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Haematological Related Perturbations in Polycystic Ovarian Syndrome: A Tertiary Centre Experience

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ABSTRACT

BACKGROUND AND OBJECTIVES: Young adolescent females on edge of living an independent life are conscious and seek medical attention for undesired physical stigma, which could be a harbinger of an underlying pathology called Polycystic ovarian syndrome. Iron and glucose molecules mutually influence each other and we wanted to have a look at that in this very group.

DESIGN AND SETTINGS: This study was a case control study conducted in our center. The study was done as joint collaborative effort between departments of Endocrinology, and department of Haematology, Sher-i-Kashmir Institute of Medical Sciences, Soura.

PATIENTS AND METHODS: All women who qualified Rotterdam 2003 criteria for a diagnosis of PCOS were informed about the study. The first step was consent attainment. The women who gave informed consent were enrolled in the study. The study population consisted of 95 subjects. All women underwent anthropometric assessment like measurement of height, weight, waist-hip circumference ratio, body mass index (BMI). Menstrual Cycle details were recorded. Hirsutism assessment was done using modified Ferriman-Gallwey score by counting nine specified body areas. Complete haemogram including red cell indices,mean platelet volume (MPV), iron kinetics and serum ferritin assays of both cases and c were done.

RESULTS: Mean hematocrit[HCT] value was 41.8±3.8 in cases and 40.0±3.7 in controls (p= 0.44). Mean Iron kinetics was found to be 62.5±54.6 in cases and 25.4±11.9 in controls which was statistically significant (p=0.001).

CONCLUSION: Despite anaemic and non-anaemic iron deficiency prevelant in this strata of our population, we found paradoxically increased red blood cell (R.B.C.) count which could have an association with insulin resistance syndrome and may further predispose this population to atherosclerotic event.

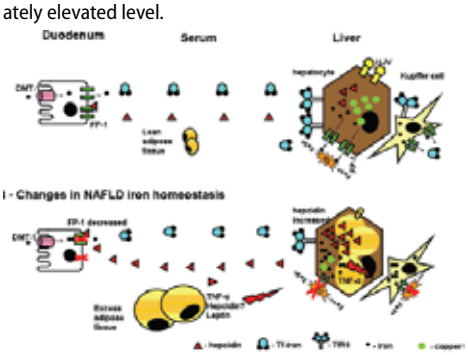
KEYWORDS:

INTRODUCTION:

The clinical association of insulin resistance (IR), hypertension, obesity, dyslipidemia, higher plasma PA-1 concentration and decreased arterial distensibility is described as insulin resistance syndrome (IRS.) There have been pointers in literarture suggesting IRS could stimulate proliferation of erythroid progenitors thereby resulting in increased R.B.C. mass.

Iron metabolism: cells acquire iron via different pathways which include uptake of transferrin bound iron by transferrin-receptors(TfR-I&TfR-2) and uptake of ferrous iron via transmembrane protein named divalent metal transporter-I(DMT-I). Thus far only one iron exporter has been characterised comprising transmembrane protein ferroportein(FP-1). Following its transfer through the duodenal baso-lateral membrane, iron undergoes oxidation by membrane bound copper containg ferro oxidase hephaestin before getting incorporated into transferrin for further transport in circulation. Iron is mainly required for haembiosynthesis in erythropiosis and other haem containing enzymes while excess iron is stored in liver,.Hepcidin is the principal iron regulatory peptide,secreted mainly by hepatocytes in response to iron perturbations. Hepcidin exerts its regulatory function on iron haemostasis .. Mutations of any of these genes is associated with inappropriately low hepcidin formation and hereditary iron overload syndromes.Though quantitatively liver is major hepcidin producing organ, macrophages and adipose tissue do also produce it.

Recently TM PRSS6 has been identified , a serin-protease required for adequate hepcidin downregulation in response to anemia . Its mutation interestingly could lead to iron deficiency owing of its inappropriately elevated level.



RESULTS:

Forty three cases and 52 controls (without the family history of diabetes) participated in the study. The mean of the patients was 22.3± 5.4 and that of controls was 18.9± 0.6 (P = <0.01).The age of menarche was 13.0±1.2 and 13.3±1.1 (P=0.4), respectively. We found 19/35 (54.3%) cases had androgenic alopecia, 28/39 (71%) had moderate to severe acne and 7/35 (20%) had acanthosis nigricans. The details of the clinical parameters are given in table 1.

Mean MCV was 87±26.7 cases vs. 93.1±5.7 ng/ml in controls (P=<0.001). using the Mann-Whitney Test the comparative analysis of ferritin levels, Iron kinetics ,platelet counts and MCV in cases and controls revealed a significant difference. Details are given in table 2.

In a study objectively designed to determine a) coagulation parameters, W.B.C. and MPV levels b) whether any association between androgens, MPV and low grade systemic coagulation in PCO subjects exists. To unravel that a total 48 subjects with non-diabetic PCO were studied, in order to evaluate and compare with a non PCO group of 52 subjects. What was found , **D-Dimer**, homeostatic model assessment (HOMA-IR), insulin, androgens, glucose, WBC and MPV concentrations were higher in women with PCOS. No difference was observed in fibrinogen, APTT, PT between two groups. Free testosterone was positively correlated with **D-Dimer**, insulin, DHEAS and MPV levels. *In multiple stepwise regression analysis, free testosterone, positively associated with D-Dimer and DHEAS. MPV was positively correlated with insulin levels, HOMA-IR values, DHEAS, free testosterone levels in these PCO subjects.**(11,7)*** Further in multiple stepwise regression analysis, MPV was positively associated with insulin and DHEAS. Deducing from these observations ,it was concluded that PCO subjects have low grade systemic coagulation and fibrinolytic activation ,evidenced by elevated by D-Dimer, increased W.B.C. and MPV levels suggesting thereby haematological parameters could potentially be used as indicators for risk factors for atherosclerosis in PCO subjects.

Table 1: Clinical parameters of patients with PCOS and controls.

Clinical Parameters	Cases (n=43) Mean ± SD	Controls (n=52) Mean ± SD	P value
Age (yrs)	22.3±5.4	18.9±0.6	<0.001
Menarche (yrs)	13±1.2	13.3±1.1	0.4
Hirsutism score	12.6±4.8	0.6±0.9	<0.001
No. of menstrual cycles/yr	8.3±3.9	11.7±0.6	<0.001
Height (cms)	156.4±5.4	157±4.7	0.70
Weight (Kg)	62.9±12.3	53.1±5.2	<0.001
Waist circumference (cms)	83.9±20.3	75.1±6.2	0.02
Hip circumference (cms)	90.8±12.1	87.1±3.3	0.09
BMI (Kg/m2)	25.8±5.3	21.6±2.4	<0.001

Table 2: Comparative description of Hemogram of between PCOS and control women.

Parameters	Cases (n=43) Mean ± SD	Controls (n=52) Mean ± SD	P value
Hemoglobin	12.4±1.4	12.4±0.9	0.46
HCT	41.8±3.8	40.0±3.7	0.44
PLT	173.0±56	132.4±60.9	0.04
MCV	87.0±26.7	93.1±5.7	<0.001
MCH	25.8±8.0	28.2±2.2	0.08
MCHC	29.4±1.6	30.4±2.8	0.01
Ferritin	30.7±38.2	11.5±1.6	0.002
Iron Kinetics	62.5±54.6	25.4±11.9	0.001

DISCUSSION:

Various cytokines and growth factors regulate the development of mature R.B.C. ,notable among them being erythropoietin which is required for survival and differentiation of erythroid progenitors.(1) Insulin in addition to other growth factors augments the role of erythropoietin in proliferation of erythroid colonies(5).The role of insulin in regulation of erythropiosis has been widely documented in vitro. Infact, studies found that physiological concentrations of insulin directly stimulates the proliferation of late erythroid progenitors(CFU-E) in culture of murine fetal liver(1) and promote growth in both human bone marrow and circulating erythroid progenitors cells in vitro(4). The mechanism of the stimulatory effects of human insulin on human bone marrow CFU-E and BFU-E has been thoroughly looked at and inferences suggest that insulin receptor itself is involved in RBC proliferation and insulin receptor (INS-R) has been detected on human erythropoietic cells at different stages of development meaning thereby that insulin acts at all stages of erythropiosis.(3)Using a serum free system, it has come to light that, insulin needs to bind with its own receptor before stimulating the erythroid progenitors, suggesting a direct action of this hormone on CFU-E and BFU-E.

The most widely accepted theory explaining how insulin affects erythropiosis is that activation of tyrosine kinase in insulin receptor could be essential for the growth-promoting action of insulin(7). Indeed, previous studies show that stimulation of insulin by erythropoietin. Deducing from multivariate analysis data, it can be safely said with fair degree of confidence that insulin activity is in synergism but not alternate to erythropoietin in promotion of erythropiosis, extrapolating it further there appears a possibility that insulin could have a role in Haematological disorders due to EPO resistance or paucity.PCO syndrome being an insulin resistance disorder encouraged us to compare various variables of disorder. Our comparative statistical analysis elaborated through tables involving these variables like anthropometry, cycles, acanthosis, alopecia, infertility,hirsuitism with haematocrit platelet, redcell parameters, iron kinetics, ferritin, hormonal assay infertility. Observations reveal significant inferences of statistical significance and could serve as a fertile template for future research.

In conclusion, our study suggests evidence of a relationship between between insulin resistance variables both physical and biochemical with red cell parameters, Iron kinetics,platelet volume and indices. we intend to look and extrapolate these parameters prospectively to unravel and substantiate haematological aspects of insulin resistance before and after treatment with insulin sensitisers and antiandrogens.

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