REVIEW ARTICLE

Skin and metabolic syndrome: A review of the possible associations

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Metabolic syndrome (MeTS) is a well-known health-related problem with several end-organ damages and the resulted side effects such as rising in the blood glucose and lipid and blood pressure. Although MeTS might show several skin symptoms such as acanthosis nigricans, skin tags, acne, and androgenic alopecia, it could also be implicated in the pathophysiology of numerous dermatologic disorders. Furthermore, some dermatologic drugs might be implicated in the incidence or exacerbation of MeTS. Consequently, MeTS and skin problem could interfere closely with each other and each one could predispose the patient to the other one and vice versa. Remembering these close relationships help us to have better therapeutic choices regarding each inflammatory skin conditions. Moreover, some of the skin symptoms should be followed cautiously to define the underlying MeTS.

Key words: Dermatology, insulin resistance, metabolic syndrome, skin

How to cite this article: Adibi N, Robati RM. Skin and metabolic syndrome: A review of the possible associations. J Res Med Sci 2021;26:16.

INTRODUCTION

Metabolic syndrome (MeTS) or X syndrome is a condition which is originated basically from insulin resistance. Those with MeTS are at increased risk of cardiovascular disease and type 2 diabetes mellitus (T2DM). The defined criterion of this syndrome is as follows: central obesity (defined by waist circumference >94 cm in male and >80 cm in female), low-density lipoproteins level (<40 mg/dl in female and <50 mg/dl in male), high triglyceride (TG) level (>150 mg/dl), elevated blood pressure (>130/85 mmHg), and elevated fasting glucose >100 mg. The diagnosis would be confirmed if a patient has three or more of this criterion. However, there are several diagnostic criteria for MeTS provided by different educational and academic societies. Some difference was also observed in sensitivity of these criteria in different populations. Therefore, it would better use the criteria with higher diagnostic sensitivity to diagnose MeTS in each population.[1-5]

Although MeTS might show several skin symptoms such as acanthosis nigricans (AN), skin tags, acne, and androgenic alopecia (AA), it could be implicated at the pathophysiology of numerous dermatologic disorders such as psoriasis, acne vulgaris, atopic dermatitis (AD), hydradenitis suppurativa, and some autoimmune skin disorders. Furthermore, chronic skin problems and the consumption of some dermatologic drugs might be implicated in the incidence or exacerbation of MeTS. Consequently, the MeTS and skin problem could interfere closely with each other and each one could predispose the patient to the other one and vice versa.[6-13]

PATHOPHYSIOLOGY

The fundamental pathophysiology of MeTS is insulin resistance, especially in the muscle, fat, and liver cells.[14] Increased free fatty acids (FFAs) due to visceral obesity will result in increasing glucose, TG, and very LDL (VLDL). On the other hand, the glucose intake

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_585_20

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Submitted: 20-May-2020; **Revised:** 14-Jun-2020; **Accepted:** 26-Aug-2020; **Published:** 27-Feb-2021

decreases in the muscle, so the glucose level will increase and the resulted insulin over-secretion produces a vicious cycle by its lipolytic effect and again an upward increase in FFA.[14]

Adipocyte originated leptin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL)-6, IL-4, and monocycle chemotactic protein 1 play an important role in the pathogenesis of both insulin resistance and some dermatologic disorders.[15] Circulating cytokines might alter the function of both keratinocytes of the skin and end organs of MeTS.[15] Oxidative stress due to deterioration in the sebum scavenger mechanism for reactive oxygen species will be followed by the increased risk of lipid abnormalities and MeTS.[16] Endocrine abnormalities like decrease in the adiponectin level which would be accompanied by MeTS, could be seen in chronic inflammatory disorders of the skin like psoriasis.[17,18]

Any problem in the metabolic mechanism of the body could result in skin disease. Insulin resistance might induce a hormonal imbalance in the circulating androgens. Hence, androgen-dependent skin diseases such as acne, AA, and hirsutism will be followed. MeTS inflammatory cytokines including IL-17, IL-23, and TNF-α are involved in inflammatory skin diseases such as AD, psoriasis, and lichen planus (LP).[19,20] Hence, the pathophysiology of MeTS and cutaneous disorders might overlap in several pathways.[2]

METABOLIC SYNDROME RELATED CUTANEOUS DISORDERS

Psoriasis

Psoriasis is defined as a multisystem inflammatory disorder of the skin.[16] Numerous studies revealed that MeTS is an independent underlying risk factor for psoriasis which might be the side effect of impaired lifestyle in these patients.[21-23]

MeTS prevalence is significantly higher in psoriatics than in normal controls.[24-26] This correlation might be related to secreted inflammatory cytokines like adiponectin, TNF-α, T-helper 1 cytokines like interferon γ, IL-12 which might be seen both in psoriatic plaques, visceral fats and atherosclerotic plaques. Adhesion molecules such as ICAM-1 and VCAM-1 are upregulated in psoriatic plaques, and these are one of the fundamental reasons in the induction of insulin resistance as well. Chronic T-cell disorganized activation and increased vascular endothelial growth factor might also be observed in both the psoriatic and atherosclerotic plaques.[16,27-31] MeTS related comorbidities, including central obesity, hypertension (HTN), hyperglycemia, and diabetes are significantly higher in psoriasis. It seems that there are even higher in inverse and nail psoriasis.[32,33] Even liver fibrosis due to fat accumulation is more common in psoriasis.[34] These findings are quite popular in children with psoriasis as well.[35]

Using insulin-sensitizing agent (such as glucagon-like peptides) can improve psoriasis emphasizing the possible effect of insulin resistance in its pathogenesis.[34] Chronic inflammation in psoriasis could downregulate insulin receptors and lead to insulin resistance. On the other hand, chronic inflammation of the MeTS could influence the skin homeostasis.[16]

Radtke *et al*. published an algorithm for psoriatic patients follow-up, and they recommended MeTS screening every 6 months for patients with severe psoriasis and every 1 year for mild cases. Furthermore, these patients should be advised for lifestyle changes.[33] Although there are some challenging data about cardiovascular risk in psoriatic patients, physicians should be aware of this risk as well.[36,37] There are some studies which show systemic methotrexate (MTX) could improve both the psoriasis severity besides MeTS and so this could be a good choice for these type of patients. However, it should be confirmed in further studies.[38]

Disorders of the hair follicle

Acne

The incidence of MeTS is higher in both males and females with acne.[39,40] Acne might be induced by polycystic ovary syndrome (PCO) in female patients due to the increased level of free testosterone. Dysfunction of pilosebaceous unit and altered sebum secretion in acne patients resulted in the accumulation of lipid and FFA which might have an inductive role in MeTS.[41,42]

The enhanced mechanistic target of rapamycin complex 1 is demonstrated both in acne patients and insulin resistance and T2DM.[43-45] Metformin plus diet showed a reduction in acne severity in male patients in the study of Fabbrocini *et al*.[46]

Hirsutism

Hirsutism and polycystic ovary and irregular menses are some predominant features of PCO in which insulin resistance is the main underlying mechanism. PCO patients have a higher risk of metabolic and cardiovascular complications. Insulin resistance should be checked in all women with hirsutism as the most common underlying cause of hirsutism in women of all ages is PCO.[47] Rezvanian *et al*., in a randomized trial, showed that addition of metformin to intense pulsed light laser would significantly improve the hirsutism score in comparison to laser alone and concluded that the treatment of underlying Mets and inducting a better insulin sensitivity in women with hirsutism is essential in any therapeutic approach to hirsutism.[48]

Rosacea

Rosacea is defined by microcirculation abnormality and pilocebaceous disease of the skin. There seems to be a correlation between rosacea and cardiovascular syndrome. In the survey by Akin Belli *et al*., the rate of insulin resistance was higher in rosacea patients than in the control group. Dyslipidemia and high-fasting glucose were also seen in rosacea patients.[49]

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a follicular occlusion syndrome due to several mechanisms including hyperandrogenism which usually affects the axilla and groin. Some studies revealed that HS might be associated with several aspects of MeTS such as dyslipidemia and diabetes even at young ages.[50,51]

Androgenetic alopecia

Androgenetic alopecia (AGA) is the most common type of alopecia. It might have a positive relation between AGA and MeTS or IR.[52] Although there are controversies about the correlation between AA and MeTS, there are several reports which show AGA both in males and females might be correlated with increased obesity, IR and HTN.[53,54] Increasing free androgen levels and oxidative stress due to MeTS might deteriorate AGA. There seem to be common genetic factors between AGA and MeTS.[55,56]

Acanthosis nigricans and skin tag

AN is defined as dark pigmented areas especially in the flexors of obese individuals. There is a confirmed association between insulin resistance and AN. AN could be prodromal of MeTS and future diabetes in children with obesity.[57,58]

There might be a correlation between skin tags and insulin resistance. Some studies showed more tissue leptin in skin tags than normal skin.[59] Raised insulin level due to the increased insulin resistance will lead to activation of insulin-like growth factor 1 receptors in the skin folds and will follow by multiple skin tags and AN.[59,60]

Skin pigmentation

A low pigment skin type is prevalent in insulin-dependent diabetes mellitus in both sexes. Insulin resistance might be associated with hyperpigmentation. In a large study on 792 healthy Japanese women, a spectrophotometer was used for measuring skin pigmentation and melanin content on arm and forehead and also fasting blood sugar and insulin and homeostatic model assessment for insulin resistance (HOMA-IR) were measured. The melanin indices were inversely correlated with insulin and HOMA-IR and they concluded that skin pigmentation is associated with insulin resistance.[61]

Skin cancers

Increased BMI and high glucose levels as some contributing factors in MeTS suggested as risk factors for malignant melanoma.[62,63] Nagel *et al*., in a large cohort study, showed that high blood pressure could be correlated with malignant melanoma. Squamous cell carcinoma could also be related to high glucose levels and abnormal lipid profiles in women.[64]

Other inflammatory skin diseases

LP is one of the most common skin diseases. 35.7% of patients with LP had MeTS. The duration of LP is shown to be higher in those with Mets. There was a higher level of fasting blood sugar (FBS) and central obesity in patients with LP as well.[65] Sadr Eshkevari *et al*., defined that cutaneous LP has a strong association with MeTS, dyslipidemia, diabetes, and HTN.[66]

Systemic lupus erythematosus and MeTS have also shown a correlation. There seems to be a secondary Mets in systemic lupus erythematosus (SLE) patients due to the high dose prednisolone therapy and increased inflammatory cytokines.[67]

DERMATOLOGIC DRUG THERAPY AND METABOLIC SYNDROME

The common dermatologic drugs which are administered in common skin disorders might have some impact on several aspects of metabolic pathways. Some of the widely used therapeutic agents like prednisolone have several definite and evidence-based metabolic side effects but there are several controversies about the others.[2,16]

Oral corticosteroids

Corticosteroids are widely used in several dermatologic conditions like dermatitis, bullous disorders, some inflammatory and immune-mediated skin disorders.[68] They might have some metabolic side effects including insulin resistance. The plasma level of glucocorticoids is important in the pathophysiology of MeTS. It has shown that the adrenalectomy in mice could decrease body weight gain. This also accompanied by reduced plasma glucose, insulin and lipid level, but all these markers increased by adding oral GC.[68] Seelig *et al*., also showed that co-administration of metformin could have a beneficial effect in the prevention of metabolic side effects of prednisolone.[69]

However, there are some controversial reports. In research on 398 rheumatoid arthritis patients who received GC, long term exposure to GC did not show any higher prevalence of MeTS.[70] In another study in Brazil on RA patients, 110 patients with RA were evaluated and they showed a very high prevalence of MeTS markers such as abdominal obesity (98.1%), HTN (80%), and low HDL (72.2%).[71]

Oral antibiotics

Early child exposure with antibiotics (AB) might elicit gut microbial perturbation, which could be followed by dysregulation of glucose metabolism in the future. It could alter glucose metabolism and pancreatic islet function and development.[72] However, Zarrinpar *et al*., showed that AB induced microbiome depletion (AIMD) alters metabolic hemostasis and metabolism. They demonstrated that AIMD decreases baseline serum glucose level and improve insulin sensitivity. There are some researches on mice that showed that low dose doxycycline therapy with its anti-inflammatory effect could improve insulin sensitivity and decrease FBS and HOMA-IR and so have a positive effect on MeTS.[73]

There are some reports about minocycline with its anti-inflammatory properties that could improve glycemic control in patients with insulin resistance and also could protect end organs from damage in diabetics.[74,75] In a study on mice by adding low dose doxycycline to the mice drinking water for 10 weeks, doxycycline could decrease peri-renal fat and hepatic cholesterol and also FBS and HOMA-IR. These data could support possible long-term usage of sub-antimicrobial doxycycline in diabetic patients.[76]

Isotretinoin

13-cis-retinoic acid (isotretinoin) is a metabolite of vitamin A and is commonly used in severe nodulocystic acne. Although some vitamin A metabolites would increase insulin sensitivity through peroxisome proliferator receptors, isotretinoin have a negative impact on insulin sensitivity and might increase total cholesterol and TG level.[77,78] There are still some controversies about the impact of isotretinoin in the induction of insulin resistance. Ertugrul *et al*., did not find any change in insulin sensitivity index (HOMA-IR) after isotretinoin therapy.[79]

However, Soyuduru *et al*., revealed that isotretinoin caused insulin resistance regardless of BMI, age and lipid levels of patients in a randomized clinical trial done on patients with severe acne.[80] In another study in 2009, Dicembrini *et al*., reported a patient whose latent immune-mediated diabetes unmasked by the usage of 30 mg/day for 1 month and so hypothesized that isotretinoin might induce or worsen insulin resistance.[81]

Cytotoxic agents (methotrexate, cyclosporine, anti tumor necrosis factor drugs)

MTX is commonly used in psoriasis, alopecia areata, morphea and LP. Owczarczyk-Saczonek *et al*., studied 24 patients with plaque type psoriasis and showed that low dose MTX might have a protective effect on the cardiovascular risk by increasing IL-10 and endocanin and decreasing C-reactive protein level and low dose short-term MTX therapy might inhibit atherosclerosis in psoriatic patients.[82] In a study by Toms *et al*., on 400 RA patients, MTX was the only disease-modifying antirheumatic drug (DMARD) that could significantly decrease the MeTS in RA patients. So MTX is a good choice for treating RA and psoriasis with protective metabolic effect especially in the elderly over 60s.[83] However, In another study by Dehpouri *et al*., the glycemic effect of MTX were evaluated in 27 psoriatic arthritis patients before and 12 weeks after MTX therapy and concluded that there is not any change in glycated hemoglobin (HbA1c) and fasting blood glucose before and after therapy.[84]

Cyclosporine is an immunosuppressant that is widely used in several dermatologic disorders like psoriasis, severe urticaria, severe AD, and several other autoimmune disorders of the skin.[85,86] In a meta-analysis on the effect of tacrolimus and cyclosporine on renal transplant patients, cyclosporin was associated with a higher incidence of hyperlipidemia.[85] In another study of post renal transplant patients, those who showed MeTS after renal transplantation have a higher median level of blood cyclosporine.[86] Cyclosporine should be used with caution in psoriatic patients, especially as a long-term treatment. Cyclosporin might adversely impact metabolic parameters such as blood glucose, lipid, and blood pressure. In a large study on psoriatic patients, HTN, diabetes, and hypercholesterolemia were more prevalent in those who received cyclosporine. Cyclosporine might also inhibit the insulin secretion from beta cells.[9,87]

TNF-α is an inflammatory cytokine that is important in the pathogenesis of psoriatic arthritis and other inflammatory disorders. TNF-α is one of the cytokines which is responsible for insulin resistance and dyslipidemia. Anti TNF-α could not only important for treating cutaneous inflammation but also ameliorating glucose and lipid metabolism.[88]

Antimalarials

Hydroxychloroquine is widely used in SLE, discoid lupus erythematosus, Lichen planopilaris, and other dermatologic disorders. It has favorable metabolic effect both on glucose and lipid profiles. It has a beneficial impact on diabetes and in dermatologic patients with diabetes, it could be a good choice. We should be also aware of its hypoglycemic effect.[89] The antidiabetic effect of chloroquine was first described by Blazar *et al*., in 1984.[90] Hydroxychloroquine increases insulin binding to its receptors and alters hepatic insulin metabolism.[89]

In a systematic review by Wondafrash *et al*., improvement of lipid profile and insulin levels and substantial diminution of HbA1c and FBS were showed in those who received hydroxychloroquine. The underlying hypothesis might be the induction of increased insulin sensitivity in the receptor level.[91]

Antihistamines

Antihistamines are widely used agents in the treatment of urticaria, pruritis, dermatitis, and other inflammatory skin conditions.[92] They could produce weight gain and MeTS. Obesity is a possible side effect of H1 antihistamines. Furthermore, they may induce a higher insulin concentration.[92] In a study by Anvari *et al*., on Nod mice (a model for human type 1 diabetes), they treated mice with 25 mg/kg of cetirizine for 2 weeks and blood glucose and insulin sensitivity were tested. They concluded that cetirizine did not affect diabetes development. However, it has a protective effect against high-fat diet-induced hyperglycemia but cetirizine did not affect insulin sensitivity.[93]

Antifungals

Systemic antifungals may adversely affect endocrine organs and produce metabolic complications such as hypo or hyperthyroidism, pancreatitis, hypernatremia, hypoadrenalism, and disturbances in electrolyte and trace elements.[94]

There are some reports that itraconazole could attenuate hepatic gluconeogenesis and promote glucose reuptake by regulating adenosine monophosphate-activated protein kinase and might be a promising candidate in the treatment of type 2 diabetes.[95] Modified released ketoconazole, a known inhibitor of cortisol secretion, were used in 72 overweight type 2 diabetes by 400 mg for 3 months. It was showed that HBA1c and FBS and total cholesterol were improved and so modified released ketoconazole might have a protective effect on MeTS.[96]

Antiandrogen

Spironolactone is an antihypertensive drug with antiandrogen effect which is used in acne, hirsutism, and female pattern hair loss. It could have a protective effect on dyslipidemia and dietary-induced MeTS by inhibition of some pathway in the pancreatic gland.[97] Furthermore, in a mice model with high fat and fructose diet, spironolactone lowered the elevation of blood glucose in mice and might have a beneficial effect on MeTS and fatty liver.[97,98]

Antiandrogenic oral contraceptives are used in hirsutism and acne. Combined estrogen-progesterone low-dose pills might have no effect on waist circumference and glucose intolerance of PCO women and showed to be safe for women with MeTS but high dose progesterone-pills should be avoided.[99]

CONCLUSION

MeTS is a well-known health-related problem with several end-organ damages and the resulted side effects like rising in the blood glucose and lipid and blood pressure. Insulin resistance is the basic pathophysiology of MeTS. There are both primary and secondary correlations between several dermatologic disorders and MeTS. Some skin disorders including psoriasis, hidradenitis supprative, hirsutism, and AN could be associated with a higher prevalence of MeTS. This association might also be observed in other dermatologic conditions such as acne, AGA, or rosacea. However, more controlled studies needed to reach a more definite conclusion in this regard.

There are also some interactions between dermatologic systemic drugs and MeTS. Some commonly used drugs in dermatology, including corticosteroids, isotretinoin, and cyclosporine could predispose some patients to develop MeTS. Other drugs such as anti-TNF agents, hydroxychloroquine, minocycline, low-dose doxycycline, itraconazole, or spirinolactone could show some protective effect against the development of MeTS. However, there are also some controversies upon the protective or predisposing effects of many drugs such as MTX or antihistamines regarding the development of MeTS.

Considering all these possible relationships help us to have better therapeutic choices regarding each inflammatory skin conditions. The skin could also serve as an indicator of MeTS in the body due to some insulin resistance manifestations. Hence, some of the skin symptoms should be followed cautiously to define the underlying MeTS.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest.

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