Te Awakairangi Health NETWORK

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Revisiting Metformin and Vitamin B-12 Deficiency

Background

Metformin is considered a cornerstone in the treatment of diabetes and is the most frequently prescribed first line therapy in type 2 diabetes. There are few disadvantages with its use, the most common side effect being gastrointestinal discomfort.

That malabsorption of vitamin B-12 occurs with metformin in many patients has been recognised for many years. By inducing B-12 malabsorption, the risk of developing B-12 deficiency may increase – a clinically important and treatable condition.

Key Messages

- Vitamin B-12 deficiency due to chronic metformin use has been reported in up to 30% of patients.
- Serum levels of vitamin B-12 under 220 pmol/L should be considered suboptimal and may be indicative of levels that could lead to an inhibition of biological function.
- The most common method for treatment of vitamin B-12 deficiency is IM hydroxocobalamin injections.
- In considering vitamin B-12 deficiency, it is important to account for both metformin dose and duration of use.
- Best practice is to monitor vitamin B-12 status annually in people on metformin, particularly for patients older than 50 years.

Vitamin B-12 deficiency

Development of vitamin B-12 deficiency can be triggered by a number of different pathways and anything that interferes with GI absorption will produce a deficiency. Some factors that may lead to eventual deficiency include:

- Nutritional deficiency – the main dietary sources are meat and dairy products therefore elderly patients with “tea and toast” diets, chronic alcoholics and strict vegans are especially at risk
- Gastric causes e.g. pernicious anaemia, gastrectomy
- Intestinal causes e.g. ileal disease/resection
- Severe pancreatic insufficiency
- Drugs e.g. oral contraceptives, metformin, long term proton pump inhibitor therapy
- Loss of gastric parietal cells that produce intrinsic factor, and the absence of hydrochloric acid may result in reduced absorption of B-12.

It can take between one and five years to develop symptoms since the liver stores B-12, and it can take that long to deplete the stores.

Metformin-induced deficiency

The exact mechanism for metformin-induced vitamin B-12 deficiency is unknown. Some of the earliest studies highlighted the significance of duration of therapy required to lower the B-12 levels. They also suggested a link between the therapeutic dose and overall decrease in the vitamin level, ie **the daily and cumulative dose of metformin are as strongly associated with lower B-12 concentrations as duration of use**.

Medsafe guidelines (Medsafe, 2009) and other studies suggest annual screening for B-12 deficiency for all patients on metformin is warranted due to the potential for irreversible neuronal damage resulting from preventable loss of the vitamin.

How reliable is the blood test for B-12?

As above, it is best practice to monitor Vitamin B12 status annually in patients on metformin. However prescribers should be aware that blood tests only tell part of the story:

- B-12 is stored in the liver, therefore the blood level does not always accurately reflect the levels of **stored** B-12.
- the appropriate normal values in a population can vary. Sometimes a result just below the normal range may not be significant and can be ignored.

Clinical relevance of B-12 deficiency

Clinically, the earliest manifestations of B-12 deficiency are numbness and paraesthesias in the feet although tiredness is the major symptoms for most patients. The development of tiredness relates to the role that B-12 plays in the regulation of sleep patterns.

Since fatigue and tiredness are also symptoms of low sugar levels, this can delay the diagnosis of B-12 deficiency. Other symptoms of diabetes may also mask B-12 deficiency. Age is an important factor too, particularly for patients older than 50 years.

A measurable reduction in B-12 levels can occur as quickly as 3-4 months after the initiation of the metformin therapy whilst symptomatic deficiency may take as long as 5 -10 years to manifest. Clinically significant deficiency of B-12 is not flagged until the patient has a serum level of <148 pmol/L.

However it has been suggested that levels **under 220 pmol/L** should be considered as suboptimal and may be indicative of levels that may lead to an inhibition of biological function.

Due to the variety of pathogenic causes for B-12 deficiency there is no 'best fit' mode of treatment. The process of vitamin B12 absorption can be impaired at the level of the stomach, where intrinsic factor is produced, or at the level of the terminal ileum, where intrinsic factor bound to vitamin B12 is absorbed. Because only a small amount of is absorbed by passive diffusion, oral doses need to be very large to be effective.

B-12 replacement is therefore usually given by intramuscular injection, initially 1000µg every week for 4-6 weeks. A maintenance dose of 1000µg every 3 months is recommended which will give B-12 levels well above the daily requirements.

References

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