REVIEW ARTICLE

Metabolic syndrome – the underbelly of Dermatology

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ABSTRACT

Metabolic syndrome, also known as syndrome X has been of tremendous importance to general physicians. However, association of this syndrome in various dermatological entities has recently been established beyond doubt. And, thus it has gained tremendous importance in the field of dermatology.

The hallmark of metabolic syndrome is a chronic inflammatory state due to persistently elevated proinflammatory cytokines like leptin, adiponectin, tumour necrosis factor (TNF) alpha, interleukin (IL) 6, adipocytokines, etc. All of these have role not only in the pathogenesis of insulin resistance but also in various cutaneous diseases. Chronic inflammatory state leads to activation of leukocytes which enter the skin or circulate after rolling on the inflamed endothelial cells. Of the numerous dermatological diseases strongly associated with the metabolic syndrome the most common ones include: Psoriasis, androgenetic alopecia, hidradenitis suppurativa, acne vulgaris, rosacea, acanthosis nigricans, lichen planus, atopic dermatitis, seborrheic dermatitis.

Establishment of proper association between cutaneous manifestations and the metabolic derangements may help faster diagnosis and better treatment of systemic diseases leading to lesser comorbidities and overall disease burden.

INTRODUCTION

Metabolic syndrome (METS), also known as syndrome X is of tremendous importance to general physicians. Gradually the importance of this syndrome in association with dermatological entities has been established. It was first described by GM Reaven in 1988.[1] METS comprises a combination of parameters that predispose individuals to the development of type 2 diabetes and cardiovascular disease (CVD). The main pathophysiology behind METS is insulin resistance.[1]

Since its description in 1988, various definitions have been proposed. Under current guidelines, revised in 2005 by the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), metabolic syndrome is diagnosed when a patient fullfils at least 3 of the following 5 criterias:[2]

1. Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia)
2. Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension)
3. Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
4. HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
5. Waist circumference ≥102 cm (40 inches) in men or ≥88 cm (35 inches) in women (if Asian American, ≥90 cm in men or ≥80 cm in women)

(The international diabetes federation [IDF] cri-

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teria allow the use of a body mass index [BMI] >30 kg/m^2 instead of the waist circumference criterion.)

Various dermatological diseases are associated with METS and/or its components. Some of the diseases include psoriasis, androgenetic alopecia, acanthosis nigricans, skin tags, lichen planus, acne inversa, systemic lupus erythematosus, etc.[3] The exact pathophysiological association of these dermatological conditions with METS is still an enigma.

PATHOPHYSIOLOGY

Metabolic syndrome and the skin: the link

METS or syndrome X though associated mainly with pathogenesis of hormones like insulin and insulin resistance, does have other factors playing a role, some of which are yet to be elucidated. Other factors like increase in proinflammatory cytokines, prothrombotic factors, homocysteine, serum viscosity, leptin and resistin levels, decrease in adiponectin, occurrence of non-alcoholic fatty liver disease and polycystic ovarian syndrome are all contributory to the pathogenesis of METS.[1]

The linkage of skin and METS may be established by the following:

1. Inflammation

The hallmark of METS is a chronic inflammatory state due to persistently elevated proinflammatory cytokines like leptin, adiponectin, tumour necrosis factor (TNF) alpha, interleukin (IL)6, adipocytokines, etc. All of the above have role not only in the pathogenesis of insulin resistance but also in cutaneous diseases.[4] Chronic inflammatory state leads to activation of leukocytes which enter the skin or circulate after rolling on the inflamed endothelial cells.[1]

Moreover, many therapeutic protocols in dermatology target proinflammatory cytokines like methotrexate and TNF-alpha antagonists which not only improve chronic dermatosis but also help to decrease insulin resistance and increase HDL.

2. Oxidative stress

The skin has certain enzymes like cytochrome P450, flavin-dependent monooxygenase, alcohol dehydrogenase, monoamine oxidase, aldehyde dehydrogenase, etc which help to metabolise xenobiotics that produce reactive oxygen species (ROS), thus maintaining a balance between ROS and antioxidants. The imbalance of the above is a major contributor to the pathogenesis of various skin conditions as well as METS.[5] The failure of elimination of ROS through the sebum leads to increased levels of lipids and cholesterol in the blood, and subsequent dyslipidemia, ultimately contributing to METS. Modern sedentary lifestyle has lead to increased intake of dietary xenobiotics and decreased excretion of ROS by sweat.[6]

Skin being directly exposed to the environmental temperature, the physiological processes of skin get influenced by the temperature, with decreased excretion of ROS in cold weather. Studies have reported increased blood pressure and cholesterol levels during winters.[7] Thus, there may be role of the effect of ambient temperature on the skin and its subsequent effect in the seasonal variation of METS.

3. Hormonal abnormalities

METS is associated with decreased secretion of adiponectin from intra-abdominal adipose tissue, increased leptins and increased levels of insulin due to insulin resistance. Low levels of adiponectin has a role in pathogenesis of chronic

skin conditions like psoriasis vulgaris. Increased leptin contributes to acute and chronic inflammation by its action on cytokines that maintain the balance between T helper cells 1 and 2.[8]

Hyperinsulinemia leads to local increase of androgens which leads to androgenetic alopecia in patients of METS.

DERMATOLOGICAL CONDITIONS ASSOCIATED WITH METS

Psoriasis

Among the various cutaneous disorders associated with METS, psoriasis has the strongest association. Psoriasis is an immune mediate inflammatory disorder and has been associated with lifestyle changes, smoking, alcohol consumption and depression. It gravely affects the quality of life of the individual and all these factors may be a forerunner of METS. METS in turn leads to obesity which creates a proinflammatory state in the body eventually exacerbating psoriasis.

Cytokines of Th1 pathway form a common link between the two conditions. In psoriasis there is an increase of Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule (VCAM-1) which promotes adhesion of inflammatory cells to the endothelium of vasculature, leading to formation of atherosclerotic plaques and obesity related insulin resistance due to oxidation of low density lipoproteins.[9]

The prevalence of metabolic syndrome ranges from 20-50% in the psoriatic patients, which is higher than the general population. Metabolic syndrome is more frequent in females with psoriasis, patients older than 40 years of age and those with high PASI scores.[10]

Even in children, psoriasis is associated with dyslipidemia, diabetes mellitus and obesity and thus there is increased risk of development of METS in children with psoriasis.[11]

The treatment of psoriasis with METS is slightly complicated, as the drugs used to treat psoriasis have an adverse effect on the metabolic diseases. Conventional treatment methods have more adverse effects compared to biologicals.

Certain tests should always be done before strating treatment with any agent in psoriasis. Renal function tests should be done before strating cyclosporine as the incidence of metabolic syndrome and diabetes mellitus is high in psoriatic population.[12] Apremilast is being increasingly used in psoriasis now because of its advantage of almost not requiring any monitoring during treatment, this drug has good safety profile and helps to induce weight loss which helps not only in psoriasis but also in METS.[13]

Anti-TNF agents may be used in psoriasis with comorbid metabolic syndrome, as it has a good safety profile and lowers the incidence of new onset type 2 diabetes as compared to patients receiving conventional treatment.[14]

Newer biologicals that target interleukin (IL) 17, 12, 23 are highly effective in psoriasis but further long-term follow up data is required to comment on their role in psoriasis with associated METS. The various adverse effects of drugs used in psoriasis on METS have been summarized in table 1.

Therefore, it is important to monitor blood pressure, body mass index, waist circumference, investigate fasting lipid profile, renal and liver function tests, fasting blood glucose and take history of smoking, alcohol consumption etc before starting a psoriasis patient on long-term treatment with any of the drugs.

Apart from medical treatment, lifestyle modi-

Table 1 Adverse effects of drugs used in psoriasis on metabolic syndrome.[15]

Drugs used in psoriasis	Adverse effects on metabolic syndrome
Methotrexate	Impaired renal and liver function
Acitretin	Dyslipidemia
Cyclosporine	Diabetes, hypertension, impaired renal function, dyslipidemia
Apremilast	None
Anti-TNF agents	Obesity
IL-17 inhibitors	None
IL-22 and IL-23 inhibitors	None

fications like quitting smoking and alcohol and weight management helps not only in metabolic syndrome but also in psoriasis.[10]

Androgenetic alopecia (AGA)

AGA is the hereditary thinning of hair leading to patterned baldness, in genetically susceptible individuals. It occurs due to miniaturization of terminal follicles under the effect of dihydrotestosterone (DHT).

An association between AGA and METS has been reported especially in males, beyond fifth decade of life, and early onset AGA associated with cardiovascular diseases.[3] The pathogenesis is speculated to be pro-inflammatory state, hyperinsulinemia due to insulin resistance and hyperaldosteronism induced by METS. Hyperinsulinemia favours vasoconstriction leading to nutritional deficiency of hair follicles as well as enhances effect of DHT leading to miniaturization of follicles. Hyperaldosteronism stimulates the hair receptors favouring progress of AGA.[16]

Patients of AGA with higher body mass index and waist circumference are more prone to develop METS. Various studies have reported association of AGA with metabolic conditions like Cushing syndrome, polycystic ovary syndrome, nutritional deficiencies and coronary artery disease all of which are contributory to development of METS.[17] Thus screening for METS may be required in patients presenting with AGA.

Hiradenitis suppurativa (HS)

HS or acne inversa is a debilitating and distressing chronic inflammatory skin disease with major negative impact on quality of life and may be associated with comorbidities.

Pro-inflammatory cytokines such as interleukin (IL)-1β, IL-10 and tumor necrosis factor-α are markedly increased in lesional and perilesional skin of HS, and patients with HS have associated comorbidities like obesity, hypertension, diabetes mellitus. The adipose tissue in obesity is characterized by a chronic ongoing low-grade inflammation with macrophages invading its stroma, angiogenesis, and activation of the leukocyte adhesion cascade. Obese adipose tissue leads to a pro-inflammatory state by releasing cytokines like TNF alpha.[18] Smoking is a risk factor for HS and also for METS. Thus, all of the above may contribute to the shared pathogenesis of HS and METS.

METS has an earlier age of onset when associated with HS.[15] All HS patients irrespective of body mass index or waist circumference should be monitored for various parameters like blood pressure, blood sugar, and serum lipid profile.

Treatment regimen for HS should be chosen carefully. Use of acitretin should be avoided in HS associated with metabolic syndrome as acitretin leads to dyslipidemia. Anti-TNF agents may help with insulin resistance working in favour of treatment of both HS and METS, but on the flip-side it may also lead to weight gain so close weight monitoring is advised.[19] Use of metformin, bariatric surgery, lifestyle modifications and quitting smoking is encouraged in pa-

tients with HS associated with METS.

Acne vulgaris

Acne vulgaris is a disease of pilosebaceous unit and is a multifactorial condition. The sebum secretion of sebaceous glands is influenced by hormones, especially dihydrotestosterone. Acne has an established association with polycystic ovary syndrome (PCOS) which itself is a part of METS. Patients with PCOS are obese, have insulin resistance, acne and hirsutism. They have low levels of sex hormone binding globulin (SHBG) leading to increased free testosterone, leading to acne.[20] The risk of insulin resistance is more in young patients with acne, and they eventually develop type 2 diabetes mellitus and METS. Thus, close monitoring of insulin resistance in young acne patients is required.

Further, in acne patients the activity of mTORC1 (mechanistic target of rapamycin complex 1) was found to be increased. mTORC signalling is a known characteristic of insulin resistance, type 2 diabetes and obesity, thus establishing the link between acne and METS.[21] mTORC inhibitors like metformin are being tried in insulin resistance skin diseases like acne vulgaris.

The secretion of sebum leads to decrease in lipid levels and dysregulation of the pilosebaceous unit may lead to development of METS. This relationship is yet to be clearly established and is an arena for future research.[22]

Rosacea

Rosacea is a complex cutaneous disorder of sebaceous glands and microcirculation which affects the face and leads to chronic inflammation. A positive correlation exists between rosacea and cardiovascular disease.[23] Dysregulation of sympathetic system, blood hypertension and effect of testosterone contributes to pathogenesis of rosacea. Recent study has found a statistically significant relationship between insulin resistance and rosacea.[23] Thus, monitoring insulin resistance, which is a forerunner of METS in patients with rosacea may be imperative.

Acanthosis nigricans (AN)

AN is also known as keratosis nigricans, it is clinically characterised by velvety thickening of skin with hyperpigmentation.

AN has been established as the most common cutaneous manifestation of obesity and has been associated with insulin resistance, dyslipidemia and hypertension. Increased insulin levels lead to proliferation of skin fibroblast and keratinocytes.[24]

Obese children with diabetes have higher risk of development of AN and cardiovascular disease eventually.[24]

Alongwith topical agents like retinoids, hydroquinone, azelaic acid, oral metformin has shown improvement in AN.

Lichen planus (LP)

LP is a chronic inflammatory papulosquamous disease which involves the skin, mucosa, hair follicles and nails.

The association of LP with METS may be explained on the basis of the inflammatory mediators. Th1 cytokines IL-2, 4, 6, 10, and TNF-α are involved in the pathogenesis of LP also play a causal role in risk factors of METS. Obesity in METS leads to a pro-inflammatory state, coupled with dyslipidemia, hypertension and insulin resistance are strong predictors of diabetes, stroke and cardiovascular diseases in patients with LP.[25]

Amongst different clinical types of LP, eruptive LP has a statistically significant association with METS especially in females in 5th decade.[25] Thus, LP may be an important cutaneous marker

for METS, so monitoring of blood sugar, lipid profile, body weight and blood pressure in LP patients may assist in better management and predict future risk of various comorbidities.

Atopic dermatitis (AD)

AD is a chronic inflammatory skin disease affecting the paediatric and well as adult patients. The association of AD with METS is quite controversial. This association is being based on the association of psoriasis with METS. The association of both skin conditions with METS has been termed as "inflammatory skin march".[1]

The common link between AD and METS lies in the dysregulation of Th2 cytokines which have a role in both conditions.[26] Severely affected patients of AD may have one or more underlying undiagnosed component of METS, therefore, screening for METS may help establish a better association between the two entities.

Seborrheic dermatitis (SD)

It is a common disease affecting mainly the scalp, nasolabial folds, eyebrows, etc. The association of SD with METS can be explained on the basis of the common role of inflammation in the pathogenesis of both the conditions.

Abdominal obesity and dyslipidemia are two of the most important components of METS. The adipose tissue functions as an endocrine organ that releases many cytokines and peptides such as TNF-α, IL-6, leptin, resistin, and adiponectin. Increased TNF-α and decreased adiponectin results in increased very-low-density lipoprotein (VLDL) and decreased peripheral clearing.[27]

Malassezia species are known to produce lipase which leads to arachidonic acid release, and subsequent inflammation. Malassezia type yeasts increase the release of inflammatory cytokines from keratinocytes such as IL-6, IL-8, and TNF-α. High density lipoproteins (HDL) is known to have antimicrobial activity. Low HDL levels may decrease antimicrobial activity leading to inflammation and SD by increasing Malassezia colonization.[27]

Thus, SD is an important warning for development of METS and dyslipidemia.

Systemic lupus erythematosus (SLE)

SLE is an autoimmune disease with systemic and cutaneous manifestation, cardiovascular causes are one of the major risk factor for mortality in SLE. METS is a cluster of risk factors for cardiovascular disease coupled with a pro-inflammatory state.

Studies report increased insulin levels in patients of SLE, this has been attributed to type B insulin resistance (severe resistance due to polyclonal IgG antibodies against insulin receptors) and hypoglycaemia (due to simultaneous release of receptors).[28] This insulin resistance is a forerunner in the pathogenesis of METS. There have been reports of increased C reactive protein (CRP) in patients of SLE and METS, especially female patients.

Several potential mechanisms, especially inflammation and inflammatory mediators like signalling kinase pathway, endothelin abnormalities, oxidative stress and dyslipidemia, linking SLE with METS may prove to be therapeutic targets for the future.

Urticaria

Chronic spontaneous urticaria is a chronic inflammatory skin disorder, its basic pathophysiology is a pro-inflammatory and pro-coagulative state similar to that of metabolic syndrome.

There is increased level of inflammatory cytokines like TNF-α, IL-1, IL-6 and CRP in patients with chronic urticaria. TNF-α, a powerful regu-

lator of the synthesis of IL-6, and CRP and complement proteins have been identified as key risk factors for insulin resistance and METS. Patients with chronic urticaria associated with METS are usually older, have higher mean urticaria activity scores, tumour necrosis factor alpha and eosinophil cationic protein.[29]

Obesity which is a key component of METS results in decreased immunological tolerance to antigens, and slanting of the immune system towards a Th2 profile, therefore, further triggering chronic urticaria.[29]

To conclude, both METS and chronic urticaria have chronic low-grade inflammation and may be mutually exacerbated or triggered.

Pemphigus

Pemphigus vulgaris and pemphigus foliaceous are autoimmune vesicobullous disorder affecting the genetically predisposed individuals.

A Brazilian study reported higher prevalence of hypertension, hypertriglyceridemia, obesity and diabetes mellitus in patients of pemphigus.[30] They also reported increased risk of cardiovascular diseases in these patients. All of the above are risk factors for METS.

Further large-scale studies may be required to establish a certain association between immunobullous skin diseases and METS as it is yet not sure if METS is secondary to use of steroids for treatment of immunobullous diseases.

Vitiligo

It is an acquired, progressive, depigmenting disorder, the pathogenesis of which is still an enigma. Autoimmunity, cytokine profile and oxidative stress are important contributors to its pathogenesis.

Oxidative stress is one of the major reasons for the development of METS. Melanocytes in the adipose tissue have anti-oxidant and anti-inflammatory effects. In vitiligo there is decreased number of melanocytes and decreased melanogenesis in the adipose tissue leading to increase oxidative stress, eventually contributing to the pathogenesis of METS. In addition to the above, insulin resistance, dyslipidemia, increased inflammatory cytokines, autoimmune reaction to melanocytes, and increased homocysteine levels may all contribute to development of METS in vitiligo patients. Female patients with long standing, active, progressing, segmental vitiligo are more prone to develop METS.[31]

Further evidence of the association lies in therapy for vitiligo which helps to improve METS and vice versa. α-melanocyte stimulating hormone, an agonist of melanin production, could be used to prevent METS. Similarly, HMG-CoA reductase inhibitors (simvastatin) that is used in dyslipidemia and cardiovascular diseases show improvement in vitiligo due to its immunomodulatory effects.[31]

Maturational hyperpigmentation (MH)

MH is an under-recognised and ill-understood clinical entity in Dermatology. It presents as asymptomatic, polygonal, brown to black pigmentation over temporal area of face, with no history of rubbing/friction, application of any chemicals or topical preparations.

It is mostly seen in middle aged adults and has been associated with obesity and prominence over patients preferred sleeping side. More than 70% patients of MH have fasting hyperglycemia and hyperinsulinemia. Thus, MH could be a potential cutaneous marker of METS.[32]

Periorbital hyperpigmentation (POH)

POH is a commonly encountered condition in dermatology, it presents as round or oval, brown

to black, hyperpigmented lesion, usually bilateral on the periorbital region. It may adversely affect the quality of life of the patient and have grave psychological impact.

POH has multitude of causes and newer associations are being discovered. It may be a manifestation of facial AN or may be associated with present or past positive history of systemic diseases like diabetes, hyperthyroidism, hypothyroidism, high cholesterol, and hypertension.[33]

Further large scale studies are required to establish this association and elicit the underlying pathophysiology behind this association.

Skin Tags

Skin tags or acrochordons are benign growth found on body folds, they may be sessile or pedunculated.

Increased level of tissue leptin has been reported in skin tags compared to normal skin linking multiple skin tags with obesity and hyperlipidemia. Raised circulating insulin levels leads to activation of insulin-like growth factor 1 receptor, leading to increased epidermal proliferation in areas of skin folds. Multiple skin tags have also been associated with type-2 diabetes, hyperinsulinemia, and insulin resistance. All of the above are fore runners of METS. Thus, skin tags though asymptomatic and benign may prove to be an important cutaneous marker for metabolic syndrome.[34]

Skin Cancer

The role of metabolic derangements in pathophysiology of skin cancer is still an enigma. Increased body mass index and blood glucose level have been established as risk factors for malignant melanoma in men and high blood pressure in both men and women.[35] High blood pressure and type 2 diabetes is a risk factor for carcinogenesis in non-melanoma skin cancer.[36]

Large scale studies with more number of subjects may be needed to establish a definite association between skin cancer and METS.

Skin ageing

Oxidative stress and upregulation of inflammatory markers underlies the pathogenesis of ageing of skin. Reactive oxygen species damage the DNA, mitochondria and lead to hormonal dysfunction leading to insulin resistance and ageing. Subsequently, glycation products cross-link with collagen bundles and interferes with its function. This is accelerated in diabetics leading to faster skin ageing. Thus, skin collagen glycation is related to both METS and skin ageing.

Oxidative stress affects fibroblast gene expression, decreases level of metalloproteinase inhibitors. Thus, increased metalloproteinases lead to more collagen degradation.[37] Moreover, collagen becomes stiffer with altered function.

All of the above contribute to skin ageing and share a common pathogenesis with METS.

CONCLUSION

Metabolic syndrome and its association with various cutaneous disorders is still an evolving field of research and discovery. Skin serves as a mirror for various metabolic and systemic diseases, and every organ of the body including the skin works in a coordinated manner. Establishment of proper association between cutaneous manifestations and the metabolic derangements may help faster diagnosis and better treatment of systemic diseases leading to lesser comorbidities and overall disease burden. This association has certain future implications like, proper blood pressure monitoring for all patients above 21 years of age, serum cholesterol to be done every

5 years starting from 20 years of age and blood glucose to be measured every 3 years in patients 45 years and above (or younger in patients with risk factor for diabetes). Apart from the above, waist circumference, body mass index, liver and renal function tests, uric acid levels should be regularly monitored. While treating the dermatological disorder patient should be advised for certain lifestyle modifications like weight loss, cessation of smoking and alcohol intake. Lifestyle modification is the cornerstone and the most important first-line of management for METS. Also, any incrimination medication should be stopped or dose should be reduced.

CONFLICT OF INTEREST

none

SOURCE OF SUPPORT

none

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