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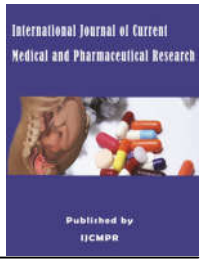

EFFECT OF PROTON PUMP INHIBITORS ON MALE FERTILITY

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ABSTRACT

Proton pump inhibitors are the most commonly used drugs for the treatment of acid peptic disorder, GERD, NSAID induced mucosal injury Z.E.syndrome and for H.pylori infection. They have been recommended to limit the extension of malignancy and reduce chemoresistance due to their property of inhibiting V- ATPases. PPIs inhibit V-ATPase and promote amyloid beta peptide formation which results in to Alzheimer disease. Infertility rate due to male counterpart is increasing. Epididymal luminal acidic pH is essential for keeping sperms in quiescence during their storage and maturation to prevent their premature entry and activation in to seminal vescicles which leads to sperm dysfunction. Specific subunits of V-ATPases present in clear cells of cauda epididymis play a crucial role in luminal acidification. These subunits are B,a4,A and E2 which are highly expressed in the clear cells of human epididymis whose inhibition by drugs like PPIs can result in to male infertility. Acrosomal membrane of sperm possess E1 and a2 isoforms of V-ATPase which are essential of intra acrosomal acidic pH necessary for processing protease zymogen needed for sperm penetration and fertilization of ovum. Their inhibition by PPI can also lead to male infertility. Long term use of PPIs is known to reduce Vit B 12 absorption which in turn affects sperm function. Many studies have observed positive effect of Vit B 12 supplementation on sperm count, morphology, maturity, motility and their DNA. It reduces reactive oxygen species in the sperms and prevent their malfunction. Vit B 12 deficiency results in to hyper homocysteinemia reduces no generation and sperm function. Thus long term use of PPIs can lead to male infertility.

INTRODUCTION

Proton pump inhibitors are commonly used drugs for treating acid peptic disorders like peptic ulcer, gastro oesophageal reflux disorders, NSAID induced mucosal injury, Zollinger Ellison syndrome and Helicobactor pylori infection.[1] They are also recommended in the treatment of malignancy to limit the tumour invasion and reduce the chemo-resistance due to their ability to inhibit vacuolar ATPases [V-ATPases] [2]Studies have demonstrated that PPIs can interfere with the degradation of amyloid beta peptide [Aβ peptide] in Alzheimers disease.[3] Clearance of fibrillar Aβ by microglia depends upon its pH and is induced by the acidification of lysosomes. PPIs are known to inhibit microglial V-ATPase proton pumps which are essential for acidic environment and result in to reduced Aβ degradation and increased Aβ levels which are the pathological features of Alzheimer's disease[4-6]V-ATPase are large multi subunit proton pumps present in eukaryotic cells. These are essential for the housekeeping acidification of membrane bound compartments of these cells. Housekeeping functions of mammalian V-ATPases include acidification of endosomes, lysosomes, phagosomes. They also acidify compartments for uncoupling receptors and ligands, autophagosomes and certain elements of golgi apparatus. [7-9] Mammalian V-ATPase is composed of 13 subunits which are divided in to 8 peripheral called as V1 and 5 membrane intrinsic called as V0. Subunits of V1 contain A,B,C,D,E,F,G and H which are also labeled as ATP6V1A[A], ATP6V1B[B], ATP6V1C[C] ,ATP6V1D[D], ATP6V1E[E], ATP6V1F[F], ATP6V1G[G], ATP6V1H[H]. Subunits of V0 are as follows- a,c",c,d and e which are also expressed as ATP6V0a[a], ATP6V0b[c"], ATP6V0c[c], ATP6V0d[d] and ATP6V0e[e] [10]

Throughout the world human fertility rate has declined in the last 3 decades[11] which poses a major health problem. Large percentage of infertility is attributed to male counterpart as a result of poor sperm motility and its interaction with oocyte.[12] The sperms are formed in testicular sertoli cells under the influence of FSH. They are transported to the epididymis for storage and maturation.[13] Epididymis is morphologically and functionally divided into- initial segment, caput, corpus and cauda.[14] Epithelial linings of epididymal lumen is formed by four types of cells- narrow, clear, principle and basal cells.

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Each cell plays an important role in the concentration, maturation, storage and viability of spermatozoa.[15,16] Epididymal luminal acidic pH is essential for keeping sperms in quiescence during their storage and maturation in epididymis.[17] Acidic pH helps the sperms to remain in dormant state by inhibiting the activation of sperm specific calcium and potassium channels.[18,19] High levels of bicarbonate in seminal vesicle fluid and in the female reproductive tract activates sperm bicarbonate sensitive adenyl cyclase and elevate cAMP in the sperm and increases their motility.[20.21] Thus pH and bicarbonate regulate sperm function. Defective acidification in epididymal lumen leading to elevation of pH and bicarbonate affects sperm maturity and enhances it's premature activation resulting into sperm dysfunction and male infertility. Clear cells are numerous in cauda epididymis and play a crucial role in the acidification in lumen where spermatozoa are stored. Specific subunits of V-ATPase like B, a4, A and E2 are highly expressed isoforms in the clear cells.[22] In additions to rat and mice, clear cells in human epididymis also express V-ATPase and their malfunction leads to sperm dysfunction and male infertility.[17] E1 and a2 isoforms of V-ATPase are located in the acrosomal membrane of the sperm. These V-ATPase isoforms are essential for intra acrosomal acidic pH which is necessary for processing protease zymogen required for sperm penetration and fertilization of ovum. Acrosome is the acidic secretory vesicle which contains hydrolytic enzymes that play a crucial role in the passage of sperm across the zona pellucida of ovum. Assembly of V-ATPase and presence of specific isoforms E1 and a2 are responsible for acrosomal acidification. [23,24]

The V-ATPase is a multi subunit enzyme which couples ATP hydrolysis to the pumping of protons across plasma membranes in eukaryotic cells. It is ubiquitously expressed. It governs the acidification of highly differentiated organelles including golgi apparatus, endosomes and secretory vesicles.[25-27] It is also found in high concentration in the plasma membrane of specialized epithelial cells. They play an important role in renal acidification, [27] bone resorption,[28] and spermatozoa capacitation.[5] Subtype of V-ATPase – ATP6 v0a2 / a2 in spermatozoa has an important role in the fertilization.[29] It is highly expressed in normal spermatozoa and weakly in spermatozoa of infertile men and also highly expressed in motile spermatozoa than in immobile one. It was found that expression of this subtype is greater in the eggs fertilized by spermatozoa than in the unfertilized eggs.[29] It was found to be localized predominantly in the acrosomal region of human normal spermatozoa and is involved in pH modulation of spermatozoa.[29] Plasma membrane V- ATPase regulates pH of intracellular organelles which play a role in the motility of spermatozoa.[30] and is responsible for acidification of acrosomal region.[31] ATP6v0a2 possibly plays a role in sperm function as pH sensor.[32] Plasma membrane V-ATPase functions in renal pH homeostasis, bone resorption and sperm maturation. It plays role in tumour metastasis also.[33,34] V-ATPase is localized in the apical membrane of epidydymal clear cells and plays an important role in keeping seminal fluid at low pH which is essential for normal maturation and storage of sperm.[5] PPIs are known to inhibit VATPases. By inhibiting epididymal V-ATPases and raising intra luminal pH locally, they can adversely affect sperm maturation, function and fertility. Components of renin angiotensin system-angiotensin I [ANG I] and angiotensin II [ANG II] are present in epididymal lumen. Angiotensin converting enzyme [ACE] exists in two forms.[35,36] These are testicular [tACE] also called as germinal ACE and somatic ACE. ANG I is converted in to ANG II by enzyme ACE. Male mice were found to be infertile due to the absence of tACE. This was as a result of sperm dysfunction and not due to its production which points towards dysfunction at post testicular tract. [37] Testicular ACE is bound to immature sperm and then gets released in to luminal fluid when sperm starts moving along epididymal fluid in the epididymal tubule.[38] Luminal ANG II interacts with ANG II type receptors and stimulates clear cells. This is followed by activation of nitric oxide [NO] cGMP pathway. Subsequently the apical accumulation of V-ATPase is triggerd by elevated cGMP in the microvilli.[39]PPIs have been shown to inhibit NO synthesis in epididymis. Apical accumulation of V-ATPases is dependent on NO c-GMP pathway. Hence PPI can affect NO c-GMP pathway and apical accumulation of V-ATPase reflecting into intra luminal pH rise in epididymis and affecting sperm motility and function. Long term use of PPIs have been associated with adverse effects like hypochlorhydria, achlorhydria, interstitial nephritis, gastro intestinal infections like that of clostridium difficile, osteoporosis and fractures, increased cardiovascular mortality due to inhibition of NO synthesis, dementia and decreased absorption of Vit B12,iron and magnessium .[1,40-42]

Role of Vitamin B12 in semen quality-Vitamin B12 is an important component of human cellular metabolism, and is essential for DNA synthesis.[43] Gastric achlorhydria and decreased availability of intrinsic factor results into the decreased Vit B12 absorption and its deficiency. Vit B12 is a co enzyme for methionine synthase enzyme which is required for synthesis of methionine from homocysteine to complete S-adenosyl methionine (SAM) cycle.[44] Conversion of SAM to S–adenosyl homocysteine results into methylation of functional units of human cells like DNA, RNA, amino acids proteins, lipids and neurotransmitters.[44,45] Vit B12 deficiency can arise as a result of malabsorption, malnutrition and due to drugs like proton pump inhibitors which elevate intragastric pH and decrease absorption of Vit B12.

In humans, Vit B12 plays an important role in spermatogenesis and in maintaining quality of semen.[46,47] It was observed that plasma Vit B12 concentration was lower in infertile men.[48,49] Various studies have confirmed the positive effect of Vit B12 on the parameters like sperm count, its motility, morphology and sperm DNA.[50-52] In these human studies, Vit B12 was administered in the form of methyl cobalamine in the dose of 1500 microgram per day. In two studies dose of 6000 microgram per day was also administered.[48,51]Animal studies done with dose of methyl cobalamine 1000microgram per kg has resulted into marked increase in sperm count in oligospermic male rats.[53] Methyl cobalamine was also found to protect against the testicular damage induced by ethylene oxide.[54] Low levels of Vit B12 reduce the catalytic activity of methionine synthase which is required for conversion of homocysteine to methionine resulting into hyper homocysteinemia.[55] Hyper homocysteinemia affects sperm quality negatively. It is also found to reduce NO production in humans by inhibiting NO synthase pathway.[56] NO synthase is present in human spermatozoa and is crucial for adequate sperm motility.[57] Thus it is possible that Vit B12 deficiency resulting into hyper homocysteinemia and reduced NO production can decrease sperm function. Increased reactive oxygen species in human semen result into enhanced oxidative injury to the sperm and its reduced count and function.[58]

Decreased Vit B12 levels in semen correlates with the increased reactive oxygen species which affect the semen quality.[59,60] Antioxidant effect of Vit B12 was found to prevent lipid peroxidation of sperm membrane under stressful conditions.[61] Studies have found powerful antioxidant activity of Vit B12.[62]In human body creatine is synthesized from the amino acids like arginine and glycine, the combination of which produce guanidinoacetate which gets methylated with the help of SAM, this being a methyl donor and produce creatine.[63,64] In human spermatozoa adenosine tri phosphate (ATP) is generated from chemical shuttle between creatine and creatine phosphate using creatine kinase.[65] Vitamin B 12 is crucial for synthesizing methionine which is a precursor of SAM. Reduced amount of SAM and amount of creatine due to low Vit B12 levels can alter sperm function by affecting rapid buffering and regeneration of ATP. Systemic inflammation is known to be associated with the reduced sperm count, sperm motility and it's abnormal morphology.[66] Supplementation of Vit B12 was found to be beneficial in the management of systemic inflammation. This suggests that Vit B12 can be beneficial to attenuate inflammation induced impairment of semen quality.[67] Similarly Vit B12 supplementation was found to control transcription factor nuclear kappa B. which is the regulator of inflammation and immune response in the sertoli cells of testis and thus prevents the excessive germ cell death and sperm loss.[67-69]

PPIs induce hypo or achlorhydria resulting in to decreased Vit B 12 absorption which is essential for sperm maturation, motility and function. Thus PPIs may affect sperm function and male fertility. Thus the long term use of PPIs in young males during their fertile age needs a careful administration of these drugs as they can affect male fertility adversely by decreasing serum levels of Vit.B 12 and by inhibition of V-ATPases in the epididymis and sperm acrosomal membrane.

References

1. Schoenfeld AJ, Grady D. Adverse Effects Associated With Proton Pump Inhibitors. *JAMA Intern Med*2016;176:172-4
2. Milito A, Canese R, Marino M, Borghi M, Lera M, Villa A. pH dependant anti tumour activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumour acidity. *Int j cancer* 2010; 127: 207-219.
3. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med* 2010;362:329-44. 19.
4. Fallahzadeh MK, Borhani Haghighi A, Namazi MR. Proton pump inhibitors: predisposers to Alzheimer disease? *J Clin Pharm Ther* 2010;35:125-6.
5. Majumdar A, Cruz D, Asamoah N, *et al*. Activation of microglia acidifies lysosomes and leads to degradation of Alzheimer amyloid fibrils. *Mol Biol Cell* 2007;18:1490-6.
6. Mattsson JP, Väänänen K, Wallmark B, *et al*. Omeprazole and bafilomycin, two proton pump inhibitors: differentiation of their effects on gastric, kidney and bone H(+)-translocating ATPases. *Biochim Biophys Acta* 1991;1065:261-8.
7. Forgac M. Vacuolar ATPases: rotary proton pumps in physiology and pathophysiology. *Nat Rev Mol Cell Biol* 2007;8:917–929.
8. Kane PM. The where, when, and how of organelle acidification by the yeast vacuolar H+-ATPase. *Microbiol Mol Biol Rev* 2006;70:177-191.
9. Wagner CA, Finberg KE, Breton S, Marshansky V, Brown D, Geibel JP. Renal vacuolar H+- ATPase. *Physiol Rev* 2004;84:1263-1314
10. Holliday S. Vacuolar H^+-ATPase: An Essential Multitasking Enzyme in Physiology and Pathophysiology. *New Journal of Science* 2014: 675430. doi:10.1155/2014/675430
11. Skakkebaek NE, Jorgensen N, Main KM, Meyts E. Rajpert-De, Leffers H, Andersson AM, *et al*. Is human fecundity declining? *Int J Androl*. 2006; 29: 2-11.
12. Aitken RJ. Sperm function tests and fertility. *Int J Androl.* 2006; 29: 69-75.
13. Cornwall GA. New insights into epididymal biology and function. *Hum Reprod Update*. 2009; 15:213-227.
14. Johnston DS, Turner TT, Finger JN, Owtscharuk TL, Kopf GS, Jelinsky SA. Identification of epididymis-specific transcripts in the mouse and rat by transcriptional profiling. *Asian J Androl*. 2007; 9: 522-527.
15. Da Silva N, Shum WWC, Breton S. Regulation of V-ATPase-dependent luminal acidification in the epididymis. *Asian J Androl*. 2007; 9: 476-482.
16. Shum WW, Da Silva N, Brown D, Breton S. Regulation of luminal acidification in the male reproductive tract via cell-cell crosstalk. *J Exp Biol*. 2009;212(Pt 11):1753-61.
17. Pastor-Soler N, Pietrement C, Breton S. Role of acid/base transporters in the male reproductive tract and potential consequences of their malfunction. *Physiology* (Bethesda). 2005; 20: 417-428.
18. Navarro B, Kirichok Y, Clapham DE, K Sper, a pH-sensitive K+ current that controls sperm membrane potential. *Proc Natl Acad Sci U S A*. 2007; 104: 7688–7692.
19. Navarro B, Kirichok Y, Chung JJ, Clapham DE. Ion channels that control fertility in mammalian spermatozoa. *Int J Dev Biol*. 2008; 52: 607–613
20. Visconti PE. Understanding the molecular basis of sperm capacitation through kinase design. *Proc Natl Acad Sci U S A*. 2009; 106: 667–668.
21. Chan HC, Ruan YC, He Q, Chen MH, Chen H, Xu WM, *et al*. The cystic fibrosis transmembrane conductance regulator in reproductive health and disease. *J Physiol*. 2009; 587: 2187–2195.
22. Pietrement C, Sun-Wada GH, Da Silva N, McKee M, Marshansky V, Brown D, *et al*. Distinct expression patterns of different subunit isoforms of the V-ATPase in the rat epididymis. *Biol Reprod.* 2006; 74: 185–194.
23. Nakanishi T, Ikawa M, Yamada S, Toshimori K, Okabe M. Alkalinization of acrosome measured by GFP as a pH indicator and its relation to sperm capacitation. *Dev. Biol*. 2001; 237:222–231.
24. Kawa G, Yamamoto A, Yoshimori T, Muguruma K, Ma tsuda T, Moriyama Y. mmunohistochemical localization of V-AT-Pases in rat spermatids. *Int. J. Androl*. 2000; 23: 278–283.
25. Futai M, Oka T, Sun-Wada G, Moriyama Y, Kanazawa H, *et al*. Luminal acidification of diverse organelles by V-ATPase in animal cells. *J Exp Biol* 2000; 203: 107–116.

26. Nelson N, Harvey WR. Vacuolar and plasma membrane proton-adenosinetriphosphatases. *Physiol Rev* 1999; 79: 361–385.
27. Wagner CA, Finberg KE, Breton S, Marshansky V, Brown D, *et al*. Renal vacuolar H+-ATPase. *Physiol Rev* 2004; 84: 1263–1314.
28. Toyomura T, Murata Y, Yamamoto A, Oka T, Sun-Wada GH, *et al*. From lysosomes to the plasma membrane: localization of vacuolar-type H+ -ATPase with the a3 isoform during osteoclast differentiation. *J Biol Chem* 2003; 278: 22023–22030.
29. Jaiswal MK, Mallers TM, Larsen B, Kwak-Kim J, Chaouat G, *et al*. V-ATPase upregulation during early pregnancy: a possible link to establishment of an inflammatory response during preimplantation period of pregnancy. *Reproduction* 2012; 143: 713–725.
30. Lishko PV, Botchkina IL, Fedorenko A, Kirichok Y. Acid extrusion from human spermatozoa is mediated by flagellar voltage-gated proton channel. *Cell* 2010; 140: 327–337.
31. Sun-Wada GH, Imai-Senga Y, Yamamoto A, Murata Y, Hirata T, *et al*. A proton pump ATPase with testis-specific E1-subunit isoform required for acrosome cidification. *J Biol Chem* 2002; 277: 18098–18105.
32. Marshansky V. The V-ATPase a2-subunit as a putative endosomal pH-sensor. *Biochem Soc Trans* 2007; 35: 1092–1099.
33. Sennoune SR, Bakunts K, Martinez GM, Chua-Tuan JL, Kebir Y, Attaya MN, *et al*. Vacuolar H+-ATPase in human breast cancer cells with distinct metastatic potential: distribution and functional activity. *Am J Physiol Cell Physiol* 2004;286:C1443–1452.
34. Hinton A, Sennoune SR, Bond S, Fang M, Reuveni M, Sahagian GG, *et al*. Function of a subunit isoforms of the V-ATPase in pH homeostasis and in vitro invasion of MDA-MB231 human breast cancer cells. *J Biol Chem* 2009;284:16400–16408.
35. Saez F, Legare C, Laflamme J, Sullivan R. Vasectomy-dependent dysregulation of a local reninangiotensin system in the epididymis of the cynomolgus monkey (Macaca fascicularis). *J Androl*. 2004; 25:784–796.
36. Corvol P, Williams TA, Soubrier F. Peptidyl dipeptidase A: angiotensin I-converting enzyme. *Methods Enzymol*. 1995; 248:283–305.
37. Hagaman JR, Moyer JS, Bachman ES, Sibony M, Magyar PL, Welch JE, *et al* Smithies O, Krege JH, O'Brien DA. Angiotensin-converting enzyme and male fertility. *Proc Natl Acad Sci U S A*. 1998; 95:2552–2557
38. Thimon V, Metayer S, Belghazi M, Dacheux F, Dacheux JL, Gatti JL. Shedding of the germinal angiotensin I-converting enzyme (gACE) involves a serine protease and is activated by epididymal fluid. *Biol Reprod*. 2005; 73:881–890.
39. Shum WW, Ruan YC, Da Silva N, Breton S. Establishment of cell-cell cross talk in the epididymis: control of luminal acidification. *J Androl.* 2011;32(6):576-86.
40. Antoniou T, Macdonald EM, Hollands S, Gomes T, Mamdani MM, Garg AX. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. *CMAJ Open* 2015; 3(2), E166–E171.
41. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. *et al*. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012;107:1011-9
42. Moledina DG, Perazella MA. Proton Pump Inhibitors and CKD. *J Am Soc Nephrol* 2016
43. Lu H, Liu X, Deng Y, Qing H. DNA methylation, a hand behind neurodegenerative diseases. *Front. Aging Neurosci.* 2013, 5, 85.
44. Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH. Homocysteine, folate, methylation, and monoamine metabolism in depression. J. Neurol. Neurosurg. *Psychiatry* 2000, 69, 228–232.
45. Banerjee RV, Matthews RG. Cobalamin-dependent methionine synthase. *FASEB J.* 1990; 4: 1450–1459.
46. Boxmeer JC, Smit M, Weber RF, Lindemans J, Romijn JC, Eijkemans MJ, *et al*. Seminal plasma cobalamin significantly correlates with sperm concentration in men undergoing IVF or ICSI procedures. *J. Androl*. 2007, 28, 521–527.
47. Watson, A.A. Seminal vitamin B12 and sterility. *Lancet* 1962, 2, 644.
48. Dhillon VS, Shahid M, Husain SA. Associations of MTHFR DNMT3b 4977 bp deletion in mtDNA and GSTM1 deletion, and aberrant CPG island hypermethylation of GSTM1 in non-obstructive infertility in indian men. *Mol. Hum. Reprod*. 2007; 13: 213–222.
49. Moriyama H, Nakamura K, Sanda N, Fujiwara E, Seko S, Yamazaki A *et al*. Studies on the usefulness of a long-term, high-dose treatment of methylcobalamin in patients with oligozoospermia. Hinyokika Kiyo 1987; 33: 151–156.
50. Isoyama R, Kawai S, Shimizu Y, Harada H. Takihara H, Baba Y *et al*. Clinical experience with methylcobalamin (CH3-B12) for male infertility. Hinyokika Kiyo 1984; 30: 581–586.
51. Kumamoto Y, Maruta H, Ishigami J, Kamidono S, Orikasa S. Kimura M *et al*. Clinical efficacy of mecobalamin in the treatment of oligozoospermia—Results of double-blind comparative clinical study. Hinyokika Kiyo 1988; 34: 1109–1132.
52. Iwasaki A, Hosaka M, Kinoshita Y, Saito K, Yumura Y, Ogawa T *et al*. Result of long-term methylcobalamin treatment for male infertility. *Jpn. J. Fertil. Steril*. 2003; 48: 119–124.
53. Ozaki S, Ohkawa I, Katoh Y, Tajima T, Kimura M, Orikasa S. Study on producing rats with experimental testicular dysfunction and effects of mecobalamin. Nihon Yakurigaku Zasshi 1988; 91: 197–207.
54. Mori K, Kaido M, Fujishiro K, Inoue N, Ide Y, Koide O. Preventive effects of methylcobalamin on the testicular damage induced by ethylene oxide. *Arch. Toxicol*. 1991; 65: 396–401.
55. Guo H, Chi J, Xing Y, Wang P. Influence of folic acid on plasma homocysteine levels and arterial endothelial function in patients with unstable angina. *Indian J. Med. Res*. 2009; 129: 279–284.
56. Stuhlinger MC, Tsao PS, Her JH, Kimoto M, Balint RF, Cooke JP. Homocysteine impairs the nitric oxide synthase pathway: Role of asymmetric dimethylarginine. *Circulation* 2001; 104: 2569-2575.
57. Miraglia E, De Angelis F, Gazzano E, Hassanpour H, Bertagna A, Aldieri E *et al*. Nitric oxide stimulates human sperm motility via activation of the cyclic

GMP/protein kinase G signaling pathway. Reproduction 2011; 141: 47-54.
58. Banihani S, Sharma R, Bayachou M, Sabanegh E, Agarwal A. Human sperm DNA oxidation, motility and viability in the presence of l-carnitine during in vitro incubation and centrifugation. *Andrologia* 2012; 44 (Suppl. 1): 505-512.
59. Chen Q, Ng V, Mei J, Chia SE. Comparison of seminal vitamin B12, folate, reactive oxygen species and various sperm parameters between fertile and infertile males. Wei Sheng Yan Jiu 2001; 30: 80-82.
60. Kifle L, Ortiz D, Shea TB. Deprivation of folate and B12 increases neurodegeneration beyond that accompanying deprivation of either vitamin alone. *J. Alzheimer's Dis*. 2009; 16: 533-540.
61. Hu JH, Tian WQ, Zhao XL, Zan LS, Xin YP, Li QW. The cryoprotective effects of vitamin B12 supplementation on bovine semen quality. Reprod. Domest. *Anim*. 2011; 46: 66-73.
62. Birch CS, Brasch NE, McCaddon A, Williams JH. A novel role for vitamin B12: Cobalamins are intracellular antioxidants in vitro. *Free Radical Biol. Med*. 2009; 47: 184-188.
63. Brosnan ME, Brosnan JT. The role of dietary creatine. *Amino Acids* 2016; 48: 1785-1791.
64. Osna NA, Feng D, Ganesan M, Maillacheruvu PF, Orlicky DJ, French S *et al*. Prolonged feeding with guanidinoacetate, a methyl group consumer, exacerbates ethanol-induced liver injury. *World J. Gastroenterol*. 2016; 22: 8497-8508.
65. Banihani SA, Abu-Alhayjaa RF. The activity of seminal creatine kinase is increased in the presence of pentoxifylline. *Andrologia* 2016; 48: 603-604.
66. Omu AE. Sperm parameters: Paradigmatic index of good health and longevity. *Med. Princ. Pract*. 2013; 22: 30-42.
67. Manzanares W, Hardy G. Vitamin B12: The forgotten micronutrient for critical care. *Curr. Opin. Clin. Nutr. Metab. Care* 2010; 13: 662-668.
68. Pentikainen V, Suomalainen L, Erkkila K, Martelin E, Parvinen M, Pentikainen MO *et al*. Nuclear factor-κB activation in human testicular apoptosis. *Am. J. Pathol*. 2002; 160: 205-218.
69. Zhao Y, Kong C, Chen X, Wang Z, Wan Z, Jia L, *et al*. Repetitive exposure to low-dose X-irradiation attenuates testicular apoptosis in type 2 diabetic rats, likely via Akt-mediated Nrf2 activation. *Mol. Cell. Endocrinol*. 2016; 422: 203-210.

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