Physiol. Res. 63 (Suppl. 3): S395-S402, 2014

Bilateral Oophorectomy May Have an Unfavorable Effect on Glucose Metabolism Compared With Natural Menopause

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Received July 21, 2014
Accepted August 4, 2014

Summary

The incidence of diabetes mellitus is rising worldwide. The aim of this prospective epidemiological study was to compare the effects of natural and surgical menopause on parameters of glucose metabolism. In a group of 587 repeatedly examined women, with a baseline age of 45-55 years, the following subgroups of women were separated: those after bilateral oophorectomy (BO, n=37) and those in natural menopause (NAT, n=380) including women menopausal already at baseline (POST, n=89). The study parameters including glycemia, insulinemia, HOMA-IR and beta-cell function using HOMA-β were determined at baseline and 6 years later. Over the study period, there was a marked rise in prediabetic and diabetic values of fasting glycemia; the percentage of women with diabetic values increased in the NAT (from 0.8 % to 3.9 %) and POST (from 2.2 % to 9.0 %) subgroups, with the highest prevalence in the BO subgroup (from 8.1 % to 10.8 %). While, among women with non-diabetic fasting glycemia, an increase in fasting glycemia was observed in all study subgroups, it was more marked in the BO subgroup than in the NAT and POST ones (p=0.02 both). This difference between NAT and BO was also found in the long-term trend of development of glycemia in non-diabetic women (p=0.014). Compared with natural menopause, bilateral oophorectomy may have an adverse effect on glucose metabolism.

Key words

Fasting glucose • Fasting insulin • Menopause • Oophorectomy • Surgical menopause

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Introduction

The incidence of obesity and type 2 diabetes is rising worldwide, particularly in nations adopting the "western lifestyle"; diabetes thus ranks among diseases that pose an increasingly significant economic burden in terms of health care expenditures also in industrialized countries. In the last decade, the conventional concept of type 2 diabetes developing as a result of obesity causing insulin resistance was expanded to include other key pathogenic factors (DeFronzo 2009); recently, major attention has been paid particularly to conditions governing pancreatic beta-cell survival and regeneration as the process seems to be more complex than believed to date (Dadon *et al.* 2012, Peiris *et al.* 2014).

Ovarian hormones, especially estrogens, play a pivotal role in the physiology of reproductive, cardiovascular, skeletal, and central nervous systems. While, in hypothalamic nuclei, ovarian hormones control body energy balance, in the skeletal muscle, liver, adipose tissue, and immune system cells, they affect insulin sensitivity and exert anti-inflammatory effects. Recent experimental data have suggested that ovarian hormones have beneficial effects on beta-cells in the pancreatic islets affecting as they do not only regulation of insulin secretion but, also, survival of beta-cells

(Mauvais-Jarvis *et al.* 2013). Estrogen can modulate menopausal women's heart rate variability (Yang *et al.* 2013). Natural menopause is a period of naturally diminished ovarian hormone secretion that usually occurs around 50 years of age making it difficult to distinguish the effects of age and natural menopause on glucose metabolism. While some authors reported a steep increase in the incidence of diabetes after the age of 50 years (Di Donato *et al.* 2005) as well as an association between diabetes and early menopause (Brand *et al.* 2013), others have not documented an association between natural menopause and the incidence of diabetes (Monterossa-Castro *et al.* 2013). Even fewer studies have sought to correlate the effects of natural and surgical menopause (Gibson *et al.* 2013, Appiah *et al.* 2014); however, there have been reports of experimental animal studies repeatedly showing that oophorectomy deteriorates insulin resistance as well as glucose tolerance (Riant *et al.* 2009, Zhu *et al.* 2014).

The aim of our 6-year prospective epidemiological study was to compare the effects of natural menopause and menopause after bilateral oophorectomy on parameters of insulin resistance and glucose tolerance.

Methods

Participants and data sources

For the present study, we used data from a population-based study. The methodology has been described elsewhere (Lejsková *et al.* 2012, Piťha *et al.* 2013). The Prague Pre- and Post- Menopausal Females study (3PMFs) used a 5 % representative and random sample of 29,440 women aged 45-54 years living in Prague selected from the registers of health insurance companies. From a random sample of 1472 women, 908 agreed to participate and came for the first examination. The first round of examinations in our prospective study was performed in the 2004-2005 period.

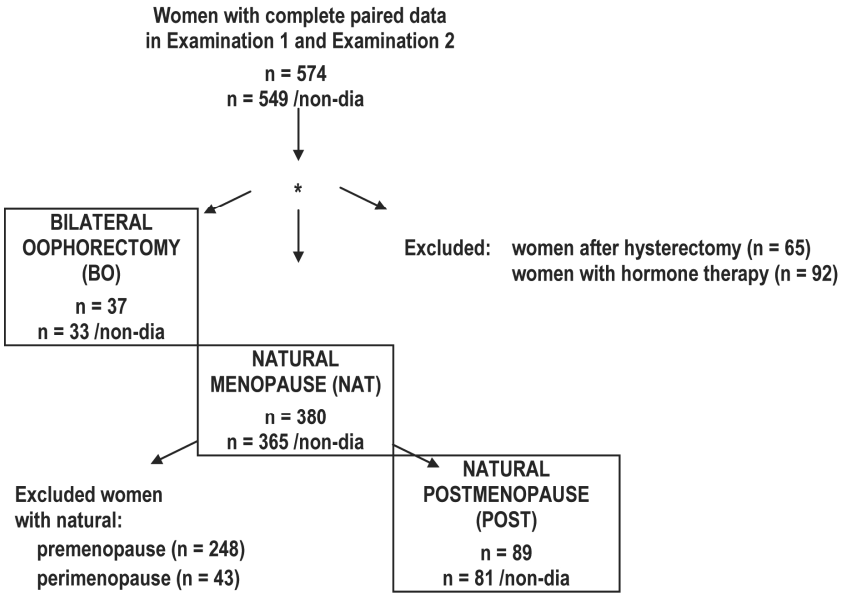

Fig. 1. Study design.

The second-round examinations of our study (Examination 2) were performed so as to keep a homogeneous time interval of 6 years between both examinations in each participant. After excluding women not fulfilling our criteria, paired data were obtained from 574 women having both examinations as per the study protocol. Using medical history data collected in the first examination, the following groups were subsequently formed (Fig. 1): 37 women with a history of bilateral oophorectomy (BO), another 65 women with a history of hysterectomy, and 92 women taking any female sex hormones at baseline. This gave us a total of 380 women with a natural course of menopause (NAT). Based on time since the last/final menstrual period at baseline (Examination 1), we divided this group of NAT women into a subgroup of 89 postmenopausal women (POST; more than 365 postmenstrual days) and subgroups of 248 premenopausal women (fewer than 33 postmenstrual days) and 43 perimenopausal women (33-365 postmenstrual days). Six years later, all perimenopausal women were in postmenopause (>365 postmenstrual days). In the premenopausal subgroup, this criterion was

met by almost three in four women. Given the study design, the individual subgroups did not differ in the time interval between both examinations, that is, all women in the subgroups were 6 years older at Examination 2 (6.16±0.16 years).

Final detailed statistical analysis of the study subgroups (BO, NAT, POST) included only data of women not treated for diabetes, with fasting glycemia values not higher than 6.8 mmol/l at either examination: the value was decreased from 6.9 to 6.8 mmol/l to unequivocally exclude women with diabetes.

Data sources

A physician-completed questionnaire including each participant's medical history, treatment of diabetes, hypertension, hyperlipidemia including the date of therapy initiation was obtained. To rule out any potential bias, the physicians carefully entered details regarding all prescribed treatments, a thorough gynecological history, drug therapy and the interval since the last menstrual bleeding.

Body weight, height, and waist circumference were measured with an accuracy of 0.1 kg and 0.5 cm, respectively. The waist-to-hip ratio and body mass index (BMI; kg/m^2) were calculated. Systolic and diastolic blood pressures were measured in the sitting position on the right arm after at least 20 minutes' rest in an outpatient clinic.

Blood samples were taken after an overnight fast. Fasting glucose and insulin were used to calculate the insulin resistance index (HOMA-IR, HOmeostasis Model Assessment of Insulin Resistance = [fasting glucose; mmol/l] × [fasting insulin; mU/l]/22.5) and the HOmeostasis Model Assessment of β-cell function [HOMA-β; %] = 20 × [fasting insulin; mU/l]/ [[fasting glucose; mmol/l] – 3.5] (Matthews *et al.* 1985).

We searched for any differences in the selected parameters of glucose metabolism among women with bilateral oophorectomy (BO), all women in the group with natural menopause (NAT) and natural postmenopausal women at Examination 1 (POST). For each of these groups, calculations were performed after excluding women with diabetic values of fasting glycemia and/or treated with antidiabetic drugs.

Statistical methods

The incidence of diabetic and prediabetic values of glycemia was assessed using the chi square test (Table 1). Results from ANOVA with repeated measures are presented in Table 2. Distributions of all continuous variables were assessed prior to performing statistical analyses. In several cases [follicle-stimulating hormone (FSH), HOMA-β, HOMA-IR, and insulinemia], log-transformed rather than original values were used in the analysis.

Results

Increasing proportion of women with higher values of glycemia

In all subgroups, there was an increase in the proportion of women with fasting glycemia at prediabetic and diabetic values. Already at Examination 1, women with diabetes made up the highest proportion of BO women ($p<0.01$); there was also one women with insulin therapy at baseline. The proportion of women with treated diabetes or a high value of glycemia (≥6.9 mmol/l), while remaining the highest in BO women at Examination 2, was not significant when using the chi square test. No other differences among the study groups were found (Table 1). More detailed analyses were only performed of data of women with unequivocally non-diabetic values.

Characteristics – changes in the parameters assessed over the 6-year period

Significant increases were seen in anthropometric parameters characterizing obesity and systolic blood pressure ($p<0.001$; only $p=0.012$ for the waist-to-hip ratio); this, however without a difference among the subgroups except for the waist-to-hip ratio showing a difference of borderline significance ($p=0.045$) between BO and NAT women (Table 2). Highly significant increases were also seen in fasting glycemia values and insulin resistance parameters ($p<0.001$), but not in HOMA-β. Although regression analysis did not demonstrate significant inter-group differences even in these parameters, the increase in glycemia values between Examinations 1 and 2 in BO women was significantly higher than that both in women in natural menopause (NAT; $p=0.015$) and in those in natural postmenopause (POST; $p=0.020$). The increase in HOMA-IR became significant only when compared with NAT women ($p=0.023$).

Table 1. Prevalence of prediabetic and diabetic values of fasting glycemia in the study groups.

	Bilateral oophorectomy (BO)				Natural menopause (NAT)				BO≠NAT (χ^2)		Natural postmenopause (POST)				BO≠POST (χ^2)	
	Exam. 1		Exam. 2		Exam. 1		Exam. 2		Exam. 1	Exam. 2	Exam. 1		Exam. 2		Exam. 1	Exam. 2
Participants non-diabetic	n = 33				n = 365				p	p	n = 81				p	p
Fasting glycemia < 5.6 mmol/l	27	81.8 %	21	63.6 %	305	83.6 %	263	72.1 %	ns	ns	65	80.2 %	53	65.4 %	ns	ns
Fasting glycemia ≥ 5.6 mmol/l	6	18.2 %	12	36.4 %	60	16.4 %	102	27.9 %			16	19.2 %	28	34.6 %		
Participants including diabetics	n = 37				n = 380				p	p	n = 89				p	p
Fasting glycemia < 5.6 mmol/l	28	75.7 %	21	56.8 %	308	81.1 %	263	69.2 %	0.002	ns	67	75.3 %	53	59.6 %	ns	ns
Fasting glycemia (5.6-6.9) mmol/l	6	16.2 %	12	32.4 %	69	18.2 %	102	26.8 %			20	22.5 %	28	31.5 %		
DM and/or Fasting glycemia ≥ 6.9 mmol/l	3	8.1 %	4	10.8 %	3	0.8 %	15	3.9 %			2	2.2 %	8	9.0 %		
DM - pharmacotherapy	n				n		n				n		n			
Insulin (+- OAD)	1				0		0				0		0			
OAD only	1				0		6				0		4			

DM, diabetes mellitus; OAD, oral anti-diabetic drugs; Exam., examination.

Table 2. Characteristics of non-diabetic participants (ANOVA with repeated measures).

Non-diabetic	Bilateral oophorectomy (BO)		Natural menopause (NAT)		NAT/BO			Natural postmenopause (POST)		POST/BO		
	n = 33		n = 365		factors			n = 81		factors		
	Exam. 1	Exam. 2	Exam. 1	Exam. 2	Repeated p	Group p	Interaction p	Exam. 1	Exam. 2	Repeated p	Group p	Interaction p
Age (years)	50.9±2.5	57.1±2.5	49.7±2.7	55.9±2.7	***	†	ns	52.5±1.7	58.7±1.7	***	†††	ns
Time since last/final menstrual period (years)	6.9±6.3	13.0±6.4	1.1±2.5	5.0±4.1	***	†††	‡‡‡	4.5±3.6	10.7±3.6	***	ns	ns
FSH (IU/l)	60±31	68±31	43±41	80±36	***	•	‡‡‡	87±30	81±28	ns	††	•
Body weight (kg)	69±7	73±8	69±12	72±13	***	ns	ns	70±11	73±12	***	ns	ns
Body mass index (BMI) (kg/m^2)	25±3	27±3	25±4	26±5	***	ns	ns	26±4	27±5	***	ns	ns
Hip circumference (cm)	102±5	104±6	102±9	103±10	***	ns	ns	103±9	104±10	***	ns	ns
Waist circumference (cm)	87±9	90±7	85±12	87±12	***	ns	ns	87±12	89±12	***	ns	ns
Waist-to-hip ratio (WHR)	0.85±0.07	0.87±0.06	0.83±0.07	0.84±0.07	*	†	ns	0.84±0.07	0.85±0.07	*	ns	ns
Systolic BP (mm Hg)	119±15	127±16	118±15	125±19	***	ns	ns	117±15	124±18	***	ns	ns
Diastolic BP (mm Hg)	78±12	80±9	78±9	79±10	ns	ns	ns	78±8	78±9	ns	ns	ns
Pulse rate (min^{-1})	68±10	71±8	71±8	70±8	ns	ns	‡	70±9	70±8	ns	ns	ns
Fasting glycemia (mmol/l)	5.08±0.58	5.51±0.63	5.09±0.46	5.29±0.49	***	ns	‡	5.12±0.46	5.28±0.56	***	ns	‡
HOMA-β (%)	89±64	79±41	87±105	77±45	ns	ns	ns	81±39	82±52	ns	ns	ns
HOMA-IR	1.4±0.8	2.1±1.6	1.4±0.8	1.6±1.1	***	ns	‡	1.5± .9	1.8±1.5	***	ns	•
Fasting insulinemia (IU/ml)	6.2±3.3	8.3±5.5	6.2±3.4	6.8±4.3	***	ns	•	6.4±3.4	7.4±5.5	**	ns	ns

FSH, follicule-stimulating hormone; BP, blood pressure; HOMA-β, HOmeostasis Model Assessment of beta-cell function; HOMA-IR, HOmeostasis Model Assessment of Insulin Resistance; Exam., examination. Significance of change in the variable between Examinations 1 and 2: * $p<0.05$; ** $p<0.01$; *** $p<0.001$. Significance of the inter-group difference in the mean of the variable: † $p<0.05$; †† $p<0.01$; ††† $p<0.001$. Significance of the inter-group difference in the change of the variable from Examination 1 to Examination 2: ‡ $p<0.05$, ‡‡‡ $p<0.001$. Borderline significance: • $0.05<p<0.1$, ns $p>0.1$.

Long-term trend in the development of glycemia

Given the inter-group differences in glycemia values, the long-term trend in the development of glycemia values by the time since the final menstrual period at Examination 2 was also assessed (Fig. 2). For comparison with BO women, only those with the time since the final period longer than 2500 days were selected from the NAT subgroup to meet the same criterion as women with BO. Both trends were shown to differ significantly (p=0.014).

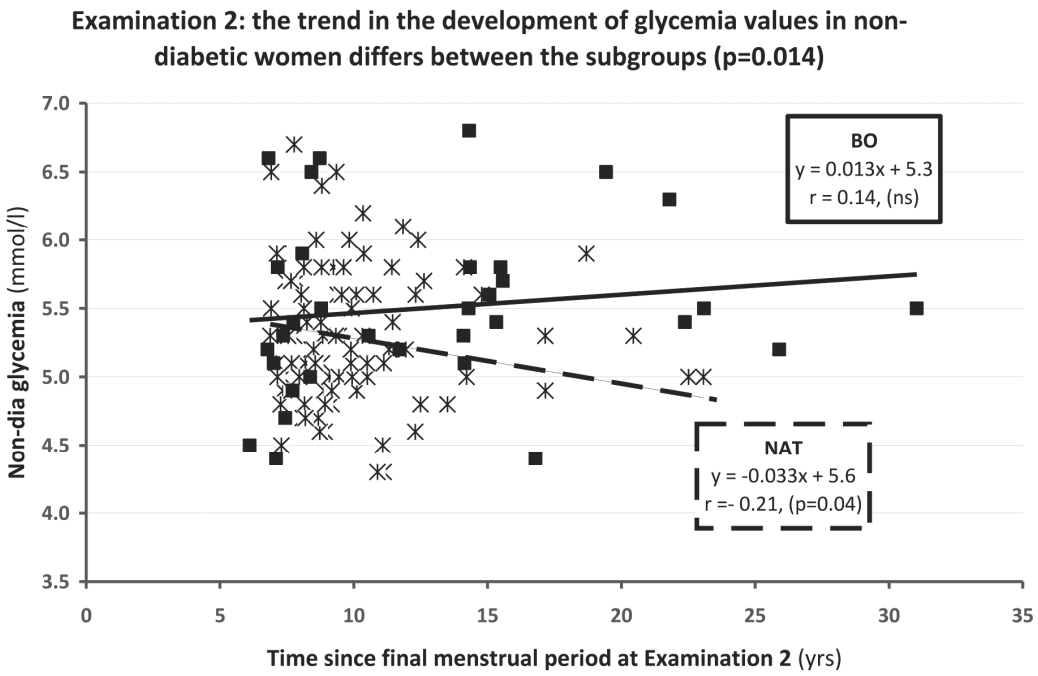

Fig. 2. Long-term trend in the development of glycemia at Examination 2 by the time since the last/final menstrual bleeding.

Discussion

Our results based on epidemiological data obtained in a prospective study in women resident in a district of Prague (Prague 4) have demonstrated that bilateral oophorectomy has a more negative effect on glucose metabolism than natural menopause. While the results reached only borderline significance, they do complement each other. Women after BO were found to have more frequent incidence of diabetes already at baseline. When excluding women with known diabetes and fasting glycemia ≥6.9 mmol/l from our analysis, mean glycemia values in BO women were not higher; however, there was a greater mean increment in glycemia over the 6-year period when compared with both NAT and POST women. This finding is consistent with the greater increment in glycemia seen also in the long-term trend (Fig. 2). The waist-to-hip ratio, slightly higher in women after BO that in NAT women, could be etiologically associated with the higher increment in HOMA-IR seen in BO women.

While no differences in HOMA-β were found among women without diabetes, the higher incidence of the disease already at Examination 1 may be related to the adverse effect of the decrease in estrogen levels following bilateral oophorectomy on pancreatic beta-cells. A search of the relevant literature did not provide evidence of reverse causality, i.e. bilateral oophorectomy being performed in women at increased risk of diabetes.

Age is the most marked predictor of the increase in anthropometric parameters, glycemia, and systolic blood pressure. In our set of compared non-diabetic subgroups of women, the age differences were minimal because of the study design, with women after BO being 1.2 years older than NAT women yet 1.6 years younger than women in POST, so the observed greater increment in glycemia as against both latter subgroups cannot be explained by age differences.

The results of our study are thus in line with the notion that bilateral oophorectomy has an adverse effect on both factors traditionally perceived as crucial for the development of type 2 diabetes: beta-cell function and insulin resistance. This concept is pathophysiologically consistent with experimental data reported in recent years showing an unfavorable effect of estrogen deficiency on a variety of tissues, particularly the insulin-sensitive ones (Mauvais-Jarvis *et al.* 2013). The adverse effects contributing to the risk of developing diabetes may

include the greater increase in BMI in the years following bilateral oophorectomy than following hysterectomy with ovarian conservation or natural menopause (Gibson *et al.* 2013). Our study documented only borderline significance for a higher waist-to-hip ratio (but not for BMI or waist circumference). The diabetogenic effect of bilateral oophorectomy was recently reported in a 9-year follow-up of a cohort of almost 2600 women (Appiah *et al.* 2014).

Nonetheless, the hormonal impacts of bilateral oophorectomy are no doubt more complex involving as they do the deficiency of a number of other hormones. Bilateral oophorectomy has been the subject of studies investigating its adverse effects on bone density, cardiovascular disease, and increased mortality and, by contrast, its beneficial effect on reducing the risk of breast cancer. Based on the outcomes of a number of studies, it is now generally accepted that salpingo-oophorectomy should not be recommended in women aged below 65 years indicated for hysterectomy for a benign disease (Ouldamer *et al.* 2013).

One limitation of this study is the relatively low number of women with surgical menopause included. Another limitation is the inclusion of women in the menopausal group based exclusively on self-reported information from the gynecological history of each patient.

In contrast, the strength of this study is its population-based design with prospective follow-up and the predefined time interval between both examinations. This allowed us to identify major differences in the basic parameters of glucose metabolism in women undergoing bilateral oophorectomy.

In summary, this prospective study found, in a population-based group of middle-aged women, that bilateral oophorectomy was associated with an unfavorable development of basic parameters of glucose metabolism compared with natural menopause. This finding is just another piece of evidence of the potential diabetogenic effect of bilateral oophorectomy. Future research into the adverse effects of bilateral oophorectomy should focus on measures preventing the development of diabetes.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This work was supported by Ministry of Health, Czech Republic – conceptual development of research organization ("Institute for Clinical and Experimental Medicine – IKEM, IN 00023001") and by grant NT 14008-3/2013 (Internal Grant Agency of the Ministry of Health of the Czech Republic).

Abbreviations

BMI, body mass index; BO, bilateral oophorectomy; BP, blood pressure; FSH, follicle-stimulating hormone; HOMA, homeostasis model assessment; IR, insulin resistance; NAT, natural menopause; POST, natural postmenopause; WHR, waist-to-hip ratio.

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