

# GLP-1 reduces metalloproteinase-9 induced by both hyperglycemia and hypoglycemia in type 1 diabetes. The possible role of oxidative stress

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## Dear editor

MMP-9 has been involved in favoring cardiovascular disease, and evidence suggests that oxidative stress favors its release. Previous studies demonstrated that during both acute hyperglycemia and hypoglycemia an oxidative stress is produced in type 1 diabetes. On the other hand, GLP-1 has shown an antioxidant power. In this study an acute hyperglycemia and hypoglycemia, with or without the simultaneous infusion of GLP-1, were produced. During both hyperglycemia and hypoglycemia, an acute increase of MMP-9 and 8-iso-PGF2 $\alpha$  plasma levels was observed. GLP-1 significantly reduced this increase. This study suggests that metalloproteinase-9 is activated by acute hyperglycemia and hypoglycemia because they generate an oxidative stress and that GLP-1 counteracts this effect.

Cardiovascular disease is a rising complication of type 1 diabetes.<sup>1</sup> MMP-9 has been involved in favoring cardiovascular disease,<sup>2</sup> and evidence suggests that MMP-9 is increased in the plasma of type 1 diabetic patients.<sup>3,4</sup> Hyperglycemia seems to favor MMP-9 expression,<sup>5,6</sup> possibly through the generation of an oxidative stress.<sup>6</sup>

Attention is paid today to the possibility that GLP-1 and GLP-1 receptor agonists can be used in the management of type 1 diabetes.<sup>7</sup> We have recently shown that, in type 1 diabetes, GLP-1 protects endothelial function and reduces inflammation during both acute hyperglycemia and hypoglycemia.<sup>8</sup> GLP-1 exerts this protection increasing intracellular antioxidant defenses and decreasing the oxidative stress generated by both hyperglycemia and hypoglycemia.<sup>8</sup> Therefore, the aim of this study has been to evaluate the impact of both acute hyperglycemia and hypoglycemia on MMP-9 plasma levels and the possible protective effect of GLP-1.

Plasma samples regarding the experiments performed in type 1 diabetes were from the study previously published.<sup>8</sup> A total of 30 type 1 diabetic patients (15 males and 15 females) participated in such study.<sup>8</sup> For this new study, 30 healthy (17 males and 13 females), aged (24.0 $\pm$ 2.3 versus [vs] 24.4 $\pm$ 2.2 years, mean  $\pm$  standard error) and body mass index (23.5 $\pm$ 2.0 vs 23.7 $\pm$ 2.2 kg/m<sup>2</sup>) matched controls were recruited. The assays for MMP-9 were performed at the same time.

The diabetic patients were divided into two groups.<sup>8</sup> In group 1, two different experiments were planned for each subject in a randomized order: a period of 2 hours of hypoglycemia (2.9 $\pm$ 0. mmol/L), with or without GLP-1 (0.4 pmol $\cdot$ kg<sup>-1</sup> $\cdot$ min<sup>-1</sup>) infusion.<sup>8</sup>

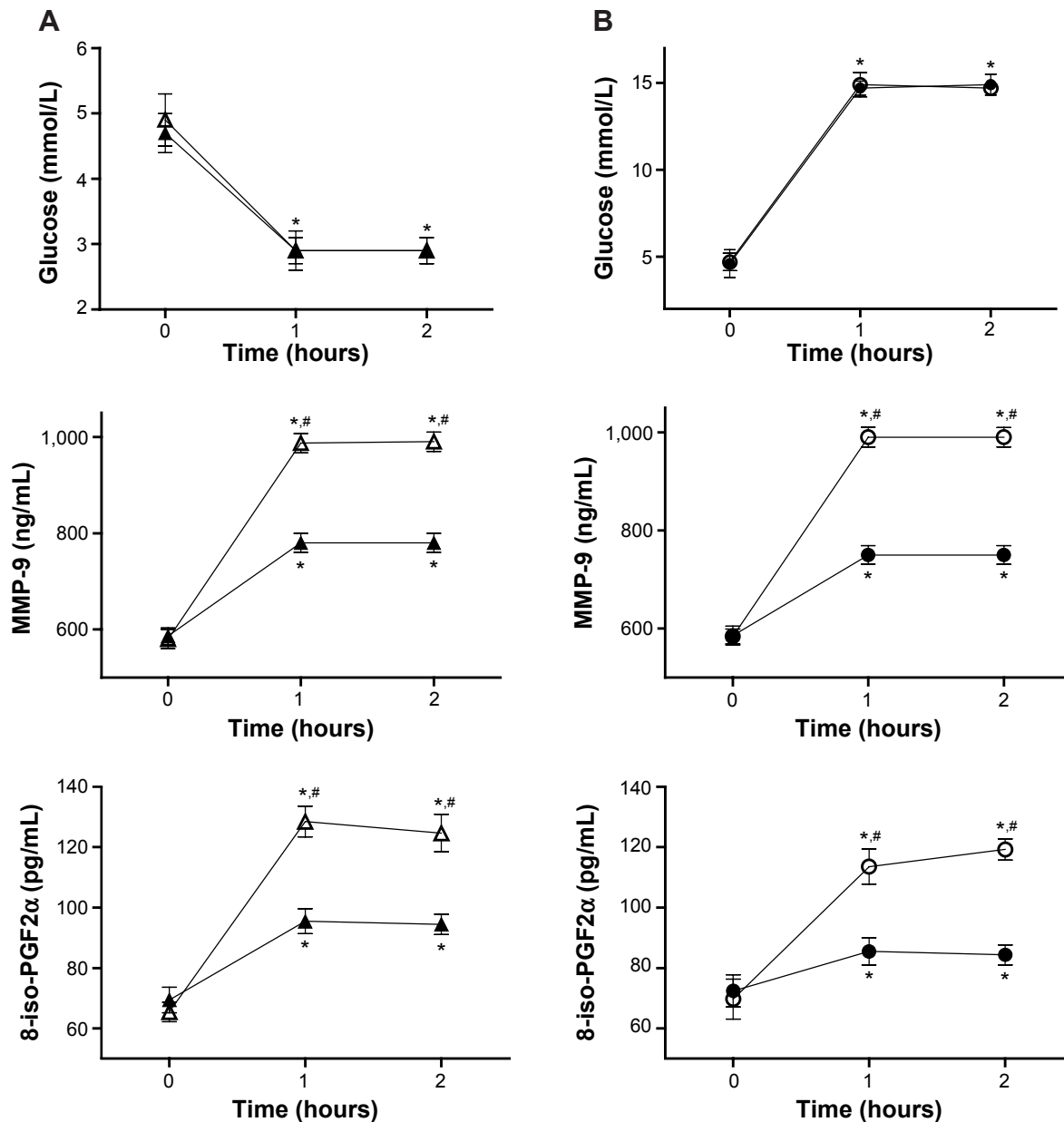
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Two different experiments were planned for each subject of group 2 in a randomized order: a period of 2 hours of hyperglycemic clamp (15 mmol/L), with or without GLP-1 (0.4 pmol·kg<sup>-1</sup>·min<sup>-1</sup>) infusion.<sup>8</sup>

At baseline and after 1 and 2 hours, glycemia, plasma 8-iso-PGF2 $\alpha$  (Cayman Chemical, Ann Arbor, MI, USA) and MMP-9 (R&D Systems, Inc., Minneapolis, MN, USA.) plasma levels were measured. For the statistics and more details about the study see Ceriello et al.<sup>8</sup>

Baseline 8-iso-PGF2 $\alpha$  (67.5 $\pm$ 4.8 vs 34.5 $\pm$ 4.5 pg/mL,  $P<0.01$ ), and MMP-9 (580.15 $\pm$ 10.9 vs 290.10 $\pm$ 12.4 ng/mL,  $P<0.01$ ) were increased in diabetic patients compared to controls.

After 2 hours of hypoglycemia, 8-iso-PGF2 $\alpha$  and MMP-9 significantly increased, compared to basal values (Figure 1). When hypoglycemia was accompanied by the simultaneous infusion of GLP-1, all these phenomena were significantly attenuated (Figure 1). Similar results were obtained in the



**Figure 1** MMP-9 and plasma 8-iso PGF2 $\alpha$  variations during acute hypoglycemia (A) and acute hyperglycemia (B), with or without GLP-1.

**Notes:** (A) Glycemia, 8-iso-PGF2 $\alpha$ , and MMP-9 in type 1 diabetes (n=15) during hypoglycemia and hypoglycemia plus GLP-1 infusion. White triangle: hypoglycemia; black triangle: hypoglycemia + GLP-1; \* $P<0.01$  vs basal; # $P<0.01$  vs hypoglycemia + GLP-1. (B) Glycemia, 8-iso-PGF2 $\alpha$ , and MMP-9 in type 1 (n=15) diabetes during hyperglycemia and hyperglycemia plus GLP-1 infusion. White circle: hyperglycemia; black circle: hyperglycemia + GLP-1; \* $P<0.01$  vs basal; # $P<0.01$  vs hyperglycemia + GLP-1. Copyright © American Diabetes Association. From Diabetes Care®, Vol 36, 2013; 2346–2350. Reprinted with permission from The American Diabetes Association.<sup>8</sup>

hyperglycemic clamp experiments. After 2 hours of hyperglycemia, 8-iso-PGF2 $\alpha$  and MMP-9 increased, compared to basal values (Figure 1). When hyperglycemia was accompanied by the simultaneous infusion of GLP-1, all these phenomena were significantly attenuated (Figure 1).

In this study, for the first time, we report that both acute hypoglycemia and hyperglycemia induce an increase of MMP-9 and that GLP-1 can counterbalance this effect. Our data suggest that MMP-9 is activated by acute hyperglycemia and hypoglycemia because they generate an oxidative stress. The data of 8-iso-PGF2 $\alpha$  support this hypothesis. GLP-1 counteracts the effects of both hyperglycemia and hypoglycemia, probably because of its antioxidant activity.<sup>8</sup>

Currently, there is huge interest in the use the GLP-1 receptor agonists for the therapy of type 1 diabetes.<sup>7</sup> Our data suggest an additional benefit of this use.

## Disclosure

The authors do not have any conflicts of interest to disclose.

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