British Journal of Medicine & Medical Research
11(2): 1-9, 2016, Article no.BJMMR.20571
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

Sulfasalazine Improves Insulin Resistance and Endothelial Dysfunction in Metabolic Syndrome Patients

Kanchan Vohra[1], Pawan Krishan[1*], Sudhir Varma[2] and Harpreet Singh Kalra[3]

[1]Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India.
[2]Department of Cardiology, Sadbhavna Medical and Heart Institute, Patiala, India.
[3]Department of Medicine, Sadbhavna Medical and Heart Institute, Patiala, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author KV designed the study, wrote the protocol and wrote the first draft of the manuscript under the supervision of authors PK and SV. Author KV managed the literature searches. Authors PK and KV managed the analyses of the study performed. Authors SV and HSK managed the experimental process. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/20571
Editor(s):
(1) Alexander D. Verin, Vascular Biology Center, Georgia Regents University Augusta, Georgia.
Reviewers:
(1) Jesus Peteiro, University of A Coruna, Spain.
(2) Ds Sheriff, Benghazi University, Benghazi, Libya.
(3) Sossa Charles, University of Abomey Calavi, Benin.
Complete Peer review History: http://sciencedomain.org/review-history/11491

Original Research Article

Received 31st July 2015
Accepted 1st September 2015
Published 21st September 2015

ABSTRACT

Aim: Metabolic syndrome (MetS) and all its components are independently characterized by the presence of low-grade chronic inflammation. The study aimed at controlling inflammation using sulfasalazine 500mg, once a day treatment in comparison to placebo in MetS patients.
Study Design: Double blind, randomized, placebo controlled study.
Place and Duration of Study: Sadbhavna Medical and Heart Institute, Patiala; and, Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, Punjab, between January-November 2014.
Methodology: 50 eligible subjects (Male / Female = 45/5, n=25/group), fulfilling the National Cholesterol education Program-Adult Treatment Panel (NCEP-ATP III) diagnostic criteria of MetS, were randomly assigned to once daily drug or placebo tablets for 20 weeks. Blood pressure, serum

**Corresponding author: Email: pawankrishan8@gmail.com;*

high sensitivity C-reactive protein (hsCRP), tumor necrosis factor–alpha (TNF-α), lipid profile, fasting plasma glucose and insulin levels, homeostatic model assessment-insulin resistance (HOMA-IR), endothelial-dependent flow-mediated dilation (FMD) of brachial artery, right common carotid artery's intima-media thickness (IMT) and artery stiffness indices [(Young elastic modulus (YEM), stiffness index (SI) and carotid arterial compliance (CAC)] by Doppler Ultrasound were assessed at baseline and after 20 weeks treatment. Tolerability of drug was also measured using hematological and biochemical analysis. Statistical significance was accepted at $p \leq .05$.

Results: FMD improved as 25.66±6.47% versus 12.41±3.22%, $p<0.01$; and insulin resistance (HOMA-IR) decreased as 7.05±3.48 versus 11.32±6.08, $p<0.01$, from baseline in drug group as compared to placebo group, whereas endothelium-independent vasodilatation (p=0.23) and baseline brachial artery diameter ($p=0.95$) remained unchanged in both the groups. Serum triglycerides ($p=0.04$), hsCRP ($p<0.01$) and TNF-α ($p<0.01$) levels were considerably altered, but there was no effect on carotid IMT, YEM, CAC and SI (all $p \geq 0.05$). Biochemical and hematological safety variables were significantly altered, but were still found with-in the normal limits.

Conclusion: Thus, sulfasalazine may prevent cardiovascular disease risk in MetS patients by reducing insulin resistance and endothelial dysfunction via halting inflammatory process. Moreover, it was found tolerable.

Keywords: Metabolic syndrome; inflammation; insulin resistance; flow mediated dilatation; endothelial dysfunction.

1. INTRODUCTION

The term "cardio-metabolic risk" delineates the increased threat of both cardiovascular and metabolic morbidity resulting from a cluster of risk factors, jointly manifested in the form of Metabolic Syndrome (MetS) [1]. The global prevalence of MetS varies from 8% in India to 24% worldwide [2]. The risk of atherosclerotic cardiovascular disease (CVD) accompanying the MetS is double than the general population [3]. Metabolic syndrome and all of its inherent components are independently characterized by the presence of low-grade chronic inflammation and an imbalance between pro-inflammatory and anti-inflammatory cytokines [4]. Pro-inflammatory cytokines induces endothelial dysfunction and accelerate atherosclerosis process by stimulating neutrophil chemotaxis, macrophage activation and superoxide production [5]. Sulfasalazine, an anti-cytokine drug, has been recently explored in established coronary artery disease patients based on its potential nuclear factor kappa B (NF-kB) and tumour necrosis factor-alpha (TNF-α) inhibitory activity [6]. The concept of immunity - inflammation - insulin resistance - endothelial dysfunction link has been now well grown. However, potential of none of the anti-cytokine drugs has been evaluated in metabolic syndrome patients. The study aimed at exploring anti-inflammatory potential of the Sulfasalazine 500mg, once a day, in comparison to placebo treatment in metabolic syndrome patients.

2. MATERIALS AND METHODS

A double-blind, placebo controlled, randomized controlled study was carried out at Sadbhavna Medical and Heart Institute, Patiala, India. 50 eligible subjects [M/F = 45/5], age ≥ 18 years and fulfilling the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) diagnostic criteria of metabolic syndrome, were recruited [7]. Presence of low grade systemic inflammation, as measured by serum high sensitivity C-reactive protein (hsCRP) level ≥ 1.0 but ≤ 10.0 mg/dl was also considered as a primary requisite for inclusion in the study. Eligible patients were randomized into two groups (n=25/per group), group A and B, and were allocated treatment as sulfasalazine and matched placebo tablets (500mg once a day, for 20 weeks) to their on-going therapeutic regimen, respectively. 1:1 randomization was carried out to expose patients equally to drug or placebo using computer assisted random number table. Patients were excluded who, at screening time, were on medications like antioxidants, multi-vitamins, non steroidal anti-inflammatory drugs or oral steroids, insulin sensitizers, disease modifying anti-rheumatic drugs (DMARDs), nitroglycerine or other vasodilators; have known or suspected allergy to the investigational medication; a history of chronic inflammatory diseases; pregnant or lactating women; currently taking another investigational study medication or had taken investigational study medication within 30 days prior to screening randomization.

Assessment of efficacy and tolerability was carried out at baseline (0 day) and after 20 weeks of treatment. The study protocol was approved (approval number- ICEC/45/2012) by the Institutional Ethics Committee (IEC) of Punjabi University, Patiala, and was conducted in accordance with "Ethical guidelines for biomedical research on human participants" issued by Indian Council of Medical Research (ICMR) and was performed in accordance with the declaration of Helsinki and the code of Good Clinical Practice.

2.1 Laboratory Measurements

Overnight fasting blood samples were withdrawn; serum and plasma were separated out and stored at -40ºC until analysis. Quantitative estimation of lipid profile [triglycerides (TG), high density lipoprotein (HDL) cholesterol and total cholesterol (TC)], fasting plasma glucose (FPG), serum creatinine, serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) were estimated using commercial kits [Agapee Diagnostics Pvt. Ltd., India; Erba® Mannheim, Transasia Biomedical Ltd., India], according to manufacturer's recommended protocol. Complete blood count (CBC) was measured using fully automated hematology analyzer (Sysmex XP-100). Inflammatory markers hsCRP and TNF-α were estimated by ELISA technique. Fasting plasma insulin (FPI) was estimated by immuno-turbidimetric assay. Insulin resistance (IR) was calculated using the homeostatic model assessment (HOMA), as the product of the FPI (µU/ml) and FPG (mg/dl) levels, and divided by 405.

2.2 Evaluation of Brachial and Carotid Artery Atherosclerosis

Assessment of endothelial-dependent flow mediated dilatation (FMD) of the brachial artery was carried out by two cardiologists, who was blinded to the treatment protocol, in accordance with the guidelines detailed by Corretti et al. [8]. FMD was calculated as FMD (%) = 100 × {(post-hyperemic diameter – basal diameter) / basal diameter}.

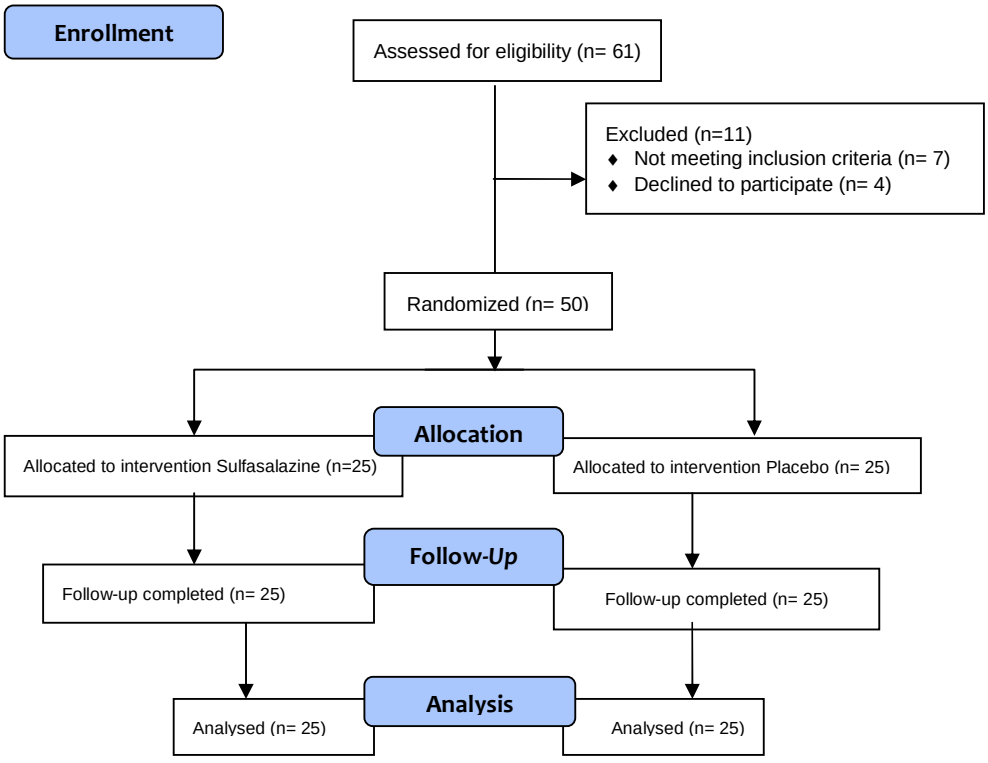

Fig. 1. Design and conduct of study

Intima-media thickness (IMT) of common carotid artery was measured using carotid ultrasonography. Diastolic (Dd) and systolic (Ds) diameter (D) of common carotid artery and, concomitant brachial blood pressure measurements (SBP and DBP) were measured to derive three parameters of arterial stiffness, *i.e.* Young's Elastic Modulus (YEM), carotid arterial compliance (CAC) and stiffness index (SI) as described by Cipolli et al. [9].

2.3 Statistical Analysis

The sample size was estimated by considering the insulin resistance as a primary response variable. To find out 25% decrease in insulin resistance (beta= 0.2, alpha= 0.05) with a standard deviation (SD) of 1.2, a sample size of total 49 patients was required [10].

Descriptive and inferential statistical analyses were performed with Sigma Stat version 3.5. Continuous variables were expressed as mean ± standard error mean and discrete variables were presented as frequencies and percentages. Statistically significance was accepted at $p \leq 0.05$. Results were compared between two groups using an unpaired t-test for normally distributed data, Mann Whitney-U test for skewed distributed data, and chi-square test for distribution free data. Pearson correlation followed by multiple linear regression analysis was applied to find independent predictors. Intra- and Inter-observer variability for cardiovascular Doppler profiling was 2.10% and 2.80% for brachial artery and 2.45% and 3.25% of the carotid artery, respectively.

3. RESULTS

The biochemical and clinical characteristics of the both groups at baseline and after treatment are presented in table 1. All patients [(n=50, Male/Female=45/5)] of MetS included were in the age range of 38-55 year. 55-64% and 8-16% of patients in both the groups had presence of 4 and 5 components of MetS, respectively. Impaired glucose tolerance/diabetes, high TG and hypertension were common in all the patients. Only 8-15% patients had low HDL levels. Patients were stable from past three weeks on drugs such as angiotensin converting enzyme (ACE) inhibitors (45%)/ or angiotensin receptor blockers (ARBs) (55%), metformin (75%) with/ or without glimepride/glipizide (45%) and fenofibrates (75%)/or statins (15%). Metformin itself has week anti-inflammatory action that may synergise action of sulfasalazine. Fidan et al. [11] had reported that metformin treatment resulted in significant improvement in metabolic parameters as well as decrease in inflammatory markers hsCRP, TNF-α and IL-6 levels. So, patients in two groups, (group A- 40% versus group B- 35%) were compared with regard to metformin treatment, but were not found significantly different ($p= 0.55$).

In comparison, no statistical significant difference ($p \geq .05$) was found for any of the variables between the two treatment groups at baseline level. TC, TG, FPI, HOMA-IR, hsCRP, TNF-α, post-hyperemic BAD and FMD were significantly changed after sulfasalazine treatment. There was no effect on carotid artery's IMT and stiffness indices. Obesity and hyperglycemia independently increase risk of CVD associated with endothelial dysfunction [12,13]. In the present study, endothelial dysfunction measured as FMD was found co-related to MetS components, dyslipidemia [{(TG), r= -.33, p=.01; (HDL), r= .28, p= .05}] only, but not with central obesity (r= -.07, p= .69), hyperglycemia (r= -.06, p= .64), and hypertension (SBP: r= -0.13, p= .34). No inter-correlation was found between FMD, HOMA-IR, IMT, stiffness indices (YEM, SI and CAC), and any other variables. Multiple linear regression analysis revealed TG (p= .01) and HDL (p=.03) as independent predictors for FMD (FMD= -16.673 - (0.103 × TG) + (0.199 × HDL). Present findings of no inter-correlation between markers of endothelial dysfunction (FMD), insulin resistance (HOMA-IR), hypertension (SBP), dyslipidemia (TG, HDL) and central obesity (Cobs) may support the fact that insulin resistance mediates all the metabolic risk factors of the metabolic syndrome but, whether it per se elicits dyslipidemia, hypertension and consequently endothelial dysfunction is not clear [3].

None of the patient had levels out of range at baseline for any of the safety parameter, viz., Hb, TLC, DLC, creatinine, SGOT and SGPT. There were no drop-outs due to adverse effects or any other reason. Serum levels of safety variables SGOT, SGPT, TLC and Cr were changed significantly (p<.05) after sulfasalazine treatment, but were still found with-in normal range. Patients' self reported adverse effects were mainly nausea (4 versus 3) and, itching of skin (7 versus 4) in drug and placebo group, respectively. Levocetrizine 5 mg OD was prescribed for itching of skin for 2 weeks.

Table 1. Patients' clinical profile (at baseline and after treatment)

Characteristics	Group A sulfasalazine (500 mg) tab	Group B placebo tab	*P*	Group A sulfasalazine (500 mg) tab	Group B placebo tab	*P* value
	At baseline			After 20 week treatment		
Age, years	42.40±4.79	43.32±4.73	0.47	-	-	-
Sex (Male/Female), number	23/3	22/3		-	-	-
Body weight, kg	90.63±7.72	91.12±7.83	0.81	-	-	
Number of MetS components (% of patients)	4 (64%)	4 (56%)	0.31			
	5 (8%)	5 (16%)	0.12			
Systolic blood pressure (SBP), mm Hg	132.68±12.24	132.48±8.96	0.45	128.52±8.96	129.72±8.53	0.23
Diastolic blood pressure (DBP), mm Hg	87.16±5.69	87.00±3.75	0.86	84.80±3.32	85.48±3.75	0.50
Metabolic and inflammatory variables						
Body mass index (BMI), kg/m^2	32.75±3.73	32.25±2.82	0.59	32.24±3.51	32.05±2.76	0.83
Waist Circumference, inches	44.48±2.46	43.48±1.76	0.10	43.72±2.24	43.20±1.53	0.34
Total cholesterol (TC), mg/dl	228.76±17.05	230.28±17.18	0.76	206.88±14.78	223.88±18.34	<0.01
Triglycerides (TG), mg/dl	162.48±10.99	164.12±12.41	0.62	148.92±15.44	156.72±11.51	0.04
High density lipoprotein (HDL), mg/dl	51.36±5.66	51.68±4.34	0.82	50.76±5.11	51.48±4.27	0.59
Fasting plasma glucose, mg/dl	144.68±28.37	138.68±26.49	0.44	125.23±15.80	136.28±25.59	0.08
Fasting plasma insulin, µU/ml	35.56±14.40	33.00±13.21	0.51	22.08±8.48	31.68±12.71	0.002
HOMA-IR	13.54±7.55	12.03±6.61	0.58	7.05±3.48	11.32±6.08	0.008
hsCRP, mg/l	5.16±1.34	5.00±1.25	0.74	2.04±0.64	4.39±0.97	<0.01
Tumor Necrosis Factor-α, pg/ml	19.08±4.33	19.16±4.53	0.91	11.40±2.72	17.64±3.26	<0.01
Brachial artery variables						
Brachial artery diameter (BAD), mm	4.52±0.39	4.54±0.38	0.85	4.51±0.38	4.51±0.39	0.95
Post hyperemic BAD, mm	5.01±0.43	4.98±0.42	0.81	5.66±0.40	5.06±0.42	<0.001
Nitroglycerine induced BAD, mm	5.35±0.46	5.34±0.48	0.75	4.89±0.15	5.26±0.40	0.32
Flow Mediated Dilation (FMD), %	11.04±4.03	09.54±2.54	0.12	25.66±6.47	12.41±3.22	<0.01
Nitroglycerine Mediated dilation, %	18.51±5.00	16.97±4.66	0.26	18.57±5.31	17.02±5.50	0.23

Characteristics	Group A sulfasalazine (500 mg) tab	Group B placebo tab	*P*	Group A sulfasalazine (500 mg) tab	Group B placebo tab	*P* value
	At baseline			After 20 week treatment		
Carotid artery variables						
Intima-Media Thickness, mm	0.76±0.08	0.74±0.07	0.63	0.75±0.08	0.74±0.68	0.79
Systolic diameter, mm	6.46±0.63	6.33±0.38	0.81	6.45±0.67	6.33±0.41	0.68
Diastolic diameter, mm	5.56±0.59	5.49±0.39	0.99	5.55±0.57	5.54±0.41	0.52
Young's Elastic Modulus, mm Hg.mm	222.82±73.87	231.94±31.65	0.68	214.94±74.71	242.00±84.90	0.23
Stiffness Index (SI)	9.89±2.99	10.38±3.02	0.30	9.87±3.07	11.08±3.27	0.08
Arterial Compliance, % per 10 mm Hg	3.67±0.97	3.45±0.83	0.39	3.81±1.00	3.37±0.94	0.12
Safety variables						
Hemoglobin (Hb), gm	11.94±1.39	12.04±1.14	0.78	11.68±1.32	11.86±1.07	0.59
Total Leukocyte count (TLC), mm^3	8836.00±1491.88	9072±1208.13	0.93	8312.0±1167.73	7268.0±1043.83	0.03
Creatinine, mg%	1.01±0.17	0.99±0.24	0.82	0.9±0.33	1.12±0.33	0.02
SGOT, U/L	25.77±8.13	24.81±8.41	0.68	38.36±5.13	29.52±7.21	<0.001
SGPT, U/L	28.20±8.74	29.67±5.78	0.89	35.08±9.28	43.72±4.97	<0.001

4. DISCUSSION

Present study results have demonstrated that inflammation is the inherent part of disease process and controlling inflammation induced endothelial dysfunction and arterial remodeling with sulfasalazine may help in improving therapeutic outcome of the disease.

NF-kB (nuclear factor kappa B), a transcription factor involved in expression of inflammatory genes, processes the transcriptional activation of pro-inflammatory cytokines [14]. TNF-α is a well-established mediator of activation of endothelial cells, which results in impaired vaso-reactivity by blocking activation of endothelial nitric oxide synthase (eNOS) or degradation of eNOS mRNA, and by activating apoptotic signaling cascade in endothelial cells [15]. CRP is also involved in decreasing eNOS activity [16]. Findings of reduced levels of hsCRP and TNF-α has proved the hypothesis that sulfasalazine plays role in halting the progression of inflammatory damage in MetS patients. This had been reflected also in improvement of insulin resistance as well as endothelial function.

Endothelial dysfunction and carotid intima-media thickness [17], both independently predict cardiovascular mortality [18,19]. Present results are in accordance with studies reporting improvement in FMD with sulfasalzine in RA [20] and CAD patients [21]. Increase in the FMD response but not the NTG response proposed that there was increased NO bioavailability but not the sensitivity of vascular smooth muscle to NO [22].

CCA-IMT has been successfully positioned as a good marker for prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study [23]. Arterial remodelling proceeds to preserve levels of endothelial shear stress [17]. At present no data is reported for effect of DMARDs and/or biological anti-TNF agents on carotid artery remodelling in MetS patients. We had found no improvement in IMT and stiffness indices.

Hyper-insulinemia is being considered as the common preceding factor of hypertension, low high density lipoprotein (HDL) cholesterol, hyper-triglyceridemia, abdominal obesity, and altered glucose tolerance [24]. Treatment with sulfasalazine had lead to significantly decrease in insulin levels as well corresponding decrease in insulin resistance. It did not adversely affect lipid profile as had been reported by Berstein et al. [25] with use of etanercpt in MetS patients on HDL levels. We found a significant decrease in triglycerides level, but, this effect could be attributed to use of fenofibrates in more than 70% patients.

The anti-inflammatory mechanism of sulfa-salazine and its role in improving insulin resistance and endothelial dysfunction is yet not established and understood. Although sulfasalazine is widely explored in rheumatic diseases, but how these mechanisms correlate with metabolic and cardiovascular effects and benefits is still need to be established. Prolonged presence of low grade systemic inflammation induces structural changes in arteries and vascular endothelium, over production of ROS, non-regulated synthesis and release of NO, impaired immune cells signalling, cytokines cascade and their interplay all impart crucial contribution for metabolic and cardio-vascular damage. Thus, overall halting inflammatory process at various levels by multiple mechanisms is the core playing component for proving efficacy of Sulfasalazine. Moreover, the drug was well tolerable for all the patients.

5. LIMITATIONS

Present study had several limitations. Mechanism of action of sulfasalazine for altering cardio-metabolic profile and NF Kappa regulated gene expression linked to insulin resistance and endothelial dysfunction was not explored. Moreover, evaluation only at one dose level in small number of subjects was carried out due to lack of funding, time and other institutional constraints.

6. CONCLUSION

Sulfasalazine was found effective in reducing insulin resistance and endothelial dysfunction by halting inflammatory process. It may prevent CVD risk in MetS patients. But, efficacy and safety must be further established in large randomized trials of long duration. Overall, it was found tolerable.

Finally, the study implies that addition of sulfasalazine to therapeutic regimen of metabolic syndrome may help in better control of sign and symptoms, and may prevent MetS induced cardio-vascular damage.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was approved (approval number-ICEC/45/2012) by the institutional ethics committee (IEC) for human research, Punjabi University, Patiala, and was conducted in accordance with "ethical guidelines for biomedical research on human participants" issued by ICMR and was performed in accordance with the declaration of Helsinki and the code of good clinical practice.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Davis SN. Contemporary strategies for managing cardiometabolic risk factors. J Manag Care Pharm. 2006;12(1):S4-S9.
2. Gogia A, Aggarwal PK. Metabolic Syndrome. Indian J Med Sci. 2006;60: 72-81.
3. Scott M. Grundy. Pre-diabetes, metabolic syndrome and cardiovascular risk. J Am Coll Cardiol. 2012;59:635-43.
4. Tousoulis D, Plastiras A, Siasos G, et al. Omega-3 PUFAs improved endothelial function and arterial stiffness with a parallel anti-inflammatory effect in adults with metabolic Syndrome. Atherosclerosis 2014;232:10-16.
5. Bilsborough W, Keen H, Taylor A, O'Driscoll GJ, Arnolda L, Green DJ. Anti-tumor necrosis factor-alpha therapy over conventional therapy improves endothelial function in adults with rheumatoid arthritis. Rheumatol Int. 2006;26:1125–1131.
6. Tabit CE, Holbrook M, Shenouda SM, Dohadwala MM, Widlansky ME, Frame AA, et al. Effect of sulfasalazine on inflammation and endothelial function in patients with established coronary artery disease. Vasc Med. 2012;17(2):101–107.
7. NCEP ATP-III executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285: 2486–97.
8. Corretti MC, Andreson TG, Emeli J, Benjamin CD, Charbonneau F and Mark A. Guideline for ultrasound assessment of endothelial dependent flow mediated vasodilation of the brachial artery. J. Am. Col. Cardiol. 2002;39:257-265.
9. Cipolli JAA, Ferreira-Sae MC, Martins RP, et al. Relationship between serum uric acid and internal carotid resistive index in hypertensive women: A cross-sectional study. BMC Cardiovas Disord. 2012;12: 52-57.
10. Vitale C, Mercuro G, Cornoldi A, Fini M, Volterrani M, Rosano GMC. Metformin improves endothelial function in patients with metabolic syndrome. J Intern Med. 2005;258:250–256.
11. Fidan E, Onder Ersoz H, Yilmaz M, Yilmaz H, Kocak M, Karahan C, et al. The effects of rosiglitazone and metformin on inflammation and endothelial dysfunction in patients with type 2 diabetes mellitus. Acta Diabetol. 2011;48(4):297-302.
12. Davies MJ, Donnelly R, Barnett AH, Jones S, Nicolay C, Kilcoyne A. Exenatide compared with long-acting insulin to achieve glycemic control with minimal weight gain in patients with type 2 diabetes: Results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. Diabetes Obes and Metab. 2009;11:1153–1162.
13. Dhindsa P, Davis KR, Donnelly R. Comparison of the micro- and macro-vascular effects of glimepiride and gliclazide in metformin-treated patients with Type 2 diabetes a double-blind, crossover study. Br J Clin Pharmacol. 2003;55:616–619.
14. Jue DM, Jeon KM, Jeong JY. Nuclear Factor κB (NF-κ B) Pathway as a Therapeutic target in Rheumatoid Arthritis. J Korean Med Sci. 1991;14:231-238.
15. Fichtlscherer S, Rössig L, Breuer S, Vasa M, Dimmeler S, Zeiher AM. Tumor necrosis factor antagonism with etanercept improves systemic endothelial vasoreactivity in patients with advanced heart failure. Circulation. 2001;(104): 3023-3025.
16. Derosa G, Salvadeo SAT. Endothelial function, blood pressure control, and risk modification: impact of irbesartan alone or

in combination. Integrated Blood Pressure Control. 2010;3:21–30.
17. Baguet JP, Asmar R, Valensi P. Effects of candesartan cilexetil on carotid remodeling in hypertensive diabetic patients: The MITEC study. Vascular Health and Risk Management. 2009;5:175–183.
18. Tikiz C, Utuk O, Pirildar T, Bayturan O, Bayindir P, Taneli F. Effects of angiotensin-converting enzyme inhibition and statin treatment on inflammatory markers and endothelial functions in patients with long term rheumatoid arthritis. J Rheumatol. 2005;32:2095–101.
19. Baldassarre D, Hamsten A, Veglia F, Faire U, Humphries SE, Smit AJ, et al. Measurements of carotid intima-media thickness and of inter adventitia common carotid diameter improve prediction of cardiovascular events. J Am Coll Cardiol. 2012;60:1489-99.
20. Guin A, Adhikari MC, Chakraborty S, Sinhamahapatra P, Ghosh A. Effects of disease modifying anti-rheumatic drugs on subclinical atherosclerosis and endothelial dysfunction which has been detected in early rheumatoid arthritis: 1-year follow-up study. Sem. Arth and Rheum. 2013;43: 48–54.
21. Vohra K, Krishan P, Varma S, Kalra HS. Exploring the potential of low-dose sulfasalazine in stable coronary artery disease patients: Randomized, double-blind, placebo-controlled study.
DOI: 10.1093/ehjcvp/pvv021.
22. Syngle A, Vohra K, Kaur L, Sharma A. Endothelial dysfunction in ankylosing spondylitis improves after tumor necrosis factor-α blockade. Clin Rheumatol. 2010; 29(7):763-70.
23. Nambi V, Chambless L, He M, Folsom AR, Mosley T, Boerwinkle E, et al. Common carotid artery intima–media thickness is as good as carotid intima–media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. Eur Heart J. 2012;33: 183–190.
24. Ferna´ndez-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocrine Reviews. 2003;24(3):278–301.
25. Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. Arch Intern Med. 2006;166:902-908.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/11491