Leukocytosis in obese individuals: possible link in patients with unexplained persistent neutrophilia


Abstract: Background: Recently, it was shown that fat tissue produces and releases inflammatory cytokines, and that obesity may be regarded as a state of low-grade inflammation. In this regard, we aimed to establish an association between obesity and persistent leukocytosis. Patients and methods: We present clinical observations of obese subjects primarily referred for further evaluation of leukocytosis without a cause and validated the link between leukocytosis and elevated body mass index (BMI) in a cross-sectional study. Results: During 1999–2005, 327 patients were referred for further investigation because of persistent leukocytosis. Of these, 15.3% were asymptomatic obese, mostly females, with mild persistent neutrophilia accompanied by elevated acute-phase reactants. After careful evaluation, no recognized cause for leukocytosis was found other than the fact that the patients were obese. During a mean follow-up of 45.6 months, the leukocytosis and the elevated acute-phase reactants persisted and no new causes for leukocytosis were evident. Furthermore, in a cross-sectional analysis of 3716 non-smoker subjects, 62 were found to have leukocytosis. Compared with the population with a normal white blood count range, these subjects with leukocytosis had higher BMI, serum C-reactive protein (CRP) levels, waist circumference, and neutrophil and platelet count (all \( P < 0.0005 \)). After logistic regression analysis, only BMI was shown to be associated with leukocytosis (\( P < 0.0005 \)). Conclusions: Obesity is recognized as a possible cause for reactive leukocytosis. Awareness of this ‘obesity-associated leukocytosis’ may help the clinician to avoid more extensive and unnecessary diagnostic work-up, particularly in similar obese subjects.

Although, in epidemiological studies, it has been shown that obese subjects have higher white blood counts than lean individuals, the absolute leukocyte count of obese subjects is generally within the normal range (1–3). On the other hand, there are almost no reports that focused specifically on leukocytosis in obesity.

In this regard, we observed that a relatively large number of patients referred for further investigation of unexplained leukocytosis, are actually obese. Even after extensive work-up, no cause could be found other than their being fat. During a relatively long follow-up, the leukocytosis was persistent and stable, and the clinical course of these subjects was benign. In a few of these subjects, who subsequently lost weight, normalization of the white blood counts occurred.

Therefore, in this study we establish a link between persistent leukocytosis and obese individuals. In our opinion, these results provide a basis for a better clinical approach for the investigation of unexplained leukocytosis in obese patients, which may avoid an extensive and unnecessary laboratory work-up in many cases.

Patients and methods

Based on our clinical observation that obesity is a possible cause for persistent leukocytosis, we started to identify patients referred because of
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unexplained persistent leukocytosis to our community outpatient hematology clinic. Using computerized patient files, we retrieved data on patients investigated for leukocytosis, during the years 1999–2005. In each case, the duration and possible causes for leukocytosis were assessed (e.g. infection, inflammation, smoking, malignancy, etc.) and all other ancillary tests were conducted. For further validation of the association between high body mass index (BMI) and leukocytosis, we analyzed data available from a large-scale population of individuals who had participated in the Tel Aviv Medical Center Inflammation Survey (4–6) in a registered databank, Data Bank Registries, Ministry of Justice, State of Israel. This survey of apparently healthy individuals is presently taking place at our medical center and includes a relatively large cohort of individuals attending the Tel Aviv Sourasky Medical Center for routine health examination. All the individuals included in the present survey gave their written consent according to the instructions of the Institutional Ethics Committee. We excluded any individuals with an underlying inflammatory disease (arthritis, inflammatory bowel disease, etc.) as well as those with any infection or other inflammatory conditions (including infection, surgery or angiography during the 6 months preceding study enrollment), patients with cancer or under immunosuppressive therapy. We also excluded individuals treated with steroid or non-steroidal anti-inflammatory medications, except for low doses of aspirin (≤ 325 mg/d). Finally, in order to minimize the effect of smoking on the leukocyte count, we excluded all current smokers.

Statistical analysis

All data were summarized and displayed as mean ± SD for the continuous variables (age, BMI, all the inflammation markers, etc.), and as number of patients plus the percentage in each group for categorical variables (e.g. cardiovascular risk factors). The crosstabs and descriptive procedures were used to calculate frequencies of categorical variables and mean (± SD) values of continuous variables. The high-sensitive C-reactive protein (hs-CRP) and the triglyceride concentration have non-normal distribution, and hence we used a logarithmic transformation converting it to normal distribution for all statistical procedures like regressions, and all the results expressed as hs-CRP are back-transformed geometrical mean and SD. The one-sample Kolmogorov–Smirnov test was used to verify the normal distribution of the logarithmic transformation.

For all categorical variables, the chi-squared and Cramer’s V statistics were used for assessing the significant difference between the individuals with and without leukocytosis, while the Student’s t-test for independent samples was used to assess those differences for all continuous variables.

To assess which of the co-factors might have contributed to leukocytosis, we used the same definition of leukocytosis as the dependent factor and age, gender, waist circumference, BMI, lipid profile including high-density lipoproteins (HDL), low-density lipoproteins (LDL) and triglycerides, systolic and diastolic blood pressure, history of cardiovascular disease, cerebrovascular or peripheral arterial disease, history of diabetes mellitus, hyperlipidemia or hypertension, and the use of statins, fibrates, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, using stepwise logistic regression.

The level of significance used for all the above analyses was two-tailed, P < 0.05. The SPSS statistical package was used to perform all statistical evaluations (SPSS Inc., Chicago, IL, USA).

Results

During the 6-yr period (1999–2005), 327 patients were referred to our hematology outpatient clinic for investigation of leukocytosis by their family physicians. In this group of cases, the commonest cause for persistent neutrophilia was smoking, while other well-recognized causes included myeloproliferative and lymphoproliferative disorders or a variety of inflammatory states, occult infections, post-splenectomy, pregnancy, and drugs. In a relatively large subgroup of patients, no obvious cause was found (Fig. 1).

The second largest group of patients (15.3%) included 50 patients, in whom no cause for leukocytosis was found other than associated obesity (BMI ≥ 30). This group of obese patients (Table 1) were predominantly middle-aged females (40 females and 10 males, mean age 53.7 ± 17.8 yr). Their leukocytosis was persistent, mild (mean WBC 13.05 ± 1.44 × 10^9/L and mean total neutrophils 8.58 ± 1.93 × 10^9/L) and was accompanied by elevated serum CRP levels (mean of 17 ± 13 mg/L) and high erythrocyte sedimentation rate (ESR) (55 ± 31). These patients were generally asymptomatic and leukocytosis was most commonly found on a routine blood cell count. On physical examination, no abnormal finding other than obesity was evident. Their mean BMI was 36.7 ± 5.6.

Based on the data available in 10 subjects, the mean waist circumference was 115.1 cm (range 100–138) and the mean hip circumference was 117.22 cm (range 106.2–140). On automated blood cell counts and peripheral blood smears, leukocytosis was characterized by neutrophilia without significant
significantly elevated acute-phase reactants. According to the white blood count distribution in males, at a mean (± SD) age of 48.5 (± 11) yr.

...collected from 3716 subjects [1333 females and 2383...

...was accompanied by a gradual reduction and normalization of the white blood count and serum CRP levels.

In three individuals, the relationship between the BMI, white blood count, and serum CRP level during weight reduction as was demonstrated in one of the patients. This figure illustrates that weight reduction is accompanied by a gradual reduction and normalization of the white blood count and serum CRP level.

...this population, leukocytosis was defined as a white blood count above 10^9/L. In this group (Table 2), 62 individuals were found to have leukocytosis. Comparison between subjects with leukocytosis and those with normal range of white blood cell counts revealed that this leukocytosis subgroup also had higher serum CRP levels (3.4 ± 3.4 vs. 1.5 ± 2.9 mg/L, *P* < 0.0005), higher BMI (28.7 ± 4.7 vs. 26.6 ± 4.1, *P* < 0.0005), greater waist circumference (98.0 ± 14.1 vs. 91.1 ± 12.3 cm, *P* < 0.0005) and waist-to-hip ratio (1.01 ± 0.12 vs. 0.96 ± 0.16 cm, *P* = 0.009), greater neutrophil counts (7.98 ± 2.03 vs. 3.85 ± 1.08 × 10^9/L, *P* < 0.0005) and higher platelet count (277 ± 69 vs. 244 ± 55 × 10^9/L, *P* < 0.0005). No significant differences in age, gender, thigh circumference, ESR and hemoglobin levels were detected in these two groups. Furthermore, in order to assess which components may have contributed to the leukocyte count, we performed logistic regression, and the results demonstrated that only higher BMI (*P* < 0.0005) was associated with leukocytosis. The odds ratio for leukocytosis was

...shift to the left and without eosinophilia or basophilia. Leukocyte acid phosphatase (LAP) analysis was performed only in nine subjects and levels were found to be elevated (median score 146, range 62–196). Further investigations were individualized based on age, medical history, physical examination, past laboratory results and other basic laboratory blood analysis. During a relatively long follow-up (mean of 45.6 ± 42 months), leukocytosis and elevated acute-phase reactants were persistent and no other new causes were found.

In three individuals, the relationship between the BMI, white blood count, and serum CRP levels was clearly demonstrated. In these cases, reduction in weight was accompanied by a gradual reduction and normalization of the white blood count and serum CRP levels (Fig. 2).

In the second part of our study, we analyzed data collected from 3716 subjects [1333 females and 2383 males, at a mean (± SD) age of 48.5 (± 11) yr. According to the white blood count distribution in

**Fig. 1.** Different etiologies for neutrophilia in a referred community-based population.

*Patients with unknown cause for leukocytosis and normal range acute-phase reactants.

1**MPD, myeloproliferative disorders.

**Table 1.** Clinical parameters and laboratory data in obese individuals obtained from selected subjects referred for evaluation of persistent leukocytosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th><em>P</em>  Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>53.7 ± 17.8</td>
<td></td>
</tr>
<tr>
<td>Female : male ratio</td>
<td>4 : 1</td>
<td></td>
</tr>
<tr>
<td>Mean leukocyte count (×10^9/L)</td>
<td>13.05 ± 1.44</td>
<td></td>
</tr>
<tr>
<td>Mean total neutrophils (×10^9/L)</td>
<td>8.58 ± 1.93</td>
<td></td>
</tr>
<tr>
<td>Mean platelet count (×10^9/L)</td>
<td>340.5 ± 92.3</td>
<td></td>
</tr>
<tr>
<td>Mean serum CRP levels (mg/L)</td>
<td>17 ± 13</td>
<td></td>
</tr>
<tr>
<td>Mean erythrocyte sedimentation</td>
<td>55 ± 31</td>
<td></td>
</tr>
<tr>
<td>Mean body mass index</td>
<td>36.7 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>Mean of time to follow-up (months)</td>
<td>45.6 ± 42</td>
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</tr>
</tbody>
</table>

**Table 2.** The results of a cross-sectional study evaluating clinical and laboratory parameters in subjects with and without leukocytosis

<table>
<thead>
<tr>
<th>Clinical and laboratory parameters</th>
<th>Leukocytosis subgroup (<em>n</em> = 62)</th>
<th>Normal white blood count population (<em>n</em> = 3654)</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>48.5 ± 11</td>
<td>46.2 ± 10.9</td>
<td>0.096</td>
</tr>
<tr>
<td>BMI</td>
<td>28.7 ± 4.7</td>
<td>26.6 ± 4.1</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>98 ± 14.1</td>
<td>91.1 ± 12.3</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>1.01 ± 0.12</td>
<td>0.96 ± 0.16</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean serum hs-CRP levels (mg/L)</td>
<td>3.4 ± 3.4</td>
<td>1.5 ± 2.9</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean total neutrophil number (×10^9/L)</td>
<td>7.98 ± 2.03</td>
<td>3.85 ± 1.08</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean hemoglobin (g/dL)</td>
<td>14.3 ± 1.2</td>
<td>14.1 ± 1.3</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean platelets number (×10^9/L)</td>
<td>277 ± 69</td>
<td>244 ± 55</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

BMI, body mass index; CRP, C-reactive protein.
1.11, which implies that for every 1 kg/m² increment in BMI, the risk of having leukocytosis is increased by 11%.

Discussion

In this study, we describe a subgroup of obese subjects with persistent leukocytosis. These subjects are mostly middle-aged asymptomatic females, who were noted to have unexplained leukocytosis and high levels of acute-phase reactants (CRP levels and ESR) on a routine blood examination. Based on medical history, physical examination, ancillary tests and a long period of follow-up, no cause for leukocytosis was evident, other than obesity. The leukocytosis was mild, consisted of neutrophilia, without a shift to the left and was stable throughout the follow-up. In three of these subjects who lost weight significantly, leukocytosis and the acute-phase reactants gradually returned to normal. Furthermore, this subgroup of obese individuals appear to constitute a relatively significant portion of the community-based patients who are referred to hematology outpatient clinics for further investigation of unexplained leukocytosis.

As this subgroup of obese patients were selected from a group of subjects who were referred for further evaluation of leukocytosis, this clinical observation could of course be biased. Because of this possible bias, we attempted to define the possible link between leukocytosis and obesity in a relatively large-scale cross-sectional analysis. In this analysis of a population of non-smokers, we found that those who had leukocytosis also had significantly higher BMI and serum CRP levels, increased waist circumference and waist-to-hip ratio, and higher neutrophil and platelet counts. Furthermore, after logistic regression analysis, only higher BMI was shown to be associated with leukocytosis.

In previous large cross-sectional epidemiological studies, obesity was shown to be associated with relatively high white blood counts and BMI was positively correlated with leukocyte count (2, 3). However, it should be noted that, although obese subjects have relatively higher white blood counts, their absolute leukocyte number is still generally within the normal range (2). In the literature, the association between absolute high white blood count and obesity did not gain any real attention and as Nanji and Freeman (7) also reported a high prevalence of leukocytosis among 42 morbid obese subjects.

The relationship between the observed leukocytosis in these obese subjects and the accompanying high levels of acute-phase reactants, can be explained by the fact that obesity may be regarded as a state of low-grade inflammation (8–14). In this respect, human adipose tissue was found to produce and release pro-inflammatory cytokines and chemokines including interleukin-6 (9), tumor necrosis factor-α (10–12), interleukin-1 (13), and interleukin-8 (14). These cytokines and chemokines can induce neutrophilia via demargination of intravascular neutrophils, acceleration of bone marrow neutrophil release or enhancement of bone marrow granulopoiesis (15–19). Furthermore, leptin the anti-obesity hormone, mostly produced in adipose tissue was shown to stimulate stem cells and produce granulocyte–macrophage colonies (20, 21).

One of the most obvious observations in our subjects was the fact that they were mostly women. In this respect, a stronger association between inflammatory markers and the indices of obesity have been observed in women when compared with men (22). It this study, it was suggested that the more prominent signs of low-grade inflammation in women may be related to the different distribution of the body fat tissue (visceral vs. subcutaneous) and the different sex hormones in women (22).

The obese subjects in our study were also characterized by an extremely high waist circumference and in the cross-sectional study those with leukocytosis also had significantly greater waist circumference values. A higher waist circumference is known to indicate a large amount of abdominal visceral fat which is considered to be a prominent promoter of inflammation (22–24). Therefore, it is not too surprising to note that these obese subjects had more pronounced parameters of inflammation, which included higher white blood counts and elevated acute-phase reactants.

In conclusion, although the white blood counts are relatively high in obese subjects, the values are still within the normal range in most of the cases. The obese subjects associated with absolute leukocytosis and raised acute-phase reactants may in fact represent a subgroup of obese subjects characterized by more pronounced parameters of inflammation. The results of our cross-sectional study further support a relationship between obesity and leukocytosis. Recognition of the association between obesity and leukocytosis may have important clinical implications. We suggest that clinicians avoid unnecessary and extensive investigation of elevated white blood counts in obese subjects who have the features presented in this study.

References

Obesity-associated leukocytosis