



Identification of a genetic risk factor for metformin-induced vitamin B12 deficiency

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- Metformin, a mainstay of treatment for type 2 diabetes, can cause vitamin B₁₂ deficiency. Clinical risk factors have been identified but genetic factors remain undiscovered. Our objective was to identify and validate genetic predisposing factors and establish clinical utility.
- Individuals with metformin-induced vitamin B₁₂ deficiency (n=487) and metformin-tolerant control individuals (n=6686) were identified in UK Biobank. Genome-wide association analysis was undertaken using logistic regression.
- Analysis identified a genome-wide significant non-synonymous SNP in the cubilin gene (CUBN, rs1801222/p.S253F) associated with metformin-induced vitamin B₁₂ deficiency.
- A large interaction with metformin use was observed, with vitamin B₁₂ deficiency occurring at 6.02% in GG, 7.96% in GA and 12.84% in AA genotype groups. When followed up from metformin initiation, 10% with the AA genotype were vitamin B₁₂ deficient by 11 years vs 21 years for 10% of the GG group.

The observed genetic association suggests that the rs180122 genotype should be considered a significant risk factor for metformin-induced vitamin B₁₂ deficiency.

