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COMMENTARY

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Uterine fibroids and risk of hypertension: Implication of inflammation and a possible role of the renin-angiotensin-aldosterone system

Decio Armanini MD[1] | Chiara Sabbadin MD[1] | Gabriella Donà PhD[1] | Luciana Bordin PhD[2] | Loris Marin MD[3] | Alessandra Andrisani MD[3] | Guido Ambrosini MD[3]

[1]Department of Medicine – Endocrinology, University of Padova, Padova, Italy

[2]Department of Molecular Medicine - Biological Chemistry, University of Padova, Padova, Italy

[3]Department of Women's and Children's Health, University of Padova, Padova, Italy

Correspondence
Decio Armanini, MD, Department of Medicine – Endocrinology, University of Padova, Padova, Italy.
Email: decio.armanini@unipd.it

1 | INTRODUCTION

Haan and colleagues[1] reported a cross-sectional study on the association between uterine fibroids (UF), hypertension, and asymptomatic organ damage. The major question that arises from this study is, Are UF directly linked to hypertension or is hypertension or some related factors involved in the onset or growth of fibroids?

Uterine fibroids are benign tumors of the muscle layer of uterus, affecting about 70% of women by age 50 years, even if only 30% of patients are symptomatic and request treatment.[2] UF can be considered a fibrotic disease starting with an invasion of inflammatory cells at the level of the uterus or alternatively by an increase of resident fibrotic cells.[3] It is well known that the female genital tract is less reactive to inflammation and autoimmunity and this pattern allows spermatozoa to exert their reproductive function still maintaining a full protection against microbial invasion.

The pathogenesis of UF involves a genetic predisposition influenced by the effect of several hormones. Both estradiol and progesterone have a role in the normal development of uterine mucosa and in the preparation of the uterus for pregnancy, but their involvement in hypertension risk is not proven. High amounts of estrogens can produce hypertension, as reported for some contraceptives, but these associations do not induce UF development or increase their volume. The hypertension caused by contraceptives has been related to the increase of angiotensinogen and activation of renin-angiotensin-aldosterone system (RAAS) or to a direct effect of estradiol at the kidney level producing sodium retention.

A previous study has shown that the risk of hypertension in UF is not influenced by hysterectomy with ovarian conservation and on the contrary hysterectomy is associated with long-term increase of cardiovascular risk.[4] These studies are consistent with an extra uterine mechanism underlying the association of hypertension and UF.

Progesterone may play an important role in UF development, stimulating cellular proliferation and fibroid growth.[5] Fibroids express elevated levels of both types of progesterone receptors (PR), PR-α and PR-β, compared to the surrounding myometrium.[6] These findings suggest a certain role of progesterone and PR in UF pathogenesis but not in hypertension, progesterone being a mineralocorticoid receptor (MR) antagonist.

Uterine fibroid size is significantly reduced in response to the PR antagonist mifepristone (RU486) or to the selective PR modulator ulipristal acetate, which are also effective at controlling uterine bleeding and reducing collagen deposits.[7] Ulipristal does not have antialdosteronic properties like progesterone and for this reason it is effective in ameliorating UF volume, but it is not effective in reducing the cardiovascular risk and hypertension.

2 | ANGIOTENSIN II AND ALDOSTERONE COMMITMENT IN UF

A previous study[8] has found a significant association between A1166C polymorphism in the angiotensin II type 1 receptor (AT1R) gene and UF. Angiotensin II and aldosterone are involved in cell proliferation, angiogenesis, inflammation, and fibrosis. Moreover, angiotensin

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II-induced proliferation of leiomyoma cells has been shown,[9] and the significant role of angiotensin II in the pathogenesis of hypertension, both directly inducing vasoconstriction and indirectly stimulating aldosterone synthesis, is well known. Considering the increased hypertension risk reported by Haan and colleagues in women with UF,[1] the involvement of the RAAS could explain a pathophysiology common to these 2 conditions. Because ACE inhibition as well as AT1R blockade have been shown to inhibit tumor angiogenesis, tumor growth, vascular density, mitotic index, and cell proliferation, ACE-inhibitors and AT1R blockers could be used to prevent or reduce tumor development in susceptible subjects bearing these polymorphisms.

Isobe and colleagues[10] reported an interesting study showing that ELT-3 leiomyoma cells express the MR and that aldosterone stimulates the cell proliferation. Preincubating the cells with the MR blockers spironolactone or eplerenone effectively repressed aldosterone-induced and angiotensin II-induced cell proliferation. These findings suggest a possible use of MR antagonists for the treatment of UF; however, only a pure MR antagonist such as eplerenone could be considered, because spironolactone is frequently associated with metrorrhagia because of its effect on PR.[11]

In the last decades many studies revaluated the role of aldosterone in the pathogenesis of inflammation and atherosclerosis.[12] The increased cardiovascular risk due to aldosterone is evident in primary aldosteronism, but even normal aldosterone values are involved in cardiovascular fibrosis and remodeling. The studies of Pitt and associates[13,14] have clearly shown a reduction of the prevalence of a relapse of heart failure and of cardio-cerebrovascular accidents through the addition of MR antagonists to the conventional treatment of many pathological conditions characterized by secondary aldosteronism. Inflammatory processes are mainly supported by peripheral blood mononuclear leukocytes (MNL) and macrophages, which both possess the MR. Prior to the development of fibrosis, aldosterone causes MNL and macrophage infiltration and increased formation of reactive oxygen species and inflammatory markers. Many in vitro and in vivo studies have demonstrated that coincubation of MNL with MR antagonists blocked the inflammatory effect of aldosterone.[15] The evidence of a central role of inflammation in the pathogenesis of UF suggests a possible involvement of RAAS.

We have hypothesized a relationship between inflammation, aldosterone, and somatic mutations.[16] Recurrent somatic mutations have been involved in increased aldosterone production and adrenal cortex cell proliferation.[17] Currently, about 50% of sporadic aldosterone-producing adenoma cases have been associated with some genetic defects. Recently, somatic mutation of MED 12 gene has been reported in UF, confirming a role of inflammation in UF development.[18]

It is also interesting to note that UF are associated with other inflammatory diseases, such as obesity, insulin resistance, and polycystic ovary syndrome (PCOS). In particular, UF are very frequent in PCOS,[19] which is often associated with increased aldosterone levels or with higher aldosterone-to-renin ratio compared with normal controls. PCOS is also linked to many aldosterone-related pathological conditions, like hypertension, Hashimoto's thyroiditis, diabetes, obesity, and preeclampsia.[20] Many of these clinical situations are evident after menopause and a precox treatment could reduce the risk of late complications.[21]

3 | CONCLUSIONS

Excluding hypertension, Haan and associates[1] did not find a correlation between UF and other factors linked to cardiovascular risk, but this finding could be related to the concomitant treatment of hypertension or to the heterogeneity of UF and of patients' age.

Local and general inflammatory status has been associated with UF development. Many other clinical situations are linked to inflammation, for example, PCOS, metabolic syndrome, insulin resistance, obesity, and diabetes. All of these situations can be associated with UF. Therefore, we believe that UF could be associated with future cardiovascular risk like all the other inflammatory-related hormonal situations frequently associated with UF.

The RAAS involvement in inflammation-linked pathological conditions could play a pathogenetic role and should be considered.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Decio Armanini http://orcid.org/0000-0002-6433-5155

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