Serum Follicle Stimulating Hormone is Associated with Reduced Risk of Diabetes in Postmenopausal women: The Hong Kong Osteoporosis Study

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ABSTRACT

Menopause is an important transition of reproductive stage in woman's life, this is also associated with diabetes. However, the role of follicle stimulating hormone (FSH), a menopause-related hormone, in the risk of diabetes is largely unknown. We evaluated the relationship between serum FSH and diabetes in 1,274 participants from the Hong Kong Osteoporosis Study aged≥55 at baseline. We also searched relevant databases for studies on serum FSH and incident diabetes and conducted a meta-analysis using fixed-effect modeling. Incident diabetes (N=60) were ascertained during a median follow-up of 10.7 years. Serum FSH was significantly associated with reduced risk of diabetes in both crude (Hazard ratio [HR] per SD increase: 0.66; 95% CI: 0.48-0.89; P=0.007) and full models after adjusted for age, sex, body mass index, factors related to risk of diabetes, and reproductive health (HR per SD increase: 0.70; 95% CI: 0.51-0.97; P=0.030), similar result was observed when FSH was analysed as quintile. In a fixed-effect meta-analysis of two studies including the current study, serum FSH>50 IU/L was associated with reduced risk of diabetes (HR=0.56; 95% CI: 0.36-0.85; P=0.006; I^2=0). In conclusion, serum FSH levels were independently associated with reduced risk of diabetes.

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INTRODUCTION

Menopause is an important transition of reproductive stage in woman's life, this is also associated with multiple adverse medical outcomes, such as osteoporosis, cardiovascular diseases, and diabetes [1]. Early menopause and surgical menopause by ovariectomy were known to be associated with increased risk of diabetes [2]. However, the underlying mechanism remains inconclusive and controversial. Menopause transition is associated with significant changes in hormone profiles, such as estradiol and follicle stimulating hormone (FSH), while these changes in hormones may play a role in disease pathogenesis [3]. The relationship between estradiol and risk of diabetes has been widely studied and reviewed [2], however the role of follicle stimulating hormone (FSH) in the risk of diabetes is largely unknown.

In a recent study from the Study of Women's Health Across the Nation (SWAN), FSH increase during menopause transition was significantly associated with reduced risk of diabetes [4]. Another cohort study showed that higher baseline FSH was significantly associated with reduced risk of incident diabetes in the simple adjusted model [5], but not in the fully adjusted model. Therefore, to gain further insight into the role of FSH in diabetes, we evaluated the relationship between serum FSH levels and diabetes in the Hong Kong Osteoporosis Study (HKOS).

MATERIALS AND METHODS

Study participants

In the current study, we analysed the data from the HKOS, details of which has been published elsewhere [6]. In brief, baseline of HKOS was conducted between 1995 and 2010, and 9,229 participants were included in the cohort. Baseline data were obtained using a structured questionnaire administered by a trained research assistant. All participants gave informed consent, and the study was conducted according to the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster Hospitals. Among all participants, 2,234 of them were post-menopausal women and with serum FSH measured at baseline (Figure 1). After excluding participants who were younger than 55 years (N=216), with missing data in the variables in the final model (N=2,36), and with prevalent diabetes (defined by self-reported and electronic medical records; N=343), 1,274 participants were included in the final analysis. The study flow is provided in figure 1.

Ascertainment of diabetes

The ascertainment of diabetes has been reported previously [7]. In brief, incident

diabetes was ascertained from the EMR in several ways: (i) having a diagnosis of diabetes (ICD-9 code 250); (ii) having a prescription record of diabetic medications; (iii) having a laboratory record of A1C ≥6.5 % or fasting plasma glucose concentration >7.0 mmol/l; and (iv) having enrolled in a diabetic complication screening program. Length of follow-up for each participant was calculated as the time from the baseline examination date to the date of first diabetes ascertainment, date of death, or 1 May 2014, whichever was earliest. The status of incident diabetes has previously been validated [7].

Assessment of serum FSH, estradiol, and other covariates

Serum FSH was measured using the microparticle enzyme immunoassay (MEIA) on the Abbott AxSYM® System (Abbott Diagnostics Division, Abbott Park, IL, USA), which was calibrated against the 2nd IRP 78/549. The inter- and intra-assay CVs are 5.4% and 4.9%, 5.8% and 5.2%, 5.4% and 5.1%, 6.7% and 6% at 5.3, 18.9, 47.8 and 79.5 mIU/l respectively [1]. Total serum estradiol was measured by competitive chemiluminescent immunoassays (Ortho-Clinical Diagnostics, Rochester, New York, USA). Total E assay had an analytical sensitivity of 10 pmol/l, with intra-assay coefficient of variation (CV) of 13.4% at 21 pmol/l, 7.3% at 85 pmol/l, and 6.1% at 236 pmol/l, and inter-assay CV of 16.5% at 23 pmol/l, 8.8% at 87 pmol/l and 9.6% at 232

pmol/l [8]. Variables related to risk of diabetes (e.g. serum calcium [7], and history of lipid-lowering and anti-hypertensive medications) and reproductive health (e.g. history of early menopause, oophorectomy, and hysterectomy, serum estradiol, reproductive lifespan, age at menopause, duration of menopause, number of full term parity, ever use of oral contraceptives, and ever use of hormone replacement therapy [9]) were also included as covariates, and details have been reported elsewhere [6, 7, 10].

Statistical methods

Variables that were not normally distributed were log-transformed. Time-to-event analyses were performed and HR, and the 95% confidence interval (CI) were calculated using Cox-proportional hazard models. Survival time was calculated from the baseline date to the date of diabetes diagnosis, death, or end of study (1 May 2014). In the Cox regression model, model 1 was crude model and model 2 was fully adjusted model (adjusted for age, body mass index [BMI], smoking status, drinking status, physical activity, history of lipid-lowering and anti-hypertensive medications, history of early menopause, hysterectomy, and oophorectomy, serum estradiol and calcium, reproductive lifespan, age at menopause, duration of menopause, number of full term parity, ever use of oral contraceptives, and ever use of hormone replacement therapy). The proportional hazards assumption was evaluated for the variables in the fully

adjusted model and found no violation. Serum FSH was analysed as quintiles (using the lowest quintile as the reference) and standardized score. To examine the dose-response relationship between serum FSH levels and incident diabetes, penalized spline was added to the Cox proportional hazard regression model, which was done using R-package "pspline". We also searched the literature using the keywords "follicle stimulating hormone", "diabetes", and "association", and 70 studies were retrieved in MEDLINE on 30 Mar 2018. Among these 70 studies, only one of them was prospective study evaluating the relationship between FSH and incident diabetes. The findings from that prospective study and the current study were meta-analyzed using the inverse variance method with fixed effect. All statistical analyses were performed using SPSS version 21.0 software (SPSS Inc, Chicago, IL) and R version 3.4.2.

RESULT

During a median follow-up of 10.7 years (range 0.1-12.6 years) and 12149.4 person/years, 60 participants developed diabetes. Table 1 shows the baseline characteristics of the studied participants. Baseline FSH levels were inversely correlated with height, weight, serum estradiol levels, and history of hyperlipidemia, and positively correlated with serum calcium ($P<0.05$). During 12149 person-years,

Table 2 shows the association between serum FSH and incident diabetes. In the crude model (Table 1), participants in quintiles 2, 4, and 5 had reduced risk of diabetes when compared to the lowest quintile with an HR of 0.42 (95% CI: 0.20-0.89), 0.40 (95% CI: 0.18-0.88), and 0.33 (95% CI: 0.14-0.77), respectively; with the trend-P of 0.009. Each SD of FSH increase was significantly associated with reduced risk of diabetes with an HR of 0.66 (95% CI: 0.48-0.89). After further adjustment in the full model, similar findings were observed, despite the associations of quintiles 2 and 5 with incident diabetes were attenuated (Table 2). The relationship between serum FSH and incident diabetes was not linear, as illustrated by the penalized regression spline (Figure 2).

Previous study evaluated the relationship between FSH of 50IU/L and incident diabetes. We first evaluated the association of this cutoff point with incident diabetes, and found that serum FSH higher than 50 IU/L was significantly associated with reduced risk of incident diabetes in both crude (HR: 0.48; 95% CI: 0.28-0.81) and full models (HR: 0.57; 95% CI: 0.33-1.00; Table 2). Similar finding was observed in meta-analysis with an HR of 0.56 (95% CI: 0.36-0.85; P=0.006; I^2=0; Figure 3).

DISCUSSION

In the current study, an inverse association between serum FSH levels and risk of

diabetes was observed.

Our study is in line with the SWAN study [4], which showed that rate of increase in FSH during menopause transition was significantly associated with reduced risk of diabetes. Previous small prospective study showed that higher serum FSH (>50 IU/L) was inversely associated with risk of diabetes, however the association was marginally insignificant (HR=0.53, 95% CI: 0.27-1.02) in the fully adjusted model [5]. The insignificant finding could be due to small sample size and hence limited statistical power. To improve statistical power, we first performed the analysis using the same cutoff point as in the literature [5] and found that serum FSH>50 IU/L was significantly associated with reduced risk of diabetes with an HR of 0.57 (0.33-1.00), P=0.048; while the subsequent fixed-effect inverse-variance meta-analysis also demonstrated a significant reduction in risk of diabetes with an overall HR of 0.56 (95% CI: 0.36–0.85, P=0.006, I^2=0 (Figure 3). Therefore, people with serum FSH>50 IU/L was significantly associated with reduced risk of diabetes. However, it should be noted that the cutoff point of 50IU/L was chosen in the previous study because it's the median of circulating FSH levels, while our analysis using regression spline showed that the slope increased after the FSH levels of ~20IU/L (Figure 2), thus future study should also explore the optimal cutoff point in predicting diabetes.

Although there was one prospective study investigating the relationship between serum FSH and incident diabetes, several cross-sectional studies have shown that serum FSH is inversely associated with cardiometabolic risk factors. In a cohort of postmenopausal women from East China, serum FSH was significantly associated with reduced 10-year atherosclerotic cardiovascular disease risk [11], and reduced odds of prediabetes [12], diabetes [12], and non-alcoholic fatty liver disease [13]. Similarly, an inverse association was observed between serum FSH and metabolic syndrome in postmenopausal Polish women [14]. In the current study, we observed a significant association between baseline FSH and prevalent diabetes in the crude model, however the association became statistically insignificant after adjustments in the full model (Supplementary Table 1). Thus, it appears that higher serum FSH levels are associated with better metabolic profile in postmenopausal women, and such beneficial effect may only observe in people without baseline diabetes.

The relationship between serum FSH and metabolic diseases in women with polycystic ovary syndrome (PCOS) has been widely studied. PCOS is known to be associated with increased risk of diabetes [15]. Serum FSH after menopause was significantly lower in women with PCOS than those without [16], while there may be cross-talk between FSH

and insulin/IGF-1 signalling pathways in granulosa cells and hence affecting energy homeostasis, and such mechanism may be defective in women with PCOS [17]. However, whether these mechanisms are applicable to healthy postmenopausal women, and its relationship with the development of diabetes, remain unknown.

Our study has strengths and limitations. To our knowledge, this was the first study evaluating the association between serum FSH and risk of diabetes in Chinese, and showing that this finding can be generalized to different ethnic groups. Incident diabetes was validated with high accuracy [7]. There are several limitations in this study. First, as in all observational study, a causal relationship cannot be inferred. Second, glycated hemoglobin, fasting glucose and insulin levels were unavailable at baseline. However, the relationship between serum FSH and incident diabetes was not confounded by these factors in the previous study [5].

In conclusion, serum FSH is significantly associated with reduced risk of diabetes.

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Contributors

CL Cheung conceived the study, constructed the study plan, analysed the data, interpreted the analyses. AW Kung and KC Tan interpreted the analyses. All authors drafted the manuscript and reviewed the final version.

Conflict of interest

The authors declare that they have no conflict of interest

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Provenance and peer review

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Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available upon request.

Table 1. Baseline characteristics of the study participants.

	Quintile 1 (N=245)		**Quintile 2 (N=271)**		**Quintile 3 (N=253)**		**Quintile 4 (N=254)**		**Quintile 5 (N=251)**		P
Age (years)	66.23	8.67	65.07	7.81	66.11	7.96	66.09	8.33	66.10	9.34	0.873
Height (meter)	1.53	0.06	1.53	0.06	1.53	0.06	1.52	0.06	1.51	0.06	0.018
Weight (kg)	58.42	10.98	55.86	8.83	54.53	9.24	51.82	8.45	50.07	8.33	<0.001
Serum FSH (IU/L)	37.30	9.68	53.31	2.97	63.88	3.08	76.85	4.49	105.69	25.05	<0.001
Serum estradiol (pmol/L)	54.16	106.83	36.83	21.63	35.03	18.92	33.15	14.18	32.83	14.45	0.002
Serum calcium (mmol/L)	2.40	0.09	2.40	0.09	2.41	0.09	2.41	0.09	2.42	0.09	0.039
Reproductive lifespan (years)	35.30	5.39	35.25	4.73	34.51	5.12	34.48	4.78	34.75	4.60	0.219
Duration of menopause (years)	16.31	10.51	15.19	9.15	17.05	9.45	16.93	9.73	16.87	10.84	0.566
Age at menopause (years)	49.92	4.93	49.88	4.00	49.07	4.72	49.16	4.51	49.24	4.13	0.094
Ever use of contraceptives	74	30.2	88	32.5	92	36.4	74	29.1	60	23.9	0.115
Ever use of HRT	29	11.8	21	7.7	27	10.7	27	10.6	28	11.2	0.812
Number of parity	2.00	2.50	1.58	2.16	1.88	2.55	1.84	2.29	1.83	2.53	0.427
Smoking											
Never	230	93.9	254	93.7	241	95.3	241	94.9	238	94.8	
Former	10	4.1	9	3.3	8	3.2	9	3.5	7	2.8	0.436
Current	5	2.0	8	3.0	4	1.6	4	1.6	6	2.4	0.809
Drinking											

Never	236	96.3	262	96.7	240	94.9	237	93.3	243	96.8	
Former	4	1.6	2	.7	4	1.6	8	3.1	4	1.6	0.967
Current	5	2.0	7	2.6	9	3.6	9	3.5	4	1.6	0.709
Physically active	135	55.1	155	57.2	155	61.3	158	62.2	137	54.6	0.907
History of hypertension	153	62.4	139	51.3	146	57.7	126	49.6	144	57.4	0.249
History of hyperlipidemia	92	37.6	76	28.0	76	30.0	82	32.3	69	27.5	0.017
Early menopause	24	9.8	21	7.7	31	12.3	36	14.2	31	12.4	0.366
History of hysterectomy or oopherectomy	24	9.8	32	11.8	32	12.6	35	13.8	29	11.6	0.527

Data are presented as mean±S.E.M. for continuous variables and percentage±S.E.M. for categorical variables.

Table 2. Association of serum FSH with incident diabetes.

Quintiles of FSH	Crude model			Full model		
	HR	95% CI	P-value	HR	95% CI	P-value
Q1	Ref			Ref		
Q2	0.42	(0.20-0.89)	0.023	0.54	(0.25-1.17)	0.116
Q3	0.58	(0.29-1.17)	0.127	0.68	(0.33-1.40)	0.300
Q4	0.40	(0.18-0.88)	0.022	0.43	(0.19-0.96)	0.039
Q5	0.33	(0.14-0.77)	0.010	0.42	(0.17-1.03)	0.057
Trend-P			0.009			0.028
Per SD change	0.66	(0.48-0.89)	0.007	0.70	(0.51-0.97)	0.030
FSH >50IU/L	0.48	(0.28-0.81)	0.006	0.57	(0.33-1.00)	0.048

[a]Adjusted for age, BMI, smoking status, drinking status, physical activity, history of lipid-lowering and anti-hypertensive medications, history of early menopause, oophorectomy, and hysterectomy, serum estradiol and calcium, reproductive lifespan, age at menopause, duration of menopause, number of full term parity, ever use of oral contraceptives, and ever use of hormone replacement therapy.

Figure 1. Flow diagram of Hong Kong Osteoporosis Study (HKOS) analysis cohort.

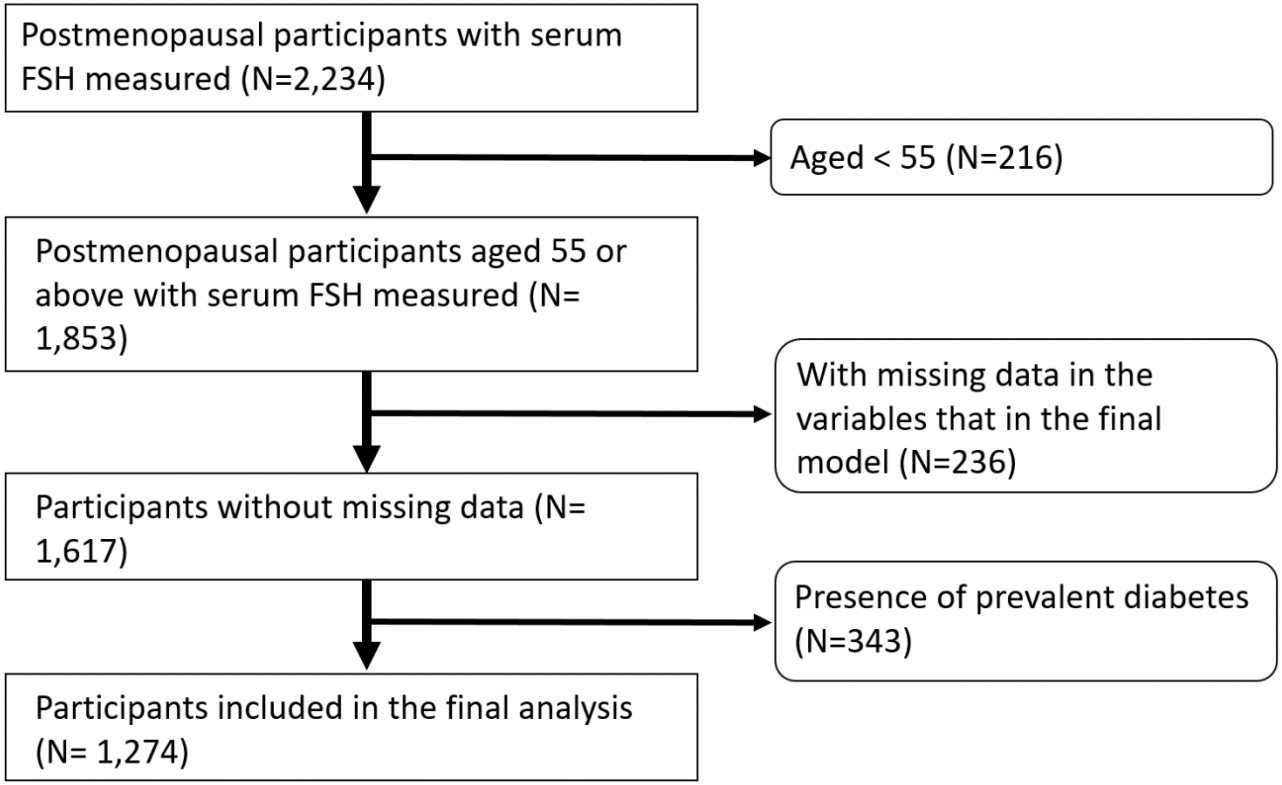

Figure 2. Association of log serum FSH levels with the log hazard ratio of an incident diabetes using penalized spline.

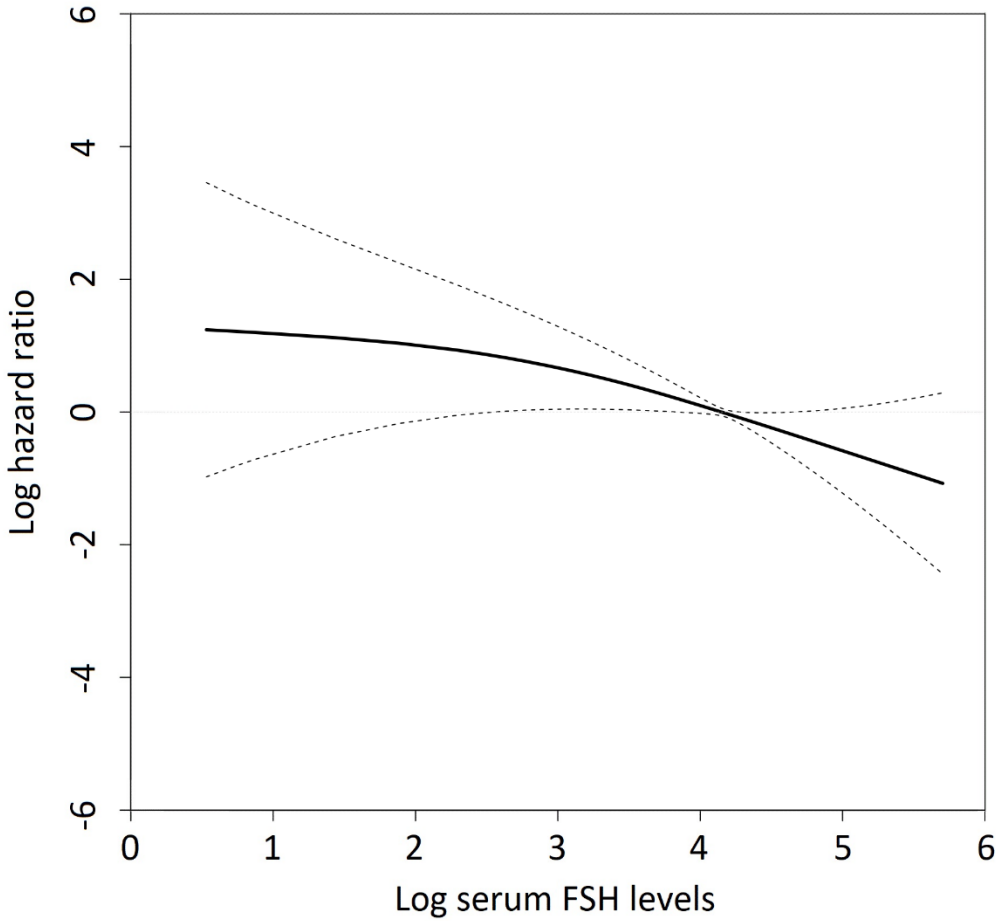

Figure 3. Meta-analysis of serum FSH levels with incident diabetes.