salsalate-treated group (24).

Overall, our findings demonstrate that treatment of persons who have prediabetes with salsalate reduces insulin resistance (without a change in body mass) and improves beta-cell function, both of which likely contribute to the observed reduction in FPG level and improvement of glucose homeostasis. Furthermore, the decrease in FPG without a significant change in the 2-hour plasma glucose level in the group treated with salsalate suggests that the effect of salsalate is more prominent in persons with IFG. In support of this premise, we found that the reduction in FPG (statistically not significant) was more prominent in study participants with IFG in comparison with those who had IGT. Further evaluation is needed to clarify the difference between the responses to salsalate among persons with IFG versus those with IGT. The A1C levels did not change significantly at the end of the study, although the A1C levels of our study subjects were not very high. Alternatively, additional treatment time and more patients may be needed to yield a statistically significant change in A1C levels. Systolic blood pressure decreased significantly with salsalate treatment, consistent with the decrements in insulin resistance and FPG. Systolic blood pressure did not decrease after salsalate therapy in the previous Targeting Inflammation Using Salsalate in Type 2 Diabetes

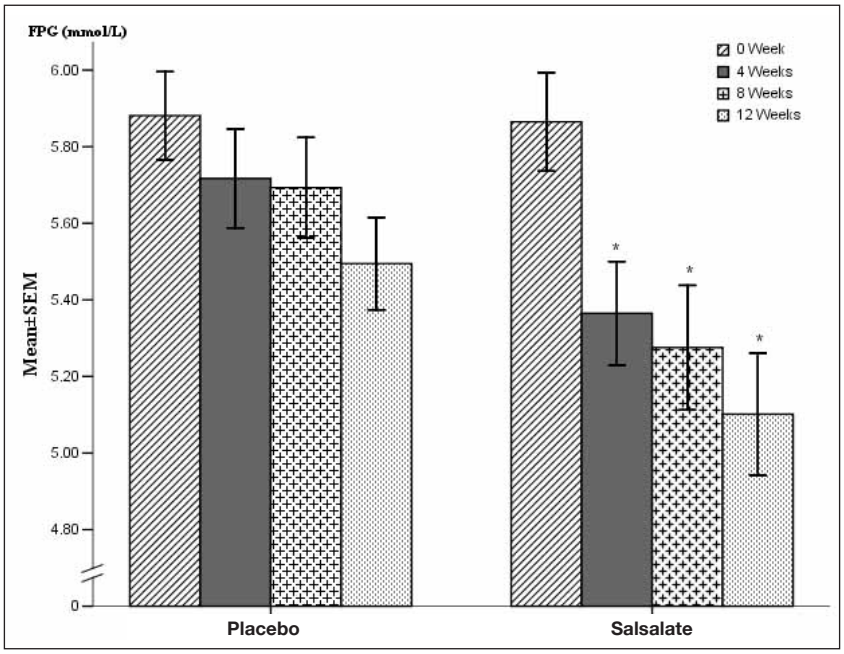

Fig. 2. Mean fasting plasma glucose (*FPG*) values, stratified by 4-week intervals during the study, in the placebo and salsalate groups. *P<.05 for comparison of FPG levels between salsalate and placebo arms. *SEM* = standard error of the mean.

(TINSAL-T2D) study (10). We found that the LDL level increased after treatment with 3 g of salsalate daily, similar to the finding in a previous report (10).

Treatment with salsalate in our current study, as well as in our previous study in patients with newly diagnosed T2DM (24), was associated with important side effects, including tinnitus, dizziness, headache, nausea, and rash. Although these side effects may preclude widespread use of this particular agent in the treatment of diabetes or the prevention of progression of prediabetes to T2DM, other antiinflammatory agents may prove useful. It may be possible to reduce the development of T2DM by intervening with lifestyle modifications and pharmacologic therapy before its onset.

In one meta-analysis, pharmacologic interventions reduced diabetes by approximately a third (18). In addition, people with prediabetes are at increased risk for cardiovascular disease, microalbuminuria, and peripheral neuropathy (25). Hence, screening for prediabetes and its treatment constitute an important public health program.

Our current study was limited in sample size and duration. Moreover, the optimal dose of salsalate to be used in persons with prediabetes is not yet known.

CONCLUSION

Salsalate treatment of persons with prediabetes improved measures of glycemic control during a 12-week trial. Novel interventions based on a better understanding of the pathophysiologic features of this condition should prove helpful in achieving reductions in the incidence of T2DM. Further large and long-term studies are necessary to ascertain the role of antiinflammatory medications in the prediabetic state.

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AUTHOR CONTRIBUTIONS

Dr. Faghihimani wrote the manuscript and researched the data. Drs. Aminorroaya, Resvanian, and Adibi reviewed and edited the manuscript. Dr. Ismail-Beigi contributed to the discussion and reviewed and edited the manuscript. Dr. Amini researched the data and contributed to the discussion.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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