Myoinositolo e infertilità maschile

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J Endocrinol Invest
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CONSENSUS STATEMENT

The use of nutraceuticals in male sexual and reproductive disturbances: position statement from the Italian Society of Andrology and Sexual Medicine (SIAMS)

A. E. Calogero[1] · A. Aversa[2] · S. La Vignera[1] · G. Corona[3] · A. Ferlin[4]

Fertility

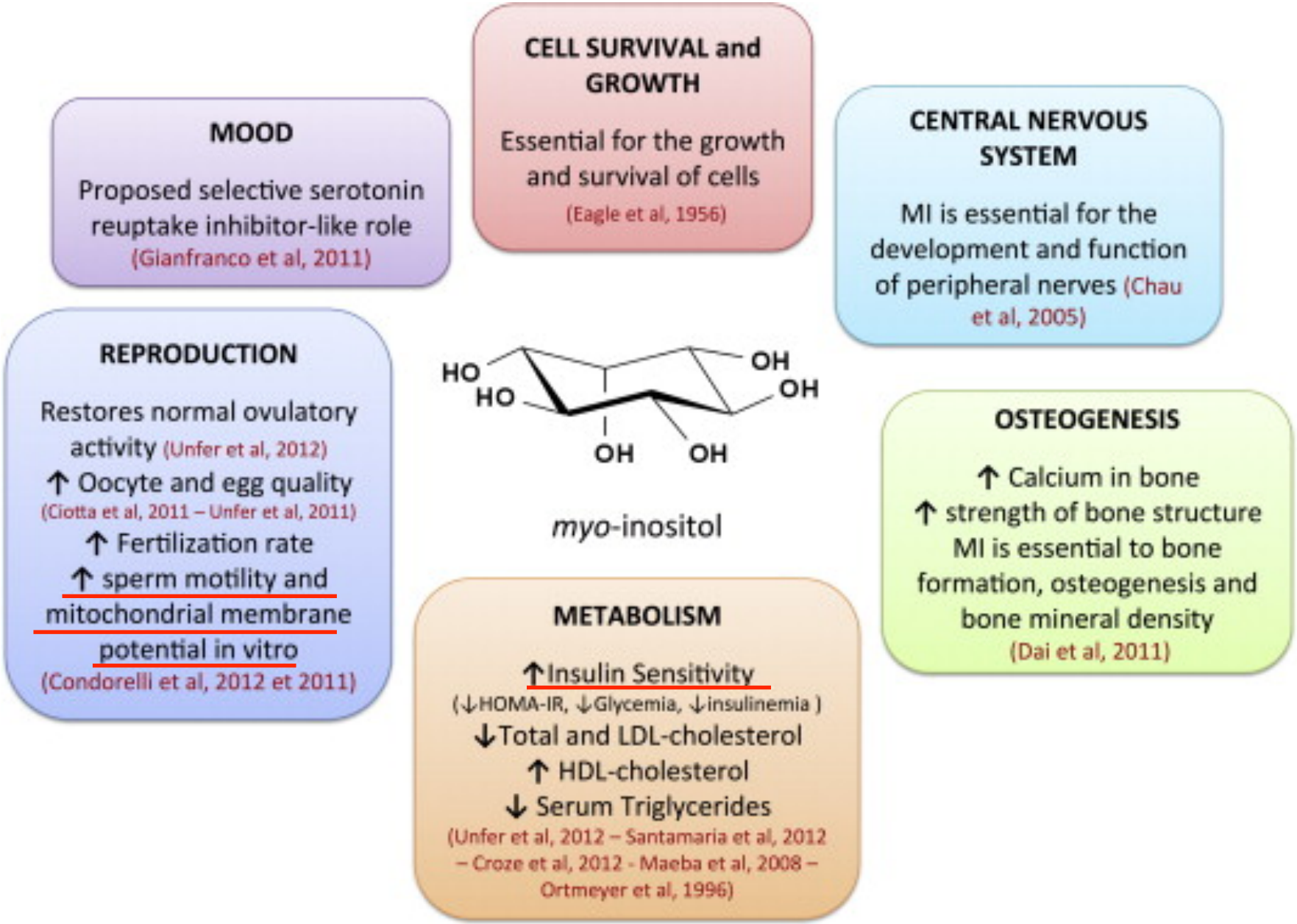
Recommendation

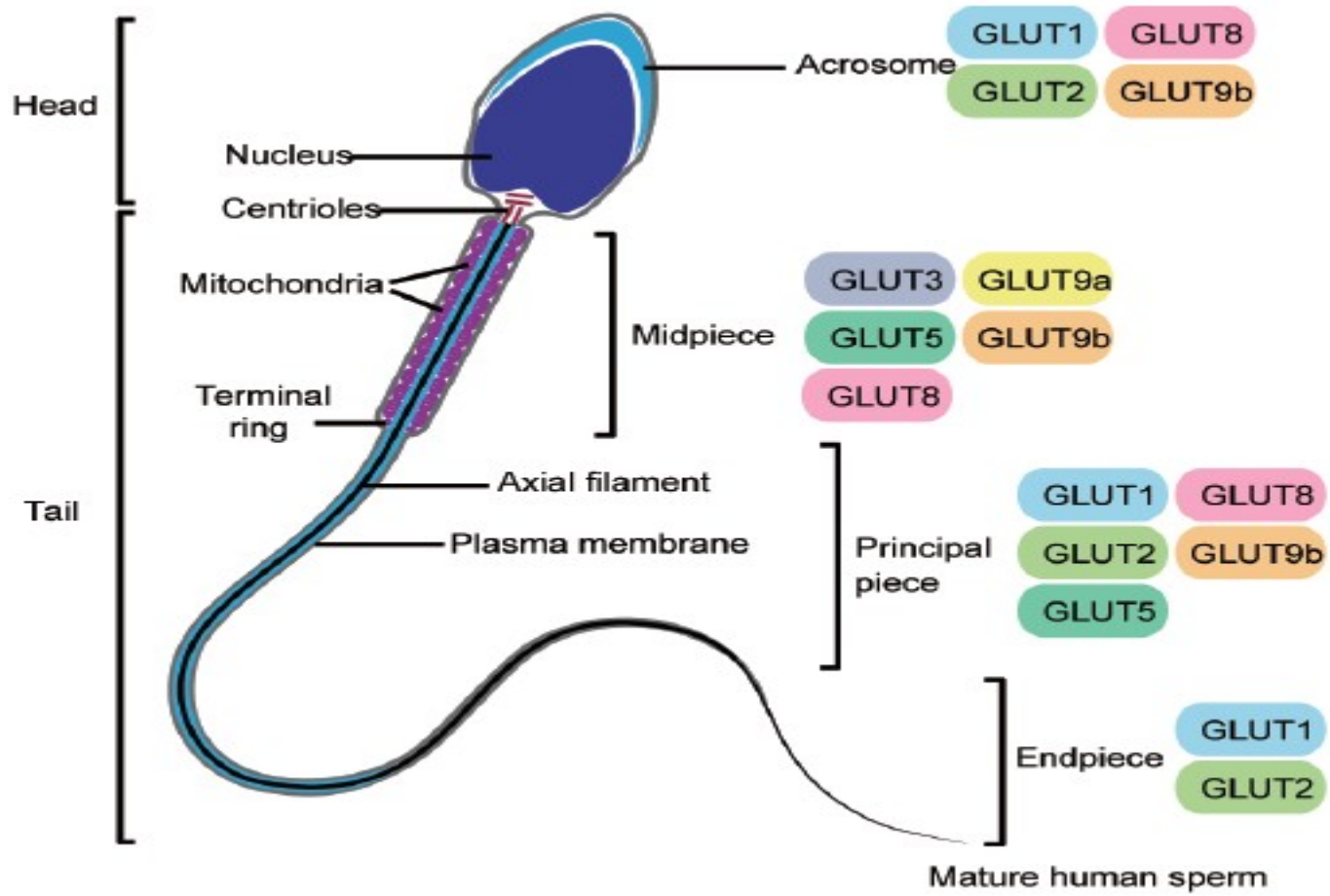
1. We recommend not prescribing antioxidants for improving sperm parameters and pregnancy rate in all subjects with sperm abnormalities before a specific diagnostic workup (1 ØØØØ).
2. We suggest the use of antioxidants in patients with idiopathic infertility in the presence of documented abnormal sperm parameters and altered sperm DNA fragmentation (SDF) only after a thorough diagnostic workup (2 ØØOO).
3. We suggest no specific antioxidants and therapeutic regimes for improving sperm parameters and pregnancy rate in patients with idiopathic infertility (2 ØØOO).

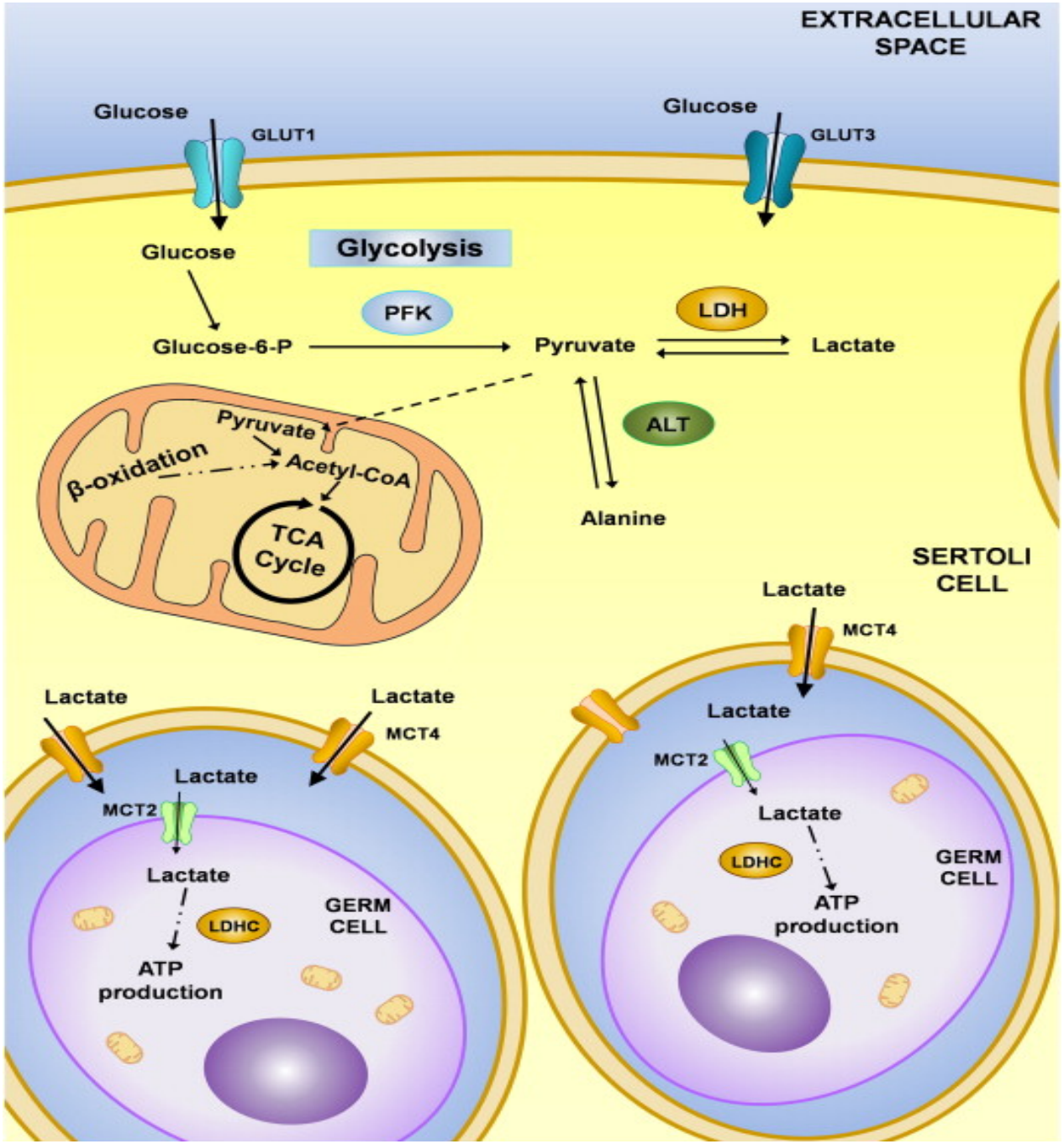
Table 1 Main nutraceuticals used for the treatment of male infertility

Nutraceuticals	Evidence	Possible indications
Ascorbic acid (vitamin C)	Its administration positively correlates with sperm count and motility [38], and negatively with sperm DNA fragmentation index [39]	Oligo-astheno-teratozoospermia
Carnitine	Improves concentration, total sperm count, and progressive motility [40–45]	Oligo-astheno-teratozoospermia
Carotenoids (lycopene, β-carotene)	Improve sperm parameters [46]	Oligo-astheno-teratozoospermia
Coenzyme Q10	Improves sperm count, motility, and morphology [47–50]	Oligo-astheno-teratozoospermia
Myoinositol	Improves sperm progressive and total motility and the mitochondrial function; increases the number of sperm recovered after swim-up technique [51–53]	Oligo-astheno-teratozoospermia
Glutathione	Improves sperm concentration, motility, and morphology [54, 55]	Oligo-astheno-teratozoospermia
N-acetyl-cysteine	Improves sperm volume, viscosity [56, 57] and motility. Prevents oxidative DNA damage [13]	Oligo-astheno-teratozoospermia
α-Tocopherol (vitamin E)	Increases sperm motility [58]	Oligo-astheno-teratozoospermia

Fig. 1. Functions and benefits of a myo-inositol diet supplement for human health.




Head
Tail
Acrosome
GLUT1
GLUT8
GLUT2
GLUT9b
Nucleus
Centrioles
Mitochondria
Midpiece
GLUT3
GLUT9a
GLUT5
GLUT9b
GLUT8
Terminal ring
Axial filament
Plasma membrane
Principal piece
GLUT1
GLUT8
GLUT2
GLUT9b
GLUT5
Endpiece
GLUT1
GLUT2
Mature human sperm



1. Glucosio penetra nelle cc di Sertoli tramite GLUT 1 e GLUT3

2. Conversione in glucosio 6 fosfato

3. Conversione in Piruvato (fosfofruttochinasi)

Piruvato (3 possibili destini metabolici)

a. Formare Acetil CoA dentro la matrice mitocondriale;

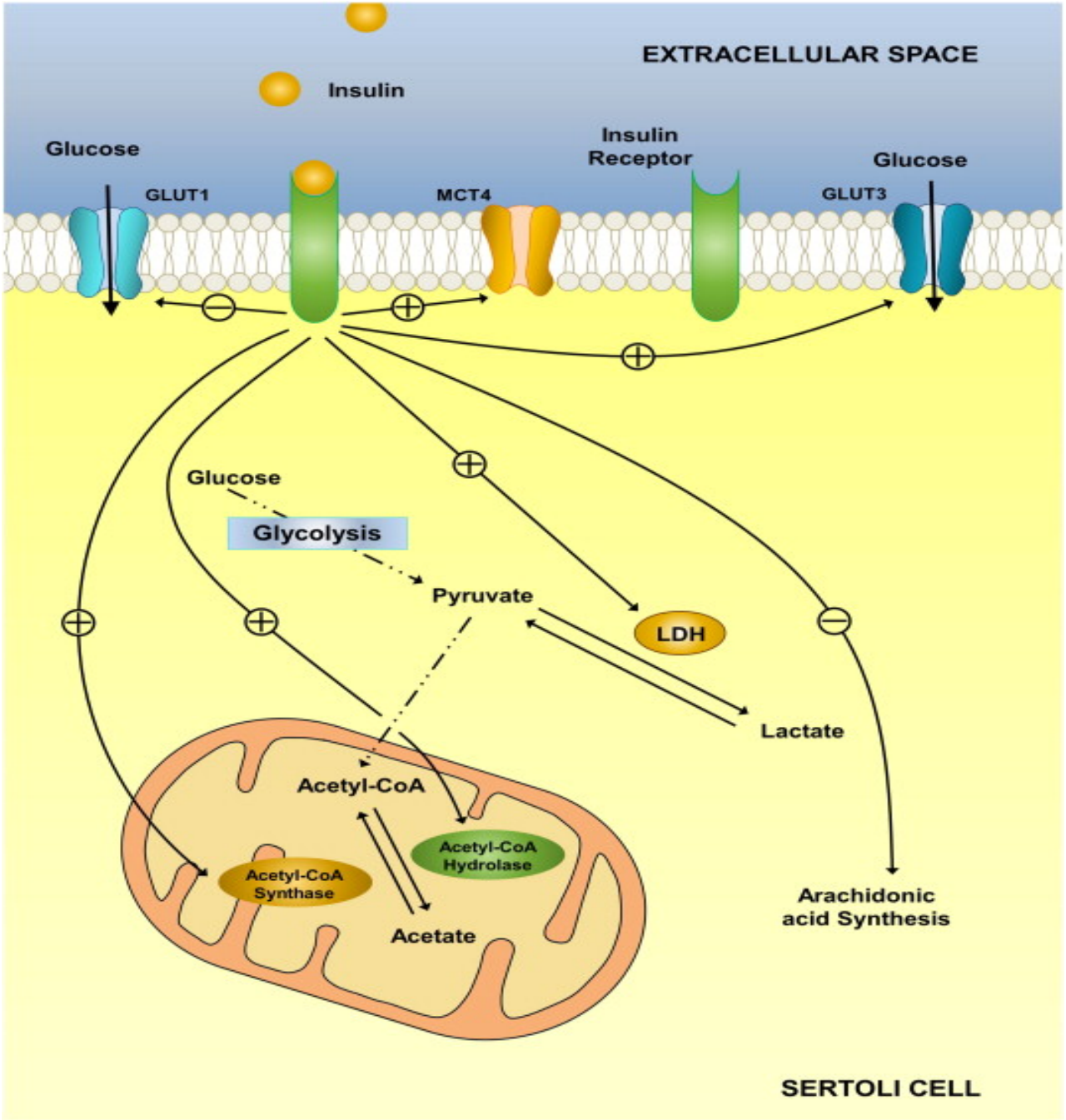
b. Conversione in lattato (LDH)

c. Conversione in alanina (ALT)

Lattato

1. Trasporto attivo nel fluido intra-tubulare (MCT4)

2. Uptake cellula germinale (MCT2)



L'INSULINA DOPO LEGAME CON IL PROPRIO RECETTORE ESERCITA EFFETTI REGOLATORI POSITIVI SU MCT4

Increased insulin resistance in men with unexplained infertility

REPRODUCTIVE BIOMEDICINE ONLINE 35 (2017) 571–575

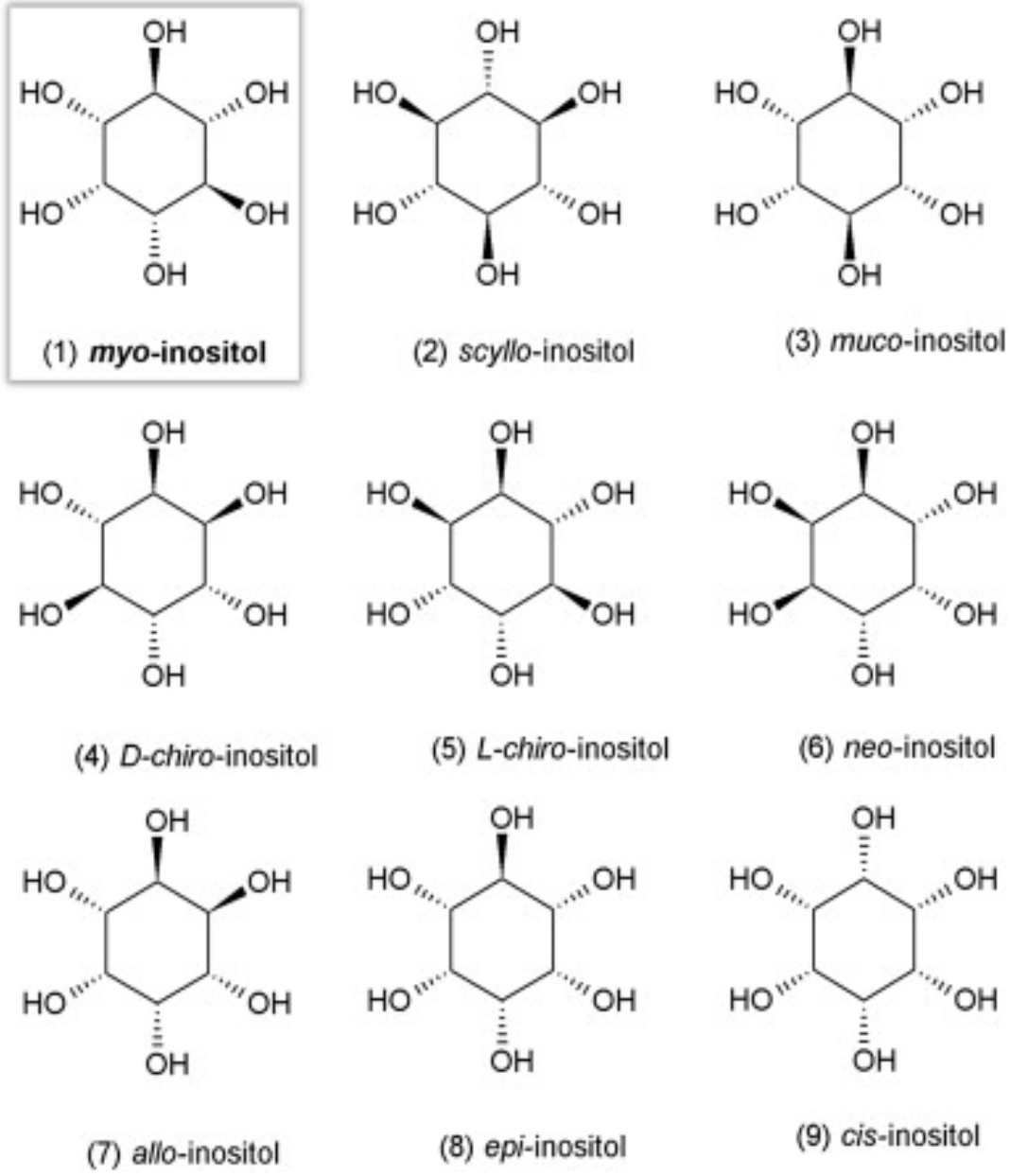
Table 1 – Participants' characteristics and study results.

	Study group (n = 160)	Control group (n = 79)	Reference ranges	P-value
Age (years)	35.12 ± 6.15	34.51 ± 5.61	–	NS
BMI	29.79 ± 3.21	29.12 ± 3.75	–	NS
Fasting serum insulin (mIU/ml)	13.67 ± 10.44	5.46 ± 3.15	0–25	<0.0001
Fasting blood glucose (mg/dl)	95.86 ± 25.22	94.41 ± 30.40	65–105	NS
Insulin resistance (inverse QUICKI)	2.99 ± 0.33	2.61 ± 0.33	–	<0.0001
Insulin resistance (HOMA)	3.07 ± 2.81	1.25 ± 0.75	–	<0.0001
Total cholesterol(mg/dl)	198.29 ± 37.52	182.45 ± 35.92	116–212	<0.05
Triglycerides(mg/dl)	142.82 ± 105.31	114.59 ± 61.42	50–150	NS
High-density lipoproteins (mg/dl)	43.15 ± 10.62	43.65 ± 15.02	40–80	NS
Low-density lipoproteins (mg/dl)	139.52 ± 106.54	140.74 ± 138.43	85–125	NS
FSH (mIU/ml)	4.71 ± 2.57	3.15 ± 1.92	1–10	<0.0001
LH (mIU/ml)	4.98 ± 2.41	3.15 ± 1.12	1.8–12	<0.0001
Prolactin (ng/ml)	12.82 ± 6.95	12.01 ± 7.96	3–15	NS
Total testosterone (ng/ml)	5.35 ± 3.02	6.62 ± 3.51	2.49–8.36	<0.001

Values presented as mean ± SD.

BMI = body mass index; NS = not statistically significant.

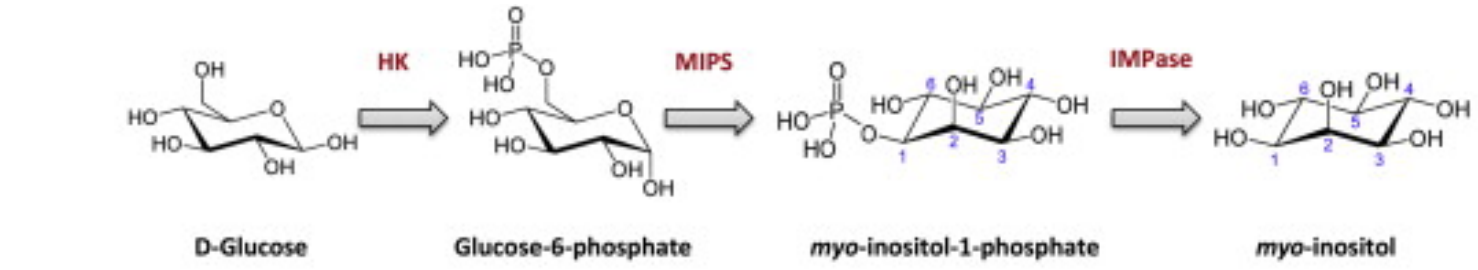
In vivo conversion of myoinositol to D-chiro-inositol can occur in tissues expressing the specific epimerase.



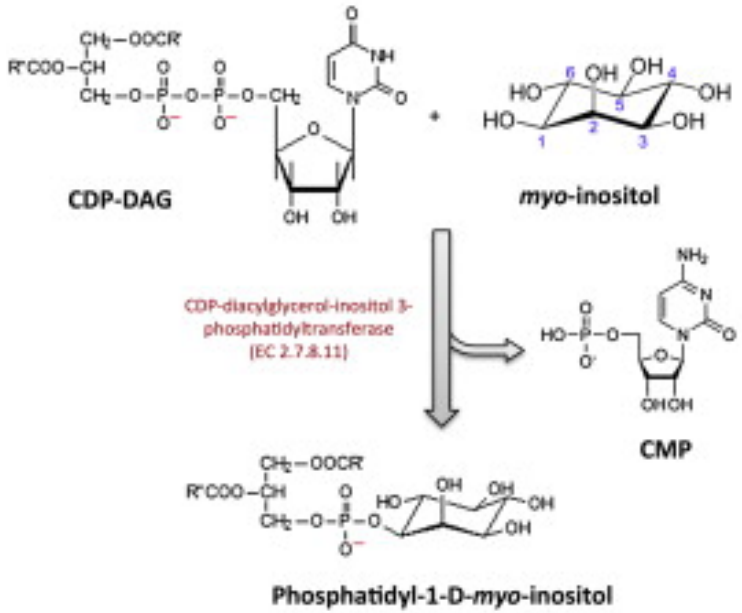
Sintesi de novo da G6P

Defosforilazione fosfolipidi membrane

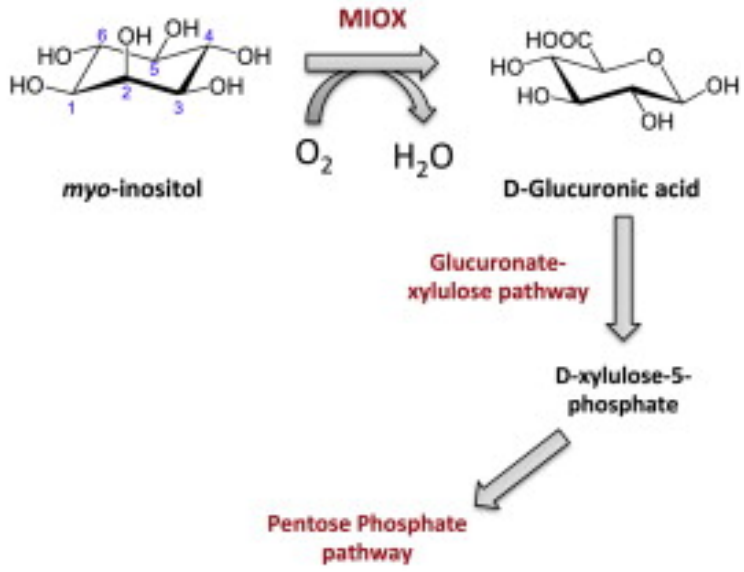
Uptake da fluido extra-cellulare (myotransporters)



MI de novo BIOSYNTHESIS from D-glucose



PHOSPHATIDYLINOSITOL synthesis from MI



MI CATABOLISM in kidney

Quali evidenze ?

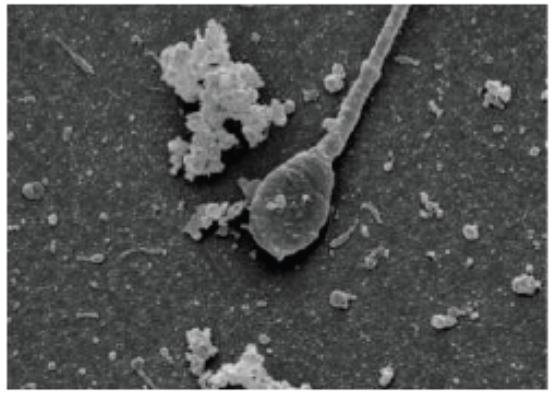
Esiste un paziente ideale ?

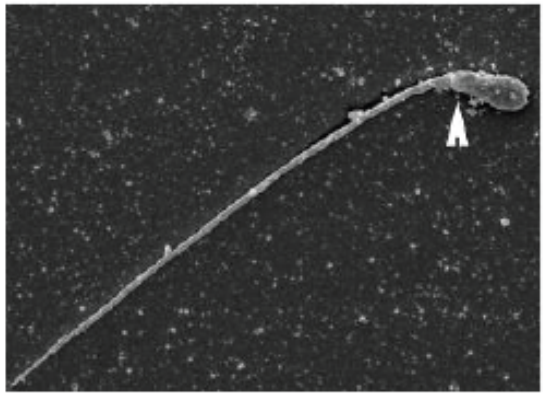
MYO-INOSITOLO: EFFETTI IN VITRO SUL SEME

AZIONE SU :MORFOLOGIA

PRIMA **DOPO MYO-INOSITOLO**

CTR

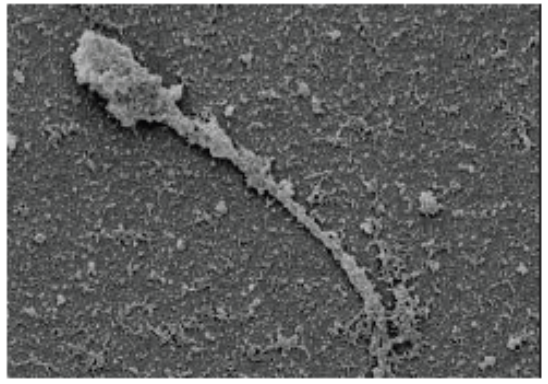


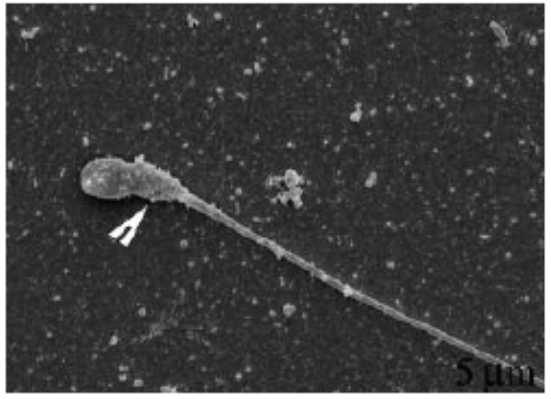


Assenza di materiale amorfo associato ad alterazioni della viscosità.

PRIMA **DOPO MYO-INOSITOLO**

OAT





Incremento del volume della guaina mitondriale, in campioni sia sani che patologici

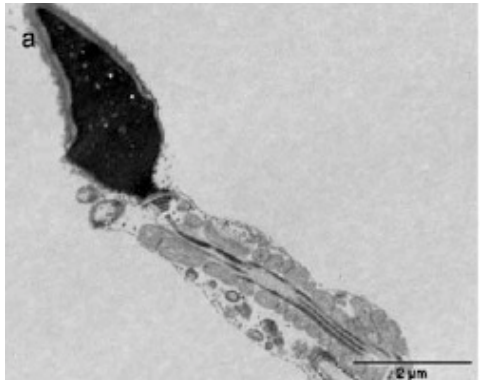
Colone M et al, Inositol activity in oligoasthenoteratospermis. An in vitro study, Eur Rew Med Pharm Sci., 2010

Microscopia SEM

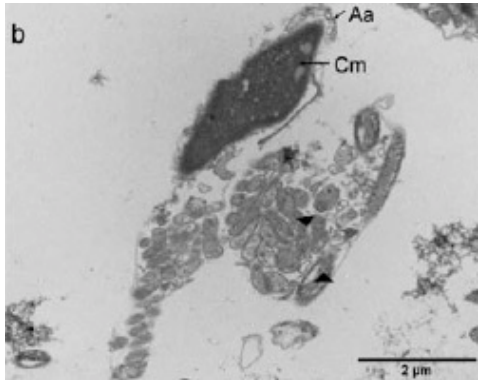
MYO-INOSITOLO: EFFETTI IN VITRO SUL SEME

Seme di pazienti OAT incubato con Myo mostra morfologia mitocondriale più simile al seme di soggetti sani

a. CONTROLLO

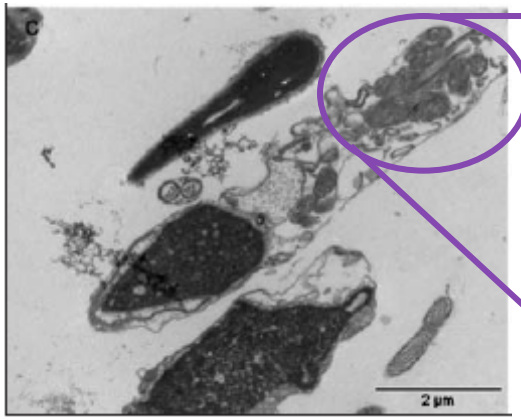


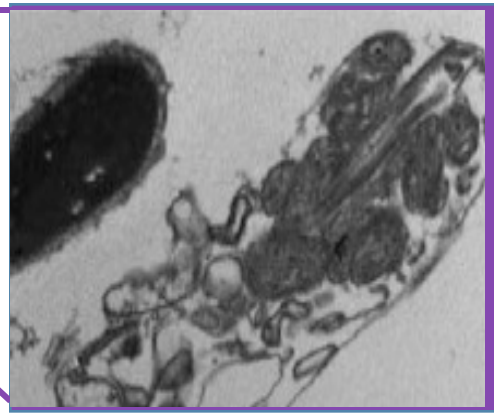
b. OAT



Microscopia TEM

c. OAT trattato con inositolo

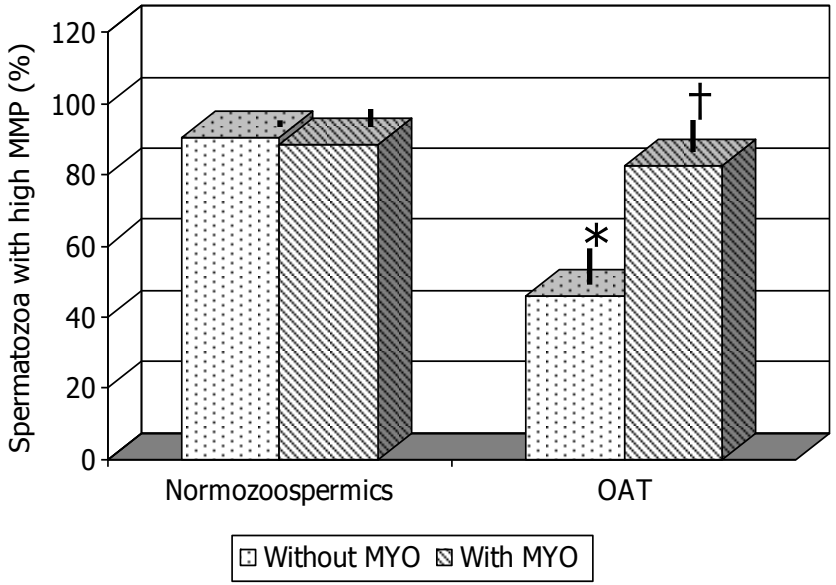




Ingrandimento del tratto intermedio di spermatozoo OAT trattato

Colone M et al. Inositol activity in oligoasthenoteratospermia – An in vitro study. Eur Rev for Med and Pharmacol Sci. 2010; 14:891-6

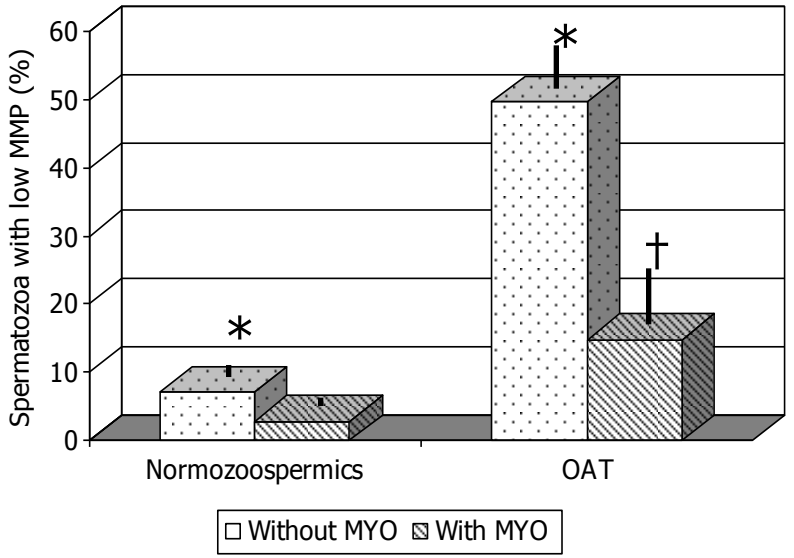
MYO-INOSITOLO: EFFETTI IN VITRO SUL SEME



*p<0.05 vs. Normo without MYO
†p<0.05 vs. OAT without MYO

% di spz con elevato PMM aumento significativo dopo incubazione con MYO nei pz con OAT

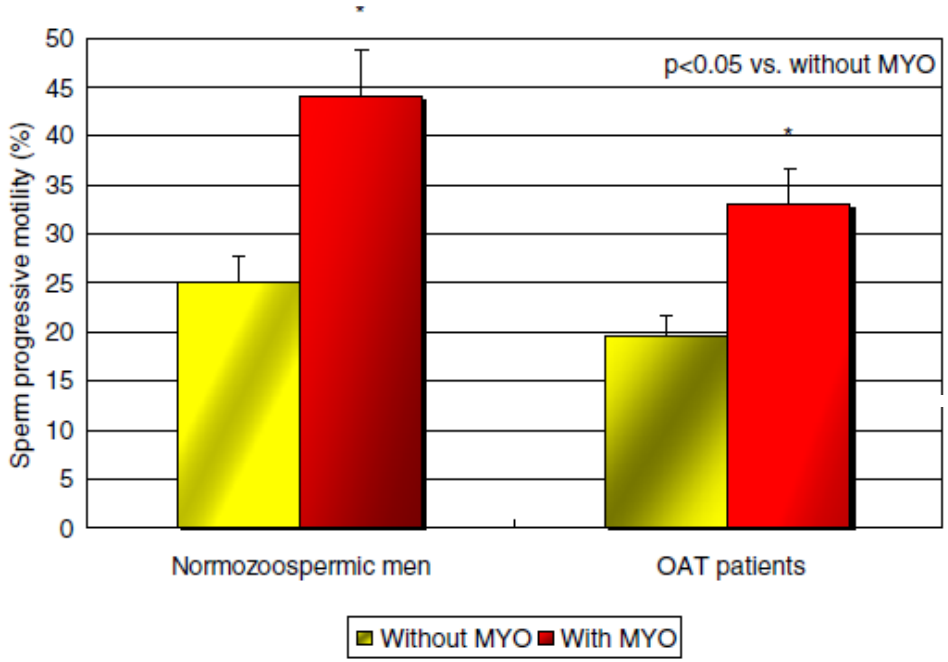
% di spz con basso PMM riduzione significativa dopo incubazione con MYO (normali e OAT)



*p<0.05 vs. Normo without MYO
†p<0.05 vs. OAT without MYO

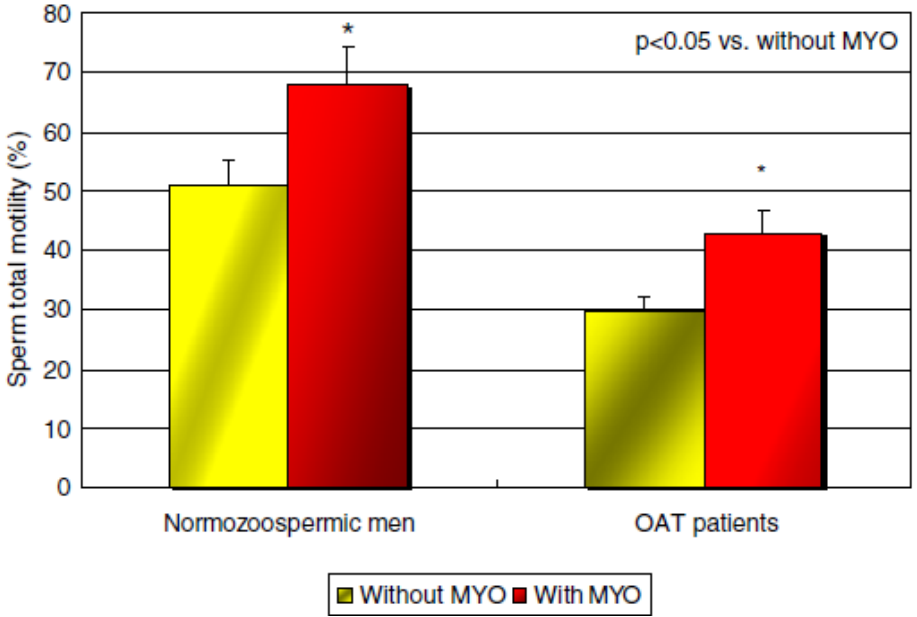
Condorelli et al., Effects of myoinositol on sperm mithocondrial function in vitro, Eur Rew Med Pharmacol Sci,2011

MYO-INOSITOLO: EFFETTI IN VITRO SUL SEME



Aumento significativo della MP

Aumento significativo della MT

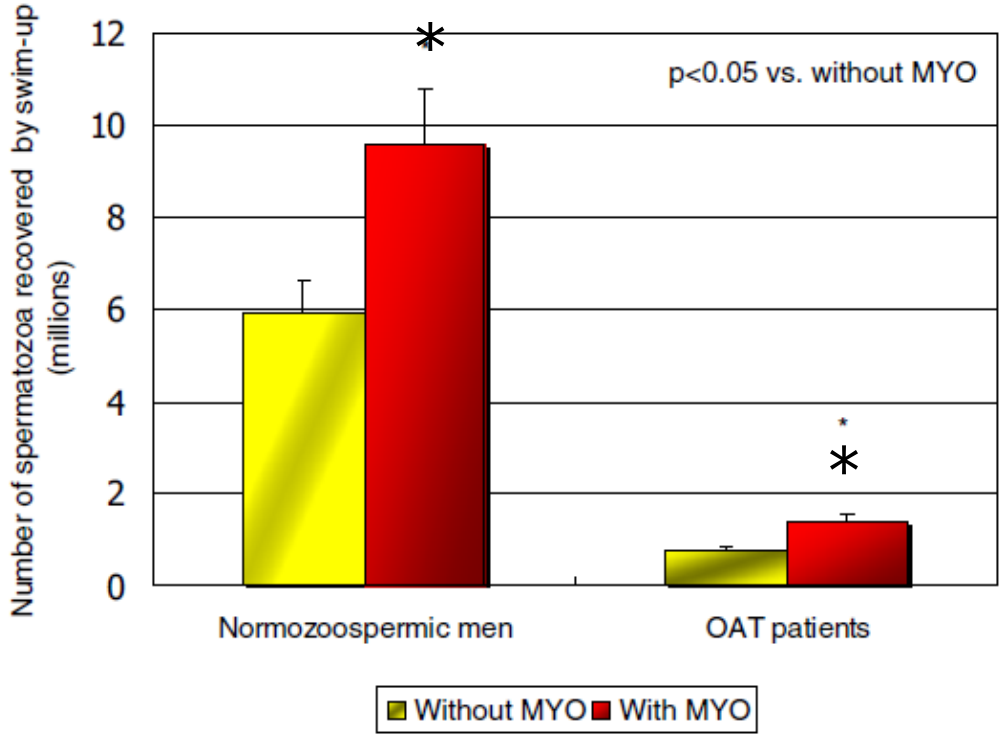


Condorelli et al., Urology. 2012 Jun;79(6):1290-5.

MYO-INOSITOLO: EFFETTI IN VITRO SUL SEME

Dopo swim up aumento del 70% di spz mobili progressivi dopo incubazione con MYO (nei normo)

Dopo swim up aumento del 91% di spz mobili progressivi dopo incubazione con MYO (nei pz OAT)



Condorelli et al., Urology. 2012 Jun;79(6):1290-5.

*p<0.05 vs. without MI

Esistono evidenze cliniche ?

Myoinositol improves sperm parameters and serum reproductive hormones in patients with idiopathic infertility: a prospective double-blind randomized placebo-controlled study

[1]A. E. Calogero, [2]G. Gullo, [1]S. La Vignera, [1]R. A. Condorelli and [3]A. Vaiarelli

[1]Section of Endocrinology, Andrology and Internal Medicine, Department of Clinical and Experimental Medicine, University of Catania, Catania, [2]Dipartimento di Ostetricia Ginecologia e Medicina Interna, Università degli Studi di Messina, and [3]Reproductive Medicine Unit, Policlinico Universitario di Messina, Messina, Italy

ANDROLOGY

ISSN: 2047-2919

ANDROLOGY

double-blind, randomized, placebo-controlled trial

Table 1 BMI, hormonal values and sperm parameters at baseline in patients treated with myoinositol or placebo

Parameters	Myoinositol ($n = 98$)		Placebo ($n = 96$)	
	Before treatment	After treatment	Before treatment	After treatment
BMI (kg/m^2)	26.6 ± 2.7	25.9 ± 2.5	26.8 ± 2.4	26.4 ± 2.2
LH (IU/L)	12.1 ± 2.6	8.8 ± 2.6*	12.4 ± 2.4	12.6 ± 2.4
FSH (IU/L)	16.7 ± 4.1	10.7 ± 4.1*	16.6 ± 4.1	16.8 ± 4.2
Prolactin (pmol/L)	374 ± 120	368 ± 118	361 ± 123	365 ± 121
Inhibin (ng/L)	86.0 ± 24.0	105.0 ± 28.0*	87.0 ± 25.0	88.0 ± 25.0
Testosterone (nmol/L)	15.8 ± 5.4	18.6 ± 5.6	15.6 ± 4.8	15.8 ± 4.6
Ejaculate volume (mL)	2.7 ± 1.3	2.7 ± 1.4	2.8 ± 1.4	2.7 ± 1.7
Sperm concentration (million/mL)	20.2 ± 4.6	26.4 ± 4.4*	20.4 ± 4.4	20.8 ± 4.3
Total sperm count (spermatozoa/ejaculate)	46.6 ± 12.6	57.6 ± 14.4*	47.2 ± 12.2	47.8 ± 11.2
Progressive motility (%)	22.2 ± 2.1	27.6 ± 1.8*	22.3 ± 2.6	23.3 ± 2.1
Acrosome-reacted spermatozoa (%)	34 ± 8	41 ± 11*	35 ± 8	36 ± 10

BMI, Body mass index; LH, luteinizing hormone; FSH, follicle-stimulating hormone. *$p < 0.05$ vs. after treatment with placebo.

2 g of MI and 200 µg of folic acid **folic acid alone**

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2016, Article ID 1674950, 5 pages
http://dx.doi.org/10.1155/2016/1674950

Clinical Study

Effect of Myoinositol and Antioxidants on Sperm Quality in Men with Metabolic Syndrome

Table 1: Metabolic and hormone profiles before and after treatment.

Analysis	Before	After	*P* value
Metabolic profile			
BMI (kg/cm^2)	28.1 ± 3.5	27.0 ± 3.1	NS
WC (cm)	107.1 ± 4.2	105.3 ± 3.3	NS
Triglycerides (mg/dL)	175.4 ± 12.5	173.2 ± 13.4	NS
HOMA index	2.8 ± 1.2	1.6 ± 0.7	<0.001
SBP	135.3 ± 12.7	128.9 ± 11.0	NS
DBP	91.2 ± 9.2	82.6 ± 9.3	NS

Table 2: Semen analysis before and after treatment.

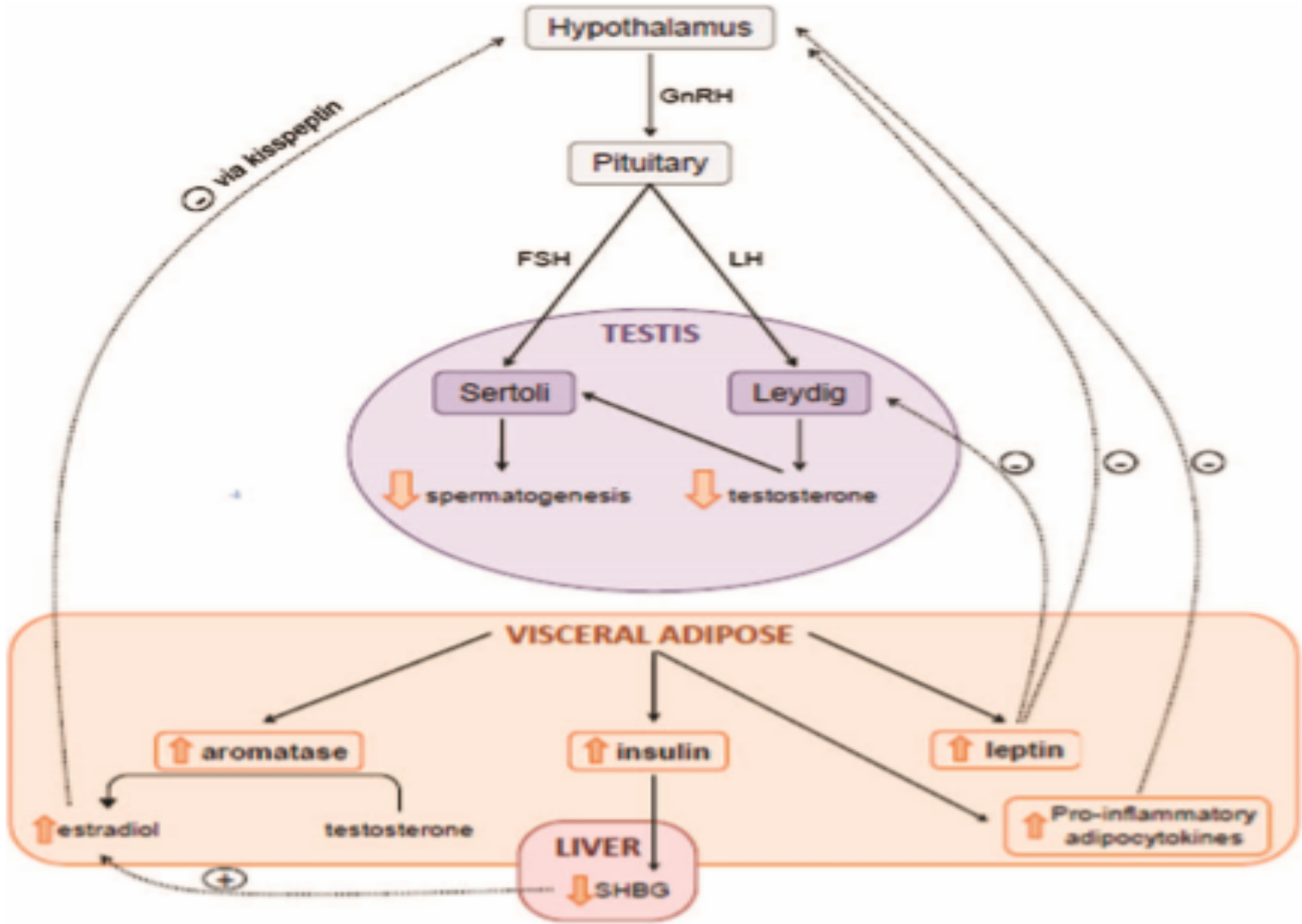
Semen parameter	Before	After	*P* value
Concentration (10^6/mL)	16.2 ± 3.4	20 ± 4.2	<0.001
Motility (%)	39.6 ± 6.1	51.4 ± 7.2	<0.001
Normal morphology (%) (normal)	24.9 ± 2.0	30.1 ± 2.3	<0.001

Data are mean ± standard deviation.

Hormone and metabolic profiles as well as semen parameters were evaluated in the relevant study at the beginning and after three months of therapy. The patients were treated by a dietary supplement administered twice a day containing 1 g MI, 30 mg L-carnitine, L-arginine and vitamin E, 55 μg selenium, and 200 μg folic acid (Andrositol, Lo.Li. Pharma s.r.l., Rome).

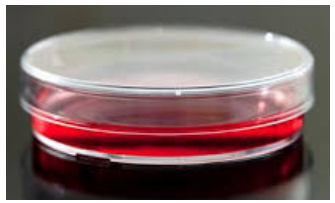
Human Fertility, 2015; 18(3): 184–193

ISSN 1464-7273 print/ISSN 1742-8149 online
DOI: 10.3109/14647273.2015.1070438



MYO-INOSITOLO

IN VITRO



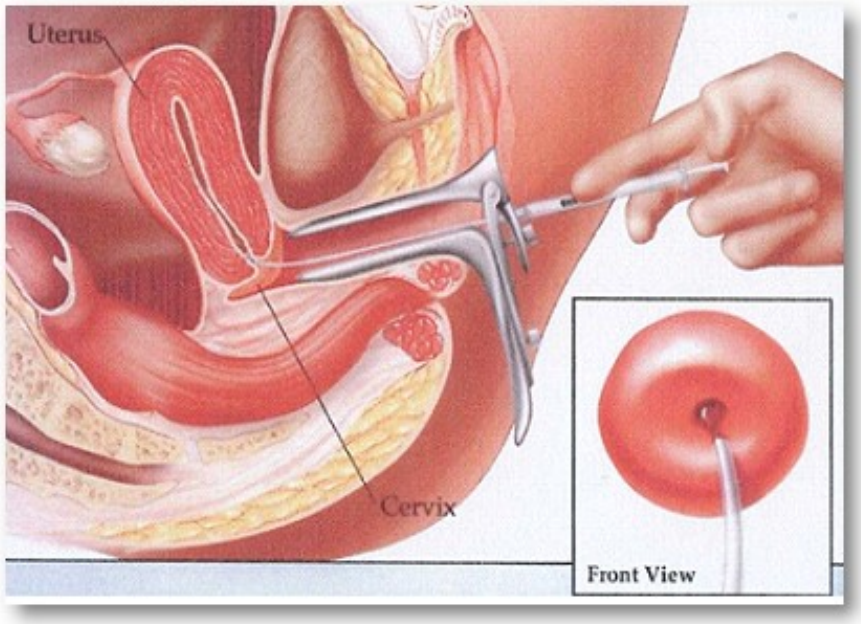
MYO-INOSITOLO
in ovuli vaginali

IN VIVO

Int J Endocrinol 2016;2016:7621942. doi: 10.1155/2016/7621942.

POST-COITAL TEST

Nasce come test diagnostico per valutare l'interazione spermatozoo-muco cervicale



PROCEDURA del post-coital test:

- introdurre in vagina uno speculum
- aspirare un campione di muco dal canale endo-cervicale
- depositarlo su vetrino porta-oggetto, coprirlo con vetrino copri-oggetto ed esaminarlo

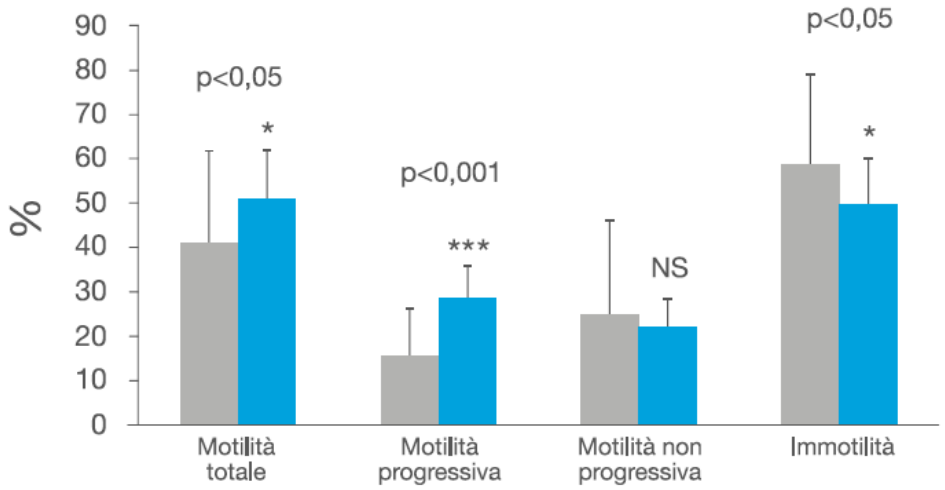
ANALISI:

-Motilità spermatica
-Proprietà del muco
-pH

Int J Endocrinol 2016;2016:7621942. doi: 10.1155/2016/7621942.

RISULTATI DA POST-COITAL TEST:
Analisi motilità spermatica

SUL SEME



1°CICLO CTRL

2°CICLO MYO-INOSITOLO

INCREMENTO

significativo della motilità progressiva e totale

Int J Endocrinol 2016;2016:7621942. doi: 10.1155/2016/7621942.

POSOLOGIA

1 ovulo a giorni alterni, preferibilmente la sera prima di coricarsi da giorno 11 in un ciclo regolare di 28 giorni

PROGRAMMARE IL RAPPORTO SESSUALE IL GIORNO SUCCESSIVO ALLA SOMMINISTRAZIONE DELL'OVULO

Dispositivo medico di classe I: ***3 ovuli vaginali da 1 gr***
2 mg di MYO-INOSITOLO

Int J Endocrinol 2016;2016:7621942. doi: 10.1155/2016/7621942.

European Review for Medical and Pharmacological Sciences 2017; 21 (2 Suppl): 60-61

Editorial – Modern approach to the infertile male: the use of andrositol® test (myo-inositol in diagnostics)

M. NORDIO

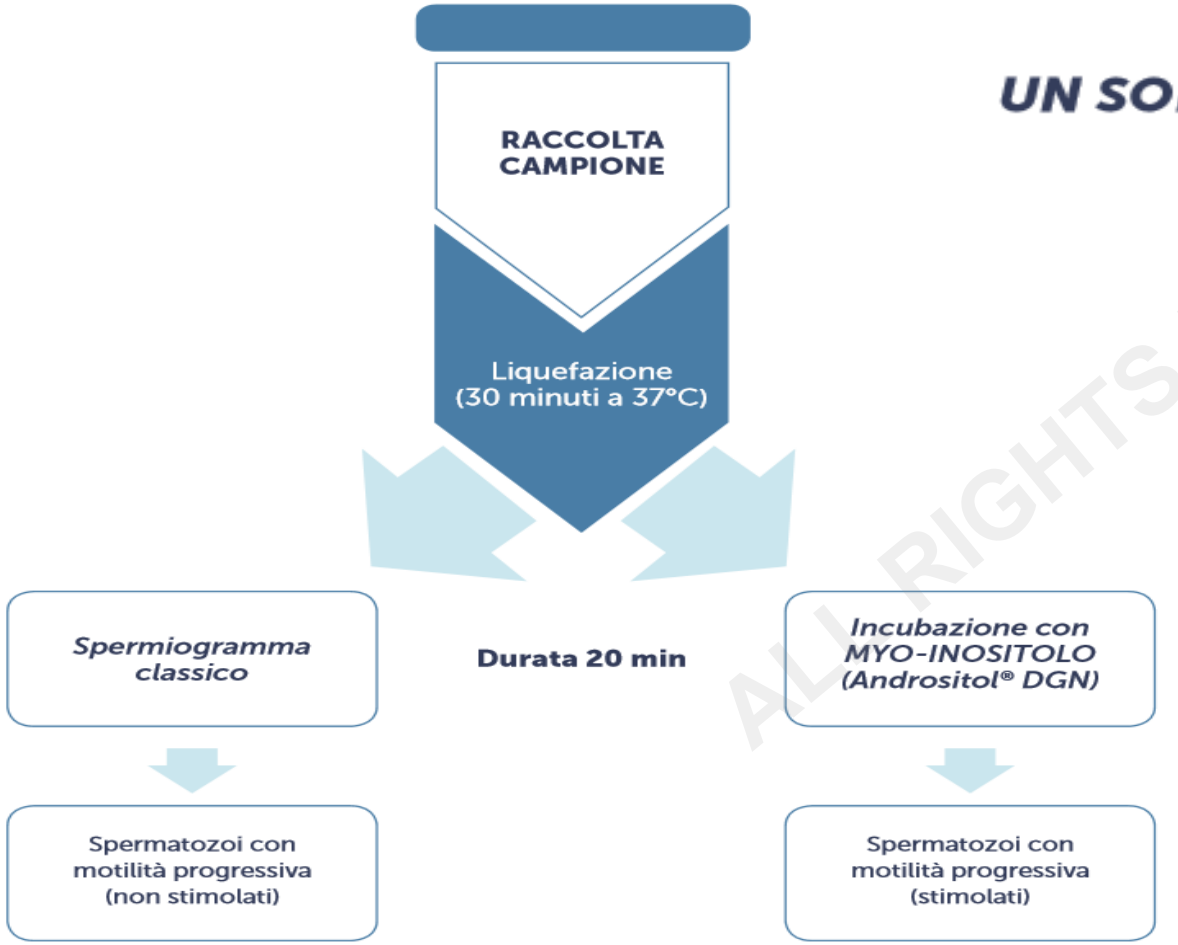
Dispositivo medico CE

Andrositol DGN 66x (µl)	VOLUME FINALE (ml)
15	1
30	2
45	3
75	5
150	10

Concentrazione finale 2 mg/ml

ANDROSITOL® Test

European patent N:2764361



UN SOLO CAMPIONE PER UN'ANALISI COMPLETA

- La fiala, una volta aperta, può essere utilizzata per 15 minuti e poi va buttata
- Una volta fatta la diluizione, la molecola di inositolo è stabile anche dopo i 15 minuti
- Dopo l'aggiunta di myo-inositolo, si lascia il campione ad incubare a 37°C per 20-30 minuti

ANDROSITOL® Test

European patent N:2764361

ESEMPIO:

a. Numero spermatozoi con motilità progressiva prima del trattamento con Andrositol DGN: 60

b. Numero spermatozoi con motilità progressiva dopo trattamento con Andrositol DGN: 90

Incremento % = (b-a)/a*100

Incremento % = (90-60)/60*100 = 50% (Medium Responder)

Interpretazione del risultato

Low responder: paziente non compromesso – molti spermatozoi con alto potenziale di membrana mitocondriale;

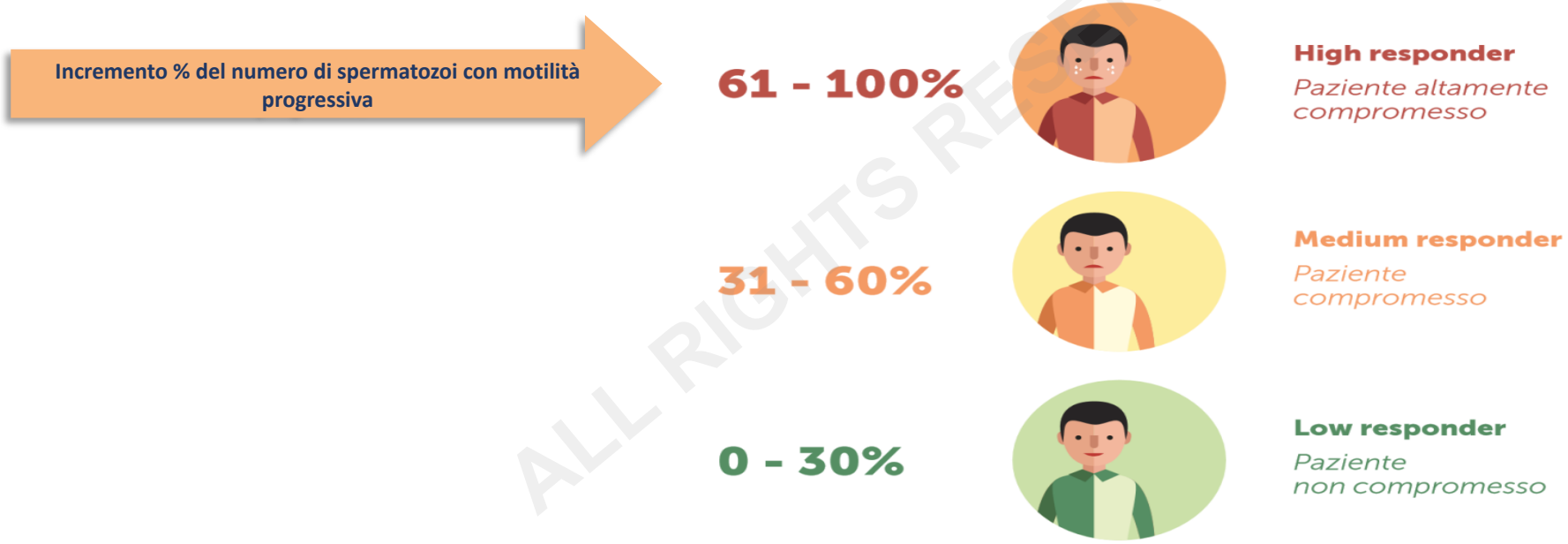
Medium responder: paziente compromesso - molti spermatozoi con basso potenziale di membrana mitocondriale;

High responder: paziente altamente compromesso - quasi tutti gli spermatozoi con basso potenziale di membrana mitocondriale.

ANDROSITOL® Test

European patent N:2764361

L'ANDROSITOL® TEST sfrutta la proporzione diretta tra carenza di myo-inositolo e incremento del numero di spermatozoi con motilità progressiva, **per riclassificare i liquidi seminali**



Questo **permette di distinguere, tra campioni identici allo spermiogramma** (ad es. i normospermici), **quelli carenti in MYO-INOSITOLO** e quindi funzionalmente e qualitativamente peggiori

A chi suggerire MYO ?
(in tema di infertilità maschile)

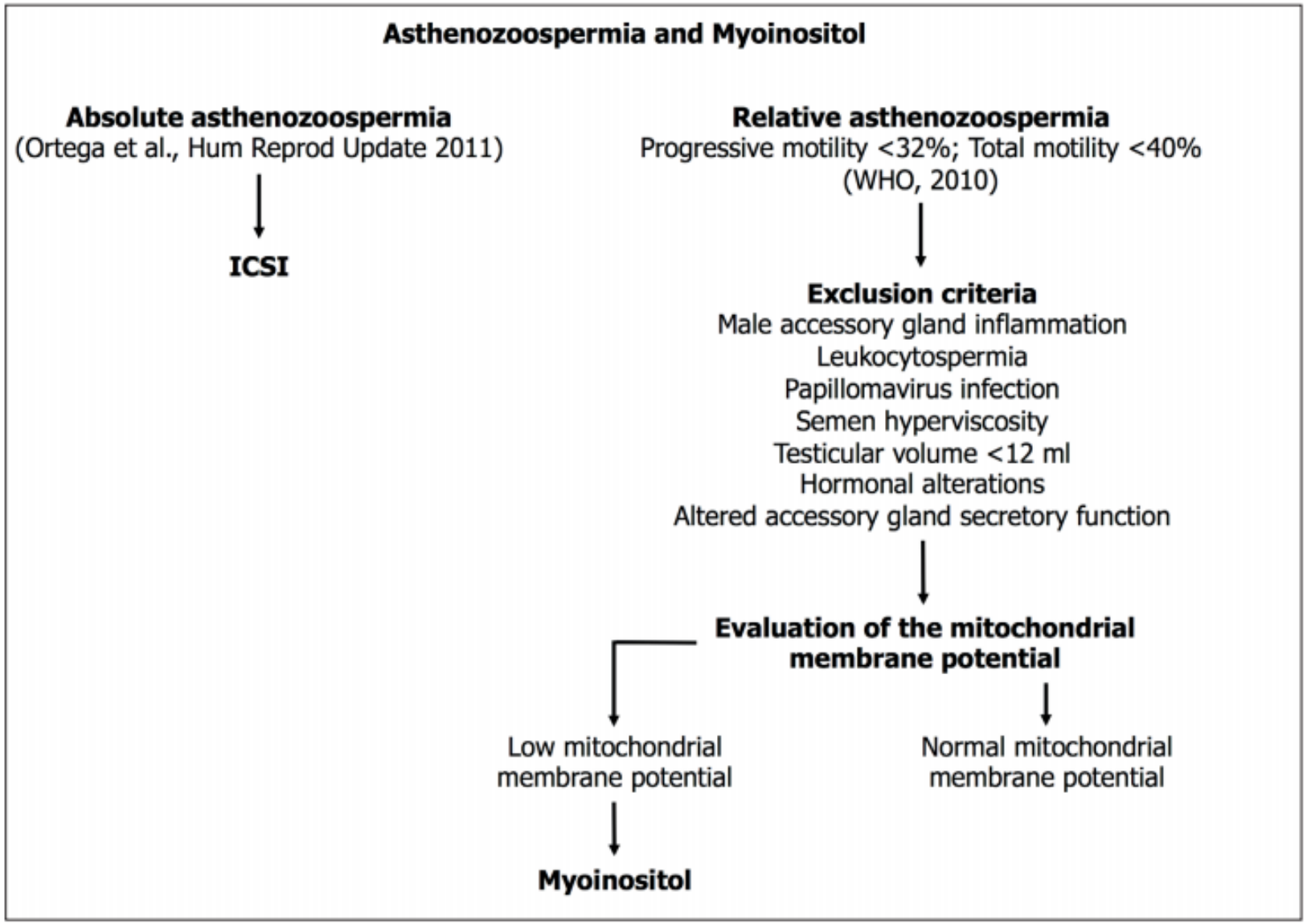


Figure 1. Possible use of MYO it patients with asthenozoospermia.

Condorelli et al., 2017

ARTICLE IN PRESS

Reproductive BioMedicine Online (2015) ■■, ■■–■■

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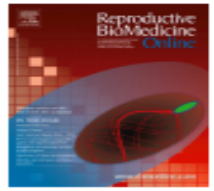

ARTICLE

Prevalence of human papilloma virus infection in patients with male accessory gland infection

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Abstract The frequency of human papillomavirus (HPV) infection in the semen of patients with male accessory gland infection (MAGI) was evaluated. One hundred infertile patients with MAGI were classified into group A: patients with an inflammatory MAGI ($n = 48$) and group B: patients with a microbial form ($n = 52$). Healthy age-matched fertile men (34.0 ± 4.0 years) made up the control group ($n = 20$). Amplification of HPV DNA was carried out by HPV-HS Bio nested polymerase chain reaction for the detection of HPV DNA sequences within the L1 ORF. Ten patients in group A (20.8%) and 15 patients in group B (28.8%) had a HPV infection; two controls (10.0%) had HPV infection. Patients with MAGI had a significantly higher frequency of HPV infection compared with controls; patients with a microbial MAGI had significantly higher frequency of HPV infection compared with patients with an inflammatory form (both $P < 0.05$). Patients with MAGI and HPV had a slight, but significantly lower sperm progressive motility and normal morphology compared with patients with MAGI HPV-negative ($P < 0.05$). Elevated frequency of HPV infection occurred in patients with MAGI, suggesting that HPV should be investigated in the diagnostic work-up of these patients.

KEYWORDS: HPV, MAGI, Prevalence

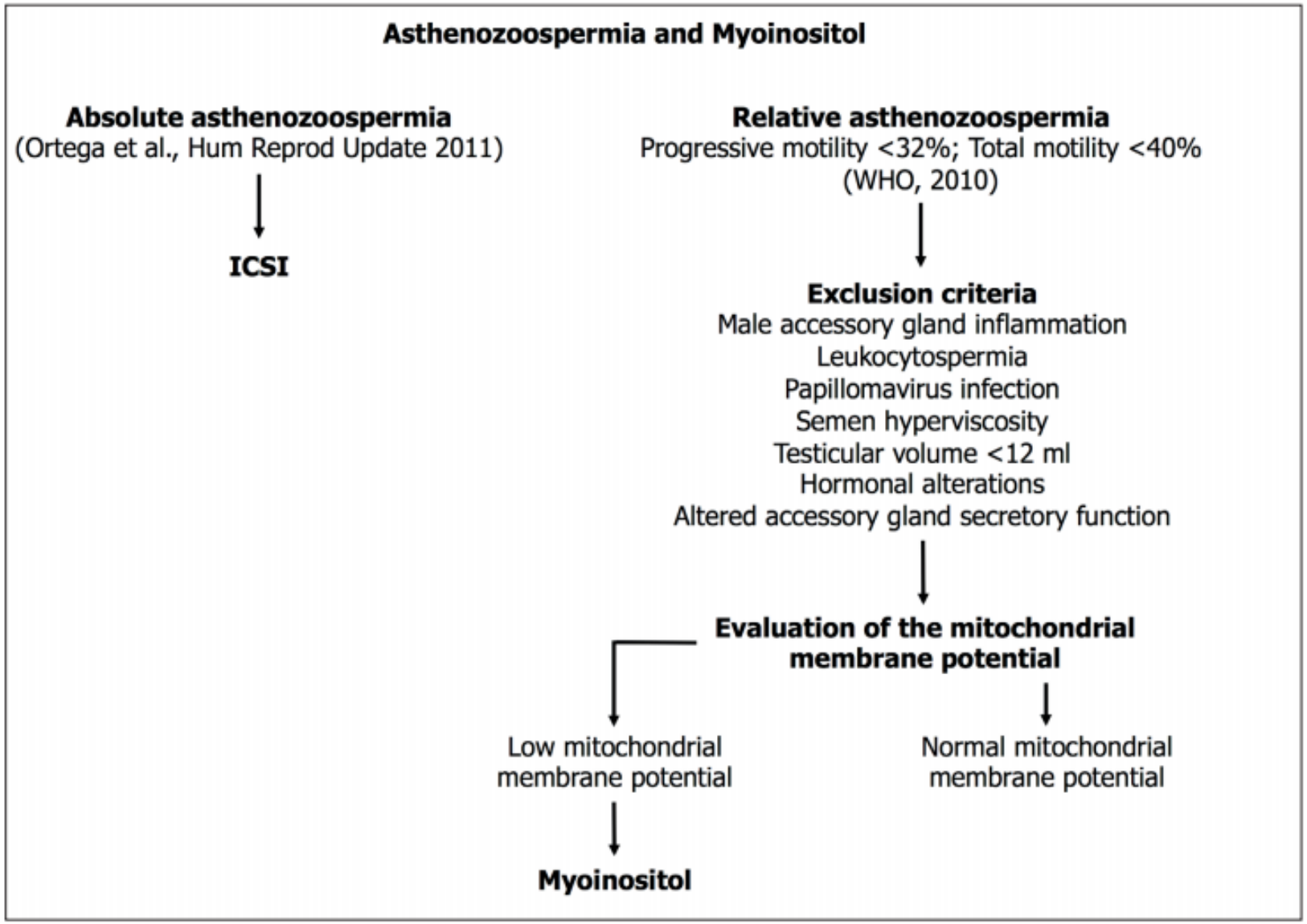
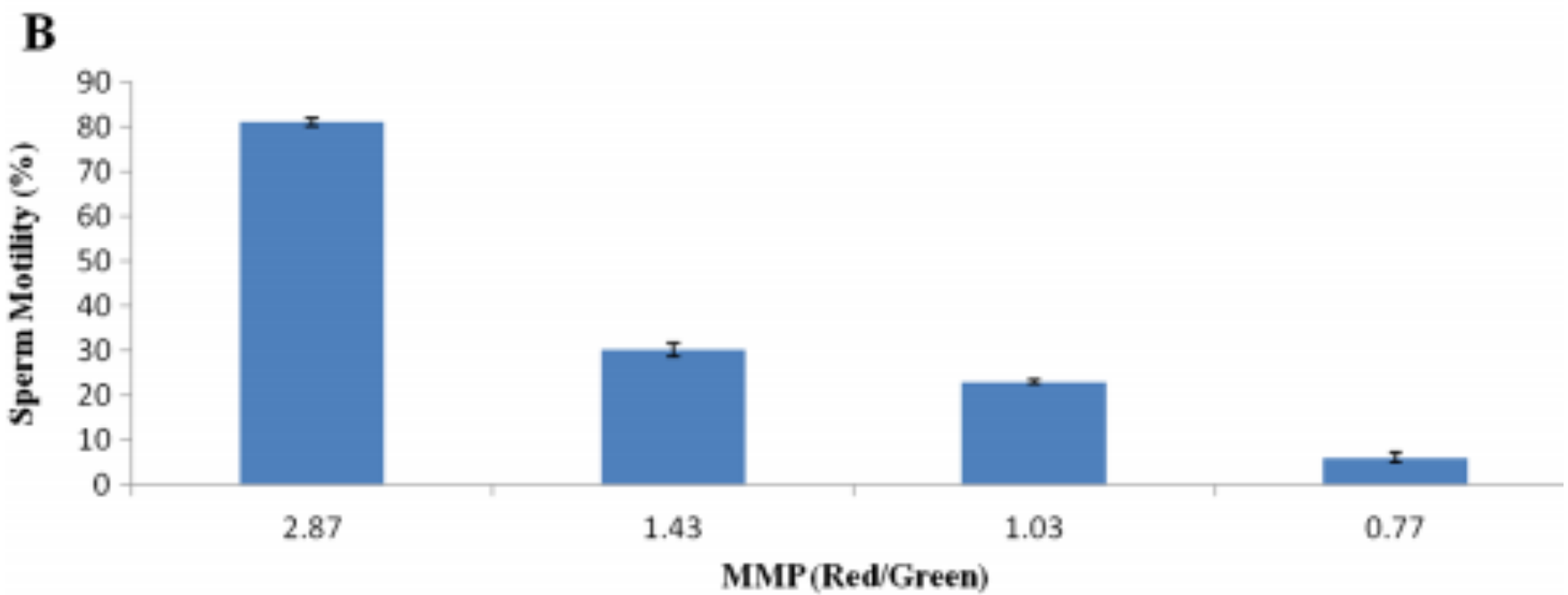


Figure 1. Possible use of MYO it patients with asthenozoospermia.

Condorelli et al., 2017

Mitochondrial membrane potential (MMP) regulates sperm motility

In Vitro Cell.Dev.Biol.—Animal (2016) 52:953–960
DOI 10.1007/s11626-016-0061-x



J Endocrinol Invest
DOI 10.1007/s40618-017-0699-6

CONSENSUS STATEMENT

The use of nutraceuticals in male sexual and reproductive disturbances: position statement from the Italian Society of Andrology and Sexual Medicine (SIAMS)

A. E. Calogero[1] · A. Aversa[2] · S. La Vignera[1] · G. Corona[3] · A. Ferlin[4]

Fertility

Recommendation

1. We recommend not prescribing antioxidants for improving sperm parameters and pregnancy rate in all subjects with sperm abnormalities before a specific diagnostic workup (1 ØØØØ).
2. We suggest the use of antioxidants in patients with idiopathic infertility in the presence of documented abnormal sperm parameters and altered sperm DNA fragmentation (SDF) only after a thorough diagnostic workup (2 ØØOO).
3. We suggest no specific antioxidants and therapeutic regimes for improving sperm parameters and pregnancy rate in patients with idiopathic infertility (2 ØØOO).

Table 1 Main nutraceuticals used for the treatment of male infertility

Nutraceuticals	Evidence	Possible indications
Ascorbic acid (vitamin C)	Its administration positively correlates with sperm count and motility [38], and negatively with sperm DNA fragmentation index [39]	Oligo-astheno-teratozoospermia
Carnitine	Improves concentration, total sperm count, and progressive motility [40–45]	Oligo-astheno-teratozoospermia
Carotenoids (lycopene, β-carotene)	Improve sperm parameters [46]	Oligo-astheno-teratozoospermia
Coenzyme Q10	Improves sperm count, motility, and morphology [47–50]	Oligo-astheno-teratozoospermia
Myoinositol	Improves sperm progressive and total motility and the mitochondrial function; increases the number of sperm recovered after swim-up technique [51–53]	Oligo-astheno-teratozoospermia
Glutathione	Improves sperm concentration, motility, and morphology [54, 55]	Oligo-astheno-teratozoospermia
N-acetyl-cysteine	Improves sperm volume, viscosity [56, 57] and motility. Prevents oxidative DNA damage [13]	Oligo-astheno-teratozoospermia
α-Tocopherol (vitamin E)	Increases sperm motility [58]	Oligo-astheno-teratozoospermia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Centro di Eccellenza SIAMS in Andrologia e Medicina della Sessualità (CEAMS)