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Myo-inositol as a male fertility molecule: speed them up!

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Abstract. – Myo-inositol (MYO) represents usually a therapeutic option for female infertility associated with insulin resistance. Recently, several evidences are accumulating about the potential use of MYO for the treatment of male infertility. This article summarizes the rationale for MYO in the treatment of male infertility. In particular, it illustrates the potential antioxidant and prokinetic role of MYO, and its importance for the modulation of hormonal regulation. In the final part of the manuscript has been added a proposal for a clinical algorithm reserved for patients with asthenozoospermia, where probably MYO could exert specific pharmacological effects.

Key Words
Sperm parameters, Male infertility, Myoinositol, Reactive oxygen species, ICSI

Male infertility and reactive oxygen species

Infertility is a worldwide problem with a negative medical and psychosocial impact on couples in reproductive age[1]. The male partner, alone or in association with the female partner, contributes to about 50% of couple infertility[2]. Conditions such as varicocele, cryptorchidism, and hypogonadism are among the many causes of male infertility. Nevertheless, a significant proportion of male infertility is undiagnosed despite an extensive diagnostic workout. This is referred to as idiopathic infertility which is characterized by sperm parameters below the World Health Organization (WHO) reference values[3-5]: i.e. oligozoospermia, asthenozoospermia and/or teratozoospermia (OAT). Idiopathic infertility is found in about 25-30% of infertile patients[6].

One of the factors that may cause male infertility is the overproduction of reactive oxygen species (ROS). ROS are represented by a broad spectrum of molecules including: a) oxygen free radicals, such as superoxide anion (O_2), hydroxyl radical (OH) and hyperoxyl radical (HOO); b) non-radical species, such as hypochlorous acid (HOCl) and hydrogen peroxide (H_2O_2); and c) reactive nitrogen species and free nitrogen radicals such as nitroxyl ion, nitrous oxide, peroxynitrite, etc.

Several conditions increase the oxidative stress in seminal fluid. These include pathological conditions involving the reproductive tract (varicocele, prostatitis)[7-12]; some life styles (smoking, alcohol abuse, drug addiction)[13-16]; environmental pollution (radiation, smog, industrial gasses) and nutritional errors (unbalanced hyperlipidic diet, etc.)[17-19].

The role of ROS in the pathophysiology of human sperm function has been emphasized in recent years. The most prolific source of ROS in sperm suspensions is a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase located in leukocytes or in spermatozoa that produces superoxide that is further converted to peroxide by the action of superoxide dismutase. Hydrogen peroxide has been recognized as the most toxic oxidizing species for human spermatozoa, which are very sensitive to lipid peroxidation owing to the high content of polyunsaturated fatty acids in their plasma membrane, though this is not the sole mechanism through which sperm function might be impaired by ROS[20].

Spermatozoa are more susceptible than other cell types to the detrimental activity of these chemical compounds. In particular, ROS can affect motility, morphology and DNA stability of spermatozoa. Mitochondria are the organ-

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elles producing the energy (adenosine triphosphate, ATP) required by spermatozoa for the performance of their function. ROS may induce changes in mitochondrial membranes and may thus compromise sperm function[21]. It has been shown that mitochondrial membrane potential (MMP) and ROS levels are inversely correlated. Such relationship could be due to two mutually interconnected phenomena: on the one hand, ROS causing damage to the mitochondrial membrane and, on the other hand, the damaged mitochondrial membrane causing increased ROS production[22].

Spermatozoa, as well as critical phases of spermiogenesis, are particularly susceptible to ROS-induced damages for several reasons. These include: a) sperm chromatin condensation is process that is very susceptible to increased oxidative stress; b) spermatozoa have very low DNA repair mechanisms; c) the sperm membrane contains high levels of poly unsaturated fatty acids; d) spermatozoa themselves produce ROS, especially during passage through epididymis; e) spermatozoa have low levels of cytoplasmic antioxidant enzymes (because most of the antioxidant enzymes are lost in spermiogenesis); and f) spermatozoa spend long periods as isolated cells in both male and female genital tracts[23-26].

Spermatozoa acquire motility during the epididymal transit, becoming able to migrate from the vagina to the Fallopian tubes, to penetrate the cumulus oophorus and to carry out all those processes involved in fertilization[27]. At first, after penetrating the cumulus oophorus of the ovum, the spermatozoon binds to the zona pellucida with its plasma membrane intact; then, it undergoes the acrosome reaction[28]. This results in the release of hydrolytic enzymes that digest the zona pellucida, allowing to the spermatozoon to penetrate into the oocyte and to fertilize it[29]. All these events are allowed by inositols and particularly by increasing intracellular Ca^{++} release through inositol-gated channels because of the protein kinase PKC activation[30].

Myoinositol

Inositol is a polyalcohol, naturally occurring as nine stereoisomers, including D-chiro-inositol (DCI) and myo-inositol (MYO) that belongs to the vitamin B complex group. MYO plays a crucial role in cell morphogenesis and cytogenesis; it is involved in cell membrane formation, lipid synthesis, cell growth and in several systemic processes and mechanisms of signal transduction in the plasma membrane as a precursor of second messengers[31].

MYO is an important precursor for the phosphatidyl-inositol (PtdIns) signaling pathway. Inositol incorporated into PtdIns is converted successively to the polyphosphoinositides, PtdInsP and PtdIns(4,5)P2. Under specific stimuli, PtdIns(4,5)P2 is hydrolyzed to produce two second messengers, diacylglycerol (DAG) and Ins(1,4,5) P3 which respectively modulate specific protein phosphorylation process and intracellular Ca^{++} concentration[32].

Despite their small size and structural simplicity, mounting evidence indicates that spermatozoa possess a sophisticated mechanism for regulation of cytoplasmic Ca^{++} concentration[33,34]. Recent studies speculate about the presence of two intracellular Ca^{++} stores and one sperm-specific Ca^{++}-permeable channel (CatSper) in the plasma membrane of the flagellar principal piece[35-39]. One of the Ca^{++}-permeable channels present in the Ca^{++} storage organelles of spermatozoa is the Ins(1,4,5)P3-sensitive Ca^{++} channel [commonly called Ins(1,4,5)P3R] that has been studied extensively in a variety of cell types including sperm [40]. This channel binds the second messenger inositol 1,4,5-triphosphate [Ins(1,4,5)P3], which leads to elevation of intracellular Ca^{++} concentration[41]. Immunolocalization experiments showed that two Ins(1,4,5)P3R-containing Ca^{++} stores are present in the sperm, one in the acrosome and the other, a much smaller Ca^{++} store, located within the redundant nuclear envelope at the back of the head[36,42-44].

Myoinositol and Male Reproduction

MYO concentration is significantly higher in the seminiferous tubules than in serum[45]. In male reproductive organs, MYO is mainly produced by Sertoli cells in response to follicle-stimulating hormone (FSH) and is involved in processes that include the regulation of motility, capacitation and acrosome reaction of sperm cells[46].

It has been suggested that MYO may play a role in the osmoregulation of seminal fluid. Indeed, both hypo- and hyper-osmotic media have been found to significantly decrease sperm progressive motility and velocities[47]. An

increased amount of a particular enzyme, Inositol-1 monophosphatase (IMPA-1), involved in the dephosphorylation of PtdIns, has been detected in asthenozoospermic patients[48]. Therefore, it is possible that increased expression of IMPA-1 in asthenozoospermic patients could alter PtdIns signaling pathway and therefore induce a reduction in sperm motility. This sustains the role of signal transduction pathways induced by PtdIns in the regulation and maintenance of male germ cell motility[49].

Few studies have investigated the role of MYO as a possible antioxidant agent both for the systemic treatment of male infertility and for the improvement in the *in-vitro* quality of the sperm used for the fertilization applied to medically-assisted reproductive procedures. An initial study has shown that the spermatozoa of patients with OAT are covered by amorphous fibrous material that increases seminal fluid viscosity and reduces sperm motility. Furthermore, the mitochondria in the intermediate tract of spermatozoa of patients with OAT had damaged cristae. However, after incubation with inositol, the amorphous fibrous material disappeared, and cristae damage decreased[50].

At a functional level, MYO acts directly on mitochondria increasing the membrane potential[51]. MMP is an apoptotic marker clearly related to the functional parameters of the sperm cells, including motility, the capacity of fertilization and embryo quality, and is therefore used as an index of fertility[52,53]. High values of MMP indicate the integrity of this structure with optimal levels of activity and are associated with high cell viability.

These morpho-functional data have recently been confirmed by evidence suggest that spermatozoa from patients with OAT incubated with MYO have a significantly higher sperm motility and a higher MMP, probably increasing cytosolic Ca^{++} and consequently inner mitochondrial Ca^{++}. In particular, a high percentage of sperm with low MMP represents a very important index of impaired sperm mitochondrial function, and MYO decreases this percentage. Moreover, when comparing patients with OAT and healthy subjects, it was found that MYO might have a stimulatory function in OAT sperm and a protective function in normal semen. These findings suggest that MYO could be used *in-vitro* in assisted reproductive techniques (ART), both to increase the number of spermatozoa to be used for intrauterine insemination and to ameliorate the sperm quality to be used for *in-vitro* ART[54,55].

As a consequence, MYO treatment of spermatozoa with different MMP level might have produced different results in fertilization rate following *in-vitro* fertilization (IVF)[52,53,56].

Rubino et al[57] reported that the oocyte fertilization rate after Intracytoplasmic Sperm Injection (ICSI) may be significantly increased when spermatozoa are treated and prepared with MYO compared with placebo supplemented media. They have also observed a statistically significant higher percentage of grade A embryos on day 3 in the MYO group. Furthermore, the efficacy and safety of MYO were investigated in a double-blind, randomized, placebo-controlled trial on 194 patients with idiopathic infertility. After 3 months of treatment, the results of this study showed that MYO is a safe supplement able to significantly rebalance serum gonadotropin and inhibin B levels and to increase sperm parameters in patients with idiopathic infertility[58]. However, a recent in vivo study has shown that exogenous administration of MYO significantly improves sperm parameters (seminal fluid volume and sperm number) both in patients with oligo-asthenozoospermia and in normal fertile men but there was no motility improvement in both groups after treatment[59].

MYO in the Andrological Clinical Practice (Therapeutic Aspects)

Based on the evidences illustrated in this article, we suggest a specific use of MYO in infertile patients with asthenozoospermia[54]. In this case, it is proper to distinguish between patients with absolute asthenozoospermia, who are candidate to ICSI, and patients with relative asthenozoospermia, who need to undergo an accurate diagnostic workup[60]. This is aimed at excluding the following pathological factors: inflammation of the male accessory glands or leukocytospermia[61], papillomavirus infection[62], increased seminal fluid viscosity[63], significant decrease of the testicular volume or of the hormonal serum levels and altered accessory gland secretory function[61,64]. Once having excluded all these, we suggest to proceed carrying on the evaluation of the MMP and to prescribe treatment with MYO to those patients who have low sperm MMP. This algorithm is illustrated in Figure 1.

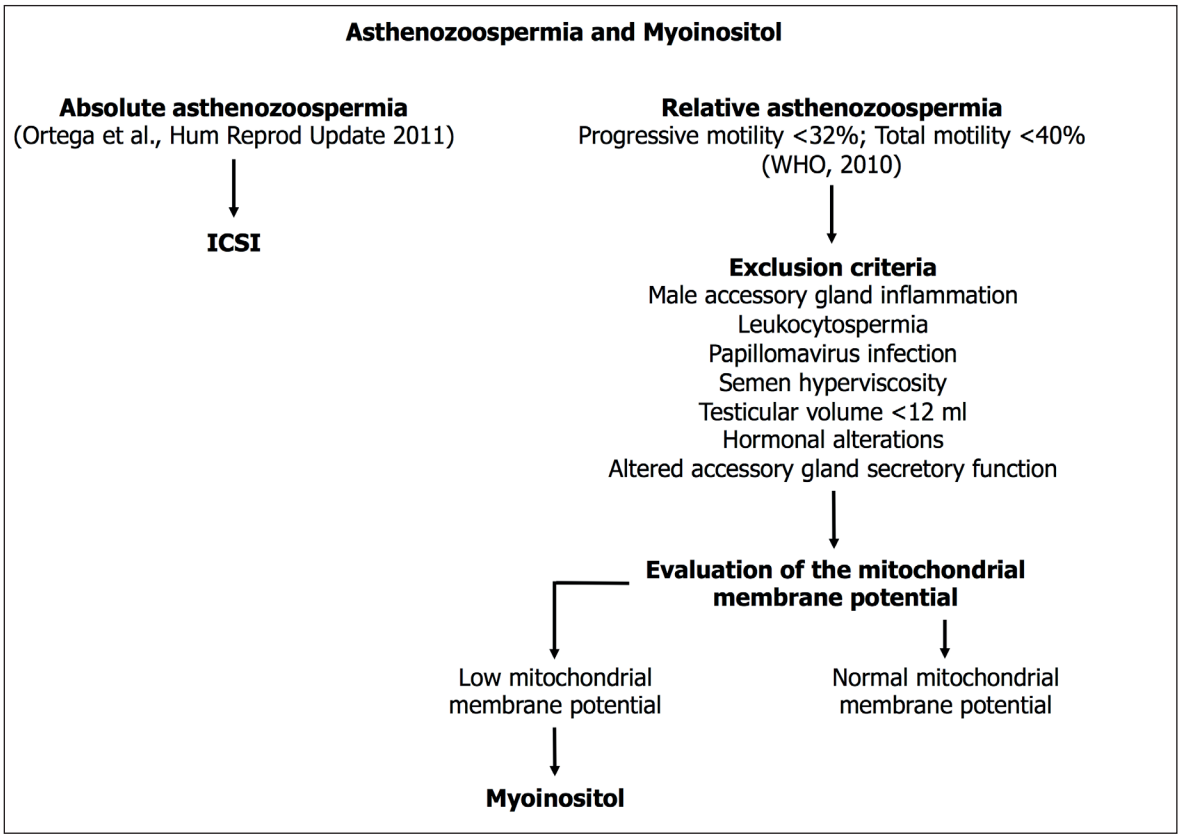

Figure 1. Possible use of MYO it patients with asthenozoospermia.

Conclusions

These data suggest that inositol is able to improve the sperm mitochondrial function, thereby improving sperm motility in patients with altered sperm parameters. Hence, patients with idiopathic infertility could take advantage by MYO supplementation. There is a need to encourage further research on all the possible benefits of MYO supplementation of culture media for human IVF procedures because the improvement of culture conditions still represents one of the main goals of the human ART research.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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