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# Should Patients on Metformin Be Screened for Vit B12 Deficiency, and if so When?

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**Our study proposes to investigate: whether there is a benefit to a formal screening recommendation and if so, at what point is it appropriate to screen for vitamin B12 deficiency in patients on Metformin.**

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# Metformin and Vitamin B12

- The first article describing this association was published in 1971 by Tomkin, Weaver and Montgomery.<sup>1</sup>
- Postulated theories
  - Alterations in small bowel motility which stimulates bacterial overgrowth and consequential vitamin B12 deficiency.<sup>2</sup>
  - Competitive inhibition or inactivation of vitamin B12 absorption.<sup>2</sup>
  - Alterations in intrinsic factor (IF) levels and interaction with the cubulin endocytic receptor.<sup>2</sup>
  - Metformin has also been shown to inhibit the calcium dependent absorption of the vitamin B12-IF complex at the terminal ileum.<sup>2</sup>
- In a meta-analysis review of 19 intermediate or high quality rated studies, it was found that metformin treatment is significantly associated with an increase in incidence of vitamin B12 deficiency and reduced serum levels. This association was dose and duration dependent.<sup>3</sup>
- A recent, randomized control trial designed to examine the temporal relationship between metformin and serum B12 found a 19% reduction in serum B12 levels compared with placebo after 4 years. Several other randomized control trials and cross-sectional surveys reported reductions in B12 ranging from 9 to 52%.<sup>4</sup>
- Despite Metformin's potential to cause vitamin B12 deficiency, there are no formal screening guidelines.
- The 2018 American Diabetes Association Standards of Medical Care position statement reports: "Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be **considered** in metformin-treated patients, especially in those with anemia or peripheral neuropathy. (Grade B)".<sup>5</sup>
- No formal recommendations have been provided by USPSTF.
- The Agency for Healthcare Research and Quality recommended that physicians consider screening patients for Vitamin B12 deficiency on long term PPI or H2 blockers (>12 months) and metformin (>4 months).<sup>6</sup>

# Study Design and Protocol

- This study is pending IRB approval (common rule changes impacting approval)
- Retrospective cohort study relying on existing administrative data without patient contact
- Study Population: Patients with HAP insurance who were exposed to Metformin
- Comparison Population: Patients with HAP insurance unexposed to Metformin

# Attrition Diagram For Exposed Population

22,648

- Patients with HAP insurance on Metformin

20,293

- Patients who filled only one prescription for Metformin

16,921

- Age <18 y/o
- Pre-existing B12 deficiency

13,489

- Less than 1 year of Metformin
- Metformin within 30 days of enrollment with HAP (concern for prior use under a different insurance)

**Final Study Population**

# Study Design and Protocol

## Variables:

- MRN (Patients with metformin use)(All available doses, brands, and combination pills for various time periods)
- Dates of Metformin prescriptions
- Dates of Vitamin B12 lab results
- Age:
  - Group 1 = 18-39
  - Group 2 = 40-49
  - Group 3 = 50-64
  - Group 4 = 65-79
  - Group 5 = >80
- Gender: Male or Female
- Race: Asian, African American, Caucasian, Hispanic, and Other
- PPI use
- Malabsorption disorder (small bowel disease, malnutrition, celiac disease, bariatric surgery)

## Outcome Variables:

- B12 Testing
- B12 Deficiency

# Comparison Population

- Total number of HAP Patients not on Metformin who were tested for B12 deficiency : **90,693**
- Total number of HAP Patients not on Metformin found to be B12 Deficient: **1,943**
- Prevalence of B12 deficiency in patients not on metformin: **2.14%**



# Results

- The overall incidence of vitamin B12 testing in our study was (6051 out of 13489, 44.86%).
- Our study demonstrated that the incidence of vitamin B12 deficiency in the exposed group (patients on metformin): 3.34%
- The average time to test was 971 days, the average time to test positive was 1925 days.
- Amongst the comparison group (patients not on metformin) the incidence of vitamin B12 deficiency was 2.14%
- Relative risk :  $3.34/2.14=1.6$
- Absolute risk increase =  $0.0334 - 0.0214 = 0.012$
- NNH=  $1 / 0.012 = 83$

**Table 1. Characteristics of the Population and Associated Testing**

	Total Number	Ever Tested	Mean Days to Test	Median Days to Test	Deficiency	Mean Days to B12 Deficiency	Median Days to B12 Deficiency
<b>Gender</b>							
Male	6247 (46.3%)	2590 (41.5%)	1037	785	81 (3.13%)	1882	1921
Female	7242 (53.7%)	3461 (47.8%)	922	675	121 (4%)	1954	2017
<b>Age</b>							
18-39	830 (6.15%)	292 (35.18%)	929	642	3 (1%)	2686	2839
40-49	1716 (12.72%)	581 (33.86%)	941	695	12 (2.1%)	2367	2397
50-64	5828 (43.21%)	2316 (39.74%)	1050	780	64 (2.8%)	2019	2397
65-79	4196 (31.1%)	2285(54.46%)	951	723	99 (4.3%)	1894	2163
>80	919 (6.81%)	577 (62.79%)	785	553	24 (4.2%)	1491	1133
<b>Race</b>							
African American	5409 (40.1%)	2251 (41.62%)	966	724	59 (2.6%)	2132	2247
Asian	499 (3.7%)	209 (41.88%)	905	864	6 (2.9%)	3212	2266
Hispanic	338 (2.5%)	149 (44.08%)	1183	791	6 (4.0%)	2230	2502
Other/ Unknown	1358 (10.3%)	573 (41.37%)	969	692	22 (3.8%)	1756	2047
White	5858 (43.4%)	2869 (48.98%)	970	723	109 (3.8%)	1811	2040
<b>Confounders</b>							
Malabsorption Disorders	694 (5.1%)	498 (7.11%)	11 (2.2%)	860	569	1863	2046
PPI use (prescriptions)	3957 (29.3%)	2173 (55%)	70 ( 3.2% )	946	703	2058	2429

Table 2. **Logistical Regression Analysis: Ever Tested for B12 deficiency**

	Odds Ratio	95%	C.I.	P-Value
<b>Age</b>	1.4569	1.402	1.5138	<0.01
<b>African American</b>	0.8531	0.7931	0.9177	<0.01
<b>Malabsorption Syndromes</b>	3.6439	3.064	4.3335	<0.01
<b>Male</b>	0.7568	0.7047	0.8126	<0.01
<b>PPI Use</b>	1.64	1.5185	1.7713	<0.01

Table 3. **Logistical Regression Analysis: B12 Deficiency**

	Odds Ratio	95%	C.I.	P-Value
<b>African American</b>	<b>0.73</b>	<b>0.5341</b>	<b>1.0014</b>	<b>0.051</b>
<b>Age</b>	<b>1.34</b>	<b>1.1412</b>	<b>1.5733</b>	<b>0.0004</b>
<b>Male</b>	0.83	0.6194	1.1072	0.2031
<b>Malabsorption Syndromes</b>	0.76	0.4068	1.4091	0.38
<b>PPI Use</b>	0.92	0.6808	1.2334	0.5645

	Days to B12 test	Days to B12 deficiency detected
<b>Shortest time to detection</b>	1	51
<b>25th percentile</b>	296	<b>1031 (~3 years)</b>
<b>Mean</b>	<b>971 (2.9 years)</b>	<b>1926 (5.2 years)</b>
<b>Median</b>	720	2287

# Discussion: Overview

- Despite the evidence associating metformin use with low vitamin B12 levels, screening for B12 deficiency in individuals treated with metformin has not been incorporated into clinical practice guidelines
- Monitoring of vitamin B12 levels because of metformin use is rarely performed in our practice
- The only factor associated with deficiency in a multivariable analysis was older age
- African American ethnicity approached significance as a protective factor for B12 deficiency ( $p = 0.051$ )

# Cost Analysis

## Cost of routine B12 Testing

- Total No. of Patients on Metformin: 22,648
- Cost/test: \$ 80.00
- Frequency of testing: Q 3 years

## Cost of Empiric B12 treatment (oral/IM)

- Oral B12 cost/year/person: \$24.00
- IM B12 cost/year/person: \$84.00

## Estimated cost burden of untreated Vit B12 Deficiency (over 15 years)

- Total No. of Patients on Metformin: 22,648
- Total Cost Burden of Untreated B12 def. over 15 year: \$50,000\*

\* Per data published in year 2000<sup>7</sup>

# Discussion: Cost analysis

- The estimated cost of disease burden to our positively tested population (3.34%) is **\$37.8 M** at the 15 year mark.
  - **\$9.4 M** for those tested positive (25%) at 1031 days
- The cost for routine testing **\$9.0 M** over 15 years
  - **\$1.8 M** at 3yrs
- The cost empiric treatment over 15 years:
  - \$8.1M (oral)
  - \$28.5M (IM)

# Screening Guidelines

Criteria for screening:

- Disease is appropriate for screening
  - Serious
  - Early treatment more beneficial
  - High prevalence of pre-clinical disease
- Program feasible and effective
  - Acceptability
  - Cost-effectiveness
  - Number of cases detected
- Valid test available



# Strengths of the study

- Large sample size
- Included participants >18 years old
- Did account for confounders ie. malabsorption, PPI use, and bariatric surgery
- Excluded pre-existing vitamin B12 deficiency, therefore we assessed incidence, not prevalence

# Limitations of the Study

- Metformin dosing or quantity: study was not stratified based on dose, combination pills were included
- Population: **HAP** Only: Selection bias does exist with HAP (premium insurance); includes few Medicare patients HAP population, not representative of the whole population
- Metformin compliance cannot be verified; however did include participants who filled their prescriptions >2 times
- Nutritional status of participants, vegans & vegetarians, participants taking supplements on their own not accounted for
- Other unmeasured patient factors likely exist



## Conclusion

Although at this time we do not have enough evidence to implement B12 screening in patients on metformin, we hope this study encourages physicians to think of the association between the two in their practice.

**Will you change your clinical practice  
based on this data?**

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