Risk factors for metformin-induced vitamin B12 deficiency and its association with peripheral neuropathy in T2DM patients

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Background

- Metformin is the cornerstone therapy in the management of T2DM

- It is routinely prescribed to 120 million diabetic patients around the world

- Inhibition of Vit. B12 absorption by metformin was first described in 1971

- Metformin interferes with Vit. B12 absorption in the terminal ileum

- Prevalence of metformin-associated Vit. B12 deficiency has shown great variation among different studies (5.8% to 52%)

- Determining the risk factors for Vit. B12 deficiency in metformin users can result in reduction in the occurrence of the deficiency

- Peripheral neuropathy is a manifestation of Vit. B12 deficiency and a complication of T2DM

- Potential of metformin-associated Vit. B12 deficiency to cause or worsen peripheral neuropathy in T2DM was investigated with conflicting results

Objectives

- To identify the risk factors for metformin-induced Vit. B12 deficiency in T2DM patients

- To examine the relationship between Vit. B12 and peripheral neuropathy in metformin-treated T2DM patients

Methods

- This cross-sectional study was conducted in diabetes clinics of two tertiary hospitals in Pretoria, South Africa

- 121 metformin-treated T2DM patients were recruited

- Peripheral neuropathy was assessed by NTSS-6 questionnaire

- Serum Vit. B12 levels were measured

- Other data were obtain from patients' records

- Stepwise (backwards) multivariable logistic regression was used to determine the risk factors for Vit. B12 deficiency

- Three initial regression models were built (to avoid the impact of multicollinearity) and reduced to a final model

- Association between Vit. B12 and peripheral neuropathy was investigated by Chi square test (binary variables) and Spearman's correlation co-efficient, rho (continuous variables)

Results

Demographic and clinical characteristics of vitamin B12-deficient patients compared to those with normal vitamin levels.

Variable	Low vit B12 (n=34)	Normal vit B12 (n=87)	P value
Age (years)	62.3 ±10.2	57.0±10.2	0.012
T2DM duration (years)	12(8.75/17)	9(5/16)	0.055
Duration of metformin use (years)	11(6.75/13.25)	8(3/13)	0.015
Total daily dose of metformin (gram)	2.6 ± 0.7	2.4±0.7	0.228
Cumulative dose of metformin (gram)	28.9(14.5/40.8)	17(7.7/31.3)	0.009
eGFR (mL/min/1.73 m^2)	100.4(78.6/129)	108.5(88/150.7)	0.093

Sex
  Women, n(%)
  Men, n(%)
	
	21(61.8)
	13(38.2)
		
		59(67.8)
		28(32.2)
			
			0.530

HbA1c (%)	7.4(6.3/9.6)	9.4(7.5/11.2)	0.001
Insulin use, yes(%)	29(85.3)	69(79.3)	0.451
Acetylsalicylic acid use, yes(%)	30(88.2)	64(73.5)	0.081
Coffee use, yes(%)	9(26.4)	14(16)	0.191

Race
  Black, n(%)
  Non-black, n(%)
	
	22(64.7)
	12(35.3)
		
		67(75.3)
		20(24.7)
			
			0.168

BMI (kg/m^2)	34.0±6.5	33.1±6.3	0.469

Number of daily doses
  One, n(%)
  Two, n(%)
  Three, n(%)
	
	0(0)
	21(63.6)
	12(36.6)
		
		3(3.5)
		40(46.5)
		43(50)
			
			0.198

Use of PPI or H2RA, yes(%)	5(14.7)	7(8)	0.271
NTSS scores	4.16(2/7.25)	4.33(2/8.33)	0.914

# Initial logistic regression models for potential risk factors of Vit. B12 deficiency

Independent variable	Model A		Model B		Model C	
	OR (95% CIs)	P value	OR (95% CIs)	P value	OR (95% CIs)	P value
Metformin duration (years)	1.03 (0.96 to 1.10)	0.481	-	-	-	-
Cumulative metformin dose (g)	-	-	1.01 (0.98 to 1.03)	0.531	-	-
T2DM duration (years)	-	-	-	-	1.03 (0.96 to 1.10)	0.374
Total daily dose of metformin (g)	1.82 (0.87 to 3.80)	0.111	1.65 (0.71to 3.85)	0.239	1.82 (0.88 to 3.78)	0.107
Age (years)	1.03 (0.96 to 1.10)	0.416	1.03 (0.96 to 1.10)	0.423	1.03 (0.96 to 1.10)	0.429
HbA1c	0.77 (0.61 to 0.98)	0.034	0.77 (0.61 to 0.98)	0.036	0.77 (0.60 to 0.98)	0.034
Coffee consumption	1.82 (0.57 to 5.80)	0.310	1.81 (0.56 to 5.74)	0.315	1.86 (0.58 to 5.96)	0.294
Race	0.30 (0.10 to 0.88)	0.029	0.29 (0.10 to 0.87)	0.028	0.30 (0.10 to 0.89)	0.031
Acetylsalicylic acid use	2.64 (0.73 to 9.58)	0.140	2.63 (0.73 to 9.51)	0.141	2.61 (0.72 to 9.47)	0.144
Number of metformin daily doses	0.84 (0.33 to 2.11)	0.705	0.84 (0.33 to 2.12)	0.707	0.82 (0.32 to 2.06)	0.669
eGFR (mL/min/1.73 m²)	0.99 (0.98 to 1.01)	0.703	0.99 (0.98 to 1.01)	0.692	0.99 (0.98 to 1.01)	0.759

## The reduced multivariable logistic regression model

Independent variable	Odds ratio (95% CIs)	P value
Total daily dose of metformin (gram)	1.96 (0.99 to 3.88)	0.053
HbA1c	0.71 (0.56 to 0.89)	0.003
Race	0.34 (0.13 to 0.92)	0.033

- Higher metformin daily dose, Lower HbA1c and being non-black South African were the risk factors significantly associated with vitamin B12 deficiency.

Status of peripheral neuropathy and Vit. B12 deficiency were not associated (P=0.209)
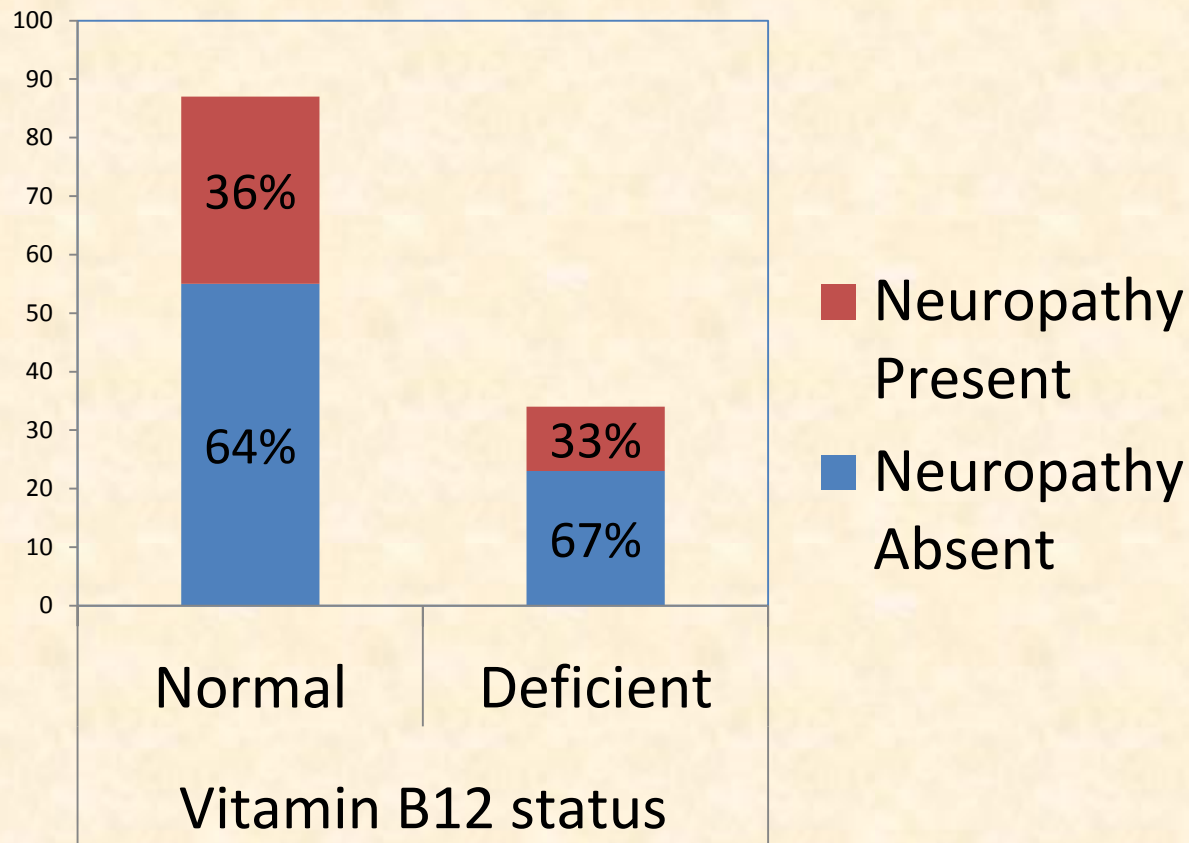
Neuropathy scores and vit B12 levels were not correlated (rho = 0.056 , P = 0.54)

NTSS scores vs Vitamin B12 levels
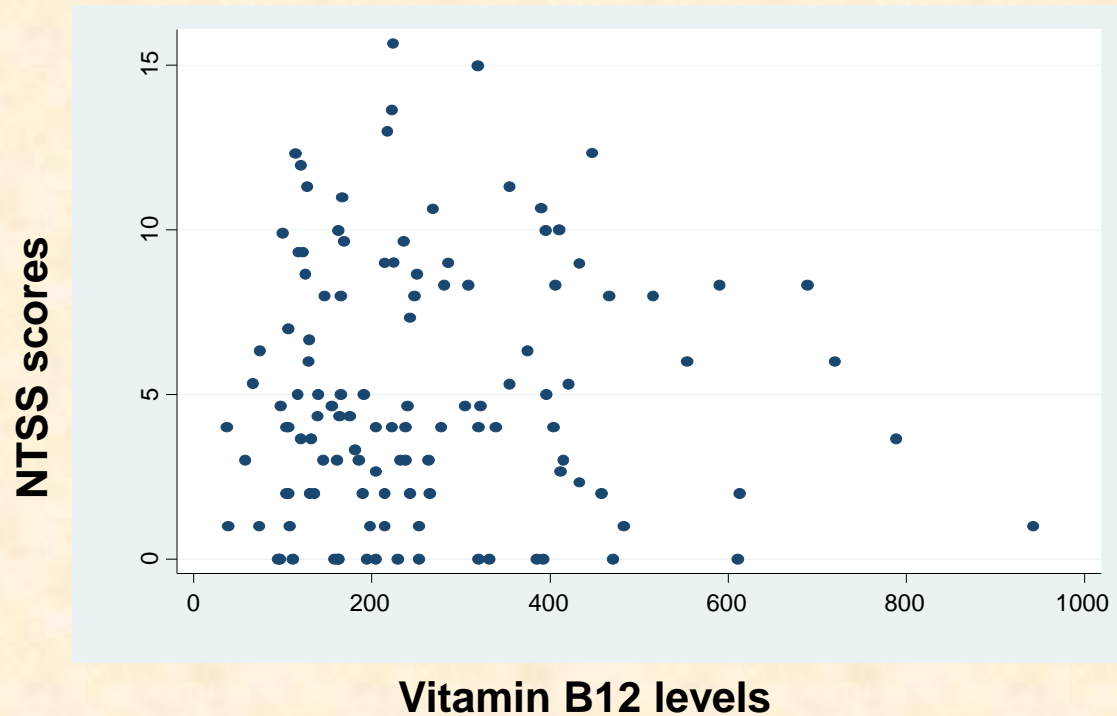
Discussion

- Relationship between HbA1c and Vit. B12 in metformin-treated T2DM patients was previously reported in the logistic regression tables of one study(1)

- Patients with better glycemic control may have better compliance to metformin and thus lower vitamin B12 levels

- Reinstatler *et al* found no statistically significant differences in vitamin B12 levels among black, white and Hispanic metformin-treated patients in the US (2)

- Higher levels of Vit. B12 binding proteins (transcobalamin II and haptocorrin) were reported in black South Africans, explaining their relatively elevated Vit. B12 levels (3)

- Absent association between Vit. B12 and peripheral neuropathy was in line with the results of two and in contrast with those of three studies

  ➢ Interpretations:

    - Animal studies showed metformin has glycemic control-independent neuroprotective effect

    - Progressive and insidious nature of neuropathy caused by metformin-induced Vit. B12 deficiency

Conclusions

- Higher metformin dose and non-black race are risk factors for Vit. B12 deficiency in T2DM patients

- Higher HbA1c was associated with elevated Vit. B12 levels

- Vit. B12 deficiency was not associated with peripheral neuropathy

Limitations

- Cross-sectional study design

- Peripheral neuropathy was only assessed by NTSS-6 questionnaire

- The study was conducted in tertiary academic specialist clinics

References

1. Kang D, Yun JS, Ko SH, Lim TS, Ahn YB, Park YM, et al. Higher prevalence of metformin-induced vitamin B12 deficiency in sulfonylurea combination compared with insulin combination in patients with type 2 diabetes: a cross-sectional study. PLoS One 2014 Oct 9;9(10):e109878.

2. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP,Jr. Association of biochemical B(1)(2) deficiency with metformin therapy and vitamin B(1)(2) supplements: the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care 2012 Feb;35(2):327-333.

3.Fernandes-Costa F, Metz J. A comparison of serum transcobalamin levels in white and black subjects. Am.J.Clin.Nutr. 1982 Jan;35(1):83-86

Thank you