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Autoimmune skin diseases and the metabolic syndrome

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Abstract The metabolic syndrome represents an important association of cutaneous maladies with cardiovascular illnesses. Chronic inflammation, shared risk factors (ie, smoking and alcohol consumption), treatment (ie, immunosuppressive agents and drugs that alter the lipid profile), and shared genetic risk loci have been proposed to the cause metabolic syndrome and cardiovascular morbidity of autoimmune diseases. There are many possible inflammatory mediators that are suggested to play a role in insulin resistance pathogenesis, such as tumor necrosis factor-α, interleukin-6, leptin, and adiponectin. These mediators are also abnormal in autoimmune skin disorders. We discuss several autoimmune skin diseases, connective tissue diseases, bullous diseases, vitiligo, psoriasis, lichen planus, chronic urticaria, and atopic dermatitis.

Introduction

The metabolic syndrome (MetS) is a culmination of several cardiovascular risk factors. Many organizations have proposed criteria for the diagnosis of MetS. According to the International Diabetes Federation (IDF) definition, in addition to central obesity, there must be at least two of the following criteria for diagnosis:

- Elevated triglyceride levels
- Reduced high-density lipoprotein cholesterol levels
- Elevated blood pressure
- Elevated fasting plasma glucose[1]

Most of the criteria for this syndrome are the consequences of insulin resistance.[1] In the case of insulin resistance, normal amounts of insulin are inadequate to produce normal insulin response from fat, muscles, and liver cells; it is a state that precedes type 2 diabetes mellitus and MetS, which affects approximately 20% of people worldwide.[2,3] People with MetS have an increased risk of myocardial infarction, stroke, type 2 diabetes mellitus, fatty liver disease, and certain types of malignancy.[4] Its description is important, because this entity may cause more attributable risk for cardiovascular disease than each component of the syndrome does individually.[5] Genetics, physical inactivity, aging, proinflammatory state, hormonal changes, and nutritional habits are all factors that can cause this syndrome. In the literature, many skin diseases have a proposed association with MetS. Recognizing MetS is becoming increasingly important for the prevention and treatment of these diseases.

Inflammatory skin diseases

Lichen planus

Lichen planus (LP) is a chronic inflammatory disease that affects skin, mucous membranes, and appendages. LP is

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Table 1 Summary of autoimmune diseases associated with Met

Behçet disease	Cardiovascular disease, Met	Chronic inflammation, adverse effect of treatment
Lichen planus	Dyslipidemia, diabetes mellitus, Met, insulin resistance, cardiovascular diseases	Chronic inflammation, disturbance of carbohydrate metabolism, drugs that alter lipid profile
Lupus erythematosus	Cardiovascular disease, diabetes, dyslipidemia	Chronic inflammation, adverse effect of treatment, chronic inflammation, oxidative stress and disturbance of lipid and glucose metabolism
Sjögren syndrome	Hypercholesterolemia, obesity	Chronic inflammation, adverse effect of treatment
Urticaria, chronic	Dyslipidemia, diabetes mellitus, Met, obesity	Chronic inflammation, elevated tumor necrosis factor, eosinophil cationic protein, complement level 3
Vasculitis	Dyslipidemia, Met, cardiovascular disease	Chronic inflammation, adverse effect of treatment

characterized by pruritic, purple (violaceous) polygonal papules and plaques with fine white lines, called Wickham striae, as well as leukoplakia of mucous membranes (Figure 1). Although the etiopathogenesis is unclear, it is proposed that there is an autoimmune reaction. It has been suggested that cytotoxic T lymphocytes attack basal keratinocytes, leading to apoptosis of the cells.[6] There are also some studies describing LP in association with dyslipidemia, diabetes mellitus, insulin resistance, and cardiovascular diseases,[7–10] suggesting its connection with MetS. With increased oxidative stress in chronic inflammation, reactive oxygen products are elevated and may cause cardiovascular diseases.[11,12] The disturbance of cellular carbohydrate metabolism affected by LP is also suggested to cause diabetes mellitus.[13] A prospective case–control study[14] noted that the prevalence of MetS in patients with LP was significantly higher than in the control group. There was also a higher prevalence of MetS in patients with mucous membrane lesions than in those who did not have mucous membrane lesions.[14] The prevalence of MetS in patients with LP was found to be 26.6% in the same study.[14]

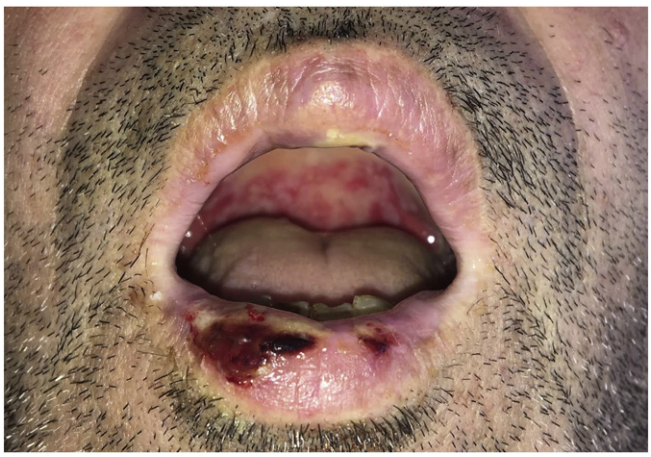

Fig. 1 Oral lesions of pemphigus vulgaris. (Courtesy of Istanbul Medeniyet University Dermatology Department.)

Allergic skin diseases

Chronic urticaria

Chronic urticaria is a common skin disorder defined by persistent or recurrent wheals and/or angioedema of at least 6 weeks (Figure 2). In the etiopathology of the disease, chronic infection and inflammation are known, but most of the cases are idiopathic.[12] In a hospital-based cross-sectional study,[15] the prevalence of MetS was significantly greater in patients with chronic urticaria than in healthy controls. In this study, approximately 30% of patients with chronic urticaria have MetS. Tumor necrosis factor, eosinophil cationic protein, and complement three levels are higher in the patients with MetS than in the control group.[15] These patients have severe urticaria that is difficult to control with antihistamines.[15] As is the case with the psoriasis–MetS association, inflammation may be responsible for this relationship. There are only a few

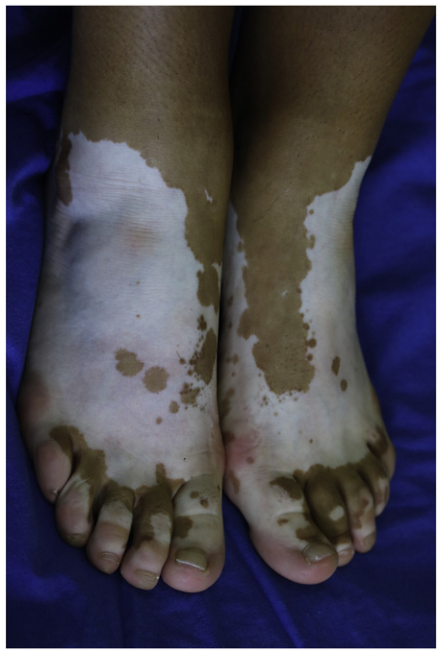

Fig. 2 Vitiligo patches on the foot. (Courtesy of Istanbul Medeniyet University Dermatology Department.)

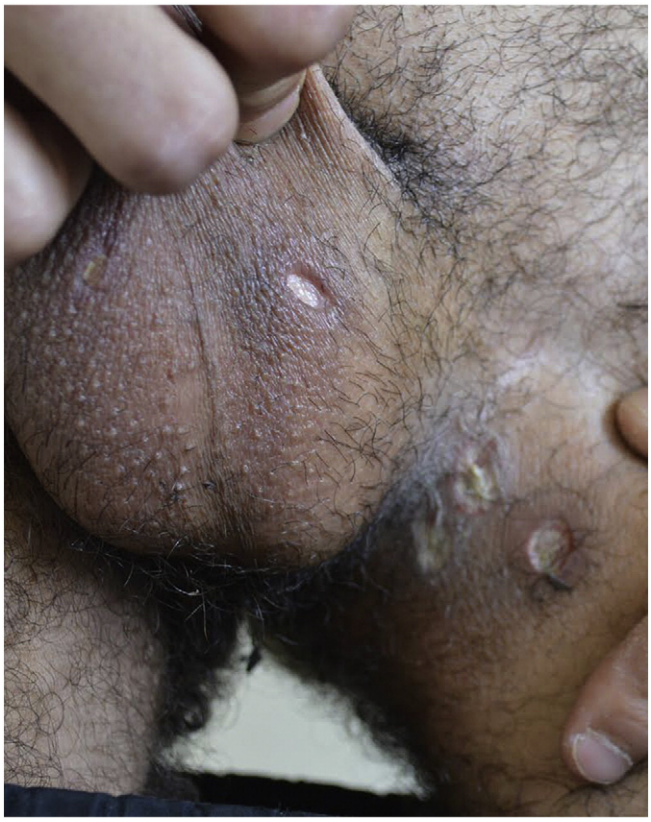

Fig. 3 Genital ulcers of Behçet syndrome. (Courtesy of Istanbul Medeniyet University Dermatology Department.)

known cases about the coexistence of chronic urticaria and MetS components.

Autoimmune bullous diseases

Autoimmune bullous diseases are a group of diverse autoimmune diseases characterized by blistering of the skin and mucous membranes (Figure 3). In the etiopathogenesis of these dermatides, there are tissue-bound and circulating autoantibodies that attack various components of the skin. Autoantibodies against desmogleins cause the intraepidermal blistering seen in pemphigus, whereas autoantibodies against hemidesmosomes are the reason for the subepidermal blistering seen in pemphigoid. Autoimmune bullous dermatoses are mainly classified in two subgroups according to the level of separation: intraepidermal or subepidermal. In the pemphigus group diseases, there is intraepidermal separation, whereas in the pemphigoid group, there is subepidermal separation. Besides the severe pain caused by erosion of these blistering lesions, the most important effect of these lesions is itching. It is speculated that autoantibodies bind to dermal mast cells, inducing their activation and secretion of mediators after being cross-linked by antigens. Among mediators, histamine directly induces itching and vessel changes, whereas tryptase potentiates itching and vessel changes in an indirect way through the actions of neuropeptides. Tryptase stimulates neurons, which in turn secrete neuropeptides. Patients also have impairment of oral intake and significant loss of fluid, electrolytes, and proteins. These complications are especially common in the case of extensive body surface involvement. There are several reports about the association of autoimmune bullous diseases between other autoimmune disorders and malignancies.[16] Treatment of these dermatoses is based on systemic corticosteroids, immunosuppressive agents, and replacement of fluid and protein loss. The side effects of glucocorticoids include osteoporosis, atherosclerosis, hypertension, insulin resistance, hyperlipidemia, and central obesity.[1] These side effects of corticosteroids are also the criteria for the diagnosis of MetS.

Several authors have proposed that there is an association between the pemphigus group of diseases and MetS.[17–19] In a retrospective population-based randomized study,[7] there is a significantly higher prevalence of hypertension, diabetes mellitus, obesity, and hypertriglyceridemia in patients with pemphigus disease than in the control group. This association may be due to the chronic use of corticosteroids. There are also reports of an association between bullous pemphigoid and MetS components.[20,21] One group noted a higher prevalence of diabetes in bullous pemphigoid patients than in the control group.[20] Bullous pemphigoid has also been found in relation to neurologic diseases.[22]

Patients with a diagnosis of autoimmune bullous diseases should be followed closely for signs of MetS, especially while being treated with systemic corticosteroid and immunosup-

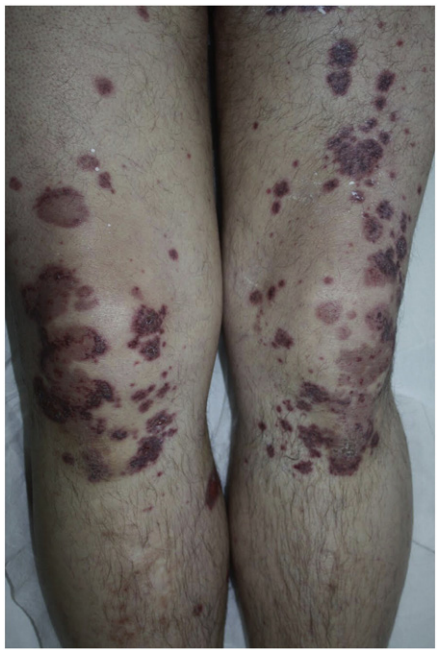

Fig. 4 Purpuric lesions of cutaneous vasculitis. (Courtesy of Istanbul Medeniyet University Dermatology Department.)

pressive agents. The advent of the use of biologics may minimize corticosteroid side effects.[17]

Pigmentation disorders

Vitiligo

Vitiligo is an acquired disease characterized by depigmented patches (Figure 4). Many factors have been described regarding the etiopathogenesis of vitiligo: genetic, immunologic, autoimmunologic, cytotoxic, neuronal, and inflammatory.[23] Vitiligo patients are often screened for autoimmune comorbidities, such as alopecia areata, autoimmune thyroid disease, Addison disease, pernicious anemia, type 1 diabetes mellitus, and myasthenia gravis.[24] Recently several authors have proposed the association between MetS and vitiligo.[24,25] This hypothesis is based on increased proinflammatory cytokines in vitiligo.[24]

There are various hypotheses describing the impairment of lipid and glucose metabolism in such patients: increased homocystine levels of vitiligo patients, lack of the antiinflammatory effect of melanin, and direct damage from reactive oxygen radicals.[26–28] Impairment of lipid metabolism and insulin resistance may also be associated with vitiligo.[29] A few vitiligo patients have been found to have decreased serum lipid levels.[29]

Connective tissue diseases and vasculitis

Lupus erythematosus

Lupus erythematosus (LE) is an autoimmune disease characterized by a wide spectrum of presenting clinical manifestations, ranging from a localized cutaneous form (cutaneous LE) to a life-threatening systemic form (systemic LE [SLE]). The literature suggests that chronic inflammation and adverse effect of medications increase the risk of developing MetS in this cohort.[30] The association of MetS and SLE has been described. In addition to the cardiovascular risk factors of MetS components, there are also lupus-specific cardiovascular risk factors, such as antiphospholipid antibodies.[30] One group[31] has suggested an alternative clinical phenotype of MetS in SLE patients, demonstrating that there is a higher prevalence of MetS in SLE patients than in the control group, despite similar measures of central obesity in both groups. Another center found the prevalence of MetS to vary from 18% to 30% in SLE patients.[30] In a third study, which was a cross-sectional and case-controlled study,[32] there was also a higher prevalence of MetS in SLE patients than in the control group.

There are several hypotheses about the etiopathogenesis of MetS in patients with LE: the adverse effects of treatment, chronic inflammation, oxidative stress, and the disturbance of lipid and glucose metabolism, as a result of chronic inflammation.[30,33] The role of treatment of MetS in SLE patients remains controversial.[30]

Many studies have revealed a relationship between cardiovascular disease and SLE due to lupus-specific or classic risk factors of cardiovascular disease. Detection of MetS in the LE population is important for preventing life-threatening complications.

Sjögren syndrome

Sjögren syndrome is a systemic chronic inflammatory disorder, presenting commonly with xerophthalmia and xerostomia. When Sjögren syndrome coexists with SLE, rheumatoid arthritis, or scleroderma, it is relabeled as mixed connective tissue disease.[34] An increasing number of studies have demonstrated that SLE is associated with cardiovascular disease and MetS.[30,31,33] The overlapping may suggest that there is an association between the MetS components and Sjögren syndrome. In a population-based multicentered cohort study,[35] there was a higher incidence of hypercholesterolemia and obesity.

Behçet syndrome

Behçet syndrome represents a chronic inflammatory disorder affecting multiple organs with generalized vasculitis. The etiology remains unclear, suggesting a multifactorial causation. Behçet syndrome may have mucocutaneous, ocular, vascular, musculoskeletal, gastrointestinal, and central nervous system involvement. There can be a high mortality rate in young patients due to arterial aneurysm rupture, neurologic involvement, or thrombosis.[36] One study revealed[37] that patients with Behçet syndrome had a 2.67-fold higher risk for MetS than healthy controls. In addition, there is an association between gastrointestinal and neurologic involvement of Behçet syndrome with MetS. There is an unproven hypothesis about the relationship between MetS and adverse effects from treatment with corticosteroids and immunosuppressive drugs.

Vasculitis

Vasculitis is an autoimmune disorder characterized by inflammation of vessels that can have an array of varying clinical presentations. Premature and accelerated atherosclerosis has been demonstrated in patients with cardiac vasculitis, and cardiovascular disease is a major cause of mortality in patients with small-vessel vasculitis. In addition to the risk of cardiovascular events due to involvement of the cardiac vessels, the association between vasculitis and MetS presents yet another risk of developing a cardiovascular event. A recent study suggested that there may be an increased risk of MetS and antineutrophil antibody-associated vasculitis. In the antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis patient group, 39 (43%) fulfilled the National Cholesterol Education Program Adults Treatment Panel III criteria for MetS compared with 22 (25%) of the controls ($P = 0.012$). Among patients with ANCA-associated vasculitis, the presence of MetS was significantly associated with increased levels of CRP and neopterin. The relapse rate was higher in patients with MetS than in those

without MetS. There were also higher C-reactive peptide levels in patients with MetS than in the control group.[38]

Conclusions

Autoimmune skin disorders represent complex diseases with an elusive underlying etiology, where a variety of immunologic, metabolic, genetic, and environmental factors play a role in the pathophysiology of the respective diseases. MetS has been hypothesized to influence several autoimmune skin disorders, where chronic inflammation may explain the link between these autoimmune diseases and MetS. Diet, physical activity, and smoking cessation should be included in the management of MetS with these autoimmune skin conditions.

References

1. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. Available from: http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf, Accessed June 11, 2011.
2. Hu G, Qiao Q, Tuomilehto J, et al. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med.* 2004;164:1066-1076.
3. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA.* 2002;287:356-359.
4. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: A review. *Am J Clin Nutr.* 2007;86:s836-s842.
5. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: A systematic review and meta-analysis of observational studies. *J Am Acad Dermatol.* 2013;68:654-662.
6. Wagner G, Rose C, Sachse MM. Clinical variants of lichen planus. *J Dtsch Dermatol Ges.* 2013;11:309-3019.
7. Dreiher J, Shapiro J, Cohen AD. Lichen planus and dyslipidaemia: A case-control study. *Br J Dermatol.* 2009;161:626-629.
8. Arias-Santiago S, Buendia-Eisman A, Aneiros-Fernandez J, et al. Lipid levels in patients with lichen planus: A case-control study. *J Eur Acad Dermatol Venereol.* 2011;25:1398-1401.
9. Powell SM, Ellis JP, Ryan TJ, et al. Glucose tolerance in lichen planus. *Br J Dermatol.* 1974;91:73-75.
10. Saleh N, Samir N, Megahed H, et al. Homocysteine and other cardiovascular risk factors in patients with lichen planus. *J Eur Acad Dermatol Venereol.* 2014;28:1507-1513.
11. Arias-Santiago S, Buendia-Eisman A, Aneiros-Fernandez J, et al. Cardiovascular risk factors in patients with lichen planus. *Am J Med.* 2011;124:543-548.
12. Chow SK. Management of chronic urticaria in Asia: 2010 AADV consensus guidelines. *Asia Pac Allergy.* 2012;2:149-160.
13. Kar BR, Panda M, Patro N. Metabolic derangements in lichen planus—a case control study. *J Clin Diagn Res.* 2016;10:WC01-WC03.
14. Baykal L, Arica DA, Yayli S, et al. Prevalence of metabolic syndrome in patients with mucosal lichen planus: A case-control study. *Am J Clin Dermatol.* 2015;16:439-445.
15. Ye YM, Jin HJ, Hwang EK, et al. Co-existence of chronic urticaria and metabolic syndrome: Clinical implications. *Acta Derm Venereol.* 2013;93:156-160.
16. Vassileva S, Drenovska K, Manuelyan K. Autoimmune blistering dermatoses as systemic diseases. *Clin Dermatol.* 2014;32:364-375.
17. Ambiel MV, Roselino AM. Prevalence of metabolic syndrome and its components in a Brazilian sample of pemphigus patients. *An Bras Dermatol.* 2014;89:752-756.
18. Cunha SF, dos Santos VM, Monteiro JP, et al. Serum lipids of pemphigus foliaceus patients on long-term glucocorticoid therapy. *Rev Soc Bras Med Trop.* 2003;36:1-4.
19. Wohl Y, Dreiher J, Cohen AD. Pemphigus and dyslipidaemia: A case-control study. *Br J Dermatol.* 2009;161:1418-1420.
20. Chuang TY, Korkij W, Soltani K, et al. Increased frequency of diabetes mellitus in patients with bullous pemphigoid: A case-control study. *J Am Acad Dermatol.* 1984;11:1099-1102.
21. Rosina P, Chieregato C, D'Onghia FS. Bullous pemphigoid and diabetes mellitus. *Acta Derm Venereol.* 1996;76:497-498.
22. Teixeira VB, Cabral R, Brites MM, et al. Bullous pemphigoid and comorbidities: A case-control study in Portuguese patients. *An Bras Dermatol.* 2014;89:274-279.
23. Pietrzak A, Bartosinska J, Hercogová J, et al. Metabolic syndrome in vitiligo. *Dermatol Ther.* 2012;25:S41-S43.
24. Alikhan A, Felsten LM, Daly M, et al. Vitiligo: A comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *J Am Acad Dermatol.* 2011;65:473-491.
25. Karadag AS, Tutal E, Ertugrul DT. Insulin resistance is increased in patients with vitiligo. *Acta Derm Venereol.* 2011;91:541-544.
26. Karadag AS, Tutal E, Ertugrul DT, et al. Serum holotranscobalamine, vitamin B_{12}, folic acid and homocysteine levels in patients with vitiligo. *Clin Exp Dermatol.* 2012;37:62-64.
27. Page S, Chandhoke V, Baranova A. Melanin and melanogenesis in adipose tissue: Possible mechanisms for abating oxidative stress and inflammation? *Obes Rev.* 2011;12:e21-e31.
28. Zhou SS, Li D, Zhou YM, et al. The skin function: A factor of anti-metabolic syndrome. *Diabetol Metab Syndr.* 2012;4:1-11.
29. Rodríguez-Martín M, de Paz NM, Mehtani P, et al. Patients with vitiligo present fewer cardiovascular risk factors: Results from a case-control study. *J Eur Acad Dermatol Venereol.* 2013;27:124-125.
30. Parker B, Bruce IN. SLE and metabolic syndrome. *Lupus.* 2013;22:1259-1266.
31. Parker B, Ahmad Y, Shelmerdine J, et al. An analysis of the metabolic syndrome phenotype in systemic lupus erythematosus. *Lupus.* 2011;20:1459-1465.
32. Akarsu S, Ozbagcivan O, Semiz F, et al. High prevalence of metabolic syndrome in patients with discoid lupus erythematosus: A cross-sectional, case-control study. *J Immunol Res.* 2017;2017, 3972706.
33. Parker B, Bruce IN. The metabolic syndrome in systemic lupus erythematosus. *Rheum Dis Clin N Am.* 2010;36:81-97.
34. Lockshin MD, Levine AB, Erkan D. Patients with overlap autoimmune disease differ from those with "pure" disease. *Lupus Sci Med.* 2015;2:1-6.
35. Bartoloni E, Baldini C, Schillaci G, et al. Cardiovascular disease risk burden in primary Sjogren's syndrome: Results of a population-based multicentre cohort study. *J Int Med.* 2015;278:185-192.
36. Demiroğlu H, Yalçın S, Büyükaşik Y, et al. Increased erythrocyte aggregation as an indicator for an aggressiveclinical course in Behcet's disease: A prospective study. *Ann Rheum Dis.* 1998;57:694-696.
37. Yalcin B, Gur G, Artuz F, et al. Prevalence of metabolic syndrome in Behcet disease: A case-control study in Turkey. *Am J Clin Dermatol.* 2013;14:421-425.
38. Peterman Smits DR, Wilde B, Kianersi Adegani M, et al. Metabolic syndrome in ANCA-associated vasculitis. *Rheumatology.* 2013;52:197-203.