



Invited Commentary | Public Health

# More Evidence of the Association of Diet With Human Testicular Function —Fish Oil Supplements

Albert Salas-Huetos, MSc, PhD

Human semen quality (ie, sperm count and concentration) has declined worldwide,<sup>1</sup> and this decrease is greater in certain geographic regions, specifically in developed and industrialized countries.<sup>2</sup> Current data suggest that this decline is associated with environmental and lifestyle factors, such as pollution, smoking, alcohol consumption, lack of physical activity, stress, and unhealthy diets.

The evidence supporting an association of diet with sperm quality is growing very rapidly. In fact, dozens of observational studies have concluded that diets rich in foods such as fish, shellfish and seafood, poultry, cereals, vegetables and fruits, low-fat dairy, and skim milk were positively associated with several sperm quality parameters.<sup>3</sup> In the case of specific foods, data come primarily from observational studies; however, in case of nutrients, the evidence comes more from randomized clinical trials (RCTs), sometimes of doubtful statistical power. To overcome this issue and to assess the precise association of nutrients with sperm quality parameters, a 2018 meta-analysis was published.<sup>4</sup> This study found that the administration of  $\omega$ -3 fatty acid supplements (ie, 1 g/d of docosahexaenoic acid and 1 g/d of eicosapentaenoic acid for 10-32 weeks) improved total sperm count (mean difference,  $18.70 \times 10^6$  spermatozoa; 95% CI,  $16.89 \times 10^6$  to  $20.51 \times 10^6$  spermatozoa), sperm concentration (mean difference,  $10.98 \times 10^6$  spermatozoa/mL; 95% CI,  $10.25 \times 10^6$  to  $11.72 \times 10^6$  spermatozoa/mL), total motility (mean difference, 7.55%; 95% CI, 7.09% to 8.01%), and morphology (mean difference, 0.91%; 95% CI, 0.69% to 1.13%). However, these results must be cautiously interpreted because of the limited sample size of the meta-analyzed studies.<sup>5,6</sup> Although RCTs represent the cornerstone of evidence-based medicine, when the observational evidence is not well determined, a well-designed RCT is extremely difficult to conceive.

An important study by Jensen et al<sup>7</sup> provides further observational evidence of the potential associations of fish oil supplements (theoretically rich in  $\omega$ -3, although the authors did not obtain information about the actual content of this fatty acid in the supplements mentioned) with better semen quality and sex hormone concentration. Although the authors tried to describe more associations between the proper function of spermatogenesis and different dietary supplements (ie, vitamin D, vitamin C, or multivitamins), only fish oil supplements reached statistical significance.<sup>7</sup> Specifically, the authors found that men with a higher consumption of fish oil supplements had larger testicular size, greater sperm volume, greater total sperm count, lower follicle-stimulating hormone concentration, lower luteinizing hormone concentration, and a higher ratio of free testosterone to luteinizing hormone than men who did not use any supplements.<sup>7</sup> While the data do not provide clear proof of dose-response associations because the authors only provided 2 cutoffs (ie, <60 or  $\geq$ 60 days of supplementation),<sup>7</sup> the association with sperm parameters and hormonal levels adds more information to the literature regarding the association of male diet with the spermatogenesis process.

This is the first well-designed study from a general population and including healthy individuals published to date, making the findings more interesting. Another strength of the study is the number of individuals analyzed (ie, 1679). Furthermore, the study by Jensen et al<sup>7</sup> included an adequate phenotypic evaluation of the men, which is uncommon in similar articles. It is important that future studies consider phenotypic and lifestyle characteristics, including but not limited to diet, obesity, medications, smoking, and physical activity, as Jensen et al<sup>7</sup> did.

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However, this study<sup>7</sup> also has some limitations. The main limitation is the lack of information about the diet questionnaire and its completion. If the participants filled out a validated Food Frequency Questionnaire, was it filled out by the participants at home? Was it checked by nutritionist-dietitian practitioners? Moreover, the cross-sectional nature of the study makes it impossible to determine causality in the results.

While these limitations are significant, the study is meaningful and insightful. Jensen et al<sup>7</sup> are to be commended for their creative study. Moreover, the article contains very interesting observational data that could affect assisted reproductive clinics if the findings are reproduced in the future by well-designed RCTs. Despite the study by Jensen et al,<sup>7</sup> much work is still required to examine the complex association between dietary supplements and semen quality and to determine whether such an association could help to improve fecundity or fecundability and the results of assisted reproductive techniques. Even more important, could the described associations affect the future generations and/or offspring health through epigenetic modification? It will be exciting to see.

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#### ARTICLE INFORMATION

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**Corresponding Author:** Albert Salas-Huetos, MSc, PhD, Andrology and IVF Laboratory, Division of Urology, Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT 84108 ([albert.salas@utah.edu](mailto:albert.salas@utah.edu)).

**Author Affiliation:** Andrology and IVF Laboratory, Division of Urology, Department of Surgery, University of Utah School of Medicine, Salt Lake City.

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