Obesity and the metabolic syndrome are significant diseases that increase the risk for developing prediabetes and diabetes.1 Prediabetes is defined as blood glucose levels that are higher than normal but not high enough for a diagnosis of diabetes. Patients with prediabetes usually have impaired glucose tolerance, impaired fasting glucose, or both.2 According to the American Diabetes Association (ADA) criteria, impaired glucose tolerance is defined as a 2-hour glucose level of 140 mg/dL to 199 mg/dL on the 75-g oral glucose tolerance test. The ADA defines impaired fasting glucose as a fasting blood glucose level ranging from 100 mg/dL to 125 mg/dL.3 Both impaired glucose tolerance and impaired fasting glucose are associated with altered insulin sensitivity and carry a risk for the progression to diabetes.4

The 3 disease states—obesity, metabolic syndrome, and prediabetes—exist in a state of chronic inflammation, leading to the production of inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, C-reactive protein (CRP), and others. Nuclear factor-κB (NF-κB) is also known to be elevated in patients with 1 of these 3 conditions, thereby increasing the production of many of the same inflammatory cytokines.3 Increased cytokine production, in turn, interferes with the regulation of glucose and insulin and may promote the progression of prediabetes to diabetes.4

With the progression to diabetes comes increased morbidity and mortality from other diseases, such as coronary artery disease, stroke, blindness, and kidney disease.1,5 It has been documented that patients with prediabetes have a 15% to 30% risk for developing type 2 diabetes within 5 years and a 50% risk for progressing to diabetes.
KEY POINTS

- The prevalence of prediabetes is rising, and with it the need for novel options to prevent the progression to diabetes, especially for obese patients.
- Although lifestyle changes are effective for this purpose, many people cannot adhere to these changes and medications are often needed.
- Salsalate is an old and inexpensive medication that belongs to the salicylate drug class, which has been shown to lower insulin resistance and reduce glucose levels, triglycerides, and free fatty acid concentrations, with minimal adverse effects.
- Recent short-term trials have shown that 3 g to 4.5 g of salicylate therapy daily can be effective for patients with prediabetes.
- When given as an anti-inflammatory therapy, salsalate reduced glycemic markers and improved the inflammatory markers in young, obese patients without diabetes.
- The effectiveness of salsalate as a treatment option for prediabetes is largely unrecognized by the medical community.
- Large clinical trials may help to establish the benefit of this inexpensive approach.

Clinical Data from 3 Recent Clinical Trials

Trial 1: Goldfine and Colleagues (2013)

In a recent study by Goldfine and colleagues, 78 participants were enrolled in a 12-week, randomized, placebo-controlled study at the Phoenix and Boston VA Health Care systems. The purpose of the study was to evaluate whether using salsalate at its maximum safe dose in patients who are at risk for diabetes could improve their insulin resistance and other metabolic abnormalities. Patients were eligible to be included in the study if they had an abnormal glucose tolerance test result or an abnormal fasting glucose level.

This trial mostly involved men, with only 3 women in both arms of the study. Persons were excluded if they were less than 80% compliant with the 3-week placebo run-in, or if they were not able to attend the scheduled study visits. Throughout the duration of the study, the participants’ weight, blood pressure (BP), oral glucose tolerance test, fasting blood lipids, inflammatory markers, endothelial function, and insulin sensitivity using a hyperinsulinemic clamp were monitored to evaluate the effects of salsalate.

The investigators found a 6% reduction in fasting glucose compared with placebo and declines in fasting C-peptide level, insulin clearance, and triacylglycerol levels in participants taking a mean dose of 3.7 g of sal-
salsalate daily. They also showed a decrease in adipose tissue NF-κB and an increase in adiponectin in the salsalate group. Many of these metabolic markers were not significantly different from the control group; however, the study was able to show a significant difference \( (P = .006) \) in the level of fasting glucose between the 2 arms of the study. Of note was the reduced insulin clearance that was seen during the use of the hyperinsulinemic clamp, which suggests that there was not a significant difference \((P = .9)\) between the C-peptide level in either arm; this also points to the need for further investigation of salsalate’s mechanism of action on glucose.4

**Trial 2: Faghihimani and Colleagues (2012)**

In the second recent trial, 66 prediabetic individuals were assigned to receive 3 g of salsalate or placebo for 12 weeks.21 The participants were instructed to consume an unrestricted diet consisting of at least 150 g of carbohydrates daily and to avoid heavy physical activity for at least 3 days before their laboratory tests. This study tested the hypothesis that giving salsalate to persons with prediabetes increases insulin sensitivity, stimulates basal insulin secretion, and thus improves glucose-insulin homeostasis.21 The measurement used to gauge insulin sensitivity is the homeostasis model assessment of insulin resistance (HOMA-IR). The HOMA-IR is calculated using the fasting plasma glucose (mmol/L) multiplied by insulin (μIU/mL) divided by 22.5. The HOMA-IR scores in the treatment group decreased from 4.2 to 3.8 \((P = .01)\) after 12 weeks of intervention; the change in HOMA-IR score in the placebo group was insignificant, from 4.2 to 4.4 \( (P = .2) \) (Table).21

<table>
<thead>
<tr>
<th>Metabolic values</th>
<th>Patients receiving placebo (N = 28)</th>
<th>Patients receiving salsalate (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Postintervention</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122.7</td>
<td>124.6</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>104.4</td>
<td>99.5</td>
</tr>
<tr>
<td>HOMA-IR, mmol/L/μIU/mL</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>HOMA-B, μIU/mL/mmol/L</td>
<td>154.7</td>
<td>180.2</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>102.5</td>
<td>94</td>
</tr>
</tbody>
</table>

*P <.05 between the 2 groups, which were compared at the end of the study.

HOMA-B indicates homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.


By the end of the study, the HOMA-B score increased in the treatment group and much less so in the placebo group (Table).21

The secondary laboratory values that showed a significant difference with the intervention included systolic BP, fasting plasma glucose, and low-density lipoprotein (LDL) cholesterol. Systolic BP decreased in the treatment group from 122.9 mm Hg to 112.7 mm Hg but increased slightly, from 122.7 mm Hg to 124.6 mm Hg \((P = .4)\), in the placebo group. The fasting plasma glucose decreased significantly \((P = .1)\) in the group receiving salsalate and insignificantly \((P = .06)\) in the placebo group. Surprisingly, the LDL cholesterol levels showed a negative trend in the salsalate group but a positive trend in the placebo group (Table).

**The secondary laboratory values that showed a significant difference with the intervention included systolic BP, fasting plasma glucose, and low-density lipoprotein cholesterol.**

Other variables that were investigated but did not show a significant difference between the 2 groups included age, waist size, body mass index (BMI), diastolic BP, 2-hour plasma glucose, insulin level, hemoglobin A1c, triglycerides, total cholesterol, and high-density lipoprotein cholesterol.21

**Trial 3: Fleishman and Colleagues (2008)**

In the third study comparing salsalate and placebo, by Fleishman and colleagues, salsalate reduced glycemia and improved inflammatory cardiovascular risk indexes in overweight individuals.22 This study investigated salsalate as an anti-inflammatory modulator and its effects on glycemic, inflammatory, and lipid markers.
The study population consisted of nondiabetic obese individuals aged <30 years with a BMI ≥30 kg/m². Participants in the salsalate group received a high dose, 4 g daily, of the active drug. Salicylate levels were therapeutic throughout the study in the salsalate group but were undetectable in the placebo group.22

The results showed that fasting glucose had decreased 8% in the salsalate group compared with a 5% increase in the placebo group (P < .002), with significant decreases in other glycemic markers, including 75-g oral glucose tolerance test area under the curve (~20%; P < .003) and glycated albumin (~16%; P < .003). Fasting and oral glucose tolerance test insulin levels remained unchanged in both groups, with the exception of the decrease in C-peptide of 24% in the salsalate group and an increase of 55 in the placebo group (P < .01). Insulin sensitivity was also assessed in this study using the calculation of HOMA-IR, which decreased 39%. By contrast, insulin levels increased 21% in the salsalate group compared with the placebo group (P < .05).22

Regarding the inflammatory parameters in the salsalate and the placebo groups, adiponectin increased by 56% with salsalate and decreased 1% in the placebo group, whereas free fatty acid and CRP markers showed no significant change. Salsalate independently predicted change in fasting blood glucose, response to an oral glucose tolerance test, and glycated albumin, with adjustment for adiponectin, free fatty acids, and CRP after multiple regression analysis.22

The side effects reported in this study included tinnitus, headache, rash, and transient elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). A total of 3 patients reported side effects, with 2 patients from the salsalate group. Dose reductions in the 2 patients resolved the side effects. The AST and ALT elevations resolved spontaneously.22

Overall, the administration of salsalate as an anti-inflammatory therapy was shown to reduce glycemic markers in this study, as well as to improve inflammatory markers in young, obese patients without diabetes. This study had a short duration and a small sample size, but it was consistent with the hypothesis of improved dysglycemia secondary to the treatment of inflammation.

The mechanism by which salsalate reduced glycemic markers was theorized by the authors to be the inhibition of the IκB/NF-κB pathway, although this effect was not evaluated during the study.22

Conclusion

Diabetes is a growing epidemic, but prediabetes is increasing at an even higher rate. Lifestyle changes are effective tools to prevent the progression of prediabetes to diabetes. However, this method is difficult to sustain lifelong; therefore, medications are sometimes needed to aid patients in their fight against glucose dysregulation. One unrecognized therapeutic intervention is salsalate. As demonstrated in the 3 recent trials discussed here, the use of salsalate therapy, at doses of 3 g to 4.5 g daily, has the ability to lower insulin resistance and reduce the levels of glucose, triglycerides, and free fatty acid concentrations through the regulation of the IκB/NF-κB pathway, with minimal side effects. This medication, which costs pennies a day, could be a useful and cost-efficient option in the treatment of individuals with prediabetes and the prevention of progression to diabetes.

Larger clinical trials are needed to convince the medical community of the benefits of this medication for the prevention of diabetes in high-risk individuals. The data presented here are encouraging and should lay the foundation for further investigation and grant funding.

Author Disclosure Statement

Dr Anderson, Dr Wherle, Dr Park, Dr Nelson, and Dr Nguyen have no conflicts of interest to report.

References

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**Payers:** Newly released 2012 data from the Centers for Disease Control and Prevention estimated that nearly 30 million Americans (9.3% of the US population) currently have diabetes.1 Approximately 8 million of these people do not know that they have diabetes. Another 86 million people (37% of US adults) are estimated to have prediabetes, a condition in which blood glucose levels are higher than normal but are not high enough to be classified as diabetes. The rates of prediabetes are similar for non-Hispanic whites (35%), non-Hispanic blacks (39%), and Hispanics (38%).1 Individuals with prediabetes are at an increased risk for type 2 diabetes, heart disease, and stroke.2 Without intervention (ie, lifestyle, drugs), 9% to 50% of them will progress to diabetes within 5 years.3

In 2012, diabetes cost the United States an estimated $245 billion—$176 billion in direct medical costs and $69 billion in indirect costs (ie, disability, work loss, premature death)—a 40% increase from 2007.1 Many studies have shown that early intervention can decrease the rate of progression from prediabetes to diabetes.4-7 The American Diabetes Association recommends lifestyle modification as the primary intervention in patients with prediabetes,4 a cheap and effective option with relatively no adverse effects. For those not responding to or unable to follow lifestyle modifications, pharmacologic options include metformin, acarbose, thiazolidinediones, and orlistat.

Anderson and colleagues review 3 recent studies regarding salsalate, an anti-inflammatory medication, as another treatment option for patients with prediabetes. These short-term trials showed that 3 g to 4.5 g of salsalate daily can lower insulin resistance and reduce glucose, triglycerides, and free fatty acid concentrations with minimal side effects. Their data demonstrate that salsalate is also effective in patients with diabetes8,9, however, its effectiveness is relatively weak compared with current medications approved for diabetes.

The most effective use of this drug, therefore, would be in individuals with prediabetes, where glucose dysregulation is not as severe as in diabetes. Long-term studies are needed to evaluate the sustainability of this treatment option.

**Patients:** Patients with prediabetes have an increased risk for diabetes, but not everyone will progress to diabetes. Evidence has shown that the glucose dysregulation at this stage is reversible with weight loss, changes in diet, and exercise.4,5 Modest weight loss (5%-10% of body weight), moderate-intensity exercise (30 minutes daily), and the use of pharmaceutical agents are proved interventions that can prevent the progression to diabetes.6,7 Salsalate may possibly be another option in the treatment repertoire for patients with prediabetes.

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