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White Blood Cell Counts, Insulinlike Growth Factor-1 Levels, and Frailty in Community-Dwelling Older Women

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Background. Elevated white blood cell (WBC) counts and decreased insulin-like growth factor-1 (IGF-1) levels are individually associated with frailty in older adults. WBC subpopulations are known to produce IGF-1 and express IGF-1 receptors in vitro. However, in vivo relationships between WBC and IGF-1 and their joint contribution to frailty have not been investigated.

Methods. Baseline data from 696 community-dwelling older women in the Women's Health and Aging Study I were included in this cross-sectional analysis. Multivariate linear regression analysis was performed to assess the relationship between WBC counts and IGF-1 levels. Odds ratios (ORs) for frailty were evaluated across tertiles of WBC counts and IGF-1 levels, adjusting for age, race, education, body mass index, and smoking.

Results. WBC counts correlated with IGF-1 levels (Spearman coefficient: .10, $p < .01$). Compared with participants in the low WBC and high IGF-1 tertiles (reference group), those in the low WBC and low IGF-1 tertiles had OR of 2.33 for frailty (95% confidence interval [CI]: 1.04–3.65, $p < .05$), those in the high WBC and high IGF-1 tertiles had OR of 3.86 (95% CI: 1.13–4.07, $p < .01$), and those in the high WBC and low IGF-1 tertiles had OR of 3.61 (95% CI: 1.64–4.97, $p < .01$), adjusting for covariates.

Conclusions. These findings demonstrate in vivo correlation between WBC and IGF-1. They suggest U-shaped joint associations of WBC and IGF-1 with frailty, with the strongest association at adverse levels of both. They also provide a basis for further investigation into the complex immune–endocrine dysregulations in frailty.

Key Words: Frailty—WBC—IGF-1.

FRAILTY is a common and important geriatric syndrome characterized by dysregulations in multiple physiological systems and increased vulnerability for serious adverse health outcomes (1–4). Substantial evidence suggests that inflammation, as marked by elevated interleukin-6 (IL-6) levels and white blood cell (WBC) counts, is a key pathophysiological factor for frailty and its associated multisystem dysregulations (5–8). Insulinlike growth factor-1 (IGF-1) is an important hormone in the growth hormone–IGF-1 axis. Decrease in the IGF-1 levels is a major endocrine dysregulation that has been implicated in frailty, disability, and mortality in older adults (8–10). WBC and its subpopulations are important cellular components of the inflammation system. They have a critical role in both innate and adaptive immunity as well. WBC subpopulations are known to produce IGF-1 and express IGF-1 receptors in vitro (11–14). On the other hand, IGF-1 regulates T-cell activation and promotes survival of T cells and granulocytes (12,15–17). However, the in vivo relationship between WBC and IGF-1 and their joint contribution to frailty in older adults have not been investigated.

In order to gain initial insight into these in vivo relationships, we conducted a cross-sectional study in the Women's Health and Aging Study (WHAS) I to test the hypothesis that WBC counts and IGF-1 levels would have significant associations with each other and multiplicative associations with frailty in community-dwelling disabled older women. Addressing this hypothesis will help advance our understanding of complex interaction between the immune and the endocrine systems and potential role of combined immune–endocrine dysregulations in the pathogenesis of frailty.

Methods

Study Population

The WHAS I is a population-based study of the causes and course of disability among moderately to severely disabled women aged 65–101 years living in the community. The study design and data collection methods of the WHAS I have been described in detail elsewhere (18,19). At baseline, 791 of 1,002 participants had blood samples drawn and 708 had total WBC counts and IGF-1 measurements. To minimize potential influence of acute bacterial infection or hematologic malignancies, 12 participants with total WBC counts more than $12 \times 10^3/mm^3$ were excluded from the analysis, yielding a final sample of 696 participants for this study.

Table 1. Selected Characteristics of the Participants in the WHAS I Cohort

Characteristics	WHAS I (N = 1,002)	Study Subsample (N = 696)	p*
Age (y), mean (*SD*)	77.7 (7.8)	77.6 (7.6)	.7
Race (% White)	71.2	71.3	.9
Education (y), mean (*SD*)	9.7 (3.6)	9.7 (3.8)	.9
Smoking status (% current or previous smokers)	46.8	47.1	.7
Body mass index (kg/m^2), mean (*SD*)	28.3 (6.8)	28.7 (6.3)	<.01
Total number of medical diagnoses, mean (*SD*)	4.0 (1.7)	4.0 (1.8)	.9
Self-reported health (%)			<.05
Excellent or very good	18.5	17.8	
Fair or good	64.0	67.6	
Poor	17.7	14.7	

Notes: WHAS = Women's Health and Aging Study.

*p Values were calculated for comparing 696 participants who were included in this study, with 306 who were excluded for reasons detailed in the text.

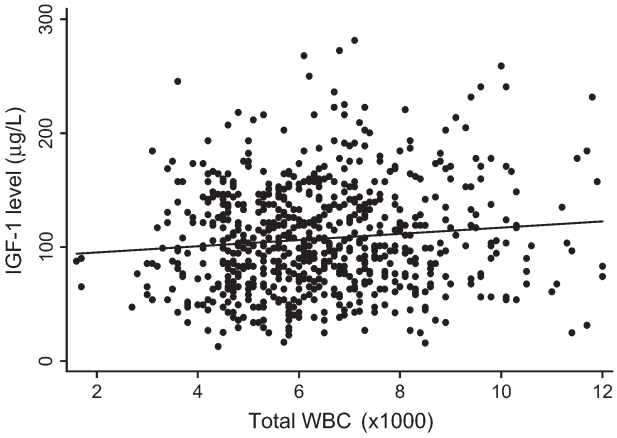

Figure 1. Scatter plot with fitted regression line showing the relationship between WBC counts and IGF-1 levels in the study population, adjusting for age, race, body mass index, education, and smoking status. IGF-1 = insulin-like growth factor-1; WBC = white blood cell.

Determination and Classification of Frailty

Participants were classified as frail, prefrail, and nonfrail according to a validated screening tool based on the presence or absence of five measurable characteristics: weakness (by grip strength), low physical activity, slowed walking speed, exhaustion, and weight loss (2). Individuals with a critical mass of 3 or more of the five components were defined as frail, those with one or two components were defined as prefrail, and those with none were defined as nonfrail.

Measurements of IGF-1 Levels and Total WBC Counts

IGF-I was measured by radioimmunoassay with ethanol extraction (Nichols Institute Diagnostics, San Juan Capistrano, CA). Total WBC counts were obtained using a Coulter Counter (Quest Laboratory, Trenton, NJ).

Statistical Analysis

Summary statistics were constructed for comparing baseline characteristics of the original WHAS I cohort (N = 1,002) with the subset of women included in this study. Distributions of sociodemographic and health characteristics, total WBC counts, and IGF-1 levels were summarized according to frailty status at baseline. The Spearman rank correlation coefficient was used to describe the correlation between WBC counts and IGF-1 levels. Linear regression analysis was used to study the relationship between total WBC counts (as dependent variable) and IGF-1 levels (as independent variable), adjusting for age, race, education, body mass index (BMI), and smoking status. Logistic regression models were used to assess the effects of WBC counts and IGF-1 levels on the risk of being frail versus nonfrail cross-sectionally at baseline. Because exploratory analyses suggested potential nonlinear associations of WBC counts and IGF-1 levels with frailty, WBC counts and IGF-1 levels were modeled as tertiles in association with frailty for ease of interpretation. Interaction terms were added to the main effects model to explore potential synergy between WBC counts and IGF-1 levels in their associations with frailty.

Results

Baseline demographic and clinical characteristics of all study participants in the WHAS I cohort and 696 participants included in this study are summarized in Table 1. Compared with the 696 participants included in the analysis, 306 participants who were not included (either did not provide blood samples or were excluded due to their WBC counts above the normal range) had lower BMI and poorer self-reported health status. There was no significant difference in age, race, education, smoking status, or total number of medical diagnoses between the two groups.

Figure 1 displays a scatter plot of WBC counts and IGF-1 levels in the study population. The mean WBC count was $6.41 \times 10^3/mm^3$, the median was $6.2 \times 10^3/mm^3$, and the range was $2.6 \times 10^3/mm^3$ to $10.2 \times 10^3/mm^3$. The mean IGF-1 level was 107.5 µg/L, the median was 101.3 µg/L, and the range was 12.8–281.3 µg/L. WBC counts and IGF-1 levels were correlated (Spearman correlation coefficient = .10, $p < .01$) such that for $1 \times 10^3/mm^3$ increase in WBC count, IGF-1 level increases by 2.54 µg/L (95% confidence interval: 0.53–4.55, $p < .01$), adjusting for age, race, BMI, education, and smoking status.

Table 2 reports baseline demographic and health-related characteristics, WBC counts, and IGF-1 levels of the study sample across frailty categories. There were significant differences in mean WBC counts and IGF-1 levels across frailty categories ($p < .001$ for stepwise increase or decrease trend). Compared with nonfrail participants, frail participants were older ($p < .001$), of non-White race ($p = .06$), and were less educated ($p < .001$).

To investigate potential joint association of WBC counts and IGF-1 levels with frailty, odds ratios (ORs) of

Table 2. Selected Demographic and Study Variables of the Study Sample Across Frailty Categories

Characteristics	Nonfrail ($N = 90$)	Prefrail ($N = 382$)	Frail ($N = 224$)	p*
Age (y), mean (*SD*)	73.0 (6.2)	77.1 (7.4)	80.6 (7.8)	<.001
Race (% White)	81.1	71.2	68.3	.06
Education (y), mean (*SD*)	10.8 (3.9)	9.8 (3.6)	9.1 (2.7)	.001
Smoking status (% current or previous smokers)	45.8	46.1	46.2	.9
BMI (kg/m^2), mean (*SD*)	27.1 (4.2)	29.1 (6.6)	27.8 (7.8)	.7
%BMI†				.5
<21.5	2.6	8.4	21.3	
21.5–24.9	31.0	15.6	16.0	
25.0–29.9	43.2	35.3	25.6	
≥30.0	23.2	40.7	37.1	
WBC (×10^3/mm^3), mean (*SD*)	6.1 (1.6)	6.4 (1.8)	6.6 (1.8)	<.001
IGF-1 (μg/L), mean (*SD*)	118.9 (43.8)	113.9 (48.6)	102.3 (46.1)	<.001

Notes: BMI = body mass index; IGF-1 = insulinlike growth factor-1; WBC = white blood cell.
*p Values were determined using Jonckheere–Terpstra trend test.
†BMI was considered a categorical variable as defined and was adjusted in all the regression models.

participants being frail versus nonfrail were assessed across tertiles of WBC counts and IGF-1 levels. As shown in Table 3, participants in the low tertile of WBC and low tertile of IGF-1, those in the high tertile of WBC and high tertile of IGF-1, and those in the high tertile of WBC and low tertile of IGF-1 had significantly higher OR of being frail compared with those in the low tertile of WBC and high tertile of IGF-1 (reference group), with OR of 2.33 ($p < .05$), 3.86 ($p < .01$), and 3.61 ($p < .01$), respectively, adjusting for age, race, BMI, education, and smoking status. These results showed that in the setting of low IGF-1 levels, both low and high WBC counts confer increased risk for frailty, and that in the setting of high WBC counts, both low and high IGF-1 levels confer increased risk for frailty, suggesting a "U"-shaped joint association of WBC counts and IGF-1 levels with frailty. The interaction terms between tertiles of WBC and IGF-1, however, were not statistically significant (data not shown).

Discussion

This study has demonstrated, for the first time, a significant in vivo association between WBC counts and IGF-1 levels in community-dwelling older women, adjusting for age, race, BMI, education, and smoking status. This finding is supported by ample in vitro evidence including (i) WBC subpopulations produce IGF-1 and IGF-binding proteins (11,14) and express IGF-1 receptor (12,13,16) and (ii) IGF-1 regulates T-cell activation and promote WBC survival (12,15–17). We did not observe multiplicative interaction in the associations of WBC counts and IGF-1 levels with frailty. Instead, the results suggest a U-shaped joint association of WBC counts and IGF-1 levels with frailty (Table 3). If this is further confirmed, it is likely that low IGF-1 cannot improve extremely low WBC and its associated immune dysregulation, whereas high IGF-1 further promotes high WBC and its associated inflammation; both inflammation and immune dysregulation are associated with frailty (5,20).

This study has two limitations. First, sample size of the subgroups in the analysis across tertiles of WBC counts and IGF-1 levels is relatively small and provide limited statistical power. Cautious interpretation of these results is warranted, and further investigation of the joint effects of WBC counts and IGF-1 levels on frailty is needed. Second, other inflammatory and immune factors including IL-6 have been identified for their interactions with IGF-1 and WBC counts as well as their associations with frailty (5,6,9,10,21). Therefore, findings from this study should be interpreted in the context of the complexity of the immune and endocrine systems as well as multifactorial nature of the frailty syndrome. Despite these limitations, results from this study do support our original hypothesis and provide a basis for further investigations into complex immune–endocrine dysregulations in frailty.

Table 3. Odds Ratios of Being Frail Versus Nonfrail of Participants Across Tertiles of WBC Counts and IGF-1 Levels

	Tertiles of IGF-1 Levels		
	Low (≤85 μg/L)	Middle (86–126 μg/L)	High (>126 μg/L)
Tertiles of WBC counts			
Low (≤5.5 × 10^3/mm^3)	2.33*	1.76	1.0 (reference)
Middle (5.6 × 10^3/mm^3 to 7.0 × 10^3/mm^3)	1.94	2.40	1.86
High (>7.0 × 10^3/mm^3)	3.61†	1.86	3.86†

Notes: IGF-1 = insulinlike growth factor-1; WBC = white blood cell.
*$p < .05$.
†$p < .01$.

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