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Short Communication

Identification of Women of Polycystic Ovary Syndrome (PCOS) At Risk for Generation of Metabolic Disease in Normal Weight PCOS: Is There a Role of Flutamide?- A Short Communication

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Polycystic ovary syndrome (PCOS) possesses the properties of ovarian hyperandrogenism (HA) from changes in the hypothalamo-pituitary-ovarian(H-P-O)axis in association with insulin resistance(IR) [1].As per the definitions, in1990 PCOS definition in women accepted by National Institute of Health (NIH) criteria [1], i.e. clinical and/or biochemical androgen excess plus oligo anovulation with exclusion of specific etiologies like hyperprolactinemia, and 21 hydroxylase deficiency, escalated androgen in general is correlated with predisposition to abdominal fat accrual, that in turn is exacerbated by obesity along with escalated incidence of generation of type2 Diabetesmellitus (T2DM), dyslipidemia as well as Metabolic Syndrome(MetS) [1-4].

As a result androgen receptors blockade with utilization of flutamide in a dosage of 600mg /day x12wk in women having PCOS as per NIH definition causes reduction in total cholesterol (TC) ,triglycerides (TG), along with low density lipoprotein(LDL)irrespective of obesity, despite akin dose of flutamide delivered orally for 1 yr in case of overweight as well as obese(PCOS women (consuming hypocaloric diets) enhances insulin sensitivity, decreases quantities of LDL in addition to reduction of intraabdominal to subcutaneous(s/c)abdominal adipose fat mass [5]. Blockade of androgen receptors with lesser dosage of 250mg /day on administration x6mths in case of women with hirsutism further decreases quantities of TC along withx18mths delivery for girls possessing functional ovarian hyperandrogenism (HA) resulted in reduction of quantities of LDL along with TG without changing the insulin sensitivity [6]. Nevertheless, other studies implicating flutamide in women with hirsutism/ PCOS could not reproduce the outcomes obtained [7].

In the form of a metabolic adaptability correlated with enhanced androgens, women possessing normal weight PCOS (by NIH definition) possesses decreased insulin sensitivity along with escalated intraabdominal fat mass in addition to adipose insulin resistance (adipose -IR) [pointing to the generation of fasting free fatty acids (FFA) along with insulin quantities) [3,8]. In case of women with PCOS HA further is correlated with exacerbated lipid accrual in the newly generated adipocytes obtained from s/c abdominal adipose stem cells (ASC's) *in vitro* facilitating s/c fat storage in the form of a compensatory mode regarding IR [9]. Seales group illustrated that the generational ranking adipose progenitors comprising of DPP-4+'interstitial progenitors" from which arise the committed ICAM1+ along with CD142+ preadipocytes are destined to differentiate into mature adipocytes. It might be advantageous to target one or greater numbers of these cell populations regarding facilitation of adaptive hyperplastic adipose for attenuation of metabolic diseases. A key observation of this work of Seales group is the localization of these DPP-4+ adipose progenitor cells in the reticular interstitium, that has only recently been noticed although not well assessed fluid containing network of collagen along with elastin fibres which surrounds numerous organs inclusive of adipose depots. Thus the probability arose from this work of Seales group that DPP-4+cells besides working as interstitial progenitors" regarding adipocytes in fat depots might participate significantly in the generation along with regeneration of other tissues[see figure1) [10].This androgen effect in PCOS correlated with changed newly generated s/c)abdominal adipocytes *in vitro* gets augmented more in s/c adipose by intracellular alpha keto reductase(AKK IC3) modulated testosterone (T) formation from androstenedione (A4)that facilitates storage of TG, as observed in case of women with normal weight PCOS by an inverse association amongst serum total T/ A4 ratio along with fasting serum TG quantities [11]. This observation takes place in parallel with catecholamines stimulated lipolysis in case of in s/c abdominal adipose tissue represents another property of PCOS in fat depot [12,13].

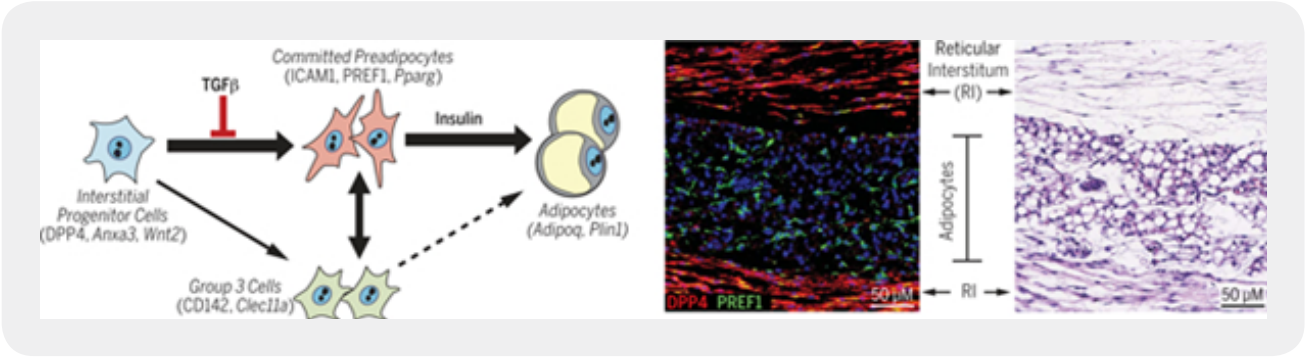

Figure 1: courtesy ref no-10 *This shows how the generational ranking adipose progenitors comprising of DPP-4+'interstitial progenitors" from which arise the committed ICAM1+ along with CD142+ preadipocytes are destined to differentiate into mature adipocytes.It might be advantageous to target one or greater numbers of these cell populations regarding facilitation of adaptive hyperplastic adipose for attenuation of metabolic diseases.A key observation of this work of Seales group is the localization of these DPP-4+ adipose progenitor cells in the reticular interstitium.*

With these observations Dumesic *et al*. [14], randomized double blind, placebo controlled Clinical trial regarding the action of lesser dosage of flutamide on working of abdominal adipocytes in case of women with PCOS. PCOS represents the commonest reproductive endocrinology disorders that gets diagnosed in women that escalates long term chances of generation of type2 diabetes mellitus (T2DM), as well as cardiovascular disease (CVD). Despite, in general the gynaecolic issues get tackled with utilization of oral contraceptives or agents for ovulation induction; there is little insight regarding the long term sequelae of PCOS, hence the other consequences of this disease might not get appreciated. Dumesic *et al*. [14], evaluated if the effects of flutamide might be utilized in overcoming the event of lipid accrual that probably aids in the generation of metabolic diseases which influence life of such patients all through life.

This pilot study was inclusive of 12 women who got the diagnosis of PCOS dependent on the NIH criteria, which got randomized for receipt of flutamide/ placebo for 6mths.The reason for utilization of NIH criteria by these researchers was the identification of women at maximization of risk of generation of metabolic conditions. Furthermore, matching of women with controls was done to guarantee that the particular populations of women were inclusive of properties individual of PCOS women (escalated androgens along with adiposity) inspite of akin age in addition to normal body mass index (BMI). Enrollment of just women with normal BMI might get hold of PCOS women at "low risk" which commonly are seen in the Clinical scenario (usually wrongly diagnosed). In case of populations of women of PCOS having normal BMI as well, flutamide resulted in reduction of abdominal fat accrual along with reduction of LDL without alterations in Luteinizing hormone(LH) in addition to androgens quantities amongst the placebo as well as treatment groups. Interestingly, the effects of flutamide are not essentially associated with the alterations of systemic androgens quantities. A prior study's observation was that flutamide resulted in enhancement of lipid types in women with PCOS irrespective of obesity. Dumesic *et al*. [14], study yields a probable mode of its effects in case of patients with PCOS giving a pathway which probably might be modulated regarding avoidance of Metabolic disease [15]. Although this adds an additional dimension, however we are still far from getting full knowledge as is the usual case with PCOS.

Conclusions

This particular study does not yield adequate proof regarding prescription of flutamide is significant enough for reduction of CVD, however it does incite greater examination in these lines. The biggest limitation is the restricted patients enrolled. Furthermore, as we already know is that flutamide possesses hepatotoxicity [16], as well as is teratogenic. The pathogenesis of PCOS has always been queried regarding what came initially chicken/egg. It is well acknowledged that insulin resistance as well as escalated androgen quantities are the ones to be blamed; nevertheless, genetic as well as environmental factors further are responsible for this complicated endocrine disorder. In view of CVD is the commonest reason for mortality along with morbidity in women greater insight of this type of "high risk" populations of women would aid in enhancement of long term health for decreasing future occurrence of Diabetes, hypertension as well as hyperlipidemia.

Normally we initiate PCOS treatment is still in the same moribund fashion. Usually additionally Clinicians facilitate healthy lifestyle; nevertheless, utilization of avoidance approaches is crucial. Thus, evaluation of pathway that result in propagation of disease might be key. Additionally, Black women with PCOS have escalated risk for metabolic Syndrome along with CVD in contrast to White women [17]. Thus, in future greater PCOS women need to be addressed regarding avoidance of metabolic diseases [18]. Recently we reviewed in the etiopathogenesis of obesity with IR, along with, pathways besides how therapeutic targeting of macrophages polarization status in the treatment of IR might be advantageous. The same is applicable in lean PCOS also needs future exploration as well as is there any variation in the pathways implicated in obese along with lean PCOS women. This needs to be looked into for avoidance of CVD as well as MetS in lean PCOS as well [19].

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