METABOLIC ENDOTOXEMIA AND MALE INFERTILITY

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SUMMARY

Infertility affects 10-15% of couples of reproductive age. Metabolic syndrome (MetS), especially in younger populations, is a risk factor for fertility disorders. Obesity and high-fat diets disrupt gut mucosal barriers, leading to endotoxemia and systemic inflammation, which negatively impact male fertility. This review examines the relationship between MetS, gut microbiota dysbiosis, and male infertility. Studies show that high-fat diets increase gut permeability and endotoxin levels, impairing spermatogenesis and sperm motility. Probiotics and prebiotics have shown promise in improving gut barrier function, reducing endotoxemia, and enhancing sperm quality. Weight loss and dietary modifications also improve semen quality and reproductive hormones. There is a need for evidence-based preconception nutritional guidance for men. Further research is necessary to explore how diet impacts male reproductive function and to develop effective treatments for idiopathic male infertility using microbiota-targeted therapies.

Keywords: Infertility, metabolic syndrome, gut microbiota, male fertility, endotoxemia, probiotics, dietary modifications.

INTRODUCTION

Infertility is a global health problem affecting 10–15% of couples of reproductive age. Lifestyle factors can impact male fertility through alterations in endocrine profiles, spermatogenesis, and sperm function. Identifying contributing factors to infertility may offer more straightforward and/or more effective therapeutic options than current treatments. The increasing worldwide prevalence of metabolic syndrome (MetS), especially in younger populations, is a risk factor for fertility disorders. Obesity and a high-fat or high-calorie diet can cause a breakdown in the gut mucosal barrier, leading to the passage of gut bacteria membrane remnants into the systemic circulation

and initiating chronic systemic inflammation. This inflammation, particularly in adipose tissue, is implicated in diet and obesity-related insulin resistance.[1] However, a direct correlation between MetS and male infertility remains unclear.

METHOD

Gómez-Elías et al.[2] induced a metabolic syndrome-like condition in (C57BL/6xBALB/c) F1 male mice by feeding them a high-fat diet (HFD, 30% fat) for 19 weeks, while controls received a normal-fat diet (NFD, 6% fat). Ning Ding et al.[3] investigated if HFD-induced gut microbiota dysbiosis could influence spermatogenesis and sperm motility. Fecal microbes from HFD-fed or regular diet (ND)--fed male mice were transplanted to mice maintained on ND. Sperm count and motility were analysed. The study explored how diet impacts male reproductive function and developed evidence-based preconception nutritional guidance for men. Dardmeh et al. investigated the effect of probiotics (Lactobacillus rhamnosus) on sperm kinematic parameters, testicular weight, lipid profiles, and reproductive hormones in male mice. Maretti and Cavallini conducted a placebo-controlled study on the impact of prebiotic/probiotic therapy on testosterone levels and sperm quality in infertile men.

RESULTS

HFD-fed mice exhibited increased body weight, hypercholesterolemia, hyperglycemia, and glucose intolerance, with more gonadal fat, lower epididymal weight, and decreased epididymal sperm count. Sperm analysis showed significant differences between HFD- and NFD-fed mice in sperm count, viability, morphology, and motility. Transplantation of HFD gut microbes into ND-maintained mice significantly decreased spermatogenesis and sperm motility and increased proinflammatory cytokines in the epididymis.[3] Obesity and high-fat diets result in changes to gut bacteria and increased intestinal permeability, leading to metabolic endotoxemia. Kelton Tremellen postulated that bacterial lipopolysaccharide (LPS) from the gut lumen into circulation is a critical inflammatory trigger underlying male hypogonadism.[4] Linn B. Hakonsen et al. observed that weight loss improved semen quality.[5] Karma L. Pearce et al. found that metabolic endotoxemia and its associated oxidative stress may drive sperm DNA damage in obese men.[6] Dardmeh et al.[7] showed probiotics could eliminate obesity's adverse effects on semen quality. Everard et al.[8] found prebiotic treatment improved gut barrier function and metabolic parameters. Valcarce et al.[9] demonstrated probiotics improved sperm quality in asthenozoospermic men. Maretti and Cavallini[10] reported a significant improvement in testosterone levels and sperm quality with prebiotic/probiotic therapy.

DISCUSSION

Obesity and a high-fat/high-calorie diet cause changes in gut bacteria and intestinal permeability, leading to metabolic endotoxemia and systemic inflammation, negatively affecting male fertility. High-fat diets are more efficient in transporting bacterial endotoxin from the gut lumen into circulation. The relationship between diet composition and obesity involves interactions between dietary macronutrients. There is a clear need to explore further how diet impacts male reproductive function to develop evidence-based preconception nutritional guidance. Probiotics and pre-

biotics can improve gut barrier function, reduce metabolic endotoxemia, and positively impact sperm quality and reproductive hormones.

CONCLUSION

Obesity and high-fat/high-calorie diets contribute to metabolic endotoxemia and systemic inflammation, negatively affecting male fertility. Lifestyle changes, including weight loss and dietary modifications, can improve semen quality and reproductive hormones. Probiotics and prebiotics offer potential therapeutic options for improving male fertility by enhancing gut barrier function and reducing metabolic endotoxemia. Further research is needed to develop evidence-based nutritional guidance for men to improve reproductive outcomes.

REFERENCES

1. Mehta NN, McGillicuddy FC, Anderson PD, Hinkle CC, Shah R, Pruscino L, Grivennikov SI, Ley K, Mosser DM, Miller LS, Toliver-Kinsky T, de Souza LS, Ferreira RA, Sierra JC, Balter A, Mandell L, Schlaepfer DD, Tabas I, Stoffel M, Reilly MP. Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. *Diabetes*. 2010; 59(1): 172-81. doi:10.2337/db09-0367
2. Gómez-Elías MD, Rodríguez-González GL, Ávila-González CC, Lara-Padilla E, Rivas-Arancibia S, Granados-Badillo A, López-Meza JE, Jiménez-Estrada M, Ortiz-Lazareno PC, Pérez-Camarillo S. Association between high-fat diet feeding and male fertility in high reproductive performance mice. *Sci Rep.* 2019; 9: 18546. doi:10.1038/s41598-019-54799-3
3. Ding N, Zhang X, Zhang XD, Zhang C, Jin J, Ma YH, Dong JY, Zhang YL, Wang YX, Ma ML, Guo YX, Huang CJ, Wei Y, Wang LH, Jin DM, Yang QL. Impairment of spermatogenesis and sperm motility by the high-fat diet-induced dysbiosis of gut microbes. *Gut*. 2020; 69(9): 1608-1619. doi:10.1136/gutjnl-2019-319127
4. Tremellen K, Pearce K. Dysbiosis of Gut Microbiota (DOGMA) – a novel theory for developing Polycystic Ovarian Syndrome. *Basic Clin Androl.* 2016; 26: 7. doi:10.1186/s12610-016-0032-1
5. Hakonsen LB, Thulstrup AM, Aggerholm AS, Olsen J, Bonde JP, Andersen CY, Bungum M, Ernst EH, Hansen ML, Gernow A, Ramlau-Hansen CH. Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men. *Reprod Health.* 2011; 8: 24. doi:10.1186/1742-4755-8-24
6. Pearce KL, Tremellen K, Lopez-Villalobos N, Kang HJ, MacDonald C, Sheedy JR. Obesity-related metabolic endotoxemia is associated with oxidative stress and impaired sperm DNA integrity. *Basic Clin Androl.* 2019; 29: 6. doi:10.1186/s12610-019-0087-y
7. Dardmeh F, Alipour H, Gazerani P, Vaegter HB, Alipour B, Nielsen HI. Lactobacillus rhamnosus PB01 (DSM 14870) supplementation affects markers of sperm kinematic parameters in a diet-induced obesity mice model. *PLoS One.* 2017; 12(10) doi:10.1371/journal.pone.0185964
8. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila

and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A*. 2013; 110(22): 9066-9071. doi:10.1073/pnas.1219451110

9. Valcarce DG, Herráez MP, Robles V. Probiotic administration improves sperm quality in asthenozoospermic human donors. *Benef Microbes.* 2017; 8(2): 193-206. doi:10.3920/BM2016.0142
10. Maretti C, Cavallini G. The association of a probiotic with a prebiotic (Flortec, Bracco) to improve the quality/quantity of spermatozoa in infertile patients with idiopathic oligoasthenoteratospermia: a pilot study. *Andrology*. 2017; 5(3): 439-444. doi:10.1111/andr.12340