Gynecologic and Obstetric Investigation

Narrative Review

Gynecol Obstet Invest
DOI: 10.1159/000545280

Received: July 25, 2024
Accepted: February 21, 2025
Published online: March 20, 2025

Endocrine Metabolic Syndrome and Metabolic Syndrome: Distinct but Interrelated Pathologies

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Keywords
Polycystic ovary syndrome · Metabolic syndrome · Obesity · Hyperandrogenism · Cardiovascular disease

Abstract
Background: Polycystic ovary syndrome, or endocrine metabolic syndrome (EMS) as recently proposed by the Expert Group on Inositol in basic and clinical research and on PCOS (EGOI-PCOS), manifests as a series of metabolic and hormonal alterations, which are primarily suspected to be underpinned by an underlying metabolic problem. Several of these metabolic issues are shared with metabolic syndrome (MetS), a separate but interrelated metabolic disorder typified by obesity, heightened glucose levels, dyslipidemia, and cardiovascular risk factors. ***Objectives:*** This review sets out to expand upon the interplay between EMS and MetS, defining the key characteristics of each condition prior to discussing treatment options that may benefit both sets of patients. ***Methods:*** A narrative review of all the relevant papers in English language was conducted. ***Outcome:*** Both EMS and MetS share common features, such as obesity, dyslipidemia, and cardiovascular risk factors, and thus can be treated in certain circumstances with similar therapeutic approaches. However, in both women and men, does not feature alterations of androgen levels, as is the case with EMS. Furthermore, these conditions tend to occur in different age groups, with MetS primarily occurring during or after menopause, while EMS occurs in women of reproductive age. ***Conclusions and Outlook:*** These two conditions share considerable overlap, and one may trigger the other in affected patients; however, the causality is currently unclear and requires further study.

Introduction

Polycystic ovary syndrome (PCOS), as it has been previously defined, is the most prevalent endocrine metabolic disorder in women of reproductive age, affecting the metabolic, hormonal, cardiovascular, and psychological health of the individual [1]. Within the clinic, patients are classified according to the revised Rotterdam criteria, which assign a phenotype (A–D) according to the presentation of three symptoms, namely, hyperandrogenism, menstrual cycle disruptions, and polycystic ovarian morphology [2]. In 2023, the Expert Group on Inositol in basic and clinical research and on PCOS (EGOI-PCOS) proposed a new classification system that formally separated the hyperandrogenic phenotypes (formally A, B, and C), and

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the normoandrogenic phenotype D [3, 4] (Fig. 1). The rationale for this change was that hyperandrogenic women frequently also exhibit impaired insulin function, resulting in elevated systemic insulin levels, which exacerbate androgen production within the ovaries [5]. Consequently, the EGOI-PCOS suggested renaming these phenotypes to the more appropriately termed endocrine metabolic syndrome (EMS), which reflected the ovaries role as a bystander of endocrine and metabolic factors rather than a root cause of the condition [6]. In contrast, the non-hyperandrogenic subset typically does not present with insulin dysfunction; thus, this condition would appear to be a truly ovarian issue, and as such these ex-phenotype D patients were labeled multi-follicular ovarian disorder (MFOD) [7].

Metabolic syndrome (MetS) is a common comorbidity of EMS and an international health concern due to worldwide rising obesity levels [8]. Presenting as a series of metabolic factors, MetS is a major risk factor for cardiovascular diseases [9]. The renaming of PCOS to EMS raises questions about the similarities of EMS and MetS and the overlap between these two conditions. This review goes into detail regarding both EMS and MetS, before comparing them and examining common therapeutic approaches, with the aim of optimizing the clinical approach to these distinct but interrelated conditions.

Metabolic Syndrome

In 1988, Reaven [10] noted that the presence of insulin resistance was involved in the etiopathogenesis of both type 2 diabetes and cardiovascular diseases. In this seminal work, Reaven [10] identified a series of metabolic abnormalities, which together with insulin resistance, were defined as syndrome X. This was later updated to become MetS X with the aim of differentiating it from the cardiovascular "syndrome X." Comprising a combination of insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, and obesity, MetS has been the subject of numerous attempts of standardization (Fig. 2). In 1998, the World Health Organization (WHO) initially proposed that MetS should be defined as the presence of insulin resistance, in addition to at least two of the following: elevated blood pressure, high triglyceride level, low HDL cholesterol, microalbuminuria and obesity (as defined by BMI) [11]. In the subsequent 1999 classification, the use of BMI to define obesity was changed to waist circumference as visceral central obesity is a more accurate representation of obesity than BMI. Furthermore, microalbuminuria did not appear in latter versions of metabolic criteria. In 2005, the NCEP:ATP III criteria differed from previous classifications of MetS in that it did not consider insulin resistance a fundamental part of the syndrome. The rationale for this change was inaccuracies or difficulties associated with measuring insulin resistance in everyday clinical practice [12]. These revised criteria identified MetS as a syndrome containing three out of five of the following: elevated fasting plasma glucose, hypertension, obesity, elevated triglycerides, and low HDL cholesterol. In 2006, the International Diabetes Federation (IDF) published a further classification method focused on improving the reproducibility between studies, making the criteria more applicable for clinicians and research groups alike. A prerequisite for the IDF criteria was the presence of central abdominal obesity in addition to two out of four of the following: elevated blood glucose, low HDL cholesterol, high triglyceride level, and elevated blood pressure [13].

Of the numerous classification criteria for MetS, the two most prevalent for diagnosis and recruitment in clinical studies are the IDF and NCEP criteria [14]. Of note, small variations can be observed in the prevalence of MetS depending on which criteria are utilized for diagnosis of the syndrome. In a cross-sectional comparative analysis by Asato et al. [15], the authors studied a multiethnic group of participants in Hawaii to evaluate prevalence of MetS according to either the NCEP, IGF, or WHO classifications. In this study, MetS was diagnosed by the WHO criteria at a rate of 22.31%, the NCEP criteria at 31.20% and the IDF criteria at 39.05%, with significant variations seen among different ethnic groups [15]. This study highlights elements of the current diagnostic criteria, for example, the definition of waist circumference, which does not adequately consider ethnic variations [16]. The lack of consistency regarding MetS hinders efforts to establish its presence in study populations.

It has been argued that a formal definition of MetS is of little importance, as it merely represents a practical approach to the management of obese patients, who have a range of cardiovascular risk factors [17]. However, the establishment of guidelines within MetS would aid in the implementation of tools to facilitate risk prevention strategies. This is of particular importance as MetS patients are not only at risk of developing cardiovascular disease but also diabetes, nonalcoholic fatty liver disease, reduced sperm quality, infectious diseases, Alzheimer's, cancer, and EMS [18–22].

While it is typically diagnosed in adults, the subject of MetS in adolescents is an area of research that has garnered attention in recent years. To date, no formal

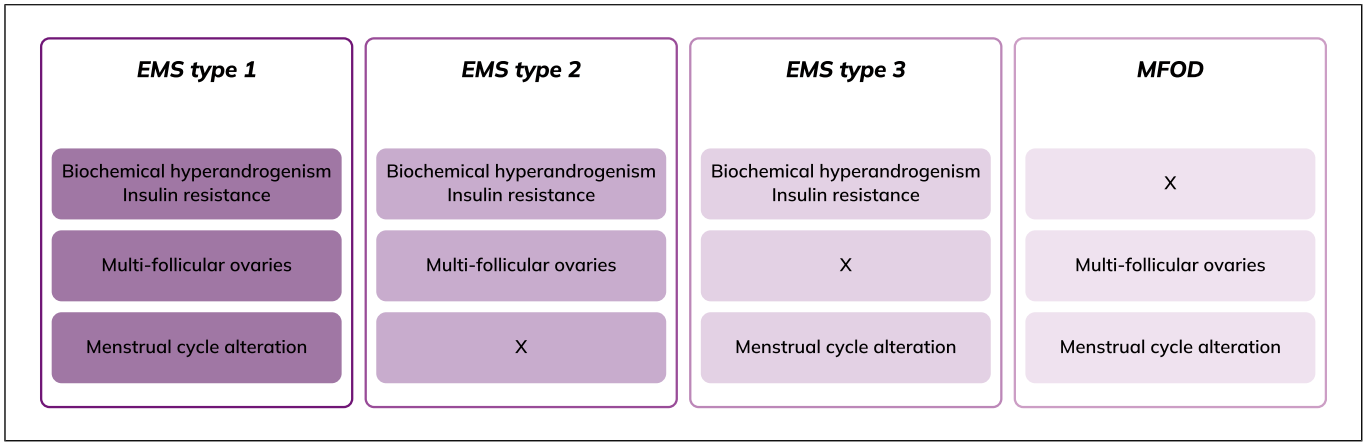

Fig. 1. EGOI-PCOS classification system. EMS, endocrine metabolic syndrome; MFOD, multi-follicular ovarian disorder.

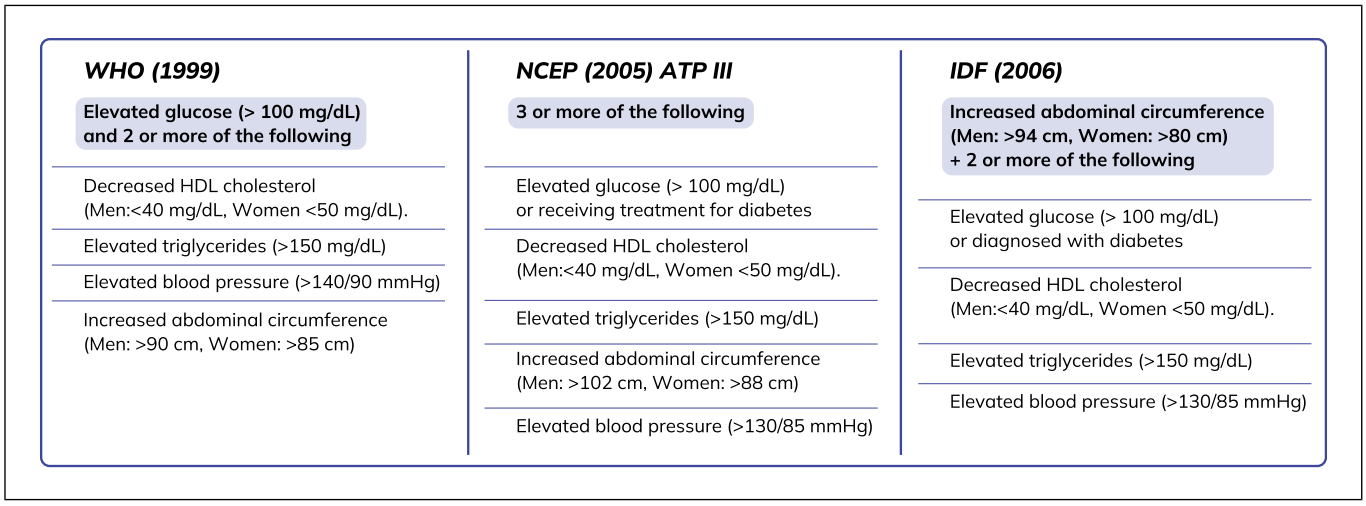

Fig. 2. Most prevalent classification systems for MetS. WHO, World Health Organization; NCEP (2005) ATP III, National Cholesterol Education Program 2005 Adult Treatment Panel III.

definition exists for MetS in children and adolescents, despite numerous attempts of standardization [23]. This has stymied attempts to calculate the prevalence of MetS in adolescents; however, a systematic review by Friend et al. [24] reported that in the general child population the prevalence of MetS was 3.3% (range, 0–19.2), growing to 11.9% in overweight children and 29.2% in obese child populations. A major limiting factor of this study was the heterogeneity in the diagnosis of MetS, introducing a degree of unreliability and bias. To account for this, a more recent meta-analysis of 20 articles investigated the prevalence of MetS in children and adolescents according to the different available diagnostic criteria [25]. This second meta-analysis agreed with the study by Friend et al. [24], finding an overall prevalence of 3.98% and 6.71%, as calculated by the IDF and the ATP III criteria, respectively. Similar results were observed in the pooled overweight and obese populations, with a 24.09% (IDF) or 36.5% (ATPIII), respectively. The clinical signs of MetS in children and adolescents mirror those observed in adult populations, namely: obesity, dyslipidemia, hypertension, and glucose intolerance. Screening in children should begin with the parents, checking for parental obesity and familial diabetes, both of which are known risk factors for childhood obesity [26].

The environmental causes of MetS are well understood, with contributing factors including diet, type and frequency of exercise, alcohol use, and the regularity of

sleeping patterns. Other contributing factors to MetS are not entirely understood; however, several contributors have been identified, including low-grade inflammation, oxidative stress, and genetic factors. In detail, chronic low-grade inflammation can occur because of a buildup of excessive visceral adipose tissue [27], and this leads to a change in the vascular and lymphatic microenvironment and to hypoxic conditions. These conditions trigger cell death of adipocytes, which may release fatty acids and the activation of pro-inflammatory pathways [28]. The inflammatory process causes the release of cytokines which affect insulin-sensitive organs, predisposing the individual to insulin resistance and increasing the risk of cardiovascular disease and type 2 diabetes. Insulin resistance in adipose tissue exacerbates lipolysis, resulting in an increase in free fatty acid release, which, in turn, further reduces the activity of insulin within these cells [29]. When insulin resistance occurs in skeletal muscle and liver cells, glucose transport and glycogen transport are perturbed leading to compensatory hyperinsulinemia, which can in time lead to type 2 diabetes.

Unraveling the genetic picture of MetS is complicated by the multifactorial and thus polygenic nature of the syndrome. Despite this, various genetic approaches are present within the literature. Candidate gene approaches have found examples of polymorphisms in or near the genes SLC6A14, GAD2, and ENPP1; however, these genetic associations have not been replicated in GWAS studies [30]. Similarly, gene-wide linkages have identified several loci for MetS; however, no specific gene has been identified for these loci. GWAS studies have identified genetic variants that predispose an individual toward MetS but are not necessarily causative. When screening for genetic factors for the individual components of MetS, van Walree et al. [31] identified 235 MetS-associated loci of which 22.5% overlapped with more than one of the MetS clinical features, demonstrating the multifactorial, complex nature of the syndrome. The largest GWAS studies to date have primarily been conducted in European populations and have identified numerous loci associated with obesity, insulin resistance, increased blood pressure, and heart disease [30]. Smaller subsequent studies have been performed in non-European patient sets and have identified distinct potential genetic biomarkers such as SIK3, YKT6, RPS6KB1, and SENP7, which have not been highlighted in the European datasets suggesting significant regional differences in genetic risk factors [32]. Aside from the small nature of this study (107,230 individuals), this study suffered from other notable limitations including a 64% female bias. Sex-specific alterations in genetic data pertaining to MetS have been observed in the literature, with certain genetic variants having a strong gender bias. A Tunisian study by Elouej et al. [33] identified that genetic variation LRPAP1-rs762861 was more influential in women, while a separate Korean study identified ZNF664-rs12310367 as only influencing BMI in women [34]. Meanwhile, in the same Korean study, KLF14-rs1562398 correlated with issues in glucose signaling in men.

Endocrine Metabolic Syndrome

EMS (formally referred to as hyperandrogenic PCOS) is defined by the presence of hyperandrogenism in combination with insulin resistance and at least one of the following symptoms: multi-follicular ovaries and/or menstrual cycle disruption. The combination of these symptoms results in three phenotypes of EMS depending on the presented symptoms [3]. Due to the inclusion of insulin resistance within the definition of EMS, it is not surprising that these patients also exhibit comorbidities associated with metabolic disturbances, such as obesity and dyslipidemia [35]. However, unlike MetS, EMS is defined by the hormonal disturbances, which typically involves elevated testosterone in addition to reduced levels of sex hormone-binding protein. This biochemical hyperandrogenism has an adverse effect on menstrual cycle frequency and may contribute to the formation of arrested follicles, in addition to causing dermatological effects of clinical hyperandrogenism such as hirsutism, acne, alopecia, seborrhea, and acanthosis nigricans [36]. Insulin resistance in these patients triggers compensatory systemic hyperinsulinemia; however, target organs, such as the ovaries, remain sensitive to insulin signaling, triggering a hyperactivation of insulin-dependent hormonal pathways [37]. In detail, insulin triggers LH-dependent androgen synthesis, in addition to increasing epimerase levels, which converts myo-inositol into D-chiro-inositol. Heightened levels of D-chiro-inositol inhibit the transcription of aromatase, which converts testosterone into estrogen, resulting in a retention of high androgen levels and worsening hyperandrogenism [38]. It should be noted that hyperandrogenism can increase insulin resistance creating a feedback loop. Specifically, Kurnaz et al. [39] observed higher systemic insulin levels in addition to serum levels of the liver protein fetuin-A in patients with hyperandrogenic congenital adrenal hyperplasia. Moreover, there was significant correlation between insulin resistance and hyperandrogenism [39].

A critical difference between the Rotterdam criteria and the EGOI-PCOS criteria is that EMS does not exclude

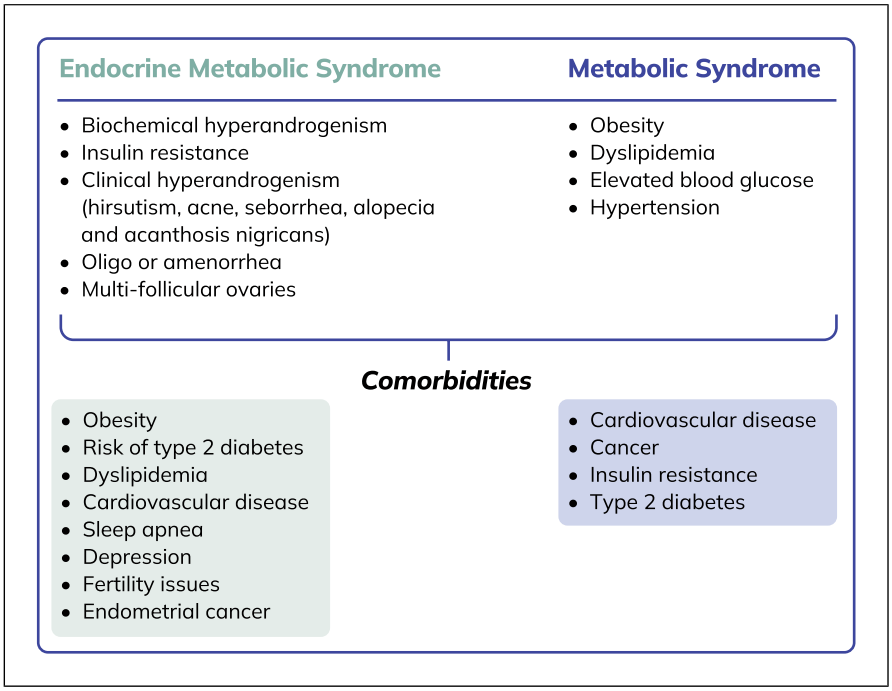

Fig. 3. Compared symptoms and comorbidities of endocrine metabolic syndrome (EMS) and metabolic syndrome (MetS).

male patients from its diagnosis. Numerous authors have described a form of "male PCOS" which occurs in men with female relatives who have PCOS [40]. These patients demonstrate similar metabolic issues to female EMS patients, including insulin resistance, dyslipidemia, and a predisposition to cardiovascular diseases. These metabolic factors are coupled with hormonal issues such as variations in androgen and SHBG levels [40]. Similarly, to female EMS patients, men with EMS demonstrate clinical signs of hyperandrogenism such as early onset balding, acne, and hypertrichosis; however, the hormonal profile of EMS differs between male and female patients. Notably, male EMS patients do not routinely demonstrate high testosterone levels with reduced Free Androgen Index (FAI) reported in prior studies [40]. Nevertheless, other androgens remain elevated; specifically, a significant increase in DHEAS in male relatives of women with EMS was observed by Lenarcik et al. [41] compared to healthy controls (310.6 ± 100.8 vs. 222.0 ± 117.0 mg/dL, $p < 0.001$). Furthermore, in the same study, 26.2% of male volunteers showed premature balding compared to 7.1% in the control group, suggesting DHEAS may be driving these clinical changes. It should be noted that this study was small consisting of only 42 male volunteers; thus, larger studies are required.

One rationale for the difference in testosterone profiles in both men and women with EMS is the ovarian versus the testicular response to insulin. As stated above, insulin signaling stimulates testosterone production in the ovaries; however, in testicular Leydig cells, excessive insulin levels inhibit steroidogenesis, leading to low levels of testosterone [42].

MetS and EMS: Two Distinct but Related Disorders

Both MetS and EMS share several common metabolic symptoms and commodities (Fig. 3), making it important to consider them within the context of one another. In detail, studies have revealed that 38–88% of women with EMS are either overweight or obese [43]. Furthermore, in a Finnish birth control study of 5,889 women, EMS was associated with dyslipidemia and increased weight gain across all age groups but especially in early adulthood [44]. In detail, BMI was significantly increased between the ages of 14 and 31 when associated with the presence of menstrual cycle dysregulation and hyperandrogenism ($p = 0.001$) or a diagnosis of EMS (termed PCOS by the original authors) ($p = 0.001$). In contrast, the same association was not observed in women between the ages of 31 and 46. As such, the authors advocated for screening methods to identify obesity and dyslipidemia in adolescents, which may avoid or postpone EMS symptoms in later life.

Both MetS and EMS share common cardiovascular risk factors, and numerous studies have demonstrated

significant increases in risk for cardiovascular conditions such as stroke, cardiovascular diseases, venous thromboembolism, and ischemic heart disease [45–47]. However, the data from these studies analyzing cardiovascular risk in EMS have largely been inconclusive as EMS patients are often overweight; thus, disentangling this possible confounder is routinely not possible. Furthermore, issues such as insufficient follow-up periods have been cited as potential reasons for contrasting datasets [48]. Similarly patients with MetS have a 50–60% increased chance of developing cardiovascular diseases at some point in their lives versus healthy populations [49]. However, it should be noted that the impact of MetS as a cardiovascular risk factor decreases with age [50].

Recent studies have also established a genetic link between EMS and metabolic conditions such as MetS. In 2020, Dapas et al. [51] evaluated whether the prior established Rotterdam phenotypes for "PCOS" were reflected in the genetic picture. This study evaluated anthropomorphic, reproductive, and metabolic features from 890 PCOS cases which were genotyped. Notably, the medium BMI was 35.4 kg/m^2, with the entire cohort demonstrating hyperandrogenism, meaning MFOD patients were not included. Cluster analysis identified a reproductive and metabolic genotype, whereby the metabolic genotype was characterized by a higher BMI, glucose and insulin levels, coupled with lower SHBG and LH levels. These metabolic factors indicate a genetic predisposition to common factors between EMS and MetS. It should be noted that further genetic studies are required, as while this work gives a snapshot of the genetic PCOS picture, the sample size for a GWAS analysis was small and requires validation through replication. In addition, the cohort included only people of European ancestry; thus, further analyses must be expanded to include a more diverse genetic pool.

Given the similarities between MetS and EMS, it is logical to conclude that the presence of one may permit evolution of the other. EMS is a common condition in adolescents and young adults, as high androgens are routinely observed as a natural part of puberty. When this is paired with a predisposition to dysmetabolism, either through genetic factors as outlined above, or as the consequence of an unhealthy lifestyle, this can lead to the development of EMS. As these patients grow older, this hyperandrogenic state may worsen metabolic parameters such as fatty liver, development of dysfunctional β-cells within the pancreas, ectopic lipid accumulation within muscle tissues, and an increase in visceral adipose tissue, all of which may lead to the development of MetS later in life [52]. In the 2007 Norwegian HUNT 2 study, MetS, as defined by the IDF criteria, had a relatively low prevalence in young populations (9.2% in women aged 20–29), which increases in older populations (49% in women aged 60–69) [53]. These trends were also observed in a recent population study, where young people between the ages of 18–30 had a prevalence of MetS (IDF 6.67%, ATPIII 10.13%) [54]. In addition, a case-control study by Pinola et al. [55] identified that women with EMS are two- to five-fold more likely than healthy populations to present with MetS. Furthermore, MetS was most common in hyperandrogenic women of late reproductive age [55]. It should be noted that this study did not consider physiological changes to androgen levels, which change with age, meaning that some hyperandrogenic women over the age of 39 may have been classified as normoandrogenic. Nevertheless, taken together, these studies indicate that this likely represents the prominent causality between EMS and MetS; however, further research is required to evaluate the relationship between the two syndromes [53]. The other direction in which this may occur is that the presence of MetS in adolescents and young women, which predisposes the individual to EMS. In detail, MetS may lead to the development of insulin resistance, leading to hyperandrogenism; however, this is thought to be less common due to aforementioned low levels of MetS in young populations.

The presence of different criteria within MetS has led us to question whether different subtypes of patients can be grouped together. Specifically, these patient phenotypes could be defined by the presence or lack of insulin resistance. The rationale behind this idea is based upon insulin role in the pathogenesis of EMS, and whether insulin resistant MetS is predisposed to develop EMS compared to the normoinsulinemic phenotypic group. To the best of our knowledge, studies identifying the causality between MetS patients and EMS have yet to be conducted; however, identification of insulin resistant MetS earlier in life may prevent the progression into EMS, suggesting the need for screening in young populations. Understanding these two interrelated but distinct conditions is vitally important to aid both diagnosis and therapeutic approach.

Consequences for Therapeutical Approaches

Treatment options for both MetS and EMS share considerable overlap, given shared underlying metabolic factors. The first recommendation in both cases is generally dietary and lifestyle changes. Within the field of MetS, the most common recommendation for patients is

weight loss. While no specific diet is recommended for MetS patients, general advice includes the reduction of trans-unsaturated fatty acids, carbohydrates, and salt, in addition to increasing dietary fiber and omega-3 fatty acid [56]. Physical exercise is crucial in preventing cardiovascular complications in MetS, with regular exercise shown to reduce triglyceride levels and blood pressure, in addition to increasing insulin sensitivity and HDL-C levels. Currently, it is clinically advised that cardiovascular risk can be reduced through 150–300 min/week of moderate-intensity exercise or 75–150 min of vigorous intensity exercise. This aerobic exercise is ideally coupled with at least twice weekly resistance training [57]. Other lifestyle changes include regular sleep patterns, as a U-shaped distribution has been identified between MetS symptoms and under or oversleeping (defined as <7 or >9 h per night). As such, the assessment of MetS is routinely accompanied with an assessment for sleep disorders such as insomnia and sleep apnea [58]. Other lifestyle changes which are routinely recommended include avoiding smoking and excessive alcohol consumption, both of which increase the incidence of MetS in comparison to healthy controls [59]. These lifestyle changes are also regularly advised to EMS patients as an initial recommendation, with a 5–10% weight reduction generally advised for EMS patients [60], coupled with regular exercise. Other treatment options for MetS address the individual symptoms, with pharmaceutical treatments including the use of statins, anti-hypertensives, anti-obesity gastric inhibitory peptide and glucagon-like peptide 1 receptor agonists, and insulin sensitizers [61–64]. Alternative approaches include the use of bariatric surgery which reduces the risk of developing diabetes by 2 years post-surgery by 96% and 78% after 15 years [65]. However, bariatric surgery is associated with surgical, nutritional, and psychiatric complications; thus, careful consideration should be given prior to the procedure [66].

Insulin sensitizers such as metformin and myo-inositol have demonstrated success in treating the underlying insulin resistance in EMS patients, leading to an improvement in metabolic and hormonal markers [67]. Meta-analyses have shown no significant difference between myo-inositol and metformin in terms of efficacy in counteracting the hormonal and metabolic abnormalities routinely seen in EMS patients including BMI ($p = 0.24$), fasting insulin ($p = 0.97$), fasting blood sugar ($p = 0.6$), HOMA ($p = 0.5$), LH/FSH ($p = 0.37$) [68]. Furthermore, myo-inositol demonstrates an improved gastrointestinal safety profile over metformin, which is associated with gastrointestinal adverse effects [69]. Oral contraceptive pills (OCPs) represent the most recommended medication for EMS [70]. Typically containing an estrogen and a progesterone component, the ethinyl estradiol component triggers hepatic production of SHBG, which binds to circulating testosterone, reducing systemic levels [71, 72]. Meanwhile, the use of progestogens binds to androgen receptors decreasing systemic androgen activity. Earlier generations of progesterone containing OCPs bind to SHBG; however, newer generations of OCPs have lower affinity for SHBG [73]. Due to feedback mechanisms between hyperandrogenism and insulin resistance, OCPs also demonstrate minor positive metabolic effects when used in combination with anti-obesity drugs such as orlistat or through the use of insulin sensitizers [74].

As both MetS and EMS share common metabolic features and comorbidities, it is desirable to pursue clinical practices which could be applied to either condition. The use of OCPs in EMS, while immediately effective at reducing androgen levels, does not address the underlying metabolic issues. Akin to painting over damp, the immediate issue is resolved; however, cessation of the therapy may leave the underlying metabolic issues to go untreated [75]. These untreated metabolic issues may lead to the development of MetS and put patients at risk of developing cardiovascular issues associated with both MetS and EMS. Therefore, it is paramount that patients taken OCPs regularly undergo metabolic assessment to check for worsening metabolic factors.

Emerging Evidence in MetS and EMS

MetS and EMS remain increasingly popular fields of research with the total number of publications increasing year after year. In a 2023 bibliometric analysis of 3,972 articles between 2012 and 2021 regarding "PCOS and metabolic dysfunction," Xu et al. [76] identified several emerging literature trends including luteinizing hormone, insulin resistance, steroids, multiple complications, therapeutic options, and notably serum metabolomics and proteomics.

These "omic" approaches may help disentangle the underlying mechanisms of MetS and EMS and potentially aid the identification of candidate biomarkers. A 2021 proteomic study, which compared 31 EMS patients and 31 healthy volunteers, identified 54 significantly downregulated and 26 upregulated proteins from the dataset [77]. Among these, up- and downregulated proteins numerous were involved in processes regulated to metabolism and inflammation. Finally, the authors confirmed through Western blot analysis the top five significantly differently expressed proteins in EMS versus the controls, namely, H4, H2A, PRDX1, TLT-1, and

SLC4A1, which may play a role in the pathogenesis of the condition. Proteomic approaches have also been employed in MetS, most notably in the recent article by Cai et al. [78], who measured over 400 proteins from approximately 20,000 proteomes and identified a proteomic fingerprint of 11 proteins that may predict MetS. Moreover, the authors report that the over or under expression of apolipoproteins, immune-related proteins, and coagulation-related proteins best correlated with the development of MetS. A potential field of future research would be to compare EMS and MetS through similar proteomic approaches, identifying key differences and similarities. Metabolomic approaches have also been utilized in the field of EMS, identifying differences in lipid metabolism, amino acid metabolism, carbohydrate metabolism, and steroid hormone biosynthesis in EMS cohorts versus control groups [79]. The use of metabolic approaches may help identify novel biomarkers to aid the early diagnosis of EMS and potential therapeutic targets.

Another emerging literature trend was therapeutic options, and this is notable as both MetS and EMS share common therapeutic approaches. Therefore, it is vital to understand the underlying biology of the two conditions to achieve correct therapeutic selection. Furthermore, according to the Rotterdam criteria, EMS patients are grouped together with phenotype D PCOS (or MFOD patients), influencing patient care and clinical study recruitment [80]. This latter subgroup does not respond in the same manner to therapies designed to treat metabolic dependent hyperandrogenism, such as metformin or inositol, and currently lack effective treatment options [3]. Thus, this normoandrogenic patient subgroup represents a potential avenue for future research.

Conclusion

EMS and MetS represent two different manifestations of underlying metabolic issues, which can cause serious health effects when untreated. The relationship between these two conditions is unclear, but it is reasonable to suppose that one may trigger the development of the other in a bidirectional manner. This review has outlined the importance of understanding the connection between EMS and MetS, in order to aid the development of lifestyle and therapeutic guidelines that may be applicable to both sets of patients. To fully differentiate these conditions and confidentiality guide clinical practice, further research is required including systematic meta-analyses, which may identify the key aspects of each condition.

Conflict of Interest Statement

S.H.M. and V.U. are employees of Lo.Li Pharma s.r.l. C.O.S. has no conflicting interests to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

S.H.M. and V.U. were responsible for the conception of the work; S.H.M. analyzed, interpreted, and reviewed the available literature and drafted the original draft; and S.H.M., C.O.S., and V.U. reviewed, edited, and approved the final version.

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