

Metformin, Oxidative Stress and Male Infertility: Way Forward

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Madam, There is an increased prevalence of infertility in male population. With reference to a variety of mechanisms, oxidative stress (OS) is responsible for alteration in structural and functional integrity of sperm leading to altered sperm parameters, hence leading to infertility¹.

Metformin though proved to be a first-line hypoglycaemic agent has demonstrated antioxidant properties in numerous tissues. It inhibits the mitochondrial respiratory chain in the liver, which leads to

stimulation of AMP-activated protein kinase (AMPK)-dependent as well as AMPK-independent mechanisms². Metformin triggers alanine production within the Sertoli cells (SCs,) balances the NADH/NAD⁺ equilibrium and provides antioxidant environment. This drug is a treatment of choice in treating females with Polycystic Ovaries (PCOS) on the basis of its capability to reduce insulin sensitivity as well as angiogenesis through the nuclear factor κ B (NF- κ B) pathway which renders it to reduce oxidant species, thus improving the reproductive environment³.

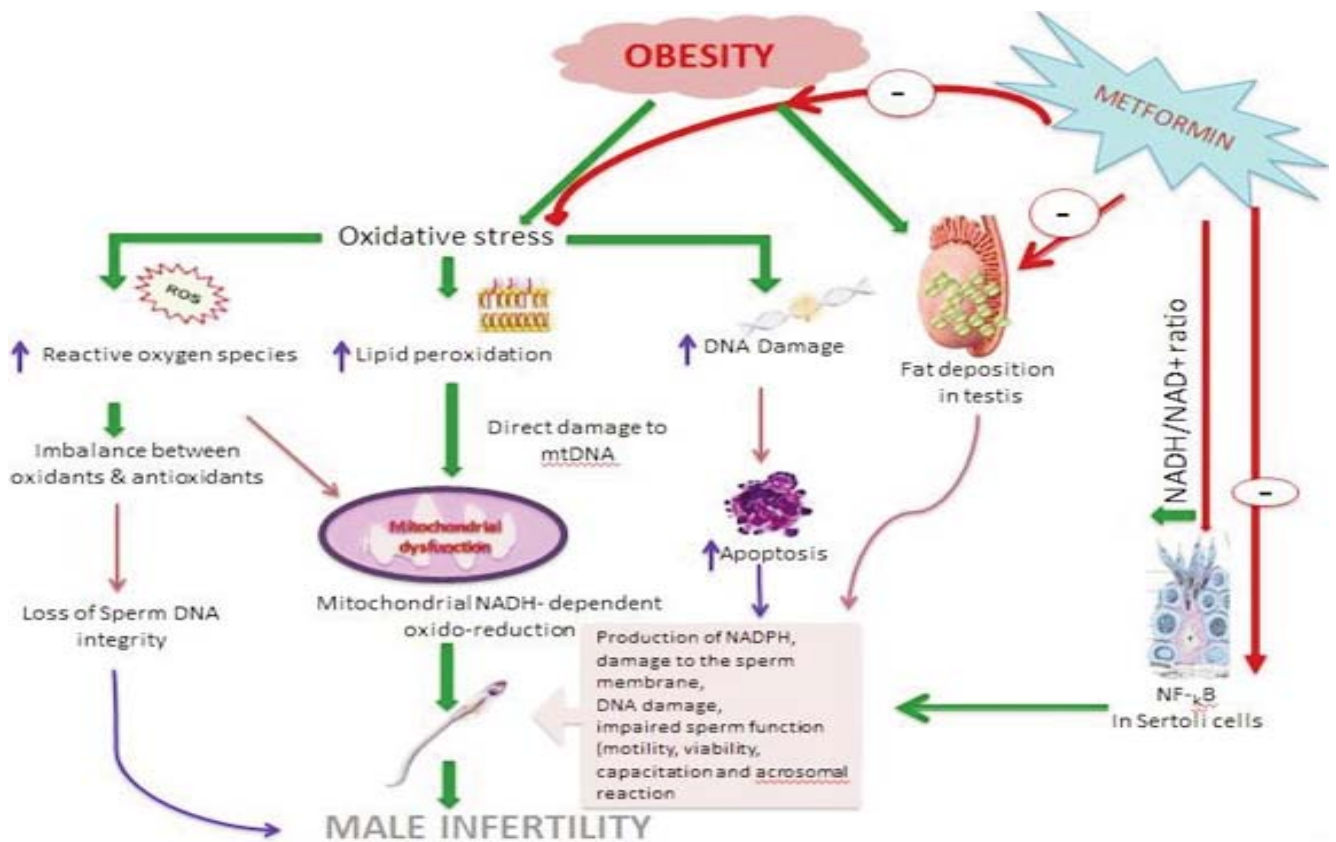


Figure: Hypothetical mechanism to elicit role of Metformin on Oxidative Stress and Male Fertility.

- Metformin minimizes Oxidative stress by increasing NADH/NAD⁺ ratio and decreasing NF- κ B in Sertoli cells

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Study on obese mice model reveals that Metformin improved male fertility by decreasing accumulation of lipid in the testis and increasing follicle stimulating

hormone (FSH) levels. The drug improved OS by reviving NF- κ B activity in SCs, remodeling of the BTB structure and rebuilding the tangled BTB-related proteins³. Furthermore, it improves fertility by inhibiting OS hence alleviating damage of blood test barrier (BTB) in testis of infertile males⁴ as illustrated in Figure. Recently metformin has proved to improve semen quality in men with hyperinsulinaemia, but the underlying molecular mechanism is unclear⁴.

We have proposed the possible mechanism of Metformin to maintain the microenvironment of the granulosa cells for restoration of fertility in females⁵.

In order to determine impact of metformin on OS and male infertility, we plan to isolate spermatozoa from infertile males by density gradient centrifugation, induce OS with H₂O₂ after incubating for 24 hours, Metformin will be added in the stressed cells and again incubated for 24 hours. To determine the OS activity, the isolated cells will be lysed, and Mishra Oxidative assay will be applied to detect changes in absorbance at 480nm⁶. Difference in expression of markers of OS will be compared before and after exposure by (OD experimental group – OD blank)/(OD control group – OD blank) \times 100%). We hypothesize that OS will be reduced with Metformin treatment. The expected reduced levels of oxidative markers in the

semen specimen /betterment of the sperm parameters after Metformin would reflect its probable role.

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Conflict of Interest: None to declare.

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