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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 ($\beta = -0.145$, $P = .019$ 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.[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.[2,3] However, the prepon-

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derance of the evidence implicated that menopausal estrogen deficiency might play a role in the increased risk of diabetes.[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,[7–9] despite that an increased postchallenge glucose concentrations was observed.[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.[11,13–15]

However, the currently approved indications for HT excluded improvement of hyperglycemia and protection against Type 2 diabetes mellitus.[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 insulinemic 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.[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/insulinemic 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.

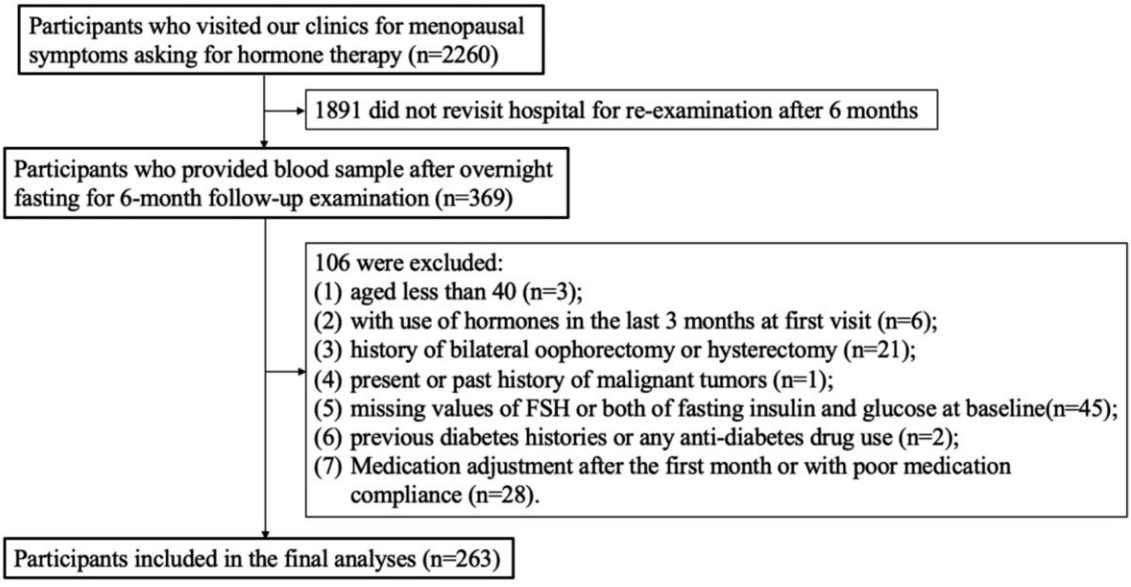

Figure 1. Flowchart of participant selection in our study.

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. Postmenopause 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 with menopausal symptoms 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-Wilk 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 Δfasting glucose formulated as $FG_{afterHT} - FG_{baseline}$. 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 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.

N	263
Age, y	49.00 (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)
Residence area	
Urban	188 (76.7)
Suburb	37 (15.1)
Rural	20 (8.2)
Economic status (yuan/mo)	
<2000	39 (17.3)
2000–5000	113 (50.2)
>5000	73 (32.4)
Education	
Primary or middle school	61 (25.0)
High school	88 (36.1)
College or beyond	95 (38.9)
Occupation	
Full-time	147 (60.5)
Part-time	21 (8.6)
Unemployed or retired	75 (30.9)
BMI, kg/m^2	21.57 (20.12–23.23)
Waist circumference, cm	74.03 ± 6.55
Waist-to-hip ratio	0.81 ± 0.05
Medication regimens	
The type of HT used	
Combined estradiol with dydrogesterone	221 (84.0)
Tibolone	42 (16.0)
The regimens	
Continuous or tibolone-used	52 (19.8)
Sequential	211 (80.2)
Dose of HT	
Standard dose	8 (3.0)
Low dose	195 (74.1)
Ultra-low dose	60 (22.8)
Route of estrogen administration	
Oral	240 (91.3)
Transdermal	23 (8.7)

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

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 insulinemic responses (Table 4). Thus, we would take further steps to investigate the association of these 2 reproductive hormones with the change of fasting glucose.

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 demorgraphics, metabolic indicators and sex hormones, only baseline FSH ($\beta = -0.159$, $P = .008$) 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 ($\beta = -0.729$, $P < .001$), BMI ($\beta = 0.276$, $P < .001$), HDL ($\beta = -0.138$, $P = .016$), and regimens ($\beta = 0.146$, $P = .020$) 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: $\beta = 0.276$, $P < .001$, stepwise model of ΔFasting glucose: $\beta = 0.072$, $P = .239$).

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

Table 2

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

	Baseline	6-month follow-up	ΔDifference	*P*-value
Metabolic parameters				
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	–0.1 (–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)	.018
ApoB, g/L†	0.88 ± 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.

Table 3

Comparison between good and poor glycemic response in baseline characteristics.

	Glycemic response		
	Good	Poor	*P*-value
ΔFasting glucose, mmol/L	≤0	>0	
N	153	102	
Demographics			
Age, y	49.00 (44.50–52.00)	48.00 (44.00–51.00)	.109
Age of menarche, y	14.00 (13.00–16.00)	14.00 (14.00–15.75)	.650
Menopause status		0.099	
Perimenopause	80 (52.3)	64 (62.7)	
Postmenopause	73 (47.7)	38 (37.3)	
Residence area		0.044	
Urban	111 (77.6)	70 (73.7)	
Suburb	25 (17.5)	12 (12.6)	
Rural	7 (4.9)	13 (13.7)	
Economic status (yuan/mo)		0.601	
<2000	25 (19.2)	14 (15.9)	
2000–5000	62 (47.7)	48 (54.5)	
>5000	43 (33.1)	26 (29.5)	
Education			.684
Primary or middle school	34 (24.1)	27 (28.1)	
High school	54 (38.3)	32 (33.3)	
College or beyond	53 (37.6)	37 (38.5)	
Occupation		0.585	
Full-time	85 (59.9)	55 (59.1)	
Part-time	10 (7.0)	10 (10.8)	
Unemployed or retired	47 (33.1)	28 (30.1)	
Baseline metabolic factors			
BMI, kg/m^2	21.48 (20.07–23.19)	21.68 (20.27–23.28)	.351
Waist circumference, cm	74.03 ± 6.17	73.84 ± 7.11	.823
Waist-to-hip ratio	0.81 ± 0.05	0.81 ± 0.04	.955
Fasting glucose, mmol/L	5.41 (5.16–5.65)	5.12 (4.81–5.37)	<.001
Fasting insulin, mU/L	5.55 (4.30–7.28)	4.95 (4.10–6.40)	.039
HOMA-IR	1.32 (1.03–1.80)	1.11 (0.86–1.50)	.002
LDL-Cholesterol, mmol/L	2.70 ± 0.63	2.59 ± 0.66	.171
HDL-Cholesterol, mmol/L	1.54 (1.31–1.75)	1.48 (1.28–1.79)	.539
Triglycerides, mmol/L	0.97 (0.75–1.42)	0.94 (0.73–1.32)	.511
Total cholesterol, mmol/L	5.21 ± 0.83	5.08 ± 0.85	.237
ApoA1, g/L	1.45 (1.29–1.66)	1.41 (1.29–1.60)	.493
ApoB, g/L	0.89 ± 0.20	0.87 ± 0.21	.515
Lipoprotein(a), mg/dL	205.00 (123.75–385.50)	194.00 (116.50–349.50)	.315
Baseline reproductive hormones			
FSH, IU/L	80.80 (66.97–106.15)	68.28 (49.81–96.25)	<.001
Estradiol, pmol/L	24.31 (18.35–182.83)	40.94 (18.35–160.25)	<.001

ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, BMI = body mass index, FSH = follicle stimulating hormone, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance.

Table 4

Comparison between good and poor insulinemic response in baseline characteristics.

	Insulinemic response		
	Good	Poor	*P*-value
ΔFasting insulin, mU/L	≤0	>0	
N	153	99	
Demographics			
Age, y	49.00 (44.00–51.00)	49.00 (45.00–52.00)	.743
Age of menarche, y	14.00 (13.00–15.25)	14.00 (14.00–16.00)	.557
Menopause status			.352
Perimenopause	91 (59.5)	53 (53.5)	
Postmenopause	62 (40.5)	46 (46.5)	
Residence area			.085
Urban	104 (72.2)	75 (83.3)	
Suburb	28 (19.4)	8 (8.9)	
Rural	12 (8.3)	7 (7.8)	
Economic status (yuan/mo)			.590
<2000	24 (18.2)	14 (16.5)	
2000–5000	65 (49.2)	42 (49.4)	
>5000	43 (32.6)	29 (34.1)	
Education			.088
Primary or middle school	42 (29.4)	18 (20.0)	
High school	43 (30.1)	39 (43.3)	
College or beyond	58 (40.6)	33 (36.7)	
Occupation			.545
Full-time	82 (58.6)	59 (64.1)	
Part-time	12 (8.6)	9 (9.8)	
Unemployed or retired	46 (32.9)	24 (26.1)	
Baseline metabolic factors			
BMI, kg/m^2	21.48 (20.00–23.31)	21.76 (20.34–23.23)	.743
Waist circumference, cm	73.99 ± 7.12	74.24 ± 5.82	.764
Waist-to-hip ratio	0.82 ± 0.05	0.82 ± 0.04	.920
Fasting glucose, mmol/L	5.33 (5.03–5.55)	5.26 (4.90–5.47)	.113
Fasting insulin, mU/L	6.00 (4.60–7.55)	4.50 (3.60–5.50)	<.001
HOMA-IR	1.41 (1.08–1.78)	1.02 (0.80–1.26)	<.001
LDL-Cholesterol, mmol/L	2.64 ± 0.64	2.69 ± 0.64	.558
HDL-Cholesterol, mmol/L	1.56 (1.31–1.80)	1.48 (1.29–1.71)	.270
Triglycerides, mmol/L	0.99 (0.79–1.35)	0.93 (0.74–1.45)	.549
Total cholesterol, mmol/L	5.16 ± 0.82	5.19 ± 0.87	.796
ApoA1, g/L	1.42 (1.30–1.67)	1.44 (1.28–1.59)	.908
ApoB, g/L	0.87 ± 0.20	0.89 ± 0.22	.513
Lipoprotein(a), mg/dL	194.00 (121.50–354.50)	209.00 (125.00–392.00)	.677
Baseline reproductive hormones			
FSH, IU/L	75.51 (64.71–101.83)	76.53 (53.04–97.48)	.148
Estradiol, pmol/L	25.23 (18.35–67.14)	32.10 (18.35–108.30)	.426

ApoA1 = apolipoprotein A1, ApoB = 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 insulinemic 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,

Table 5

Multivariable linear regression with stepwise variable selection for ΔFasting glucose and ΔFasting insulin (N = 263).

Dependent variables	Crude model*	Standar-dized β	*P*-value	Stepwise model†	Standar-dized β	*P*-value
ΔFasting glucose	Constant	–	<.001	Constant	–	<.001
	Age	−0.086	.147	Age	−0.080	.166
	BMI	−0.145	.049	BMI	0.072	.239
	Baseline fasting glucose	−0.589	<.001	Baseline fasting glucose	−0.574	<.001
				Baseline FSH	−0.159	.008
ΔFasting insulin	Constant	–	.102	Constant	–	.597
	Age	0.005	.932	Age	−0.068	.275
	BMI	0.294	<.001	BMI	0.276	<.001
	Baseline fasting insulin	−0.703	<.001	Baseline fasting insulin	−0.729	<.001
				Baseline HDL-C	−0.138	.016
				Regimens		
				Sequential	Reference category	
				Continuous	0.146	.020

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-Cholesterol, HDL-Cholesterol, triglycerides, total cholesterol, apoA1). If fasting insulin was included in the crude model, HOMA-IR was dispendable for stepwise selection. It is because that these 2 biomarkers were highly correlated (rs for spearman correlations = 0.983, $P < .001$).

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,[21] 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,[10] 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 β of −0.574 (stepwise model, $P < .001$, Table 5).

Standardized coefficients of baseline FSH (stepwise model, $\beta = -0.159$, $P = .008$, Table 5) in this model was negative which led to the conclusion that higher FSH was associated with greater beneficial change of fasting glucose in magnitude. To our knowledge, our study was the first one to illustrate that baseline FSH levels could be a potential determinant of glucometabolic improvement during HT in addition to baseline fasting glucose.

Emerging studies have explored the associations between FSH and diabetes in cross-sectional and longitudinal studies. From the cross-sectional analysis of SPECT-China, FSH and prevalence of diabetes in older postmenopausal women was found to be negatively correlated even adjusting for metabolic factors like adiposity.[22] The secondary analyses of Hong Kong Osteoporosis Study (HKOS) also demonstrated that higher baseline FSH was associated with reduced risk of incident diabetes during a median follow-up of 10.7 years.[23] In line with HKOS, Kuopio Ischaemic Heart Disease Risk Factor (KIHD) 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 ($P = .065$) 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.

FSH 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 hypogonadal 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]

Table 6

Characteristic comparison between high versus low-FSH group.

	FSH range		*P*-value
	≤76.53 IU/L	>76.53 IU/L	
N	132	131	
Demographics			
Age, y	48.00 (45.00–52.00)	49.00 (44.00–52.00)	.855
Age of menarche, y	14.00 (13.00–16.00)	14.00 (13.00–15.00)	.543
Menopause status			.041
Perimenopause	83 (62.9)	66 (50.4)	
Postmenopause	49 (37.1)	65 (49.6)	
Residence area			.994
Urban	95 (76.6)	93 (76.9)	
Suburb	19 (15.3)	18 (14.9)	
Rural	10 (8.1)	10 (8.3)	
Economic status			.848
<2000 RMB	20 (17.5)	19 (17.1)	
2000–5000 RMB	59 (51.8)	54 (48.6)	
>5000 RMB	35 (30.7)	38 (34.2)	
Education			.084
Primary or middle school	38 (31.1)	23 (18.9)	
High school	41 (33.6)	47 (38.5)	
College	43 (35.2)	52 (42.6)	
Occupation			.020
Full-time	65 (52.4)	82 (68.9)	
Part-time	11 (8.9)	10 (8.4)	
Unemployed or retired	48 (38.7)	27 (22.7)	
Baseline metabolic factors			
BMI, kg/m^2	22.18 (20.70–23.93)	20.90 (19.68–22.47)	<.001
Waist circumference, cm	75.88 ± 6.39	72.13 ± 6.18	<.001
Waist-to-hip ratio	0.83 ± 0.05	0.80 ± 0.04	<.001
E2, pmol/L	36.64 (18.35–180.85)	22.53 (18.35–48.32)	.001
Fasting glucose, mmol/L	5.31 (4.91–5.59)	5.27 (5.04–5.50)	.828
Fasting insulin, mU/L	5.40 (4.30–7.60)	5.00 (4.10–6.50)	.065
HOMA-IR	1.26 (1.00–1.77)	1.18 (0.93–1.58)	.093
LDL-C, mmol/L	2.73 ± 0.63	2.59 ± 0.65	.080
HDL-C, mmol/L	1.43 (1.25–1.69)	1.60 (1.33–1.83)	.002
Triglycerides, mmol/L	1.03 (0.76–1.46)	0.93 (0.72–1.28)	.201
Total cholesterol, mmol/L	5.16 ± 0.89	5.16 ± 0.79	.991
ApoA1, g/L	1.38 (1.26–1.57)	1.48 (1.34–1.69)	.019
ApoB, g/L	0.90 ± 0.20	0.85 ± 0.20	.050
Lipoprotein(a), mg/dL	192.00 (123.25–350.75)	209.00 (119.00–386.75)	.579
ΔFasting glucose, mmol/L	−0.04 ± 0.56	−0.13 ± 0.47	.037
ΔFasting insulin, mU/L	−0.62 ± 2.43	−0.50 ± .00	.669

ApoA1 = apolipoprotein A1, ApoB = apolipoprotein B, BMI = body mass index, FSH = follicle stimulating hormone, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance, HDL-C = high-density lipoprotein, LDL-C = low-density lipoprotein.

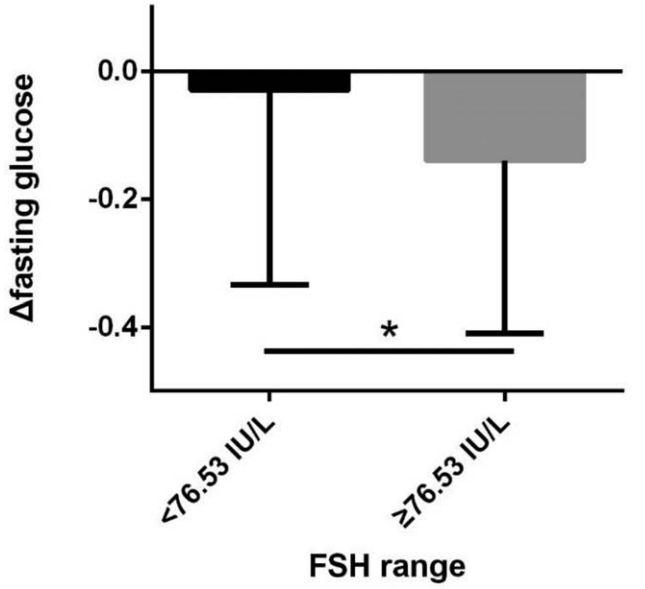

Figure 2. The change of fasting glucose plotted as median with interquartile by FSH dichotomization in 263 peri- and postmenopausal women. FSH = follicle stimulating hormone.

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 biomarker than a protective molecule in menopausal women. We could postulate that the faster FSH reaches high levels during the menopausal transition, the better adaptive capacity and responses to HT of this individual. It was a good evidence that in the well-known SWAN study,[28] rate of elevation in FSH during the menopausal transition was found to be associated with reduced risks of diabetes.

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 in 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 ΔFasting 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 ΔFasting 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[32] and osteoporosis[33] 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 heathy 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 the 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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