Change in metabolic parameters and reproductive hormones from baseline to 6-month hormone therapy

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Abstract
Adequate evidence showed hormone therapy (HT) reduces the risk of new-onset diabetes in midlife women by decreasing fasting glucose and insulin. However, the improvement of these diabetic biomarkers varied with each individual in clinical observations. The objective of our study was to investigate potential baseline factors associated with the change of fasting glucose and insulin during HT.

A retrospective cohort study was performed among 263 midlife participants aged 40 to 60 years with menopausal symptoms who have received 6-month individualized HT. Demographic information and laboratory indicators including reproductive hormone, lipid profiles, diabetic indicators were collected and measured at baseline and were followed-up. A series of statistical analyses were performed to confirm the effectiveness of HT and compare the baseline factors between participants with different glycemic or insulinemic response. Multivariable linear regression model with stepwise variable selection was further used to identify the associated factor with the change of fasting glucose and insulin.

Of all participants, fasting glucose \((P = .001)\) and fasting insulin \((P < .001)\) were significantly decreased after individualized HT. Significant differences in baseline reproductive hormones were observed in participants with different glycemic response to HT \((P < .001\) for both follicle stimulating hormone \([FSH]\) and estradiol). Stepwise linear regression model showed that in addition to baseline fasting glucose levels, baseline FSH was also independently associated with the change of fasting glucose \((\beta = -0.145, P = .019 \text{ for baseline FSH})\) but not fasting insulin. Greater reduction in fasting glucose in women with higher FSH levels was observed even though they have already been in better metabolic conditions \((P = .037)\).

Midlife women with higher baseline FSH levels have greater reduction in fasting glucose but not fasting insulin. FSH could be an independent predictor of glycemic response to HT in peri- and postmenopausal women.

Abbreviations: BMI = body mass index, FG = fasting glucose, FI = fasting insulin, FSH = follicle stimulating hormone, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance, HT = hormone therapy.

Keywords: fasting glucose, fasting insulin, follicle stimulating hormone, hormone therapy, menopause

1. Introduction
Menopause characterized by exhaustion of ovarian sex hormones is a milestone for women, which accelerates chronological aging.\textsuperscript{[1]} As life expectancy increases, the long-term management of chronic disease like type 2 diabetes has gradually become a critical public health issue. For a time, increasing incidence of diabetes in postmenopausal women was seen as a concomitant phenomenon of chronological aging.\textsuperscript{[2,3]} However, the prepon-
derance of the evidence implicated that menopausal estrogen deficiency might play a role in the increased risk of diabetes.\textsuperscript{[4–6]}

Hormone therapy (HT) has been an effective treatment to alleviate menopausal symptoms such as hot flashes, insomnia, and bone loss. Besides, HT also has favorable effects on glycemic control among midlife women. Several well-known large HT-randomized controlled trial studies showed a 12\% to 35\% reduction in the incidence of diabetes among baseline non-diabetic women receiving HT,\textsuperscript{[7–9]} despite that an increased postchallenge glucose concentrations was observed.\textsuperscript{[10–12]} Further investigations revealed that this antidiabetic effect of HT was mainly attributed to a lower fasting glucose and better insulin sensitivity in women receiving HT.\textsuperscript{[11,13–15]}

However, the currently approved indications for HT excluded improvement of hyperglycemia and protection against Type 2 diabetes mellitus.\textsuperscript{[16]} It is not only because of inadequate evidence of randomized controlled trials examining HT on diabetes prevention as a primary outcome, but also partially due to incomplete understanding of the potential factors affecting the improvement of HT on glycemic and insulimic indicators. Especially in clinical observations, glycemic improvement after HT was significant but still varied from person to person.

Therefore, the aim of our study was to evaluate the potential baseline factors associated with the change of fasting glucose and insulin after HT in peri- and postmenopausal women. We thereby conducted a retrospective cohort study of 263 non-diabetic women to identify the related determinants for predicting the improvement.

2. Materials and methods

2.1. Study population and data collection

From October 2010 to November 2017, 2260 women with menopausal somatic symptoms asking for HT were recruited at the Department of Gynecology at Women’s Hospital of Zhejiang University located in Hangzhou, Zhejiang Province, China. Only patients who have never received HT before the first visit were included. The sociodemographic characteristics, gynecological history, and medical history were collected through a face-to-face interview. Every patient was given a thorough measurement of anthropometric, endocrinological, and metabolic parameters including weight, height, waist and hip circumferences, sex hormones, lipid, and glycemic profiles. Height and weight were measured in light clothing without shoes using a stadiometer and a calibrated scale. Waist circumference was the measurement taken around the abdomen at the level of the umbilicus. Hip circumference was measured at the level of the widest circumference over the great trochanters.\textsuperscript{[17]} Anthropometric information was collected by trained interviewers.

Patients were recommended to revisit the doctors to evaluate the therapeutic effect in 6 months. The purpose of this retrospective cohort study was to track HT users’ menopausal transition and therapeutic process; to investigate influencing factors associated with individual differences of HT response. Good glycemic/insulimic response to HT means fasting glucose/insulin has decreased after 6-month HT, while poor response means fasting glucose/insulin has increased or not changed.

Considering that the onset of metabolic improvements lagged behind the reliefs of somatic symptoms, baseline, and 6-month follow-up medical records of these patients were accessed to conduct data analyses. Women who revisited our clinic for 6-month follow-up and provided blood samples after overnight fasting were included in this study. Therefore, the medical records of 369 women were retrieved. Since re-examination was non-obligatory, 1891 women did not revisit hospital on time after 6 months. The further exclusion criteria of this study included: aged <40; with use of hormones in the last 3 months at first visit; history of bilateral oophorectomy or hysterectomy; present or past history of malignant tumors; missing values of FSH or both of fasting insulin and glucose at baseline; previous diabetes histories or any anti-diabetes drug use; medication adjustment after the first month or with poor medication compliance. Finally, a total of 263 patients were included in our retrospective cohort study. Selection flowchart was showed in Fig. 1.
2.2. Ethical approval

Informed consent was obtained from every participant at the initial interview. This study protocol was approved by the ethical committee of Women’s Hospital, School of Medicine, Zhejiang University (No. 20170187).

2.3. Hormone therapy

HT regimen and dose were individually formulated under integrative consideration of multiple factors, such as age, menopausal status, symptom severity, medicine availability in local clinics, and personal preference. For example, low dose was most commonly used, while ultra-low dose was usually prescribed in the further adjustment of treatment scheme in order to attain the optimization of HT regimen for those who had concerns for estrogen use. Standard doses were more likely to be prescribed if earlier onset of menopausal symptoms, in which age 45 could be an empirical threshold for the definition of early menopause. Sequential progestogen regimen was more likely to be adopted for perimenopausal women who had ever menstruated in the last few months, while continuous progestogen regimen or tibolone was for postmenopausal women. However, personal preferences (i.e., whether maintaining menstruation or not, administration route) and medicine availability would also be taken into consideration for final HT regimen. Moreover, HT regimen and dose would be adjusted and settled to reach a balance between symptom relief and personal preference within the first month of treatment. Referring to the methods of the previous studies,[18] the type of HT used (combined estradiol with dydrogesterone or tibolone), medical regimens (continuous or sequential progestogen), dose of HT (standard, low, ultra-low dose), route of administration (oral or transdermal) were used to describe individualized medication and be analyzed among glycemic-response associated factors. Tibolone was considered as continuous progestogen and dose of HT was categorized according to the previous article.[19]

2.4. Menstrual status

Based on self-reports of menstrual history and serum hormone test, menopausal status was defined according to the Stages of Reproductive Aging Workshop +10 (STRAW+10).[20] Perimenopause is defined as the period that begins at Stage-2 and ends 12 months after the final menstrual period which includes Stage-2, -1, and +1a. Stage-2 is characterized as persistent difference of 7 days or more in the length of consecutive cycles. Persistence is defined as recurrence within 10 cycles of the first variable length cycle. Stage-1 is marked by the occurrence of amenorrhea of 60 days or longer and with FSH levels greater than 25 IU/L. Post-menopause was defined as complete cessation of menstruation over 12 months which includes Stage +1b and beyond here.

2.5. Biochemical measurements

Blood samples were collected at baseline and every follow-up after overnight fasting. If women had menopausal symptoms who had menstrual cycles, blood samples were collected on days 2 to 5 of the follicular phase. If not, blood was collected at the time of interview. The reproductive hormones were determined by an automated Roche Modular Analytics E170 analyzer (Roche Diagnostics, Mannheim, Germany). Metabolic profiles were determined by an Architect c16000 automated analyzer (Abbott Laboratories, Abbott Park, IL).

2.6. Statistical analysis

We analyzed all of the data with IBM SPSS statistics, version 24 (IBM corporation, Armonk, NY). A 2-sided P-value <.05 was considered significant. Demographic characteristics, hormones levels, and metabolic markers at baseline and 6-month follow-up were presented. The normality of all continuous indicators was examined by Shapiro–Wilks test. Thus, the normally distributed variables were presented as mean±SD. They were compared using student t test between the 2 groups or using paired-sample t test when analyzing the improvement before and after HT. The variables that did not meet the normality were summarized as median with interquartile range. They were compared using Mann–Whitney U test between the 2 groups or using paired t test/ Wilcoxon signed-rank test when analyzing the improvement before and after HT. Categorical variables were showed as number with proportion and compared using Pearson chi-squared test between the 2 groups. The change of fasting glucose (FG) was defined as $\Delta$fasting glucose formulated as FG$_{\text{after HT}}$– FG$_{\text{baseline}}$. So was the change of fasting insulin (FI). Glycemic and insulinemic response to HT were stratified by the change of fasting glucose and insulin bordered by 0. A Crude model was established which included potential variables such as age, body mass index (BMI), and baseline fasting glucose/insulin. Stepwise linear regression model was adopted to screen out the significant factors in the change of FG and FI based on crude model. All demographic information, reproductive hormones, and metabolic parameters at baseline and follow-up were included in the models. To investigate the role of baseline FSH in glucometabolic response to HT, the population was dichotomized according to median FSH level into low- and high-FSH group.

3. Results

3.1. Baseline characteristics of study participants and effectiveness of hormone therapy

Baseline characteristics and medication regimens of study participants receiving HT were presented in Table 1. Study participants with the median (interquartile) age of 49.00 (44.00, 52.00) have FSH and estradiol respectively at the median of 52.00) have FSH and estradiol respectively at the median of 76.53 IU/L and 27.19 pmol/L. Individualized HT regiments were formulated for these 263 participants according to age, severity of menopausal symptoms, menstruation change, and personal preferences. Among this population, 149 (56.7%) women were perimenopausal while 114 (43.3%) were postmenopausal. As shown in Table 2, fasting glucose ($P=.001$) and insulin ($P < .001$) were significantly improved after 6-month HT as well as the other metabolic parameters except for high-density lipoprotein ($P = .264$). Increased serum estradiol levels and decreased FSH were observed proving for effective sex hormones replacement ($P < .001$ for both).

3.2. Comparison of baseline characteristics according to glycemic and insulinemic response

In order to figure out the related factors with the improvement of diabetic biomarkers, glycemic and insulinemic response to HT were stratified by the change of fasting glucose and insulin...
Table 1  
Baseline characteristics of the 263 women receiving hormone treatment.

| Characteristics          | Values |
|--------------------------|--------|
| N                        | 263    |
| Age, y                   | 40.00 (44.00–52.00) |
| Age of menarche, y       | 14.00 (13.00–16.00) |
| FSH, IU/L                | 76.53 (59.90–100.20) |
| Estradiol, pmol/L        | 27.19 (18.35–72.72) |
| Menopause status         |        |
| Perimenopause            | 149 (56.7) |
| Postmenopause            | 114 (43.3) |
| Education                |        |
| Urban                    | 188 (76.7) |
| Suburb                   | 37 (15.1) |
| Rural                    | 20 (8.2) |
| Economic status (yuan/mo) |      |
| <20000                   | 39 (17.3) |
| 2000–5000                | 113 (50.2) |
| >5000                    | 73 (32.4) |
| Occupation               |        |
| Full-time                | 147 (60.5) |
| Part-time                | 21 (8.6) |
| Unemployed or retired    | 75 (30.9) |
| BML, kg/m²               | 2.157 (20.12–23.22) |
| Waist circumference, cm  | 74.03 ± 6.55 |
| Waist-to-hip ratio       | 0.81 ± 0.05 |
| Medication regimens      |        |
| Continuous or tibolone-used | 52 (19.8) |
| Sequential               | 211 (80.2) |
| Route of estrogen adm     |        |
| Oral                     | 240 (91.3) |
| Transdermal              | 23 (8.7) |

BMI= body mass index, FSH=follicle stimulating hormone.

Table 2  
Metabolic parameters and reproductive hormones before and after 6-month HT.

| Metabolic parameters          | Baseline | 6-month follow-up | ΔDifference | P-value |
|-------------------------------|----------|-------------------|-------------|---------|
| Fasting glucose, mmol/L       | 5.29 (5.01–5.54) | 5.16 (4.93–5.46) | -0.1 (-0.37, 0.165) | .001 |
| Fasting insulin, mU/L         | 5.20 (4.18–6.90) | 4.90 (3.70–6.30) | -0.5 (-1.8, 0.75) | <.001 |
| HOMA-IR                       | 1.24 (0.96–1.65) | 1.14 (0.84–1.51) | -0.106 (-0.46, 0.196) | <.001 |
| LDL-Cholesterol, mmol/L       | 2.66 ± 0.64 | 2.56 ± 0.65 | -0.11 (-0.413, 0.19) | .001 |
| HDL-Cholesterol, mmol/L       | 1.53 (1.30–1.78) | 1.54 (1.30–1.76) | 0.03 (-0.12, 0.172) | .264 |
| Triglycerides, mmol/L         | 0.95 (0.75–1.34) | 0.92 (0.68–1.24) | -0.05 (-0.312, 0.203) | .027 |
| Total cholesterol, mmol/L     | 5.16 ± 0.84 | 4.89 ± 0.79 | -0.22 (-0.57, 0.153) | <.001 |
| ApoA1, g/L                    | 1.43 (1.29–1.63) | 1.47 (1.30–1.67) | 0.045 (-0.098, 0.167) | .108 |
| ApoB, g/L                     | 0.89 ± 0.20 | 0.84 ± 0.20 | -0.04 (-0.13, 0.05) | <.001 |
| Lipoprotein(a), mg/dL         | 197.00 (122.50–371.25) | 155.50 (85.25–292.00) | -38.5 (-106.5, 10.75) | <.001 |
| Reproductive hormones         |        |                   |             |         |
| FSH, IU/L                     | 76.53 (59.90–100.20) | 53.29 (36.01–70.26) | -24.9 (-43.132, -8.968) | <.001 |
| Estradiol, pmol/L             | 27.19 (18.35–72.72) | 129.40 (59.22–243.77) | 73.8 (1.445, 192.365) | <.001 |

HOMA-IR=Fasting glucose × Fasting insulin/22.5
ApoA1=apolipoprotein A1, ApoB=apolipoprotein B, HDL-C=high-density lipoprotein, HOMA-IR=Homeostatic Model Assessment for Insulin Resistance, LDL-C=low-density lipoprotein. 
* Wilcoxon rank-sum test.
† Paired t test.

3.3. Multivariable stepwise linear regression models to investigate the related factors with the improvement of diabetic biomarkers

We next examined the change of fasting glucose/insulin in relation to all variables using stepwise linear regression (Table 5). After stepwise selection for variables including demorographics, metabolic indicators and sex hormones, only baseline FSH (β = -0.159, P = .008) remained significant in the model of fasting glucose, while baseline estradiol lost significance. When we conducted the same analyses of the change of fasting insulin, baseline fasting insulin (β = -0.729, P < .001), BMI (β = 0.276, P < .001), HDL (β = -0.138, P = .016), and regimens (β = 0.146, P = .020) were found to be related to ΔFasting insulin. However, it was showed that both reproductive hormones were excluded in this stepwise model which was distinguished from the analyses of the change of fasting glucose above. BMI reached notable significance in the analyses of ΔFasting insulin, while no interaction was found between BMI and ΔFasting glucose (stepwise model of ΔFasting insulin: β = 0.276, P < .001, stepwise model of ΔFasting glucose: β = 0.072, P = .239).

3.4. Comparison of baseline characteristics, the change of fasting glucose and insulin in FSH-dichotomized groups

Thus, considering that the extragonadal role of FSH was being gradually revealed, the potential association between baseline bordered by 0 (Tables 3 and 4). Relatively high fasting glucose levels were observed in participants with good glycemic response to HT (P < .001, good vs poor glycemic response), as well as fasting insulin (P = .039) and Homeostatic Model Assessment for Insulin Resistance (P = .002), which together indicated a relative worse glycemic status. Surprisingly, baseline serum FSH and estradiol turned out to have great statistical significance between the groups with different glycemic responses (both P < .001). However, this kind of difference was absent between the groups of good and poor insulimic responses (Table 4). Thus, we would take further steps to investigate the association of these 2 reproductive hormones with the change of fasting glucose.
Baseline reproductive hormones
FSH, IU/L 80.80 68.28 <.001
(66.97–106.15) (49.81–96.25)
Estradiol, pmol/L 24.31 40.94 <.001
(18.35–182.83) (18.35–160.25)

Ap0A1 = apolipoprotein A1, Ap0B = apolipoprotein B, BMI = body mass index, FSH = follicle stimulating hormone, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance.

FSH and the change of fasting glucose through HT was further investigated. The whole population was dichotomized into 2 groups according to baseline FSH. All demographic characteristics, metabolic factors, and reproductive hormones were compared respectively (Table 6). There was significant difference in ΔFasting glucose (P = .037) but not ΔFasting insulin (P = .669) between high and low-FSH group (Table 6, Fig. 2). In addition, the distribution of individual with different glycemic responses was significantly different between the 2 groups (P = .007), while that of insulineemic response was not (P = .861). These above reconfirmed the findings of the stepwise regression models in another perspective. What deserves to be mentioned is that participants in the high FSH group tended to be postmenopausal and have lower BMI, waist circumference, and higher HDL.

4. Discussion
In this study, higher baseline FSH levels were associated with greater beneficial changes of fasting glucose but not fasting insulin after 6-month hormone therapy. These associations persisted after controlling for baseline fasting glucose, a potential significant factor. Other baseline metabolic indicators, estradiol,
and medication regimens were examined to be not involved with the improvement of fasting glucose. Taken together, our study showed that FSH level at baseline was an independent influencing factor in the glycemic response to hormone therapy.

Linear regression model used in the analyses preserved baseline fasting glucose and FSH as the associated factors of the change of fasting glucose among various potential influencing parameters. It is reasonable to observe that high baseline fasting glucose leads to greater reduction. In a meta-analysis of 107 HT randomized trials, a 2.5% reduction of fasting glucose and a 9.3% reduction of fasting insulin were observed after HT among women without diabetes. The reduction of fasting glucose was almost twice as much as that in our study (median 1.7% reduction of FG), while the reduction of fasting insulin was similar with that in our study (median 10.0% reduction of FI). This reduction was much more pronounced in diabetic women with high fasting glucose reported by this article. In the preliminary PEPI study, the greatest benefit for glycemic control from HT was obtained in the women with the highest levels of fasting glucose and insulin. In line with these studies, baseline fasting glucose appeared to be the most significant factor in the model with the standardized coefficient $\beta$ of $-0.574$ (stepwise model, $P < .001$, Table 5).

Table 5

| Dependent variables | Crude model* | Standardized $\beta$ | P-value | Stepwise model† | Standardized $\beta$ | P-value |
|---------------------|--------------|----------------------|---------|-----------------|----------------------|---------|
| $\Delta$ Fasting glucose | Constant | $-$ | $<.001$ | Constant | $-$ | $<.001$ |
|                     | Age         | $-0.086$             | $0.147$ | Age             | $-0.080$             | $0.166$ |
|                     | BMI         | $-0.145$             | $0.049$ | BMI              | $0.072$             | $0.239$ |
|                     | Baseline fasting glucose | $-0.589$             | $<.001$ | Baseline fasting glucose | $-0.574$             | $<.001$ |
| $\Delta$ Fasting insulin | Constant | $-$ | $0.102$ | Constant | $-$ | $0.597$ |
|                     | Age         | $0.005$              | $0.932$ | Age              | $-0.068$             | $0.275$ |
|                     | BMI         | $0.294$              | $<.001$ | BMI              | $0.276$             | $<.001$ |
|                     | Baseline fasting insulin | $-0.703$             | $<.001$ | Baseline fasting insulin | $-0.729$             | $<.001$ |

BMI = body mass index, FSH = follicle stimulating hormone, HDL-C = high-density lipoprotein.
* Age, BMI and baseline fasting glucose or insulin are potential relevant variables which are included in the crude model.
† Included variables for stepwise selection: demographics (age of menarche, menopause status, residence area, economic status, education, occupation), baseline metabolic factors (E2, FSH, fasting insulin or HOMA-IR, LDL-C, HDL-C, triglycerides, total cholesterol, apoA1). If fasting insulin was included in the crude model, HOMA-IR was dispensable for stepwise selection. It is because that these 2 biomarkers were highly correlated (r for spearman correlations = 0.983, $P < .001$).

Ischaemic Heart Disease Risk Factor (IHFD) conducted in Finland between 1998 and 2008, found the relationship between higher FSH at baseline and lower fasting insulin at follow-up approximately 7 years later which suggested better insulin sensitivity.[24] These findings indicated that baseline FSH could be a potential predictor of diabetes predisposition in the remaining life of menopausal women.

Accumulating evidence showed that high FSH could be a protective biomarker against metabolic disorders. Metabolic syndrome (MetS) is characterized as abdominal obesity, elevated blood pressure, hyperglycemia, high triglyceride, and low high-density lipoprotein. FSH was found to be significantly inversely associated with the probability of incident MetS after adjusting for MetS-associated features in postmenopausal women.[25] Consistent with previous studies, lower BMI, smaller waist circumference, and higher HDL were observed in the high FSH group which suggested better metabolic profiles (Table 6). It was worth mentioning that in our study no difference was detected in fasting glucose ($P = .828$) and fasting insulin ($P = .063$) at baseline after FSH dichotomization, which slightly disagrees with the results of SPECT-China.[22] This could be attributed to the different population sources. The population in SPECT-China was selected based on the age over 55 and considered as postmenopausal, whereas our study sample was perimenopausal or postmenopausal people willing to receive HT. However, greater fasting glucose reduction ($P = .037$, Table 6) after individualized HT was observed in the high-FSH group despite the absence of difference in fasting glucose at baseline, which was consistent with the results of linear model.

FH is likely to have a long-standing influence on extragonadal tissues independent of estrogen as evidenced by recent laboratory and clinical studies. The latest laboratory findings reported by Quinn et al.[26] highlighted the role of FSH in the induction of hepatic glucocorticoid (GC) hypersensitivity in the hypothalamic female mice independent of estrogen. Given that GC is well known to promote hepatic gluconeogenesis, the decreased GC sensitivity after HT could be caused by greater reduction of FSH. In addition, FSH was found to enhanced hepatic gluconeogenesis through GRK2-mediated AMPK hyperphosphorylation.[27]
Thus, greater reduction of FSH in the high FSH group (Table 6, \( P < .001 \)) can be an explanation of better glycemic responses. Moreover, it also indicated that FSH may be more a protective factor associated with insulin resistance. On the other hand, lower FSH was linked to increasing BMI, which disagree with previous studies to some extent. Our study also provided evidence that FSH could be a full mediator of association between FSH and the reduction of fasting insulin that represented improving insulin sensitivity.

In our study, association of FSH with insulin did not attain significance, which disagree with previous studies to some extent. Baseline FSH levels in postmenopausal women was inversely correlated with fasting insulin whether at baseline or approximately 7 years later.\(^{24,25}\) However, there were some aspects that could not be neglected. Firstly, the most important is that FSH change and metabolic improvement during hormone therapy was not their interest in these previous studies. Secondly, the majority of our study was metabolically healthy but suffered from menopausal symptoms, while the studies mentioned above either was population-based or focused on patients with metabolic syndrome. In the stepwise regression model of \( \Delta \)Fasting insulin, BMI was a significant factor (\( \beta = 0.276, P < .001, \) Table 5). On the one hand, BMI was a measure of fat distribution that was related with insulin resistance. On the other hand, lower FSH was generally observed in obesity partially due to increased production of estrogen by adipose tissue.\(^{29-31}\) So, BMI could be a full mediator of association between FSH and the reduction of fasting insulin that represented improving insulin sensitivity. However, the significance of FSH persisted in the analyses of \( \Delta \)Fasting glucose while that of BMI lost. This probably suggested the independent role of FSH in the glucose metabolism additionally.

Our study has some strengths. This is the first study to identify FSH as an independent determinant in the glycemic response to HT. Currently, instead of estrogen replacement only, FSH has come up to be expected as a novel target for co-treating obesity and osteoporosis in menopausal women. Further exploration of the extragonadal role of FSH in the glucose metabolism was warranted. Another strength of our study was the extensive information on biochemical and clinical factors, which enable us to evaluate potential confounding and effect modification in the stepwise linear regression model.

Our study has some limitations as well. Firstly, the duration of HT use was not a variable through the whole analyses. Our study only assessed the association of FSH with the reduction of fasting glucose between 6-month follow-up and baseline. However, it was enough to observe metabolic improvement during 6-month...
HT in clinical observations. Secondly, our conclusion may be limited because of moderate sample size and generally metabolically healthy participants. Thirdly, it cannot be denied that a single blood sample for sex hormone in only a menstrual cycle was not enough to make a validated conclusion. Finally, selection bias and follow-up bias might be inevitable owing to the nature of our clinic-based retrospective design and non-obligatory reevaluation during HT treatment. More evidence would be needed to determine both the reproducibility and clinical importance in the future.

5. Conclusions

To our knowledge, this is the first clinic-based study to illustrate the role of FSH as a predictor of glycemic response to HT in midlife women. These results suggest that women with higher baseline FSH levels may be more likely to have greater reduction in fasting glucose even though they have already been in better metabolic conditions. Identifying the predicting role of FSH in HT may not only advance the understanding of its extragonadal effect, but also help establish the population whose metabolic profiles would benefit from HT. However, due to the limitations of our study, the potential clinical implications are still uncertain. Additional researches are warranted to validate our conclusion and make clear whether prevention of diabetes should be included in the indications of HT.

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