Original article

Relationship Between Serum Ferritin Levels, Arterial Hypertension and Shift Work in Women. A Cross-sectional Analysis

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Abstract

Introduction: The aim of this study was to use cross-sectional research to determine the relationship between serum ferritin levels and arterial hypertension in women who work in shifts and women with regular daytime working hours.

Methods: The respondents included 67 female nurses divided into two groups: nurses working in 12-hour shifts (7 am to 7 pm/7 pm to 7 am) were the test group, while nurses regularly working for 8 hours (7 am to 3 pm) were the control group. Data collection included information on associated diseases, chronic medication, last menstruation, duration of menopause, cigarette smoking, number of years of employment in shift work and regular daytime work, laboratory and anthropometric parameters and blood pressure levels.

Results: In all respondents, there was a significant and positive relationship between ferritin and CRP levels, i.e. the higher the CRP levels, the higher the ferritin levels (Rho = 0.401; P = 0.001). Among respondents who have regular daytime working hours, there was no significant association between ferritin and other indicators, while in the group of those who work in shifts, there was a significant and positive association between ferritin and CRP (Rho = 0.468; P = 0.002). Finally, a positive correlation was found between the number of years of employment in shift work and systolic blood pressure levels, i.e. higher systolic pressure was observed in those respondents who worked longer in shifts (Rho = 0.424, P = 0.03).

Conclusion: The study demonstrated a significant correlation between the number of years of employment in shift work and systolic blood pressure. A positive correlation between serum CRP and ferritin levels was also observed in all respondents, and especially in shift workers.

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Introduction

Iron is a trace element that is necessary for the normal functioning of numerous metabolic processes in living beings [1]. Accumulation of iron in organs such as the liver, heart and endocrine glands can lead to pathological changes and dysfunction of the organs [2]. Ferritin is an intracellular protein that serves to store and release iron, and by determining its serum level, insights into the body's iron stores are obtained [3, 4, 5]. In addition to storing and releasing iron, ferritin plays a role in cell proliferation, angiogenesis, immunosuppression and atherosclerosis [6]. Atherosclerotic lesions have been shown to contain ferritin; this means that iron is a potent catalyst for oxidation of lipids found in LDL cholesterol, which plays a major role in atherogenesis [7, 8].

It is known that the presence of ferritin is a result of the inflammatory response of the acute phase of systemic infections, because its synthesis is increased under the influence of cytokines and its serum level increases in inflammatory events [9]. Observational studies have shown a positive correlation between serum ferritin levels and the development of chronic diseases such as atherosclerotic coronary artery disease and cancers, while certain other studies have failed to show a correlation between high serum ferritin levels and chronic diseases [10, 11]. Arterial hypertension is one of the leading causes of morbidity and mortality in the population, with a continuous correlation between blood pressure levels and cardiorenal events [12]. Previous studies have found a higher prevalence of arterial hypertension in men who had higher iron stores and serum ferritin levels [13, 14, 15]. Likewise, a positive correlation has been shown between serum ferritin levels and the prevalence of arterial hypertension in shift workers [16]. Compared to regular daytime (morning and afternoon) work, shift work (day and night shifts) leads to circadian rhythm disorders and, additionally due to lifestyle changes, to an increase in stress levels, which can trigger an inflammatory response. Such an inflammatory response has an important role in all stages of atherosclerotic plaque formation and development [17].

Previous research has confirmed the association between increased arterial stiffness and the development of atherosclerotic plaque [18, 19]. A positive correlation between serum ferritin levels and arterial stiffness in adult men and women has also been confirmed [20]. Unlike in men, serum ferritin levels in women change before and after menopause. During the reproductive period, serum ferritin levels in women are low due to menstrual bleeding, but in menopause, after menstrual cycles stop, serum ferritin levels increase. Natural postmenopause is defined by the absence of menstrual bleeding over a period of 12 months (excluding exogenous factors such as hysterectomy) [21]. In addition, serum ferritin levels in women of childbearing age are difficult to assess because throughout life, a number of factors can affect the levels, such as pregnancy, hormone therapy and gynaecological diseases [22]. Consequently, the association between serum ferritin levels and arterial hypertension in women has been insufficiently investigated.

To our knowledge, there are no studies concerning the association between serum ferritin levels, arterial hypertension and shift work in women. Therefore, the aim of this article was to use cross-sectional research to determine the relationship between serum ferritin levels and arterial hypertension in women who work in shifts and those with regular daytime working hours.

Respondents and Methods

Respondents

Of the total number of healthcare professionals who underwent a health check-up at the "Dr. Josip Benčević" General Hospital in Slavonski Brod, Croatia, in the period from May to July 2021, 67 female nurses were included in this study.

The respondents were female nurses who were divided into two groups: nurses working in 12-hour shifts (7 am to 7 pm/7 pm to 7 am) were the test group, while nurses regularly working for 8 hours (7 am to 3 pm) were the control group. The inclusion criteria were female gender, age of respondents between 18 and 65 for both groups, consent to participation in the survey and signed informed consent. Exclusion criteria included any form of iron replacement therapy, malignant disease, chronic renal failure, chronic liver disease, severe anaemia, acute illness, hormone replacement therapy, immunomodulatory therapy, reluctance to participate in the research.

The study was conducted in accordance with the Declaration of Helsinki. All participants in the survey signed a written informed consent form. The research was approved by the Ethics Committee of the "Dr. Josip Benčević" General Hospital in Slavonski Brod (Ethical Approval No. 04000000/21-46).

Data collection

The questionnaire was given and the physical examination was performed as part of the annual internal medicine examination. The questionnaire consisted of a report on medical history and primary health: it included data on chronic medication (for chronic conditions such as arterial hypertension, dyslipidaemia, diabetes, chronic obstructive pulmonary disease, osteoarthritis, depression), last menstruation, duration of menopause, cigarette smoking, number of years of employment in shift work and regular daytime work (at least one year for both groups). Regular cycles were the marker of premenopausal women, while absence of menstruation for the last 12 months or longer was a criterion for postmenopausal women [21]. Cigarette smoking habits were recorded as smoker, ex-smoker and non-smoker. Blood pressure was measured after 5 minutes of rest. Three measurements were performed at 1-minute intervals, with the respondents in a sitting position and using their right arm. Omron M6 Comfort® blood pressure monitor and Omron HEM-FL31® upper arm cuff with circumference of 22–42 cm were used to measure blood pressure. Levels of systolic pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg were used to define arterial hypertension, in accordance with the current guidelines for arterial hypertension of the European Society of Cardiology [12]. The blood pressure level of the respondents was calculated as the mean value of the second and third measurements. Respondents who had previously taken antihypertensive therapy were placed in the group with proven arterial hypertension. Height and weight were measured to the nearest 0.1 cm and 0.1 kg (using the SECA® scale and altimeter). During the measurement, the respondents were asked to take off their clothes and put on a disposable dress for the examination. Waist circumference (WC) was measured to the nearest 0.1 cm at the midpoint between the lower costal arch and the iliac crest. Body mass index (BMI) was calculated as weight/height ratio2 (kg/m2); values ≥ 25 kg/m2 indicated that the respondent is overweight, while values ≥ 30 kg/m2 indicated obesity.

Serum ferritin concentration was measured using the ALINITY® immunochemical analyser (Abbott). Laboratory parameters tested using fasting blood samples were as follows: erythrocytes (E), haemoglobin (Hb), haematocrit (Htc), mean corpuscular volume (MCV), leukocytes (L), platelets (Tr), iron (Fe), unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (Tg), C-reactive protein (CRP), blood glucose (BG), haemoglobin A1c (HbA1c) and vitamin D. Complete blood count was determined using the SYSMEX XN-1000® haematology analyser by fluorescence flow cytometry. Vitamin D levels were determined by chemiluminescent immunochemical assay using the ALINITY® immunochemical analyser (Abbott). Haemoglobin A1c in venous blood was determined using the DxC 700 AU® biochemical analyser. Finally, biochemical parameters CRP, BG, TC, Tg, HDL, LDL, Fe and UIBC were determined using the biochemical part of the integrated ALINITY® system (Abbott).

Statistical analysis

General characteristics of the respondents, according to the groups (shift work/regular daytime work), were derived using a descriptive method for continuous variables and using the Chi-squared test for categorical variables after data weighting. The data were sorted into quartiles based on the respondents' serum ferritin concentrations: quartile 1 (Q1) ≤ 26.11 ng/mL, quartile 2 (Q2) 26.12–47.74 ng/mL, quartile 3 (Q3) 47.75–93.5 ng/mL, and quartile 4 (Q4) > 93.5 ng/mL. The respondents' basic characteristics according to ferritin levels in the quartiles were derived using the Chi-squared test and Fisher's exact test. By dividing data into quartiles, four groups were obtained with an almost equal number of respondents. Appropriate nonparametric tests were used to compare two or more independent groups. The Mann–Whitney U test was used to compare age, BMI, number of years of work and blood pressure levels between the test and control groups. The Kruskal–Wallis test (Conover post-hoc) was used to compare age, BMI, number of years of work, blood pressure levels in relation to groups, according to ferritin levels in the quartiles. The Chi-squared test was performed to divide the respondents according to ferritin levels and the presence of arterial hypertension. Spearman's correlation coefficient was used to assess the association of ferritin and other biochemical values between groups and to assess the association of shift work with arterial pressure and ferritin levels. The level of statistical significance was set at $p < 0.05$. Statistical analysis was performed using the SPSS for Windows 11.0.3 software (SPSS Inc., Chicago, IL, USA).

Results

The research was conducted on 67 respondents, of whom 43 (64%) work in shifts and 24 (36%) regularly work 8 hours. There were 45 (67.2%) obese or overweight respondents. There were 42 (62.7%) respondents in postmenopause, and in regard to comorbidities, arterial hypertension was recorded in 22 (32.8%) respondents, while diabetes was present in 3 of them (4.5%). Out of a total of 51 respondents who gave an answer about smoking, 19 (62.7%) respondents smoked cigarettes daily. Antihypertensive therapy was taken by 19 (37.3%), statins by 6 (9%), and vitamin D by 3 (4.5%) respondents. There were no significant differences in general characteristics between the groups (Table 1).

Table 1. Basic characteristics of the respondents

	Number (%) of respondents			
	Regular daytime work (n = 24)	**Shift work (n = 43)**	**Total**	***P****
BMI kg/m²				
< 25, normal	7 (29.2)	15 (34.9)	22 (32.8)	0.71
25–30, overweight	12 (50)	17 (39.5)	29 (43.3)	
> 30, obese	5 (20.8)	11 (25.6)	16 (23.9)	
Postmenopause	14 (58.3)	28 (65.1)	42 (62.7)	0.58
Smoking	6 (28.6)	13 (43.3)	19 (37.3)	0.28
Arterial hypertension	11 (45.8)	11 (25.6)	22 (32.8)	0.09
Diabetes mellitus	2 (8.3)	1 (2.3)	3 (4.5)	0.25
Antihypertensive therapy	10 (41.7)	9 (20.9)	19 (37.3)	0.07
Statins therapy	4 (16.7)	2 (4.7)	6 (9)	0.09
Vitamin D therapy	1 (4.2)	2 (4.7)	3 (4.5)	0.93

*χ^2 test

A statistically significant interquartile difference was observed in postmenopausal respondents (Table 2)..

Table 2. Basic characteristics of the respondents according to ferritin levels

	Number (%) of respondents according to ferritin levels					
	< 26.11 (n = 17) Q1	26.12–47.74 (n = 17) Q2	47.75–93.5 (n = 17) Q3	> 93.5 (n = 16) Q4	Total	P*
BMI kg/m²						
< 25, normal	8 (47.1)	7 (41.2)	4 (23.5)	3 (18.8)	22 (32.8)	0.61
25–30, overweight	6 (35.3)	6 (35.3)	8 (47.1)	9 (56.3)	29 (43.3)	
> 30, obese	3 (17.6)	4 (23.5)	5 (29.4)	4 (25)	16 (23.9)	
Postmenopause	4 (23.5)	11 (64.7)	13 (76.5)	14 (87.5)	42 (62.7)	**0.001**
Smoking	5 (38.5)	5 (31.3)	5 (50)	4 (33.3)	19 (37.3)	0.79
Arterial hypertension	2 (11.8)	7 (41.2)	7 (41.2)	6 (37.5)	22 (32.8)	0.20
Diabetes mellitus	1 (5.9)	1 (5.9)	1 (5.9)	0	3 (4.5)	> 0.99†
Antihypertensive therapy	1 (5.9)	7 (41.2)	5 (29.4)	6 (37.5)	19 (28.4)	0.08†
Statins therapy	0	2 (11.8)	2 (11.8)	2 (12.5)	6 (9)	0.56†
Vitamin D therapy	0	0	2 (11.8)	1 (6.3)	3 (4.5)	0.32†

**2 test; † Fisher's exact test*

The median age of the respondents was 57 (interquartile range of 45 to 60 years), with respondents ranging from 25 to 65 years old and no significant difference between the groups. There were no significant differences in BMI, WC, postmenopausal duration, systolic and diastolic pressure and number of years of treatment for arterial hypertension with respect to the groups. Nurses working in shifts had more work experience, compared to nurses working only in the morning shift, with a median of 35 years (interquartile range from 25 to 39 years) (Mann–Whitney U test, P < 0.001) (Tables 3 and 4).

Table 3. Age, BMI, years of experience, blood pressure levels in relation to groups

	Median (interquartile range)				
	Regular daytime work (n = 24)	Shift work (n = 43)	Difference *	95% CI	P†
Age (years)	56.5 (44.5–60.75)	57 (45–59)	0	-4–4	0.98
BMI (kg/m²)	26.62 (24.33–29.43)	27.1 (23.9–30.1)	-0.11	-2.5–1.9	0.90
WC (cm)	95 (85–99.25)	89 (75–94)	-5	-11–2	0.18
Years of experience (years)	12.5 (4.25–24.75)	35 (25–39)	18	12–24	**< 0.001**
Duration of menopause (years)	9 (5–15.5)	8 (6–10)	0	-5–3	0.73
Systolic pressure (mmHg)	128 (118–137.25)	121 (115–130)	-5	-12–2	0.20
Diastolic pressure (mmHg)	79.5 (74.88–85.25)	78 (72–84)	-2	-6.5–2.5	0.41
Years of arterial hypertension	8 (2.8–11)	9 (6–13.5)	2.5	-	0.54

*CI – confidence interval, *Hodges–Lehmann median difference, †Mann–Whitney U test*

Table 4. Age, BMI, years of experience and blood pressure levels in relation to groups, according to ferritin levels (quartile)

	Median (interquartile range)				
	< 26.11 (n = 17) **Q1**	26.12–47.74 (n = 17) **Q2**	47.75–93.5 (n = 17) **Q3**	> 93.5 (n = 16) **Q4**	*P**
Age (years)	45 (37.5–53)	57 (49–61)	58 (48–61.5)	58.5 (53.5–61.8)	**0.006**ǂ
BMI (kg/m²)	26.4 (22.65–28.44)	27.3 (24.34–29.9)	26.8 (24.5–31.2)	27.3 (26–30.3)	0.70
WC (cm)	87 (72–94)	88 (77.5–96)	94 (85–102.5)	92 (80.8–97)	0.50
Years of experience (years)	21 (7–26)	26 (8.5–37)	35 (17.5–38)	31.5 (14.3–40)	0.08
Duration of menopause (years)	4.5 (2.5–8)	7 (4.5–12)	9 (7.3–15.8)	8.5 (7–10.3)	0.16
Systolic pressure (mmHg)	120 (106.5–126.5)	128 (119.5–133)	128 (118–141.8)	119.5 (114.3–131.8)	0.08
Diastolic pressure (mmHg)	73 (65–80.5)	81 (73–84.5)	80 (74.8–84.5)	79.8 (73.8–87.5)	0.16
Years of arterial hypertension	5 (n =1)	6 (2–11.8)	11 (9–12)	11 (8–15)	0.30

**Kruskal–Wallis test (Conover post-hoc)*
ǂat the confidence level P < 0.05 there were significant differences in Q1 vs. Q2; Q1 vs. Q3; Q1 vs. Q4.

Arterial hypertension was present in 22 respondents, 2 of whom (9.1%) had ferritin concentrations in the lowest quartile (< 26.11 ng/ml). There were 45 respondents without arterial hypertension, of which 15 (33.3%) had serum ferritin concentrations in the lowest quartile (< 26.11 ng/ml). Likewise, there was no statistically significant difference between ferritin and the presence of arterial hypertension (Figure 1).

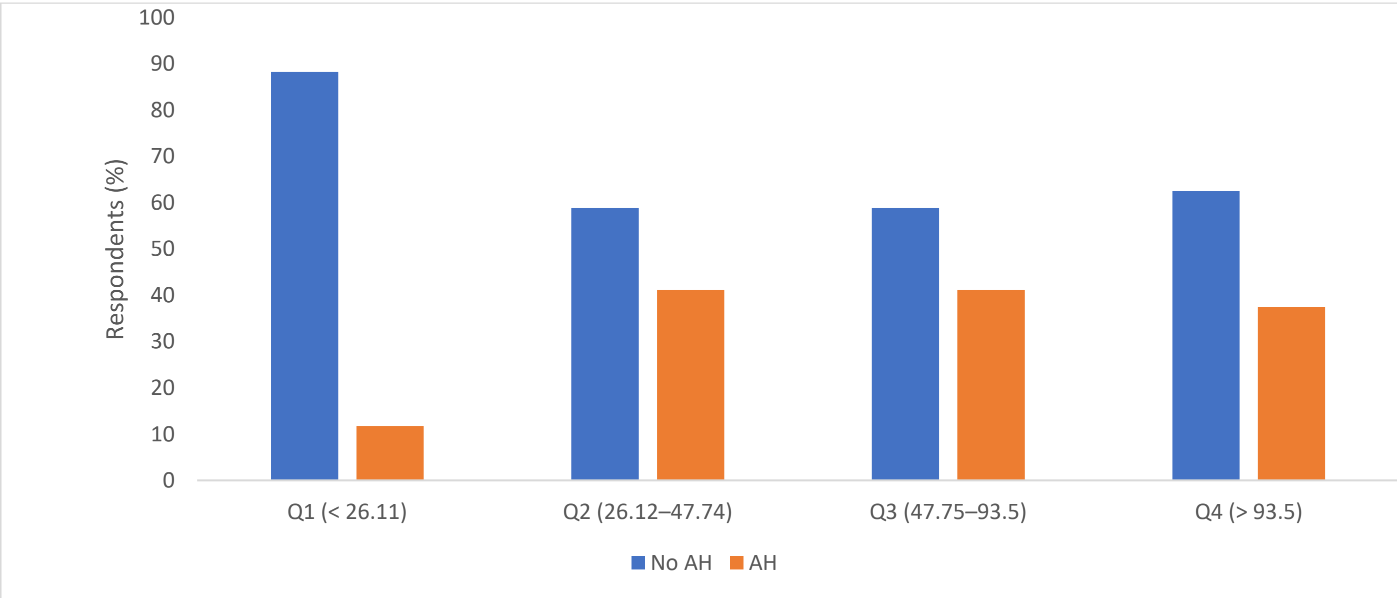

Figure 1. Distribution of respondents according to ferritin levels and the presence of arterial hypertension
AH – Arterial hypertension

The correlation coefficient of ferritin with other biochemical values was evaluated using Spearman's correlation coefficient. In the group of all respondents, there was a significant and positive relationship between ferritin and CRP levels, i.e. the higher the CRP levels, the higher the ferritin levels (Rho = 0.401; P = 0.001). Among respondents who regularly work 8 hours, there was no significant association of ferritin and other indicators, while in the group of those who work in shifts, there was a significant and positive association of ferritin and CRP (Rho = 0.468; P = 0.002) (Table 5).

Table 5. Association of ferritin and other biochemical values between the groups

	Ferritin*	*P* value
All respondents		
TC (mol/L)	0.195	0.11
HDL (mmol/L)	0.103	0.41
LDL (mmol/L)	0.163	0.19
Tg (mmol/L)	0.161	0.19
BG (mmol/L)	-0.102	0.42
HbA1c (%)	0.072	0.56
CRP (mg/L)	**0.401**	**0.001**
Vitamin D (nmol/L)	-0.013	0.92
Regular daytime work		
TC (mol/L)	0.232	0.28
HDL (mmol/L)	0.039	0.86
LDL (mmol/L)	0.281	0.18
Tg (mmol/L)	-0.063	0.77
BG (mmol/L)	-0.119	0.58
HbA1c (%)	0.227	0.29
CRP (mg/L)	0.291	0.18
Vitamin D (nmol/L)	0.084	0.70
Shift work		
TC (mol/L)	0.178	0.26
HDL (mmol/L)	0.139	0.38
LDL (mmol/L)	0.109	0.49
Tg (mmol/L)	0.215	0.17
BG (mmol/L)	-0.086	0.59
HbA1c (%)	-0.027	0.86
CRP (mg/L)	**0.468**	**0.002**
Vitamin D (nmol/L)	-0.068	0.67

**Spearman's rank correlation coefficient (Rho)*

Spearman's correlation coefficient was used to assess the relationship between the number of years of employment in shift work with blood pressure and ferritin levels, and a positive correlation was found between number of years of employment in shift work and systolic pressure, i.e. higher systolic pressure was observed in those respondents who worked longer in shifts (Rho = 0.424, P = 0.03) (Table 6).

Table 6. Relationship of shift work length with blood pressure and ferritin

	Length of work in shifts*	*P* value
Systolic	0.424	**0.03**
Diastolic	0.202	0.34
Ferritin (ng/mL)	-0.005	0.98

**Spearman's rank correlation coefficient (Rho)*

Discussion

This study was conducted to determine the relationship between serum ferritin levels, arterial hypertension and shift work in women. This study demonstrated the persistent link between shift work and systolic blood pressure. A positive correlation between serum CRP and ferritin levels was also demonstrated in all respondents, and especially in shift workers. The reason for the expected higher levels of arterial pressure in shift workers, in addition to changes in the circadian rhythm, is increased exposure to psychophysical stress that leads to an inflammatory response [16, 23]. Due to the rapid modernization of many sectors, there is a growing need for 24-hour availability of the healthcare system, which creates the need for shift work. According to a 2010 European Union report, 23% of men and 14% of women work in shifts [24]. The consequences can be different, but the most significant ones are those that affect the cardiovascular system. Previous research has confirmed that shift workers, compared to regular daytime workers, have a higher incidence of ischemic heart disease and myocardial infarction, and more commonly develop arterial hypertension [25, 26]. Of noncardiac consequences, a higher incidence of gastric ulcer, obesity, and diabetes has been observed [27–29].

In previous studies, a proportional association between CRP levels and blood pressure was confirmed, i.e. higher levels of the inflammatory marker are associated with higher blood pressure levels [30–31]. In the Framingham Offspring Study, Rutter and colleagues showed that elevated CRP is associated with a higher risk of insulin resistance and metabolic syndrome in women [32].

Such a phenomenon can be explained by the fact that higher CRP levels are present in conditions that represent risk factors for development of arterial hypertension, such as obesity, metabolic syndrome, smoking and arterial stiffness [33–36]. CRP additionally reflects chronic low-grade inflammation of the arterial wall at the site of atherosclerotic plaque [37]. The mechanism of action is mediated by increased expression of adhesion molecules with receptor function, such as vascular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), on endothelial cells of blood vessels [38]. Receptors have chemotactic function for macrophages which, by infiltrating the vessel wall, lead to an inflammatory reaction, mediated by proinflammatory cytokines – interleukin-1, interleukin-6 and tumour necrosis factor. Furthermore, CRP binds to the cell membrane of damaged cells, activating the inflammatory response, which leads to cell dysfunction and atherosclerosis by reducing the synthesis of nitric oxide [39, 40].

There is growing evidence that oestrogen depletion during menopausal transition promotes a systemic inflammatory condition. This condition is characterized by systemic proinflammatory cytokines derived from reproductive tissue, as well as by changes in the cellular immune profile [41].

An inverse relationship between oestrogen and ferritin concentrations is to be expected, i.e. a decrease in oestrogen concentration due to the weakening of ovarian function leads to an increase in ferritin levels in the absence of menstrual bleeding [42]. According to the results of the research by Milman and Kirchhoff, it follows that during the perimenopausal period, iron stores increase 2–3 times, i.e. an increase in serum ferritin concentration by 1 μg/L corresponds to 120 μg of stored iron per kilogram of body weight [43]. Just like CRP, ferritin is a good indicator of the inflammatory response in the body, reflecting the degree of acute and chronic inflammation [44]. However, serum ferritin levels are directly linked to the occurrence of insulin resistance and diabetes mellitus, especially if it is accompanied by elevated CRP levels [45].

Although the obtained results are in line with previous findings, the authors point out four important limitations of the research. First, of the respondents included in the research who were in the group of regular daytime workers, 91.7% had previously worked in shifts with a median duration of such work of 18 years (interquartile range 11.5–26.0). Second, cross-sectional testing cannot establish a causal relationship, which is why large population and prospective studies are needed. Third, as ferritin is an acute-phase protein, it may be elevated in inflammatory or other chronic events that may have remained unrecognized prior to the inclusion of respondents in the study. Finally, the uneven distribution of respondents, i.e. a higher share of postmenopausal women working in shifts, is possibly a consequence of personal financial circumstances.

Conclusion

The obtained data show a significant correlation between the length of work in shifts and systolic blood pressure levels, as well as a connection of shift work with higher ferritin and CRP levels. Further studies on a large sample are needed to determine the association between serum ferritin levels and arterial hypertension. To the best of the authors' knowledge, this is the first study conducted on women who work in shifts in the healthcare system. The question for further research remains whether the length of shift work should be limited and whether shift workers should undergo more frequent medical examinations due to the increased risk of adverse cardiovascular events.

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Competing interests. None to declare

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