Abstract. – OBJECTIVE: Endometrial cancer (EC) is a complex gynecological neoplasm with several clinical, histopathological and genetic features. Different hormonal, metabolic and biochemical axes are involved in pathogenesis. Obesity is a well-known risk factor for this disease and the role of local and systemic effects of adipose tissue, especially in the promotion of subclinical chronic inflammation, is an important issue. Indeed, inflammation is related to the pathogenesis of different tumors, including EC. This review aims to remark the role of obesity and inflammation in the pathogenesis of EC cancer through an exploration of the current literature.

MATERIALS AND METHODS: We performed a comprehensive review of the literature through a PubMed search using key words and including English language papers looking at this topic.

RESULTS: Only few authors analyzed the role of inflammatory cytokines released by adipose tissue in visceral abdominal fat depots. Tumor Necrosis Factor-α, Interleukin-6, Interleukin-1 Receptor Antagonist, Nuclear Factor-kB, Leptin, Adiponectin and C Reactive Protein were studied for cancer risk prediction models, risk stratification or targeted therapies. Furthermore, genetic studies evaluated the effect of inflammatory cytokines secreted by visceral adipocytes in the modulation of angiogenesis and signaling pathways such as PI3K/AKT/mTOR, that result altered in the pathogenesis of EC.

CONCLUSIONS: The identification of inflammatory biomarkers released by adipose tissue, in the pathogenesis of EC, could be useful in improving diagnostic accuracy, identifying targets of therapy, suggesting useful lifestyle behaviors. A deeper knowledge of the genetic background of alterations in inflammatory pathway genes could better define the population exposed to a higher susceptibility to EC due to genetic polymorphisms. Future studies are needed to better understand this field.

Key Words: Endometrial Cancer, Inflammation, Cytokines, Obesity.

Introduction

Endometrial cancer (EC) is the most common female genital tract malignancy in industrialized countries and the second most common in developing countries. It counts 140 000 new cases every year worldwide, about 6% of new cancer cases and 3% of cancer death per year. Historically, EC has been classified on the basis of clinical, endocrine and epidemiological characteristics into Type I (80-90%) and Type II (10-20% of cases). Histopathological classification further divided tumors into endometrioid and non-endometrioid. Nevertheless, all these classifications didn’t take into account the complexity of this disease. Recently, the mapping of genomic landscape of ECs by the Cancer Genome Atlas Research Network has enriched the knowledge of this kind of neoplasia, underlying the great molecular heterogeneity and defining four molecular subgroups: (1) POLE ultramutated; (2) MSI-hypermutated; (3) copy number low; (4) copy number high. These differences are fundamental to better understand the endometrial tumorigenesis and to predict its variable prognosis and sensitivity to treatment. Among the proven risk factors for endometrial neoplasia, those related to an excess of estrogens and typical clinical features recur. High Body Mass Index (BMI), metabolic syndrome, hypertension, type 2 diabetes mellitus, hypertriglyceridaemia, nulliparity, infertility, polycystic ovarian syndrome, early menarche, late menopause, unopposed estrogen therapy are the most common examples. All these conditions are characterized by an excess of biologically available estrogen or an excess of estrogen related to progesterone. After menopause, adipose tissue represents the primary source of estrogen, whose
levels correlates with elevated BMI\textsuperscript{11}. Although these factors are linked to endometrioid EC, their impact on clinical and histological phenotype is poorly understood and several ongoing studies are aimed to clarify molecular mechanisms connected to its genesis. Furthermore, a number of other hormonal, metabolic and biochemical axes have been associated with the risk. In the huge field of these observations, obesity and inflammation have been hypothesized to play a role in EC development, either by mediating estrogens action and as independent factors\textsuperscript{12,13}. This review is aimed to remark the role of obesity and inflammation in the pathogenesis of EC through an exploration of the current literature

**Materials and Methods**

We performed a comprehensive review of the literature through a PubMed search using the key terms “endometrial cancer”, “inflammation”, “cytokines”, “obesity”. We then surveyed the English language literature for studies looking at this topic. The authors identified the most relevant studies through the selection of abstracts, including systematic reviews, studies with the longest follow-up, and studies discussing molecular basis and pathophysiology of the studied disease. The search yielded a total of 44 papers, which were reviewed by the authors.

**Results**

**Obesity, Inflammation and Cancer**

The role of inflammation in cancer development is well known. Inflammatory pathways influencing tumorigenesis can be intrinsic or extrinsic. The first is sustained by genetic mutations able to initiate cancer transformation and further up-regulate the expression of inflammatory mediators. The second is related to a chronic inflammatory condition leading to the initiation of cancer and further production of inflammatory mediators\textsuperscript{14}. Even if genetic mutations seem to be the most important initiating factor, contribution to tumor initiation and growth is really complex and several elements influence it. Among them, obesity represents a key predisposing condition\textsuperscript{15}. Obesity, defined as excess in adipose tissue, with its increasing incidence, represents a challenge to global health. Adipose tissue is a complex heterogeneous organ acting in the metabolic homeostasis of the organism through the interaction of many different cell types, such as adipocytes, pre-adipocytes, macrophages, endothelial cells and many immune cells. It is already clear that obesity is associated with an increased frequency of many types of cancer, but the relative roles of the different cells and the molecular pathways involved in carcinogenesis are still unclear\textsuperscript{15}. The hypertrophied adipose tissue secretes a large amount of factors such as leptin, hepatocyte growth factor, angiotensin 1, Vascular Endothelial Growth Factor (VEGF) and many others. All of them are crucial for communication among different cell types and tissue growth\textsuperscript{16}. Some of these factors, such as adipokines derived from adipocytes, are associated with the inflammatory system. The most studied, because of their relation with cancer risk, are leptin, a potent inflammatory agent, and adiponectin, with anti-inflammatory activity\textsuperscript{17}. The cytokines secreted by adipose tissue can activate macrophages or other inflammatory cells, and promote cancer\textsuperscript{18}. It has already been defined that macrophage infiltration has an important role in tumor microenvironment and contributes to tissue invasion, angiogenesis and metastasis\textsuperscript{18}. In summary, a large body of literature demonstrates that a combination of factors secreted by adipocytes, such as increased leptin, decreased adiponectin and increased inflammatory cytokines secretion (Tumor Necrosis Factor, Interleukin 6 and others), in addition to secondary effects of obesity, i.e. hyperinsulinemia and hyperlipidemia, results in a higher risk of developing different types of neoplasms, such as breast, bladder, stomach, blood, colon and liver cancer\textsuperscript{14,19}. It’s not easy to assess which is more important in increasing the likelihood of carcinogenesis, whether adipose tissue itself or consequences of obesity; several ongoing studies are aimed to explore the different roles\textsuperscript{15}. Insights about the complex biology of adipose tissue have defined a new classification based on the risk of metabolic complications of obesity. This divides Metabolically Healthy Obesity (MHO) from Metabolically Unhealthy Obesity (MUO), with differences in terms of body fat distribution\textsuperscript{20,21}. Furthermore, it is proven that ectopic fat tissue depots surrounding organs and blood vessels, mostly prevalent in MUO, have several local and systemic effects promoting sub-clinical chronic inflammation. This is due to the infiltration of adipose tissue by macrophages and to the deregulation of cytokines and secreting growth factors\textsuperscript{22}. All these conditions are already
considered as proven risk factors for cardiovascular diseases and may contribute to several other pathologies, including implications in cancer epidemiology\textsuperscript{17,20}.

**Obesity, Inflammation and Endometrial Cancer**

Evidence supporting the critical role of inflammation in initiation, promotion, malignant degeneration, invasion and metastasis has been confirmed in the pathogenesis of different neoplasms. Less is still known about EC, the most common gynecological malignancy\textsuperscript{23,24}. Obesity is an important independent risk factor for both type 1 and type 2 EC. Nevertheless, the metabolic, immunogenic and inflammatory environment regulating the underlying biological relation between obesity and the different subsets of this neoplasia are still poorly understood. High visceral abdominal fat exerts an independent metabolic and endocrine activity, different from that of subcutaneous fat tissue. It is thought to promote carcinogenesis by inducing a state of low-grade chronic inflammation and is considered relevant in terms of pathogenic and prognostic value\textsuperscript{18}. Since adipose tissue and uterus are highly vascularized and interconnected through blood vessels, growth factors secreted by adipocytes can easily alter uterine physiology. The differences in terms of molecular pathways such as KRAS activation and inflammation in the pathogenesis of endometrioid EC and its precursors in obese patients seem to be different if compared to non-obese women\textsuperscript{11}. Few studies tried to improve the knowledge of this complex interaction of elements and the involved mechanisms. Modugno et al\textsuperscript{13} in 2005 first hypothesized a relation between a chronic inflammation state and endometrial cellular division, higher risk for replication errors and ineffective DNA repair. They put in evidence that an inflammatory milieu in endometrial tissue with the release of cytokines and growth factors was related to initiation and promotion of EC. Furthermore, they underlined that all the known risk factors for neoplasia were directly related to inflammation or were indirectly involved in modulation of the inflammatory pathway. For example, unopposed estrogen action was related to increased pro-inflammatory response in the endometrium. Obesity, diabetes mellitus, polycystic ovarian syndrome were associated to an increased pro-inflammatory milieu. Early menarche, late menopause and menorrhagia were associated to increased exposure to inflammation due to longer menstruation\textsuperscript{15}. Among all the known pro-inflammatory cytokines, Tumor Necrosis Factor-\(\alpha\) (TNF-\(\alpha\)) is one of the most powerful. Its relationship with EC has been analyzed in a case-control study by Dossus et al\textsuperscript{26} in 2011, with data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort\textsuperscript{27}. They analyzed serum TNF-\(\alpha\) and plasma TNF soluble receptors (sTNFR1 and sTNFR2). The results from 270 cases and 518 controls, showed a positive association of TNF-\(\alpha\) and sTNFRs with endometrial proliferation and angiogenesis promotion. As a matter of fact, TNF-\(\alpha\) was related to known risk factors for EC, such as enhanced local estrogen synthesis, increased development of insulin resistance and type 2 diabetes mellitus. Researches could not exclude that the presence of a tumor itself could enhance the levels of circulating inflammatory mediators, but results supporting the role of TNF-\(\alpha\) and its receptors were of particular interest in terms of therapeutic possibilities with TNF-\(\alpha\) inhibitors\textsuperscript{29}. The same group further analyzed the role of circulating cytokines and acute phase reactants in the pathogenesis of EC\textsuperscript{28}. A case-control study, nested within the EPIC study\textsuperscript{27}, aimed to investigate the association of C-Reactive Protein (CRP), Interleukin-6 (IL6) and IL1Ra with EC risk and to what extent these factors can relate obesity and EC. Blood samples from 305 cases taken prospectively prior to EC diagnosis, who were incidentally found with disease during follow up, and 574 healthy controls were analyzed. In conclusion, high blood concentrations of cytokines were significantly associated with EC risk and their association was largely dependent on the levels of patients’ adiposity, thus indicating modulators of aromatase activity of cytokines within the adipose tissue\textsuperscript{29}. Another investigation within the data of the EPIC cohort\textsuperscript{27} included 233 cases and 446 controls. Dossus et al\textsuperscript{26} analyzed a large set of serum biomarkers, taken from pre-diagnostic blood samples, including hormones, growth factors and cytokines, in order to examine their association with EC. This analysis confirmed that TNF-\(\alpha\) and sTNFRs, along with IL-6 and CRP, were inflammatory factors associated with an increased risk of EC in post-menopausal women. Dossus et al\textsuperscript{26} concluded underlying the complex interrelation of all the physiological pathways related to EC pathogenesis, including insulin resistance/metabolic syndrome, steroids and finally inflammation. Trabert et al\textsuperscript{29} in 2016 in a nested
case-control study within the PLCO Screening Trial measured blood level of 64 inflammatory biomarkers in 284 cases of endometrial cancer and 284 controls. They found a higher risk for endometrial cancer among obese women with the highest inflammation scores and several inflammation markers, such as adipokines, inflammatory cytokines, angiogenic factors and acute phase proteins. Only VEGF-A was recognized as a risk factor independent of BMI. Sahoo et al\textsuperscript{16} investigated the effect of cytokines secreted by adipose tissue and, in particular, visceral adipocytes in the modulation and stimulation of angiogenesis and EC proliferation through the action of VEGF. They confirmed that VEGF stimulates the PI3K/AKT/mTOR signaling pathway, a regulator of cellular growth and survival, the most frequently altered pathway in EC. Their results indicate that VEGF expression is directly linked to BMI: the large amount of visceral adipose tissue in obese women is linked to up-regulated VEGF signaling, resulting in more tumor vascularization and higher mTOR activity in the promotion of EC. These results have an increasing interest in terms of pathways-targeted therapies, since mTOR and VEGF inhibitors treatments could be a promising option to reduce the occurrence of EC in obese women\textsuperscript{16}. Biomarkers related to EC risk including steroid hormones, factors linked to metabolic syndrome, insulin resistance and inflammation can be found in visceral abdominal fat depots. Their recognition in peripheral serum as a potential tool for cancer risk prediction models is interesting in risk stratification. This setting has been studied with un-univocal results, since Fortner et al\textsuperscript{10,11} achieved only a modest improvement in identification of pattern of high-risk patients. More research\textsuperscript{10-13} is needed to recognize hormones, etiologic markers and confirmed genetic markers useful in improving discrimination of patients.

Conclusions

The aim of this study was to review the current knowledge about the complex mechanisms underlying the pathogenesis of EC, related to well known risk factors such as obesity and pro-inflammatory conditions. The identification of the involved biomarkers could be useful in improving diagnostic accuracy and identifying targets of therapy, defining systemic treatment strategies and suggesting useful lifestyle behaviors\textsuperscript{14-37}. A deeper understanding of the genetic background of alterations in inflammatory pathway genes could better define populations exposed to a higher susceptibility to EC due to genetic polymorphisms\textsuperscript{38-42}. Furthermore, a better understanding of these molecular pathways could be useful for those patients who could take advantage of conservative treatments such as women with endometrial atypical hyperplasia who want to preserve fertility or to those with EC who are inoperable\textsuperscript{13,44}.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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