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A Comprehensive Metaanalysis and Systematic Review on Effect of Genistein on Metabolic Syndrome

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ABSTRACT

Background: Isoflavones such as genistein have shown substantial efficacy over the days in treatment of circulatory and cardiovascular diseases. Similarly metabolic diseases were also known to be ameliorated and greatly relieved from genistein. Some studies reported the ameliorative effect of genisteine on metabolic syndrome in relation to biochemical as well as physical parameters. The present investigation was carried to demonstrate the relation between genistein and metabolic syndrome. **Materials and Method:** A comprehensive search was conducted on following search engines: Pubmed, EMBASE, Google Scholar, Medscape, Plosone and Scopus. The following terms were used as key words in the database search: "Genistein", "Metabolic syndrome", "association" and "Randomized controlled trial". Data was analyzed using RevMan v 5.0 analysis software. **Results:** Biochemical parameters representing metabolic syndrome such as low-density lipoprotein, triglycerides, total cholesterol, blood glucose levels, shown the substantial weight skewed in the favor for genistein treatment. On the contrary high-density lipoprotein remained uninfluenced with the treatment of genistein. The base line characteristics such as systolic and diastolic blood pressure have shown significant difference when compared to control arm, whereas, body mass index did not shown any considerable change. **Conclusion:** Genistein is effective in the treatment of metabolic syndrome but necessity of large number of high quality clinical trials remains obligatory.

Key words: Genistein, metaanalysis, metabolic syndrome, systematic review

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INTRODUCTION

Genistein is one of the few known isoflavones. Genistein are found in an integer of plants together with fava beans, lupin, kudzu, psoralea and soybeans being the principal food source (Behloul and Wu, 2013). It occours in the many medicinal plants such as *Flemingia vestita* and coffee. Isoflavones have been made known to interact with human estrogen receptors, causing effects in the body analogous to those caused by the hormone estrogen. Isoflavones too produce non-hormonal effects (Choi *et al*., 2012).

A metabolic disorder eventually leads to metabolic syndrome comprising of abdominal obesity, insulin resistance and dyslipidemia (Kandhare *et al*., 2012a; Kandhare *et al*., 2012b; Visnagri *et al*., 2012). Recently, genistein has acquired the good attention in relation to their beneficial role in metabolic disorders and reduction in risk of cardiovascular diseases (Bitto *et al*., 2009; Choi *et al*., 2012). Additionally, it has been also verified to be efficient in reducing cardiovascular risk in postmenopausal women (Kaufman *et al*., 1997). It's prospective in the prevention of modern lifestyle disorders namely cardiovascular diseases, osteoporosis and hormone related cancers is undoubtedly proven by multiple clinical studies as well pilot trials (Ghosh *et al*., 2012a; Kandhare *et al*., 2012a).

The discourse concerning special effects of genistein conducted on animals and humans exposed additional dimensions of its biomedical influence. Genistein has ability to alter metabolic states at the cellular rank as well as in the entire organism. While reducing the everyday food intake it reduces the adipose tissues. It also alters the metabolism of variety of hormones such as insulin, leptin and brings appropriate biochemical

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modifications (Behloul and Wu, 2013; Friso *et al*., 2010). Moreover, alteration in lipid parameters like cholesterol and triglycerides were also noticed as a result of genistein administration (Jenkins *et al*., 2002). Furthermore, alteration in ATP synthesis along with distorted lipogenesis and affected lipolysis were also observed after genistein administration in preclinical studies. Subsequently, the pragmatic changes in expression of genes in lipid metabolism with troubled glucose transport in to cells were also found (Alves *et al*., 2010).

Therefore, in this meta-analysis of studies designed as RCTs and open-label, single-arm trials, we aimed to evaluate the effect of each PAH agent on exercise capacity in patients with CTD-PAH compared with patients with all forms of PAH. The present study was designed to investigate the effects of genistein on various risk factors of metabolic syndrome.

MATERIAL AND METHODS

Search strategy, selection criteria and inclusion criteria and data abstraction: A comprehensive in depth search was conducted on following search engines: Pubmed, EMBASE, Google Scholar, Medscape, Plosone and Scopus. The following terms were used as keywords in the database search: "Genistein", "Metabolic syndrome", "association" and "Randomized controlled trial" till March 2013. Only reports fulfilling the following inclusion criteria were included in the meta-analysis.

The inclusion studies that contained the minimum information necessary to estimate the weighted mean difference (i.e., 95% Confidence Interval (CI), z value and p-value of the significance of the estimate). Randomized controlled trials published as original articles. Articles were reviewed and data extracted and cross-checked independently by 3 investigators (Any disagreement was resolved by common consensus among the 3 reviewers). A total of 8 articles were identified by computerized search of databases and, from these, 4 were excluded due to non-compliance with exclusion criteria. Excluded studies were mainly duplicates, study designs other than randomized controlled trials, studies on animals and studies published in languages other than English. Abstracts of the remaining 4 studies and those identified by the screening of references of relevant original and review articles were scrutinized by the three reviewers. From this process, a total of 3 articles were potentially eligible. Finally, 3 studies were selected for metaanalysis (Fig. 1).

Data synthesis and analysis: Data was analysed using RevMan v 5.0 analysis software. The data of experimental and control group was represent as Mean±SD and 95% confidence interval. Tau^2, Chi^2, I^2 i.e., heterogeneity value were calculated overall. The entire data was plotted and represented in the form of Forest plot depicting the mean difference with 95% confidence interval of mean difference. Mean difference and 95% confidence interval

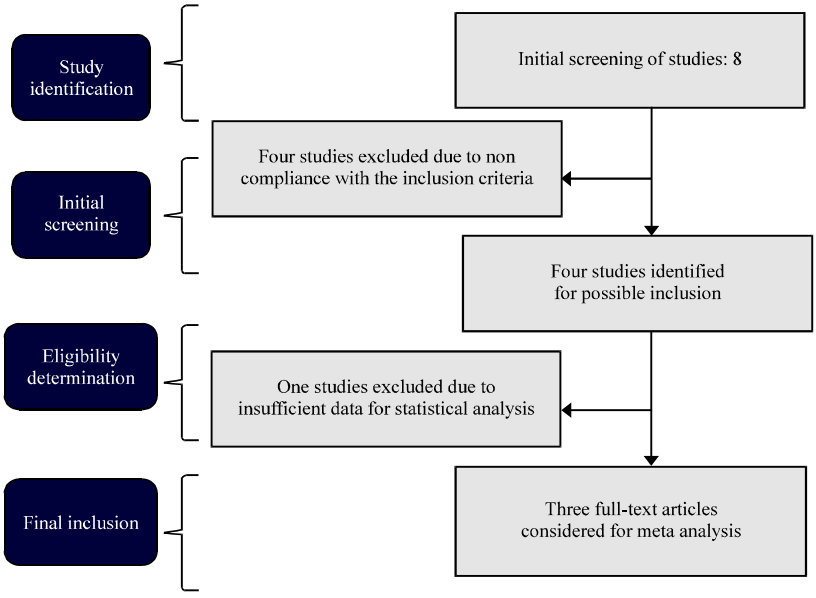

Fig. 1: Process of selecting articles for inclusion in the review

(95% CI) was calculated for the cardiac and metabolic profile in control and treatment groups respectively. Mean difference and 95% CIs were calculated for each individual study and for all studies combined. For forest plot analysis we used Random-effects model (DerSimonian-Laird method).

RESULTS

The three trials were fulfilled the above criteria and thus included in the study. Table 1 summarizes key data from these publications.

A randomized, placebo controlled trial performed by Villa *et al*. (2009) on post-menopausal women to assess the cardiovascular risk factors for the differential effect of the phytoestrogen genistein. Subjects (n = 30) were randomized to receive 50 mg day^{-1} genistein while subjects (n=20) were treated with placebo for 24 weeks. Main efficacy outcome measures were hormonal and lipid assays, oral glucose tolerance tests with glycemic, insulin and C peptide evaluations, anthropometric measures indexes of insulin sensitivity and endothelial function and euglycemic-hyperinsulinaemic clamps were performed. In conclusion, glycoinsulinemic metabolism and the endothelial function were significantly influenced by genistein. In particular, normoinsulinemic patients showed an improvement in glycemic and vascular reactivity indexes. Conversely, an improvement in the insulin sensitivity indexes was noted in hyperinsulinemic patients.

Han *et al*. (2002) performed double blind, randomized, placebo controlled study on menopausal women to assess cardiovascular risk factors in response to 4 months of daily 100 mg soy isoflavone. There were 80 women randomly assigned to isoflavone (n = 40) and placebo (n = 40) treatment. Main efficacy outcome measures were plasma lipid levels, blood glucose levels, body mass index and blood pressure in the participants. In conclusion isoflavone 100 mg regime treatment may be a safe and effective alternative therapy for menopausal symptoms and may offer a benefit to the cardiovascular system.

Jenkins *et al*. (2002) performed a randomized crossover study on forty one hyperlipidemic men and postmenopausal women for three 1-mo diets: A low-fat dairy food control diet and high-(50 g soy protein and 73 mg isoflavones daily) and low-(52 g soy protein and 10 mg isoflavones daily) isoflavone soy food diets. Main efficacy outcome measures were total cholesterol, estimated CAD risk and ratios of total to HDL cholesterol, LDL to HDL cholesterol and apolipoprotein B to A-I. In conclusion, Substitution of soy foods for animal products, regardless of isoflavone concentration, reduces the CAD risk because of both modest reductions in blood lipids and reductions in oxidized LDL, homocysteine and blood pressure.

All the studies included in the present investigation comprise an underlying relation between Genistein and lipid profile. Included studies in the present investigation elucidated the effect of genistein on the lipid profile.

The WMD of TG was found out to be 24.7 (19.44, 29.96), -2.65 (-2.75, -2.55), 16.9 (-6, 39.8) by Han *et al*. (2002), Jenkins *et al*. (2002) and Villa *et al*. (2009) respectively. The z value and p-value were computed to be equal to 1.9 and 0.28, respectively and heterogeneity in the studies was found to be 98% (Fig. 2a).

The data synthesis of the various studies fulfilling the inclusion criteria revealed the following findings about HDL: The study conducted by Han *et al*. (2002) Weighted Mean Difference (WMD) was found out to be 0.40 (-0.30, 1.10). The study conducted by Jenkins *et al*. (2002) the Weighted Mean Difference (WMD) was found out to be 0.77 (0.75, 0.79). The study conducted by Villa *et al*. (2009) WMD was found out to be -14 (-21.61, -6.39). The z value and p-value were computed to be equal to 0.28 and 0.78, respectively and heterogeneity in the studies was found to be 87% (Fig. 2b). The diamond represents the overall mean in forest plot.

The WMD of LDL was found out to be -18.7 (-20.79, -16.61), -12.76 (-12.81, -12.71), -4.4 (-32.95, 24.15) by Han *et al*. (2002); Jenkins *et al*. (2002) and Villa *et al*. (2009) respectively. The z value and p-value were computed to be equal to 5.3 and 0.00001, respectively and heterogeneity in the studies was found to be 94%.

The WMD of Total Cholesterol (TC) was found out to be -27.8 (-30.75, -24.85), -12.37 (-12.42, -12.32), -17.1 (-47.58, 13.38) by Han *et al*. (2002); Jenkins *et al*. (2002) and Villa *et al*. (2009) respectively. The z value and p-value were computed to be equal to 2.77 and 0.006

Table 1: Description of the study designs and patients' characteristics for trials included in the meta-analysis

Jaddad score	Study design	Patients randomized (n)	No. of patients evaluated	Countries	Treatment duration (month)	Reference
0	Pilot prospective study	-	12	Italy	6	Romualdi *et al*. (2008)
1	Crossover RCT	41	73	Canada	4	Jenkins *et al*. (2002)
3	RCT	26	50	Italy	12	Villa *et al*. (2009)
4	RCT, parallel design	80	80	Brazil	4	Han *et al*. (2002)

RCT: Randomized controlled trial

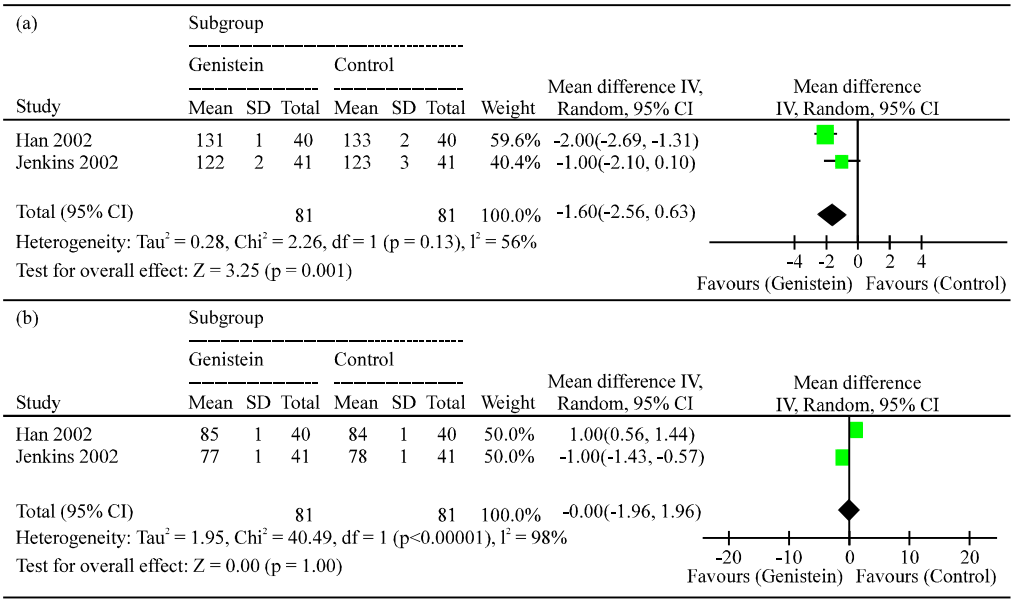

Fig. 2(a-b): A forest plot depicting the metaanalysis of the association of (a) Triglycerides and (b) HDL with genistein. It shows mean difference, 95% CI (confidence interval)

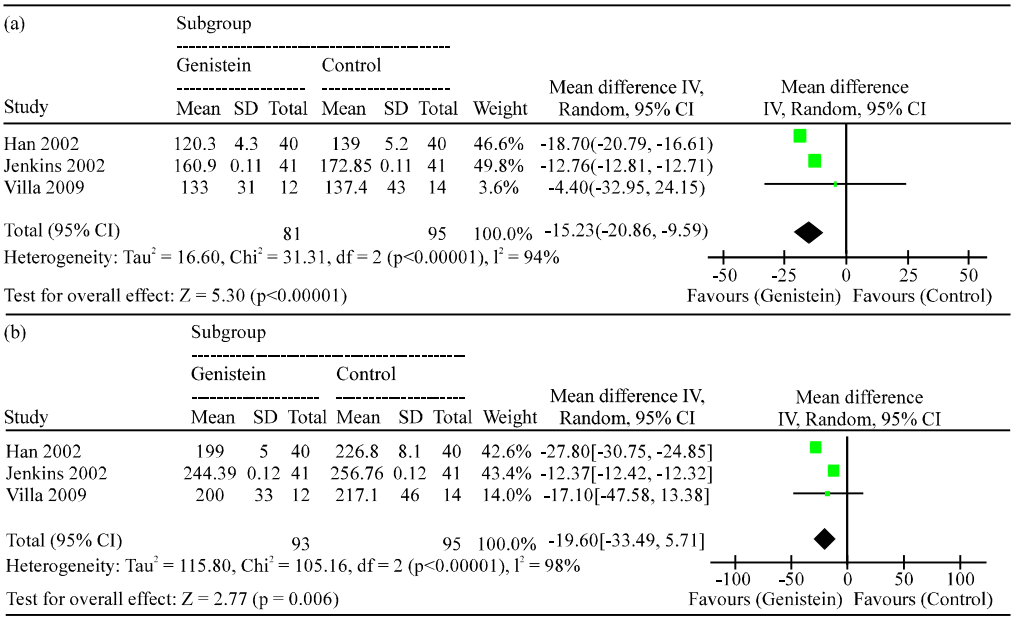

Fig. 3(a-b): A forest plot depicting the metaanalysis of the association of (a) LDL and (b) Total cholesterol with genistein. It shows mean difference, 95% CI (confidence interval)

respectively and heterogeneity in the studies was found to be 98%. As shown in forest plots (Fig. 3a and b) of LDL and total cholesterol, the mean difference significantly skewed in favor of genistein treatment.

The WMD of Systolic blood pressure was found out to be -2 (-2.69, -1.31), -1 (-2.1, 0.1) by Han *et al.* (2002) and Jenkins *et al.* (2002), respectively. The z value and p-value were computed to be equal to 3.25 and 0.001, respectively and heterogeneity in the studies was found to be 56%. Mean difference of included studies tilted in favor of genistein treatment (Fig. 4a).

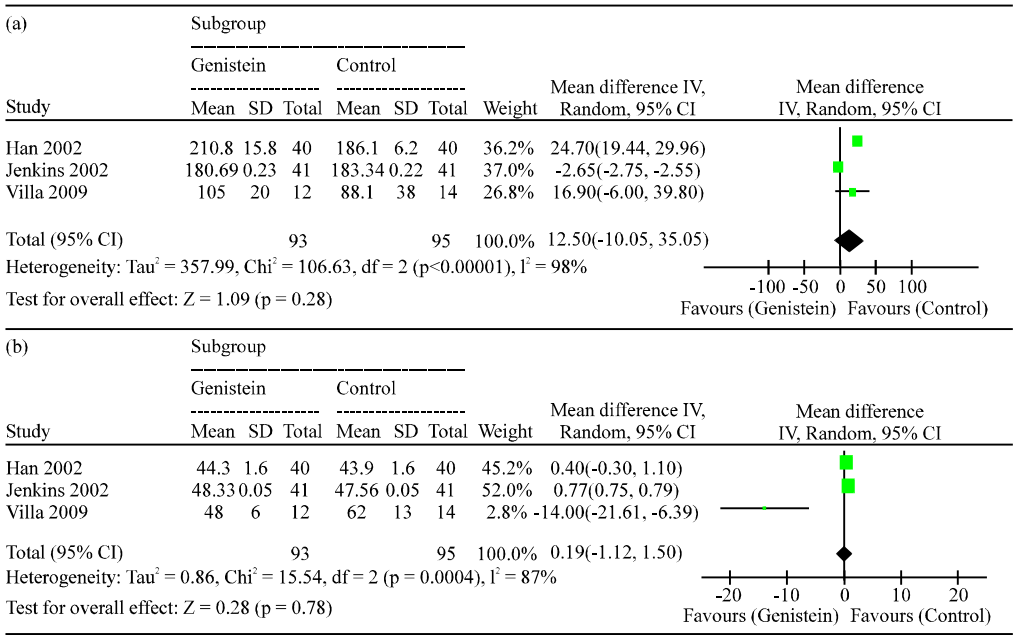

Fig. 4(a-b): A forest plot depicting the metaanalysis of the association of (a) Systolic blood pressure and (b) Diastolic blood pressure with genistein. It shows mean difference, 95% CI (confidence interval)

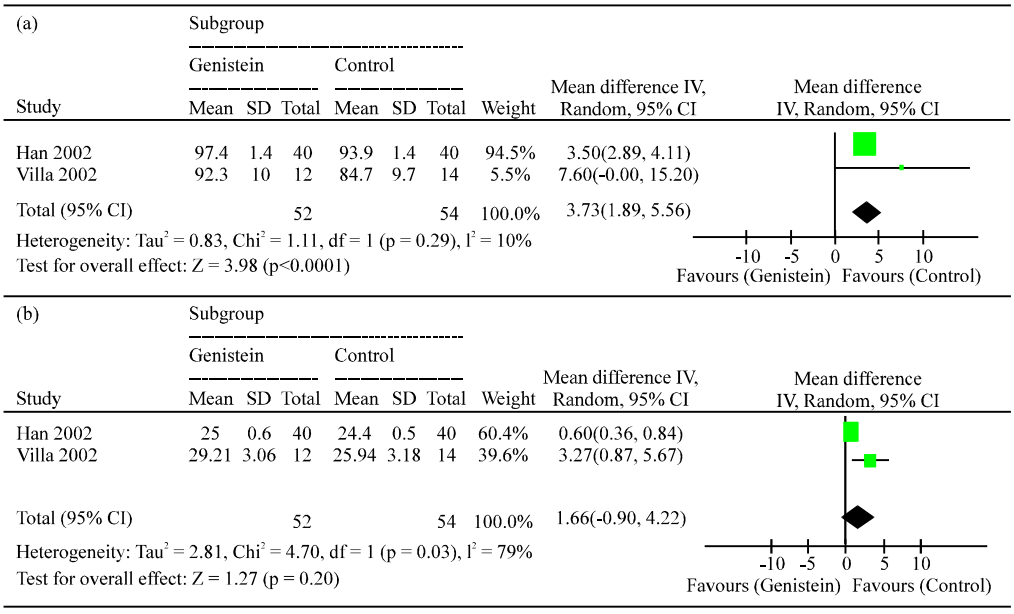

Fig. 5(a-b): A forest plot depicting the metaanalysis of the association of (a) Blood glucose level and (b) BMI with genistein. It shows mean difference, 95% CI (confidence interval)

The WMD of Diastolic blood pressure was found out to be 1 (0.56, 1.44), -1 (-1.43, -0.57) by Han *et al*. (2002) and Jenkins *et al*. (2002), respectively. The z value and p-value were computed to be equal to 0.0 and 1, respectively and heterogeneity in the studies was found to be 98%. Figure 4b showing forest plot of the association between diastolic blood pressure and genistein treatment.

The WMD of Glucose level was found out to be 3.5 (2.89, 4.11), 7.6 (-0.0, 15.2) by Han *et al*. (2002) and

Villa *et al*. (2009) respectively. The z value and p-value were computed to be equal to 3.98 and 0.0001 respectively and heterogeneity in the studies was found to be 10%.

The WMD of BMI was found out to be 0.6 (0.36, 0.84), 3.27 (0.87, 5.67) by Han *et al*. (2002) and Villa *et al*. (2009), respectively. The z value and p-value were computed to be equal to 1.27 and 0.21, respectively and heterogeneity in the studies was found to be 79%. Forest plots of glucose level and BMI association with genistein treatment were shown in (Fig. 5a and b).

DISCUSSION

Metabolic syndrome is a very prominent feature of metabolic risk factors which is a cluster of conditions such as hypertension, an elevated blood sugar level, excess body fat around the waist and abnormal cholesterol levels that together increase risk of heart disease, stroke and diabetes (Ghosh *et al*., 2012b; Kamble *et al*., 2013; Kandhare *et al*., 2012b; Visnagri *et al*., 2013; Visnagri *et al*., 2012). Metabolic syndrome mainly presents in up to 85% of adults patients. It has been reported that metabolic syndrome is a useful and simple tool in clinical practice for earlier detection of type 2 diabetes and cardiovascular disease (Ghosh *et al*., 2012b; Gosavi *et al*., 2011a; Gosavi *et al*., 2011b). Hyperglycemia-caused imbalances in metabolic pathways as well as microvascular changes lead to development of diabetic complications such as neuropathy, nephropathy, retinopathy and cardiomyopathy (Ghosh *et al*., 2012b; Kamble *et al*., 2013, Kandhare *et al*., 2012b; Visnagri *et al*., 2012).

In present study, metaanalysis of these three published, fair-quality studies suggests that genistein offers some benefit to patients with metabolic syndrome. In the present investigation it is evident that the studies in which subgroup consisted of biochemical parameters representing metabolic syndrome such as LDL-C, triglycerides, total cholesterol and blood glucose levels shown the substantial weight skewed in the favor for genistein treatment. On the contrary HDL-C remained uninfluenced with the treatment of genistein. The base line characteristics such as systolic and diastolic blood pressure have shown significant difference when compared to control arm, whereas, body mass index did not shown any considerable change. This metaanalysis of 3 published, randomized controlled trials suggests that genistein improves functioning of patients with metabolic syndrome by affecting various associated risk factors like LDL, total cholesterol, triglycerides and blood glucose levels. There is less number of trials available which may not fulfill the quality of the analysis in effect of genistein on metabolic syndrome. Therefore, there is an urgent requirement for high quality trials to reduce the heterogeneity among the outcome variables which leads to definite conclusion for the efficacy of genistein over metabolic syndrome.

CONCLUSION

In addition to optimal screening and follow-up, it has been recommends that patient with metabolic disorder, physicians and other members of the multidisciplinary team should help educate and motivate patients with metabolic disorder to improve their lifestyle through use of behavioural interventions including dietary measures and exercise. Therefore, it is useful that family members and caregivers be offered education regarding the increased risk of patients with metabolic syndrome and ways to mitigate this risk. Although, clinically genistein may prove efficacious for the treatment of metabolic syndrome, but limited data are available regarding its efficacy in the management of metabolic syndrome hence, there is need for more number of interventional randomized controlled trials remains refutable. However, general lifestyle improvements should be used as an adjuvant to genistein for management of metabolic syndrome. Further more, refined meta-analysis studies are needed to address some of the issues involved in answering these questions and clinical implications of these findings.

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