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ORIGINAL ARTICLE

Salsalate improves glycemic control in patients with newly diagnosed type 2 diabetes

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Abstract Chronic inflammation contributes to insulin resistance and type 2 diabetes mellitus (T2DM). We investigated whether treatment with salsalate, an anti-inflammatory medication, improves glycemia in a group of newly diagnosed drug-naïve patients with T2DM. The study was a randomized, double-blind, placebo-controlled trial. Diagnosis of T2DM was made within 2 months of enrollment, and participants had not received any anti-glycemic agent. Sixty adults were randomized to receive salsalate (3 g/day) or placebo for 12 weeks. Fasting plasma glucose and insulin, glucose 2 h after 75 g oral glucose, HbA1C, lipid profile, HOMA-IR, and HOMA-B were determined before and after treatment. Salsalate reduced fasting glucose from 6.3 ± 0.2 mmol/l to 5.4 ± 0.2 mmol/l ($P < 0.01$) and TG from 1.9 ± 0.2 mmol/l to 1.5 ± 0.2 mmol/l ($P < 0.03$). Fasting insulin levels were increased in the salsalate group from 18.8 ± 1.6 to 21.6 ± 3.9, while they decreased in the placebo group. HbA1c rose in the placebo group from 6.2% ± 0.2 to 7.9% ± 1.1 mmol/mol, but decreased in the intervention group from 6.1% ± 0.5 to 5.6% ± 0.2 mmol/mol ($P < 0.04$ for between-group comparison). HOMA-IR did not change but HOMA-B increased ~1.7-fold ($P = 0.06$) in the salsalate group. The results show that salsalate is effective in improving glycemic control in newly diagnosed naïve patients with T2DM. The optimal duration of treatment with salsalate and sustainability of its effect requires further study (IRCT138709011465N1).

Keywords Salsalate · Type 2 diabetes · Glycemic control

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Introduction

Type 2 diabetes mellitus (T2DM) is a serious rising health problem in the world [1]. In addition to the genetic factors and excess body fat, chronic inflammation plays an important role in increasing insulin resistance and in development of T2DM [2, 3]. Epidemiologic studies have shown that circulating concentrations of acute phase reactants such as CRP directly correlate with obesity and T2DM [4, 5]. Other studies have shown that blood levels of proinflammatory cytokines including TNF-α, IL6, resistin, leptin are elevated in diabetic patients [6–10], and pathophysiological studies have focused on intracellular pathways that activate inflammation. Two pathways that play an important role in the development of insulin resistance in obesity as well as in T2DM are the JNK and IKKβ/NF-κB pathways [11]. Increased lipid deposition in adipose and other tissues leads to production of pro-inflammatory cytokines that can activate the JNK and NF-κB pathways [11–13]. Activation of these pathways release nuclear factors to translocate into the nucleus to promote the expression of numerous genes, including mediators of inflammation. These mediators, in turn, interfere with insulin action by suppressing insulin signal transduction and contribute to insulin resistance [11–15].

Based on the above, suppression of inflammation represents a novel interventional approach for treatment of T2DM. Use of salicylates, a traditional anti-inflammatory agent, in patients with various inflammatory disorders in

conjunction with type 2 diabetes has been reported to reduce serum glucose concentrations [15]. Additionally, in a few small clinical trials, high doses of salicylates improved fasting and postprandial glucose levels in diabetic patients [15, 16]. Finally, recent studies have shown that salsalate, a non-acetylated and better tolerated form of salicylate, acts similarly to salicylates as a suppressor of NF-κB pathway and reduces the subclinical inflammation and hyperglycemia in patients with T2DM [17–21].

We initiated this study to investigate the effects of salsalate on glycemic control in patients with T2DM. The study was conducted in newly diagnosed and medication-naïve patients with T2DM with a positive family history of T2DM in one or more first-degree relative.

Methods

Study design

This study was a double-blind placebo-controlled clinical trial. All participants were selected from the first-degree relatives of T2DM, who were screened during a diabetes primary preventive program in Isfahan Endocrinology and Metabolism Research Center. Patients in whom the diagnosis of T2DM was made within the previous 2 months of enrollment were considered to have "newly diagnosed" T2DM and were deemed eligible to participate in the study. Participants were between 30 and 70 years of age. Diabetes was diagnosed by fasting plasma glucose (FPG) level of 7.0 mmol/l or a 2-h blood glucose level of >11.1 mmol/l following a 75 g of orally administered glucose (2-h PG) according to ADA 2010 Standards of Care [22]. We excluded those with FPG higher than 13.8 mmol/l or concomitant illness or conditions, including peptic ulcer disease or recent gastrointestinal bleeding, renal or hepatic failure, asthma, aspirin allergy, current usage of corticosteroid or use of any hypoglycemic agents; pregnant or lactating women, and patients with type 1 diabetes mellitus were excluded from the study. All participants were enrolled in a lifestyle modification program emphasizing proper diet and exercise. They were introduced to a nutritionist, for a low calorie diet according to their BMI. We expected to lose weight by 5–10% at 6 months. All participants encouraged to walk about 30 min every other day.

We assessed a total of 370 people for eligibility and 124 persons did not meet the criteria (see Consort Diagram in Fig. 1). The remaining 176 patients were invited to participate in the study following a briefing session informing them about diabetes, its complications, and the effects of different medications on control of the disease. They were also informed about the possible effects and side effects of salsalate and the work plan of the project. From this group, 60 patients consented to participate in the study. The randomization sequence was computer generated. Patients and study personnel were masked to treatment assignment. Thirty participants each were randomized to receive 3.0 g of salsalate in two divided doses orally per day (Caraco Pharmaceutical Laboratories, Detroit, MI) or identical placebo tablets for 12 weeks.

Pretreatment baseline evaluation and a 12-week treatment period with visits at 4, 8, and 12 weeks after random assignment were done in our center. Study patients had fasting blood sampling in each visit. Drug adherence was assessed by pill count. Of this group, 24 and 25 participants in the salsalate and placebo arms, respectively, completed the study.

The study protocol and consent form was approved by the Ethics Committee of Isfahan University of Medical Sciences. All participants signed a written informed consent form prior to enrollment in the study (IRCT138709011465N1).

Assays

Plasma glucose concentrations, cholesterol, TG, and HDL levels were determined by the enzymatic method. (Pars Azmoon, Iran). Insulin was determined by immune-radiometric assay (Biosource Europe S.A, Belgium). HbA1c was measured by a chromatographic-spectrophotometric assay (Biosystem S.A., Spain).

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. HOMA-B, an indirect estimate of β-cell function, was calculated as fasting insulin (μIU/ml) $\times$ 20/[FPG (mmol/l) $-$ 3.5].

Statistical analysis

Data obtained in participants who completed the 3-month intervention protocol was used. Analysis of significance was performed using software SPSS. The end point was the change from baseline in fasting plasma glucose and insulin, HOMA-IR, and HOMA-B measured within and between salsalate and placebo groups. All data were near-normal in distribution and are presented as mean $\pm$ SEM. Unpaired (salsalate vs. placebo) and paired (before vs. after treatment) students t-test was used. We used ANOVA to determine the exact effect of salsalate on glycemia after adjustment of BMI, age, waist circumferences and insulin levels. Results were considered significant with a P-value of <0.05.

Results

Table 1 lists baseline characteristics of 60 participants enrolled in the study. On average, participants were

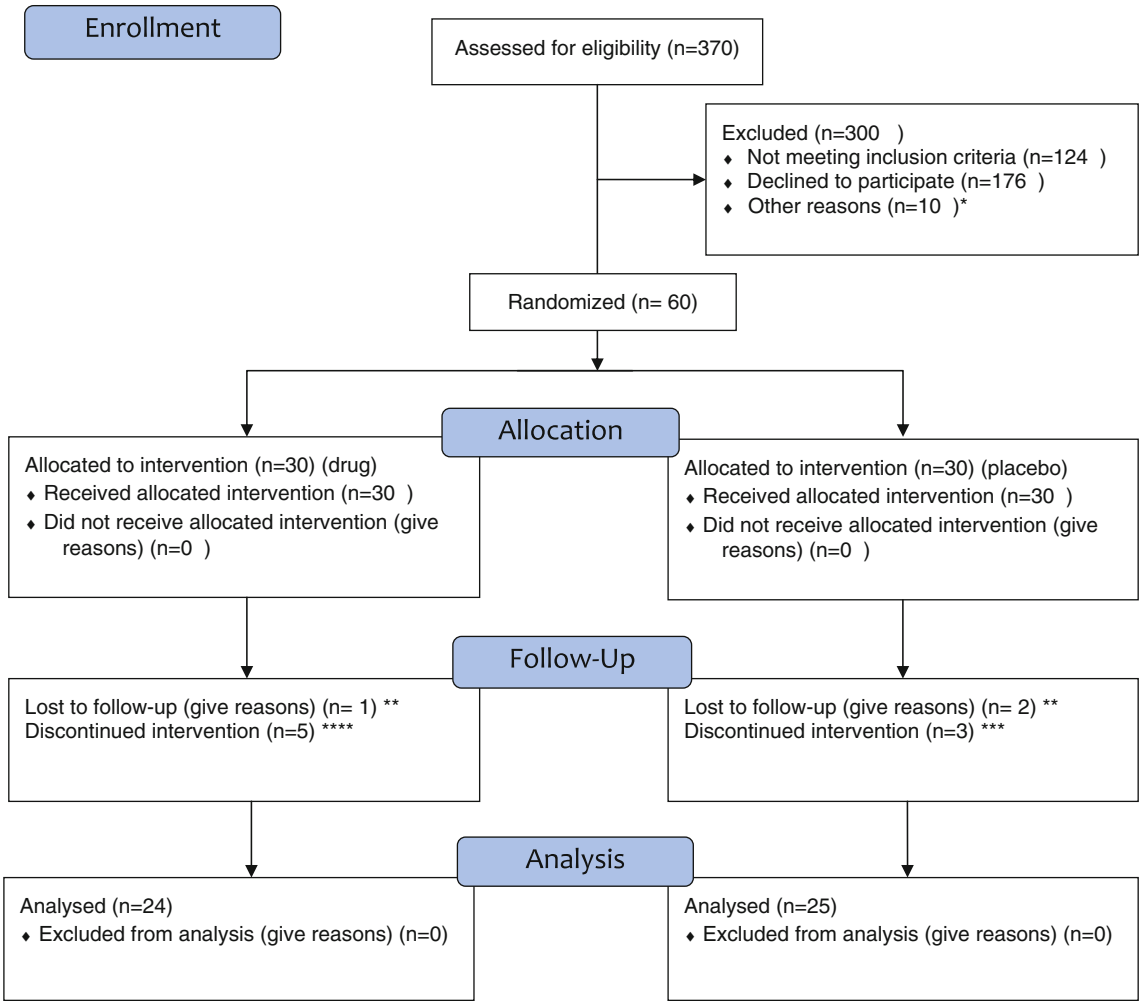

Fig. 1 CONSORT flow diagram. *They were women who could not begin the study because of some family problems (refusal by other family members). **They lived far from the city and could not return for the hematologic tests. ***They had some mild GI upset, but refused to continue the study. ****Two participants did not tolerate the drug because of tinnitus and dizziness. Other two patients complained of macular rash, One patient withdrawn the drug because of sever GI upset, such as nausea, vomiting, and flatulence

$\sim$49 years old, 30% men, with a BMI of $\sim$30 kg/m^2, fasting and 2 h post glucose values of $\sim$7.3 mmol/l and 11.6 mmol/l, respectively, and HbA1c value of $\sim$5.9% (41.5 mmol/mol), with no significant differences between the groups. Mean of waist circumferences in men and women were 94.8 $\pm$ 4.1 cm and 90.6 $\pm$ 1.5 cm, respectively. The difference was not statistically significant. From 42 women who participated in the study, 12 women were at menopausal state. Menopause had no extra effect on the results of the study. Forty-nine participants—24 in salsalate and 25 in the placebo group completed the study. Comparison of variables between men and women showed no gender related differences.

Table 2 shows a summary of variables measured at baseline and after the 3-month intervention period in participants who completed the study. Similar to the data in Table 1, there were no differences in baseline characteristics between the two groups, and compared to those listed in Table 1. Fasting blood glucose decreased from 6.3 $\pm$ 0.2 to 5.4 $\pm$ 0.2 ($P < 0.01$) in the salsalate group. The 2-h PG level in the salsalate group decreased, and the fasting and 2-h PG levels in the placebo group increased during the intervention period, but these changes did not reach statistical significance. There was no demonstrable change in HOMA-IR in the salsalate group. Interestingly, HOMA-B was rose $\sim$1.7-fold, but the change was shy of significance ($P < 0.06$). There were also significant decreases in TG and WBC levels in the salsalate group. Treatment with salsalate resulted in no changes in BMI, BP, fasting insulin, HbA1c, total cholesterol, and HDL. At the end of the study, diastolic blood pressure decreased, significantly in placebo group but there was not so changes in salsalate group.

Table 1 Baseline characteristics of patients with newly diagnosed and drug-naïve type 2 diabetes at enrollment

Variables Mean ± SEM	Salsalate $N = 30$	Placebo $N = 30$	*P*-value
Age (years)	47.9 ± 1.2	50.8 ± 1.6	<0.15
Waist (cm)	91.7 ± 1.3	92.0 ± 2.9	<0.93
BMI (kg/m$^{2)}$	30.0 ± 0.7	29.2 ± 1.2	<0.59
Systolic BP (mmHg)	121.2 ± 3.0	127.1 ± 3.8	<0.24
Diastolic BP (mmHg)	80.2 ± 2.5	84.2 ± 1.7	<0.19
FPG (mmol/l)	6.4 ± 0.2	6.8 ± 0.4	<0.47
2-h PG (mmol/l)	09.9 ± 0.5	11.1 ± 0.5	<0.13
Insulin (μU/ml)	17.5 ± 1.6	18.2 ± 1.6	<0.19
HOMA-IR (mmol/l/ μU/ml)	5.6 ± 0.6	5.7 ± 0.5	<0.88
HOMA-B (μU/ml/ mmol/l)	106.0 ± 12.4	118.0 ± 14.7	<0.54
HbA1C (%) mmol/ mol	(5.8 ± 0.2) 40.6 ± 2.5	(5.9 ± 0.1) 41.5 ± 1.8	<0.80
TG (mmol/l)	2.0 ± 0.2	1.6 ± 0.1	<0.30
Cholesterol (mmol/l)	4.3 ± 0.1	4.2 ± 0.1	<0.76
HDL (mmol/l)	0.9 ± 0.05	0.9 ± 0.05	<0.80
LDL (mmol/l)	2.6 ± 0.1	2.6 ± 0.1	<0.86
WBC (cell/μl)	7,677.7 ± 447.7	6,911.1 ± 557.4	<0.29

The time course of changes in fasting glucose measured in participants in the salsalate and placebo groups is shown in Fig. 2. Fasting glucose decreased in the salsalate group and was significantly different from the placebo group at the end of the first month; levels remained low at the 3-month time-point. In contrast, glucose levels remained relatively constant (and rose slightly) in the placebo group.

The *P*-value for the percent change in various parameters between the two groups at 3 months is also listed in Table 2, and some of the changes are depicted in Fig. 3. As can be appreciated, FPGs fell in the salsalate group, while the values rose in the placebo group. Similar to FPG, in-between group changes were also significant for plasma insulin, HOMA-B, HbA1c, and TG levels in the salsalate group favoring improved glucose control. Two hour PG values decreased in salsalate group and increased in placebo group, although not significant. Insulin adjusted analysis of FPG values showed significant differences between salsalate and placebo groups ($P < 0.05$).

Safety and tolerability

The dose of 3.0 g of salsalate, a dose that has been used in patients with rheumatological diseases, was well tolerated

Table 2 Variables before and after the 3-month intervention period in participants who completed the study

Variables Mean ± SEM	Salsalate $n = 24$			Placebo $n = 25$			*P*-value for % change
	Baseline	3 Months	*P*-value	Baseline	3 months	*P*-value	
Waist (cm)	92.5 ± 1.4	92.5 ± 1.3	<1.00	90.5 ± 4.4	89.7 ± 3.9	<0.61	<0.74
BMI (kg/m$^{2)}$	30.0 ± 0.7	29.7 ± 1.0	<0.58	29.2 ± 1.2	27.8 ± 1.3	<0.14	<0.13
Systolic BP (mmHg)	121.2 ± 3.0	119.4 ± 2.7	<0.80	127.1 ± 3.8	117.6 ± 3.5	<0.15	<0.06
Diastolic BP (mmHg)	80.2 ± 2.5	82.1 ± 1.4	<0.28	84.2 ± 1.7	77.6 ± 2.06	<0.05	<0.03
FPG (mmol/l)	6.3 ± 0.2	5.4 ± 0.2	<0.01	6.1 ± 0.3	6.6 ± 0.9	<0.38	<0.01
2-h PG (mmol/l)	9.9 ± 1.0	7.8 ± 1.0	<0.29	9.6 ± 1.4	11.7 ± 1.9	<0.13	<0.13
Insulin (μU/ml)	18.8 ± 1.6	21.6 ± 3.9	<0.49	20.5 ± 2.2	15.1 ± 2.1	<0.00	<0.02
HOMA-IR (mmol/l/ μU/ml)	5.7 ± 0.52	5.3 ± 1.11	<0.75	6.02 ± 0.81	5.1 ± 1.1	<0.27	<0.54
HOMA-B (μU/ml/ mmol/l)	119.0 ± 15.4	201.6 ± 37.8	<0.06	131.5 ± 23.6	89.3 ± 22.4	<0.08	<0.02
HbA1C (%) mmol/mol	(6.1 ± 0.5) 43.1 ± 5.6	(5.6 ± 0.2) 37.7 ± 2.9	<0.41	(6.2 ± 0.2) 44.6 ± 2.9	(7. 9 ± 1.1) 62.8 ± 12.0	<0.18	<0.04
TG (mmol/l)	1.9 ± 0.2	1.5 ± 0.2	<0.03	1.7 ± 0.2	1.8 ± 0.3	<0.20	<0.04
Cholesterol (mmol/l)	4.3 ± 0.1	4.2 ± 0.2	<0.61	4.2 ± 0.3	3.5 ± 0.2	<0.10	<0.19
HDL (mmol/l)	1.0 ± 0.05	0.9 ± 0.03	<0.35	0.9 ± 0.09	0.8 ± 0.06	<0.30	<0.41
LDL (mmol/l)	2.5 ± 0.1	2.6 ± 0.1	<0.92	2.5 ± 0.3	1.9 ± 0.1	<0.07	<0.07
WBC (cell/μl)	7,366.6 ± 512.8	5,711.1 ± 546.5	<0.01	7,850.0 ± 1,294.5	4,750.0 ± 647.4	<0.16	<0.51

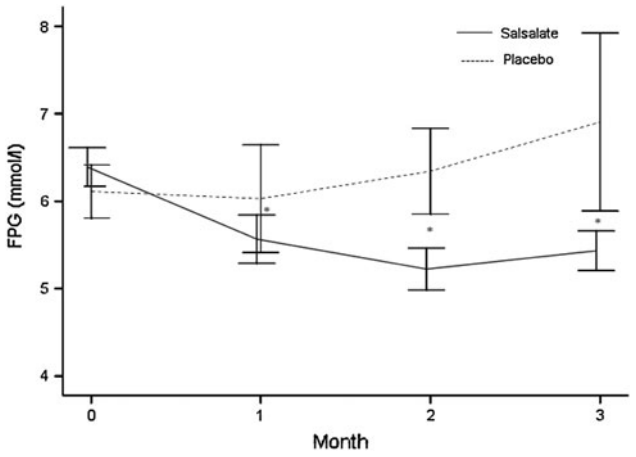

Fig. 2 Fasting plasma glucose in participants who completed the trial. *P-value < 0.05

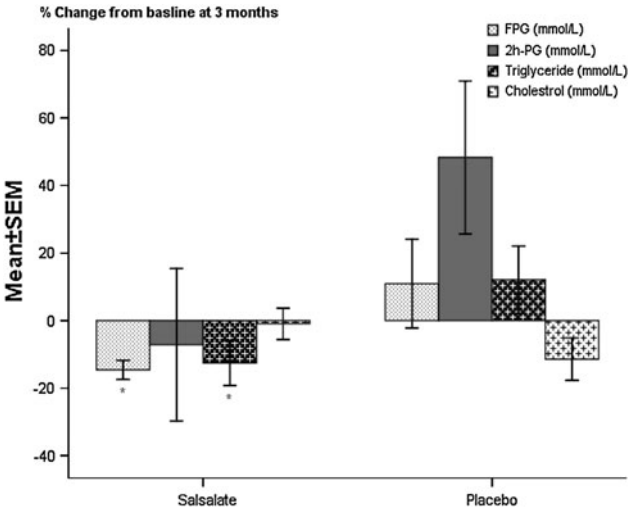

Fig. 3 The effect of salsalate versus placebo on selected parameters at study end. *P-value < 0.05

by most participants. However, five participants in the salsalate group withdrew from the study: two participants could not tolerate the drug due of tinnitus and dizziness, and two other patients complained of a macular rash and withdrew from the study; one additional patient was withdrawn because of severe GI upset including nausea, vomiting, and flatulence. Three patients in the placebo group withdrew because of mild GI side effects. A few participants complained of generalized "puffiness", but there was neither edema on physical examination nor significant change in body weight. There were no important changes in laboratory results of renal function, liver enzymes or electrolytes. No cardiovascular or respiratory distress was noted, and there were no hypoglycemic event in either group.

Discussion

In the present study, we evaluated the effects of salsalate, an oral anti-inflammatory agent, on newly diagnosed drug naive patients with T2DM using a randomized, double-blind, placebo-controlled design. We determined the effect of salsalate on several parameters including fasting plasma glucose and insulin levels, plasma glucose level 2-h PG load, HbA1c, lipid profile, HOMA-IR, and HOMA-B before and after 3 months of treatment. In the salsalate-treated group, there was a 14.5% reduction in FPG associated with a nonsignificant 14.8% rise in fasting insulin. FPG was also measured in both groups on a monthly basis. FPG in the salsalate group was significantly reduced at 1 month and remained low at months 2 and 3. HbA1c was 6.1% and 5.6% at baseline and at 3 months, respectively, but the change was not significant. No significant change was noted in HOMA-IR, and the nominal $\sim$70% increase in HOMA-B was shy of significance ($P < 0.06$). Plasma triglyceride and WBC count significantly decreased. In the placebo group, there appeared to be some deterioration of the diabetic state during the 3-month interval with non-significant increases in FPG, 2-h PG, and HbA1c levels and decreases in fasting insulin and HOMA-B. HOMA-B as a marker of β-cell function has nearly decreased in placebo arm after 3 months. It means that not only insulin resistance (we could not get appropriate result by HOMA-IR), but also β-cell dysfunction may result increment of blood glucose in placebo group. The significant decrease in insulin level in placebo group can be the consequence of β-cell dysfunction. At the end of the study, diastolic blood pressure decreased in placebo group but there was a not so change in salsalate group. Lifestyle changes during the study can induce decrease of DBP. Salsalate have induced a mild increase in DBP, so the effect of lifestyle changes on DBP is not apparent in this group.

Comparison of values at the 3-month time-point between salsalate and placebo groups revealed significant in-between group changes in FPG and insulin levels, 2-h PG, HbA1c, and TG level favoring improvement of the diabetic state in the salsalate versus the placebo group. Interestingly, there was no in-between change in HOMA-IR, while there was a significant increase in HOMA-B in the salsalate-treated participants compared to the control group at 3 months. In general, our observations on the effect of a daily dose of 3 g salsalate on blood glucose levels is in keeping with results of the TINSAL-T2D study conducted over a 14-week period[23].

Our data are consistent with previous studies demonstrating the positive effect of salsalate on control of hyperglycemia in patients with T2DM [15]. A large body

of evidence indicates the contributory role of inflammation in the pathogenesis of T2DM [24–27]. Salsalate, a dimeric non-acetylated salicylate comprised of two esterified salicylate moieties, has been shown to inhibit the IKKβ/NF-kB and JNK signaling pathways leading to a suppression of inflammation, and thereby increasing insulin sensitivity [20, 21]. Experimental evidence generated in obese nondiabetic individuals as well as in patients with T2DM treated with acetyl-salicylic acid or salsalate suggests that improved glucose metabolism is mediated by enhanced insulin sensitivity [17, 19, 23] while other studies emphasize the role of increase in plasma insulin concentrations in the response [16, 28]. The increase in concentration of insulin has been reported to be mediated by decreased plasma clearance of insulin [16, 20, 23, 27, 29], and/or by increased secretion of insulin by beta-cells [28]. Our results do not directly address these points. Nevertheless, we found no change in HOMA-IR but a near-significant rise in HOMA-B in the group treated with salsalate, with the latter being consistent with either increased insulin secretion—perhaps mediated by a decrease in inflammation within the islets or decreased hepatic insulin clearance. It is important to note that neither HOMA-IR nor HOMA-B is a robust measure of insulin resistance and insulin secretion [30]. Although, insulin levels have increased in our study, but insulin adjusted analysis of fasting plasma glucose levels showed significant difference between salsalate and placebo group ($P < 0.05$) at the end of the study, indicating factors other than insulin level may affect glycemic improvement. Nevertheless, the apparent increase in HOMA-B in our participants is intriguing and raises the possibility that the relative effect of salsalate on insulin resistance and insulin secretion may differ according to the stage and phenotype of T2DM.

We observed some adverse events associated with usage of salsalate. A total of 5 participants (out of 30 in the salsalate group) withdrew from the study: two participants developed tinnitus and dizziness, two developed a macular rash, and one developed severe nausea and vomiting with flatulence. None of the above events were seen in the placebo group. No cardiovascular or respiratory distress was noted, and although transient elevation of ALT and AST has been reported with use of salicylates [18], we observed no significant changes in liver enzymes in either group. There were no hypoglycemic events.

Our study has some novelties and strengths. This is the first time that the clinical effect of salsalate has been examined in newly diagnosed and drug-naïve patients with T2DM. In addition, we employed a randomized double-blind design in this study. Our study was limited by the relatively small sample size. In addition, the absence of robust physiological measurements limits mechanistic interpretation of our observations.

In summary, we find salsalate to be an effective agent in the management of glycemia in patients with newly diagnosed T2DM. Its use was associated with significant reduction in blood glucose with no major change in fasting insulin levels. The adverse events associated with its use, however, may limit its utility in general clinical practice.

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Conflicts of interest Nothing to declare.

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