Metformin induces reductions in plasma cobalamin and haptocorrin bound cobalamin levels in elderly diabetic patients

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Introduction

Since the first published series of putative metformin induced cases of clinical B12 deficiency in 1971 [1], many studies in adult diabetic populations have documented that the initiation of metformin use is typically associated with reductions of 10–20% in plasma cobalamin levels [2–4]. This association has not been previously documented in an elderly population, although this demographic is known to have a high prevalence of subclinical cobalamin deficiency. The cause and significance of a metformin induced reduction in plasma cobalamin remains controversial [1,5–7] as it has not been clarified to which extent cobalamin bound to transcobalamin (HoloTC) or to haptocorrin (HC-Cbl) decreases. If metformin induces a decrease in the functional measure of circulating cobalamin, HoloTC, elderly patients with subclinical B12 deficiency may be at particularly high risk for clinical B12 deficiency.

Methods

Twenty patients (10 males, 10 females) with type 2 diabetes (1–17 years of duration), aged 67–91 years old were recruited between 2004 and 2007 at the Diabetes Centre at the Vancouver General Hospital, Vancouver, Canada. Ten were assigned to treatment with metformin and 10 served as controls. Plasma samples were taken at baseline (prior to allocation and start of treatment) and 3 months later. HbA1c was measured by turbidometric immunoassay (Dimension RXL®, Dade-Behring), total cobalamin by chemiluminescent immunoassay (Centaur©, Bayer) and methyl malonic acid by gas chromatography mass spectrometry as previously described [8]. HoloTC, total transcobalamin, haptocorrin and HC-Cbl assays were performed as previously described [9,10]. Differences in levels of all analytes at 3 months as compared to baseline were evaluated by paired t-tests.

Results

HbA1c values ranged from 5.7 to 8.6% and showed a significant decrease (p<0.01) in treated patients but not in the control group (data not shown). Other measurements are summarized in the Table 1. The methylmalonic acid levels remained unchanged in both the control and the treated group. Total cobalamin, total haptocorrin, and HC-Cbl showed a significant decrease in the treated group while no change was observed in the control group. While HoloTC decreased to a similar degree in both the treated and the control groups, the study was underpowered to detect significant differences (power<10% in
bound cobalamin; TtlHC, total haptocorrin; MMA, methyl malonic acid.

Table values for the baseline, delta and delta/baseline indicate mean values for the respective study groups. Confidence limits refers to mean plus and minus 2 standard deviations. P-values are for paired 2-tailed t-tests in the respective study groups.

Abbreviations: T2, measurement at 3 months; T1, measurement at baseline; TlCbl, total cobalamin; HoloTC, holotranscobalamin; TlTTC, total transcobalamin; HC-Cbl, haptocorrin bound cobalamin; TlHHC, total haptocorrin; MMA, methyl malonic acid.

treatment group, 56% in control group). There was no significant change for total transcobalamin levels.

Discussion

Our results show that reductions in circulating levels of cobalamin and HC-Cbl are present after 3 months of metformin therapy in an elderly diabetic population. The decrease in total cobalamin levels on average 24%, is similar to that observed in the previous studies of metformin induced B12 deficiency. The mechanism for the cobalamin decrease remains unclear as both HoloTC and HC-Cbl are decreased in the treated group (14% p = 0.06, 19% p = 0.0001). Furthermore, HoloTC decreased to a similar non-significant degree in both the treated and control groups making conclusions impossible regarding the potential effect of metformin on HoloTC. In contrast, HC-Cbl decreased unambiguously and specifically in the metformin treated patients.

Both of the major cobalamin binding proteins were measured in all patients with the total haptocorrin but not the total transcobalamin levels showing a specific and significant decrease in metformin treated patients. The relevance of these latter observations with regard to the mechanism of metformin induced changes in cobalamin status remains uncertain. However, the observation that both total haptocorrin and HC-Cbl levels decreased significantly with metformin therapy highlights the importance of monitoring functional B12 measures in monitoring the effect of metformin on cobalamin status. Although functional measures of cobalamin status were measured in this study, the study size was underpowered to detect a modest decrease in HoloTC levels. Depending on the mechanism of action, the short duration of the metformin exposure may also have been insufficient to document a slower decline in functional B12 measures.

In conclusion, our preliminary study results indicate that metformin induced reductions in plasma cobalamin levels are partially attributable to reductions in non-functional measures of cobalamin status. Further larger and longer studies are warranted to clarify the effect of metformin therapy on functional B12 measures to determine if this drug is a clinically relevant risk factor for clinical B12 deficiency.

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Disclosure

The authors have no relevant conflict of interest to disclose.

References

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