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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 a woman's life. It is associated with diabetes, but 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 1274 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. Cases of 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 a crude model (hazard ratio [HR] per SD increase: 0.66; 95% CI: 0.48-0.89; P = 0.007) and a full model with adjustment 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); a similar result was observed when FSH was analysed in quintiles. 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 diabetes.

1. Introduction

Menopause is an important transition of reproductive stage in a woman's life, and is associated with multiple adverse medical outcomes, such as osteoporosis, cardiovascular diseases, and diabetes [1]. Early menopause and surgical menopause by ovariectomy are 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).

2. Materials and methods

2.1. 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 9229 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, 2234 of them were post-menopausal women and with serum FSH measured at baseline (Fig. 1). After excluding participants who were younger than 55 years (N = 216), with missing data in the variables in the final model (N = 236), and with prevalent diabetes (defined by self-reported and electronic medical records; N = 343), 1274

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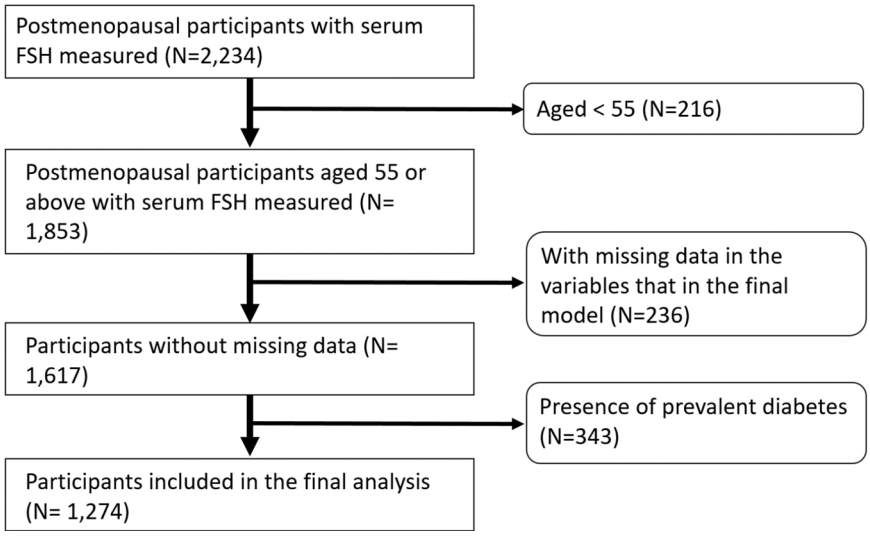

Fig. 1. Flow diagram of Hong Kong Osteoporosis Study (HKOS) analysis cohort.

participants were included in the final analysis. The study flow is provided in Fig. 1.

2.2. 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].

2.3. 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].

2.4. 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.

3. Results

During a median follow-up of 10.7 years (range 0.1–12.6 years) and 12,149.4 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 12,149 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 (Fig. 2).