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Impact of body iron store on sexual function: a comprehensive review and pilot cohort study in midlife women

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Abstract

Purpose Both iron deficiency (ID) and female sexual dysfunction (FSD) affect more than 25% of the world population. The aim of this study was to identify a connection between these two conditions based on the existing literature and to investigate this interrelation in a small pilot cross-sectional study.

Methods A database search for publications referring to ID and FSD was conducted. The resulting common denominators were used to formulate hypotheses regarding the interaction of these diseases. Simultaneously, 45 healthy middle-aged women completed questionnaires about their sexual function and provided a blood sample for the purpose of determining ferritin and haemoglobin levels. The main outcome measures included an analysis of responses to questions on sexuality and partnership and of blood ferritin and haemoglobin levels. The secondary outcomes included an assessment of further influences on libido, such as sex hormones, menopausal status, health, and life satisfaction.

Results Altered monoaminergic cerebral metabolism, hyperprolactinaemia and hypothyroidism, impaired socioemotional interaction, increased anxiety, and depression in both, ID and FSD, account for the most comprehensive explanations for the postulated association between the two conditions. Despite a feasible assumption, our empirical findings failed to demonstrate any correlation between ID and FSD. We identified a certain impact of menopausal hormonal status on sexual function.

Conclusion ID has no influence on FSD in the given population, although the literature suggests that FSD may at least be partly due to ID. Further research seems justified given the potential advantages for sexual health, considering that ID is an easily treatable disease.

Keywords Iron deficiency (anaemia) · Ferritin · Sexual (dys)function · Libido · Healthy midlife women

Introduction

Iron deficiency (ID) is the most prevalent nutrient deficiency. According to the World Health Organization (WHO), ID affects approximately two billion people worldwide, and its prevalence continues to increase [1]. ID is associated with many physical and psychological symptoms, including fatigue, listlessness, dizziness, decreased immunity, impaired performance and activity, altered hormonal metabolism, depression, anxiety, and cognitive impairment [2–16]. Similarly, female sexual dysfunction (FSD) is among the most widespread health issues, affecting at least 25% of women worldwide, reaching even a higher prevalence of up to 86.5% in postmenopausal women [17]. Female sexual function changes with age and is susceptible to various sources of disruption, including overall physical and mental health states, partnership quality and sociocultural as well as socioeconomical factors [18]. Furthermore, ovarian sex steroids have a major impact, as their decline due to menopause has been found to be associated with an increased incidence of FSD [19–21].

However, given the wide spectrum of symptoms caused by ID and the equally multifaceted causes of FSD, as well as

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the congruency, an emerging question is whether ID exerts an influence on female sexual function. Indeed, a short-duration intervention study recently revealed a significant correlation between ID anaemia and FSD in middle-aged women, Gulmez et al. [22]. The aim of the present publication was to (1) provide a comprehensive literature review on the association between ID and FSD and (2) assess the impact of body iron levels on female sexual function in a cross-sectional pilot cohort study in healthy, non-anaemic midlife women.

Materials and methods

Literature research

In November 2018, a literature research was conducted through PubMed, PubMed Central, MedPilot, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, SOMED, and Google Scholar databases without limitations on year of publication, sex, age, or species. The keywords "iron, ferritin, transferrin, transferrin receptor, iron deficiency, iron-deficiency an(a)emia, iron loss, hypochromia, sideropenia, low ferritin, low serum iron, iron depletion, iron metabolism, h(a)emoglobin deficiency", and their truncated forms were linked to the keywords "sexual dysfunction, dyspareunia, vaginismus, sexual arousal (disorder), sexual desire (disorder), sexual interest, libido, lubrication, sexual activity, orgasm (disorder), sexual pain disorders, frigidity, sexual function, sexual response cycle, sexual satisfaction, female sexual disorder, FSD", and their variations. Inclusion criteria for this comprehensive literature review were a citation index of at least 70 if published before 2010 and publication in a renowned journal (impact factor > 2 and, if available, h5-index > 20). Animal studies were only considered if they were prospective and controlled, with appropriate animal models and measurements (e.g., dopamine metabolism in rats). Human studies were considered only if the results for males and females were presented separately. In addition, studies that included subjects who were seriously ill were not included due to the negative influence of severe diseases on sexual function [23, 24]. This search strategy identified 580 articles. Titles and abstracts were screened for the prespecified inclusion and exclusion criteria and in case of uncertainty the full-text articles were obtained and evaluated. 77 articles were eligible for this review.

Pilot study characteristics

This was a single-center, cross-sectional, observational, non-interventional trial in midlife women. 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. To form our study group, we recruited German-speaking women between November 2013 and June 2015 at the Department of Obstetrics and Gynecology, Inselspital Bern, Switzerland. Recruitment was performed by the principle investigator, Petra Stute M.D., a study nurse and three doctoral students (Conny Joanna Hartmann, M.D., Barbara Stutter, M.D. and Manuela Fehr, M.D.) 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 and shopping centers). Advertisements and flyers already listed inclusion and exclusion criteria, so that interested women would only contact the investigators by phone or mail if they met the criteria or if they had further questions about it. After making clear that the interested person fulfilled the criteria, an appointment was made for further explanation, questionnaires and collection of blood samples.

Inclusion criteria were as follows:

1. Age between 45 and 65 years.
2. Stable and confiding heterosexual relationship for at least 1 year.

Women suffering from diseases or taking drugs that are well-known causes of FSD or women with diagnosed sexual problems such as mentioned below could not participate, since this would have made it clearly more difficult to distinguish between iron deficiency and the well-known risk factors as the real cause of possibly detected sexual problems in study participants. Therefore, exclusion criteria were as follows:

1. Depression [Hospital Anxiety and Depression Scale (HADS-D) score < 8] [25].
2. Diseases such as cancer, multiple sclerosis, diabetes mellitus, Parkinson disease, or thyroid dysfunction.
3. Psychiatric disorders, substance abuse (drugs, more than one package of cigarettes), or acute stress.
4. History of sexual abuse, diagnosed dyspareunia, vaginism, orgasm disorder, or urinary incontinence.
5. Use of the following medication during eight 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 (androgens and PDE5 inhibitors).

All participants followed a standardized battery of assessments (Fig. 1) including age, social status (partnership, having children, satisfaction with relationship and sex life),

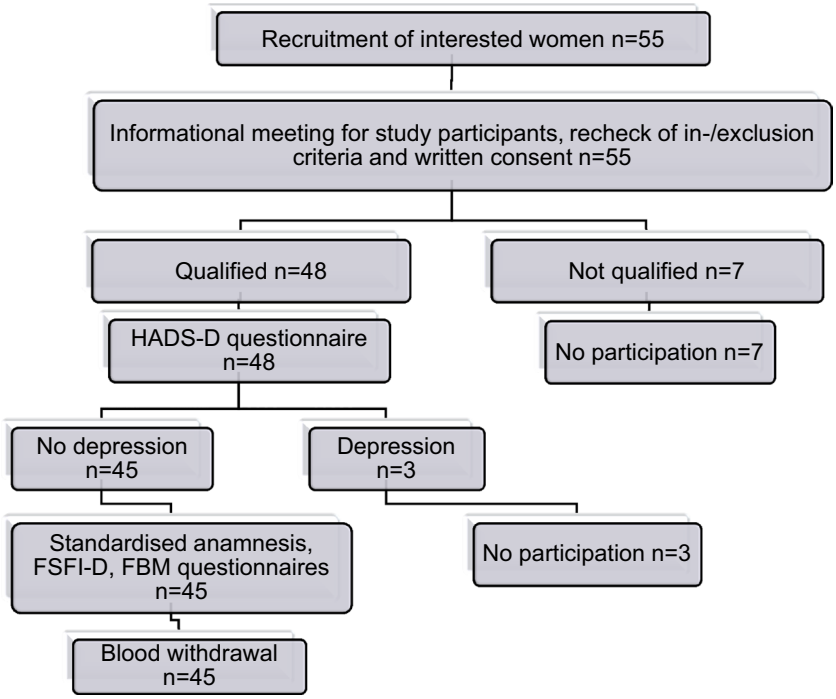

Fig. 1 Flowchart of the study protocol

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 disease, metabolic disorder, skin and/or hair disease, neuromuscular and psychiatric disorder as well as bone and joint disease. 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). In addition, we used segments of a multidimensional standardized questionnaire on subjective health status, satisfaction with life and sexuality in women above age 45 that has been developed by Bucher et al. [26]. 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, sexual intercourse). Female sexual function was assessed by the multidimensional standardized, validated questionnaire FSFI-D [27]. It features 19 items measuring 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 six 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. Fasting venous blood samples (1 EDTA tube, 7.5 ml; 1 EDTA tube, 2.7 ml; 2 serum tubes, 7.5 ml) were obtained from each subject between 8 and 10 a.m. In premenopausal women, blood was withdrawn on menstrual cycle days 1–5. Serum tubes were centrifuged at 4000 rpm for 10 min. Blood chemistry analyses were performed by UNILABS Laboratory (Murtenstrasse 143, 3008 Bern). The hormones luteinizing hormone (LH), follicle stimulating hormone (FSH), oestradiol (E2), free 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 globuline (SHBG) was analyzed by an assay by Siemens (LOT number 345). Haemoglobin (Hb), C reactive protein (CRP), and ferritin were analysed by Sysmex SLS-hemoglobin method (sodium-lauryl-sulfate) (LOT numbers for Hb: D5002, CRP: 40270Y600, ferritin: 48906UI01).

Statistical analysis

Participants were divided into two groups based on menopausal status using FSH, LH and E2 serum-level thresholds (postmenopausal FSH: 18–150 U/l, postmenopausal LH: 5.2–62.0 U/l, postmenopausal E2: < 103 pmol/l). To assess the correlations between FSFI-D subscales and blood values, Pearson correlation coefficients were calculated, and Mann–Whitney tests were performed. The correlation size was classified according to Cohen's (1988) rules of thumb (|0.1| is classified as small, |0.3| as medium and |0.5| as large) and effect size [28]. Furthermore, the Mann–Whitney test, Pearson and Spearman correlations, and the Kruskal–Wallis test were applied to assess the associations between blood chemistry, sexual function, socioeconomic data, and menopausal and health states, respectively. Statistical tests were chosen based on data quality and quantity.

Results

Comprehensive literature review on the association between iron deficiency and female sexual dysfunction

So far, the relation between ID anaemia and sexual function in women of reproductive age has only been assessed by one prospective pilot study [22]. Herein, 3 months of oral iron supplementation in women with ID anaemia significantly improved their sexual function and decreased their anxiety, so that researchers concluded that ID anaemia let to increased anxiety which in turn resulted in impaired sexual function. However, as there was no control group the impact of ID itself or anaemia on sexual function could not be evaluated. Furthermore, results were not adjusted for menstrual cycle phase and sex hormones. To substantiate the findings of Gulmez and to justify further research on this topic, it appeared to be reasonable to construct a theoretical synopsis, based on the existing literature, pathophysiologically linking ID and FSD. Postulating ID as a possible cause of FSD, databases were searched for health consequences of ID as well as causes of FSD. Whenever such causes and consequences were superimposable, theoretical plausible connections were hypothesized. We found such connections on the basis of enzymatic, neurotransmissional, hormonal, psychological, and sociobehavioural commonalities (Fig. 2).

Neurotransmitter systems

The production of the neurotransmitters dopamine and norepinephrine is dependent on iron-containing tyrosine hydroxylase. Thus, it has been presumed that ID alters neurotransmitter synthesis and metabolism. Indeed, research demonstrated an increase in steady-state extracellular dopamine concentration [12], a decreased expression of dopamine transporter (DAT), D1 and D2 receptors, and dopamine uptake in iron-deficient rodent striatum [5, 14, 29]. Neither DAT nor D1 and D2 receptor expression levels normalized with iron repletion following the early postnatal period of ID in rodent models [30]. Thus, early life ID may result in long-term brain abnormalities that manifest as behavioural

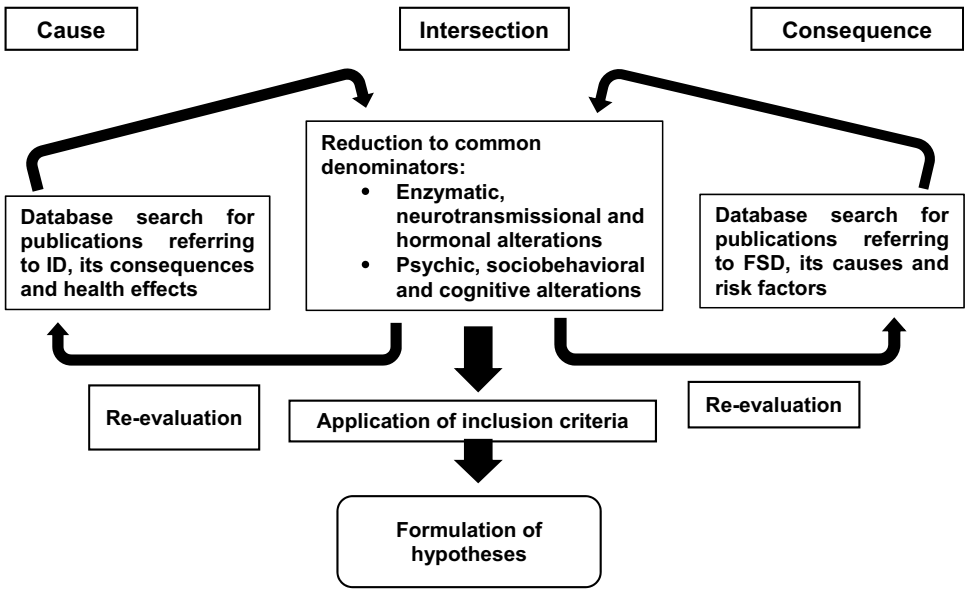

Fig. 2 Theoretical synopsis pathophysiologically linking iron deficiency and female sexual dysfunction

and cognitive deficits. Accordingly, it was demonstrated that formerly iron-deficient individuals showed deficits in documented frontal-striatal-dependent set-shifting tasks, implicating dopamine dysfunction, whereas control subjects performed better [31]. Dopamine is a well-known modulator of female sexual behaviour. It leads to increased sensorimotor integration and response to sexual stimuli, and influences appetence, motivation, orgasm and reward via various dopaminergic cerebral pathways [32]. The higher FSD prevalence during the intake of antidopaminergic drugs, e.g., antipsychotics, supports dopamine as a stimulating factor. Moreover, dopamine seems to influence cerebral progesterone receptor expression, whose stimulation in turn increases mating habits in rats [33–36]. Thus, the diminished functionality of the dopaminergic system may be one of the most important biochemical connection between ID and FSD. There is conflicting evidence regarding whether other monoaminergic systems, i.e., serotonin and norepinephrine, are sensitive to changes in brain iron level [8, 10, 37–40]. ID rodent brains showed diminished concentrations of serotonin transporters as well as reduced serotonin uptake by some subgroups of serotonin receptors [11, 14, 38, 41]. As expected, changes to extracellular serotonin concentration can be observed 30. Serotonin is a well-known inhibitor of sexual function in both sexes. Accordingly, sexual dysfunction can present as side effect of various antidepressants [36, 42]. However, whether serotonin itself or its dopamine-inhibiting effect is the underlying FSD cause remains unknown [43]. Regardless, both the increased concentration of extracellular serotonin and the diminished function of dopaminergic system in ID individuals may favour sexual dysfunction. In respect to the noradrenergic system, ID has been reported to favour a sympathotonic condition represented by elevated concentrations of serum and urine norepinephrine and its metabolites [2, 13]. Furthermore, norepinephrine reuptake from the synaptic space seems to be diminished in ID subjects [12], and accordingly, elevated interstitial levels of norepinephrine have been measured [44–46]. Norepinephrine displays an excitatory effect via α1 receptors and is involved in modulating attention and sensory afference [33]. Furthermore, it stimulates the receptivity of female rats via α- and β-receptors and enhances blood flow in female genitals, which in turn facilitates sexual arousal and orgasm [33, 42]. Thus, based on these results, it could be assumed that if an ID induced change in norepinephrine metabolism had any effect on sexual function at all, it would be beneficial. Even though the evidence is weak, some trials showed a slightly elevated concentration of β-endorphins, the body's own opioid, in ID rat brains [6, 16]. Depending on exposure duration, synthetic opioids seem to have positive as well as negative effects on sex drive [36]. A long-term application lowered sexual desire and arousal and increased the risk of anorgasmia, while orgasm itself has been found to be associated with a short-term endorphin increase [36, 42].

Endocrine systems

ID has been found to be associated with an altered prolactin receptor expression in peripheral tissues as well as with hyperprolactinaemia [6]. Prolactin acts as an inhibitor of sex drive [42, 47]. Accordingly, FSD is a well-known phenomenon in breast-feeding or otherwise hyperprolactinaemic women or in those taking dopamine-antagonistic drugs [34, 36, 42]. ID also reduces pituitary TSH release resulting in reduced T3 and T4 serum levels. These changes can be partly explained by the reduced enzyme activity of thyreoperoxidase and hepatic deiodinase in ID subjects and by the interactions of dopamine, prolactin, thyrotropin-releasing hormone (TRH), and TSH, all of which are somewhat unbalanced in ID [2, 13]. Recently, FSD has been found to be associated with manifest as well as subclinical hypothyroidism [48]. Since ID leads to a hypothyreotic condition, FSD may be a consequence of the former.

Psychological domain

ID has been reported to be associated with a higher prevalence of chronic fatigue, concentration difficulties, anxiety and depressive mood as well as with lower scores on standardized tests for overall mental health, vitality and quality of life [1, 49–52]. Positive correlations between depressive symptoms and ID as well as between anxiety and ID have been replicated reliably [50, 53–57]. Loss of libido and FSD have been shown to be typical symptoms of (sub)clinical depressive disorders and dysthymia [23, 31, 58, 59]. Even years after a depressive episode, some women still reported FSD [60]. Therefore, ID-induced depressive mood should have a detrimental effect on sexual function. Similarly, anxiety may be a cause of FSD with particularly negative effects on sexual appetence [4, 58, 59, 61–67]. Pronounced anxiety disorders can even lead to sexual aversion [31]. As ID may favour anxiety and avoidance behaviour, it seems likely that it also results in FSD.

Sociobehavioural domain

ID subjects have been found to have deficits in socioemotional development, showing more wariness, fear, hesitancy and shyness as well as fewer or slower approaches to strangers or unfamiliar objects, less social referencing and faster return to their mothers [53, 68–72]. ID infants exhibit an overall blunted positive affect as well as a reduced tendency to initiate social interactions using language or approach and

a more passive attitude in play [53, 73, 74]. This reduced tendency to interact with the environment may exacerbate the abovementioned cognitive impairments, resulting in a cycle of underperformance, known in the literature as the "functional isolation hypothesis" [75, 76]. ID subjects scored higher on measures of anxiety, depression, social problems, delinquent behaviour, aggression, feelings of detachment and negative emotions and reported lower emotional health [54, 77], even years after iron supplementation. Furthermore, ID subjects suffer from fatigue, lassitude and lethargy, delayed motor development, disturbed arousal and sleep–wake cycles, less spontaneous activity, and an overall lower level of activity; they also exhibit proneness to attention deficit hyperactivity disorder [78] and restless leg syndrome later in life [72, 79, 80]. Similarly, ID rats displayed less exploratory locomotion [81]. In general, these behaviours may decrease the probability of sexual interaction and activity. In addition, emotional bonds with partners or feelings of acceptance in a relationship are critical factors for sexual motivation [82]. Early bonding experiences and emotional and physical interactions in childhood, which appear to be disordered in ID individuals, seem to be equally important and formative factors in the development of healthy sexual function [23, 31, 59, 82]. Especially, a lack of emotional intelligence seems to be associated with FSD and orgasmic disorder [83]. Recently, East et al. succeeded to prove that ID and ID anaemia in childhood were related to high-risk sexual behaviour in adolescence through poorer emotional regulation and frequent rule breaking [84]. Therefore, ID, or even ID in childhood, are apparent risk factors for developing FSD.

Cross-sectional pilot cohort study in healthy, non-anaemic, midlife women

Characteristics of the cohort

In total, 45 Caucasian women were recruited. Detailed characteristics of the cohort have been reported recently [85] Briefly, mean age was 52.8 ± 5.1 years, partnership duration was 19.3 ± 10.8 years, 60% were married, 62% had at least two children, and 20% had a degree from a university or advanced technical college. 42.2% of the women had a monthly gross income below 5000 Swiss Francs (according to the Swiss Federal Statistical Office the average income in Switzerland is 5979 Swiss Francs per month), whereas 6.7% often worried about money, 37.8% worried about it from time to time and the others did not or seldom worry about it. 21% of participants reported regular alcohol consumption at least twice a week. Most of the participants were non-smokers (71.1%) and physically active (until sweating, 77%). The mean body mass index (BMI) was 23.3 ± 3.8 kg/m^2, with 11 subjects (24.4%) being overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2) and three (6.6%) being obese (BMI ≥ 30 kg/m^2).

Based on their hormonal profiles, 26.7% ($n = 12$) of the participants were premenopausal, 4.4% ($n = 2$) were perimenopausal, and 68.9% ($n = 31$) were postmenopausal, with 16.1% ($n = 5$) taking hormone replacement therapy. 73.3% of subjects reported to have menopausal symptoms with mean impairment being moderate (score 14.2 ± 3.5). When being asked if sexual function has changed during the menopausal transition ($n = 33$), one half of women reported an unchanged function (51.5%), while the other half had observed a decline (48.5%). Subjective health status was described to be "good" or "very good" by 95.5% of participants. The prevalence of being disease free was 97.7% ($n = 44$), with only one woman suffering from mild ulcerative colitis (no regular medication). In particular, none but one woman was currently affected by slight anaemia. Most participants were content with themselves and pleased with their body, which was reflected by a high mean score of 16.6 ± 1.62 (range 4 = not content at all to 20 = completely pleased with themselves). Use of any type of medication was reported by 53.3% of participants ($n = 24$ reports). The major medication group was analgesics ($n = 13$, 28.8%).

Sexual function and body iron stores

Table 1 presents descriptive statistics of FSFI-D, blood haemoglobin and serum ferritin. Mean FSFI-D total score was 25 (maximum 36). All mean FSFI-D subscale results were comparable with 'Desire' scoring the lowest indicating FSD. Mean ferritin and haemoglobin levels were within the normal range with only one woman suffering from mild anaemia (Hb 118 g/l, ferritin 11 µg/l). However, 13.3% ($n = 6$) of participants had completely depleted iron stores (ferritin < 15 µg/l), 6.7% ($n = 3$) had empty or scarce iron

Table 1 Descriptive statistics of FSFI-D, blood haemoglobin, and serum ferritin

Variables of FSFI-D	Mean	Median	SD	Quartile	
				1st	3rd
'Desire'	3.32	3.60	0.98	2.40	4.20
'Arousal'	4.14	4.50	1.5	3.30	5.10
'Lubrication'	4.23	4.80	1.84	3.45	5.85
'Orgasm'	4.24	4.80	1.89	3.40	5.80
'Satisfaction'	4.61	4.80	1.54	3.80	6.00
'Pain'	4.40	5.20	2.1	4.40	6.00
Total score	24.97	28.90	8.59	20.35	31.50
Ferritin µg/l	69.80	63.00	51.84	36.50	93.00
Haemoglobin g/l	137.44	138.00	7.73	132.50	142.00

Maximal score is six points per subgroup and 36 points in total

FSFI-D Female Sexual Function Index, German version

stores (ferritin 15–30 µg/l) and 20% ($n=9$) had a potentially functional ID (ferritin 30–50 µg/l). The remaining 60% ($n=27$) had normal iron stores (ferritin > 50 µg/l). Due to the small sample size, the participants were divided into 'iron-sufficient' (ferritin > 50 µg/l) and 'iron-deficient' (ferritin < 50 µg/l) groups for further analysis [86]. In all women, serum CRP was negative.

In a next step, correlation analysis was performed between FSFI-D subscales and blood iron values (ferritin, Hb) (Table 2). There was a significantly positive correlation within FSFI-D subscales and total score. In contrast, there was no significant correlation between FSFI-D and ferritin and Hb, respectively. The effect sizes of correlation coefficients were small (approximately |0.1|) or small to medium (approximately |0.2|).

Similarly, when differentiating between 'iron-sufficient' (ferritin > 50 µg/l) and 'iron-deficient' (ferritin < 50 µg/l) groups, FSFI-D total score and subscales did not differ significantly (Table 3). Nevertheless, the effect sizes of the FSFI-D subscales 'Arousal' and 'Pain' were comparatively large, and the difference between medians for 'iron-sufficient' and iron-deficient' individuals almost reached statistical significance for the FSFI-D subscale 'Pain' ($p=0.06$). 20% ($n=9$) of participants reported a history of anaemia, one of whom still suffered from completely depleted and two others from empty to scarce iron stores at the time of measurement. There was no significant correlation between female sexual function and history of anaemia (data not shown).

Sexual satisfaction and body iron stores Table 4 presents descriptive statistics of the personal history and FBM questionnaire addressing sexual satisfaction. Most participants had a good overall satisfaction with their sex life, enjoyed caresses, petting and sexual intercourse, found their partners

Table 2 Correlation analysis between FSFI-D subscales and blood iron values

Variable FSFI-D	Coefficient	2	3	4	5	6	7	8	FSFI-D Total score
Ferritin (1)	Pearson	0.06	0.2	− 0.07	− 0.06	0.06	− 0.03	− 0.23	− 0.05
	p value	0.7	0.18	0.63	0.71	0.67	0.84	0.12	0.75
Haemoglobin (2)	Pearson		0.02	0.05	0.03	0.08	0.16	0.13	0.09
	p value		0.92	0.77	0.83	0.6	0.29	0.39	0.55
'Desire' (3)	Pearson			0.6**	0.45**	0.5**	0.53**	0.38**	0.62**
	p value			< 0.001	0.002	< 0.001	< 0.001	0.01	< 0.001
'Arousal' (4)	Pearson				0.82**	0.86**	0.81**	0.77**	0.94**
	p value				< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
'Lubrication' (5)	Pearson					0.85**	0.75**	0.76**	0.91**
	p value					< 0.001	< 0.001	< 0.001	< 0.001
'Orgasm' (6)	Pearson						0.79**	0.70**	0.92**
	p value						< 0.001	< 0.001	< 0.001
'Satisfaction' (7)	Pearson							0.72**	0.89**
	p value							< 0.001	< 0.001
'Pain' (8)	Pearson								0.87**
	p value								< 0.001

*Significant at $p < 0.05$ level,

**Significant at $p < 0.01$ level

Table 3 Female sexual function when differentiating between 'iron-sufficient' and 'iron-deficient' individuals ($n=45$)

	'Desire'		'Arousal'		'Lubrication'		'Orgasm'		'Satisfaction'		'Pain'		Total score	
p value	0.97		0.1		0.26		0.98		0.96		0.06		0.29	
1r	− 0.005		− 0.25		− 0.17		− 0.003		− 0.007		− 0.29		− 0.16	
ID	y	n	y	n	y	n	y	n	y	n	y	n	y	n
Median	3.60	3.60	4.80	4.50	5.05	4.20	4.90	4.80	4.80	5.00	5.80	4.80	29.20	28.60

Statistical analysis by Mann–Whitney *U* test

ID iron deficient, *y* yes, *n* no, $1r = Z/\sqrt{N}$ effect size according to Tomczak [28]

attractive, and had no serious difficulties in talking about sexual requests.

Correlation analysis between all questions addressing sexual satisfaction (Table 4) and body iron stores (ferritin, Hb) revealed a significantly positive correlation between ferritin serum level and the statement 'Sexual activity decreases with age' ($p=0.04$, Spearman $r=0.31$), and a significantly negative correlation between blood haemoglobin and the statements 'Enjoyment of intercourse' ($p=0.049$, Spearman $r=-0.3$) and 'I think my partner is desirable' ($p=0.002$, Spearman $r=-0.46$), respectively. *This indicates that if ferritin tends to be lower, participants agree more to the statement thatsexual activity decreases with age. In addition, satisfaction with sexual intercourse and appraisal of attractiveness of the partner are higher if blood haemoglobin tends to be higher* (as lower numbers represent higher agreement, satisfaction, and attractiveness).

Satisfaction with partnership and body iron stores

Table 5 presents descriptive statistics of the personal history and FBM questionnaire addressing satisfaction with partnership. Overall, participants tended to be pleased or very pleased with their partnership. Correlation analysis between all questions addressing satisfaction with partnership (Table 5) and body iron stores (ferritin, Hb) revealed a significantly positive correlation between the statement 'Sometimes I feel neglected by my partner' ($p=0.016$, Spearman $r=0.36$), indicating that higher ferritin serum levels are associated with stronger feelings of neglect.

Discussion

Based on our comprehensive literature review, we found numerous potential associations between ID and FSD, such as (1) altered dopaminergic, noradrenergic, and

Table 4 Descriptive statistics of the personal history and FBM questionnaire addressing sexual satisfaction

Variables	Mean	Median	SD	Quartile	
				1st	3rd
Satisfaction with sex life, personal history (1 = not at all, 5 = very); $n=45$	3.58	4.00	1.33	3.00	5.00
Satisfaction with sex life, FBM (1 = very, 5 = not at all); $n=45$	2.31	2.00	1.15	1.00	3.00
Sexual activity decreases with age (1 = total agreement, 5 = total disagreement); $n=45$	3.69	4.00	1.18	2.00	5.00
Experienced caresses during the last 3 months (1 = 1x/day 2 = 2–3x/week, 3 = 1x/week, 4 = 2–3x/month, 5 = 1x/month, 6 = < 1x/month, 7 = never); $n=45$	1.93	1.00	1.44	1.00	2.00
Enjoyment of caresses (2 = great, 3 = pleasing, 4 = mediocre, 5 = annoying, 6 = very annoying); $n=45$	2.64	2.00	0.83	2.00	3.00
Experienced petting during the last 3 months (same scale as above); $n=45$	3.60	3.00	1.79	2.00	4.50
Enjoyment of petting (2 = great…6 = very annoying); $n=43$	2.74	3.00	1.07	2.00	3.00
Experienced intercourse during the last 3 months (1 = 1x/day 2 = 2–3x/week, 3 = 1x/week, 4 = 2–3x/month, 5 = 1x/month, 6 = < 1x/month, 7 = never); $n=45$	3.71	3.00	1.58	2.50	5.00
Enjoyment of intercourse (2 = great … 6 = very annoying); $n=44$	2.93	3.00	1.19	2.00	3.00
Frequency of masturbation during the last 3 months (1 = 1x/day 2 = 2–3x/week, 3 = 1x/week, 4 = 2–3x/month, 5 = 1x/month, 6 = < 1x/month, 7 = never); $n=45$	5.50	6.00	1.25	5.00	7.00
Satisfaction with sex life during the last 3 months (1 = very, 5 = not at all); $n=45$	2.45	2.00	1.37	1.00	3.75
No problems talking about sexual wishes and phantasies with partner (1 = total agreement, 5 = total disagreement); $n=45$	1.69	1.00	0.87	1.00	2.00
Wish for more caresses (1 = total agreement, 5 = total disagreement); $n=45$	4.07	4.00	1.16	3.75	5.00
Partner shows too little enthusiasm for sex (1 = total agreement, 5 = total disagreement); $n=45$	4.55	5.00	0.99	5.00	5.00
Partner demands things I do not want (1 = total agreement, 5 = total disagreement); $n=45$	4.76	5.00	0.48	5.00	5.00
My partner has sex appeal (1 = total agreement, 5 = total disagreement); $n=45$	1.67	1.00	1.05	1.00	2.00
Feeling inhibited to communicate my sexual wishes (1 = total agreement, 5 = total disagreement); $n=45$	4.12	4.00	0.94	3.75	5.00
Partner responds well to my desires (1 = total agreement, 5 = total disagreement); $n=45$	1.76	1.00	1.01	1.00	2.25
My partner is exceedingly prude (1 = total agreement, 5 = total disagreement); $n=45$	4.71	5.00	0.67	5.00	5.00
Sexual demands of my partner are too extreme (1 = total agreement, 5 = total disagreement); $n=45$	4.52	5.00	0.94	4.00	5.00
I think my partner is desirable (1 = total agreement, 5 = total disagreement); $n=45$	1.57	1.00	0.94	1.00	2.00

FBM = multidimensional standardized questionnaire on subjective health status, satisfaction with life and sexuality in women. Note that two women did not experience petting and one woman did not experience sexual intercourse during the last 3 month; therefore, their answers in terms of enjoyment have been disregarded to not distort the ordinal scale of measurement for statistical analysis

SD standard deviation

Table 5 Descriptive statistics of the personal history and FBM questionnaire addressing satisfaction with partnership ($n = 45$)

Variables	Mean	Median	SD	Quartile	
				1st	3rd
Satisfaction with partnership, personal history (1 = not at all, 5 = very)	4.40	5.00	0.84	4.00	5.00
Satisfaction with partnership, FBM (1 = very, 5 = not at all)	1.67	2.00	0.83	1.00	2.00
Partner listens to me if needed (1 = true, 5 = not true)	1.60	1.00	0.84	1.00	2.00
I often feel a certain distance between us (1 = true, 5 = not true)	4.02	4.00	1.12	3.50	5.00
Partner fully understands my cheers and sorrows (1 = true, 5 = not true)	1.84	2.00	0.88	1.00	2.00
Sometimes I feel neglected by my partner (1 = true, 5 = not true)	3.71	4.00	1.29	3.00	5.00
I feel lonely even with my partner (1 = true, 5 = not true)	4.04	4.00	1.02	3.50	5.00
Troubles with my partner (1 = often, 4 = never)	2.84	3.00	0.64	2.50	3.00

FBM = multidimensional standardized questionnaire on subjective health status, satisfaction with life and sexuality in women

SD standard deviation

serotoninergic cerebral metabolism, (2) altered hormonal conditions such as hyperprolactinaemia and (subclinical) hypothyroidism, (3) higher prevalence of psychiatric disorders such as depression and/or anxiety, and (4) impaired socioemotional interaction.

As the discussed neuroendocrine systems only operate successfully in close interplay with one another, questions regarding cause and effect cannot be answered conclusively. Alterations in the neurotransmitter and endocrine systems in both, ID and FSD, suggest at least a mutual interference with disrupted dopamine metabolism seeming to be the main culprit. Eventually, alterations in neuroendocrine metabolism may lead to certain behaviours. ID-induced emotional and social interactive deficits [50, 53–57, 68–77, 79, 80] may increase the risk for depression and anxiety which all together are risk factors for developing FSD [4, 23, 31, 58–67, 82–84]. However, such complex psychological phenomena are prone to bias and, therefore, must be interpreted carefully. In addition, our literature review is based on a theoretical construct according to the procedure explained in Fig. 2. It is exploratory and, therefore, does not fully meet the PRISMA criteria for a systematic review. Furthermore, it needs to be kept in mind that iron overload also might have negative effects on sexual function [87, 88].

So far, the hypothesized association between ID and FSD has been supported by one pilot study only showing that iron supplementation in women with ID improved sexual function [22]. However, this study was not designed to show a causal relationship between ID and FSD. Therefore, we aimed to assess the association between sexual function and body iron stores in a cross-sectional pilot cohort study in healthy midlife women. Herein, we (1) did not find a correlation between body iron store (Hb, ferritin) and female sexual function, and satisfaction with sex life and partnership, respectively. This was also true when differentiating between 'iron-sufficient' (ferritin > 50 µg/l) and 'iron-deficient' (ferritin < 50 µg/l) participants. However, women in our study were non-anaemic. Thus, we were not able to compare non-anaemic and anaemic women in respect to sexual function. However, (2) we made some interesting observations. For example, participants with lower ferritin serum levels tended to believe that sexual activity declined with age. This result could reflect, to some extent, the restriction in social interaction, its negative effects on emotion and stress tolerance, the higher rates of listlessness, lethargy, lassitude, chronic fatigue, anxiety and depressive mood, and the lower overall mental health, activity, vitality, and quality of life in ID subjects [1, 49, 50, 52, 53, 59, 68–72]. Furthermore, we found that lower ferritin serum levels were associated with weaker feelings of neglect by partners, although none of the participants felt neglected on a regular basis, and most did not feel neglected at all. This could reflect the decreased requirement for social interaction and bonding in ID individuals, although single statements from the FBM questionnaire must be interpreted in the context of the entire document. Clearly, our study has some limitations. The sample size was small, and women were non-anaemic. On the other hand, the strength of our study was its well characterized cohort of generally healthy midlife women living in a long-term heterosexual partnership. As ID is highly prevalent and an easily treatable disease its worth to invest in future studies comparing sexual function in women with and without ID anaemia and assessing the efficacy of iron supplementation in ID anaemic women.

Conclusions

Based on current literature, there are many potential associations between body iron store and sexual function making ID a possible risk factor for developing FSD. Accordingly, iron supplementation has been shown to be beneficial for sexual function in ID anaemic women. However, slight differences in body iron stores do not have a tremendous impact on sexual function as in non-anaemic midlife women sexual function, satisfaction with sex life

and partnership did not differ between 'iron-sufficient' and 'iron-deficient' women.

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Author contributions CJH: project development; data collection, and analysis and management; manuscript writing/editing. BS: project development and data collection, analysis, and management. MF: project development and data collection, analysis, and management. PS: project development and supervision.

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Compliance with ethical standards

Conflicts of interest Blood chemistry analysis was financially supported and performed by Unilabs SA, Berne. All authors declare that they have no conflicts of interest with the contents of this article.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Ethics approval The study protocol was approved by the Cantonal Ethics Committee Bern (Ref.-Nr. KEK-BE: 087/13).

Informed consent Informed consent was obtained from all individual participants included in the study.

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