Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2164–2169

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Strategies to ameliorate endothelial dysfunction associated with metabolic syndrome, where are we?

Sigfrid Casmir Shayo, Shigeru Kawade, Kazuma Ogiso, Nishio Yoshihiko

Department of Diabetes and Endocrine Medicine Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima, 890-8520, Japan

ARTICLE INFO

Article history:
Received 20 April 2019
Accepted 12 May 2019

Keywords:
Metabolic syndrome
Endothelial-dependent vasodilation
Endothelial function

ABSTRACT

There is a paucity of aggregated clinical trials on strategies of ameliorating endothelial dysfunction associated with Metabolic Syndrome (MS). We reviewed clinical trials conducted between 2008 and 2017, reporting on strategies of improving endothelial function in patients with MS. A comprehensive search of published articles by the Google Scholar and PubMed were carried out. Only studies involving non-invasive, objective measurement of endothelial function were included. Thirty (30) studies were selected for analysis, in which physical exercise training, diet modification, calcium channel blockers + alpha-lipoic acid, bezafibrate, allopurinol, mesoglycan, and L-arginine supplementation significantly improved Endothelial-Dependent Vasodilation (EDV) in patients with MS but without cardiovascular diseases. Large multicenter clinical trials are required to address the question of generalizability of these findings.

1. Introduction

Metabolic syndrome (MS) is a global epidemic of our time. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII, 2005), MS is defined as the presence of three [3] of the following five [5] criteria; visceral obesity assessed by waist circumference of greater than 40 inches and 35 inches in males and females respectively, fasting blood glucose of greater than or equal to 100 mg/dl, serum triglycerides of greater than or equal to 150 mg/dl, serum HDL-cholesterol of less than 40 mg/dl and 50 mg/dl in males and females respectively and systolic blood pressure and diastolic blood pressure values of greater than 130 mmHg and 85 mmHg respectively [1.] It is estimated that about 20–25% of the adult population globally have MS. People with MS, are two times more likely to die from heart attack and stroke than their counterparts. Additionally, people with MS are five times more likely to develop type 2 diabetes mellitus, which further accelerates their risk of cardiovascular morbidity and mortality [2]. Impaired endothelial-dependent vasodilatation (EDV), also known as an impaired endothelial function is an early pathogenic event that happens before stroke and heart attack and has been proved by studies to be prevalent in people with metabolic syndrome [3–8]. Studies have shown that there is a well-established clinical association between vascular endothelial cell dysfunction, atherosclerosis, stroke and cardiovascular events [9–12]. Vascular endothelial dysfunction is thought to play a crucial role in the pathogenesis of Acute coronary syndrome (ACS) and Sudden Cardiac Death (SCD). Measurement of vascular endothelial function in humans is currently done in clinical settings. There are both invasive and non-invasive methods of measuring EF but there has been a growing interest in the non-invasive examination of endothelium-dependent Flow-mediated dilation (FMD) of the conduit brachial artery by using vascular Ultrasound. FMD is safe, faster, non-invasive, physiological, and highly correlates with endothelial dysfunction in the coronary circulation. On the other hand, serum circulating levels of soluble Intercellular cell adhesion molecules (sICAM), soluble vascular cell adhesion molecules (sVCAM), E-selectin, Von Willebrand factor, tissue plasminogen activator, and plasminogen activator inhibitor-1 can also be used to evaluate the extent of endothelial dysfunction [13]. (see Table 1)

Accumulating evidence shows that endothelial dysfunction associated with metabolic syndrome and diabetes can be improved by both lifestyle and pharmacological interventions. However, in the literature, there is a paucity of aggregated randomized controlled trials and prospective studies showing the current strategies of ameliorating endothelial dysfunction in patients with

E-mail addresses: shayosigfrid@yahoo.com, sigshayo@m.kufm.kagoshima-u.ac.jp (S.C. Shayo), fk_ks0926@yahoo.co.jp (S. Kawade), nomushi7@m.kufm.kagoshima-u.ac.jp (K. Ogiso), ynishio@m3.kufm.kagoshima-u.ac.jp (N. Yoshihiko).

https://doi.org/10.1016/j.dsx.2019.05.005
1871-4021/

Table 1
Summary of few included studies.

No	Author's year of Publication	Study design	Sample size (n)	Intervention group	Comparison/ control group	Intervention time	Outcome measure p-value	Author's conclusion
1	Silva et al., 2011, Brazil	RCT	31	High-intensity aerobics	Low intensity aerobics	6 weeks	FMD $p < 0.005$	High intensity aerobic training improved EF in patients with MS and T2DM
2	Seligman et al., 2011, Brazil	RCT	75	Accessible healthy eating (AHE) &3-times-a-week fitness (>75% peak VO2) program	AHE & 10 000-steps-a-day or AHE&1-h walking-a day.	12 weeks	FMD $P = 0.036$	Intensive exercise (fitness) combined with sugar restriction can modulate Endothelial-dependent Vasodilatation, EDV.
3	Vaccarino, 2013, America.	RCT	44	Consciously Resting Meditation (CRM) 2xday for 20 min	Health education	12 months	FMD ($p = 0.51$)	CRM cannot improve EDV significantly.
4.	Stull at.al,2015, America	RCT	68	45 g/day of blueberries	Placebo	6 weeks	RHI ($p = 0.0023$)	Daily consumption of blueberries over a period of 6 weeks improved EF in subjects with MS
5.	Katz et al., 2012 America	RC-XT	46	ad libitum diet enriched with 56 g/day of shelled English walnut/day	ad libitum diet without walnut enrichment.	8 weeks (washout period = weeks)	FMD ($p = 0.019$)	Daily consumption of walnuts by overweight adults with Visceral obesity improves EF.
6.	Tousoulis et al., 2013 Greece	RCT	29	2 g/day of Omega 3-PUFA	Placebo	12 weeks	FMD ($p < 0.001$	Omega-3 PUFA treatment improves EF, arterial stiffness and systemic inflammation in MS
7	Hwang et al., 2015 America	RCT	04	100 mg/day of eplerenone	Placebo	FMD ($p = 0.4$)	1month	Selective mineralocorticoid receptor blockade has a limited role in improving EF and Insulin resistance in adults with MS.
8.	Ohno et al., 2014 Japan	RCT	10	400 mg/day of Bezafibrate	Cross-over	4 weeks	FMD ($P = 0.04$)	Bezafibrate significantly decreased postprandial endothelial dysfunction
9	O.Yiginer et al., 2008 Turkey	RCT	50	Allopurinol 300 mg/day/PO	Placebo	1month	FMD ($p < 0.01$)	Treatment with Allopurionol, a Xanthine oxidoreductase inhibitor, improves EF and oxidative stress by lowering Myeloperoxidase levels in patients with MS
10	Valvano A. et al., 2015 Italy.	RCT	30	-Intramuscular Mesoglycan 60 mg STAT -Cap mesoglycan 50 mg twice a day, for 90 days	Placebo	3 months	FMD -Acute administration ($p < 0.05$) -Chronic administration ($p = 0.04$)	Acute and chronic administration of mesoglycan, causes significant improvement in vascular physiology, detected by improvement in EDV
11	Bobby V. et al. 2010, America	RCT -Cross-over design	40	-Quinapril (40 mg/day) for 8 weeks -Quinapril + ALA (600 mg/day) for 8 weeks	Cross-over design	2 months	FMD -p<0.055 versus baseline for Quinapril -P<0.005 vs baseline for Quinapril+ ALA	In patients with hypertension and MS, quinapril (ACE inhibitor) improves EDV, and its effect is strongly potentiated by Alpha lipoic acid
12	Barona et al., 2012 Colombia	RC-XT 3 weeks washout	25 men	Grape supplements	Placebo	1 month	FMD ($P < 0.0001$)	Grape polyphenols consumption reduce systolic blood pressure, improves EDV and lowers soluble cell adhesion molecules in MS.
13	Telichowska S.K et al., 2014	RCT	40	High dose egg -derived phospholipid supplement	Olive oil preparation	1 month	FMD	High dose egg-derived phospholipid causes significant improvement in EDV and a decrease in waist/hip ratio in patients with MetS
14	Monti D. et al., Italy	RCT	15	6.6 g of L-arginine enriched biscuit snack/day	Placebo	2 weeks	PI-BF $P < 0.01$	L-arginine enriched biscuit snacks improved vascular endothelial function (increased PI-BF), glucose metabolism and insulin sensitivity in patients with obesity, MS and IGT
15	Reverri J.et al., America	RCT Cross-over design	17	Soy nut snack	Macronutrient-matched control snack	4 weeks (2-week washout period)	RHI ($P > 0.05$)	Soy consumption has a modest effect on EDV but significantly improves arterial stiffness.

RCT-Randomized controlled trial, FMD; Flow-mediated dilatation, T2DM; Type 2 diabetes, EF; Endothelial function, RHI; Reactive hyperemia Index, MS; Metabolic Syndrome, EDV; Endothelial-dependent Vasodilatation, RC-XT; Randomized Controlled Cross over study, ALA-Alpha lipoic acid, ACE; Angiotensin Converting Enzyme, PI-BF; Post-Ischemic Blood Flow, IGT; Impaired Glucose Tolerance Test, RHI-Reactive Hyperemia Index.

metabolic syndrome. Knowledge of strategies of ameliorating endothelial dysfunction in metabolic syndrome is important because it might help to prevent or delay the onset of atherosclerosis, and hence reducing the incidence of stroke and heart attack. In this review we shall describe the current strategies of improving endothelial function in patients of metabolic syndrome as reported by prospective and randomized control trials conducted between 2008 and 2017 inclusively.

2. Methods

2.1. Data sources and selection criteria

This review was carried out with a comprehensive search of

published articles in PubMed and Google Scholar databases in January 2018. The review was guided by the question; What are the strategies of ameliorating endothelial dysfunction in metabolic syndrome as reported by RCTs and prospective studies between years 2008–2017? Keywords used in the searching process; metabolic syndrome, endothelial function. In this review, minimal requirements laid down by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were achieved. (see Fig.1).

2.2. Inclusion criteria

We included studies reporting on strategies for improving endothelial function in patients with metabolic syndrome. These studies must have involved non-invasive, objective measurement of Endothelial-dependent Vasodilation, such as the FMD and Endo-PAT.

2.3. Exclusion criteria

We excluded studies reporting on strategies of ameliorating endothelial dysfunction in medical conditions other than the metabolic syndrome. In addition, studies published in a language other than English or published before the year 2008 were excluded.

2.4. Synopsis of articles included in the analysis

2.4.1. Non-pharmacological interventions for improving vascular endothelial function in MS

A review of articles published between years 2008–2017 inclusively, has shown that endothelial dysfunction associated with MS can be modified by several non-pharmacological interventions. Below is the summary of non-pharmacological interventions and their role in altering endothelial dysfunction associated with MS.

2.5. The role of physical exercise training

Studies have established that physical exercise increases vascular shear stress and intracellular calcium availability, both of which promote EDV through the production of nitric oxide. In a

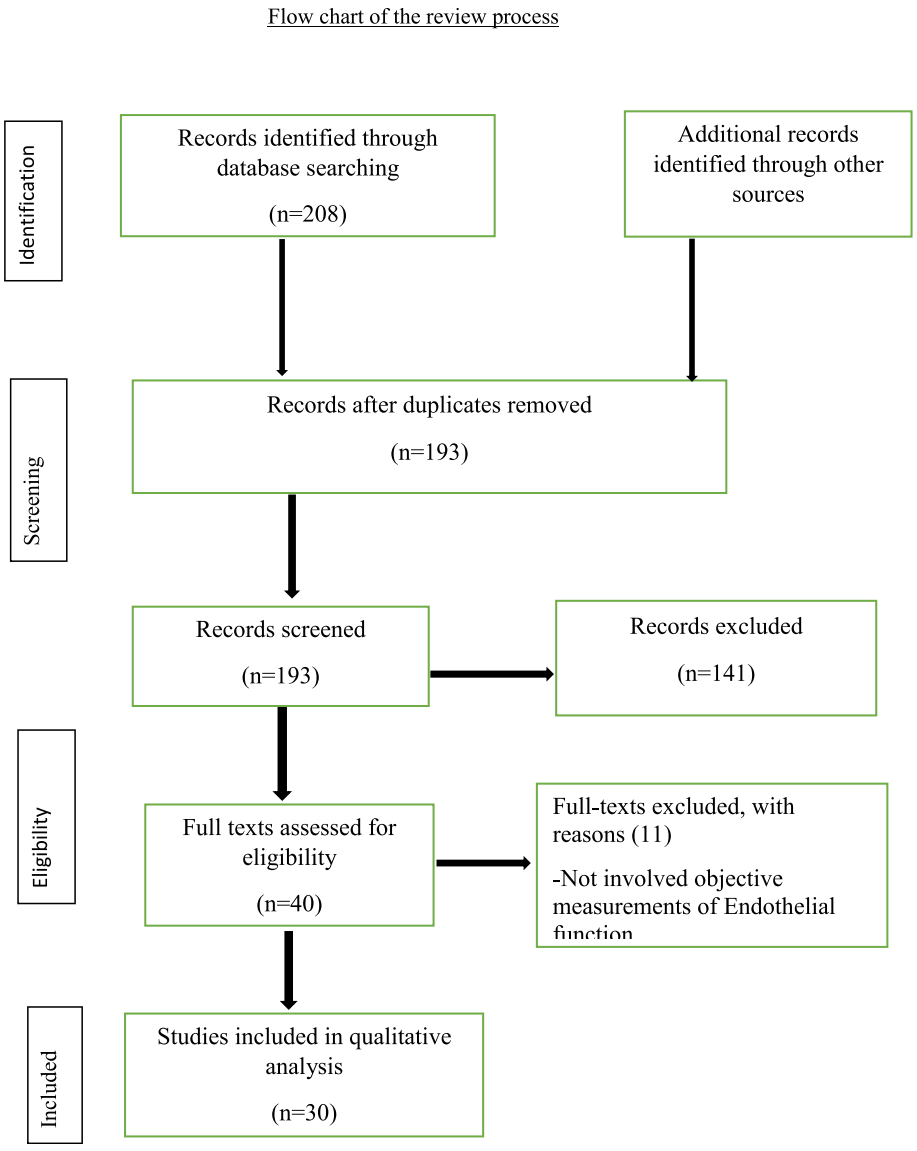

Fig. 1. PRISMA flow diagram showing how the articles included in the review were obtained.

randomized controlled trial done in Brazil, six [6] weeks of high-intensity aerobic exercise training in patients with diabetes and MS significantly improved the brachial arterial flow-mediated EDV. Parallel with this, high-intensity aerobic exercise also significantly improved the glycemic profile and reduced LDL-cholesterol [14].

2.6. The combined role of exercise and diet modification

Doing physical exercises parallel with modifying one's diet is thought by many researchers to have a favorable effect MS parameters. The role of restricting sugars and saturated fatty acids in promoting cardiovascular health has also been extensively researched. A study done among 75 Brazilian men with MS shows that 12 weeks of high-intensity exercise (achieving 75% of individual's maximum heart rate) going hand-in-hand with carbohydrate restriction, led to more significant improvement in brachial arterial FMD than a tailored low-fat diet with 1 h of walking per day [15]. Contrary to this finding, a non-randomized controlled interventional study among 52 individuals (26 with MS and 26 without MS), lifestyle modification (aerobic exercise and Mediterranean-style diet) prescribed by family physician over a period of 24 weeks resulted in a significant change of other metabolic syndrome components but not forearm flow-mediated dilation [15].

2.7. The role of relaxation techniques

Evidence from studies conducted in man and experimental animals shows that mental stress is one of the culprits for impaired endothelial-dependent vasodilation. In a randomized controlled trial among 75 black Americans with MS, mantra meditation, one of the forms of consciously resting meditation done by Hindus, relatively but not significantly improved brachial artery flow-mediated dilation (FMD%) [16].

2.8. The role of antioxidant foods

It is well known that oxidative stress from any cause results in impaired EDV via different mechanisms, such as decreasing nitric oxide availability. A randomized, double-blind, placebo-controlled clinical trial among 44 subjects with MS showed that consumption of 45 g/day of antioxidant-rich blueberries over a period of six weeks, significantly improved vascular endothelial function [17]. Also, consumption Longevinex, modified resveratrol with antioxidant activity, significantly increased the fore-arm flow-mediated dilation (FMD) in Japanese patients with MS who were on standard treatment [21]. In Colombia, a randomized controlled cross over study showed that consumption of 46 g/day of grape polyphenols over a period of one month, resulted in significant improvement in systolic blood pressure, endothelial function and circulating cell adhesion molecules in 24 men with metabolic syndrome (17). On the other hand consumption of quercetin, a major dietary flavonoid naturally occurring in many plant foods especially onions, for a period of 8 weeks did not improve EF in MS patients when compared to placebo [18].

2.9. Mediterranean diet and metabolic syndrome

Consumption of Mediterranean diet is well known to have cardiometabolic benefits. A randomized controlled trial in Athens showed that reinforcement of Mediterranean diet consumption over a period of 2 months in 90 subjects with abdominal obesity, significantly improved the fore-arm flow-mediated dilation (FMD %) [19]. It is suggested that Mediterranean food fights oxidative stress and low-grade systemic inflammation. Besides, its favorable effect in lipid profile might account for the improvement in endothelial function.

2.10. The role of foods rich in polyunsaturated fatty acids (PUFA)

Consumption of polyunsaturated fatty acids contained in either fish oil or in concentrated pharmaceutical preparations has demonstrated appreciable cardiovascular benefits. In a randomized placebo-controlled trial done among Greek patients with MS, 2 g/day daily consumption of omega- 3 polyunsaturated fatty acids improved endothelial function with a concomitant anti-inflammatory and lipid-lowering effect [20].

2.11. The role played by nuts

Nuts are better known to be highly rich in polyunsaturated fatty acids, monounsaturated fatty acids, and antioxidant minerals such as selenium, manganese, and copper. The role of nuts in improving EDV in MS is still controversial. Daily ingestion of 56 g/day of shelled English walnuts for a period of 8 weeks, has been shown to improve EDV significantly in overweight American adults with visceral obesity. However, a similar study done by Uriarte et al. among Spanish subjects with MS showed that a daily serving of mixed nuts (walnuts, almonds, and hazelnuts) has no effect on EDV [25,26].

2.12. Encapsulated fruit and vegetable concentrates

Commercially available fruits and vegetable concentrates were tested for the ability to improve endothelial function associated with MS. Randomized, double-blind, placebo-controlled crossover clinical trial with three treatment arms involving 64 patients with MS demonstrated that 8 weeks consumption of encapsulated fruit and vegetable concentrates could not improve EDV [22].

2.13. The role of isoflavones

It is well known that the risk of cardiovascular disease in women increases on the transition to menopause because of a relative decline of estrogen hormone. In a randomized controlled trial, consumption of a phytoestrogen, genistein supplement at a dose of 54 mg/day significantly improved the fore-arm FMD and lipid profile in postmenopausal women with MS in Italy [19]. However, in a randomized controlled crossover trial, consumption of soy nuts which are known to be highly rich in isoflavone had only a modest benefit on endothelial function [21].

2.14. Moderation of carbohydrate and saturated fatty acids intake

In MS patients with atherogenic dyslipidemia, consumption of carbohydrate-restricted diet (1504 Kcal, carbohydrate: fat: protein = 12%:59%:28%) for 12 weeks significantly improved 3 h postprandial fore-arm FMD as compared to low fat diet (1478 Kcal, carbohydrate: fat: protein = 56%:24%:20%). In a similar study, consumption of moderate fat diet (fat: carbohydrate = 40en%:45% en) for 4 weeks, improved the atherogenic dyslipidemia of MS more than low-fat diet (fat: carbohydrate = 20%en:65%en), but with no significant difference in insulin resistance or endothelial function [27,28]. Furthermore, consumption of a diet rich in high monounsaturated fatty acids and phospholipids, significantly improved the EDV (29) (30). Low-fat milk taken as a breakfast (following a night of fasting), also improved the EDV more significantly than isocaloric rice milk in patients with MS (31).

2.15. The role of L-arginine supplementation

Many studies have underscored the role of L-arginine supplementation in improving EF in cardiometabolic diseases. Mont et al. did a randomized double-blind crossover study in 15 obese subjects with impaired glucose tolerance and MS. In this study, patients received either 6.6 g of L-Arginine enriched biscuits or placebo biscuits in 1600 Kcal of diet for 14 days. L-Arginine supplementation resulted in a significant improvement of vascular EF, glucose tolerance, insulin secretion and sensitivity (22).

2.15.1. Pharmacological interventions for improving endothelial function in metabolic syndrome

Quite a number of studies have tried to shine a light on the vascular endothelial benefit of the conventional medications used in the management of diabetes and hypertension. The endothelial protective role of selective mineralocorticoid receptor antagonist, eplerenone in patients with metabolic syndrome has been studied. Hwang et al. did a randomized double-blind, placebo-controlled, cross over study among adults (62.6 ± 3.2) with metabolic syndrome whose results did not support the protective role of eplerenone to the vascular endothelium, but showed that 100 mg/day of eplerenone improved systolic hypertension in these patients [23]. Similar cross over study done by Khan et al. in Atlanta showed that the use of calcium channel blocker, quinapril (40 mg/day for 8 weeks) alone or in combination with alpha-lipoic acid improved vascular endothelial function as measured by forearm FMD in diabetic patients with metabolic syndrome [24]. The incretin hormone, Glucagon-like peptide 1 (GLP-1), apart from its ability to lower blood sugar, it can also have some vascular protective function. An experimental study done in Italy indicates that GLP-1 enhanced the insulin-stimulated vasodilator responsiveness in patients with obesity-related metabolic syndrome [25].

The role of lipid-lowering drugs in improving EF in MS has also been researched. Ohno et al. conducted a crossover study among 10 middle-aged Japanese patients with MS in which 400 mg/day of bezafibrate daily for a period of 4 weeks significantly improved postprandial EF. Bezafibrate use in this study was also associated with a reduction of postprandial Triglyceride-Rich Lipoproteins (TRL). A crossover study by Westerink et al., also demonstrated that statins and cholesterol-lowering drug (ezetimibe) have a modest effect on the endothelial-dependent vasodilation in patients with MS [26]. Studies have evidenced that elevated levels of uric acid which points towards the high activity of the enzyme Xanthine oxidoreductase (XOR) is implicated in the pathogenesis of atherosclerosis. Yiginer et al. did a randomized, placebo-controlled trial among Turkey patients with MS in which the use of 300 mg/day of allopurinol over a period of one month, resulted in significant improvement of oxidative stress and EF measured by forearm FMD ($p < 0.01$) [27].

Finally, acute and long-term administration of mesoglycan, a glycosaminoglycan compound which is harvested from porcine intestinal mucosa has demonstrated vascular health benefits. In a randomized, placebo-controlled trial done in Italy involving 30 human subjects with MS, acute administration of 60 mg of intramuscular mesoglycan, and 50 mg twice a day oral dosage of mesoglycan for 90 days resulted in significant improvement in endothelial-dependent vasodilation as measured by FMD(28).

3. Conclusion

Our review reveals that in patients with MS but without cardiovascular diseases, both lifestyle modification and pharmacological interventions can help to improve EDV**.** Aerobic exercise in order of increasing intensity, diet modification (Mediterranean diet consumption, carbohydrate restriction, consumption of marine PUFA, anti-oxidant foods e.g. blueberries, and L-arginine supplementation) significantly improved EDV. Furthermore, in postmenopausal women with MS, consumption of a phytoestrogen, the so-called genistein appreciably improved the EDV. On the other hand, prescription of a combination of calcium channel blockers and alpha-lipoic acid, LDL-cholesterol and Triglyceride lowering drug (bezafibrate), xanthine oxidoreductase inhibitor (allopurinol), and mesoglycan is a promising intervention in improving EDV in MS without cardiovascular diseases. Nevertheless, because most trials were done in the developed world and involved small sample size, large multicenter clinical trials should be done to ensure inclusivity and generalizability these findings.

References

[1] Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech [Internet] 2009;2(5–6):231–7. Available from: http://dmm.biologists.org/cgi/doi/10.1242/dmm.001180.

[2] Idf. Epidemiolgy and Prevention. IDF worldwide definition of the metabolic syndrome, vol. 50. International Diabetes Federation; 2005. p. 514211. Available from: http://www.idf.org/metabolic-syndrome.

[3] Esposito K, Ciotola M, Carleo D, Schisano B, Saccomanno F, Sasso FC, et al. Effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome. Diabetes Care 2006;29(5):1071–6.

[4] Hamburg NM, Larson MG, Vita JA, Vasan RS, Keyes MJ, Widlansky ME, et al. Metabolic syndrome, insulin resistance, and brachial artery vasodilator function in framingham offspring participants without clinical evidence of cardiovascular disease. Am J Cardiol 2008;101(1):82–8.

[5] Lteif AA, Han K, Mather KJ. Obesity, insulin resistance, and the metabolic syndrome: determinants of endothelial dysfunction in whites and blacks. Circulation 2005;112(1):32–8.

[6] Bahia L, Aguiar LG, Villela N, Bottino D, Godoy-Matos AF, Geloneze B, et al. Relationship between adipokines, inflammation, and vascular reactivity in lean controls and obese subjects with metabolic syndrome. Clinics 2006;61(5):433–40. Available from: http://www.scielo.br/pdf/clin/v61n5/31806.pdf.

[7] Koh KK, Oh PC, Sakuma I, Lee Y, Han SH, Shin EK. Rosuvastatin dose-dependently improves flow-mediated dilation, but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients. Int J Cardiol 2016;223:488–93.

[8] Dell'Omo G, Penno G, Pucci L, Mariani M, Del Prato S, Pedrinelli R. Abnormal capillary permeability and endothelial dysfunction in hypertension with comorbid Metabolic Syndrome. Atherosclerosis 2004;172(2):383–9.

[9] Landmesser U. Endothelial function: a critical determinant in atherosclerosis? Circulation 2004;109(21_suppl_1). II-27-II-33 Available from: http://circ.ahajournals.org/cgi/doi/10.1161/01.CIR.0000129501.88485.1f.

[10] Volpe M, Cosentino F. Abnormalities of endothelial function in the pathogenesis of Stroke : the importance of endothelin. J Cardiovasc Pharmacol 2000;35(4 S2):S45–8.

[11] Lerman A, Zeiher AM. Endothelial function. Circulation 2005;111:363–8.

[12] Widlansky ME, Gokce N, Keaney JF, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003;42:1149–60.

[13] Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Endothelial dysfunction in metabolic syndrome: prevalence, pathogenesis and management. Nutr Metabol Cardiovasc Dis 2010;20:140–6.

[14] Silva CA da, Ribeiro JP, Canto JCAU, Silva RE da, Silva Junior GB, Botura E, et al. High-intensity aerobic training improves endothelium-dependent vasodilation in patients with metabolic syndrome and type 2 diabetes mellitus. Diabetes Res Clin Pract 2012;95(2):237–45.

[15] Aizawa K, Shoemaker JK, Overend TJ, Petrella RJ. Metabolic syndrome, endothelial function and lifestyle modification. Diabetes Vasc Dis Res 2009;6(3):181–9.

[16] Vaccarino V, Kondwani KA, Kelley ME, Murrah NV, Boyd L, Ahmed Y, et al. Effect of meditation on endothelial function in black Americans with metabolic syndrome: a randomized trial. Psychosom Med 2013;75(6):591–9.

[17] Barona J, Aristizabal JC, Blesso CN, Volek JS, Fernandez ML. Grape polyphenols reduce blood pressure and increase flow-mediated vasodilation in men with metabolic syndrome. J Nutr 2012;142(9):1626–32. Available from: http://jn.nutrition.org/cgi/doi/10.3945/jn.112.162743.

[18] Pfeuffer M, Auinger A, Bley U, Kraus-Stojanowic I, Laue C, Winkler P, et al. Effect of quercetin on traits of the metabolic syndrome, endothelial function and inflammation in men with different APOE isoforms. Nutr Metabol Cardiovasc Dis 2013;23(5):403–9.

[19] Rallidis LS, Lekakis J, Kolomvotsou A, Zampelas A, Vamvakou G, Efstathiou S, et al. Close adherence to a Mediterranean diet improves endothelial function in subjects with abdominal obesity [cited 2018 Jan 16] Am J Clin Nutr 2009 Aug 1;90(2). 263–8, http://www.ajcn.org/cgi/doi/10.3945/ajcn.2008.27290. Available from:.

[20] Tousoulis D, Plastiras A, Siasos G, Oikonomou E, Verveniotis A, Kokkou E, et al.

Omega-3 PUFAs improved endothelial function and arterial stiffness with a parallel antiinflammatory effect in adults with metabolic syndrome. Atherosclerosis 2014;232(1):10–6. Available from: https://doi.org/10.1016/j.atherosclerosis.2013.10.014.

[21] Marsh R, Stefan M, Bansal R, Hao X, et al. Soy provides modest benefits on endothelial function without affecting inflammatory biomarkers in adults at cardiometabolic risk. Mol Nutr Food Res 2016;77(7):616–23.

[22] Monti LD, Casiraghi MC, Setola E, Galluccio E, Pagani MA, Quaglia L, et al. L-Arginine enriched biscuits improve endothelial function and glucose metabolism: a pilot study in healthy subjects and a cross-over study in subjects with impaired glucose tolerance and metabolic syndrome. Metabolism [Internet] 2013;62(2):255–64. Available from: https://doi.org/10.1016/j.metabol.2012.08.004.

[23] Hwang M-H, Yoo J-K, Luttrell M, Meade TH, English M, Christou DD. Effect of selective mineralocorticoid receptor blockade on flow-mediated dilation and insulin resistance in older adults with metabolic syndrome [cited 2018 Jan 16] Metab Syndrome Relat Disord 2015 Oct;13(8). 356–61. Available from: http://online.liebertpub.com/doi/10.1089/met.2015.0044.

[24] Khan BV, Rahman ST, Haque T, Merchant N. Quinapril and lipoic acid improve endothelial function and reduce markers of inflammation: results of quinapril and lipoic acid in the metabolic syndrome (quality) study. J Am Coll Cardiol 2010;55(10). A54.E510. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0735109710605116.

[25] Hirlanda GIG. Effects of GLP-1 on forearm vasodilator function and glucose disposal during. 2013.

[26] Westerink J, Deanfield JE, Imholz BP, Spiering W, Basart DC, Coll B, et al. High-dose statin monotherapy versus low-dose statin/ezetimibe combination on fasting and postprandial lipids and endothelial function in obese patients with the metabolic syndrome: the PANACEA study. Atherosclerosis 2013;227(1):118–24.

[27] Yiginer O, Ozcelik F, Inanc T, Aparci M, Ozmen N, Cingozbay BY, et al. Allopurinol improves endothelial function and reduces oxidant-inflammatory enzyme of myeloperoxidase in metabolic syndrome. Clin Res Cardiol 2008;97(5):334–40.

[28] Valvano A, Bosso G, Apuzzi V, Riccone F, Saccà L, Oliviero U. Mesoglycan improves vascular reactivity and insulin sensitivity in patients with metabolic syndrome. Atherosclerosis 2015:407–13.