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Controversies in Endometrial Cancer with Metabolic Syndrome

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Abstract

Introduction: All dysfunctions that contribute to metabolic syndrome have been found to be independently associated with increased risk of endometrial cancer. Also metabolic syndrome on its own with dyslipidaemia seems to increase the risk of many cancers, particularly EC.

Objective: Was to look into existing challenges about association of metabolic syndrome and EC.

Results: Diabetes Mellitus (DM), Hypertension (HTN), Polycystic Ovarian Syndrome (PCOS), Tamoxifen use and others are known to be associated with increased incidence of EC. However observations linking hypertension, glucose metabolism, and insulin resistance to EC have come mostly from retrospective studies. It has been assumed that elevated endogenous estrogen in PCOS patients led to EC. Obesity and insulin resistance were not fully recognized as potential risk factors for EC. Also DM has been found to be a risk factor for Type I EC (Oestrogen dependent), but not Type II EC (nonoestrogen dependent) and needs more research. Impact of metformin on ovarian or EC, outcomes, recurrence or overall survival has also been reported. Weight loss and exercise, the most effective steps which women could take to prevent developing metabolic syndrome, could reduce EC too, but still a lot needs to be known.

Conclusion: Literature reveals metabolic syndrome with or without obesity has linkage to EC but a lot of research is still needed.

Introduction

Metabolic syndrome (also known as syndrome X or dysmetabolic syndrome) is a cluster of health consequences associated with increased BMI, high blood pressure, abnormal levels of cholesterol and triglycerides in the blood, and insulin resistance (Table 1)[1]. Metabolic syndrome is being linked to many cancers and whatever dysfunctions constitute. Metabolic syndrome have been linked to endometrial cancer separately too. Actually it was decades back that Sommers SC et al. reported that EC patients were prone to a 'habitus' which consisted of obesity, glucose intolerance or diabetes, and hypertension [2]. Even after the researchers accounted for excess weight, Metabolic syndrome was still linked to up to a 21% increased risk of EC [1]. Studies reported direct association between EC risk and individual components of the Metabolic syndrome i.e. obesity, diabetes, hypertension, and dyslipidemia, however a few epidemiological studies considered the association with overall Metabolic syndrome [3]. Variations seem to be because different definitions of Metabolic syndrome have been suggested. Over the years various researchers recognized many risk factors, like diabetes mellitus [4], hypertension [5,6], PCOS [7], and tamoxifen [8,9]. However findings linking blood pressure, glucose metabolism, and insulin resistance to EC came mostly from retrospective studies which provided less conclusive evidence because of self-reported disease history and anthropometry or an absence of adjustment for body mass [10]. And a lot does not seem to be known.

Objective

Was to look at association of endometrial cancer and Metabolic syndrome.

Results

The researchers have observed that each distinct metabolic syndrome condition that they could evaluate within the database, excessive weight, high blood pressure, high triglycerides, and impaired fasting glucose was associated with an increased risk for EC. However it has also been reported that about one-fourth of people

Table 1: Definitions used to define metabolic syndrome factors [1].

Factor	Code-based definitions
Overweight/obesity	A diagnosis of unspecified or overweight /obesity morbid obesity or central adiposity (specifically ICD-9:278, 278.0.278.00, 278.01,278.02, 278.03, 278,1, V77.8[a]) [a]Code for central adiposity (V77.8) only available from 2001-2007 A diagnosis of type 2 diabetes or impaired fasting glucose (ICD-9:250.X0.250.X2, 790.2.790.21.790.22.790.29)[b]
Impaired fasting glucose	[b]Codes 250, 250X were not included because they generically reference both type 1 and 2 diabetes, and codes 250 X1 and 250 X3 were not included because they also include type 1 diabetes
High blood pressure	A diagnosis of hypertensive disease (ICD-9:401-405)
Low HDI, Cholesterol	A diagnosis of lipoprotein deficiency (ICD-9:272.5.272.5X)
High triglycerides	A diagnosis of pure hyperglycemia, mixed hyperlipidemia, hyperchylomicronemia or other unspecified hyperlipidemia (ICD-9:272.1, 272.IX, 272.2, 272.2X, 272.3, 272.3X, 272.4, 272.4X) [c]Codes 272, 272.0, 272.0X are not included.
Dysmetabolic syndrome	A diagnosis of metabolic syndrome (ICD-9:277.7, started use in 2001)

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who do not have diabetes have Metabolic syndrome [11]. Trabert B et al. performed a case-control study using data from the SEER-Medicare linked database [12]. They analyzed data of 16,323 women diagnosed with EC and 100,751 women without EC between 1993 and 2007. A diagnosis of Metabolic syndrome was associated with an increased EC risk of 39 percent and 103 percent, respectively.

Age

According to the results of a study women with Metabolic syndrome who were of age 65 or older, had an increased risk of EC. The increased risk was found regardless of their BMI [11]. Trabert B et al. have reported that metabolic syndrome was associated with a 39% to 103% increased risk for EC in women aged 65 years and older [12]. It was revealed that among women of age 65 and older, metabolic syndrome, and its components individually, increased risk of EC, similarly across EC subtypes. A recent study suggested that women under 50 years with PCOS were at four times risk of EC compared with controls. Increased risk remained even when Body Mass Index (BMI), was controlled, however there was no adjustment made for IR [13]. A 10-fold increased risk has been reported with a family history of EC at age younger than 50 years or breast or ovarian cancer [14,15].

Obesity

Obesity has been known as a risk factor for EC, however Metabolic syndrome, regardless of whether the woman is obese or not has higher risk for EC. Weiderpass E et al. reported an increased association of hypertension with EC in obese women and many others have also reported the same [7,16-18]. However, obesity and IR have not been fully recognized as potential risk factors for EC. Brinton LA et al. reported that women with a BMI of 32 kg/m^2 or greater were four times as likely to develop EC as women with a BMI of less than 23 kg/m^2 [19]. Women with a BMI of 35 kg/m^2 or greater, had six times the risk. Swanson CA et al. also reported that heaviest women were at the highest risk of developing EC [20]. Many researchers have reported that a woman's current weight and weight gain throughout adulthood were most predictive of risk of developing EC. Larger weight gains over a woman's life have been reported to increase the risk [16]. As such obesity as a risk factor for EC has been reported to account for 17 to 46% of all cases [21]. Researchers have reported an increase in obesity and Metabolic syndrome amongst married women of reproductive age from 11% to 15% in India, and the rural population was not an exception and research needed to be continued about effects on EC burden [22,23]. Saltzman BS et al. reported an effect of hypertension among obese women, compatible with the hypothesis that metabolic syndrome including obesity, hypertension and insulin resistance were the risk factors for EC [24].

Diabetes

Many authors have reported Type 2 diabetes to be an independent risk factor for developing EC [10,25]. These studies found a persistent elevated risk of developing EC in diabetic patients, when either adjusting for weight or studying nonobese women [16]. Vigneri P et al. reported that the relative risk for EC was greatest (about twofold or higher) with diabetes [26]. There was further evidence that obese diabetic women, had the highest risk of developing EC [27]. Ko EM et al. also reported DM as a risk factor for Type I EC, however the association was not found in Type II EC [28]. The same was also supported by Nevadunsky NS et al. [29]. As such Type IEC and Type II EC seem to be completely different in etiology and behavior.

Insulin-Resistance

In a study 66% of patients were found to have IR at the time of diagnosis of EC. Interestingly, half of the women with IR did not have a history of diabetes in another study [30]. High endogenous estrogen related to IR, obesity and PCOS are both known to be associated with IR, which lead to elevated insulin levels and increased insulin-like growth factor I (IGF-I) expression. Elevated IGF-I expression, which may occur through decreased sex hormone-binding globulin, the phosphorylated-akt (p-akt) pathway, and/or the aromatase pathway, caused high local and/or systemic estrogen concentrations [31]. Further work is needed to know the exact role of IR in the development of EC. Soliman PT et al. reported that women with EC were more likely to have low adiponectin levels than controls, even after adjusting for BMI [32]. This suggested that IR was independently associated with EC.

Others

A relationship between EC and polycystic ovary syndrome (PCOS) was first suggested in the 1940s - 1950s [33]. Some studies revealed up to 30% premenopausal patients of EC having PCOS [34]. It was assumed that elevated endogenous estrogen in PCOS patients led to EC. Given that many women with PCOS are obese and have IR, it is unclear whether PCOS is truly an independent risk factor. Friedenreich CM et al. reported that Metabolic syndrome with dyslipidaemia increased the risk of developing various cancers specially EC [35]. Three prospective studies have evaluated circulating estrogen levels and EC risk in postmenopausal women, with consistent strong positive association, but the relationship was not studied in premenopausal women [36-38].

Data from a case-control study of 454 women with EC and 798 controls admitted to the same hospitals as cases for acute conditions, revealed a direct association between various components of metabolic syndrome besides overweight, and risk of EC [3]. Metabolic Syndrome marked by a combination of different medical conditions, low levels of high-density lipoprotein (HDL), the so-called 'good' component of cholesterol, and high levels of circulating triglycerides have been found to be associated with a 39% increased risk of EC, or a 21% increased risk after taking into account whether a woman was obese or overweight [11].

Discussion

Because of the higher risk of developing cardiovascular events, EC and peripheral vascular disease in patients with Metabolic syndrome it is becoming a rising issue in woman's health. A new study from the National Institutes of Health demonstrated that Metabolic syndrome was associated with increased risk of EC. The researchers found women with Metabolic syndrome as determined by the ATP III criteria were 39% more likely to develop EC, and those with Metabolic syndrome as determined by International Diabetes Foundation criteria were 109% more likely to develop EC. After accounting for overweight or obesity among the women, the risk of developing EC was 21% and 17% higher, respectively [39].

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Theoretically, metformin, a drug widely used to treat infertile women with PCOS, might have a role in preventing endometrial hyperstimulation by lowering insulin concentrations and restoring ovulation. However, the long-term effects of this drug in women with PCOS are not known and more studies are required before suggesting its use for preventing EC [40]. Several studies have evaluated the impact of metformin on ovarian or EC outcomes, cancer recurrence or overall survival [41,42]. However, there has been scant evidence regarding the impact of metformin upon the development of EC. Koet EM al. reported that in a population-based cohort of >500,000 women, patients using metformin compared to those using sulfonylurea were not associated with a reduced risk of developing EC [43]. Trabert B et al. have reported weight loss and exercise, the most effective steps, women could take to prevent developing metabolic syndrome and may be EC too [12].

Way forward

More research is needed to better understand the association between Metabolic syndrome and EC as the strategies to reduce the prevalence of Metabolic syndrome might potentially have a favorable effect on the reduction of EC.

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