Relationship between sex hormones levels and $^{18}$F-FDG uptake by the ovaries in premenopausal woman

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Background. The study was conducted to evaluate the effect of sex hormones on F-18 fluorodeoxyglucose (F18-FDG) uptake by normal ovaries.

Patients and methods. A total of 197 premenopausal women were included in this study. Based on F18-FDG positron emission tomography/computed tomography (PET/CT) images obtained from these subjects, the association of ovarian F18-FDG uptake with levels of sex hormones, including estradiol, progesterone, testosterone, follicle-stimulating hormone, and luteinizing hormone was investigated. We also analysed the relationship between the menstrual cycle and ovarian F18-FDG uptake.

Results. The highest ovarian F18-FDG uptake occurred at 2 weeks after the onset of menstruation (median maximum standardized uptake value [SUVmax] = 3.40, median mean SUV [SUVmean] = 2.20), and the lowest ovarian F18-FDG uptake was observed during the first week of the menstrual cycle (median SUVmax = 1.60, median SUVmean = 1.20). Ovarian F18-FDG uptake was weakly positively correlated with progesterone levels ($\rho = 0.28$, $p < 0.001$ for SUVmax, $\rho = 0.30$, $p < 0.001$ for SUVmean), and this pattern was consistently observed in subjects in the follicular-phase group ($\rho = 0.29$, $p = 0.003$ for both SUVmax and SUVmean) but not in subjects in the luteal-phase group.

Conclusions. Based on PET images, ovarian glucose metabolism in premenopausal women tended to increase slightly with increasing progesterone concentration.

Key words: ovary; fluorodeoxyglucose F18; positron-emission tomography; gonadal steroid hormones

Introduction

$^{18}$F-FDG PET, which utilizes a radiolabeled analogue of glucose, is widely used clinically in patients with cancer to evaluate staging and the therapeutic response. However, $^{18}$F-FDG uptake may be high not only in malignant lesions but also in normal tissues. High uptake of $^{18}$F-FDG in the pelvic region of women, particularly by the ovaries, can be confusing for nuclear-medicine physicians interpreting PET images. The ovary is a major reproductive organ characterized by cyclic changes in sex hormones, which are believed to affect the degree of $^{18}$F-FDG uptake by the ovary. Ovarian $^{18}$F-FDG uptake is typically negligible in postmenopausal women; if incidental ovarian $^{18}$F-FDG uptake is found on PET, the possibility of a malignant lesion is sufficiently high to recommend further evaluation by magnetic resonance imaging (MRI) or ultrasonography. However, in premenopausal women, ovarian $^{18}$F-FDG uptake occurs even under normal or be-
In benign conditions such as a follicular ovarian cyst or hemorrhagic corpora lutea.7 Therefore, in daily practice, nuclear-medicine physicians do not routinely recommend further radiographic evaluation in the event of ovarian 18F-FDG uptake. This makes it difficult to draw conclusions about ovarian 18F-FDG uptake in premenopausal women. We investigated physiological ovarian 18F-FDG uptake, since previous studies on ovarian 18F-FDG uptake in premenopausal women are limited and most focused on the degree of change in 18F-FDG uptake during the menstrual cycle.5,6,8,9 Furthermore, how sex hormones affect this uptake has not been clearly determined.

The purpose of this study was to investigate the relationship between sex hormones levels and 18F-FDG uptake by ovaries in premenopausal woman.

Patients and methods

Patients

This study included 197 premenopausal women (median age, 44 years) who were diagnosed with breast cancer between March 2015 and July 2017 and underwent 18F-FDG PET/CT to determine pre-treatment status, as well as sex-hormone assays (including estradiol, progesterone, testosterone, follicle-stimulating hormone [FSH] and luteinizing hormone [LH]). Hormone assays were performed on the same day as PET. The date of the last normal menstrual period (LNMP) of all patients was also recorded and used to divide the women into two groups based on their menstrual phase on the day of the tests: a follicular-phase group (days 1–13) and a luteal-phase group (days 14–31). We also noted how many weeks had elapsed since the date of onset of menstruation. Patients were excluded if they had a history of ovarian disease, sex hormone therapy or an irregular menstrual cycle of more than 31 days.10

The clinical design of this retrospective study was approved by the Institutional Review Board of Ajou University (AJIRB-MED-OBS-18-354). The need for informed consent was waived.

18F-FDG PET/CT protocol

After fasting for at least 6 hours, patients were administered 5 MBq/kg 18F-FDG intravenously. The blood glucose level at the time of the 18F-FDG injection was < 8.3 mmol/L in all patients. Patients were instructed to rest comfortably for 60 min, and to urinate before the scan. Whole-body PET/CT images were obtained with a Discovery ST 8 slice CT scanner or Discovery STE 16 slice CT scanner (GE Healthcare, Milwaukee, WI, USA). Seven or eight frames (3 min/frame) of PET emission data were acquired in three-dimensional mode after a non-contrast CT scan from the base of the skull to the upper thigh (120 kV, 30–100 mA in the AutomA mode; section width = 3.75 mm). Emission PET images were reconstructed using an iterative method (ordered-subsets expectation maximization with two iterations and 20 subsets; field of view = 600 mm, slice thickness = 3.27 mm) and attenuation was corrected with noncontrast CT.

Image analysis

A nuclear-medicine specialist with 13 years of PET experience, blinded to the clinical data, reviewed the 18F-FDG PET/CT images on an AW workstation (version 4.4; General Electric Healthcare, Chicago, IL, USA). The volume of interest (VOI) was placed on the ovarian area showing higher 18F-FDG uptake than the background activity on the PET image. If there was no PET uptake, the VOI was drawn on the right and left ovarian areas on the CT image. The SUVmax and SUVmean were calculated from these VOIs based on injected dose and body weight. The higher values of the right and left ovarian SUVs were used for the statistical analysis.

Statistical analysis

All statistical analyses were done using MedCalc Statistical Software (ver. 18.5; MedCalc Software bvba, Ostend, Belgium). First, we calculated the required sample size. A significance (a) level of 5% and statistical power (1 − b) of 80 % were considered acceptable for the purposes of the study. A sample size of 145 patients was required to attain an appropriate confidence range; thus, the obtained sample size (N = 197 patients) was sufficient for the statistical analysis.

The Kolmogorov–Smirnov test was used to assess whether the data were normally distributed. None of the data followed a normal distribution, so they are presented as medians and interquartile range (IQR). The Mann–Whitney test was used to compare groups distinguished based on the menstrual phase. The Kruskal–Wallis test was used to compare ovarian 18F-FDG uptake among groups distinguished based on weeks since onset of menstruation. If the Kruskal–Wallis test was significant, a post-hoc analysis was performed for pairwise
comparisons of the subgroups. Spearman’s rank coefficient correlation test was used to examine the correlations between the ovary SUVs and levels of sex hormones. Correlations were classified as very weak (\( \rho < 0.20 \)), weak (\( \rho = 0.20–0.39 \)), moderate (\( \rho = 0.40–0.59 \)), strong (\( \rho = 0.60–0.79 \)), or very strong (\( \rho \geq 0.80 \)). All P values < 0.05 were considered significant.

**Results**

Of all patients, 100 (50.8%) underwent \(^{18}\text{F-FDG}\) PET in the follicular phase and 97 (49.2%) in the luteal phase. Progesterone levels were significantly higher in the luteal-phase group than in the follicular-phase group (12.30 vs. 1.62 nmol/L, \( p < 0.001 \)) and FSH was significantly higher in the follicular-phase group than in the luteal-phase group (5.7 vs. 2.9 mIU/mL, \( p < 0.001 \)). Age, and the levels of all other sex hormones measured (estradiol, testosterone, and LH), did not differ significantly between the two groups. The median SUVmax and SUVmean values of the ovaries in all subjects were 2.00 and 1.40, respectively, and these values were significantly higher in the luteal-phase group than in the follicular-phase group (2.10 vs. 1.70, \( p = 0.030 \) for SUVmax, 1.60 vs. 1.30, \( p = 0.015 \) for SUVmean). The patient characteristics are summarized in detail in Table 1.

| Table 1. Patient characteristics |
|---------------------------------|
| **Menstrual phase on test day**  | **Follicular phase** | **Luteal phase** | **Total** | **p-value** |
| Number of patients, n [%]        | 100 (50.8)           | 97 (49.2)        | 197 (100) | 0.150       |
| Age, years                       | 45 (42–47)           | 44 (38–47)       | 44 (40–47) |             |
| Sex hormone levels               |                     |                 |           |             |
| Estradiol, pg/ml                 | 125 (76–176)         | 150 (84–182)     | 126 (81–179) | 0.292       |
| Progesterone, ng/ml              | 1.62 (1.26–2.53)     | 12.30 (3.85–18.95)| 2.71 (1.42–12.11) | < 0.001*   |
| Testosterone, ng/ml              | 0.34 (0.21–0.52)     | 0.37 (0.23–0.51) | 0.36 (0.23–0.51) | 0.342       |
| FSH, mIU/ml                      | 5.7 (3.9–8.1)        | 2.9 (1.7–4.1)    | 3.7 (2.4–6.1)   | < 0.001*    |
| LH, mIU/ml                       | 5.9 (2.9–8.6)        | 3.6 (2.5–6.6)    | 4.6 (2.7–7.8)   | 0.105       |
| SUVmax of ovary                  | 1.70 (0–2.70)        | 2.10 (1.50–3.63) | 2.00 (0–3.23)   | 0.030*      |
| SUVmean of ovary                 | 1.30 (0-1.85)        | 1.60 (0.9–2.40)  | 1.40 (0-2.10)   | 0.015*      |

All continuous variables are shown as medians (interquartile range). *p-value < 0.05

\( FSH = \) follicular-stimulating hormone; \( LH = \) luteinizing hormone; \( SUVmax = \) maximum standardized uptake value; \( SUVmean = \) mean standardized uptake value

The results for the entire cohort showed that the ovarian SUVmax and SUVmean values were weakly positively correlated with progesterone levels (\( \rho = 0.28, p < 0.001 \) for SUVmax, \( \rho = 0.30, p < 0.001 \) for SUVmean) (Figure 2). Levels of the other sex hormones (estradiol, testosterone, FSH, and LH) were not correlated with ovarian \(^{18}\text{F-FDG}\) uptake. The ovarian SUVmean was very weakly correlated with age (\( \rho = 0.15, p = 0.035 \)).
Analysis of the phase groups revealed that when progesterone levels were high, ovarian \(^{18}\)F-FDG uptake was slightly higher \((\rho = 0.29, p = 0.003\) for both SUVmax and SUVmean\) in the follicular-phase group. In the luteal-phase group, no correlation was found between sex-hormone levels and ovarian \(^{18}\)F-FDG uptake. The data and statistical analysis results are shown in detail in Table 2.

**Discussion**

Ovarian \(^{18}\)F-FDG often presents a challenge to nuclear-medicine physicians interpreting \(^{18}\)F-FDG PET/CT images. Ovarian \(^{18}\)F-FDG uptake can occur depending on the phase of the menstrual cycle, particularly in premenopausal women\(^{6,9}\), but a clear mechanism for this remains unclear. We postulated that sex hormones are associated with ovarian \(^{18}\)F-FDG uptake and aimed to evaluate this relationship.

Our study found that progesterone was weakly positively correlated with ovarian \(^{18}\)F-FDG uptake in all subjects in the follicular-phase group, but none of the sex hormones was correlated with ovarian \(^{18}\)F-FDG uptake in the luteal-phase group. Progesterone acts on the endometrium and plays a major role in preparing the uterus for implantation.
Progesterone secretion switches from the adrenal is regulated by unknown elements in the ovary. Progesterone is secreted from the adrenal cortex; this secretion during most of the follicular phase is the result of a complex interaction between the adrenal cortex and the ovaries, which may account for the correlation between progesterone levels and ovarian glucose metabolism. We acknowledge that this hypothesis is speculative and further research will be needed for confirmation. Estradiol and FSH, which play important roles in follicular growth, and LH, which plays a key role in ovulation, were not correlated with ovarian 18F-FDG uptake; this has rarely been reported, so interpreting this finding is difficult. The relationship between the ovaries and sex-hormone levels is very complex and therefore difficult to elucidate. This study is significant in that it is the first to reveal a relationship between ovarian 18F-FDG uptake and sex hormone levels, but more research will be needed to clarify the mechanism of their relationship.

Another noteworthy result of this study was that ovarian 18F-FDG uptake was very weakly negatively correlated with age. With aging, the ovaries gradually decrease in function. Our results show that changes in ovarian metabolism due to aging are reflected in 18F-FDG uptake.

Lerman et al. reported that 18F-FDG uptake was detectable in normal ovaries during the ovulatory phase in premenopausal women. Nishizawa et al. reported increased ovarian 18F-FDG uptake from the late follicular phase to the early luteal phase. Kim et al., demonstrated that increased ovarian 18F-FDG uptake occurs mainly 10–25 days after the onset of menstruation, which corresponds to the late follicular, ovulatory, and early to mid-luteal phases. Our results do not differ from those of previous studies. In our study, ovarian 18F-FDG uptake was highest at 2 weeks after the onset of menstruation, when the follicle is actively proliferating, implying 18F-FDG uptake by the pre-ovulatory follicle. In addition, ovarian 18F-FDG uptake was higher during the luteal phase than during the follicular phase, which may have been due to increased 18F-FDG uptake by the corpora lutea in this phase. A possible reason for the increased 18F-FDG uptake by the pre-ovulatory follicle and corpus luteum is as follows. Active growth of pre-ovulatory follicles has been associated with increased metabolic demand and glucose-transporter-3 expression, which is regulated by interleukin-1β during the peri-ovulatory phase, leading to increased 18F-FDG uptake.

Angiogenesis and the cytokine-mediated inflammatory reaction have been suggested as being involved in 18F-FDG uptake by the

| Parameters       | Correlation with SUVmax of ovary | Correlation with SUVmean of ovary |
|------------------|----------------------------------|----------------------------------|
| Age              | 0.12 (0.07-0.30)                 | 0.235 (0.13-0.32)                |
| Estradiol        | 0.07 (0.24-0.38)                 | 0.657 (0.01-0.28)                |
| Progesterone     | 0.29 (0.09-0.45)                 | 0.003                       |
| Testosterone     | -0.08 (-0.27-0.12)               | 0.428 (0.13-0.07)               |
| FSH              | -0.18 (-0.37 to -0.01)           | 0.082 (0.18-0.10)               |
| LH               | 0.07 (-0.24-0.38)                | 0.657 (-0.01-0.28)              |

**TABLE 2. Correlation between ovarian 18F-FDG uptake and sex hormone levels**

- p < 0.05
- CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SUVmax = maximum standardized uptake value; SUVmean = mean standardized uptake value

and pregnancy from the late proliferative phase to the luteal phase. The finding that progesterone levels correlated with ovarian glucose metabolism in the follicular phase may be explained as follows. During most of the follicular phase, progesterone is secreted from the adrenal cortex; this secretion is regulated by unknown elements in the ovary. Progesterone secretion switches from the adrenal cortex to the ovaries before ovulation. In other words, progesterone secretion during the follicular phase is the result of a complex interaction between the adrenal cortex and the ovaries, which may account for the correlation between progesterone levels and ovarian glucose metabolism during this period. We acknowledge that this hypothesis is speculative and further research will be needed for confirmation. Estradiol and FSH, which play important roles in follicular growth, and LH, which plays a key role in ovulation, were not correlated with ovarian 18F-FDG uptake; this has rarely been reported, so interpreting this finding is difficult. The relationship between the ovaries and sex-hormone levels is very complex and therefore difficult to elucidate. This study is significant in that it is the first to reveal a relationship between ovarian 18F-FDG uptake and sex hormone levels, but more research will be needed to clarify the mechanism of their relationship.

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Angiogenesis and the cytokine-mediated inflammatory reaction have been suggested as being involved in 18F-FDG uptake by the ovaries.
corpus luteum, because the mechanism of corpus luteal formation is similar to those of wound healing and tumour formation. In our study, the lowest 18F-FDG uptake observed was at 1 week after the onset of menstruation, which may have been due to lower 18F-FDG uptake in small follicles before growth.7

This study included only subjects with regular menstrual cycles, and excluded those who had a menstrual cycle exceeding 31 days. Patients with irregular menstrual cycles were excluded from the study because of a concern that their sex hormones would not be in balance. Most previous reports included subjects with irregular menstrual cycles5,8,9, and the results of those studies are likely to have been biased accordingly. Therefore, a strength of the present study was that it excluded such subjects.

In this study, progesterone was higher in the luteal-phase group than in the follicular-phase group, while FSH levels were significantly higher in the follicular-phase group than in the luteal-phase group. Changes in sex hormones during the menstrual cycle have been well documented, and the high progesterone levels observed during the luteal phase and elevated FSH levels observed during the follicular phase are consistent with previous data.10 The results demonstrate that the self-reported LNMP data of our subjects accords with the actual levels of the sex hormones, thus demonstrating the accuracy and objectivity of this study.

The limitations of this study were as follows. First, the ovarian status of the subjects was evaluated using non-contrast enhanced CT, as part of the PET/CT examination. The ovary can be examined more precisely by contrast-enhanced CT, MRI, or ultrasonography, but this study was retrospective, so it was not possible to perform these radiological examinations in all patients. However, the ovaries of the subjects showed no pathological lesions on non-enhanced CT. Future studies will require more detailed radiological examinations to validate our results. Second, this study did not report results regarding uterine 18F-FDG uptake, although numerous studies have reported 18F-FDG uptake by the endometrium as well as the ovaries.5,6,8,20 However, in our study, many subjects had small or large uterine myomas (51/197; 25.8%), so it was difficult to determine normal uterine 18F-FDG uptake. Myomas are associated with varying levels of 18F-FDG uptake, so we judged that assessing physiological uterine 18F-FDG uptake would be problematic. Finally, this study included patients with breast cancer, but the design might have been more appropriate for healthy volunteers; unfortunately, we were constrained to retrospective use of 18F-FDG PET/CT data in patients with breast cancer, albeit that we attempted to evaluate physiological ovarian uptake by omitting patients who had a previous history of ovarian disease or hormone therapy.

Conclusions

Ovarian 18F-FDG uptake in premenopausal women was positively correlated with progesterone levels. This correlation was detected during the follicular phase of the menstrual cycle, while the other sex hormones measured (estradiol, testosterone, FSH, and LH) were not associated with ovarian 18F-FDG uptake.

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