Caloric Restriction Dramatically Hinders the Lesion Growth in Mouse with Experimentally Induced Endometriosis

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Introduction: Caloric restriction (CR), defined as a reduction of total caloric intake without malnutrition, has been well-documented to have many health benefits in animal experimentations. However, its effect on endometriosis has not been published. CR is reported to impact on multiple key signaling pathways involved in metabolism, angiogenesis, estrogen activity, insulin sensitivity and autophagy. Since all these pathways have been reported to be involved in the pathophysiology of endometriosis, CR may also exert its protective effect on endometriosis. In this study, we performed two mouse experimentations to evaluate the effect of CR by 30% decrease in calorie intake before and after the induction of endometriosis on the development of endometriosis, and to test the hypothesis that CR can hamper the development of endometriosis in mice.

Materials and Methods: In experiment 1, 20 female adult Balb/C mice were randomly assigned in equal size to either AL group that was fed ad libitum, or to CR group fed 30% less in caloric intake than AL. CR was initiated 2 weeks prior to the induction of endometriosis and was continued for 2 additional weeks after implantation. In experiment 2, 2 weeks after induction of endometriosis, 20 mice were divided randomly in equal sizes into 2 groups: the AL-p group that was fed ad libitum, and the CR-p group that was fed 30% less in caloric intake than AL. The diet intervention lasted for 4 weeks until the sacrifice of mice. In both experiments, we measured bodyweight, lesion weight, and hotplate latency, and, for endometriotic lesions, performed Masson trichrome staining as well as immunohistochemistry analysis of proliferating cell nuclear antigen (PCNA), vascular endothelial growth factor (VEGF), CD31, insulin-like growth factor-1(IGF-1), phosphorylated protein kinase B (p-Akt), mammalian target of rapamycin (mTOR), microtubule-associated protein light chain 3 (LC3), phosphorylated adenosine monophosphate-activated protein kinase (p-AMPK), phosphorylated cyclic adenosine monophosphate response element-binding protein (p-CREB), steroidogenic acute regulatory protein (StAR) and sirtuin 1 (SIRT1).

Results: CR significantly inhibited the growth of endometriotic lesions, reducing the lesion weight by an average of 88.5% as compared with AL. Similarly, the lesion weight in the CR-p group was reduced by 93.0% as compared with the AL-p group. CR significantly reduced the extent of fibrosis and microvessel density in endometriotic lesions. Endometriotic lesions from CR mice also showed significantly lower staining levels of PCNA, VEGF, IGF-1, p-Akt, mTOR, p-CREB and StAR but higher staining levels of LC3, p-AMPK, and SIRT1. Similar findings were also seen in the mouse experiment 2.

Conclusion: CR significantly and dramatically hinders the growth of endometriotic lesions and fibrogenesis through reduced angiogenesis and key growth factor levels, down-regulation of PI3K/Akt-mTOR signaling pathway, enhancement of autophagy, reduced estrogen production, and up-regulation of AMPK/SIRT1 pathway in ectopic implants, even when CR was instituted well after the endometriotic lesions are established. While extreme caution should be exercised when extrapolating this finding to humans, our study should simulate more research on the possible dietary prevention or intervention for endometriosis, which should yield new insight into possible prevention and treatment of endometriosis.

Keywords : mTOR / autophagy / angiogenesis / caloric restriction / endometriosis / mouse
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