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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Androgen receptor gene polymorphism and sexual function in midlife women

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Abstract

Purpose To assess the impact of serum androgen levels and androgen receptor CAG polymorphism on sexual function in 45 healthy midlife women living in a heterosexual relationship.

Methods Cross-sectional study [Cantonal Ethics Committee Bern (Ref.-Nr. KEK-BE: 087/13)]. Main outcome measures: Association between androgen serum levels, androgen receptor CAG polymorphism and sexual function was assessed by the FSFI-d questionnaire.

Results In our cohort of healthy, midlife, well-educated, middle-class, mostly postmenopausal women living in a heterosexual satisfying partnership, sexual function was perceived to remain stable or to decline during menopausal transition with sexual desire scoring lowest (FSFI-d 3.3 ± 0.9). Androgen serum levels did not correlate with sexual function. Mean CAG repeat number was 21.6 ± 1.9. There was a highly inverse though non-significant correlation between female sexual function and AR CAG repeat polymorphism with specifically higher numbers of CAG repeats being significantly positively correlated to more frequent or more severe pain during or after sexual intercourse.

Conclusion The AR polymorphism is a non-negligible factor in female sexual function. Future studies on female sexual (dys)function should incorporate its assessment.

Keywords Androgen receptor gene polymorphism · CAG repeat · Sexual function · Libido · Serum testosterone · Healthy midlife women

Introduction

Female sexual function changes with aging. Biopsychosocial factors such as physical and mental health, partnership quality, and sociocultural and economic aspects are crucial determinants for an intact sexual function [1–3]. Furthermore, ovarian sex steroids have a major impact, and their decline due to menopause has been found to be associated with an increased incidence of female sexual dysfunction (FSD) [4–6]. During menopause, women do not only experience a decline of estrogen but also androgen production. Androgens are believed to play a key role particularly in centrally guided aspects of sexuality such as desire, arousal and sexual responsiveness [7]. However, despite beneficial effects of testosterone therapy on female sexual function, research keeps struggling to prove a significant direct association between serum androgen levels and female sexual function [8, 9]. One reason may be technical issues when measuring women's relatively low androgen serum levels [10]. Furthermore, serum androgens may be

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insufficient to extrapolate their action on target tissues as the target tissue itself may contribute to androgen production [9, 11] and/or may aromatize androgens to estrogens [8, 11, 12] which then act via the estrogen (ER) or androgen receptor (AR), respectively [13].

Interestingly, by application of selective AR modulators (SARMs), sexual responsiveness and motivation were improved in female rats. As SARMs are non-aromatizable, they do not cross-react with the ER emphasizing the AR as another critical determinant in regulating female libido [12]. The genetic code for the AR lies proximal on the long arm of the X-chromosome. It consists of eight exons that encode for the AR subunits. Cytosine, adenosine and guanine (CAG) repeats within the first exon (range 8 to > 30 repeats) are coding for a polyglutamine sequence in the NH2 terminal domain and thereby determine the grade of transcriptional activity of the AR. The length of the sequence inversely correlates with the AR sensitivity to androgens and, therefore, with its activity level [14]. It has to be kept in mind though, that in women, each cell expresses gene products from one X-chromosome only. Thus, women exhibit a mosaic of either one of the two AR gene alleles throughout their body which may result into different intrapersonal organ-specific sensitivities to the same amount of free androgens [15]. So far, the length of the AR gene polymorphism has been linked to serum androgen levels [16–18] and pathogenesis of various diseases [19–23]. However, the role of the AR gene polymorphism in female sexual function is unclear.

Thus, the aim of our cross-sectional study in healthy midlife women was to assess the role of the AR gene polymorphism in female sexual function taking serum androgen levels into account.

Materials and methods

Study design

This was a single-center, cross-sectional, observational, non-interventional trial. All the participants followed a standardized battery of assessments consisting of a personal and family history, questionnaires about sexual function [Female Sexual Function Index (FSFI-d)] [24] and questionnaire about health, life satisfaction and sexuality in middle-aged women (supplementary file 1) [25], and a blood test (serum hormones and AR gene polymorphism). The assessments are further described in "Assessment procedures". The study protocol was approved by the Cantonal Ethics Committee Bern (Ref.-Nr. KEK-BE: 087/13), and written informed consent was obtained from each participant.

Study population

German-speaking women were recruited between November 2013 and June 2015 at the Department of Obstetrics and Gynecology, Inselspital Bern, Switzerland. Recruitment was performed by the principle investigator (PS), the study nurse (DG) and three doctoral students of the medical school, University of Bern, via personal contact (patients, colleagues, family, and friends), online advertisement (internet, intranet Inselspital Bern, and social media), and flyers (fitness or shopping centers). Inclusion criteria were age between 45 and 65 years, a stable and confiding heterosexual relationship for at least 1 year, and the absence of depression (Hospital Anxiety and Depression Scale (HADS-D) score < 8) [26]. Exclusion criteria were severe diseases such as cancer, multiple sclerosis, diabetes mellitus, or Parkinson disease; thyroid dysfunction; psychiatric disorders; a history of sexual abuse; substance abuse (drugs and more than one package of cigarettes); acute stress; dyspareunia; vaginism; urinary incontinence; orgasm disorder; and use of the following medication during 8 weeks prior to study entry: systemic corticosteroids, antihypertensives (beta blockers, diuretics, ACE inhibitors, and spironolactone), antidepressants or hypericum, antipsychotics of the first generation, anticonvulsants, benzodiazepine, opioid analgetics, hormonal contraceptives, antiandrogens, and potential libido enhancers.

Assessment procedures

Personal and family history

Briefly, we assessed age, social status (partnership, having children, satisfaction with relationship and sex life), lifestyle (alcohol, tobacco, sport, and sleep), and job status (highest educational degree, current field of work, job position, working hours, monthly gross income, presenteeism, and absenteeism). Personal and family history further comprised information about malignancy, cardiovascular disease, breathing disorder, abdominal and urogenital diseases, metabolic disorder, skin and/or hair diseases, neuromuscular and psychiatric disorders as well as bone and joint diseases. Quality of sleep was assessed in a 4-point scale (1 = very good, 4 = very bad). Satisfaction with partnership and sex life was assessed on a 5-point scale (1 = not at all satisfied, 5 = very satisfied) (supplementary file 2).

In addition, we used segments of a multidimensional standardized questionnaire on subjective health status and satisfaction with life and sexuality in women above

the age of 45 years that has been developed by Bucher et al. [25, 27]. Subjective health status was assessed on a 5-point scale (1 = very good, 5 = very bad). Medical condition comprised 15 aspects that were each assessed on a 3-point scale indicating how much the respondent was affected by the condition during the preceding 3 months (1 = not affected, 2 = somewhat affected, 3 = severely affected; score 15 = no overall impairment, score 45 = severe impairment in all aspects). Impairment by seven menopausal symptoms was assessed on a 4-point scale (1 = not affected, 2 = somewhat affected, 3 = moderately affected, 4 = severely affected; score 7 = no overall impairment, score 28 = severe impairment by menopausal symptoms). Satisfaction with oneself covering four aspects was assessed on a 5-point scale (1 = not satisfied, 5 = absolutely satisfied; score 4 = no general satisfaction with oneself, score 20 = high satisfaction with oneself in all aspects). Furthermore, women were asked to evaluate sexual function during the menopausal transition including the desired and actually experienced sexual activity (caresses, petting, and sexual intercourse).

Female sexual function

The FSFI-d (Female Sexual Function Index, German version) is a multidimensional standardized, validated questionnaire [24]. It measures six aspects of female sexual function, e.g., desire, arousal, lubrication, orgasm, satisfaction and pain. Each item ($n = 19$) is rated on a 5-point scale assessing how often one has experienced a certain situation within the past 4 weeks. The sum of each subgroup is multiplied by a certain factor resulting in a score of maximal 6 points per subgroup and 36 points in total, respectively. A low score implies sexual dysfunction, whereas a high score indicates a pronounced sexual activity, satisfaction and successful sexual function.

Blood chemistry

Fasting venous blood samples (one EDTA tube containing 7.5 ml, one EDTA tube containing 2.7 ml, and two serum tubes each containing 7.5 ml) were taken from each subject at 8–10 am. In premenopausal women, blood was withdrawn within menstrual cycle day 1–5. Serum tubes were centrifuged at 4000 rpm for 10 min. Blood chemistry analysis was performed by UNILABS Laboratory (Murtenstrasse 143, 3008 Bern). The hormones luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), total testosterone (TT), dehydroepiandrosterone sulfate (DHEAS), prolactin (PRL), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) were analyzed by assays from Abbott (LOT numbers for LH: 47903UI02, FSH: 49908UI02, E2: 57929UI0, TT: 10413UP00, DHEAS: 01514L000, PRL: 50903UI00, TSH: 54900UI00, fT3: 49914UI00, fT4: 50914UI00). Sexual hormone-binding globulin (SHBG) was analyzed by an assay by Siemens (LOT number 345), and hemoglobin (Hb), C reactive protein (CRP) and ferritin by Sysmex SLS-hemoglobine method (sodium-lauryl-sulfate) (LOT numbers for Hb: D5002, CRP: 40270Y600, ferritin: 48906UI01), respectively.

Androgen receptor (AR) polymorphism

AR CAG repeats were determined from an EDTA blood sample. The method has been described in detail before [22]. Briefly, DNA was isolated from blood samples using the commercial Nucleon BACC Kit (GE Healthcare, Freiburg, Germany). A fragment of exon 1 of the AR was amplified using polymerase chain reaction (PCR). The number of CAG repeats was calculated by comparing the detected PCR fragment to sequencing reactions that are run in parallel to the samples and serve as molecular size marker. In addition, PCR samples with known numbers of CAG repeats (15, 20 and 30 CAG repeats as determined by cloning and sequencing the corresponding AR exon 1 fragments) were used as internal standards for the calculation.

Statistical analysis

Non-parametric spearman rank analyses were performed on original data, and log transformation was performed for parametric multiple regression models (stepwise backwards method). To further elucidate significant interdependent net effects within the steroid hormone profile in GD patients, the multivariate statistical tool of factor analysis was used to determine cluster structures. A principal component analysis with orthogonal rotation (varimax) was applied. When factors correlate among each other, this can be used to determine and explain interrelationships of a higher level between the respective clusters. Variables included the hormones mentioned above. Each variable included in such a factor correlates with it in either a positive or negative fashion ranging from − 1 to 1. Prior to calculation, the matrix variables were tested for sphericity according to Bartlett and the measure of sampling adequacy was determined according to Kaiser–Mayer–Olkin (KMO).

Results

Characteristics of the cohort

In total, 45 Caucasian women were recruited. Information on age, social and job status, life style, health status, and prevalent medication is provided in Table 1. Briefly, mean

Table 1 Characteristics of the cohort

	N (%)	Mean (standard deviation)
Job and social status		
Number of children		
0	11 (24.4)	
1	7 (15.5)	
2	19 (42.2)	
3	8 (17.7)	
Educational degree		
None	1 (2.2)	
Vocational school	35 (77.7)	
University, technical college	9 (20)	
Monthly gross income		
< 5000 Swiss Francs	20 (44.4)	
5000–10,000 Swiss Francs	22 (48.8)	
> 10,000 Swiss Francs	3 (6.6)	
Person that decides on expenses		
Partner	1 (2.2)	
Together	26 (57.7)	
Woman (respondent)	3 (6.6)	
Own income	15 (33.3)	
Subjective health status and lifestyle		
Alcohol consumption		
None	1 (2.2)	
< 2 ×/week	35 (77.7)	
≥ 2 ×/week	9 (20)	
Tobacco consumption		
Non-smoker	32 (71.1)	
Smoker	13 (28.9)	
Physical activity		
None	2 (4.4)	
< 2 ×/week	31 (68.9)	
≥ 2 ×/week	12 (26.7)	
Body mass index (BMI) (kg/m^2)		23.3 (3.8)
> 25 and < 30	11 (24.4)	
≥ 30	3 (6.6)	
Prevalence of chronic conditions/diseases		
None	44 (97.8)	
Mild colitis ulcerosa	1 (2.2)	
Subjective health status (score 1–5)		1.58 (0.66)
Very good (1), good (2)	43 (95.5)	
Neither good nor bad (3)	1 (2.2)	
Rather bad (4)	1 (2.2)	
Bad (5)	0	
Impairment by medical condition (score range 15–45)		20.6 (3.2)
Impairment by menopausal symptoms (score range 7–28)		14.2 (3.5)
Sleep		
Quality (score range 1–5)		2.7 (0.6)
Very good (1), good (2)	37 (82.2)	
Duration (h)		6.8 (1.5)
Satisfaction with oneself (score 4–20)		16.6 (1.6)

Table 1 (continued)

	N (%)	Mean (standard deviation)
Sick days		
Being at work despite being sick (presenteeism)	27 (60)	
Missing < 5 h in the preceding month due to being sick (absenteeism)	34 (75.5)	
Medication		
Reports of medication use	24 (53.3)	
Analgesics	13 (28.9)	
Menopausal hormone therapy	5 (11.1)	
Hypnotics	4 (8.9)	

age was 52.8 ± 5.1 years. 60% had at least two children while 24.4% were childless. 20% had a degree from university or advanced technical college, respectively. 44.4% of the women had a monthly gross income below 5000 Swiss Francs. 20% reported regular alcohol consumption at least twice a week. The majority of participants (71.1%) were non-smoker and physically active (till sweating, 77%). Mean BMI was 23.3 ± 3.8 with 11 subjects (24.4%) being overweight and 3 obese (6.6%). The prevalence of being disease free was 97.7% ($n = 44$), with only one woman suffering from mild ulcerative colitis (no regular medication). 95.5% of the participants rated their health status to be good or very good. Similarly, impairment by medical conditions was rather low (score 20.6 ± 3.2). 73.3% of the subjects reported to have menopausal symptoms with impairment being moderate (score 14.2 ± 3.5). Mean sleep duration was 6.8 ± 1.5 h, and sleep quality was rated to be (very) good by 82.2%. Most participants were content with themselves and pleased with their body, respectively (score 16.6 ± 1.6). The good objective and subjective health status and well-being was reflected in the low numbers of sick days. 53.3% of the participants reported use of any kind of medication ($n = 24$ reports). The major medication group was analgesics ($n = 13$, 28.9%). Five women (11.1%) were using menopausal hormone therapy. Four women (8.9%) were taking hypnotics from time to time.

Partnership and sexual function

All recruited women were living in a heterosexual partnership, and 60% were married. Mean duration of partnership was 19.3 ± 10.8 years. Mean age difference between partners was 3.3 ± 5.7 years with the female being older than the male partner in 13.3%. 89% of the subjects rated their partnership to be (very) good, and 57.8% were (very) pleased with their sex life. Only one in four women ($n = 12$, 26.7%) at least partly agreed to the statement that the general sexual activity in women declines with age. When being asked if sexual function has changed during the menopausal transition ($n = 33$), one half of the women reported an unchanged function (51.5%) while the other half had observed a decline (48.5%).

Sexual function (desire, arousal, lubrication, orgasm, satisfaction, pain, and total score) was then assessed more specifically by the FSFI-d with a low score implying sexual dysfunction (Table 2). Desire was the sexual function domain with the lowest mean score. However, there were women with the lowest scores in almost all other domains indicating that they might have had sex without any arousal, orgasm, lubrication but pain.

More detailed information with respect to desired and actually experienced sexual activity (caresses, petting, and sexual intercourse) during the preceding 3 months was gained by the questionnaire about health, life satisfaction and sexuality in middle-aged women (Table 3). The majority of women (95.5%) desired caresses several times per week which came true for 77.8% with 86.7% of all enjoying being caressed. The desired and actual frequency of petting and sexual intercourse displayed a quite different pattern. 84.4% desired petting and 46.7% sexual intercourse at least once per week. Indeed, more than half of the women (51.1%) practiced petting at the desired frequency with 71.1% of all women feeling (very) good in

Table 2 Sexual function assessed by FSFI-d ($n = 45$)

Sexual function domain	Mean (standard deviation)	Minimum (0 points) … maximum (6 and 36 points, respectively)
Desire	3.3 (0.9)	1.2 … 4.8
Arousal	4.1 (1.5)	0.0 … 6.0
Lubrication	4.2 (1.8)	0.0 … 6.0
Orgasm	4.2 (1.9)	0.0 … 6.0
Satisfaction	4.6 (1.5)	0.8 … 6.0
Pain	4.4 (2.1)	0.0 … 6.0
Total score	24.9 (8.6)	3.2 … 34.8

Each item is rated on a 5-point rating scale assessing how often one has experienced a certain situation within the past 4 weeks

Table 3 Desired frequency versus experienced frequency of caresses, petting and sexual intercourse, assessed by the questionnaire about health, life satisfaction and sexuality in middle-aged women [25]

	Every day	Several times per week	Once per week	Several times per month	Once per month	Less than once monthly	Never
Desired frequency of caresses	36	7	1	0	1	0	0
Experienced frequency of caresses	24	11	6	1	0	2	1
Desired frequency of petting	12	13	13	4	2	0	1
Experienced frequency of petting	4	11	8	11	3	3	5
Desired frequency of sexual intercourse	2	15	21	5	1	1	0
Experienced frequency of sexual intercourse	1	10	13	9	5	5	3

Table 4 Blood chemistry

Blood parameter (reference value range)	Mean (standard deviation)
Luteinizing hormone (LH) (2.0–7.8 U/l, postmenopause 5.2–62.0 U/l)	23.3 (0.2)
Follicle-stimulating hormone (FSH) (3.9–8.8 U/l, postmenopause 18–150 U/l)	48.9 (0.2)
Estradiol (E2) (78–266 pmol/l, postmenopause < 103 pmol/l)	148.8 (1.0)
Total testosterone (TT) (0.3–3.8 nmol/l, postmenopause 0.4–4.5 nmol/l)	0.9 (0.9)
Sexual hormone-binding globulin (SHBG) (17.0–112.2 nmol/l)	55.4 (0.3)
Free androgen index (FAI) (TT × 100/SHBG)	1.9 (1.8)
Dehydroepiandrosterone sulfate (DHEAS) (1.5–7.7 µmol/l)	5.3 (6.5)
Prolactin (PRL) (5.2–26.5 µg/l)	11.6 (5.0)
Thyroid-stimulating hormone (TSH) (0.3–4.3 mU/l)	2.0 (2.0)
Free triiodothyronine (fT3) (2.6–5.7 pmol/l)	4.3 (− 0.5)
Free thyroxine (fT4) (9.0–19.0 pmol/l)	11.9 (0.2)
Hemoglobin (Hb) (121–154 g/l)	137.4 (− 0.4)
C reactive protein (CRP) (<5 mg/l)	1.7 (4.6)
Ferritin (< 15 completely depleted, 15–30 empty or scarce, 30–50 functional iron deficiency possible)	69.8 (1.8)

doing so. In women desiring sexual intercourse at least once per week, satisfaction was (very) good for 75.6%. On the other hand, women that desired petting or sexual intercourse several times per month or less experienced more petting and sexual intercourse than they wished for. Five women (11.1%) stated they did not have any sexual intercourse during the preceding 3 months due to lack of libido (4.4%), dyspareunia (2.2%) or health/libido issues of the partner (6.6%).

Blood chemistry

The blood chemistry results are presented in Table 4. On an average, blood parameters were within the normal range. Based on their hormonal profiles, the majority of women ($n = 34$, 75.6%) were postmenopausal (E2 < 103 pmol/l and FSH > 40 U/l), while 20% ($n = 9$) were pre- and only 4.4% ($n = 2$) perimenopausal.

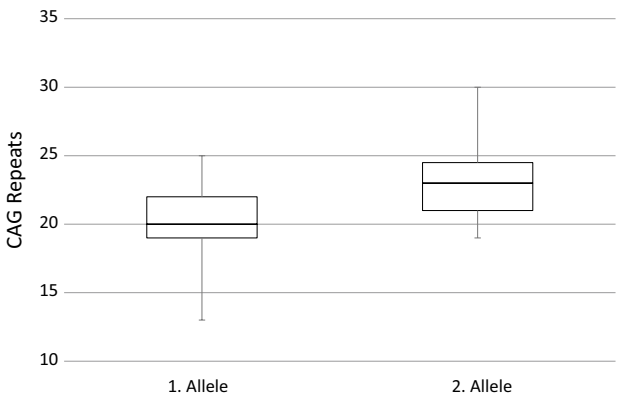

Fig. 1 CAG repeat number on the first and second allele of the AR (box plot). *CAG* cytosine, adenosine and guanine

Table 5 Correlation between sexual function (FSFI-d) and CAG repeat length

Correlation between sexual function subdomains (FSFI-d) and CAG repeat length	Spearman correlation coefficient	*p* value
Desire		
Total	−0.11	0.48
Frequency	−0.12	0.50
Level	−0.09	0.59
Arousal		
Total	−0.29	0.06
Frequency	−0.19	0.21
Level	−0.31	0.05
Confidence	−0.28	0.07
Satisfaction	−0.31	*0.04*
Lubrication		
Total	−0.26	0.09
Frequency	−0.31	*0.04*
Difficulty	−0.29	0.06
Frequency of maintaining	−0.23	0.14
Difficulty in maintaining	−0.26	0.09
Orgasm		
Total	−0.19	0.23
Frequency	−0.19	0.21
Difficulty	−0.23	0.14
Satisfaction	−0.18	0.25
Satisfaction		
Total	−0.26	0.09
With closeness to partner	−0.20	0.19
With sexual relationship	−0.31	*< 0.05*
With overall sex life	−0.29	0.06
Pain		
Total	−0.37	*0.02*
Frequency during vaginal penetration	−0.40	*0.01*
Frequency following vaginal penetration	−0.45	*< 0.01*
Level during or following vaginal penetration	−0.43	*< 0.01*
Total score	−0.67	0.22

Significant correlations are highlighted by italics

CAG cytosine, adenosine and guanine

Androgen receptor (AR) polymorphism (CAG repeat sequence)

Mean CAG repeat number was 21.6 ± 1.9. Figure 1 presents the CAG repeat number on the first and second allele of the AR. In a next step, we analyzed the association between CAG repeat length and sexual function (FSFI-d) (Table 5). There was a significantly inverse correlation between CAG repeat length and frequency with lubrication, dyspareunia, satisfaction with arousal and satisfaction with sexual relationship. Accordingly, higher numbers of CAG repeats were associated with more frequent or more severe pain during or after sexual intercourse which might have negatively affected arousal and satisfaction with the sexual relationship. To further analyze the association between pain and CAG repeat length, we incorporated the parameter serum FSH into our model (multiple regression analysis) (Table 6). We found that serum FSH levels as well as CAG repeat length had an impact on dyspareunia. Accordingly, higher serum FSH levels and/or CAG repeat length were correlated with more pain during or after vaginal penetration. For example, if CAG repeat length increased by 1 the FSFI-d score for total pain would decrease by 0.16, and the FSFI-d subscores for pain frequency during and following vaginal penetration by 0.13 each. The same principle applied to serum FSH levels. However, there was no significant correlation between serum androgen levels, CAG repeat length and other FSFI-d (sub-)domains, respectively. All the data were controlled for age and blood iron status.

The variables examined in this investigation were largely interrelated, that is, they were most likely influencing each other. In such a case, a factor analysis is adequate to describe general patterns of mutual influence within the whole set of variables (called matrix). This matrix passed the required Bartlett test as well as the measure of sampling adequacy (KMO measure 0.63: mediocre to meritorious) and a factor analysis was possible. Hence, we performed a principal component analysis with varimax rotation including Kaiser normalization which yielded a two-dimensional model. This model explains 71% of the variance of all assessed data ($p < 0.001$). That is, about three quarters of all aspects of postmenopausal sexual well-being can be explained by these factors. These two dimensions influencing the woman's sexual well-being were named "sexuality" and "hormonal status" and they consisted of various parameters (Table 7). In detail, the subdomains of the FSFI (excitement, satisfaction, lubrication, orgasm, lack of pain, and desire) defined the dimension "sexuality" in a positive way. Hormone-related parameters (CAG repeats, FSH and LH) also belonged to this dimension of sexual well-being. In this case, the higher the value of each parameter, the less positive sexuality was experienced. The dimension "hormonal status" was defined by high serum levels of LH and FSH as well as low levels of E2, indicating a postmenopausal state. Desire as such was strong in these women; nevertheless, the other sexual functions such as excitement, satisfaction, lubrication and orgasmic ability were not present. This may indicate that after menopause, sexual desire was still and markedly present, but sexual fulfillment became more difficult. The factor analysis did not show any significant impact of SHBG, DHEAS and TT on female sexual well-being.

Table 6 Association between pain, CAG repeat length and serum FSH (multiple regression analysis)

	Regression coefficient (standard deviation)	*t* test	*p* value
Pain total	9.49 (1.70)	5.57	*< 0.001*
Serum FSH	− 0.04 (0.01)	− 4.17	*< 0.001*
CAG repeat length	− 0.16 (0.08)	− 2.07	*< 0.05*
Regression equation: pain = 9.49 − 0.04 serum FSH − 0.16 CAG repeat length			
Pain frequency during vaginal penetration	8.03 (1.46)	5.49	*< 0.001*
Serum FSH	− 0.03 (0.01)	− 4.29	*< 0.001*
CAG repeat length	− 0.13 (0.07)	− 1.99	0.05
Regression equation: pain frequency during vaginal penetration = 8.03 − 0.03 serum FSH − 0.13 CAG repeat length			
Pain frequency following vaginal penetration	8.06 (1.56)	5.15	*< 0.001*
Serum FSH	− 0.03 (0.01)	− 3.69	*0.001*
CAG repeat length	− 0.13 (0.07)	− 1.86	0.07
Regression equation: pain frequency following vaginal penetration = 8.06 − 0.03 serum FSH –0.13 CAG repeat length			
Pain level during or following vaginal penetration	8.42 (1.39)	6.06	*< 0.001*
Serum FSH	− 0.03 (0.01)	− 4.41	*< 0.001*
CAG repeat length	− 0.16 (0.06)	− 2.49	*0.017*
Regression equation: pain level = 8.42 − 0.03 serum FSH − 0.16 CAG repeat length			

Significant correlations are highlighted by italics

CAG cytosine, adenosine and guanine, *FSH* follicle-stimulating hormone

Table 7 Factor analysis resulting in a two-dimensional model of sexual well-being in midlife women

	Sexuality	Hormonal status
Excitement	0.94	
Satisfaction	0.89	
Lubrication	0.89	
Orgasm	0.86	
Pain	0.86	
Desire	0.64	0.39
AR CAG repeats	− 0.32	
Serum E2 level		− 0.79
Serum LH level	− 0.37	0.78
Serum FSH level	− 0.52	0.71

AR androgen receptor, *CAG* cytosine, adenosine and guanine, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *E2* estradiol, *TT* total testosterone, *DHEAS* dehydroepiandrosterone sulfate

Discussion

The prevalence of sexual dysfunction, specifically desire disorders, has frequently been reported to increase with age [28–30] and during menopause [5, 31]. Most studies focused on the impact of changing androgen serum levels [10, 32–34] and androgen therapy [7–9, 35–39] on female sexual function.

To our knowledge, we are the first to study the association between AR CAG repeat polymorphism and female sexual function. In our cohort of healthy, midlife, well-educated, middle-class, mostly postmenopausal women living in a heterosexual satisfying partnership, we found that (1) sexual function was perceived to remain stable or to decline during menopausal transition with (2) sexual desire scoring lowest, (3) most women desired and received caresses and petting, and mostly enjoyed it, (4) women who desired weekly sexual intercourse also enjoyed it, while on the other hand (5) some women experienced less petting and sexual intercourse than they wished for. (6) Androgen serum levels did not correlate with sexual function, and (7) mean CAG repeat number was approximately 22. There was (8) a highly inverse though non-significant correlation between female sexual function and AR CAG repeat polymorphism with specifically (9) higher numbers of CAG repeats being significantly positively correlated to more frequent or more severe pain during or after sexual intercourse. Interestingly, (10) postmenopausal women still experienced sexual desire but sexual fulfillment was restricted due to missing/decreased excitement, satisfaction, lubrication, and orgasmic ability.

Similar to previous studies on female sexual function and ageing and menopause [5, 28–31], respectively, most women in our cohort confirmed that the prevalence of sexual dysfunction had increased during the menopausal transition. None described an increase of sexual function. Yet, the range between observed and experienced sexual function in midlife women across the FSFI subdomains was big.

However, reduced sexual function is not always associated with personal distress [29, 31]. Accordingly, more than half of the subjects in our study were still satisfied with their sex life.

Androgens are thought to have a non-negligible impact on female sexual function [8]. However, previous studies have yielded conflicting results as to if and to which extent serum androgen levels are correlated to female sexual function [7, 8, 10, 33, 34, 40–42]. In our study, we did not observe a correlation between serum androgen levels (DHEAS, TT) and sexual function across all FSFI subdomains. Still, several studies found a positive impact of androgen therapy on menopausal women complaining of female sexual dysfunction [7–9, 37–39]. So far, there is no established parameter to predict responsiveness to androgen treatment in an individual woman [12]. Possibly, efficacy of androgen treatment is based on the activity degree of the corresponding receptor, the AR. In men, the length of AR gene CAG repeats has been found to inversely correlate with androgen function [43–46]. In women, an association was found between androgen effects and the prevalence of the polycystic ovary syndrome [47, 48]. However, so far, there has been no study on the impact of the length of AR gene CAG repeats on female sexual function. In male-to-female transsexuals, longer length of CAG repeats was associated with higher free testosterone but not total testosterone serum levels. In the same study, subjects with moderate length of CAG repeats and low testosterone serum levels were more likely to have lower sexual desire than those with longer or shorter length of CAG repeats [16]. However, as the sample size was small, it was difficult to find a biological explanation for this finding [16]. In our study, we found a highly inverse though non-significant correlation between female sexual function and AR CAG repeat polymorphism. However, when analyzing the different FSFI subdomains, we found a significantly positive correlation between length of CAG repeats and dyspareunia. This finding supports a previous study showing that women using combined hormonal contraception had an increased risk of vestibulodynia when having long CAG repeats [17]. Indeed, the vaginal wall has been shown to express AR [49], and the studies in ovariectomized mice reported an increase in the density of nerve fibers within the lamina propria and sympathetic fibers within the muscularis after treatment with the androgenic pro-hormone DHEA [50]. Thus, not only sex hormone serum levels but also the genetic setting facilitating hormone action seems to have an influence on sexual function in women. The age-related decline of androgens, therefore, accentuates the relevance of the genetically determined and thus lifelong AR activity. However, assessment of the length of CAG repeats is neither part of routine laboratory workup in women with sexual dysfunction nor in any other endocrine condition, e.g., idiopathic hyperandrogenism. Yet, experts advise to assess AR CAG repeat sequence in target patients with elevated risk for adverse effects, such as postmenopausal women and overweight men [51]. Assessment of the AR CAG repeat sequence could also allow for more easily finding the individual appropriate androgen dosage for sexual dysfunction treatment. Still, unpredictable responses to androgen therapy might still occur given the mosaic like pattern of AR distribution within the female body [14, 15].

Clearly, our study also has some limitations. The sample size was small. Thus, it was not possible to adjust our data to other factors that may influence female sexual function such as socioeconomic status, overall satisfaction with life and partnership specifically, objective and subjective physical and mental health, respectively. Furthermore, serum androgen levels are influenced by, e.g., age, menstrual cycle phase, seasons, circadian rhythm, and medication [52]. However, we did our best to control those influencing factors.

On the other hand, our study has strengths too. We chose strictly defined inclusion criteria. Thus, we were sure to not have biased the results by severe comorbidities, partnership issues or the use of, e.g., psycho-pharmaceuticals, respectively. Also, the prevalence of MHT use was low. As the laboratory workup was within the normal range, we were confident to have excluded hormonal disorders, e.g., hypothyroidism as being the cause for sexual dysfunction. By applying a standard validated questionnaire, FSFI, our results will be comparable to future studies. Furthermore, the rotated matrix of components with factor loadings in our study confirmed the validation of the FSFI. Our results displayed a wide range of sexual function which is comparable to previous studies in elderly women [31, 53, 54].

In conclusion, our results suggest that the AR polymorphism is a non-negligible factor in female sexual function. Especially, women with less active AR were shown to suffer more frequently or more severe from pain during or after sexual intercourse. Given the importance of this subdomain of sexual disorders, incorporating the assessment of the AR CAG length could improve multidisciplinary treatment of affected patients.

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Author contributions BS, MF, CH: data collection and manuscript writing; SS: providing the questionnaire about health, life satisfaction and sexuality in middle-aged women; MZ: protocol development, data analysis, and manuscript writing; PS: protocol/project development, funding, and manuscript writing.

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Conflict of interest B Sutter, M. Fehr, C. Hartmann, S. Schmid, M. Zitzmann and P. Stute declare to have no conflict of interest in context of this manuscript.

Data statement Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

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