Observational Studies

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Association between clinical laboratory indicators and WOMAC scores in Qatar Biobank participants: The impact of testosterone and fibrinogen on pain, stiffness, and functional limitation

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Abstract

Objectives – The association between baseline laboratory parameters and experienced well-being in healthy individuals remains uncertain. This study explored the relationship between clinical laboratory profiles and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for pain, stiffness, and physical functional limitation in healthy individuals in Qatar.

Methods – Clinical laboratory data were collected from 1,764 Qatar Biobank participants who also completed the WOMAC questionnaire: lipid profiles (high-density lipoprotein, low-density lipoprotein, cholesterol, and triglycerides), endocrine markers (TSH, T3, T4, estradiol, and testosterone), and two inflammatory markers (CRP and fibrinogen). Multiple linear regression was used with 11 clinical indicators as independent variables and the subscale and total WOMAC scores as dependent variables. Multivariate effects of each indicator on the outcomes were assessed, and univariate effects were examined when significant.

Results – Testosterone had a significant impact on all WOMAC subscales (pain, stiffness, and functional limitation) and the total WOMAC score. Higher testosterone levels were associated with a reduction in pain (β = −0.03, t = −3.505, p < 0.001, 95% CI = −0.052, −0.015), stiffness (β = −0.01, t = −2.265, p = 0.024, 95% CI = −0.018, −0.001), physical dysfunction (β = −0.08, t = −3.265, p = 0.001, 95% CI = −0.135, −0.034), and total WOMAC scores (β = −0.127, t = −3.444, p < 0.001, 95% CI = −0.199, −0.055). Elevated fibrinogen levels were associated with an increase in stiffness (β = 0.155, t = 2.241, p = 0.025, 95% CI = 0.019, 0.290), physical dysfunction (β = 1.17, t = 2.808, p = 0.005, 95% CI = 0.354, 1.997), and total WOMAC scores (β = 1.610, t = 2.691, p = 0.007, 95% CI = 0.437, 2.784).

Conclusion – Testosterone may protect against pain, stiffness, and physical dysfunction, while high fibrinogen levels might be a surrogate of systemic inflammation that enhances stiffness and limits physical function. Measuring multiple clinical and laboratory markers in healthy individuals may enhance our understanding of the molecular mechanisms underlying pain.

Keywords: arthralgia, biological specimen banks, inflammation, Qatar, surveys and questionnaires, testosterone

1 Introduction

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used self-assessed instrument [1]. It is commonly used to evaluate patients with osteoarthritis in the hip and knee joints. The WOMAC questionnaire assesses pain during various activities involving these joints, measures the level of stiffness experienced (particularly in the morning or after rest), and evaluates experienced difficulties in everyday physical function, including walking, climbing stairs, or sitting. It is useful for assessing the symptom severity and treatment effectiveness in patients with osteoarthritis. However, its potential as a tool for assessing pain and quality of life (QoL) in healthy individuals, particularly in exercise and sports medicine research, has

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also been studied [2–5]. In healthy individuals, WOMAC serves as a valuable tool to investigate the relationship between pain and various factors such as age, gender, and physical activity levels, offering a comprehensive assessment of musculoskeletal symptoms in the absence of defined pathological conditions [3,6]. It is also helpful for identifying potential risk factors for musculoskeletal conditions and informing the development of preventive strategies and interventions to maintain or improve musculoskeletal health in the general population.

Clinical laboratory tests play a pivotal role in health assessments, offering objective measures of various physiological parameters. Given that WOMAC is a robust pain and QoL measure, exploring potential associations between clinical laboratory parameters – such as inflammatory markers [7], lipid metabolism [8], and sex hormones (progesterone, estradiol, testosterone, and estrogen) [9,10] – and musculoskeletal health as assessed by WOMAC could provide insights into the underlying pathobiology. An interdisciplinary approach between the laboratory and clinic recognizes that pain and systemic physiology may be interconnected, and assessing both aspects and understanding their interactions could provide a more comprehensive understanding of the underlying pathophysiology and an individual's health.

Overall, few studies have used WOMAC in healthy individuals. The Qatar Biobank is a prospective project that started in 2012 that aimed to recruit Qatari nationals and residents living in Qatar for over 15 years aged 18 years and older. By the end of 2021, the Qatar Biobank had recruited >25,000 participants. Participants attend the biobank voluntarily with a prior appointment, and the visit can last up to 5 h. Participants are provided with self-administered sociodemographic and lifestyle questions that capture information on age, gender, educational level, employment status, work pattern, smoking habits, reproductive health, and consanguinity-related questions. The Qatar Biobank also allows its volunteers to take the WOMAC survey. We, therefore, exploited this resource to examine associations between clinical laboratory test results and WOMAC scores in healthy individuals in Qatar. The aim of the study was to investigate the relationship between total and subscale WOMAC scores (pain, stiffness, and physical functional limitation) with biochemical parameters including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), total cholesterol (TC), T3, T4, estradiol, thyroid-stimulating hormone (TSH), testosterone, CRP, and fibrinogen.

2 Methods

2.1 Study design and data source

This was a cross-sectional study of 1,764 healthy Qatari and non-Qatari (resident for over 15 years) participants of both sexes aged 18 and above and attending the Qatar Biobank with available WOMAC data. The Qatar Biobank is linked to the largest medical service in Qatar, Hamad Medical Corporation (HMC). This longitudinal project aims to track recruited individuals over a long period of time to capture relationships between clinical and biological variables and disease occurrence. The details of the Qatar Biobank are published elsewhere [11]. All laboratory and clinical investigations were carried out at Qatar Biobank and HMC.

The Qatar Biobank started administering the WOMAC survey in 2017, and data for the current study were requested in 2021. There was good to excellent reliability for the WOMAC subscales for pain (Cronbach's alpha 0.872), stiffness (Cronbach's alpha 0.821), and physical functional limitation (Cronbach's alpha 0.962) and for the total WOMAC scale (Cronbach's alpha 0.966). In addition to the WOMAC, data for demographic variables such as age, gender, citizenship, education level, employment status, night work, BMI, and smoking status were collected.

In a *post hoc* power analysis, a sample size of 430 per outcome (four outcomes in total) was able to detect small effect sizes (effect size *f*-square 0.02; F critical 1.811, at alpha 0.05 with 11 predictors), making a sample of 1,720 sufficient to detect a small effect size. Our smallest F value was 4.2, and we were powered to detect a critical F value of 1.811.

2.2 WOMAC

The survey typically takes 10–15 min to complete and consists of 24 five-point Likert scale [12] questions categorized into 3 sections: pain (5 questions), stiffness (2 questions), and physical functional limitation (17 questions) summed to give a total score of 0–120 [13]. Scores are calculated for the three subdomains: a pain score between 0 and 25 points, where a higher score is equivalent to greater pain and, consequently, poorer knee or hip outcomes; a stiffness score between 0 and 10; and the functional limitation score between 0 and 85 [2–4,14].

2.3 Demographic questions

In addition to the WOMAC, demographic data were collected: age, gender, citizenship, education level, employment status, night work, BMI, and smoking status (smoker, stopped smoking, and non-smoker).

2.4 Inclusion and exclusion criteria

The inclusion criteria were complete sociodemographic data, clinical test profiles, and WOMAC surveys. The inclusion criterion was any chronic condition that might potentially have an effect on the WOMAC index, including diabetes, hypertension, osteoporosis, osteoarthritis, rheumatoid arthritis, high cholesterol and lipid diseases, stroke, kidney diseases, cancer, thyroid diseases, Parkinson's disease, and autoimmune diseases. The purpose of excluding individuals with chronic conditions was to minimize interference with clinical parameters or WOMAC scores since our goal was to establish associations in healthy individuals.

2.5 Clinical laboratory tests

Blood samples were collected using standard phlebotomy procedures. Standard automated laboratory protocols were applied to evaluate TC, TG, and high-density lipoprotein cholesterol (HDL-C) with Hitachi-917 analyzers (Gmbh Diagnostic, Mannheim, Germany). LDL-C was calculated using the Friedewald formula. CRP, T3/T4, TSH, estradiol, and testosterone were measured using enzyme-linked immunosorbent assay kits (Mercodia, Uppsala, Sweden). Fibrinogen was assessed using plasma according to the Clauss method [15].

2.6 Statistical analysis

All statistical analyses were conducted using SPSS v28.0.0 (IBM Statistics, Armonk, NY, USA). Multiple linear regression was used, where the 11 clinical indicators were inserted as the independent variables, and the 3 WOMAC subscales, as well as the total WOMAC score, were all inserted as dependent variables, resulting in 4 models. The multivariate effects of each indicator on each outcome were observed. For significant effects, we observed parameter estimates and noted the beta coefficient and 95% confidence intervals (CIs). We ran linear regressions for the clinical indicators with each outcome to compute the Mahalanobis distances. Then, we compared the Mahalanobis distances to chi-square distributions corresponding to the same degrees of freedom and calculated a p-value of the right-tail for the chi-square distribution and any case with a probability value less than 0.001. Out of 1,764, 44 cases significantly deviated from the chi-square distribution and were thus deemed outliers and excluded, leaving 1,720 cases for the analysis.

Ethics statement: Data were obtained from the Qatar Biobank under reference number E-2021-QF-QBB-RES-ACC-00050-0172, and the study was conducted with the approval of QU-IRB under reference number 1648-E/22. All patients provided written informed consent.

3 Results

Demographic data of the study participants are summarized in Table 1. About 76.7% (n = 1,353) of the study cohort were Qatari and 23.3% (n = 411) were non-Qatari but long-term residents in Qatar; 27.2% of the participants worked at night (n = 1,281), 77.2% (n = 1,361) were employed or self-employed, while 22.8% were unemployed, retired, or housewives. Only 20.1% of the participants were smokers, 63% had quit smoking, and 16.9% were non-smokers. About 50.3% (887) of the participants were female. Table 2 displays the mean values and standard deviations of the clinical indicators and WOMAC outcomes used in this study, and Figure 1 shows the distribution of subscale and total WOMAC scores.

The effects of the models containing the 11 clinical indicators on each outcome are shown in Table 3. All models had a significant effect on each outcome. Of all tested indicators, testosterone and fibrinogen predicted most WOMAC outcomes, while the other indicators did not have a significant effect on any WOMAC outcome (Table 4). Testosterone had a significant effect on all three WOMAC subscales and the total WOMAC score, predicting reduced pain (β = −0.03, t = −3.505, p < 0.001, 95% CI = −0.052, −0.015), reduced stiffness (β = −0.01, t = −2.265, p = 0.024, 95% CI = −0.018, −0.001), reduced functional limitation (β = −0.08, t = −3.265, p = 0.001, 95% CI = −0.135, −0.034), and total WOMAC scores (β = −0.127, t = −3.444, p < 0.001, 95% CI = −0.199, −0.055). Fibrinogen had a significant effect on stiffness and functional limitation, as well as the total WOMAC scores but not the pain subscale. Fibrinogen predicted greater stiffness (β = 0.155, t = 2.241, p = 0.025, 95% CI = 0.019, 0.290), greater functional limitation (β = 1.17, t = 2.808, p = 0.005, 95% CI = 0.354, 1.997), and greater total

Table 1: Sociodemographic characteristics of the study cohort from the Qatar Biobank

Variable	Total (n = 1,764)	Statistics	
		Count	Percentage (%)
Gender			
Female		887	50.3
Male		877	49.7
Age (years)			
18–27		545	30.9
28–37		605	34.3
38–47		413	23.4
48–57		161	9.1
58 or above		40	2.3
Citizenship			
Qatari		1,353	76.7
Non-Qatari		411	23.3
Night work			
No		1,281	72.8
Yes		479	27.2
Education level			
Did not attend school		28	1.6
Up to secondary school		801	45.4
Post-secondary school		109	6.2
University degree or higher		836	46.8
BMI			
Underweight		55	3.1
Normal weight		481	27.3
Overweight		648	36.7
Obese		580	32.9
Employment status			
Employed		1,361	77.2
Unemployed		403	22.8
Smoking status			
Smoker		355	20.1
Stopped smoking		1,111	63.0
Non-smoker		303	16.9

Table 2: Mean values and standard deviations for the clinical indicators and WOMAC outcomes

Variable	Mean	SD
HDL	1.408	0.381
LDL	2.854	0.799
TC	4.784	0.847
TG	1.151	0.641
Free triiodothyronine	4.443	0.879
Free thyroxine	14.731	2.343
TSH	2.216	1.607
Testosterone	9.402	9.610
Estradiol	240.233	282.830
Fibrinogen	3.205	0.602
CRP	4.630	4.023
WOMAC (pain)	7.162	3.109
WOMAC (stiffness)	2.905	1.404
WOMAC (physical function)	22.162	8.548
WOMAC (total)	32.229	12.22

WOMAC score (β = 1.610, t = 2.691, p = 0.007, 95% CI = 0.437, 2.784). Given that fibrinogen and testosterone were the two biochemical parameters with significant effects on WOMAC outcomes, we tested the correlation between them as an *ad hoc* analysis. Interestingly, fibrinogen and testosterone were negatively and weakly correlated (r = −0.283, p < 0.001).

In this sample, there was a large proportion of overweight participants, warranting a sensitivity analysis where the sample was stratified by the BMI score (normal: ≤25 vs high: >25). The effect of testosterone on pain (β = −0.05, t = −4.074, p < 0.001, 95% CI = −0.075, −0.026), stiffness (β = −0.019, t = −3.326, p < 0.001, 95% CI = −0.030, −0.008), functional limitation (β = −0.153, t = −4.275, p < 0.001, 95% CI = −0.223, −0.083), and total WOMAC score (β = −0.222, t = −4.405, p < 0.001, 95% CI = −0.321, −0.123) remained significant, but only for individuals with high BMI and with mostly higher regression weights than the collapsed sample. However, fibrinogen no longer had an effect on stiffness, function limitation, or total WOMAC score when the sample was stratified by BMI.

4 Discussion

In this cross-sectional study of 1,720 healthy men and women completing the WOMAC survey as part of Qatar Biobank assessments, we detected an association between testosterone levels and pain intensity, stiffness, and functional limitation outcomes. Specifically, in both men and women, each one-point increase in serum testosterone levels resulted in a decrease in WOMAC pain, stiffness, and physical functional limitation scores. This might indicate that testosterone levels protect against joint pain and stiffness and decrease the risk of physical dysfunction in healthy individuals. Notably, these associations were independent of age, BMI, and gender. In addition, we detected an effect of fibrinogen on both WOMAC stiffness and function scores, with higher fibrinogen levels associated with increased stiffness and functional limitation scores but not pain intensity. The fact that testosterone and fibrinogen are negatively but inversely associated with WOMAC outcomes is interesting and intuitive, as they have distinct but opposing biological roles in inflammation, tissue repair, and musculoskeletal health. Finally, our sensitivity analysis revealed that the effect of testosterone on WOMAC outcomes was BMI-specific, as the effects were only significant for the subgroup of individuals with overweight and

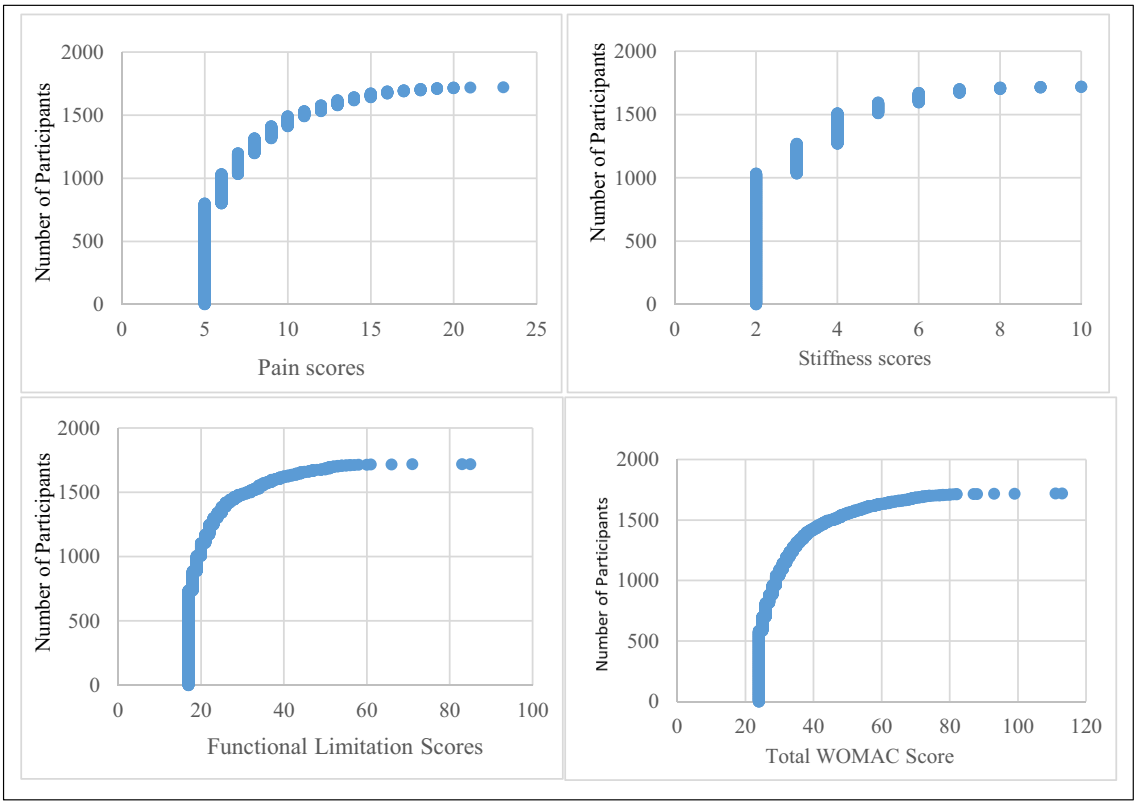

Figure 1: Distribution of the WOMAC subscale scores and total scores. Scores were calculated for the three subdomains: Pain score ranges from 0 to 25 points, where a higher score is equivalent to greater pain and, consequently, poorer knee or hip outcomes; stiffness ranges from 0 to 10; and functional limitation scores range from 0 to 85. The total WOMAC score is the sum of the scores from all three dimensions (pain, stiffness, and physical function), and it ranges from 0 to 120.

Table 3: Multivariate effects of each clinical indicator on WOMAC outcomes

Outcome	Sum of squares	df	Mean square	*F*	*p*-value	R^2
Pain	442.279	11	40.207	4.244	<0.001	0.027
Stiffness	96.956	11	8.814	4.572	<0.001	0.029
Function	4711.682	11	428.335	6.051	<0.001	0.038
Total WOMAC	9799.055	11	890.823	6.162	<0.001	0.038

obesity. However, the effect of fibrinogen was not BMI-specific, and stratifying the sample by BMI diminished the effect of fibrinogen on WOMAC outcomes.

Elevated serum testosterone has been associated with reduced WOMAC pain scores independent of age, BMI, and physical activity [16]. In addition, several studies have shown that lower testosterone levels are associated with an increased risk of chronic pain, inflammation, and metabolic diseases [17–20]. One study described a non-significant inverse association between testosterone levels and WOMAC limited physical function scores in women and WOMAC stiffness in men with symptomatic knee osteoarthritis [16,21]. Moreover, low sex hormone levels have been linked to chronic and musculoskeletal pain in elderly women, irrespective of lifestyle and health-related variables [22]. Another study reported an association between testosterone levels and the risk of developing arthritis, with the arthritis group having lower testosterone levels than the non-arthritis group [23]. In a study of arthritis patients, lower serum testosterone was associated with lower WOMAC stiffness scores in males and higher WOMAC limited physical function scores in females [21,23]. These studies support our finding that testosterone could play a role in reducing pain and increasing the pain threshold. Indeed, testosterone has been reported to protect against pain in males [24]. Testosterone can play a role in limiting the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), thereby contributing to significant antinociception in males compared with females, who have lower testosterone levels [25]. Additionally, testosterone reduces capsaicin receptor-mediated signals in dorsal root ganglion neurons, underscoring its pain-relieving properties [24]. Testosterone could play a significant role in influencing pain perception,

Table 4: Effect of clinical indicators on each WOMAC outcome

Indicator	Outcome															
	Pain				Stiffness				Functional limitation				Total			
	B	Std. Error	*t*	*p*	*B*	Std. Error	*t*	*p*	*B*	Std. Error	*t*	*p*	*B*	Std. Error	*t*	*p*
HDL	1.19	1.79	0.66	0.51	0.07	0.80	0.08	0.94	3.43	4.89	0.70	0.48	4.68	6.98	0.67	0.50
LDL	1.21	1.78	0.68	0.50	−0.04	0.80	−0.05	0.96	3.32	4.87	0.68	0.50	4.49	6.96	0.65	0.52
TC	−1.17	1.78	−0.65	0.51	0.06	0.80	0.08	0.94	−3.19	4.88	−0.66	0.51	−4.30	6.97	−0.62	0.54
TG	0.61	0.80	0.76	0.45	0.01	0.36	0.03	0.98	1.92	2.19	0.88	0.38	2.54	3.13	0.81	0.42
Free triiodothyronine	−0.11	0.11	−1.04	0.30	−0.04	0.05	−0.76	0.45	−0.39	0.30	−1.28	0.20	−0.54	0.43	−1.25	0.21
Free thyroxine	0.00	0.04	−0.08	0.94	−0.02	0.02	−1.17	0.24	−0.01	0.11	−0.05	0.96	−0.03	0.16	−0.19	0.85
TSH	0.00	0.02	−0.10	0.92	0.01	0.01	0.41	0.68	−0.01	0.07	−0.13	0.90	−0.01	0.10	−0.07	0.94
Testosterone	−0.03	0.01	−3.59	<0.001	−0.01	0.00	−2.53	0.01	−0.08	0.03	−3.39	<0.001	−0.13	0.04	−3.58	<0.001
Estradiol	0.00	0.00	−0.86	0.39	0.00	0.00	−1.38	0.17	0.00	0.00	−1.17	0.24	0.00	0.00	−1.20	0.23
Fibrinogen	0.24	0.15	1.63	0.10	0.17	0.07	2.48	0.01	1.07	0.40	2.66	0.01	1.48	0.58	2.57	0.01
CRP	0.02	0.02	1.16	0.25	0.01	0.01	1.08	0.28	0.08	0.05	1.54	0.12	0.11	0.08	1.50	0.13

potentially contributing to lower pain severity in individuals with higher testosterone levels.

Fibrinogen is considered an inflammatory marker, and when elevated, it indicates a systemic acute inflammatory reaction [26,27]. A study assessing patients with osteoarthritis receiving the anti-inflammatory drug pycnogenol or placebo measured CRP and fibrinogen [26] and found a significant reduction in WOMAC scores, CRP (3.9 to 1.1 mg/L), and fibrinogen (62.8% decrease) in the group receiving the drug compared with initial measurements ($p < 0.05$) [26]. Interestingly, pain severity may be inversely associated with the intensity of the inflammatory reaction, with one study showing that as pain severity increased, CRP levels decreased. However, despite this inverse association, no significant correlation was observed between CRP levels and WOMAC scores in patients with osteoarthritis [28]. This finding is consistent with our study, indicating that while inflammation may play a role in pain perception, the relationship between CRP levels and pain severity, as assessed by the WOMAC scale, may not be straightforward nor consistent across all populations.

Fibrinogen, vital for blood clotting, plays a crucial role in the initial reaction to musculoskeletal injury and in healing and disease processes [27]. Its primary role is to create fibrin clots and facilitate tissue repair [27,29]. However, fibrinogen and its derivatives risk exacerbating inflammation and consequent tissue damage, leading to increased pain [29]. Moreover, fibrinogen can interact with nociceptive receptors and signaling pathways, influencing pain perception [29]. Interestingly, within our study population, we did not observe a significant effect of fibrinogen levels on the reported WOMAC pain score. Despite its known involvement in inflammatory processes and pain modulation, the specific relationship between fibrinogen levels and pain severity did not emerge as a significant factor in our analysis. While fibrinogen may play a role in pain perception and inflammation in general, its impact on musculoskeletal pain, as assessed by the WOMAC pain score in our study, may be influenced by other factors or mechanisms not captured in our analysis.

A few studies have correlated lipid profiles with WOMAC scores. One study reported an association between LDL cholesterol levels and WOMAC subscale scores [30]. In the study, a moderate correlation was found between LDL cholesterol and higher pain intensity ($r = 0.44$ and 0.34; $p < 0.05$). Moreover, the study detected a significant association between LDL cholesterol and higher physical function scores, suggesting poorer physical function in individuals with early OA. These findings contradict our results since we did not detect a significant effect for any of the four lipid profile parameters. We did not detect an association between other lipid parameters and WOMAC scores. However, one study reported that higher HDL-C levels are associated with lower WOMAC scores ($p < 0.001$) [31].

Despite its usefulness, WOMAC has its limitations when used in healthy individuals. One notable limitation is the potential for floor effects, especially in populations where participants may report minimal pain, stiffness, or functional limitations. Healthy individuals might exhibit low WOMAC scores due to the absence of significant musculoskeletal pathology, potentially limiting the sensitivity of the tool in detecting subtle variations in pain perception [32]. Furthermore, the subjective nature of self-reported

measures, such as those used in WOMAC, introduces the possibility of response bias or variations in individual interpretation. Pain perception is a complex phenomenon influenced by psychological, social, and cultural factors. While WOMAC captures the physical aspects of pain, it may not fully account for the psychological components, necessitating a comprehensive approach that combines WOMAC with additional assessments, such as psychological questionnaires or objective physical measurements, for a more holistic understanding of pain in healthy populations [33]. Longitudinal studies may be useful to assess changes in WOMAC scores over time to provide a better understanding of the natural progression of musculoskeletal disorders and the impact of demographic and clinical parameters on WOMAC scores.

In conclusion, we report a possible effect of both testosterone and fibrinogen on pain, stiffness, and physical functional limitations in healthy individuals. Our findings suggest that the measurement of multiple clinical laboratory markers in healthy individuals may be useful for determining the causes of pain.

Research ethics: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013). Data were obtained from the Qatar Biobank under reference number E-2021-QF-QBB-RES-ACC-00050-0172, and the study was conducted with the approval of QU-IRB under reference number 1648-E/22.

Informed consent: Informed consent was obtained from all individuals in this study.

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Artificial intelligence/Machine learning tools: Not applicable.

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