International Journal of Research in Medical Sciences
Kalal C et al. Int J Res Med Sci. 2020 Oct;8(10):3746-3748
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20204266

Case Report

Polycythemia: a mystery solved by history

Chetan Kalal*, Atif Patel, Adinath Wagh, Harshad Joshi, Samit Jain, Ravindra Surude, Shobna Bhatia, Chetan Bhatt

Department of Gastroenterology, Sir H. N. Reliance Hospital and Research Centre, Mumbai, Maharashtra, India

Received: 01 August 2020
Revised: 06 September 2020
Accepted: 08 September 2020

***Correspondence:**
Dr. Chetan Kalal,
E-mail: chetan.kalal@rfhospital.org

ABSTRACT

Testosterone is responsible for increased muscle mass. Leaner body mass helps control weight and increases energy. High levels of testosterone help build muscles and also stimulate growth in strength. Androgenic-anabolic steroids (AAS) are drugs that are structurally related to the cyclic steroid rings system and have similar effects to testosterone in the body. Athletes who abuse steroids do so for muscle growth and quick recovery. Testosterone - whether it's injected, applied via a patch or cream, or taken orally - allows athletes to rapidly increase muscle mass beyond their usual capacity, and also reduces their recovery time which allows them to train continuously with little need to rest their bodies in between workouts. Physiologically, erythrocytosis is defined by an erythrocyte mass that exceeds 125% of that predicted for sex and body mass. Much of the concern with the use of testosterone involves increase in blood viscosity, resulting from increased red blood cell mass causing a potential increased risk for venous thromboembolism (VTE), myocardial infarction (MI), and cerebrovascular accidents (CVA). We report a case of secondary polycythemia related to testosterone therapy.

Keywords: Polycythemia, Testosterone induced polycythemia, Androgenic-anabolic steroids

INTRODUCTION

Testosterone could be a hormone which is liable for increased muscle mass. Lean body mass helps to control weight and also increases energy. High levels of testosterone not only helps build muscles but also stimulate growth in strength. Anabolic androgenic steroids (AAS) are the drugs which are related structurally to the cyclic steroid rings and have effects kind of like testosterone within the body. Many athletes abuse steroids for the aim of muscle growth and quick recovery. Athletes can rapidly increase muscle mass beyond their usual capacity, and also reduces their recovery time by using testosterone, which may be injected, applied via a patch or cream, or be taken orally allowing them to coach continuously with little need to rest their bodies in between workouts.

Erythrocytosis is defined by an erythrocyte mass which exceeds 125% of that predicted for sex and body mass physiologically.[1] Use of testosterone leads to an increased red blood cell mass causing an in blood viscosity causing a potential increased risk for cerebrovascular accidents (CVA), myocardial infarction (MI), and venous thromboembolism (VTE).[2] We report a case of secondary polycythemia related to testosterone therapy.

CASE REPORT

A 47-year old male known diabetic on oral hypoglycaemic agents (OHA) came into emergency with multiple episodes of loose, watery, non-bloody stools and vomiting for a day and abdominal pain (generalized in nature), for two days. Associated complaints involved fever 100.3 degrees, on and off crampy abdominal pain. No history of

(h/o) dysentery, altered sensorium, chest pain or decreased urination.

On examination, pulse (P): 98/min, blood pressure (BP): 150/90 mm Hg, respiratory rate (RR): 20/min. Patient had h/o abdominal surgery done 7 years back for Meckel's diverticulum. History of umbilical hernia repair 8 years back. His computed tomography CT abdomen was done which was suggestive of segmental groove pancreatitis. His haemoglobin was 20.8 gm/dl, hematocrit (HCT) 61.6%, with red blood cells (RBC) count 7.17 x 1012/l, mean corpuscular volume (MCV): 85.88 fl, mean corpuscular hemoglobin (MCH): 29 pg, and mean corpuscular hemoglobin concentration (MCHC): 33.8 g/dl. White blood cells (WBC) was 14370 with neutrophils 84%. His serum lipase was 157 u/l. The serum erythropoietin level (EPO) was 13.70 IU/l (normal range 4.3-29) despite the erythrocytosis. His V617F Janus kinase 2 (JAK2) mutation test was negative.

He had a history of taking injection testosterone 100 mg intramuscular (IM) every week since a year. He had used steroid stacking for 6 weeks; creatinine powder 6 scoops (18 gm)/day for 5 days a week since 18 months, whey protein powder, 8 scoops (200 gm protein)/day since 18 months. He had taken the same supplements, ten years ago. The polycythemia was attributed to testosterone injections and thus was discontinued and he has since been observed without evidence of disease progression.

DISCUSSION

Often secondary polycythemia develops as a response to chronic hypoxemia, triggering an increased production of erythropoietin by the kidneys. One of the most common causes of secondary polycythemia includes obstructive obesity hypoventilation syndrome, chronic obstructive pulmonary disease (COPD), sleep apnea, and drugs.[3] Secondary polycythemia has to be differentiated from primary polycythemia and relative polycythemia (in which plasma volume is contracted but the RBC numbers are normal). Dehydration or to reduced venous compliance can cause a reduction in plasma volume; the latter is also termed stress polycythemia or Gaisbock syndrome, and is seen typically in middle-aged obese men who are receiving diuretics for the treatment of hypertension. Erythrocytosis is a predictable although under-recognized effect of testosterone.[4]

Erythrocytosis is defined as an increase in the number of erythrocytes and objectively with a haemoglobin level more than 185 g/l and HCT percent more than 49% in men, or 165 g/l and 48%, respectively, in women.[5]

An approach to erythrocytosis includes to distinguish a primary bone marrow disorder like polycythemia vera or other myeloproliferative neoplasms from possible secondary causes. Primary erythrocytosis is will have a low level of serum erythropoietin and secondary causes will have normal or high erythropoietin levels.

Secondary erythrocytoses are further sub categorized into congenital and acquired causes. The congenital causes includes germline mutations that results in high oxygen affinity hemoglobinopathies, enhanced erythropoietin receptor signaling, or altered intracellular oxygen sensing pathways. Though erythrocytosis is acquired more commonly. Chronic hypoxic states such as lung disease, heavy smoking, intracardiac shunting, hypoventilation syndromes and local renal hypoxia (e.g. in renal artery stenosis) stimulates erythropoietin pysiologically. Drugs that stimulate erythropoietin, including thiazide diuretics, darbopoietin or androgen therapy (i.e. testosterone or anabolic steroids) are also commonly found to be the acquired causes for erythropoiesis. Alternatively, erythropoietin secretion can be pathological in erythropoietin-producing malignant diseases like renal cell carcinoma, pheochromocytoma and hepatocellular carcinoma.[1]

Historical studies in preclinical models have suggested that testosterone does induce a motivating factor for erythropoiesis, which was measured by a bioassay employing a polycythemia mouse model in these studies.[6] But, human studies haven't provided clear evidence that testosterone stimulates EPO secretion. For instance, in healthy young and older men, whose endogenous testosterone production was suppressed employing a long acting gonadotropin releasing hormone agonist, administration of graded doses of testosterone, did increase haemoglobin and HCT levels dose dependently but it failed to change the EPO levels consistently after 20 weeks even at supraphysiologic doses of testosterone.[7] Hep3B cells are an EPO-secreting cell line which are sensitive to hypoxic induction. Testosterone didn't activate EPO transcription directly in Hep3B cells, thus suggesting that any EPO dependent mechanism for testosterone-induced erythrocytosis might be indirect, of modest magnitude, and/or transient.[8] Alternative mechanisms of testosterone-induced erythrocytosis have been suggested, for instance direct effects on bone marrow erythroblasts and on red cell survival.[6]

An American study which had evaluated the results of testosterone in graded doses on erythropoiesis found that the share of HCT had begun to increase within one month of beginning of the treatment and had continued to extend after three months in an exceedingly linear dose dependent manner. This study had also reported that increase in HCT were rather more in older men (60-75 years of age) as compared to young men (19-35 years of age). For instance, in the younger men group who were taking a 125 mg dose, 42% achieved peak HCT percentages after 12 weeks as compared with 75% within the older group.[7]

Initiation of testosterone therapy must be limited to those patients who show both biochemical and clinical evidence of androgen deficiency so on avoid complications caused by unnecessary exposure of the drug. Physicians should regularly monitor the HCT percentage during testosterone replacement. Indications for testosterone must even be re-

evaluated to confirm that the patients are receiving clinical benefit, warranting the need for ongoing treatment.[4]

Evidence based guidelines for the management of secondary erythrocytosis with testosterone therapy are lacking, and current guidelines supported expert consensus are variable. The American guideline advises stopping testosterone at a HCT percentage above 54%, whereas the EU guideline advises phlebotomy to be considered at this level.[9,10] This 54% value of HCT was derived from the Framingham cohort study. Testosterone therapy is restarted at lower doses if the haematocrit percentage drops to less than 50%, and no other secondary causes of erythrocytosis are found.[9]

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Keohane C, McMullin MF, Harrison C. The diagnosis and management of erythrocytosis. BMJ. 2013;347.
2. Brækkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Hansen JB. Hematocrit and risk of venous thromboembolism in a general population. The Tromsø study. Haematologica. 2010;95(2):270-5.
3. Nadeem O, Gui J, Ornstein DL. Prevalence of venous thromboembolism in patients with secondary polycythemia. Clin Appl Thromb. 2013;19(4):363-6.
4. Morales A, Bebb RA, Manjoo P, Assimakopoulos P, Axler J, Collier C, et al. Diagnosis and management of testosterone deficiency syndrome in men: Clinical practice guideline. CMAJ. 2015;187(18):1369-77.
5. Barbui T, Thiele J, Vannucchi AM, Tefferi A. Rationale for revision and proposed changes of the WHO diagnostic criteria for polycythemia vera, essential thrombocythemia and primary myelofibrosis. Blood Cancer J. 2015;5(8):337.
6. Mirand EA, Gordon AS, Wenig J. Mechanism of testosterone action in erythropoiesis. Nature. 1965;206(4981):270-2.
7. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab. 2008;93(3):914-9.
8. Blanchard KL, Acquaviva AM, Galson DL, Bunn HF. Hypoxic induction of the human erythropoietin gene: cooperation between the promoter and enhancer, each of which contains steroid receptor response elements. Mol Cell Biol. 1992;12(12):5373-85.
9. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536-59.
10. EAU Guidelines: Male Hypogonadism | Uroweb. https://uroweb.org/guideline/male-hypogonadism/. Accessed September 23, 2020.

Cite this article as: Kalal C, Patel A, Wagh A, Joshi H, Jain S, Surude R, Bhatia S, Bhatt C. Polycythemia: a mystery solved by history. Int J Res Med Sci 2020;8:3746-8.