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Review

Association between metformin and vitamin B_{12} deficiency in patients with type 2 diabetes: A systematic review and meta-analysis

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Abstract

Aim. – Metformin is the most widely used oral hypoglycaemic drug, but it may lower B_{12} status, which could have important clinical implications. We undertook a systematic review and meta-analysis of the relationship between metformin use and vitamin B_{12} deficiency in persons with type 2 diabetes.

Methods. – Electronic database searches were undertaken (1st January 1957–1st July 2013) using the Cochrane library, Scopus, CINAHL, Grey literature databases, Pub Med Central, NICE Clinical Guidelines UK, and ongoing clinical trials. Included studies were of any study design, with data from patients with type 2 diabetes of any age or gender, taking any dose or duration of metformin. Planned primary outcomes were serum vitamin B_{12} levels, % prevalence or incidence of vitamin B_{12} deficiency and risk of vitamin B_{12} deficiency.

Results. – Twenty-six papers were included in the review. Ten out of 17 observational studies showed statistically significantly lower levels of vitamin B_{12} in patients on metformin than not on metformin. Meta-analysis performed on four trials demonstrated a statistically significant overall mean B_{12} reducing effect of metformin of 57 pmol/L [WMD (fixed) = –0.57 (95% CI: –35 to –79 pmol/L)] after 6 weeks to 3 months of use.

Conclusion. – The evidence from this review demonstrates an association between metformin usage and lower levels of vitamin B_{12} by 57 pmol/L, which leads to frank deficiency or borderline status in some patients with type 2 diabetes. This suggests that it is prudent to monitor B_{12} levels in these patients who are at increased risk of deficiency.

Keywords: Diabetes mellitus; Meta-analysis; Metabolic adverse effects; Oral hypoglycaemic agents; Primary care; Vitamin deficiency

1. Introduction

The worldwide prevalence of diabetes mellitus is rising. For western countries, it is currently projected that there will be a 17% increase in persons with diabetes in France and Belgium by 2035 [1], with a 22% increase in both the USA and United Kingdom, a 31% increase in Canada, and a 3% to 37% increase in other European Union countries [1].

The most widely used class of drugs in persons with type 2 diabetes are the biguanides (e.g. metformin), which increase insulin sensitivity, and contribute to weight loss [2]. However, one of the side effects of metformin is to reduce vitamin B_{12} status. Vitamin B_{12} deficiency is under diagnosed and under-treated [3,4]. Severe deficiency (e.g. pernicious anaemia) can result in macrocytic anaemia, peripheral neuropathy and mental-psychiatric changes. Also, milder symptoms, such as weakness, tiredness, and memory loss can occur before frank anaemia [5–7].

Metformin-related vitamin B_{12} deficiency has been known for over 40 years. However, a systematic analysis of the data concerning B_{12} status and metformin usage has not been carried out to date specifically in patients with type 2 diabetes. Two recent meta-analyses [8,9] have shown a reduction in B_{12} levels in populations with metformin use but both used a mixed population of patient types (e.g. diabetes, polycystic ovary syndrome,

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hyperlipidaemia). Therefore, their results may differ from that of patients specifically with a diagnosis of diabetes mellitus and a systematic review and meta-analysis is now required in this specific patient group.

Our objective was to perform the first systematic review and meta-analysis of the published literature (observational and intervention studies) on the association between metformin use and vitamin B_{12} deficiency (as measured by serum vitamin B_{12}) in patients with diabetes mellitus and to consider the potential implications for practice.

2. Method

2.1. Literature search

As recommended by the Cochrane Database of Systematic Reviews (http://www.cochranelibrary.com/); electronic, hand, web and reference list searches were made of the literature to date. Core health bibliographic databases were searched from 1st January 1957 (year of the first metformin clinical trial) to 1st July 2013. These databases included the Cochrane library, national, regional and subject specific databases, Scopus, CINAHL, Index to theses, Grey literature databases, Conference abstract databases, Pub Med Central, Zetoc, NICE Clinical Guidelines UK, ongoing trials and other electronic databases (e.g. Nexis). No ethical approval was required for this review as only analysis of already published data was used.

The full search strategy for each database is available in the online supplementary material (eSearches). A combination of Medical Subject Heading (MeSH) and free-text terms were used. The exact search phrases were: "(diabetics OR diabetes OR type 1 OR type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent Diabetes OR non-insulin dependent Diabetes OR non-insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM) AND (metformin OR metformin hydrochloride OR biguanides OR biguanide) AND (B_{12} OR B_{12} deficiency OR Vitamin B_{12} OR Vitamin B_{12} deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)". Reference lists from the search results were checked for relevant papers and experts in the field and study authors were contacted to enquire about additional published or unpublished studies, ongoing trials and background data.

2.2. Eligibility criteria for inclusion and data extraction

All human studies of cross-sectional, cohort or intervention (metformin vs. placebo or other control) design published in the English language from the 1st January 1957 to 1st July 2013 were assessed. Studies reporting data from all patients of any age or gender with diabetes mellitus and taking metformin were considered for inclusion. No papers were found assessing patients with type 1 diabetes, so the review subsequently focussed only on patients with type 2 diabetes. Intervention studies were included in the systematic review and meta-analysis if they assessed oral metformin in patients with diabetes vs. placebo (or no intervention, i.e. comparison with background data for the population). Due to the anticipated small number of intervention studies in this subject area, we did not plan to carry out any subgroup analyses. Data presented in conference abstract form was not included in the analysis.

2.3. Primary and secondary outcomes

The primary outcomes were serum vitamin B_{12} levels, % prevalence or incidence of vitamin B_{12} deficiency and odds or risk of vitamin B_{12} deficiency. Diagnosis of vitamin B_{12} deficiency was based upon a serum vitamin B_{12} level below 150 pmol/L, with borderline deficiency between 150 and 220 pmol/L. In this paper, all B_{12} measurements reported are that of serum vitamin B_{12} (pmol/L), unless otherwise stated. Secondary outcomes eligible for inclusion included reported symptoms, active B_{12} (holotranscobalamin II; HoloTC), homocysteine (Hcy), methylmalonic acid (MMA), haemoglobin (Hb), mean cell volume (MCV), estimates of economic costs, and quality of life data. Due to lack of data on these secondary outcomes, only the primary outcomes were included in the text of the systematic review and in the meta-analysis.

2.4. Statistical analysis

For cross-sectional surveys, mean ± standard deviation (SD) and correlation coefficients (r) were obtained where available. Relative risk (RR), odds ratios (OR) or hazard ratios (HR) were extracted for case-control studies, and mean and standard deviations extracted for intervention studies. The number of participants (n) as well as P values and 95% confidence intervals for effect estimates were extracted for all study types. Multivariate adjusted analyses were used where possible to reduce the effects of confounding.

Review manager (RevMan5.2, Cochrane Collaboration) [10] was used to perform the meta-analysis and for observational studies multivariate adjusted data used where possible to reduce the effects of confounding. All estimates are presented as mean ± standard deviation unless otherwise stated. The Jadad scale and CONSORT statement were used to assess the quality of the design and conduct of the randomised controlled trials (RCT's) [11–13]. The international GRADE working group grading system was used to link the quality of the evidence into recommendations [14,15].

3. Results

The 26 databases identified 7257 records from which 25 studies were included in this review. Fig. 1, based on the PRISMA statement (http://www.prisma-statement.org/), illustrates the results and the process of screening and selection. The online supplement contains full results of searches (Appendix A; Table A.1–A.3; see supplementary material associated with this article online), with details of reasons for exclusions of