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Short Communication

Advancements in the Etiopathogenesis, Pathophysiology and Treatment of Polycystic Ovary Syndrome (PCOS)

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The polycystic ovary syndrome (PCOS) portrays an endocrine impairment correlated with numerous metabolic conditions, inclusive of, insulin resistance (IR), type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), NAFLD, non alcoholic steatohepatitis (NASH), along with enhanced infertility rate. Recently PCOS has been considered to be a condition with low grade chronic inflammation (LGF) [1,2]. As summarised by Dabravolski., *et al*. [3] mitochondrial impairment is substantially responsible for PCOS generation and propagation [3].

Mitochondrial mutations, impaired mitophagy, diminished ATP generation and liberated ROS further aids in the related symptoms, primarily IR, MetS and obesity generation. Future investigations might focus on acquisition of a greater advantageous insight of the etiological part of nuclear and mitochondrial gene mutations, epigenetic, environmental apart from lifestyle factors on the aetiopathogenesis of PCOS and the associated symptoms.

They summarised the mtDNA mutations identified in PCOS patients. They combined outcomes obtained from case studies (one patient/family) and wide population assessment. Listed mutations were identified backwards from PCOS-diagnosed patients (Rotterdam criteria-dependent), and healthy people were utilized as a control. Mutations have been highlighted on the human mitochondria genetic map (Figure 1).

In total, 33 PCOS correlated mtDNA mutations have been. Twelve mutations have been observed in tRNA genes and just 2 in OXPHOS system. The majority of the identified mutations (20) were identified in the displacement (D) -loop regulatory region, suggesting it as a hot-spot for PCOS-associated mtDNA mutations. Despite various papers have posited mtDNA mutations in the form of etiologic agent for PCOS generation, there are certain arguments against such a causative relation. The main arguments are as follows: (1) the homoplasmic nature of the identified mutations are not associated with other severe clinical symptoms usual for mtDNA mutations that lead to premature ageing and death; (2) some mutations are also present in healthy controls; (3) skeletal muscle functions are not affected [4,5]. Additionally, we have to note that the obtained results have originated from only two ethnic groups (Chinese Han and South Indian), so we cannot rule out selection bias. It is possible that the observed mutations are an example of natural mtDNA variation because wide-population mtDNA analysis of those ethnic groups is still missing. The next crucial point is the lack of standardisation in phenotype description (levels of hormones, degree of oligo/anovulation, and related symptoms like DM, IR, MetS, hypertension, CVD and others) [6].

Present PCOS treatments depend on efficacious insulin-reducing, anti-inflammatory and symptom-targeted drugs apart from lifestyle and diet therapies. Innovative methods imply the administration of synthetic and natural compounds to ameliorate mitochondrial func-

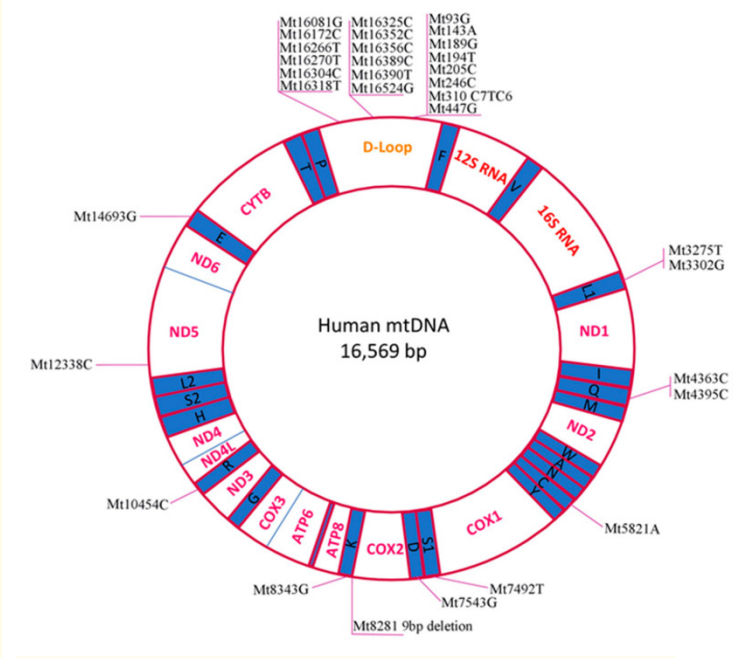

Figure 1: *Courtesy ref no-3-Simplified map of the human mitochondrial genome. The mtDNA mutations associated with PCOS, are marked.*

tion and decreased ROS quantities and OS injury. As PCOS is the commonest reproductive disease, it is key to find markers for early diagnosis and define treatments. In view of PCOS is considered a low-grade chronic inflammation disease, inflammation mediators and correlated signalling molecules might portray an innovative target for therapeutic ventures. Recent analyses has aided in identification of lncRNAs as a new controlling modes implicated in PCOS pathogenesis and, thereby, a target for medical approaches. Thereby the probability of utilization of new markers for early diagnosis, combined with target phenotype- and genotype- particular therapies, hold attractive avenues for PCOS patients for which no specific treatment exists to completely cure it.

The group of Muscogiuri initially posited that of the 2 isoforms of inositol, myo in addition to D-chiro, might be possessing a key part in tackling metabolic along with endocrine paradigms towards homeostasis that counters the signs and symptoms canonical of PCOS. Additionally, certain recent studies concentrated ion Mediterranean diet (MD) along with ketogenic diet (KD) to yield positive outcomes in patients who were influenced by overweight/obesity and T2DM, hence these diets might be of use in PCOS [7].

Furthermore, very low-calorie ketogenic diet (VLCKD) is rapidly proving to be advantageous not only in obesity but also in the treatment of other metabolic diseases. Recently we highlighted the promising benefits of KD over MD in overweight/obesity and T2DM patients. In view of PCOS shares LGF with these metabolic disease lot of work has accumulated in MD along with VLCKD in cases of PCOS [8].

For aiding its management, lifestyle/dietary interventions have been assessed, very low-calorie ketogenic diet (VLCKD) is revealing at a fast pace advantageous outcomes apart from obesity; in the treatment of other metabolic diseases as well. Recently Barrea., *et al*. [9], reviewed for assessment of the scientific proof validating this dietary fashion in the form of efficacious approaches for PCOS treatment in

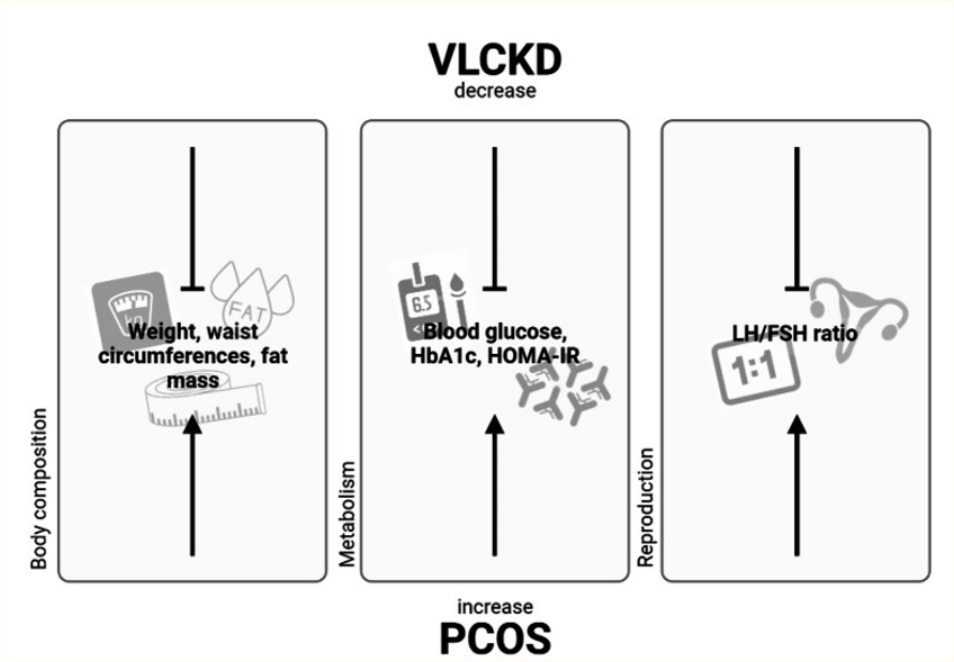

Figure 2: *Courtesy ref no9--Metabolic and reproductive effects of VLCKD on PCOS.* VLCKD *very low-calorie ketogenic diet,* PCOS *polycystic ovary syndrome.* ⊥ *indicates a decrease, while ↑ indicates an increase.*

addition to the metabolic conditions correlated with it. The initial outcomes pointed significant enhancement in body weight besides its constitution, metabolic characteristics (glucose, serum insulin, triglycerides, total low-density lipoprotein (LDL) cholesterol), as well as insulin resistance (IR) subsequent to VLCKD. Nevertheless, there is still paucity of this proof which warrants it to get further corroborated. Thus they summarized that weight loss in PCOS women has been illustrated to result in improvement of metabolic abnormalities along with body constituents. Nevertheless, no agreement exists with regards to ideal dietary fashion or macronutrient constitution. There is certain validation the possible corroborating part of the Mediterranean diet in improvement of infertility (in addition to other well-known metabolic advantages) in women with PCOS. Noticeably, VLCKD might be believed to be probable strategy for the short-term treatment of PCOS. However it needs prescription in addition to needs precise supervision by professionals [9].

Recently Cicione., *et al*. [10], from the same group of Muscogiuri and Barrea (an authority on diet management) tried assessment of PCOS with KD in overweight/obese patients with PCOS in addition to analysed probable advantageous actions on metabolic along with endocrine paradigms in contrast to standardized, balanced hypocaloric diet like MD. Enrolled patients were divided in a 1: 1 ratio, randomized to receive KD or MD. In all patients anthropometric parameters, metabolic along with endocrine paradigms were taken at baseline subsequent to dietetic treatment. Their outcomes revealed significant alterations in anthropometric parameters along with bio-chemical paradigms which were statistically significant ($p < 0.001$) in both groups subsequent to both types of diet treatments. Despite, the decrease of all paradigms were significantly greater in KD in contrast to MD group. Thus concluding that decrease of carbohydrates by KD might be of in Pharmacologic therapy of PCOS [10]. Nevertheless, it is significant to note that these dietetic therapies are only meant for obese PCOS whereas in lean PCOS weight gain is advised [9]. Future trials are still needed for standardization of components of MD and KD (precise restriction of carbohydrates).

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