Polycystic Ovary Syndrome and Leucocytosis

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex heterogeneous female reproductive endocrine disorder with multiple pathological mechanisms. Persistent leucocytosis, reflecting an underlying inflammation, is well recorded in obesity and diabetes; diseases with an underlying Insulin resistance (IR). Leucocytosis in PCOS has not been widely studied in spite of IR being considered as the important aetiopathological mechanism. The present communication explores the occurrence of leucocytosis in thirty patients of PCOS as compared to that in twenty six healthy regularly menstruating women.

Introduction

Leucocytosis is defined as an increase in the number of white blood cells above the normal range (4000-10000) per cubic millimeter of blood.[1] This can be detected by routine haematological profiling. Increase in white blood cell count (WBC) occurs in response to infections or it reflects an underlying low grade chronic inflammatory state as seen in non communicable diseases like obesity, and type 2 diabetes.[2-6] Hyperinsulinaemia and insulin resistance are common pathophysiological mechanism for both obesity and type 2 diabetes and chronic inflammation is the link between obesity and insulin resistannce.[7] It is of importance to explore presence of leucocytosis in the other insulin resistant disorders like PCOS.[8,9] In the present communication we have explored for the presence of leucocytosis amongst women with PCOS (N=30) as compared to its presence in healthy women (N=26) with the history of regular menstrual cycles. The studied cycles in the control group were documented for the presence of ovulation.

Subjects and Methods

It was a retrospective study design to compare the WBC count in a group of PCOS patients and controls. Consecutive 30 patients belonging to teen age and / or young adult group with identified PCOS attending a reproductive endocrine clinic provided the material for this study. Permission for the study of the healthy control group was obtained from ISBEC, an independent ethics committee and written informed consents were obtained from the participants.

Pelvic ultra sonography in the study group was carried out by trans-abdominal method. Polycystic ovary was identified if the ovaries had at least one of the following: either 12 or more follicles measuring 2 – 9 mm in diameter and increased ovarian volume (> 10 cm^3).[10] Ultrasonography was not done in the control group.

PCOS was defined as per the Rotterdam consensus, which is taken to be present when two of the following criteria are diagnosed in a patient.[11] 1. Oligo/Anovulation 2. Hyperandrogenism. 2a. Hirsutism (or clinically less male pattern alopecia) and/or 2b. Biochemical (raised free androgen index or free testosterone). 3. Polycystic ovaries on ultrasound. Known cases of autoimmune disease, diabetes, hypothyroid, thyroid, platelet dysfunction were excluded.

Comprehensive evaluation included detailed history. Family history of diabetes mellitus (DM) in 1st and 2nd degree relatives was recorded. Physical examination

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included anthropometry; height in cm and weight in kg. Height was measured in centimetres on a Harpenden stadiometer and weight in kg by an electronic scale (AMCO, India). BMI was calculated as kg/m^2.

A healthy control group was provided by adolescent girls and young women who gave history of regular menstrual cycles. Subjects from the control group did not have any history of the first degree relative with either type 2 diabetes mellitus or hypertension. Subjects from the control group were also screened for the presence of acne and /or hirsutism. Their studied cycles were also screened for biochemical hyperandrogenism. Anyone with clinical or biochemical evidence of hyperandrogenism were excluded.

Blood samples for various biochemical and endocrine tests were taken after 12 hour overnight fast in both the groups. Fasting sample was analysed for blood glucose, serum insulin, complete blood count, ESR, total cholesterol, HDL and LDL cholesterol, serum triglyceride. The complete blood count was done using fully automated cell counter (PCE210,ERMA IMC) and the differential count was obtained from the blood smear (stain with Field's stain) using Light microscope (Micron Optik). The diagnosis of leucocytosis was done when the WBC was more than 10000/cmm.[12]

Fasting blood sample was collected after 12 hours overnight fast. Then patients were given a 75 grams glucose to drink and blood samples were collected after 1 and 2 hrs. Blood glucose was estimated using GOD/POD (Accurex Biomedical Pvt Ltd). Fasting blood sugar of ≥ 110 & < 126 mg% is impaired fasting glucose (IFG). The post glucose blood sugar of ≥ 140 & < 200 mg% in response to glucose challenge is considered as impaired glucose tolerance (IGT) which is also considered as a prediabetic state. The diagnosis of type 2 diabetes was made if the fasting blood sugar level was ≥ 126 mg% and post glucose blood sugar levels ≥ 200 mg%. Serum insulin was estimated by Radioimmunoassay (Immunotech). The ratio of fasting glucose to fasting insulin of ≤ 4.5 identified insulin resistance and /or if the 2 hour post glucose insulin levels were higher than 80 μIU/ml.[13] Insulin levels were not available for 6 of the study group.

Results

Over weight (20%) and obesity (40.1%) constituted 61.3% of the PCOS group as per WHO classification of BMI.[14] However, when classified according to the criteria for Indian women, the overall rate rose to 63.3% in the group.[15] One patient from the study group had impaired glucose tolerance. She had shown both the IGT and marked hyperinsulinaemia and IR inspite of having normal BMI. This lean patient with PCOS showed definite leucocytosis. The rest of the patients had normal fasting and post glucose blood sugar levels. Insulin resistance defined by FG:FI ratio showed 8 (33.3%) of the 24 PCOS women having insulin resistance. While those having IR on the basis of delayed hyperinsulinaemia were observed in 12 (50%); of these six also had the overlapping IR according to their FG:FI ratio of < 4.5. This indicates that totally 14 of the 24 (58%) PCOS were insulin resistant and none from the control group showed any evidence of insulin resistance.

The WBC count in PCOS ranged from 4300-12100 and the definable count for the diagnosis of leucocytosis (≥ 10000) was observed in 5 (16%) of them. Subjects from the control group showed WBC ranging from 5300-10000/cmm. However definable leucocytosis (≥ 10000) was observed in only one of the control group. The mean WBC count of the control group was 6825/cmm ± 2292.6 and the median was 6100/cmm. Whereas the study group showed a higher mean count of WBC (7897/cmm ± 2044.8) and median (7150/cmm). However, the differences of WBC in the study group was not statistically significant as compared to the control group. The number showing actual leucocytosis and the higher side of normal WBC were more amongst the study group as compared to the control group. WBC count more than 7000/cmm was identified in 56% of the study group, while the control group had only 19.2 percent of them having more than 7000/cmm.

Discussion

Currently obesity, prediabetes, and type 2 diabetes are considered as chronic inflammatory diseases.[4,7,8] Leucocytosis, a simple haematological investigation reflects the presence of underlying inflammation and insulin resistance in these conditions.[2-5] Unexplained persistent leucocytosis was observed in association with the concomitant increase in the acute phase reactants in obese patients.[3] The authors have alerted that obese patients should be spared of unnecessary investigations for such leucocytosis.

We have earlier shown that patients with PCOS have hyperinsulinaemia, insulin resistance and underlying chronic inflammation.[16] Thus it was of interest to look for the presence of leucocytosis amongst patients of PCOS.

Some investigators have reported higher white blood cells amongst women with PCOS as compared to non PCOS group.[17,18] However, the literature is scant regarding the presence of leucocytosis in patients of PCOS. The leucocytosis was ascribed only in PCOS conditions and not to the obesity or insulin resistance.[18] In the present study however, all the five patients with definable leucocytosis had presence of insulin resistance including the one who was lean with normal BMI. Increased sympathetic drive amongst PCOS due to sleep apnoea is proposed as a possible mechanism in unexplained leucocytosis.[19]

Leucocytosis in the present group of PCOS was observed in 56% of patients. Though the number showing a definable diagnosis of leucocytosis is small, several of them showed counts in the higher range of normal. Similar results have been observed by others investigating the presence of leucocytosis in obese, those with prediabetes or with diabetes.[3,6,20,21] A persistent unexplained leucocytosis was observed in obese patients during a long term follow up of more than 45 months.[3] The investigators had also observed a concomitant increase in the acute phase reactants. They also found that the others who had high BMI had higher side of normal WBC along with high CRP and ESR. In the present study, we also found that > 50 percent of PCOS group had higher side of normal WBC count.

Conclusion

Leucocytosis in polycystic ovarian syndrome can form a simple marker of underlying insulin resistance. We observed that there was a presence of leucocytosis in patients of PCOS irrespective of their BMI.

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References

1. Shapiro MF, Greenfield S. The complete blood count and leukocyte differential count. An approach to their rational application. *Ann Intern Med*. 1987; 106: 65–74.
2. Perfetto F, Mancuso F, Tarquini R. Leukocytosis and hyperleptinemia in obesity. *Haematologica*. 2002; 87 :(05) ELT25.
3. Herishanu Y, Rogowski O, Polliack A, Marilus R. Leukocytosis in obese individuals: possible link in patients with unexplained persistent neutrophilia. Eur J *Haematol*. 2006; 76:516-20.
4. Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes*. 2002; 51:455–461.
5. Sefil F, Ulutas KT, Dokuyucu R, Sumbul AT, Yengil E, Yagiz AE, et al. Investigation of neutrophil lymphocyte ratio and blood glucose regulation in Patients with type 2 diabetes mellitus. *Journal of International Medical Research*. 2014; 42:581-588.
6. Twig, G, Afek A, Shamiss A, Derazne E, Tzur D, Gordon B, Tirosh A. White Blood Cells Count and Incidence of Type 2 Diabetes in Young Men. *Diabetes Care*. 2013; 36: 276-282.
7. Dandona P., Aljada, A., Bandyopadhyay, A. Inflammation: The link between insulin resistance, obesity and diabetes. *Trends Immunol*. 2004; 25:4–7.
8. Shoelson SE, Lee J, Goldfine AB.Inflammation and insulin resistance. *J Clin Invest*. 2006 July; 116(7):1793-801.
9. Bastard J P, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B.Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw*. 2006; 17:4-12.
10. Halen A, Laven J.SE, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. *Hum Reprod Update*. 2003; 9: 505-514.
11. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and Sterility*. 2004; 81: 19-25.
12. Godkar P.B.and Godkar D.P. Section III Hematology, In: Godkar P.B.and Godkar D.P editors. Textbook of Medical Laboratory, Second Edition, Bhalani Publishing House Mumbai, 2003; p. 721:774.
13. Shringi MS, Vaidya RA, Vaidya AB et al. Insulin resistance in polycystic ovarian syndrome. *Indian Journal of endocrinology and metabolism*. 2003; 1: 19-23.
14. WHO. Physical status. The use and interpretation of anthropometry- Report of a WHO expert committee. WHO Technical Series 854, Geneva World Health Organization; 1995.
15. Misra A. Revision of cutoff of body mass index to define overweight and obesity are needed for the Asian-Indian groups. *Int J Obesity*. 2003; 27 : 1294-1296.
16. Vaidya RA, Pandey SN, and Vaidya ADB. Polycystic ovary syndrome:Is it a chronic inflammatory disease?Chapter 3, ECAB Clinical Update: *Obstetrics and Gynecology*. 2008;1:42-73.
17. Herlihy AC1, Kelly RE, Hogan JL, O'Connor N, Farah N, Turner MJ, Polycystic ovary syndrome and the peripheral blood white cell count. *J Obstet Gynaecol.* 2011; 31(3):242-4.
18. Phelan N1, O'Connor A, Kyaw Tun T, Correia N, Boran G, Roche HM, Gibney J. Leucocytosis in women with polycystic ovary syndrome (PCOS) is incompletely explained by obesity and insulin resistance. *Clin Endocrinol* (Oxf). 2013 Jan; 78(1):107-13.
19. Morton A. Neutrophil leucocytosis and polycystic ovarian syndrome--could elevated noradrenaline levels due to obstructive sleep apnoea be a contributing mechanism? *Clin Endocrinol* (Oxf). 2013 Oct; 79(4):591.
20. Hansen LK, Grimm RH jr, Neaton JD. The relationship of white blood cell count to other cardiovascular risk factors. *Int J Epidemiol*. 1990; 19:881–888.
21. Ohshita K, Yamane K, Hanafusa M, Mori H, Mito K, Okubo M et al Elevated White Blood Cell Count in Subjects with Impaired Glucose Tolerance. *Diabetes Care*. 2004; 27:491–496.