

**BRIEF REPORT**

# Edema from Taking Cinnamon for Treatment of Diabetes: Similar Biochemistry and Pathophysiology to Thiazolidinedione Medications

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**We present a report of cinnamon bark powder 1000 mg daily associated with edema that resolved after stopping the supplement in an adult male. Thiazolidinediones (TZDs) cause fluid retention in those with diabetes or prediabetes. Some medications in this class have been implicated in increased cardiac deaths from this side effect. While medications are effective for diabetes, many people have turned to natural remedies to treat their diabetes instead of conventional pharmaceuticals. Cinnamon is a common agent used, and it has received extensive lay press attention. Chemically, cinnamon bark powder activates peroxisome proliferated activated receptors similar to TZDs. It is reasonable to hypothesize that cinnamon bark powder can cause edema. This case demonstrates that cinnamon bark powder may have a similar side effect profile. Physicians should be aware that consumption of cinnamon bark powder could cause fluid retention and possibly worsen congestive heart failure. (J Am Board Fam Med 2018;31:809–811.)**

**Keywords:** Cinnamon, Edema, Heart Failure, Peroxisome Proliferator-Activated Receptors, Thiazolidinediones

While cinnamon as an herbal remedy has existed for thousands of years, cinnamon as a dietary supplement specifically for lowering glucose has enjoyed increasing popularity in the press. Most lay press articles make a positive connection between cinnamon and prediabetes and type 2 diabetes, but they do caution that studies involving cinnamon for the treatment of prediabetes and type 2 diabetes are few, small, and have had mixed results. This has not stopped patients from supplementing their diets with cinnamon, either in capsule form or by sprinkling cinnamon powder on foods such as oatmeal. Published studies show that cinnamon was one of

the most commonly used herbal products in Palestine,<sup>1</sup> Australia,<sup>2</sup> and Austria.<sup>3</sup>

Few studies have examined the adverse effects of cinnamon. Patients experienced dyspepsia when the amount of refined cinnamon ingested was 85 mg the first month, 250 mg the second month, and 500 mg the third month.<sup>4</sup> There have also been cases of allergic contact dermatitis/stomatitis from a cinnamal patch test and from cinnamon chewing gum.<sup>5,6</sup> One case report of an elderly woman reported a diagnosis of cinnamon statin combination-induced hepatitis.<sup>7</sup> Another case report of an elderly white woman found that 2 weeks of using cinnamon oil pills 500 mg daily exacerbated the patient's rosacea.<sup>8</sup> It is critical that potential adverse events from cinnamon are reported, and we report a case of peripheral edema from taking cinnamon.

## Case Report

A 57-year-old male with hypertension and type 2 diabetes was enrolled in a clinical trial evaluating the effect of cinnamon bark powder (*Cinnamomum cassia*) 1000 mg daily versus oral extended release metformin 1000 mg daily versus Cinnulin PF 500

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mg daily on lowering hemoglobin A1C at least 0.5% in patients with previously diagnosed type 2 diabetes mellitus. On study enrollment, he had trace lower-extremity edema and a recent normal echocardiogram with normal exercise tolerance. Except for hemoglobin A1C of 6.5%, he had a normal blood count and normal renal and liver function.

He was randomized to take 1000 mg of cinnamon bark powder daily, and within 1 week of starting his study medication, he presented with rapid increase in leg swelling. Investigators stopped his cinnamon bark powder at this time, and his treatment was unblinded. Physical examination revealed no extra heart sounds, jugular venous distension, or hepatojugular reflux, all classic signs of heart failure, but he did have 4+ pitting edema to the knees bilaterally. Renal, liver, and urine tests drawn on that day were normal. Within 5 days of discontinuing cinnamon bark powder, swelling improved to baseline.

Over the next 16 months, the patient developed congestive heart failure with normal ejection fraction, grade 1 diastolic dysfunction and periodic edema.

## Discussion

Five point eight million units of pioglitazone, a thiazolidinedione (TZD), was prescribed in the United States in 2015.<sup>9</sup> One of the most common side effects of TZDs is peripheral edema. Approximately 5% of patients using TZDs develop peripheral edema; when TZDs are used with other antidiabetic drugs, the risk of patients developing peripheral edema increases to 18%.<sup>10,11</sup>

Cinnamon supplements and TZDs have similar molecular mechanisms of action. Peroxisome proliferated activated receptors (PPARs) are ligand-activated nuclear hormone receptors with the isoforms PPAR $\alpha$  ( $\alpha$ ), PPAR $\gamma$  ( $\gamma$ ), and PPAR $\delta/\beta$  ( $\delta/\beta$ ).<sup>12</sup> PPAR $\alpha$  is expressed mainly in brown adipose tissue and the liver, while PPAR $\gamma$  is mainly expressed in adipose tissue, and PPAR $\delta/\beta$  is expressed throughout many tissues. Evidence shows that activation of PPAR $\alpha$  lowers plasma triglycerides and elevates plasma high density lipoprotein cholesterol levels,<sup>13</sup> and that the activation of PPAR $\gamma$  increases insulin sensitivity and therefore results in antidiabetic effects.<sup>14</sup>

Cinnamon has been shown to upregulate mRNA expression of PPAR $\gamma$ .<sup>15</sup> Cinnamaldehyde, an active

component of cinnamon, was found to induce activation of PPAR $\delta$ , PPAR $\gamma$ , and retinoid X receptor (RXR). Cinnamaldehyde may activate PPAR $\gamma$  in a different manner than pioglitazone, as cinnamon selectively stimulated PPAR $\gamma$  S342A mutant whereas pioglitazone did not. To gather the biological evidence that cinnamaldehyde increases PPARs transcription, researchers measured the expressions of PPAR $\delta$  and PPAR $\gamma$  target genes in 3T3-L1 adipocytes. The data showed that cinnamaldehyde induced the expression of PPAR $\delta$  and PPAR $\gamma$  target genes, namely aP2 and CD36, in differentiated adipocytes. As a result, PPAR $\delta$ , PPAR $\gamma$  and their heterodimeric partner RXR seem to play a part in cinnamaldehyde action in the target tissues, causing an enhancement in insulin sensitivity and fatty acid  $\beta$ -oxidation and energy uncoupling in skeletal muscle and adipose tissue.<sup>16</sup> Data also suggest that cinnamon in its water extract form can act as a dual activator of PPAR $\alpha$  and  $\gamma$ , and may be an alternative to PPAR $\gamma$  activators.<sup>17</sup> In mice, the PPAR $\alpha$  mRNA (liver) and PPAR $\gamma$  mRNA (adipose tissue) expression levels were increased significantly in the cinnamon-treated group ( $P < .05$ ).<sup>18</sup>

TZDs also activate PPAR $\gamma$  receptors, and TZD activated PPAR $\gamma$  have been shown to cause edema. In 1 double-blind randomize-controlled 4-way crossover study, pioglitazone and placebo were examined for their effect on renal, systemic, and hormonal responses to changes in sodium intake. Pioglitazone was found to increase diurnal proximal sodium retention in diabetic and hypertensive patients.<sup>19</sup> One study makes the supposition that because TZDs are PPAR full agonists, a side effect of TZDs is fluid retention with associated peripheral edema due to the alteration of sodium and water reabsorption in the distal collecting ducts of the kidney.<sup>20</sup> In a meta-analysis assessing the overall risk for developing edema from TZD, there was a 2-fold increase in the risk for developing edema with a TZD compared with placebo, oral antihyperglycemic agents, or insulin.<sup>21</sup>

Coumarin, a chemical precursor to the drug warfarin, is present in cinnamon. In doses above 0.1 mg/kg, coumarins may cause liver dysfunction (and subsequent fluid retention) in humans. The cinnamon bark powder in this clinical trial was assessed (ExperTox, Deer Spring, TX) to have 0.5% coumarin, or 5 mg per daily dose. All patients in the

trial weighed greater than 50 kg; thus coumarin intake was never in the toxic range.

In the current case report, we hypothesize that cinnamon bark powder may have caused edema in this subject through similar mechanisms to TZDs.

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