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RESEARCH LETTER

WILEY

Pyridoxamine does not reduce arterial stiffness in an 8-week randomized double-blind placebo-controlled intervention trial with abdominally obese individuals

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1 | BACKGROUND

Arterial stiffening is associated with cardiovascular disease (CVD). Several studies suggest an association of arterial stiffness with advanced glycation end products (AGEs).[1,2] The accumulation of AGEs in long-lived proteins such as collagen may lead to cross-linking and possibly to increased arterial stiffness. The dicarbonyl compound methylglyoxal (MGO), a reactive metabolite mainly formed as a by-product of glycolysis, is the major precursor in the formation of AGEs. MGO levels are elevated in obesity and MGO has been associated with the development of many age-related complications[3] and incident CVD in diabetes.[4,5]

Pyridoxamine (PM), a B6 vitamer and scavenger of MGO, was able to reduce diabetes-induced artery calcification[6] and was able to prevent aortic stiffening in rat and old mouse models.[7–9] We recently showed that PM prevents vascular dysfunction in mice.[10] These findings suggest the role of PM in reducing arterial stiffening by targeting the formation of MGO stress and AGE-induced collagen cross-linking.

In an RCT with abdominally obese individuals, we recently demonstrated a reduction in MGO and endothelial dysfunction markers by 8 weeks of PM supplementation.[11] In this post-hoc analysis of the RCT study, we aim to investigate the effects of this 8 week PM supplementation on arterial stiffness.

2 | MATERIALS AND METHODS

Apparently, healthy individuals with abdominal obesity (54% female; mean age 50 years; mean body mass index 32 kg/m^2) were randomized to an 8-week intervention with either placebo ($n = 36$), a low dose of 25 mg PM ($n = 36$) or a high dose of 200 mg PM ($n = 36$).

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An overview of the population characteristics and enrolment log is provided in Table S1 and Figure S1. For a complete overview of the study design, population characteristics and in- and exclusion criteria, see.[11]

All measurements were performed at baseline (BL) (test day before participants started taking PM capsules) and at follow-up (FU) (after the 8-week intervention period). Regional stiffness measurements (carotid-femoral pulse wave velocity (cfPWV) and augmentation index (AIx)), as well as local carotid artery stiffness measurements (compliance coefficient (CC), distensibility coefficient (cDC), carotid intima-media thickness (cIMT), pulse wave velocity (cPWV) and Young's elastic modulus (cYEM)), were performed and corrected for office blood pressure. An overview of these vascular measurements and corresponding calculations is described in the supplementary methods. Treatment effects were evaluated by one-way analysis of covariance with adjustment for baseline values.

The study was registered at the ClinicalTrials.gov database as NCT02954588 and was approved by the Ethics Committee of Maastricht University Medical Centre.

3 | RESULTS

The total study population comprised 112 participants, of which 108 finished all primary outcome measurements. Table S1 gives an overview of the general characteristics at baseline, Figure S1 describes the enrolment log. The mean compliance during the intervention was >80% based on the number of returned capsules. A dose-dependent trend of pyridoxamine plasma metabolites over the three groups was apparent ($p < 0.01$) as previously published.[11]

3.1 | Dicarbonyl compounds, advanced glycation end products and skin autofluorescence

We previously found a significant reduction of plasma MGO of −22 [−39, −4] nmol/L (mean [95% CI]; $p = 0.017$) in the high dosage group compared to the placebo.[11] Furthermore, the high dose of PM decreased protein-bound MG-H1 in plasma with −211 [−371, −52] nmol/L ($p = 0.010$). There were no significant changes in skin autofluorescence over the 8-week intervention period (Tables 1 and 2).

TABLE 1 Blood pressure, stiffness and skin autofluorescence measures at baseline and follow-up per treatment group.

	Placebo		PM 25 mg/day		PM 200 mg/day	
	BL	FU	BL	FU	BL	FU
Blood pressure						
Systolic BP (mmHg)	128.4 ± 12.7	128.4 ± 14.6	130.1 ± 13.6	127.1 ± 14.1	126.6 ± 13.1	123.5 ± 14.0
Diastolic BP (mmHg)	79.5 ± 8.0	78.9 ± 8.3	80.4 ± 9.7	79.1 ± 8.5	79.3 ± 10.3	76.9 ± 9.2
MAP (mmHg)	99.8 ± 10.4	99.3 ± 10.7	101.0 ± 12.0	99.1 ± 10.5	98.9 ± 12.1	96.1 ± 11.1
Regional stiffness measures						
AIx (%)	19.9 ± 13.0	19.5 ± 13.2	17.4 ± 15.1	16.9 ± 18.9	17.9 ± 13.8	17.5 ± 11.6
cfPWV (m/s)	9.8 ± 2.4	10.0 ± 2.7	10.0 ± 2.2	10.0 ± 2.2	9.4 ± 1.5	9.8 ± 2.2
Carotid stiffness measures						
cIMT (μm)	890 ± 189	863 ± 163	831 ± 112	831 ± 126	832 ± 140	821 ± 138
CC (MPa^{-1})	0.81 ± 0.31	0.9 ± 0.4	0.77 ± 0.36	0.8 ± 0.3	0.85 ± 0.53	0.8 ± 0.4
cDC (MPa^{-1})	15.0 ± 5.1	15.6 ± 5.8	15.2 ± 6.7	16.0 ± 7.4	16.8 ± 7.3	18.1 ± 9.1
cPWV (m/s)	8.5 ± 2.3	8.3 ± 1.9	8.5 ± 1.8	8.3 ± 1.7	8.0 ± 1.5	8.0 ± 2.2
cYEM (MPa)	0.71 ± 0.40	0.69 ± 0.27	0.72 ± 0.32	0.68 ± 0.27	0.62 ± 0.22	0.66 ± 0.53
Carotid stiffness measures corrected for blood pressure						
$cIMT_{corr}$ (μm)	890 ± 191	862 ± 166	830 ± 119	829 ± 132	831 ± 145	816 ± 143
cDC_{corr} (MPa^{-1})	15.3 ± 5.0	15.7 ± 5.6	15.4 ± 5.7	15.8 ± 6.4	16.8 ± 6.6	17.3 ± 7.5
$cPWV_{corr}$ (m/s)	8.4 ± 2.0	8.3 ± 1.6	8.4 ± 1.5	8.3 ± 1.5	8.0 ± 1.4	8.1 ± 2.0
$cYEM_{corr}$ (MPa)	0.70 ± 0.36	0.68 ± 0.24	0.70 ± 0.28	0.67 ± 0.24	0.62 ± 0.22	0.68 ± 0.46
Skin autofluorescence						
Skin autofluorescence (AU)	1.98 ± 0.36	2.03 ± 0.37	2.12 ± 0.34	2.11 ± 0.44	1.91 ± 0.30	1.92 ± 0.37

Note: Data are presented as mean ± SD. $n = 108$ for cfPWV, AIx and skin autofluorescence measurements, $n = 105$ for local stiffness measures and blood pressures.

Abbreviations: Aix, central pressure augmentation index; BL, baseline; BP, (office) blood pressure; CC, compliance coefficient; cDC, carotid distensibility coefficient; cfPWV, carotid-to-femoral pulse wave velocity; cIMT, carotid intima-media thickness; '$_{corr}$', stiffness measures corrected for individual blood pressure; cPWV, carotid pulse wave velocity; cYEM, carotid Young's elastic modulus; FU, follow-up; MAP, mean arterial pressure; PM, pyridoxamine; SD, standard deviation.

TABLE 2 ANCOVA regression analysis with correction for baseline measures.

	Treatment effect - change			
	PM 25 mg/day – placebo		PM 200 mg/day – placebo	
	(Δdifference (95%-CI))	*p*	(Δdifference (95%-CI))	*p*
Blood pressure				
Systolic BP (mmHg)	−2.8 (−6.8–1.2)	0.16	−3.3 (−7.2–0.6)	0.10
Diastolic BP (mmHg)	−0.5 (−2.6–1.6)	0.64	−1.8 (−3.9–0.2)	0.08
MAP (mmHg)	−1.1 (−3.9–1.7)	0.43	−2.4 (−5.2–0.3)	0.08
Regional stiffness measures				
AIx (%)	−0.3 (−3.4–2.9)	0.87	−0.1 (−3.3–3.1)	0.96
cfPWV (m/s)	−0.1 (−0.9–0.6)	0.74	0.1 (−0.6–0.9)	0.71
Carotid stiffness measures				
cIMT (μm)	9.9 (−34.5–56.2)	0.64	−1.0 (−47.3–45.3)	0.97
CC (MPa^{-1})	−0.07 (−0.20–0.06)	0.28	−0.04 (−0.17–0.08)	0.50
cDC (MPa^{-1})	0.2 (−1.7–2.1)	0.82	0.8 (−1.1–2.7)	0.41
cPWV (m/s)	−0.02 (−0.60–0.57)	0.95	0.05 (−0.54–0.63)	0.88
cYEM (MPa)	−0.01 (−0.16–0.14)	0.88	0.04 (−0.11–0.19)	0.61
Carotid stiffness measures corrected for blood pressure				
$cIMT_{corr}$ (μm)	10.4 (−36.3–57.1)	0.66	−3.8 (−50.1–42.6)	0.87
cDC_{corr} (MPa^{-1})	0.1 (−1.6–1.7)	0.95	0.2 (−1.5–1.9)	0.82
$cPWV_{corr}$ (m/s)	0.03 (−0.50–0.56)	0.90	0.12 (−0.41–0.65)	0.65
$cYEM_{corr}$ (MPa)	−0.01 (−0.14–0.13)	0.94	0.04 (−0.09–0.17)	0.52
Skin autofluorescence				
Skin autofluorescence (AU)	−0.03 (−0.18–0.11)	0.65	−0.06 (−0.21–0.08)	0.37

Note: Treatment effect after 8 weeks presented as the mean difference between treatment and placebo group, corrected for baseline measurements. $n = 108$ for cfPWV, Aix and skin autofluorescence measurements, $n = 105$ for local stiffness measures and blood pressures.
Abbreviations: Aix, central pressure augmentation index; BL, baseline; BP, blood pressure; CC, compliance coefficient; cDC, carotid distensibility coefficient; cfPWV, carotid-to-femoral pulse wave velocity; cIMT, carotid intima-media thickness; 'corr', stiffness measures corrected for individual blood pressure; cPWV, carotid pulse wave velocity; cYEM, carotid Young's elastic modulus; FU, follow-up; MAP, mean arterial pressure; PM, pyridoxamine; SD, standard deviation.

3.2 | Blood pressure

No significant changes versus placebo were observed in systolic office blood pressure (low PM −2.8 mmHg [−6.8–1.2], $p = 0.16$; high PM −3.3 mmHg [−7.2–0.6], $p = 0.10$). Diastolic blood pressure was also not significantly altered by the intervention (low PM −0.5 mmHg [−2.6–1.6], $p = 0.64$, high PM −1.8 mmHg [−3.9–0.2], $p = 0.08$; Tables 1 and 2), though the borderline statistical significance for the high dosage should be noted. None of the blood pressure measures were confounded by age or sex (all $p > 0.05$).

3.3 | Pulse wave velocity and augmentation index

Following the 8-week intervention period, no changes in cfPWV versus placebo were observed: (low PM −0.1 [−0.9–0.6] m/s, $p = 0.74$; high PM −0.1 [−0.6–0.9] m/s, $p = 0.71$; Tables 1 and 2). Results were not confounded by age or sex ($p = 0.18$, $p = 0.11$ respectively). In addition, no significant changes in AIx were observed (low PM −0.3 [−3.4–2.9], $p = 0.87$; high PM −0.1 [−3.3–3.1], $p = 0.96$; Tables 1 and 2). AIx was significantly confounded by age ($p = 0.02$), but the changes in Aix remained non-significant.

3.4 | Uncorrected and pressure-corrected carotid stiffness measures

cDC, cYEM and cPWV did not change after treatment with low or high doses of PM over the 8-week intervention period. cPWV was significantly confounded by age ($p = 0.01$). cIMT also did not change after treatment with low or high doses of PM during the 8-week intervention period (Tables 1 and 2). cIMT was confounded by age as well as sex ($p = 0.002$ and $p = 0.047$, respectively).

The pressure-corrected carotid measures did not demonstrate materially different results (Tables 1 and 2). As with the uncorrected measures, age was a confounder of $cPWV_{corr}$ ($p = 0.004$), whereas $cIMT_{corr}$ was influenced by age and sex ($p = 0.003$, $p = 0.04$ respectively). Additionally, cDC_{corr} was influenced by age ($p = 0.03$). All primary outcome measures remained statistically insignificant after correction for age and sex.

4 | DISCUSSION

In this RCT with abdominally obese individuals, we found no treatment effect of an 8-week intervention with PM on arterial stiffness.

Experimental studies have previously described significant improvements in vasculature after PM treatment.[6–8,10,12,13] We previously found a reduction of MGO, MG-H1 and the endothelial dysfunction markers sICAM-1 and sVCAM-1 by PM.[11] Although these studies are of great value to assess the effect of PM in cardiovascular disease, limited clinical studies are available to determine its effect on the macrovasculature in humans.

MGO may affect the arterial wall by both structural and functional alterations. MGO can react irreversibly with lysine and arginine residues to form cross-links, affecting the properties of the arterial wall. In addition to structural alterations of the arterial wall, MGO can affect vascular cell function via intracellular glycation of proteins. Furthermore, the MGO-derived MG-H1 is known to bind to the receptor for AGEs (RAGE) which may lead to low-grade inflammation, all indirectly linked to vascular stiffness.

Although PM supplementation reduces plasma MGO and MG-H1 and improves endothelial function, as estimated by specific biomarkers, this clinical trial also had several limitations. For safety reasons, we used a moderate dosage of PM, and our study population consisted of apparently healthy individuals. As a result, the PM concentration may have been too low, and the participants were too healthy to observe significant improvements in the arterial wall structure. An intervention involving diabetic individuals, who typically exhibit more pronounced structural changes in the vasculature, might yield greater effects on these outcomes. Furthermore, the 8-week intervention may have been too short, although several studies have reported changes in vascular stiffness within an 8-week timeframe.[14] Additionally, the lack of statistically significant findings could be attributed to limited statistical power. To fully elucidate the clinical effect of PM on arterial stiffening, it remains of great interest and relevance to study the effects of PM supplementation over a longer intervention period and/or in patients whose vascular health tends to be more heavily compromised.

5 | CONCLUSION

In this RCT with abdominally obese individuals, we showed that PM supplementation reduces plasma MGO and MG-H1 levels but does not influence arterial stiffness over an 8-week period.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16524.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The current study was approved by the Ethics Committee of Maastricht University Medical Centre (METC163003).

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REFERENCES

1. van Eupen MG, Schram MT, van Sloten TT, et al. Skin autofluorescence and pentosidine are associated with aortic stiffening: the Maastricht study. *Hypertension*. 2016;68(4):956-963.
2. Sveen KA, Dahl-Jørgensen K, Stensaeth KH, et al. Glucosepane and oxidative markers in skin collagen correlate with intima media thickness and arterial stiffness in long-term type 1 diabetes. *J Diabetes Complications*. 2015;29(3):407-412.
3. Schalkwijk CG, Stehouwer CDA. Methylglyoxal, a highly reactive dicarbonyl compound, in diabetes, its vascular complications, and other age-related diseases. *Physiol Rev*. 2020;100(1):407-461.
4. Hanssen NMJ, Scheijen JLJM, Jorsal A, et al. Higher plasma methylglyoxal levels are associated with incident cardiovascular disease in individuals with type 1 diabetes: a 12-year follow-up study. *Diabetes*. 2017;66(8):2278-2283.
5. Hanssen NMJ, Westerink J, Scheijen J, et al. Higher plasma methylglyoxal levels are associated with incident cardiovascular disease and mortality in individuals with type 2 diabetes. *Diabetes Care*. 2018;41(8):1689-1695.
6. Brodeur MR, Bouvet C, Bouchard S, et al. Reduction of advanced-glycation end products levels and inhibition of RAGE signaling decreases rat vascular calcification induced by diabetes. *PLoS One*. 2014;9(1):e85922.
7. Wu ET, Liang JT, Wu MS, Chang KC. Pyridoxamine prevents age-related aortic stiffening and vascular resistance in association with reduced collagen glycation. *Exp Gerontol*. 2011;46(6):482-488.
8. Chang KC, Liang JT, Tsai PS, Wu MS, Hsu KL. Prevention of arterial stiffening by pyridoxamine in diabetes is associated with inhibition of the pathogenic glycation on aortic collagen. *Br J Pharmacol*. 2009;157(8):1419-1426.
9. Reeve EH, Kronquist EK, Wolf JR, et al. Pyridoxamine treatment ameliorates large artery stiffening and cerebral artery endothelial dysfunction in old mice. *J Cereb Blood Flow Metab*. 2023;43(2):281-295.
10. Maessen DE, Brouwers O, Gaens KH, et al. Delayed intervention with Pyridoxamine improves metabolic function and prevents adipose tissue inflammation and insulin resistance in high-fat diet-induced obese mice. *Diabetes*. 2016;65(4):956-966.
11. Van den Eynde MDG, Houben A, Scheijen J, et al. Pyridoxamine reduces methylglyoxal and markers of glycation and endothelial dysfunction, but does not improve insulin sensitivity or vascular function

in abdominally obese individuals: a randomized double-blind placebo-controlled trial. *Diabetes Obes Metab*. 2023;25(5):1280-1291.
12. Alderson NL, Chachich ME, Youssef NN, et al. The AGE inhibitor pyridoxamine inhibits lipemia and development of renal and vascular disease in Zucker obese rats. *Kidney Int*. 2003;63(6):2123-2133.
13. Watson AM, Soro-Paavonen A, Sheehy K, et al. Delayed intervention with AGE inhibitors attenuates the progression of diabetes-accelerated atherosclerosis in diabetic apolipoprotein E knockout mice. *Diabetologia*. 2011;54(3):681-689.
14. Scholtes RA, Mosterd CM, Hesp AC, Smits MM, Heerspink HJL, van Raalte DH. Mechanisms underlying the blood pressure-lowering effects of empagliflozin, losartan and their combination in people with type 2 diabetes: a secondary analysis of a randomized crossover trial. *Diabetes Obes Metab*. 2023;25(1):198-207.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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