ISSN: 2572-9462
Journal of Thrombosis and Circulation: Open Access

OPEN ACCESS Freely available online

Research Article

Polycythaemia- Clinical Profile and Impact of Lifestyle Change and Weight Reduction

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ABSTRACT

Introduction: Polycythaemia is an increase in the absolute Red Blood Cell (RBC) mass with increase in hemoglobin levels and haematocrit. It can be primary and secondary. Management depends on the causes and can be pharmacological and non-pharmacological.

Objectives of the study: To determine the clinical profile of patients with all types polycythaemia and to study the impact of weight reduction with diet and lifestyle changes on behaviour of polycythaemia.

Methods: We enrolled 92 consecutive subjects with confirmed polycythaemia during a period of one year, subjected them to diet and lifestyle changes with an intention to achieve weight reduction. It was a hospital based prospective study between January 2020 to June 2021. Patients who were confirmed to have polycythaemia by symptoms, signs and laboratory features were included. They were classified into primary or secondary polycythaemia based on clinical judgement, laboratory parameters and World Health Organization (WHO) 2016 criteria for Polycythaemia Vera. The enrolled patients in both the groups were given clear advice on diet and lifestyle changes with an intention to achieve weight reduction, cessation of smoking and alcohol along with the standard care. They were then followed up monthly, for re-counselling for lifestyle changes and weight recording at each visit, for six months to maximum of one year.

Results: All subjects, irrespective of the causes of polycythaemia, had change in wellbeing, symptom relief, reduced frequency of venesections, haematocrit levels and other blood parameters (p value<0.05). There were 22 patients out of 92 (24%) with secondary polycythaemia due to overweight or obesity and they all had reversal of polycythaemia after weight reduction.

Conclusion: The study showed that commonest cause of secondary polycythaemia in the study group was due to weight gain or obesity, and interventions by diet and lifestyle modification leading to weight reduction, could completely reverse polycythaemia in this subgroup. The same interventions, gave statistically significant changes in hematological outcomes of all subjects with primary and secondary polycythaemia. The weight reduction needed to get benefit varied from 4 Kg to 15 Kg with a mean of 9.13 Kg.

Keywords: Polycythaemia; Reversal of polycythaemia; Lifestyle; Diet; Weight reduction

INTRODUCTION

Absolute polycythaemia or erythrocytosis is an increase in Hb in blood, due to overproduction of red cells and resultant increase in red cell numbers or red cell mass. Spurious polycythaemia reflects plasma volume contraction, due to dehydration or a decrease in plasma volume due to any cause [1,2]. Absolute polycythaemia may be primary with no physiological stimulus for erythrocytosis, the prototype of which is Polycythaemia Rubra Vera (PRV), due to *JAK2* (V617F) mutation [3]. Absolute polycythaemia may be secondary with a physiological stimulus for erythropoiesis like hypoxia, or a pathological overproduction of erythropoietin/erythropoietin like substances. Differentiating between primary and secondary causes

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Received: 06-Sep-2023, Manuscript No. JTCOA-23-22866; **Editor assigned:** 08-Sep-2023, PreQC No. JTCOA-23-22866; **Reviewed:** 22-Sep-2023, QC No JTCOA-23-22866; **Revised:** 29-Sep-2023, Manuscript No. JTCOA-23-22866 (R); **Published:** 09-Oct-2023 DOI: 10.35248/2572-9462.23.9.241.

Citation: Rahim SA, Sasidharan PK (2023) Polycythaemia- Clinical Profile and Impact of Lifestyle Change with Weight Reduction. J Thrombo Cir. 9:241.

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is a challenge, but our experience is that it is easily achieved by good clinical evaluation and common laboratory tests rather than using erythropoietin levels [4,5]. With hypoxia as a physiological stimulus, the causes for polycythaemia are living at high altitude, smoker's polycythaemia, chronic lung disease like Chronic Obstructive Pulmonary Disease (COPD) and Interstitial Lung Disease (ILD), cyanotic heart disorders and obesity related. In response to the hypoxia, there is overproduction of erythropoietin from the renal interstitial peritubular capillary cells. But reduced perfusion of the renal interstitium due to a local cause could also be a hypoxic stimulus for erythropoietin release as in renal artery stenosis, polycystic kidney disease, hypernephroma, hydronephrosis, and nephrocalcinosis [6]. Pathological overproduction of erythropoietin like substances is seen rarely in hepatoma, atrial myxoma, and cerebellar hemangioblastoma.

Irrespective of the cause, patients with polycythaemia have non-specific symptoms like fatigue, heaviness of head, headache, dizziness, transient blurring of vision or thrombotic events in venous or arterial circulation. They may have ruddy complexion and cyanosis as a manifestation of polycythaemia. Patients with PRV may present with erythromelalgia and symptoms due to hyperuricemia. Presence of splenomegaly, thrombocytosis or leucocytosis suggests PRV as the diagnosis [6,7]. Before diagnosing PRV, it is mandatory to rule out secondary causes by good clinical evaluation, rather than doing *JAK 2* mutation or serum erythropoietin upfront to make a diagnosis [1,2,4,7-9]. It is mandatory to elicit chronic smoking to suggest smoker's polycythaemia and history of weight gain in all patients, even if the weight gain is just two kilograms more from previous normal, to look for chronic hypoventilation as a possible cause [6,7,9].

Treatment of polycythaemias may require phlebotomy, but PRV may need hydroxyurea and low dose aspirin in addition. Ruxolitinib is giving promising results in some selected patients with PRV [10]. The mainstay of treatment of secondary causes is to manage the underlying disease [8,9]. The effects of non-pharmacological measures like weight reduction and lifestyle modification in the management of primary and secondary polycythaemia is not studied before. Literature search showed no studies that have ventured on lifestyle modification on polycythaemia.

MATERIALS AND METHODS

This study was the outcome of our observation that weight gain and the consequent chronic hypoventilation is a common cause for secondary polycythaemia, and that weight reduction by diet and lifestyle modification had helped in reversal of polycythaemia [6,7,14-16]. Besides that weight reduction had improved other comorbidities, like hypertension, diabetes and Non-Alcoholic Steatohepatitis (NASH) [14,15,16]. In those with overweight, the adipocyte size and mass expand and the white adipose tissue becomes hypoxic, leading to inflammation and cellular dysfunction. Thus it could be possible that weight reduction and lifestyle modifications would help decrease the impact pro-inflammatory mediators and hence improved outcomes [11,12]. Despite extensive literature search we could not get any study that evaluated the clinical and hematological profile, risk factors and the impact of lifestyle modifications in the polycythaemias group as a whole.

It was a prospective observational study, from January 2020 to June 2021. Approval of the institutional ethics committee was obtained. The cut-off for inclusion was Hb>15 g/dl and haematocrit>45 % in women, and Hb>17g/dl and haematocrit>50 % in men. Patients with relative polycythaemias, on erythropoietin, anabolic steroids, hydroxyurea or aspirin and those who would not be compliant with the lifestyle modification, as those with cognitive impairment or psychiatric diseases were excluded. We enrolled 92 subjects of polycythaemia who satisfied the inclusion criteria. Clinical and laboratory evaluation for secondary causes were done and the subjects were divided into primary or secondary polycythaemia based on clinical and laboratory parameters. PRV was diagnosed using WHO 2016 diagnostic criteria for PRV [13]. As the study was done among low income population, initially we planned to do *JAK2* only where categorization into primary and secondary was difficult, but we ended up having *JAK2* assay in most patients as it had already been done before the patients were referred to us. Erythropoietin estimation was not done by plan as the study was in a low-resource setting and it was our experience that it almost never helped in differentiating. Clinical presentation, dietary habits, history of any weight gain, from the previous normal, causes of that weight gain, history of tobacco smoking and alcohol intake, height, weight and Body Mass Index (BMI) were recorded. The lowest weight when the subjects were healthy and active was also recorded. BMI more than 23 Kg/m^2 was taken as overweight and above 28 Kg/m^2 as obesity. Frequency of venesection before and after the intervention was recorded. Weight was measured using same electronic weighing machine throughout the study and height measured using a stadiometer. The baseline blood pressure was recorded in all at enrolment and during follow up. Food questionnaire was used to collect details regarding each item, using a 24-hour dietary recall method on an average for a week's period.

Diet plan

All the enrolled patients were given advice on balanced diet with emphasis on calorie restriction, lifestyle modification for weight reduction and cessation of smoking and alcohol. A comprehensive diet plan with a pictorial representation of the proportions between different components was used [11,12]. Each meal containing all five components with adequate intake of protein (any one of the pulses, yogurt, fish, egg or meat), adequate vegetables (preferably raw or steamed and never over cooked), fresh seasonal fruits, one source of calorie in least possible amounts, and adequate water intake were explained in detail [11,12]. The subjects were advised to consume only half the capacity of their stomach and leave the rest empty at each meal. Calorie rich foods were reduced and replaced that portion with fibre rich vegetables constituting the major proportion of any individual meal. They were instructed to restrict eating to a maximum of three times a day and to avoid all snacks. Water consumption was ensured to be adequate to produce sufficient urine output (2 L/day-2.5L/day). Consumption of junk food, fried foods, snacks, all fast foods and processed food items were taken note of and was advised to avoid [11,12].

Physical activity

Physical activity was assessed by noting the type, duration and frequency and the sedentary nature of work. They were advised to carry out any physical activity requiring a moderate amount of exertion for at least 30 minutes a day.

Standard care

In those with PRV were advised phlebotomy, aspirin and

hydroxyurea as per individual clinical profile. In subjects with secondary polycythaemia, phlebotomy was advised in the initial visits only, when haematocrit was high (>50%), or when they had some symptoms presumed to be due to hyper viscosity. The participants were reviewed every month for re-counselling, and adherence to diet and physical activity was re-emphasized at each visit. Weight, blood pressure, Hb, haematocrit, liver function tests and blood sugar were checked at each visit. They were periodically assessed for 6 months at least and the final weight, hematological parameters and frequency of venesection were reviewed and recorded.

Statistical methods

Data was entered in Excel and analyzed using Stata 14.2. Variables were summarized appropriately. The percentage of individuals with different forms of polycythaemia and the presence of *JAK2* mutation were summarized as frequency and proportions. Association between weight status, *JAK2* mutation, smoking status, alcohol status, clinical symptoms, hematological profile and comorbidity status and the type of polycythaemia were done using Chi square test / Fischer's exact test. Dietary status (carbohydrate, protein, fast food intake etc.), and physical activity levels (mild, moderate, and severe) along with the different patterns of polycythaemia were also checked using the Chi-square test / Fischer's exact test. A P-value of < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

There were 37 cases of primary polycythaemia and 55 cases of secondary polycythaemia. Majority were males (88%) and the age ranged from 20 to 74 years with a mean age of 46.5 years. The most common symptoms were tiredness, fatigue, heaviness of head or headache in both groups. Arterial thrombosis, tinnitus and blurring vision, cardiac symptoms, and aquagenic pruritis were found to be more common in primary polycythaemia. Eye congestion, palmar erythema and plethoric face was seen in both, but splenomegaly was seen only in primary polycythaemia group. Hepatomegaly was significantly more common in secondary group. *JAK 2* mutation was done in 73 subjects, none of the secondary group had *JAK 2* positivity, while 83% of the primary polycythaemia had *JAK 2* positivity. The distribution of clinical presentation are described in Tables 1 and 2.

Table 1: Distribution of demographic and comorbidity patterns among types of polycythaemia, n=9.

Characteristics	Primary polycythaemia n = 37 No. (%)	Secondary polycythaemia n = 55 No. (%)	P value
Mean age (SD)	59.4 (7.8)	37.8 (8.1)	<0.001
Female	7 (19)	3 (5)	0.08
Male	30 (81)	52 (95)	
JAK 2 positive	24 (83)	0 (0)	<0.001
JAK 2 negative	5 (17)	44 (100)	
Current smokers	11 (30)	31 (56)	<0.001
Stopped smoking	12 (32)	2 (4)	
Never smoked	14 (38)	22 (40)	
Type 2 DM	18 (49)	20 (36)	0.24
Hypertension	21 (57)	19 (35)	0.04
COPD	0 (0)	2 (3.6)	0.51
OSAS	0 (0)	1 (1.8)	1
ILD	0 (0)	1 (1.8)	1

Note: Chronic Obstructive Pulmonary Disease (COPD); Obstructive Sleep Apnea Syndrome (OSAS);
Interstitial Lung Disease (ILD).

Table 2: Distribution of clinical presentation among the types of polycythaemia, n=92.

	Primary polycythaemia (n = 37) No. (%)	Secondary polycythaemia (n = 55) No. (%)	p value (chi square)
Asymptomatic	9 (24)	11 (20)	0.62
Tiredness	11 (29.7)	24 (44)	0.18
Arterial thrombosis	5 (13.5)	1 (1.8)	0.04
Venous thrombosis	3 (8)	4 (7)	1
Headache	22 (60)	23 (42)	0.1
Dizziness	14 (38)	12 (22)	0.09
Erythromelalgia	3 (8)	0 (0)	0.06
Aquagenic pruritus	6 (16)	0 (0)	0.003
Plethoric face	9 (24)	7 (13)	0.15
Eye congestion	27 (73)	24 (44)	0.006
Palmar erythema	14 (38)	14 (25)	0.21
Splenomegaly	32 (87)	0 (0)	<.001
Hepatomegaly	5 (13)	34 (62)	<.001

The percentage of weight reduction in the whole group ranged from 2.7% to 25% with an average of 12.3 percentage. Table 3 shows the BMI pattern in different types of polycythaemia. A striking observation was that all the 22 patients with polycythaemia due to weight gain normalised their Hb and haematocrit after weight reduction. The weight reduction in this group ranged from 4 Kg to 15 kg with a mean of 9.13 kg. One patient in this subgroup had normal BMI but had a history of weight gain from his previous normal weight. On reducing that excess weight the haematocrit normalised without venesection (Table 4).

Table 3: BMI and the categories of polycythaemia, n=92.

	Normal N (%)	Overweight N (%)	Obese N (%)
Polycythaemia vera (n=37)	21 (57)	12 (32)	4 (11)
Smokers' polycythaemia (n=18)	16 (89)	2 (11.)	0 (0)
Polycythaemia of overweight (n=22)	1 (4.6)	4 (18.2)	17 (77)
Polycythaemia of mixed causes (n=11)	0 (0)	1 (9)	10 (91)

Table 4: Pre and post-intervention, subgroup analysis of change in haematological parameters.

	Pre intervention Mean (SD)	Post-intervention Mean (SD)	p value
Polycythaemia rubra vera patients (n=37)			
Hb (gm/dl)	20.5 (1.9)	19.8 (1.4)	0.003

PCV (%)	55.9 (4.1)	53.0 (2.9)	<0.001
SGPT (IU/ml)	42.1 (8.7)	40.0 (8.7)	0.02
Weight (kg)	57.44(6.7)	54.35 (5.4)	0.03
Smokers' polycythaemia managed without Venesection (n=7)			
Hb (gm/dl)	18.4 (0.3)	15.8 (1.7)	0.004
PCV (%)	51.8 (1.1)	44.6 (4.4)	0.005
SGPT (IU/ml)	36.4 (3.0)	34.7 (1.9)	0.21
Weight (kg)	58.5(3.9)	57.5(2.9)	0.53
Smokers' polycythaemia managed initially with Venesection (n=11)			
Hb (gm/dl)	20.1 (1.0)	17.6 (2.1)	0.002
PCV (%)	55.4 (2.2)	48.7 (6.0)	0.002
SGPT (IU/ml)	33.4 (12.1)	32.7 (5.4)	0.8
Weight (kg)	56.8(5.8)	55.6(5.1)	0.62
Overweight related polycythaemia managed initially with venesection (n=22)			
Hb (gm/dl)	19.9 (2.0)	16.7 (1.6)	<0.001
PCV (%)	54.4 (4.5)	46.8 (4.3)	<0.001
SGPT (IU/ml)	69.3 (22.9)	52.5 (12.6)	<0.001
Weight (kg)	71.9(12.3)	62.5(11.1)	0.01
Polycythaemia due to mixed causes managed initially with venesection (n=11)			
Hb (gm/dl)	19.9 (1.3)	16.2 (1.4)	<0.001
PCV (%)	53.9 (2.8)	45.1 (2.0)	<0.001
SGPT (IU/ml)	50.4 (17.3)	40.0 (11.9)	0.001
Weight (kg)	66.9 (8.7)	57.2(7.3)	0.01

Note: Packed Cell Volume (PCV); Serum Glutamic Pyruvic Transaminase (SGPT).

Table 5 shows the subgroup with polycythaemia of overweight separately. There was complete normalization of hemoglobin and haematocrit levels after weight reduction in this group. The difference was statistically significant with all p values <0.001. Out of 22 patients with polycythaemia of overweight / obesity, 13 were diabetic and 8 were having hypertension and 19 were having raised Serum Glutamic Pyruvic Transaminase (SGPT) levels. Hb, Packed Cell Volume (PCV), SGPT became normal in all of them, and did not require any more venesections. In addition there was a significant drop in all these parameters after weight reduction among PRV and polycythaemia due to mixed causes too. The frequency of venesections became much less in PRV after weight reduction. In the smokers' polycythaemia group, Hb and PCV dropped significantly after cessation of smoking.

Table 5: Overweight related polycythaemia who were managed initially with Venesection (n=22).

	Pre intervention	Post intervention	p value
Hb gm/dl (SD)	19.9 (2.0)	16.7 (1.6)	<0.001
PCV % (SD)	54.4 (4.5)	46.8 (4.3)	<0.001
SGPT IU/ml (SD)	69.3 (22.9)	52.5 (12.6)	<0.001

Note: Packed Cell Volume (PCV); Serum Glutamic Pyruvic Transaminase (SGPT).

DISCUSSION

After the intervention with weight reduction, there was significant relief of symptoms, Hb and PCV in both primary and secondary polycythaemia. The secondary polycythaemia due to overweight or obesity (40% of the secondary causes), was independent of smoking, heart, lung or kidney diseases, and this appears due to chronic hypoventilation probably due to reduced chest wall compliance. They all normalized their Hb and PCV after achieving weight reduction. Out of 22 patients with polycythaemia of overweight/ obesity, 19 were having fatty liver disease (NASH) which was the commonest association of secondary polycythaemia. Diabetes and hypertension were the other common associations among the overweight or obese. Along with reversal of polycythaemia, the elevated liver enzymes, diabetes and hypertension too became better after weight reduction. The difference was statistically significant with all p values less than 0.001. Three other studies before, in the same setting, showed reversal of diabetes, NASH and hypertension on weight reduction and some of them who had polycythaemia too reversed and that was the reason for initiating this study [14,15,16]. Since the overweight patients with secondary polycythaemia were also having either NASH, hypertension or diabetes or some of them had all of these, and all these reversed after weight reduction means that secondary polycythaemia can be yet another lifestyle disorder. They were consuming excess carbohydrates with decreased intake of vegetables and became overweight, hence developed polycythaemia of overweight.

Previously there were only case reports of polycythaemia with hypertension and erythrocytosis without splenomegaly or leucocytosis, which were being described as Gaisbock syndrome [2]. We are now certain that the originally described Gaisbock syndrome was in fact secondary polycythaemia due to weight gain. Interestingly one subject, in the overweight category with secondary polycythemia had a BMI less than 23 only, but he had 5 Kg weight gain from his previous normal, and after weight reduction by 4 Kg, the Hb and haematocrit normalized. This points to another hypothesis that the assessment of desired normal weight based on some arbitrary or imaginary normal range has to go and the desired weight and BMI has to be individualized.

Another useful observation of the study was that all secondary polycythaemias were seen in the age group between 30 and 39 years, while PRV was seen in the 5th decade of life only. In other words we should not evaluate those below 30 years for PRV, unless there are sufficient justification to do that. Males were more commonly affected with all types of polycythaemias, similar was the findings in other studies [6,7]. We found *JAK2* positivity in 83% of those with primary polycythaemia [3,7,17]. Though *JAK 2* mutation is highly sensitive for picking up PRV, we observed that it is most often not needed, as its cost-effectiveness and usefulness in diagnosis are questionable, unless we have a plan to start *JAK 2* inhibitors upfront [3,4,7,18]. In addition *JAK 2* negative does not rule out primary polycythaemia, since *JAK2* exon 12 have been described in *JAK2*V617F negative patients with PRV [19,20]. At the time of writing this article, we got the follow up of one subject who was originally labelled as PRV since *JAK 2* was positive, and was getting hydroxyurea. He had normalized his Hb, PCV and the liver enzymes, which were elevated, after weight reduction and is no longer on hydroxyurea. In this patient there was anyway a need for weight reduction for the NASH and to our surprise all these reversed and for the last one year he has normal haematocrit and no longer

needed venesection. We need to diagnose PRV with clinical features and hemogram [6,7]. Just because *JAK 2* is positive one should not conclude that the polycythaemia is entirely due to PRV.

There were only very few studies evaluating the effect of lifestyle interventions. Excess carbohydrate intake was the primary reason for polycythaemia of weight gain and obesity and they contributed to adverse outcomes with PRV as well. One previous study had evaluated the effect of fruits, vegetables, and coffee intake in myeloproliferative neoplasm and shown that those taking more carbohydrate had a higher risk of PRV compared to those with lower carbohydrate intake [21]. Even patients with PRV after weight reduction had improved well-being and needed less frequent venesections without increasing hydroxyurea or *JAK 2* inhibitors [21,22,23]. It could be even possible that *JAK 2* mutation and the subsequent development of PRV could be the end result of this prolonged presence of inflammatory meditators due to weight gain.

Majority of patients with polycythaemia vera and polycythaemias of mixed causes consumed fast foods, and consumed vegetables less than once per week. Research works exploring diet and physical inactivity as risk factors of haematological neoplasms are many, but only a few interventional studies have established the protective effect of diet and physical activity in delaying disease progression and improving clinical and hematological outcomes. After extensive literature review, our study is the first of its kind to evaluate the effect of dietary and physical activity in patients with primary and secondary polycythaemias.

CONCLUSIONS AND RECOMMENDATIONS

Diet and lifestyle interventions gave significant improvements in the clinical and haematological outcomes of both primary and secondary polycythaemias. Weight gain was the commonest reason for secondary polycythaemia in the subjects. There was complete reversal of polycythaemia after weight reduction in this subgroup. The comorbidities they had were, NASH, diabetes, and hypertension which all improved or reversed after weight reduction. Polycythaemia due to weight gain is yet another lifestyle disorder. The study suggests that the originally described Gaisbock syndrome is secondary polycythaemia due to weight gain. One should not consider PRV as a clinical possibility in patients below 30 years. Findings stress on the importance of advocating diet and lifestyle modification for all polycythaemias along with usual care, to improve the management outcomes. Future research is warranted in the same line to evaluate the effect of lifestyle modifications of polycythaemias in varied study settings

STRENGTHS AND LIMITATIONS

It is one among the very few studies to determine the risk factors associated with polycythaemias. It showed that the commonest cause of secondary polycythaemia in the study population is weight gain, and they are all reversible with weight reduction. It is probably the first study that has evaluated the effect of weight reduction and lifestyle modification in all types of polycythaemias including PRV to facilitate the management. The limitation was smaller sample size, and it was conducted only in one centre. Other similar studies are warranted to consolidate the observations.

ACKNOWLEDGEMENT

The authors acknowledge the help of the superintendent and management of PVS Sunrise hospital CALICUT in permitting us to do the study

CONFLICT OF INTEREST

All authors agree for the publication. For all authors, there are no competing interests to declare.

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