Salsalate Improves Glycemia and Inflammatory Parameters in Obese Young Adults

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Running Title: Salsalate Improves Glycemia in Obesity

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ABSTRACT

Objective: Sedentary lifestyle and western diet promote subacute-chronic inflammation, obesity and subsequently dysglycemia. The aim of the current study was to evaluate the efficacy of the anti-inflammatory drug salsalate to improve glycemia by reducing systemic inflammation in obese adults at risk for the development of type 2 diabetes mellitus.

Research Design and Methods: In a double-masked placebo controlled trial, we evaluated 20 obese non-diabetic adults at baseline and after one-month of salsalate or placebo.

Results: Compared to placebo, salsalate reduced fasting glucose 13% (p<0.002), glycemic response following an oral glucose challenge 20% (p<0.004), and glycated albumin 17% (p<0.0003). While insulin levels were unchanged, fasting and OGTT C-peptide levels decreased in the salsalate treated subjects compared to placebo (p<0.03), consistent with improved insulin sensitivity and a known effect of salicylates to inhibit insulin clearance. Adiponectin increased 57% following salsalate compared with placebo (p<0.003). Additionally, within the group of salsalate treated subjects, circulating levels of CRP were reduced by 34% (p<0.05).

Conclusions: In this proof-of-principle study, salsalate reduces glycemia and may improve inflammatory cardiovascular risk indexes in overweight persons. These data support the hypothesis that subacute-chronic inflammation contributes to the pathogenesis of obesity related dysglycemia, and targeting inflammation may provide a therapeutic route for diabetes prevention.

CLINICAL TRIAL REGISTRATION  NCT00258115, clinicaltrials.gov
Obesity, occurring at epidemic rates worldwide, is a major risk factor for diabetes and cardiovascular disease. Thus, there is urgent need for effective interventions to prevent diabetes in obese populations. The importance of lifestyle modification obesity and diabetes is well recognized. However, disappointing long-term results of these treatments have led to increased interest in pharmaceutical intervention. Obesity and high fat Western diets activate inflammatory processes which promote development of insulin resistance (1; 2). Thus, targeting the inflammatory pathway may be a novel pharmacologic intervention for diabetes prevention and treatment.

Salicylates are among the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs). The benefits of salicylates for treatment of diabetes have long been appreciated (3; 4). High doses of the salicylate aspirin (4-7 gram/day) improve fasting and postprandial hyperglycemia in patients with diabetes (5-7). Recent studies reinvestigated hypoglycemic actions of salicylates and identified the molecular target to be the IKKβ/NF-κB pathway (8; 9), a central integrator of proinflammatory signals (2). The therapeutic potential of high dose aspirin is limited by bleeding risk. Salsalate, a dimer of salicylic acid, has an established safety profile after decades of use for rheumatic pain. As a non-acetylated salicylate, salsalate is an equipotent inhibitor of NF-κB but has a lower bleeding risk than aspirin (10; 11).

To our knowledge, this is the first study to assess metabolic changes with administration of salicylates to obese persons without diabetes. We hypothesized salicylates administered for one month would improve glycemia in obese young adults.

SUBJECTS, MATERIALS AND METHODS

The Joslin Diabetes Center IRB approved the double-masked placebo controlled study. Written informed consent was obtained. Subjects were <30 years and obese, with body mass index (BMI) ≥30 kg/m². Participants were excluded for recent blood donation, change in weight >5% in the preceding 6 months, use of medication known to alter glucose metabolism, acute febrile illness, biochemical evidence of renal or hepatic dysfunction, aspirin allergy, history of gastritis or gastrointestinal bleeding, or diabetes. Women were excluded for pregnancy, lactation, or lack of contraception use.

Participants were instructed to consume a high-carbohydrate diet (250-300 grams/day) and abstain from strenuous exercise for three days prior to evaluations, and not to alter dietary or exercise habits during the study. Blood pressure was measured twice (DINAMAP® PRO-100, General Electric Healthcare, USA) with the patient supine for 10 minutes. Fasting lipids and cytokines were measured, and oral glucose tolerance tests (OGTT) were performed with glucose, insulin, and C-peptide levels measured prior to and 30, 60, 90 and 120 minutes after 75-gram glucose load. All subjects were non-diabetic based on American Diabetes Association guidelines (12). Insulin resistance was determined using homeostasis model assessment (HOMA-IR) for insulin and C-peptide as described using the modified formula HOMA-IR$_{C$-peptide}=(fasting C-peptide * fasting glucose)/22.5 (13).

Subjects were randomized by a research pharmacist to receive salsalate, 4.0 grams/day (Caraco Pharmaceutical Laboratories Ltd., Detroit, MI) divided in two doses, or identical placebo for 4 weeks. Participants and study personnel were blinded to treatment assignment. Starting dose was selected based on tolerability data in patients with arthritis (14). A dose reduction plan was specified a priori with stepped reductions of 500 mg for symptoms related to salicylate use, such as tinnitus or headache. Compliance was evaluated by salicylate levels.

27 subjects were enrolled. One subject became ineligible after blood donation.
following screening. Three subjects withdrew consent due to personal conflicts and were considered non-informative; two had been randomized to placebo and one to salsalate. Three subjects were withdrawn due to rash.

**Assays.** Glucose was measured by glucose oxidation, cholesterol and HDL by cholesterol esterase assay, triglycerides via hydrolysis to glycerol and FFA (Beckman Synchro CX3delta and CX9, Beckman Coulter, Brea, CA), and glycohemoglobin by HPLC (Tosho 2.2, Tosoh Bioscience, San Francisco, CA). Immunoassays were performed in duplicate by commercial assay including RIA for insulin and C-peptide (Diagnostic Systems Laboratories, Webster, TX), and adiponectin (Linco research, St.Charles, MO, USA); ELISA for free fatty acids (WAKO chemicals, Richmond, VA, USA), and IL-6 and VCAM-1 (R& D Systems, Minneapolis, MN, USA). CRP was analyzed by immunoturbidometry (WAKO chemicals, Richmond, VA, USA). Salicylate levels were assessed commercially by colorimetric assay (Quest Laboratories, Cambridge, MA, USA). Glycated albumin was evaluated by Hitachi 911 lipid and protein analyzer and kits from AsahiKasei (Tokyo, JP). Glycated albumin was calculated by determining (a) the colorimetric measurement of total albumin; (b) partial enzymatic digestion of albumin at glycated sites; (c) re-assessment of albumin; (d) = a-c.

**Statistical analysis.** The primary endpoint was change from baseline in glycemic measures between salsalate and placebo groups. Secondary outcomes were also assessed as change from baseline within group. Data are presented as mean ± standard error. Unpaired (salsalate vs. placebo) and paired (pre vs. post) Student t- tests were performed. Treatment effects were determined by calculating percent change for each participant. Repeated measures and area under curve analyses were performed to compare response to OGTT before and after treatment. Completer analysis was pre-specified. Multiple regression analysis was performed to evaluate the contribution of covariates to the primary endpoints. Results were considered significant with two-tailed p-values <0.05.

**RESULTS**

**Subject Characteristics.** 20 participants completed the protocol. Subject baseline characteristics were similar (Table 1) in both groups. All participants had central obesity (15), and normal fasting glucose values. Three subjects (2 in placebo and 1 in treatment group) had baseline 120 minute OGTT glucose values consistent with impaired glucose tolerance. No subject had diabetes at baseline.

In salsalate-treated participants, mean serum salicylate levels were in the therapeutic range established in rheumatology practice (0.7-2.2 mmol/L), 1.35±0.18 mmol/L at 2 weeks and 1.23±0.25 mmol/L at 4 weeks. Salicylate levels were undetectable in placebo treated persons. There were no significant changes in weight, systolic or diastolic blood pressure, or standard lipid profiles in either group.

**Glucose Metabolism.** Fasting glucose decreased 13% in the salsalate compared with placebo group after one month (-0.4±0.2 mmol/L vs. +0.2±0.1 mmol/L, respectively, p<0.002) (Figure 1a, left). Glucose area under the curve following 75 gram OGTT was also significantly reduced in salsalate compared to placebo treated subjects (-130±53 mmol*min/L vs. +38±15 mmol*min/L, p<0.004) (Figure 1a, middle). Likewise, within groups the glycemic response to OGTT improved following salsalate treatment (repeated measure analysis p<0.01), but not placebo (Figure 1b). Consistently, we found a 17% reduction in the percent of glycated albumin between salsalate and placebo (-2.2±0.5 vs. -0.1±0.1%, p<0.0003), (Figure 1a, right). Therefore, glycemia, assessed by fasting, post-glucose load and glycated albumin, was significantly reduced following salsalate when compared to placebo. No hypoglycemia was noted in either group.
Fasting insulin and levels during OGTT remained unchanged after salsalate or placebo (Figure 1c). However, the reduction in fasting C-peptide comparing salsalate and placebo treated groups was significant (-0.53±0.14 nmol/L vs. +0.06±0.1 nmol/L, respectively, p<0.01). The percent difference in C-peptide AUC post OGTT between groups was also significant (-19±6% vs. +2±6%, p<0.03) (Figure 1d).

As salicylates have previously been demonstrated to reduce insulin clearance (7), we assessed insulin sensitivity by homeostasis model assessment of insulin resistance calculated using C-peptide (HOMA IR\(_{\text{C-peptide}}\)), which was significantly lowered by 29±10% after salsalate and increased 10±7% after placebo (between groups, p<0.004). However, HOMA-IR using insulin was not significantly changed in either group (4.3±0.9 vs. 4.2±0.6 and 3.5±0.5 vs 3.7±0.4, pre- vs post-salsalate and placebo, respectively), with no difference in the change between groups (p=0.7). These findings are consistent with reduced insulin clearance and improved insulin sensitivity contributing to the improved glycemia.

**Cytokines and Adipokines.** In secondary analyses, cytokines and adipokines were assessed to evaluate the anti-inflammatory mechanism for improvement in glycemia. Importantly, adiponectin increased significantly comparing salsalate and placebo treated groups (+5.6±1.8 vs. -0.3±0.4 mg/L, respectively, p<0.003), (Figure 2a). In change from baseline within group analysis, CRP concentrations decreased 34% (-18.0 ±7.7 nmol/L, p<0.05) following salsalate, with no-significant decrease following placebo (-2.8±7.2 nmol/L, p=0.7), and fasting non-esterified fatty acids (FFA) showed a tendency to decline by 14% following salsalate (-0.20±0.10 mEq/L, p=0.07) with no change following placebo (-0.06±0.05 mEq/L, p=0.6) (Figure 2b), although the between group comparisons did not reach statistical significance. Additional inflammatory markers II-6 and soluble VCAM-1 did not change significantly following salsalate therapy (data not shown). Using multiple regression analysis, salsalate assignment independently predicted the change in fasting blood glucose (p<0.009), response to glucose load (p=0.05), and glycated albumin (p<0.003) when adjusting for the change in adiponectin, FFA, and CRP.

**Safety and tolerability.** A priori, the protocol specified dose reduction for signs of salicylism so the maximum tolerable dose was evaluated for efficacy. Three participants required dose reduction due to complaints of tinnitus, headache or dizziness. Two of the three participants were on active medication, one tolerated 3.5 grams/day, one tolerated 3.0 grams/day, and both completed the trial without symptoms. There were no noted changes in laboratory analyses of renal function, electrolytes, or anion gap. Three participants who received active therapy were withdrawn for rash. No respiratory distress was noted. There was no statistically significant change in mean alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in the treatment or placebo groups (p>0.1). However, one participant had an isolated rise in ALT to less than twice the upper range of normal, and a second participant had a similarly mild elevation in ALT and AST. Both resolved spontaneously.

**DISCUSSION**

Obesity is an established risk factor for development of type 2 diabetes and is associated with a chronic inflammatory process (16; 17). Higher fasting glucose levels within the normoglycemic range independently predict risk for diabetes (18). In this proof-of-principle study, we evaluated whether the widely prescribed anti-inflammatory agent salsalate could impact glycemia in obese young adults. In a randomized, double masked, placebo controlled study, we demonstrate reductions in glycemia, both fasting and post OGTT, and reduced glycated albumin following one month of salsalate. As evidence of the anti-inflammatory effects of this therapy, we
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demonstrate increased adiponectin, and a trend toward reduction in CRP and free fatty acid levels which may also be important for reducing diabetes and cardiovascular risk. This is the first human trial to demonstrate salsalate can cause significant improvements in glycemia and adiponectin in obese persons. Although limited in sample size and study duration, our data are consistent with the hypothesis that targeting inflammation may provide a potential treatment for dysglycemia and method for diabetes prevention.

Both sodium salicylate and acetylsalicylic acid (aspirin) have been shown to improve glycemia in humans with type 2 diabetes (7; 19; 20). Previous human studies have been of one-two weeks. The current study is the first to suggest effects may be sustained over longer durations. Rarely, salicylates have been noted to cause hypoglycemia. Notably, there was no symptomatic or measured hypoglycemia in our study group. Additionally, our data suggest improved insulin sensitivity may contribute to reduced glucose levels. Evaluation of insulin resistance was limited by the fact that insulin clearance has been shown to be reduced by salicylates, demonstrated during a hyperinsulinemic-euglycemic clamp before and after two weeks of high dose aspirin (7). Although we did not directly assess insulin clearance in this cohort, altered insulin clearance would confound interpretation of insulin sensitivity based on circulating insulin levels. No effect of salicylates on C-peptide clearance has been demonstrated. Thus, the finding of an improvement in insulin sensitivity was based on interpretation of HOMA-IR\textsubscript{C-peptide}, as previously described (13), and supported by increased adiponectin.

Mechanism(s) by which salicylates lower glucose have historically been poorly understood and attributed to prostaglandin suppression (21). However, aspirin doses required for both anti-inflammatory and glucose lowering effects exceed levels necessary for inhibition of COX enzymes and prostaglandin synthesis. Nonacetylated salicylates, such as salsalate, lack an acetyl group and do not effectively inhibit COX enzymes (22), thus are unlikely to act via this proposed mechanism. Recently, high doses of salicylates have been recognized to inhibit NF-κB activity (9), possibly through inhibition of IKKβ (23). The direct role of the IKKβ/NF-κB pathway in development of diet induced obesity and insulin resistance has been validated in animal models (24; 25). In addition, insulin resistance in suppressor of cytokine signaling 3 (SOCS3) knockout mice is improved by sodium salicylate, suggesting an inflammatory mechanism of action. While we did not directly assess NF-κB or SOCS3 activity, we hypothesize the mechanism by which salsalate improves glycemia is via the established effect of salicylates on IKK/NF-κB signaling pathways.

Other mechanisms could contribute to the altered metabolic parameters demonstrated. Adiponectin is an adipocyte-derived cytokine, which has insulin sensitizing, anti-inflammatory and antiatherosclerotic properties (27; 28) and is decreased in obese populations (29). Increased adiponectin could affect glucose homeostasis. Likewise, although modest, the reduction in levels of free fatty acids could also contribute to the improvements in glycemic parameters and insulin sensitivity through the decreased activation of inflammatory mediators (30). Multiple regression analyses suggest that observed changes in the measured circulating inflammatory cytokines do not fully account for the glycemic lowering effects of salsalate. Although no weight change was noted in our current study, the impact of alterations in food intake or energy expenditure precipitated by salsalate therapy cannot be excluded. Future mechanistic studies are required to confirm the hypothesis that salsalate improves glycemia by impacting the IKK/NF-κB signaling pathways in humans.

Although efficacious for treatment of patients with diabetes, the adverse safety profile of high doses of aspirin, particularly the risk of bleeding, limits clinical therapeutic utility. Nonacetylated salicylates, such as salsalate,
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Individuals in this proof-of-principle trial do not inhibit platelets and have reduced risk of bleeding (10; 11). Additionally, salsalate is not soluble in the acidic gastric environment with resultant lack of gastrointestinal side effects (31). Salsalate has been administered to humans for decades and has an established long term safety profile. Therefore, the choice of salsalate, a salicylate dimer that is an equipotent inhibitor of NF-κB activity without adverse effects on platelet aggregation and bleeding risk is a logical choice for study.

Side effects reported in the current study were tinnitus, headache, rash and transient elevation in ALT and AST. Tinnitus, an expected side effect, was reported in two patients on active therapy and one on placebo. Symptoms resolved with dose adjustment as anticipated. Rash occurred at a rate higher than reported by registration trials (32). There was no evidence of respiratory distress or anaphylaxis in our participants. The increased rate of this side effect is not explained in this group without a history of allergy to NSAIDs. The transient, mild ALT and AST elevation is a rare reported side effect and attribution to the medication is unclear. Obesity itself is associated with mild elevations in serum ALT and AST, associated with hepatic steatosis and/or inflammation (33). Recent estimates suggest >33% of obese individuals may have hepatic steatosis (34). Therefore, mild elevations in hepatic enzymes may be consistent with expected findings in the obese population. Salsalate has been widely prescribed for more than a half century and no specific concerns in overweight persons have been noted. However, safety in obese subjects needs to be monitored and established in larger, long term studies.

This study is limited by the relatively small sample size and short-term duration. However, the excellent efficacy to lower glycemia and improve adiponectin in obese

ACKNOWLEDGEMENTS

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REFERENCES

**TABLE 1.** Baseline Subject Characteristics

There were no significant differences in the baseline characteristics between the salsalate and placebo groups. Characteristics presented as mean ± standard error. (W= white, non hispanic, H= Hispanic, B = African-American, BMI = body mass index).

<table>
<thead>
<tr>
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<th>Salsalate Therapy</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1M/8F</td>
<td>2M/9F</td>
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<td>Ethnicity</td>
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<td>5W/1H/4B/1other</td>
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<td>Age (years)</td>
<td>23.5 ± 1.1</td>
<td>24.1 ± 1.0</td>
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<td>BMI (kg/m$^2$)</td>
<td>36.3 ± 2.2</td>
<td>38.9 ± 2.5</td>
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<td>Waist circumference (cm)</td>
<td>106 ± 5</td>
<td>116 ± 6</td>
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<td>Current smoking</td>
<td>3 of 9</td>
<td>2 of 11</td>
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<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.0 ± 0.3</td>
<td>4.6 ± 0.2</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.2</td>
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<tr>
<td>Systolic BP</td>
<td>121 ± 4</td>
<td>123 ± 4</td>
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<tr>
<td>Diastolic BP</td>
<td>67 ± 3</td>
<td>71 ± 3</td>
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<td>Fasting glucose (mmol/L)</td>
<td>5.0 ± 0.2</td>
<td>4.8 ± 0.1</td>
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<td>120 minute glucose (mmol/L)</td>
<td>6.7 ± 0.4</td>
<td>6.8 ± 0.4</td>
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TABLE 2. Glycemic, Inflammatory, Lipid, and Body Composition Parameters

(FFA= free fatty acids, CRP= C-reactive protein, LDL= low density lipoprotein, BMI = body mass index, W/H = waist to hip) Data presented as mean ± standard error. *= p < 0.05 for within group analysis

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>One month</th>
<th>Percent change from baseline</th>
<th>Baseline</th>
<th>One month</th>
<th>Percent change from baseline</th>
<th>P-value for comparison of change between groups</th>
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<td>Glucose (mmol/L)</td>
<td>5.0 ± 0.2</td>
<td>4.6 ± 0.1*</td>
<td>-8%</td>
<td>4.8 ± 0.1</td>
<td>5.1 ± 0.1*</td>
<td>+5%</td>
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<td>Glycated albumin (%)</td>
<td>12.4 ± 0.4</td>
<td>10.3 ± 0.3*</td>
<td>-17%</td>
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<td>Glucose AUC (mmol*min/L)</td>
<td>905 ± 42</td>
<td>776 ± 50</td>
<td>-14%</td>
<td>801 ± 40</td>
<td>840 ± 42</td>
<td>+6%</td>
<td>&lt;0.004</td>
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<tr>
<td>C-peptide (nmol/L)</td>
<td>1.6 ± 0.2</td>
<td>1.1 ± 0.2*</td>
<td>-24%</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>+5%</td>
<td>&lt;0.01</td>
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<tr>
<td>Insulin (pmol/L)</td>
<td>112 ± 21</td>
<td>124 ± 18</td>
<td>+27%</td>
<td>97 ± 12</td>
<td>98 ± 10</td>
<td>+6%</td>
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<td>HOMA IR c-peptide</td>
<td>1.1 ± 0.2</td>
<td>0.7 ± 0.1*</td>
<td>-29%</td>
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<td>1.0 ± 0.1</td>
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<td>&lt;0.004</td>
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<td><strong>Inflammatory parameters</strong></td>
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<td>Adiponectin (mg/L)</td>
<td>10.6 ± 1.7</td>
<td>16.2 ± 2.7*</td>
<td>+56%</td>
<td>10.8 ± 1.5</td>
<td>10.5 ± 1.5</td>
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<td>&lt;0.003</td>
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<td>FFA (mEq/L)</td>
<td>0.46 ± 0.08</td>
<td>0.25 ± 0.05</td>
<td>-14%</td>
<td>0.42 ± 0.06</td>
<td>0.37 ± 0.08</td>
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<td>CRP (nmol/L)</td>
<td>48.2 ± 10.5</td>
<td>30.2 ± 7.4*</td>
<td>-34%</td>
<td>45.4 ± 8.4</td>
<td>42.7 ± 9.6</td>
<td>-8%</td>
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<td>LDL (mmol/L)</td>
<td>2.9 ± 0.3</td>
<td>2.8 ± 0.2</td>
<td>-5%</td>
<td>3.3 ± 0.2</td>
<td>3.2 ± 0.2</td>
<td>-4%</td>
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<td>Triglycerides (mmol/L)</td>
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<td>0.8 ± 0.1</td>
<td>-12%</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>+15%</td>
<td>0.08</td>
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<td>BMI (kg/m²)</td>
<td>36.3 ± 2.2</td>
<td>36.5 ± 2.2</td>
<td>+0.5%</td>
<td>38.9 ± 2.5</td>
<td>38.8 ± 2.5</td>
<td>-0.3%</td>
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</table>
FIGURE LEGENDS

**Figure 1:** Changes in Glycemia, Insulin, and C-peptide
1a: Fasting glucose, post oral glucose challenge glucose area under the curve (AUC), and glycated albumin were reduced in salsalate treated subjects when compared to placebo. Black bar = salsalate, Grey bar = placebo
1b: The salsalate treated group showed improvements in glycemia post oral glucose challenge compared to placebo. Mean and standard error data for the oral glucose tolerance test are demonstrated before and 30, 60, 90 and 120 min following 75 g oral glucose. Baseline data is depicted by the dashed line and open circle, and post treatment data by the solid line and closed circle.
1c and 1d: Insulin (1c) and C-peptide (1d) are demonstrated before and 30, 60, 90 and 120 min following 75 g oral glucose load. Baseline data is depicted by the dashed line and open circle, and post treatment data by the solid line and closed circle.

**Figure 2:** Changes in Inflammatory Markers and Mediators
2a: Adiponectin increased significantly in the salsalate compared to the placebo group. Black bar = salsalate, Grey bar = placebo.
2b: C-reactive protein (CRP) and Free Fatty Acids (FFA) were lower following salsalate, but unchanged following placebo by within group analysis. (* = p< 0.05). Dotted bar = baseline, Black bar = post therapy
FIGURE 1: Changes in Glycemia, Insulin, and C-peptide

1a: Fasting glucose, post oral glucose challenge glucose area under the curve (AUC), and glycated albumin were reduced in salsalate treated subjects when compared to placebo. Black bar = salsalate, Grey bar = placebo  

1b: The salsalate treated group showed improvements in glycemia post oral glucose challenge compared to placebo. Mean and standard error data for the oral glucose tolerance test are demonstrated before and 30, 60, 90 and 120 min following 75 g oral glucose. Baseline data is depicted by the dashed line and open circle, and post treatment data by the solid line and closed circle.  

1c and 1d: Insulin (1c) and C-peptide (1d) are demonstrated before and 30, 60, 90 and 120 min following 75 g oral glucose load. Baseline data is depicted by the dashed line and open circle, and post treatment data by the solid line and closed circle.
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**Figure 1c**

**Figure 1d**

<table>
<thead>
<tr>
<th>Salsalate</th>
<th>Placebo</th>
<th>Salsalate</th>
<th>Placebo</th>
</tr>
</thead>
</table>

**Insulin (pmol/L)**

- **Time (minutes):** 0, 60, 120
- **Baseline**
- **Salsalate**
- **Placebo**

**C-peptide (nmol/L)**

- **Time (minutes):** 0, 60, 120
- **Baseline**
- **Salsalate**
- **Placebo**

ANOVA p < 0.03
FIGURE 2. Changes in Inflammatory Markers and Mediators

2a: Adiponectin increased significantly in the salsalate compared to the placebo group. Black bar = salsalate, Grey bar = placebo. 2b: C-reactive protein (CRP) and Free Fatty Acids (FFA) were lower following salsalate, but unchanged following placebo by within group analysis. (* = p< 0.05). Dotted bar = baseline, Black bar = post therapy