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Skin disease related to metabolic syndrome in women☆,☆☆

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ABSTRACT

Sex hormones are involved in pathways of metabolic syndrome (MetS), an observation supported by animal studies. The relationships of sex hormones with components of MetS, such as insulin resistance and dyslipidemia, have been studied in pre- and postmenopausal women. High testosterone, low sex hormone-binding globulin, and low estrogen levels increase the risks of MetS and type 2 diabetes in women. Cutaneous diseases that are sex hormone mediated, such as polycystic ovary syndrome, acanthosis nigricans, acne vulgaris, and pattern alopecia, have been associated with insulin resistance and increased risk for MetS. Furthermore, inflammatory skin conditions, such as hidradenitis suppurativa and psoriasis, increase the risk for MetS. Patients with such skin conditions should be followed for metabolic complications, and early lifestyle interventions toward these populations may be warranted.

Contents

Introduction

The metabolic syndrome (MetS) comprises a combination of interconnected physiological, biochemical, clinical, and metabolic

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factors that predispose for cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and increased all-cause mortality (Kaur, 2014). Many definitions of MetS have been proposed, with the most recent comprising five equal criteria: elevated waist circumference (WC; within population-specific criteria), elevated triglyceride (TG) levels, elevated fasting glucose, low high-density lipoprotein cholesterol (HDL-C) levels, and elevated blood pressure (BP; Alberti et al., 2009). The presence of at least three of these criteria is necessary and sufficient for a diagnosis of MetS.

There has been ongoing interest in comorbidities, such as skin disease, associated with MetS and the mechanisms that underlie these associations. Any pathophysiologic dysfunction, such as insulin resistance (IR), that results in metabolic alterations can also result in cutaneous disease (Stefanadi et al., 2018: Wu et al., 2012). A body of literature has demonstrated that sex hormones are linked to pathways of MetS (Ahmed et al., 2017; Kroumpouzos, 2013; Laaksonen et al., 2004; Roth et al., 2018). Obesity induces chronic inflammation associated with MetS, and the bidirectional relationship of sex hormones with obesity has been validated in several studies (Brown et al., 2010). The relationships between sex hormones and MetS are illustrated in Figure 1. The main pathophysiologic mechanisms that underlie the link between MetS and skin disease are presented in Table 1. Herein, we describe sex hormone–mediated or –affected skin diseases associated with MetS and elaborate on associations with components of MetS.

Table 1
Main mechanisms of metabolic syndrome in women with skin disease

Main mechanisms	Condition
Hyperandrogenism + insulin resistance	Polycystic ovary syndrome
Insulin resistance	Acanthosis nigricans Acne vulgaris
Potential insulin resistance	Acrochordons Pattern alopecia Systemic lupus erythematosus
Chronic inflammation + insulin resistance	Hidradenitis suppurativa Psoriasis vulgaris
Chronic inflammation	Lichen planus
Unknown	Atopic dermatitis Squamous cell carcinoma Seborrheic dermatitis

Animal studies on sex hormones and metabolic syndrome

Developmental exposure to excess testosterone (T) causes neuroendocrine, ovarian, and metabolic deficits (Padmanabhan and Veiga-Lopez, 2011). Dihydrotestosterone treatment induces polycystic ovary syndrome (PCOS) features in mature female rats (Caldwell et al., 2014). These include polycystic ovaries displaying unhealthy antral follicles, increased body fat, hypercholesteremia, anovulation, and acyclicity. Furthermore, elevated androgen levels in female rats have been demonstrated to impair glucose-stimulated insulin secretion, partly through the dysfunction of pancreatic β cell mitochondria (Wang et al., 2015). Chronic administration of estradiol has been shown to improve insulin sensitivity in rodents (Hevener et al., 2015).

Effects of endogenous sex hormones

Sex hormone–binding globulin affects the bioavailable fraction of hormones and sequesters the actions of androgens and estrogens (Ding et al., 2009). Additionally, serum SHBG can directly affect cells by binding to its receptor and acting as a hormone (Rosner et al., 2010). Low levels of SHBG have been associated with impaired glucose control, suggesting a link between SHBG and glucose regulation (Ding et al., 2006, 2009; Kajaia et al., 2007; Maggio et al., 2007; Sutton-Tyrrell et al., 2005). Low SHBG and high free androgen index are significantly associated with cardiovascular risk factors (Sutton-Tyrrell et al., 2005). Furthermore, higher SHBG levels are associated with a reduced risk of MetS (Brand et al., 2011). Increases in SBGH after lifestyle interventions in postmenopausal women are associated with a favorable impact on fasting and postchallenge glucose levels (Kim and Halter, 2014).

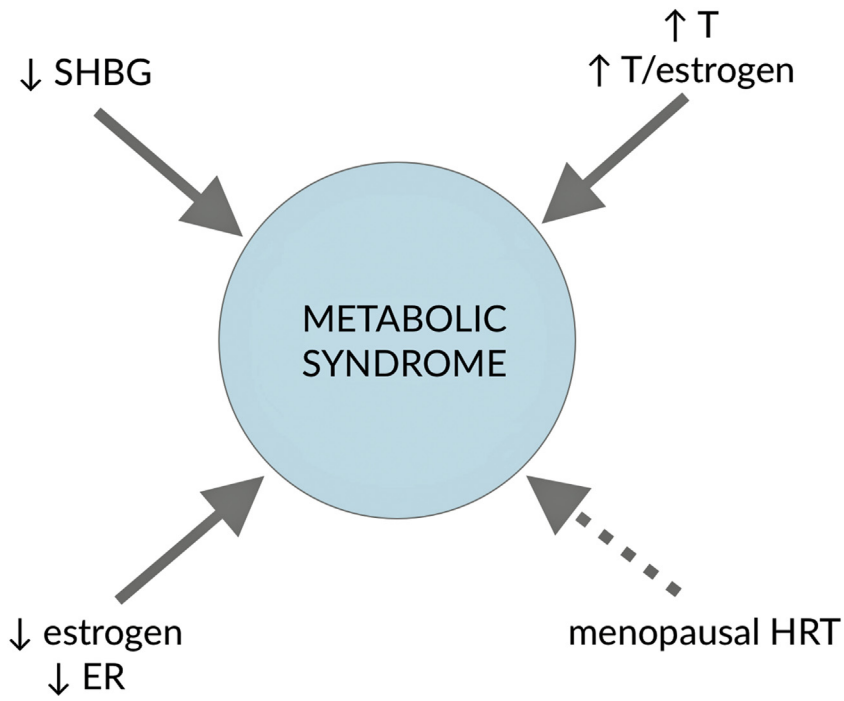

Fig. 1. Relationships between sex hormones and metabolic syndrome in women. ER, estrogen receptor; HRT, hormone replacement therapy; SHBG, sex hormone-binding globulin; T, testosterone. Solid arrows indicate a triggering effect on metabolic syndrome; dotted arrow indicates an inhibitory/preventive effect.

Several observational studies have demonstrated that total and free T levels are higher in women with MetS (Brand et al., 2011). Additionally, higher T levels in women increase the risk of T2DM (Ding et al., 2006). Furthermore, the T/estradiol ratio and its rate of change during the menopausal transition increase the incidence of MetS (Torréns et al., 2009). A vast number of studies indicate a critical and protective role for estrogen receptor alpha in the maintenance of metabolic homeostasis and insulin sensitivity (Hevener et al., 2015). Estradiol and estrogen receptor alpha–specific agonists promote energy homeostasis; improve body fat distribution; and ameliorate IR, β cell function, and inflammation (Hevener et al., 2015).

Effects of exogenous sex hormones

Menopausal hormone replacement therapy (HRT) has shown beneficial effects on women's metabolic profile in several studies (Lovre et al., 2016). HRT was associated with a 20% diabetes risk reduction and improvement of insulin sensitivity (Manson et al., 1992; Salpeter et al., 2006). In addition, HRT has been associated with lower levels of fasting glucose and total cholesterol (TC) and decreased systolic BP, body mass index (BMI), WC, and waist-to-hip ratio among both diabetic and nondiabetic women (Kim et al., 2019). Studies on postmenopausal HRT showed that oral estrogen increased HDL-C and TG and decreased low-density lipoprotein cholesterol (LDL-C) levels (Godsland, 2001; Miller et al., 1995). Estrogen-induced increases in HDL-C and TG were opposed according to the type of progestogen (Godsland, 2001).

Metabolic syndrome through female life cycle

Features of MetS may begin in childhood and continue through adolescence (Hadjiyannakis, 2005). The prevalence of MetS in children is unknown because of a lack of diagnostic criteria in the pediatric population (Hadjiyannakis, 2005; Weiss et al., 2013). Factors such as obesity, IR, genetic predisposition, environment, and ethnic heritage may be involved in MetS development during childhood (Roth et al., 2018). Early menarche, especially among low-birth-weight females, increases the risk of MetS during young adulthood (Kim and Je, 2019; Lim et al., 2016; Vryonidou et al., 2015). In this population, high TG and low HDL-C levels are the most common MetS components (Akter et al., 2012). Puberty is associated with a 30% decrease in insulin sensitivity during the progression from Tanner stage II to IV (Amiel et al., 1991; Hadjiyannakis, 2005).

Pregnancy is characterized by increased physiologic requirements associated with a relative degree of IR and hyperlipidaemia, which catapults women into a metabolic state (Sattar, 2002; Vryonidou et al., 2015; Williams, 2003). These metabolic changes could be considered stress tests of maternal carbohydrate and lipid pathways and vascular function (Sattar, 2002). The contribution of sex hormones to metabolic adaptations during pregnancy is supported by a body of literature (reviewed by Zeng et al., 2017). Obesity during pregnancy increases the risk of gestational diabetes mellitus (GDM) and hypertension (HTN; Bartha et al., 2008; Grieger et al., 2018). Women with MetS are at a higher risk for preeclampsia and GDM (Grieger et al., 2018), and women with GDM are at a higher risk for T2DM and CVD later in life (Bartha et al., 2008; Chatzi et al., 2009; Kaufmann et al., 1995; Williams, 2003). Preeclampsia is an additional risk factor for T2DM and CVD (Bartha et al., 2008). Many studies have indicated a positive association between the number of children and a mother's later risk for CVD (Rich-Edwards et al., 2014). However, parity and CVD risk might be affected by other socioeconomic and lifestyle factors (Rich-Edwards et al., 2014).

Natural menopause is associated with an acceleration of risk of MetS independently of aging (Ziaei and Mohseni, 2013).

Table 2
Conditions associated with hyperandrogenism

Idiopathic hyperandrogenism
Adrenal dysfunction
Congenital adrenal hyperplasia (classical, nonclassical)
Ovarian dysfunction (abnormal gonadal development, stromal hyperthecosis)
Polycystic ovary syndrome
Hyperandrogenic insulin-resistant acanthosis nigricans syndrome
Cushing syndrome
Hyperprolactinemia
Thyroid dysfunction
Acromegaly
Androgen-secreting tumor (ovarian or adrenal)
Gestational hyperandrogenism (theca lutein cysts, luteomas)
Exogenous androgen
Drug-induced (e.g., cyclosporine, progestin, diazoxide, minoxidil, phenytoin)

Table modified from Roth et al., 2018.

Menopause is characterized by hormonal changes that substantially increase the risk for CVD and MetS. The onset of MetS during menopause is mainly due to a deficiency of estrogens, which exert a cardioprotective role (Vryonidou et al., 2015). Furthermore, relative androgen excess during the menopausal transition is predictive of MetS (Torréns et al., 2009). Elevated T and decreased SHBG levels are the most significant factors correlated to MetS in postmenopausal women (Ziaei and Mohseni, 2013).

Mechanisms underlying the skin: Metabolic syndrome connection

IR, hyperandrogenism, chronic inflammation, and oxidative stress are the main mechanisms that link skin disease to MetS. These mechanisms are involved in complex interactions; for example, the chronic inflammation that is often linked to obesity makes IR more likely to occur. Sex hormones have complex interactions with obesity, inflammation, and MetS (Roth et al., 2018). IR, possibly related to a postreceptor defect in adipose tissue, plays a paramount role in MetS.

Conditions associated with hyperandrogenism are shown in Table 2 (Carmina et al., 2006a, 2006b; Keen et al., 2017; Meek et al., 2013; Mihailidis et al., 2015; Roth et al., 2018; Schmidt and Shinkai, 2015). Acne is the most common manifestation of cutaneous hyperandrogenism (Clark et al., 2014). Other cutaneous manifestations include hirsutism, acanthosis nigricans (AN), female pattern alopecia (PA), and skin tags (STs) (Clark et al., 2014; Roth et al., 2018). The clinical assessment of hyperandrogenism should be followed by a biochemical assessment (Meet et al., 2013). Of note, clinical features of cutaneous hyperandrogenism can be present without evidence of biochemical hyperandrogenism (Ozdemir et al., 2010).

Polycystic ovary syndrome

PCOS is the most common endocrine abnormality in women of reproductive age (Teede et al., 2010). Its prevalence among women of reproductive age is 6.5% to 8.0% per the National Institutes of Health 1990 criteria and increases to 15% to20% when the Rotterdam 2004 criteria are used (Goodarzi and Azziz, 2006; Sirmans and Pate, 2013). The clinical features of PCOS include acne, hirsutism or less severe excessive hair growth, AN, alopecia, amenorrhea, oligomenorrhea or dysfunctional bleeding, anovulatory infertility, and central obesity (Ozdemir et al., 2010; Schmidt et al., 2016). The acne severity in women with PCOS is associated with higher total and free T levels and free androgen index value (Franik et al., 2012).

IR, combined with androgen excess and abnormal gonadotropic functions, plays a crucial role in the pathogenesis of PCOS

(Alemzadeh et al., 2010; Amato et al., 2008; Lee and Zane, 2007). Insulin may increase androgen serum levels (Lee and Zane, 2007), and women with both PCOS and MetS tend to manifest hyperadrogenemia, lower serum SHBG levels, and AN more often than women who have PCOS alone (Apridonidze et al., 2005). On the other hand, MetS shows a substantially higher prevalence (ranging from 8.2% in Italy to 43%-47% in the United States) in women with PCOS than in age-matched women in the general population (Carmina et al., 2006a, 2006b; Dokras et al., 2005; Glueck et al., 2003).

Dyslipidemia is often observed in women with PCOS who have low HDL-C, high LDL-C, and high TG levels (Diamanti-Kandarakis et al., 2007; Legro et al., 2001). Increased WC and low serum HDL-C levels are the most commonly documented components of MetS in women with PCOS (Dokras et al., 2005; Zahiri et al., 2016). Women with PCOS and MetS have higher values of BP, BMI, and ovarian size and increased levels of TG, TC, fasting blood sugar, and 2-hour blood sugar compared with women with PCOS but without MetS (Zahiri et al., 2016).

Obesity is reported in 61% to 76% of women with PCOS (El Hayek et al., 2016). Furthermore, obese individuals with PCOS have a worse metabolic profile than normal weight controls (Lim et al., 2019). Although not required for a diagnosis of PCOS, IR plays a prominent role in PCOS. Women with PCOS have an increased prevalence of impaired glucose tolerance and T2DM (Moran et al., 2010). IR in PCOS occurs independently of obesity, and lean women with PCOS were found to have a higher risk for CVD compared with healthy controls (Dunaif, 1997; Dunaif et al., 1989). Asprosin, a newly discovered peptide, is associated with BMI, glucose metabolism, insulin homeostasis, and inflammation (Li et al., 2018). Increased asprosin levels were associated with a higher possibility of having PCOS (Alan et al., 2019). A higher risk of HTN, especially among PCOS patients aged $\leq$40, has been shown (Behboudi-Gandevani et al., 2018).

The MetS/PCOS overlap significantly increases the risk of developing atherothrombosis and T2DM (Alexander et al., 2009; Cussons et al., 2008; Essah and Nestler, 2006). Insulin-sensitizing agents, such as biguanide metformin, and lifestyle changes are beneficial in the treatment and prevention of metabolic abnormalities in women with PCOS (Essah and Nestler, 2006; Pugeat et al., 2000). Generally, the administration of oral contraceptives, the traditional pharmacological therapy for PCOS, leads to improved menstrual patterns and serum androgen levels compared with metformin, but metformin is more effective than oral contraceptives in reducing fasting insulin and lowering TG levels (Costello et al., 2007).

Psoriasis

Psoriasis is increasingly recognized as a systemic inflammatory disorder (Takeshita et al., 2017a). A number of studies have shown that the prevalence of MetS is higher among patients with psoriasis, both in pediatric and adult populations (Armstrong et al., 2013; Gutmark-Little and Shah, 2015; Langan et al., 2012). The association between psoriasis and MetS is directly correlated with the severity of psoriasis (Langan et al., 2012; Stefanadi et al., 2018). Psoriasis is an independent factor for CVD (Takeshita et al., 2017a). The severity of disease and nail pitting are risk factors of CVD (Gelfand et al., 2016; Stefanadi et al., 2018). Risk factors for CVD occur with higher incidence in patients with psoriasis than in the general population (Kaye et al., 2008; Neimann et al., 2006). The risk of myocardial infarction is significant even for patients with mild psoriasis (Armstrong et al., 2013; Takeshita et al., 2017a). Longer course of disease is associated with a greater risk for CVD (Armstrong et al., 2012), and women with psoriasis are at high risk for HTN (Qureshi et al., 2009). Furthermore, patients with psoriasis appear to have more difficult-to-control HTN compared with nonpsoriatic, hypertensive patients (Armstrong et al., 2011; Takeshita et al., 2015).

Dyslipidemia has been associated with psoriasis; however, the directionality between these conditions remains unclear (Ma et al., 2013; Takeshita et al., 2017a; Wu et al., 2014). Obesity is an independent factor for psoriasis, and the risk in women increases with a higher BMI score (Kumar et al., 2013; Langan et al., 2012; Setty et al., 2007). Heterogeneous randomized weight loss clinical trials showed that patients who received weight loss interventions had a greater reduction in the severity of psoriasis when compared with controls (Upala and Sanguankeo, 2015). Lastly, weight loss in obese patients on biologic treatment showed an increase in drug efficacy (Al-Mutairi and Nour, 2014). Obesity seems to favor psoriasis in predisposed individuals because of the proinflammatory state and release of mediators, such as adipokines that contribute to inflammation (Padhi and Garima, 2013). Adiponectin, an anti-inflammatory protein, is decreased among patients with psoriasis compared with healthy controls (Cerman et al., 2008; Kaur et al., 2008; Shibata et al., 2009; Wang et al., 2008).

Women with psoriasis are at increased risk of diabetes independently of their BMI (Qureshi et al., 2009). The likelihood of IR relates to psoriasis severity (Azfar et al., 2012; Langan et al., 2012). Additionally, diabetic patients with psoriasis are more likely to be under pharmacologic treatment and report vascular complications than diabetic patients without psoriasis (Armstrong et al., 2015; Azfar et al., 2012; Takeshita et al., 2017b).

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is more prevalent in women than in men in the United States (Vazquez et al., 2013). Changes in HS activity have been reported during times of fluctuating hormones, such as during premenstrual periods, pregnancy, and menopause (Clark et al., 2017; Riis et al., 2016). Estradiol and progesterone levels decline during the premenstrual period, and premenstrual HS flares occur in 44% of 63% of patients (Riis et al., 2016). The decline of estrogen and progesterone levels during menopause has been associated with a decline in HS symptoms and cases (Barth et al., 1996; Burger et al., 2007; Clark et al., 2017).

The role of androgens in HS remains unclear. Although there is no increase in serum androgen levels in most patients with HS, there is evidence supporting the efficacy of anti-androgen medications (i.e., spironolactone, finasteride, and dutasteride) in HS (Kraft and Searles, 2007; Khandalavala and Do, 2016). There is a lack of supportive data regarding the use of oral contraceptive pills for HS treatment (Clark et al., 2017).

The association of HS with MetS has been consistently identified in a number of studies (Sabat et al., 2012; Shlyankevich et al., 2014; Tzellos et al., 2015). The relationship to MetS applies also to young HS patients and those with mild disease (Ergun, 2018). IR is common among patients with HS (Vilanova et al., 2018). Compared with the general population, patients with HS are three times more likely to have diabetes (Bui et al., 2018) and are more likely to have hyperlipidemia, obesity, and/or HTN (Shalom et al., 2015). Patients with HS are also at an increased risk for myocardial infarction, ischemic stroke, CDV-associated death, and all-cause mortality (Egeberg et al., 2016). The severity of HS is a risk factor for CVD (Stefanadi et al., 2018). Mean resting heart rate, a risk factor for CVD, is higher in patients with severe HS compared with healthy individuals (Juhl et al., 2018).

Acrochordons

Acrochordons, or STs, are more common among overweight individuals and may be a marker of MetS (El Safoury et al., 2011; Shah et al., 2014). STs have been associated with impaired insulin

homeostasis (i.e., glucose intolerance and diabetes; Behm et al., 2012; Margolis and Margolis, 1976; Sari et al., 2010) and hypercholesterolemia (Platsidaki et al., 2018). A recent study demonstrated that the lipid profile of patients with STs is characterized by high levels of LDL-C, TC, and TG, but the mean HDL-C level was lower (Shah et al., 2014). Individuals with STs have higher systolic and diastolic BP than controls (Shah et al., 2014). The number and presence of mixed-colored STs has been related to obesity (El-Safoury & Ibrahim, 2011). Serum leptin levels are higher in patients with STs than in controls (Wali and Wali, 2016). Although the pathophysiologic mechanism by which leptin is related to STs is unknown, the mitogenic effect of leptin on keratinocytes may be involved (Stallmeyer et al., 2001).

Acanthosis nigricans

AN is linked to obesity, PCOS, T2DM, and IR (Higgins et al., 2008). Hyperinsulinemia is associated independently with AN; it leads to the stimulation of epidermal keratinocytes, producing the characteristic lesions that are most commonly noted in skin folds (Roth et al., 2018; Stoddart et al., 2002). This link appears to start early, and a systematic review demonstrated the relationship between AN and IR/T2DM in children with obesity (Abraham and Rozmus, 2012). Periorbital pigmentation in a female patient with AN was proposed as an alarming sign of MetS (Zawar et al., 2019).

Acne vulgaris

Pathogenetic mechanisms involved in the development of acne, including excess sebum production, release of inflammatory mediators, and follicular keratinization, are affected by excess androgen activity (Bhat et al., 2017; Bagatin et al., 2019). The activation of mammalian target of rapamycin complex 1 signaling is involved in both acne pathogenesis and IR (Melnik et al., 2013). Acne in women has been linked with IR and lipid profile alterations independent of hyperandrogenism (Emiroğlu et al., 2015; Kartal et al., 2016). Nonetheless acne has not been established as a prognostic factor for MetS (Roth et al., 2018).

Rosacea

Studies have linked rosacea to risk factors for CVD (Akin Belli et al., 2016; Duman et al., 2014). Patients with rosacea have higher TC, LDL-C, and C-reactive protein levels than controls (Akin Belli et al., 2016; Duman et al., 2014). Furthermore, patients with rosacea are also more likely to report a family history of CVD (Duman et al., 2014). IR and elevations in systolic and diastolic BP are significantly associated with rosacea (Akin Belli et al., 2016). Furthermore, dysregulation of sympathetic system and T effect may be involved in cases of rosacea linked to MetS (Leroith, 2012).

Female pattern alopecia

PA in women has been linked to MetS, and the severity of the condition is associated with CVD (Stefanadi et al., 2018). A population-based survey shopwed that female patients with PA are more likely to have CVD, dyslipidemia and obesity (Kim et al., 2018). Among MetS traits, WC and HTN are the most important factors associated with PA (El Sayed et al., 2016). Furthermore, WC increases with the severity of PA (El Sayed et al., 2016). Women with PA have higher TG, LDL-C, and TC levels and lower HDL-C levels than nonalopecic controls (Arias-Santiago et al., 2010a, 2010b; Bakry et al., 2015). Hyperglycemia or diabetes was more common among patients with alopecia (Arias-Santiago et al., 2011a, 2011b). A relationship with IR (Matilainen et al., 2003) has been disputed (Nabaie et al., 2009). Additionally, patients with hyperglycemia and alopecia have significantly lower SHBG levels than individuals with hyperglycemia.

Hirsutism

Hirsutism in women is defined as excessive hair growth in androgen-dependent areas (Messenger et al., 2010). Hirsutism results from an interaction between androgen and hair follicle sensitivity to this sex hormone (Mihailidis et al., 2015). Idiopathic hirsutism is the most common form, but the condition can be associated with PCOS or medication (Unlühizarci et al., 2004; Mihailidis et al., 2015). Hirsutism is associated with IR and increased prevalence of impaired glucose tolerance in obese patients (Unlühizarci et al., 2004).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) shows a female predilection. Women with SLE have a greater than five-fold risk for coronary artery disease events (Parker et al., 2015). The risk of MetS is significantly higher in patients with SLE compared with healthy controls (Hallajzadeh et al., 2018). Among MetS components, elevated TG levels and HTN were the most strongly linked to SLE (Hallajzadeh et al., 2018).

Miscellaneous conditions

Lichen planus has been associated with MetS, and the MetS criteria most frequently reported in patients with lichen planus are elevated TG, WC, and low HDL-C levels (Arias-Santiago et al., 2011a, 2011b). Atopic dermatitis is possibly related to MetS, and female sex was suggested as a risk factor (Furue and Kadono, 2017). In a study, women with squamous cell carcinoma had a tendency toward increased glucose and TG levels (Nagel et al., 2012). Another study indicated that seborrheic dermatitis is a predictive factor for MetS (Imamoglu et al., 2016).

Xanthelasma palpebrum (XP) appears predominantly in middle-aged women (Kavoussi et al., 2016). Significantly elevated mean TC and TG levels, very low density lipoprotein levels, and low HDL-C values in patients with XP compared with controls have been reported (Kavoussi et al., 2016). XP may be a marker of atherosclerosis irrespective of lesion size or serum lipid levels (Pandhi et al., 2012). However, Ozdöl et al. found that hyperlipidemia was significantly more common in patients with XP than in the control group, but there was no increase in the observed risk of CVD (Ozdöl, 2008). The prevalence of MetS in XP has not been adequately studied, and the risk for CVD requires further investigation.

Conclusion

The constellation of MetS, IR, and CVD can be present in a wide spectrum of cutaneous conditions. The health care provider should be familiar with skin diseases associated with MetS and promptly recognize MetS-relevant comorbidities, such as CVD in patients with these skin diseases. Establishing an early diagnosis of MetS is crucial to management and facilitates counseling that may include lifestyle interventions. IR and dyslipidemia should be managed, and tighter glycemic control and HTN screening should be pursued. A multidisciplinary approach is required to address the multifaceted aspects of MetS linked to skin disease.

Appendix A. Supplementary data

For patient information on this topic please click on Supplemental Material to bring you to the Patient Page. Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijwd.2019.06.030.

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