

Androgen Excess-Induced Endocrine-Metabolic Dysfunctions: Novel Strategy for Treatment in the Polycystic Ovary Syndrome Overweight/Obese Phenotype

Eduardo Spinedi¹ and Daniel P Cardinali²

¹Centre for Experimental and Applied Endocrinology (CENEXA, UNLP-CONICET, La Plata Medical School, La Plata, Argentina

²Department of Teaching and Research, UCA Medical School & BIOMED-UCA-CONICET, Buenos Aires, Argentina

Transient, early in life, hyperandrogenemia predisposes the organism to develop Polycystic Ovary Syndrome (PCOS is a hormonal disorder common among women of reproductive age. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries may develop numerous small collections of fluid (follicles) and fail to regularly release eggs). Genetic and environmental (epigenetic) factors also play relevant roles in PCOS development. PCOS and Metabolic Syndrome (MS) female phenotypes share common characteristics. Indeed, hyperadiposity and sleep disturbances have been reported to increase in PCOS women and obstructive sleep apnea is a common feature in both phenotypes. Maturation of the LH-RH secretion pattern in pubertal girls is closely related to changes in the sleep-wake cycle, and could have relevance in the pathogenesis of PCOS. When analyzed the impact of neonatal² androgenization (testosterone propionate, TP; sc 1.25 mg/rat-pup) on endocrine-metabolic biomarkers and ovarian function in female rats over development (juvenile and adult ages), TP individuals displayed accelerated growth, hypertrophic adiposity (expressing high and low mRNA levels of leptin and adiponectin, respectively), enhanced peripheral concentrations of non-esterified fatty acid (NEFA), plasminogen activator inhibitor-1 (PAI-1), leptin and insulin. These features were accompanied by early vaginal opening, permanent estrous cycle and dysfunctional ovarian steroidogenesis, with conserved glomerulosa cell endocrine function. Indeed, studies of juvenile TP ovaries rats indicated that primary and antral follicle frequencies were 3- and 15-fold higher and lower, respectively; whereas secondary and atretic follicle frequencies were 3- and 5-fold lower and higher, respectively, large cystic images without corpus luteum were found in adult TP rats. These data strongly suggest that neonatal hyperandrogenemia induced metabolic-endocrine and ovarian misprogramming, suggesting that this phenotype is highly susceptible to develop an enhanced risk of MS, overweight/obesity, type 2 Diabetes Mellitus and cardiovascular disease (CVD). It has also been found that melatonin-treated diet-induced obese (DIO) rodents are protected against several obesity co-morbidities.

The clinical management of PCOS (PCOS is a hormonal disorder common among women of reproductive age. Women with

PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries may develop numerous small collections of fluid (follicles) and fail to regularly release eggs women should include precise phenotype identification,

namely the PCOS-MS one, and as a consequence, lifestyle modifications, insulin therapy, and drug treatments that promote insulin sensitization (such as metformin) and insulin secretion (such as glibenclamide), dipeptidyl peptidase-4 inhibitors, sodium glucose co-transporter 2 inhibitors and anti-hyperlipidemic therapy. In general, these approaches are designed to manage symptoms of IR/ β - cell dysfunction and dyslipidemia, and are used either alone or together .

Although overweight/obesity is a preventable condition, its prevalence is continuously increasing worldwide and, because it's frequently related to other cardiovascular risk factors and high mortality, obesity has become an important public health problem and a heavy socioeconomic burden for society as a whole. Environmental factors, androgen excess or stressors of so-called contemporary "24/7" societies have pronounced circadian clock disruptive effect. Indeed, people whose work involves irregular time schedules, night/shift workers, show significant distortion in sleep architecture and enhanced prevalence for MS development. These evidences strongly suggest that the body's system fails to adjust properly to environmental and/or stressor changes disrupting overall homeostasis.

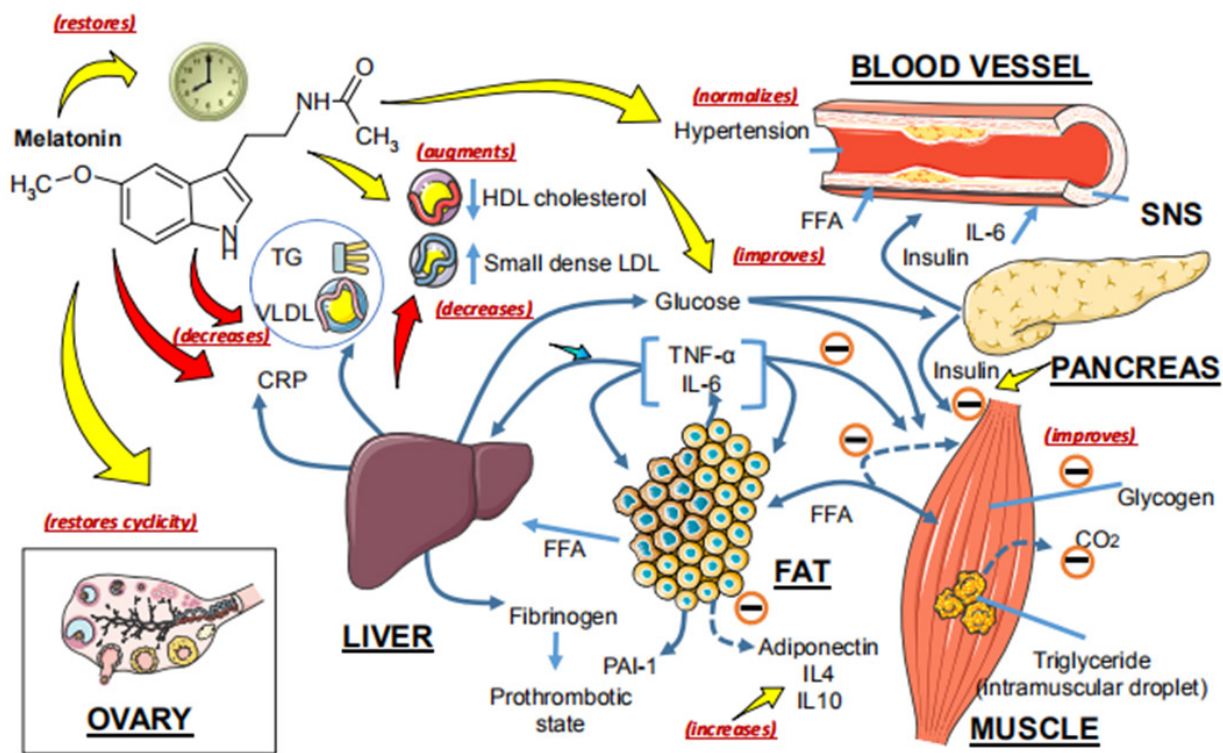
Drug therapies for PCOS individuals are expensive worldwide, and in some cases have been associated with adverse secondary events including pancreatitis, hypoglycemia and osteoporosis. Therefore, a need remains for new and cost-effective diabetes presenting limited additional health risks. Melatonin may provide an innovative strategy in PCOS by combining its chronobiotic effect on circadian rhythm with cytoprotective properties and insulin-sensitivity enhancers. Indeed, melatonin protects against several MS co-morbidities in PCOS (PCOS is a hormonal disorder common among women of reproductive age. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries may develop numerous small collections of fluid

(follicles) and fail to regularly release eggs, such as diabetes and concomitant oxy-radical mediated damage, inflammation, microvascular disease, atherothrombotic risk and ovary dysfunction. Melatonin may therefore have an area from the initial phases of PCOS treatment. Its high safety profile and reduced toxicity distinguishes it from many pharmaceutical agents utilized in PCOS-MS patients. However, studies using 2-5 mg of melatonin per day are not adequate to provide an adequate comparison with data on the protection of PCOS or MS derived from animal studies.

Hence clinical trials with doses in the 40-100 mg/day range are urgently needed. It should be noted that melatonin is remarkably non-toxic, and its safety is very high. The lethal dose 50 for the i.p. injection of melatonin was determined for rats (1,168 mg/kg) and mice (1,131 mg/kg), but that for the p.o. administration of melatonin (tested up to 3,200 mg/kg in rats) and s.c. administration of melatonin (tested up to 1,600 mg/kg in

rats and mice) could not be determined. In humans, melatonin has a high safety profile and, in general, is very well tolerated. Unfortunately, the pharmaceutical industry is refractive to support those studies because of the lack of protective patents for a natural compound. Hence, only with the involvement of governmental and non-profit organizations such a goal can be achieved. At present, the only option for the attending physician interested in the use of melatonin as a cytoprotective is that the off-label indication of the drug.

In conclusion, an appropriately classical pharmacological treatment combined with melatonin should be considered in PCOS-MS individuals to restore endocrine-metabolic and reproductive functions. Therefore melatonin may have a place from the initial phase of the pharmacological treatment in the PCOS-MS woman phenotype to further reversion of endocrine-metabolic and reproductive dyfunctions (see figure below).



Treating PCOS-MS women with melatonin could normalize high blood pressure (BP) and inflammation; moreover, It also improves insulin sensitivity and restores disrupted circadian rhythms. Additionally, melatonin directly affects ovarian function by ameliorating granulosa cell steroidogenesis and follicular function in humans. (Adapted from Reiter RJ, et al. Fertil Steril 2014;102:321-8)