Metabolic Syndrome and Gynaecological Cancers: An Emerging Public Health Concern

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Abstract- Metabolic syndrome (MetS), which is defined by central obesity, insulin resistance, dyslipidaemia, and hypertension, has become a significant global health concern. Its growing prevalence corresponds with the increasing incidence of non-communicable diseases and is heavily influenced by sedentary lifestyles, high-calorie diets, and obesity. Emerging research underscores a strong link between MetS and the onset and progression of gynaecological cancers, such as endometrial, ovarian, cervical, and breast cancers. The mechanisms that connect MetS to cancer development are complex and involve chronic low-grade inflammation, elevated insulin levels, insulin-like growth factor (IGF-1) signaling, oxidative stress, hormonal imbalances, and disturbances in adipokines. These biological changes encourage tumor formation, increase cell proliferation, prevent programmed cell death, and facilitate metastasis by fostering an environment conducive to cancer growth. Among the various gynaecological cancers, endometrial cancer exhibits the most significant epidemiological relationship with MetS, showing a two- to four-fold increased risk, particularly in postmenopausal women. Furthermore, obesity-related changes in estrogen metabolism and immune functions heighten the risk of cancer.

Despite abundant evidence, MetS is still often overlooked and insufficiently managed in standard gynaecological oncology care. Implementing early screening and thorough management of MetS through lifestyle changes, nutritional interventions, weight loss, and medication may significantly lower the risk of gynaecological cancers and enhance long-term outcomes. Incorporating metabolic health into initiatives for cancer prevention and treatment is a crucial approach to reducing the global disease burden. This review provides an overview of the latest epidemiological findings, pathogenic mechanisms, and public health consequences, emphasizing the critical need for multidisciplinary prevention strategies and policy interventions.

Keywords: Metabolic syndrome; Gynaecological cancer; Obesity; Insulin resistance; Inflammation; Endometrial cancer; Public health.

I. INTRODUCTION

A growing global public health concern is the co-occurrence of gynaecological malignancies with metabolic syndrome (MetS). The metabolic syndrome is a collection of related metabolic disorders, such as central obesity, insulin resistance, dyslipidaemia, and hypertension, rather than a single illness. Although this group of risk factors greatly raises the chance of getting type 2 diabetes and cardiovascular disease, there is growing evidence that it also has substantial oncological implications [1]. Among the most prevalent cancers in women are the principal gynaecological malignancies, endometrial, ovarian, and cervical cancers. The systemic metabolic dysregulation that characterizes MetS is increasingly associated with the prevalence of these cancers. This review's main goal is to summarize the available data that connects metabolic syndrome to the etiology, prognosis, and treatment of various cancers in order to shed light on the biological processes and therapeutic ramifications of this risky combination. The epidemiological landscape of MetS in women and a brief summary of the pertinent gynaecological cancers will be established before this study navigates the intricate link between these illnesses [2]. We will then explore the fundamental pathophysiological connections and particular molecular processes that

propel carcinogenesis in a state of metabolic dysfunction. We will then examine the clinical data from observational studies, evaluate how MetS affects the prognosis of cancer, and talk about the screening and prevention implications. In order to provide a whole framework for comprehending and resolving this expanding issue in women's health, we will lastly examine therapeutic treatments and highlight important research gaps [3].

II. EPIDEMIOLOGY OF METABOLIC SYNDROME IN WOMEN

It is strategically critical to comprehend the epidemiology of metabolic syndrome, particularly in women. In addition to providing information for public health policy and resource allocation, prevalence data helps physicians to improve risk assessments for a variety of diseases unique to women, such as gynaecological malignancies. The burden of MetS is increasing as the world's population ages and leads increasingly sedentary lives, which makes it a crucial area of study for preventive medicine [4].

The prevalence of metabolic syndrome among women is startlingly high worldwide. For instance, according to data from the National Health and Nutrition Examination Survey (NHANES) in the United States, the prevalence of MetS in women has risen to over 35%, with the percentage increasing with age. Increased waist circumference (central obesity), higher triglycerides, decreased HDL cholesterol, high blood pressure, and elevated fasting glucose are the five main criteria that must be present for the diagnosis [5]. Trends show a dramatic rise in incidence that is consistent with the worldwide obesity crisis. A vast, susceptible population is put at increased risk for a variety of chronic diseases due to the widespread presence of a pro-inflammatory and metabolically dysregulated condition. Given how common MetS is, more research is required to fully understand how it specifically affects hormone-sensitive and inflammation-driven cancers, like those of the female reproductive system [6].

III. OVERVIEW OF GYNAECOLOGICAL CANCERS

Prior to examining their intricate relationship with metabolic disorders, it is imperative to have a basic understanding of the main gynecological malignancies. These cancers are a major cause of morbidity and mortality globally and start in the female reproductive system. Despite their differences in biology and clinical presentation, they are all susceptible to systemic causes such as chronic inflammation and hormone imbalances, which are characteristics of metabolic syndrome [7].

In this context, endometrial, ovarian, and cervical cancer are the three most important gynaecological cancers that are the subject of this review.

- The lining of the uterus is the site of endometrial cancer, the most prevalent gynaecological cancer in wealthy nations. Prolonged exposure to unopposed estrogen is its strongest known risk factor, and obesity exacerbates this illness. The epidemiological association is very significant; studies indicate that the risk of endometrial cancer increases by around 1.6 times for every 5 kg/m² increase in body mass index (BMI) [38].
- Although less frequent, ovarian cancer is much more deadly and frequently discovered at an advanced stage. Hormonal dysregulation and chronic inflammation are thought to contribute to its development, indicating believable links to the metabolic state, even though its risk factors are less well established [6].
- The main cause of cervical cancer is an ongoing high-risk human papillomavirus (HPV) infection. Nonetheless, host variables including systemic inflammation and altered glucose metabolism that affect immune response and viral persistence are becoming more widely acknowledged as significant co-factors in the virus's progression from infection to malignancy [8].

Knowing the baseline risk profiles for these cancers gives you the background you need to understand how metabolic syndrome's systemic disturbances might cause or hasten the development of these malignancies through common biological pathways [7].

IV. THE PATHOPHYSIOLOGICAL LINK BETWEEN METABOLIC SYNDROME AND CANCER

There is much more to the relationship between metabolic syndrome and cancer than just a correlation. It is important to understand that MetS is a systemic, pro-tumorigenic state that fosters a microenvironment that supports the initiation, spread, and metastasis of

cancer rather than just a group of separate risk factors. In order to prevent and cure cancer in the large and expanding population of women who suffer from metabolic dysfunction, it is essential to comprehend this systemic relationship [9]. Numerous important biological pillars serve as the foundation for the broad pathophysiological relationships between the elements of MetS and cancer. Excess visceral adipose tissue causes persistent, low-grade inflammation, which emits a constant flow of pro-inflammatory cytokines that can encourage DNA damage and cellular proliferation. Through the signalling pathways for insulin and insulin-like growth factor (IGF-1), insulin resistance and the resulting compensatory hyperinsulinemia simultaneously offer a potent stimulant for cell development [10]. Lastly, the development of hormone-sensitive cancers is directly fueled by severe sex hormone imbalances, specifically the elevated synthesis of estrogen in adipose tissue. The threshold for carcinogenesis is systematically lowered by the synergistic environment created by these interrelated disturbances. This broad picture will be broken down into the particular molecular processes that convert metabolic dysregulation into malignant transformation in the section that follows [11].

V. MECHANISMS OF CARCINOGENESIS

We must break down the general pathophysiological links into precise, empirically supported molecular and cellular pathways in order to completely understand the relationship between metabolic syndrome and gynaecological malignancies. This level of specificity is crucial for both clinical and scholarly purposes since it aids in the identification of possible treatment targets for halting the consequences of metabolic illness that promote cancer. Hormonal imbalance, altered adipokine signalling, chronic inflammation, and hyperinsulinemia are the main causes [10].

5.1 Insulin Resistance and Hyperinsulinemia

Hyperinsulinemia results from the pancreas manufacturing too much insulin to compensate for insulin resistance. Insulin and insulin-like growth factor 1 (IGF-1), which have structural similarities, are both powerful mitogens. They attach to their corresponding receptors on malignant and precancerous cells when they are in high concentrations, triggering downstream signalling cascades including PI3K/Akt/mTOR that directly support cell growth, survival, and proliferation [33]. Additionally, especially in hormone-sensitive tissues like the endometrium, these pathways prevent apoptosis, or programmed cell death, which permits damaged cells that would otherwise be destroyed to survive and collect mutations, ultimately aiding in the creation of tumours [12].

5.2 Chronic Low-Grade Inflammation

A characteristic of central obesity in MetS, visceral adipose tissue is an active endocrine organ that secretes a variety of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). This results in a persistent, low-grade inflammatory environment throughout the body [13]. Through a variety of ways, this inflammatory state aids in the development of cancer. It can cause DNA damage by generating reactive oxygen species, encourage the growth of new blood vessels (angiogenesis), which provide nutrition to tumors, and make it easier for tumour cells to invade and spread. Tumor genesis and progression across a range of cancer types are facilitated by this inflammatory environment [14].

5.3 Dysregulation of Sex Hormones

Sex hormone metabolism is drastically changed by central obesity, a process that has significant consequences for endometrial cancer. Peripheral aromatization, the process by which the enzyme aromatase transforms androgens into estrogens, primarily occurs in adipose tissue. This becomes the primary source of estrogen in postmenopausal women. This process is markedly increased in the setting of MetS and excess adiposity, which results in elevated amounts of estrogen in the blood [15]. This "unopposed estrogen" continuously promotes the growth of the endometrial lining in the absence of progesterone's counterbalancing effects, raising the risk of hyperplasia and malignant transformation. The potent dose-response connection seen in epidemiological research is directly explained by this exact mechanism [16].

5.4 Adipokines and Growth Factors

Adipokines are a class of signalling molecules secreted by adipose tissue that are dysregulated in metabolic syndrome. It is essential that these aspects be balanced. Obesity raises the hormone leptin, which has pro-tumorigenic effects by encouraging angiogenesis and cell proliferation. On the other hand, adiponectin, which is decreased in people with MetS, usually possesses anti-inflammatory and anti-proliferative qualities, which may make it protective against cancer [37]. Therefore, the cellular milieu is shifted in favor of tumor growth and survival due to the typical imbalance of MetS, which is high leptin and low adiponectin. The clinical and epidemiological evidence linking MetS to gynecological malignancies in patient populations is well supported by these biological processes [17].

VI. CLINICAL EVIDENCE AND OBSERVATIONAL STUDIES

Numerous clinical and epidemiological studies have examined the relationship between metabolic syndrome and the risk of gynaecological cancer, progressing from biological plausibility to practical correlation [39,40]. The main conclusions from significant cohort and case-control studies that have confirmed this association are outlined in this part, showing how the mechanistic connections result in measurable health effects for women. However, the association's strength differs greatly depending on the type of cancer [18].

1. Endometrial Cancer: There is substantial, reliable, and convincing evidence that metabolic syndrome is associated with endometrial cancer. According to a 2021 meta-analysis published in Gynaecologic Oncology, MetS was linked to a 2.5 (95% CI: 2.1-3.0) pooled relative risk of endometrial cancer. Even after controlling for specific factors like obesity, the link remains strong, highlighting the synergistic role of the entire syndrome in fostering this cancer [19].

2. Ovarian Cancer: MetS and ovarian cancer have a more complex association. Emerging evidence suggests that the connection may be higher for particular histological subtypes, even though several large cohort studies have not established a substantial association with overall risk. According to a pooled analysis, there was a significant increase in risk for non-serous subtypes, especially endometrioid tumors (OR = 1.88, 95% CI: 1.45-2.43), which are similar to endometrial cancer in their hormonal sensitivity [18].

3. Cervical Cancer: MetS is not the primary cause of cervical cancer; rather, it is a crucial co-factor in this indirect relationship. The body's capacity to eradicate a persistent HPV infection may be hampered by the systemic and local immune responses being weakened by the chronic inflammation and decreased glucose metabolism linked to MetS. According to data, women with MetS are more likely to experience HPV persistence and progression to cervical intraepithelial neoplasia, which raises the risk of invasive malignancy [17].

These results demonstrate that metabolic syndrome has a burden that goes beyond cardiovascular disease, directly affecting cancer risk and laying the groundwork for its effects on patient outcomes following a diagnosis.

VII. IMPACT ON CANCER PROGNOSIS AND SURVIVAL

Beyond carcinogenesis, metabolic syndrome has a significant impact on treatment outcomes and patient survival following a diagnosis of gynecological cancer. When MetS and its constituent parts are present at the time of diagnosis, the biological environment may be more conducive to aggressive tumour behaviour and less amenable to conventional treatments. As a result of this realization, the clinical paradigm is changing to a more comprehensive perspective of the patient, where metabolic health is seen as a crucial component of cancer treatment and prognosis [21]. Numerous studies have shown evidence that a worse prognosis is linked to the existence of metabolic syndrome upon diagnosis. Higher-grade tumours and more advanced stages of the illness are more common in patients with MetS. It has a substantial quantitative impact; for instance, a large cohort study revealed that patients with endometrial cancer who had MetS had a 40% higher

all-cause mortality rate (HR = 1.40, 95% CI: 1.15-1.71). The same underlying processes that drive carcinogenesis—hyperinsulinemia, inflammation, and hormone dysregulation—also likely underlie this detrimental effect, as they continue to feed tumour growth and foster resistance to radiation and chemotherapy. The urgent need for proactive therapeutic treatments to control metabolic dysfunction in this patient population is highlighted by these prognostic implications [19,20].

VIII. SCREENING AND RISK STRATIFICATION

It is clinically necessary to convert these epidemiological data into practical screening and risk assessment procedures because of the obvious correlation between metabolic syndrome, cancer risk, and worse outcomes [34]. Moving past a reactive approach to cancer therapy and proactively identifying high-risk individuals who stand to gain the most from focused preventative measures is the main objective. A significant chance to reduce the risk of cancer before it appears is presented by including metabolic health assessment into standard gynaecological care [21]. Although obesity is known to be a risk factor for endometrial cancer, metabolic syndrome is not now formally included as a separate risk factor in clinical guidelines for gynecological cancer screening [32]. More careful monitoring or risk-reducing counseling for impacted women is being recommended as a result of the growing consensus that MetS should be regarded as an independent risk factor in clinical decision-making. For instance, a postmenopausal woman with MetS presenting with abnormal uterine bleeding might be triaged for an endometrial biopsy with a higher index of suspicion [30]. Creating user-friendly, validated scoring systems that assist doctors in measuring this risk and directing individualized patient care is an opportunity. This naturally brings up the next important query: what can be done to reduce the danger when high-risk persons have been identified [22].

IX. PREVENTION AND LIFESTYLE MODIFICATIONS

Primary and secondary prevention play a significant role in breaking the relationship between metabolic dysfunction and gynaecological cancer. Because it addresses the underlying causes of the condition—excess adiposity, insulin resistance, and chronic inflammation—lifestyle modification is the main tactic for reducing the cancer risk linked to metabolic syndrome. One of the best strategies to lessen the long-term cancer burden on women is to provide them with the information and resources they need to enhance their metabolic health.
Numerous important lifestyle changes that can reverse or improve the elements of MetS and hence reduce the risk of cancer are well supported by the evidence [23].

- Dietary Interventions: Developing wholesome eating habits is essential. It has been demonstrated that diets high in fruits, vegetables, whole grains, and lean proteins—like the Mediterranean diet—improve insulin sensitivity, lower inflammatory markers, and aid in weight management. Reducing consumption of refined sugars and processed meals is similarly important [31].

- Physical Activity: Frequent exercise has significant metabolic advantages that go beyond weight loss. It lowers systemic inflammation, improves insulin sensitivity, and aids in hormone regulation. According to guidelines, strength training should be combined with at least 150 minutes of moderate-intensity aerobic activity per week [24].

- Weight Management: Achieving and maintaining a healthy body weight is crucial because central obesity is the main cause of MetS. In addition to lowering important inflammatory markers like C-reactive protein by up to 25%, even a small weight loss of 5–10% of total body weight can result in notable improvements in blood pressure, lipid levels, and glycaemic control, dismantling the pro-tumorigenic environment that the syndrome has created.

Surgery and medication may be necessary if these non-pharmacological methods are not enough to completely address metabolic imbalance [25,39].

- Pharmacological and Surgical Interventions

Pharmacological and surgical therapies may present a substantial opportunity to manage both metabolic health and related cancer risk when lifestyle changes

alone are not enough to control the components of metabolic syndrome. These strategies focus on the underlying pathophysiology of MetS, and new research indicates that they may have advantages beyond cardiovascular protection, such as preventing cancer and improving oncologic outcomes.

The utility of particular therapies for controlling MetS in relation to the risk of gynaecological cancer is supported by an increasing amount of research [26].

- Metformin: Due to its possible anti-cancer effects, this popular anti-diabetic medication has attracted a lot of interest. In addition to increasing insulin sensitivity, metformin may stop the development of cancer cells by activating AMPK and blocking the mTOR pathway. Although conclusive evidence from randomized trials is still available, a meta-analysis of observational studies suggested a possible survival benefit among metformin users with gynaecological malignancies.

- Other Pharmacotherapies: Other medication classes used to treat aspects of MetS might be involved, albeit the evidence is less clear. Because of their anti-inflammatory qualities, statins, which reduce cholesterol, may help lessen the risk of cancer. To confirm a direct role for these medicines in preventing gynaecological cancer, more research is necessary [25].

- Bariatric Surgery: The most successful treatment for causing significant and long-lasting weight loss in people with extreme obesity is bariatric surgery, which frequently results in the metabolic syndrome being completely resolved. Crucially, extensive research has demonstrated that bariatric surgery is linked to a significant decrease in the chance of acquiring cancers linked to obesity, with endometrial cancer showing a particularly significant risk reduction of up to 81% [23].

Although these interventions have a lot of potential, there are still a lot of unsolved issues, which emphasizes how important it is to establish future research goals in this area.

X. FUTURE DIRECTIONS AND RESEARCH GAPS

Even while it is now widely known that metabolic syndrome is linked to gynaecological cancers, especially endometrial cancer, there are still a lot of unanswered questions. To improve treatment approaches, deepen our understanding, and eventually lessen the burden of these diseases, more targeted and ongoing study is necessary. Resolving the existing gaps in our understanding will open the door to more individualized and successful prevention and treatment strategies [27]. To progress the discipline, a number of important research gaps and future directions need to be given top priority:

I. Elucidating Molecular Pathways: The precise molecular signalling pathways and genetic variables that mediate the impact of MetS on various gynaecological tumour types require more investigation. Finding new targets for targeted medicines depends on this study [35].

II. Prospective Clinical Trials: Observational studies provide a large portion of the available evidence. Randomized controlled trials (RCTs) that are intended to prospectively assess the effects of certain MetS interventions—like metformin, structured diet and exercise regimens, or bariatric surgery—on cancer incidence, recurrence, and survival are desperately needed [28].

III. Biomarker Development: To more accurately determine whether women with metabolic syndrome have the highest absolute risk of getting gynaecological cancer, trustworthy biomarkers must be developed and validated. By using these indicators, screening and prevention efforts could be more effectively targeted to the people who stand to gain the most [36,41].

IV. Health Disparities: In order to affect the incidence and results of gynaecological cancer, it is imperative to look into the ways that socioeconomic status, race, and ethnicity interact with the prevalence of metabolic syndrome. Targeted public health interventions and the identification of vulnerable populations can both benefit from this field of study [29].

Answering these concerns will be essential to converting our present knowledge into better therapeutic results and directly contributes to the review's main findings.

XI.CONCLUSION

A strong and clinically significant correlation between metabolic syndrome and gynaecological cancers has been confirmed by the synthesis of the available data. The epidemiological scope of the issue, the biological mechanisms at play (such as insulin resistance, chronic inflammation, and hormonal dysregulation), and the compelling clinical evidence that links MetS to a higher risk of cancer and worse patient outcomes have all been outlined in this review. Although there are also clear links to some ovarian cancer subtypes and the advancement of cervical cancer, the association is strongest for endometrial cancer, where MetS increases the risk by 2.5 times.

A paradigm change in clinical practice is required due to the convergence of these two significant public health concerns. Managing gynaecological cancer risk and metabolic health separately is no longer adequate. Recognizing and treating metabolic dysfunction as a crucial and modifiable part of gynaecological cancer prevention and care is essential for healthcare professionals, including primary care physicians, gynaecologists, and oncologists. We may proactively minimize risk, enhance prognoses, and ultimately lessen the increasing burden of these interrelated diseases by incorporating metabolic screening, lifestyle counselling, and targeted medical therapies into normal practice.

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