Importance of vitamin D-calcidiol and calcitriol in endometriosis

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Abstract

Background: Vitamin D has multiple extra-skeletal functions. Among them are some important roles in reproductive system and many aspects are still under evaluation. It is not surprising because vitamin D seems to be involved in almost every physiological process that takes place in the reproductive system. Active form of vitamin D –calcitriol – 1,25OH2D3 plays a significant role in anti-proliferative and immunosuppressive processes in the body. Evaluation of endometriosis in some studies showed changed vitamin D metabolism in tissue and advanced parallel activation and degradation of calcitriol in cells of endometriosis.

Aim: We aimed to observe literature to review current knowledge about the connection of endometriosis and vitamin D – calcidiol and calcitriol. Our main interest is to summarize latest studies, based on them make some conclusions and suggest directions for future studies. Key interest is to find out how affects vitamin D endometriosis and vice versa in both clinical and experimental studies.

Materials and Methods: Electronic databases such: PubMed, Medline, Cochrane Library, Web of Science, Science Direct, Springer were searched. 75 articles were reviewed. 29 articles that had statistically significant results were included in our review.

Results: Clinical studies from the last few years are more about the associative connection of low 25OHD3 and endometriosis. Researchers are concentrated more on calcidiol-25OHD3 and do not pay much attention to calcitriol-1,25OHD3. Mainly they see low calcidiol as a risk factor for endometriosis and few think that low 25OHD3 may be the consequence of active conversion of 25OHD3 to 1,25OHD3. Association between low calcidiol -25OHD3 and endometriosis is studied the most. Most of the studies have found that patients with endometriosis have lower levels of 25OHD3. Only two studies measured both calcitriol and calcidiol in blood of women with endometriosis and result are controversial. Evidence is low and insufficient to discuss about the reasons and consequences of changed metabolism.

Conclusions: According to reviewed research we do not have enough data to insist that vitamin D metabolism is different in endometriosis. But it seems to be so. It is important to understand which is risk factor for another- low 25OHD3 raises risk of endometriosis or vice versa? If high activation of 25OHD3 to 1,25OHD3 and following high degradation of 1,25OHD3 occurs during endometriosis in endometrial tissue, what is the consequence of it in blood and are these consequences important enough to notice? May it affect calcium homeostasis? It should be mentioned that experimental treatment of endometriosis with calcitriol analogs shows promising effects. If management of endometriosis with help of calcitriol analogs will be available in the future, it will be important to have some basic knowledge about primary calcitriol and calcidiol levels in blood during endometriosis. Outcome of this different vitamin D metabolism in endometrial tissue may be high, low or normal calcitriol levels in blood. But substrate for conversion – 25OHD3 calcidiol should be theoretically low, because of high demand. Persistent hypercalcitriolemia may lead to hypercalcemia and cause harm to multiple organ systems. Thus, normalization of vitamin D metabolites should receive proper attention and be corrected as well. **TCM-GMJ December 2023; 8 (2):P3-P6)**

Keywords: vitamin D; endometriosis; calcidiol; calcitriol; 25OHD3; 1,25OHD3;

Introduction

Vitamin D is pleiotropic hormone. Active form of vitamin D is calcitriol - 1,25OHD3, which is responsible for its functions. There is a huge interest about vitamin D worldwide. Beside calcium homeostasis vitamin D has multiple extra-skeletal functions. Among them are some important roles in reproductive system and many aspects are still under evaluation.

D vitamin deficiency worldwide looks like pandemic. Despite a high deficiency prevalence, low vitamin D level is associated with many diseases. Vitamin D deficiency is an industrial health issue. In the last century the world has changed its lifestyle. People spend more time indoors, buildings are taller, and air is polluted. This may be one of the most important reasons for such dramatic vitamin D deficiency. Another reason may be climate changes – longer winters and decreased UV B radiation due to changed angle of the sun (1).

Vitamins are micronutrients, whereas chemical substances that body can produce and that act like messengers are classified as hormones. Thus, vitamin D is recognized as a hormone. Vitamin D is synthesized from cholesterol - similar to well-known steroid hormones. It is activated twice and the final active compound- calcitriol - 1,25OHD3 is bound to nuclear receptors - VDR (vitamin D receptor). This complex binds to DNA and up or down-regulates multiple gene transcription (2). It is no longer questionable that vitamin D is not different from other steroid hormones. The only difference is that it may be consumed from food sources also, but that occurs in insignificant quantities. Until 1979 it was not possible to measure vitamin D status. Since then, normal ranges of vitamin D were established and it turned out that about a billion people are either deficient or insufficient.

Deficiency of vitamin D is a well-known health problem. During centuries deficient-children were affected with rickets. In 1822 Sniadecki found a connection between sun exposure and rickets (3). In the early 1900s Huldschinsky began to treat children with rickets with help of ultraviolet irradiation (4). Scientists also noted that cod liver oil improved skeletal abnormalities in rickets. So, in the early 19th century there was already a hypothesis about an antirachitic factor that was both - a nutrient and a hormone. Many countries started to fortify food with vitamin D. In the mid-20th century, the problem of rickets seemed to be more or less resolved, but an outbreak of hypercalcemia led the governments to stop fortification. In 1979 due to increased rickets cases fortification of milk was reintroduced. (1) As we can see these days, fortification is not enough to overwhelm vitamin D deficiency.

Evidence is growing about extra-skeletal functions of vitamin D. Its deficiency is related to many autoimmune, inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, autoimmune thyroiditis and many more. Active form of vitamin D – calcitriol – 1,25OH2D3 plays a significant role in anti-proliferative and immunosuppressive processes in the body (5).

Reproductive health is closely related to vitamin D status. In general infertility and many gynecological diseases are associated with vitamin D deficiency. Most evidence we have about PCOS, hyperandrogenism and insulin resistance (6,7,8). Dysmenorrhea, PMS, pregnancy complications-such preeclampsia and gestational diabetes are also influenced by vitamin D deficiency (9,10,11,12,

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13). It is not surprising because vitamin D seems to be involved in almost every physiological process that takes place in the reproductive system of both sexes (14). Experimental study shows that rats that are calcitriol deficient are infertile due to interrupted folliculogenesis and hypoplastic uterus (5).

1889 vitamin D deficiency and female fertility were connected to each other for the first time. At that time high incidence of rickets led to deformed pelvis in women and childbirth was in many cases fatal. Surgeon Murdock Cameron began to perform routinely C-sections in order to save lives (1).

In 1980-1990 years, scientists discovered that activation of cholecalciferol 25OHD3 to calcitriol 1,25OHD3 occurs not only in kidneys, but also in other organs such as the uterus and placenta (15). Enzyme 1alpha-hydroxylase, which converts 25OHD3- calcidiol to active 1,25OH2D3 calcitriol, is synthesized in stromal and epithelial cells of endometrium. It is important to notice that vitamin D receptor VDR is also identified in endometrium, myometrium, ovary and mammary gland (15). Reproductive system has all the needed components to let vitamin D fulfill its actions, but not all the functions are clear.

In the 1950s scientists noticed some connection between active vitamin D – calcitriol and pregnancy. Calcitriol and progesterone act synergistic in order to maintain normal pregnancy. (16) Pregnancy is a state of high calcitriol levels that is independent from calcium metabolism and should have some other explanation, which is not understood properly until now (17)(18).

Chemical structure of calcitriol stands near progesterone's structure. They are both steroid hormones. Some scientists suggest the hypothesis that calcitriol has the ability to bind to progesterone's nuclear receptor due to structural similarity and activate it, but this opinion is not proven yet (19).

According to basic studies calcitriol and progesterone cooperate in following ways: Vitamin D treatment increases m RNA of progesterone receptor (PR) in both - women who underwent IVF and were diagnosed with RIF (Repeated implantation failure) and in healthy controls. For this study endometrial stromal cells biopsy samples were evaluated. Results show that vitamin D treatment upregulates progesterone receptor and may improve progesterone receptivity, which is the main interrupted pathway in the development of endometriosis (20).

On the other hand, another study suggests that vitamin D receptor VDR is induced by progesterone in human and mice T cells and in uterine cells of mice (21).

One study concluded that vitamin D directly stimulates progesterone production in the human ovary. Vitamin D enhances 3-beta-HSD expression in granulosa cells, which is essential step in converting pregnenolone to progesterone. Study was carried out in 54 IVF patients. Follicular fluid and granulosa cells were collected from follicles. Adding vitamin D significantly ($P < 0.05$) increased progesterone levels in granulosa cells in 24 hours, compared with control group (22).

Endometriosis is estrogen-dependent, progesterone-resistant chronic inflammatory disease that affects about 10% of women worldwide. 50% of women with chronic pelvic pain and infertility are diagnosed with endometriosis. Impaired reception to progesterone has main role in pathogenesis of interrupted decidualization and occurrence of ectopic endometrial implants. Endometrial cells during endometriosis fail to downregulate genes needed for cell cycle regulation and decidualization. This leads to unlimited proliferation. Progesterone has anti-inflammatory effect in endometrium, but its effects are limited due to decreased response of receptors and inflammation during endometriosis, that worsens this resistance further (23).

Endometriosis often leads to infertility but it also affects women's quality of life. Diagnosis and treatment of endometriosis is a big challenge for practitioners. Often clinical examination and imaging are not enough to diagnose endometriosis and diagnostic laparoscopy is needed.

Conservative treatment is also not always satisfactory and surgery is performed. In many cases either surgery is insufficient way of management, because endometriosis is chronic recurrent disease. Researchers are looking for specific noninvasive diagnostic markers and better conservative treatment options.

We are aware that vitamin D, mainly its active form - 1,25OHD3 calcitriol, has important role in pathogenesis of endometriosis. Synergistic actions of vitamin D with progesterone and its anti- inflammatory and anti-proliferative properties are reasons why the link between vitamin D and endometriosis may be important. Many researchers found interactions, but there is still a big gap in knowledge and inconsistent data.

Aim

We aimed to observe literature to review current knowledge about the connection of endometriosis and vitamin D – calcidiol and calcitriol. Our main interest is to summarize latest studies, based on them make some conclusions and suggest directions for future studies. Key interest is to find out how affects vitamin D endometriosis and vice versa in both clinical and experimental studies? What is different in vitamin D metabolism in case of endometriosis?

Results

The evidence about vitamin D metabolism in case of endometriosis can be divided into two categories. These are basic studies about pathophysiology and clinical studies which are more of associative character.

As far as we are informed, in 1989 Hartwell was first who evaluated that women with endometriosis have elevated levels of calcitriol in blood. Blood concentration of vitamin D metabolites were studied in 42 women with endometriosis and compared to control group. Women with endometriosis had higher calcitriol 1,25OHD3 levels then healthy women.

25OHD3 and 1,25OHD3 levels were not associated with age or menopause status. 25OHD3 was dependent on season but 1,25OHD3 was not (24).

Basic studies followed this clinical study. According to them in women with endometriosis there is local enhanced activation of calcidiol (25OHD3) to calcitriol (1,25OHD3) due to elevated levels of enzyme 1-alpha-hydroxylase in endometrial cells which is responsible for this conversion. For this study endometrium samples of 77 women were collected. They underwent laparoscopy for unexplained infertility. 27 had endometriosis, Samples of endometriosis of 9 patients were taken from peritoneal lesions and endometrial cysts for histology. Decidual tissue of control group were obtained from 38 healthy women who underwent elective termination of p r e g n a n c y (5, 25).

Latest research shows that expression of vitamin D receptor (VDR) is lower in ectopic endometrium compared to eutopic. Study included 32 patients with genital endometriosis and 20 healthy women in control group. Expression of vitamin D receptor VDR was measured. VDR expression in the endometrial heterotopias was statistically significantly lower compared to eutopic endometrium in patients with genital endometriosis. Also, VDR cyclic variations were not present in genital endometriosis group in contrast to the control group (26).

Progesterone and calcitriol cooperate not only in a theoretical way. CYP24A1 is a calcitriol deactivating protein that causes calcitriol-induced self-limitation. Progesterone shows the ability to inhibit this CYP24A1. That allows calcitriol to work more effectively as an antiproliferative factor in case of endometrial cancer (27)(28)(28)(29). This inactivation of calcitriol due to CYP24A1 protein appears to be important in endometriosis as well. In endometriosis stromal cells are upregulating genes for CYP24A1 protein to 369 times in response to calcitriol (30). This means too much deactivated calcitriol. During endometriosis cells cannot respond properly to progesterone because of resistance, so progesterone's action as CYP24A1 inhibitor may be diminished. Theoretically this may be the reason for enhanced calcitriol deactivation, which leads to further uncontrolled cell proliferation.

It looks like endometriosis changes vitamin D metabolism and advanced activation and degradation of calcitriol are parallel processes in cells of endometriosis. Is this process balanced or not we do not know for sure. Outcome of this different vitamin D metabolism in endometrial tissue may be high, low or normal calcitriol levels in blood. But substrate for conversion – 25OHD3 calcidiol should be theoretically low, because of high demand besides other risks of deficiency.

One important discovery made in recent years from basic science is that vitamin D is connected with HOXA10 genes. HOX genes are a transcription factor family that are critically important for implantation

and early embryo development. Expression of these genes occur in the female reproductive tract, mainly in the uterus. Regulation of HOXA10 genes appears to be due to estrogen and progesterone. During implantation these genes are up regulated by sex hormones. They are important for implantation and decidualization. Experimental study showed that calcitriol directly upregulates HOXA10 transcription in endometrial stromal cells.

Patients with some genetic mutation in calcitriol producing chain, have defect of decidualization (31)(32).

Expression of HOXA10 is cyclic and peaks during the implantation window. During endometriosis mid-luteal peak is absent and this maybe one reason of infertility in endometriosis (33).

Clinical studies from the last few years are more about the associative connection of low 25OHD3 and endometriosis. Researchers are concentrated more on calcidiol-25OHD3 and do not pay much attention to calcitriol-1,25OHD3. Mainly they see low calcidiol as a risk factor for endometriosis and few think that low 25OHD3 may also be the consequence of active conversion of 25OHD3 to 1,25OHD3. In case of endometriosis this process may lower concentration of main vitamin D reserve in blood, which is 25OHD3.

We found only one study after Hartwell that assessed both calcitriol and calcidiol in the blood of women with endometriosis. In this case-control study of 2007 year women with endometriosis (n87) and healthy controls (n53) were evaluated. Study results were surprising - 25OHD levels were higher in the endometriosis group. Levels of 1,25OHD were also higher in women affected with endometriosis compared to control group, but these results regarding 1,25OHD were not statistically significant (34).

In recent years some researchers concluded opposite - higher 25OHD appears not to be associated with higher risk of endometriosis. On the contrary low levels of calcidiol 25OHD in blood shows to have predisposing effect regarding endometriosis. One study found also association between calcium intake and endometriosis and calcium intake shows to be beneficial in women with endometriosis (35). Another study included medical data of 737,712 women, who underwent gynecological surgery for different reasons between 1991-2005 years. This follow – up concluded that women who consume 3 or more servings of dairy food (that is fortified with vitamin D and high in calcium) have 18% less chance to be diagnosed with endometriosis then women who consume only 2 servings per day (36).

We found few meta-analyses regarding endometriosis and vitamin D. Latest and largest of them is published in 2020 and includes only nine original studies. According to them women with endometriosis have lower calcidiol 25OHD3 levels in blood than healthy women. Also, 25OHD3 status is in negative correlation with the degree of endometriosis. But this result was statistically insignificant (37).

Newest systemic review of 2023 included data of 29 studies.13 of them were clinical, 12 preclinical. 8 of 11 clinical studies found association between low vitamin 25OHD and endometriosis and only 1 study reported high vitamin D levels in endometriosis. Others did not find any associations. Most results show the correlation between low 25OHD and endometriosis (38).

In the majority of above-mentioned studies only one fraction of vitamin D- calcidiol 25OHD is measured. Evidence about association is also inconclusive and low.

Beside that data, we reviewed interventional researches.

Attention should be paid to one study regarding experimental treatment in women with endometriosis. 440 patients were included in group of endometriosis with morphologically confirmed diagnoses and 30 healthy women were in the control group. Inclusion criteria was pain associated with endometriosis. Combination treatment with aGnRH 3,75mg +cholecalciferol showed greater improvement in pain then aGnRH 3,75mg alone, but dienogest 2mg monotherapy showed greater efficiency (26). In this study is used cholecalciferol, but studies with calcitriol analogs are also available and show promising results.

Analogs of calcitriol were used in experimental animal studies to treat endometriotic lesions. In 2012 Journal "Human Reproduction " published a study about VDR selective agonist elocalcitol. It was used to treat endometriosis in rats. Elocalcitol reduced peritoneal inflammation.Elocalcitol 100 mcg/kg in 3 weeks reduced endometriotic lesion by 70% (39). Similar experiment was conducted with calcitriol in mice. Endometriotic lesions shrank in size in this case also (40).

In human study of 2015 year calcitriol showed positive influence on stromal cells in women with endometriosis. Eutopic and ectopic stromal cells from 25 women with endometriosis and samples of 20 healthy women were investigated in vitro. Proliferation and invasion of cells were reduced (41).

Conclusion

According to reviewed research we do not have enough data to insist that vitamin D metabolism is different in endometriosis. But it seems to be so. Association between low 25OHD3 and endometriosis is studied the most. But this evidence is also insufficient. It is important to understand which is risk factor for another- low 25OHD3 raises risk of endometriosis or vice versa? If high activation of 25OHD3 to 1,25OHD3 and following high degradation of 1,25OHD3 occurs during endometriosis in endometrial tissue, what is the consequence of it? What levels of calcidiol and calcitriol do we receive in blood? Do we have important differences enough to notice? May it affect calcium homeostasis?

There are many questions left unanswered and more research is needed. It is important to understand vitamin D metabolism better in endometriosis and then according to this knowledge search for better treatment options.

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