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Presentation Abstract

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Title: **Metformin, methylmalonic acid and the risk of neuropathy: a randomised placebo-controlled trial**

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Abstract: **Background and aims:** Metformin lowers serum vitamin B12 (B12) and increases serum methylmalonic acid (MMA), the gold standard biomarker for tissue B12 deficiency. However, the clinical relevance of metformin-associated decreases in B12 is still controversial, since relevant clinical outcomes are lacking. Current guidelines mention B12 deficiency as a disadvantage of metformin, but do not yet give recommendations on the detection and prevention of B12 deficiency, waiting for more clinical evidence. Therefore, we studied whether the increase in MMA was associated with the onset or deterioration of neuropathy.
Materials and methods: In the HOME trial, 390 insulin-treated patients with type 2 diabetes were treated with 850 mg metformin or placebo up to three times daily for 52 months. We analyzed the association between metformin and changes in HbA1c, MMA and the Valk Score, a validated neuropathy score. We used structural equation modeling (SEM) analysis to estimate the mediation effects of MMA and HbA1c in the total effect of metformin on neuropathy score. We excluded patients with B12 deficiency at baseline or with B12 supplementation (n=15).
Results: In mixed model analysis, metformin, as compared to placebo, was associated with an increase of MMA at the end of the study (0.04 µmol/L, 95%CI 0.02 - 0.06, p=0.001). There was no significant difference in neuropathy score after 52 months between placebo (increase from 0.8±2.2 to 2.2±1.6) and metformin (1.1±2.1 to 3.7±1.3; ANCOVA: 0.03; 95% CI -0.03 - 0.08, p=0.41). However, SEM analysis showed that the effect of metformin on the neuropathy score consisted of a beneficial effect through lowering HbA1c (-0.02 per gram year of metformin) and an adverse effect through increasing MMA (0.04 per gram year). The model satisfied the goodness-of-fit test (χ^2=4.0; df=2, p=0.13; normated fit index = 0.98). In addition, during the study, MMA did not differ significantly between treatment groups when stratified for B12 concentration, showing that metformin did not affect the biological relation between B12 and MMA.
Conclusion: Metformin not only reduces B12, but also progressively increases MMA. The increase of MMA in metformin users was associated with significant worsening of the neuropathy score. Furthermore, metformin did not affect the biological relation between B12 and MMA. These results indicate that metformin-related B12 deficiency is clinically relevant. Monitoring of B12 and, when available, MMA, in users of metformin should be considered.

Clinical Trial Registration Number: NCT00375388