


The use of insulin-like growth factor I improved the parameters of the seminogram in a patient with severe oligoasthenoteratozoospermia

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Abstract

Male patients suffering from oligoasthenoteratozoospermia typically failed to achieve pregnancy, even with assisted reproductive technologies. Growth hormone and insulin-like growth factor I have been shown to regulate sperm quality parameters; therefore, the insulin-like growth factor I supplement could improve sperm parameters. Here, we determine the effect insulin-like growth factor I has on sperm parameters in a patient suffering from oligoasthenoteratozoospermia. A 47-year-old male was administered once a day 1.5 IU of insulin-like growth factor I by intradermal injection for 2 months. Seminogram analysis was performed before and after. Treatment with insulin-like growth factor I resulted in a 15.5-fold improvement in sperm concentration (1.1×10^6 vs 18.3×10^6 per mL), 71.4% change in volume (0.7 vs 1.2 mL), increased progressive motility (2% vs 43%), and the total volume of sperm with progressive motility (0% vs 23.6%). Here, we show that administering a daily dose of insulin-like growth factor I can improve sperm quality parameters.

Keywords

Growth hormone, insulin-like growth factor, oligoasthenoteratozoospermia, sperm quality

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Introduction

The connection between growth hormone, especially insulin-like growth factor I (IGF-1), and testicular development and spermatogenesis has been well described (for review, see Hull et al.¹); however, there is limited information focusing on humans. What can be surmised is that hepatic IGF-1 or paracrine IGF-1 is key for spermatogenesis. For example, using frozen/thawed semen samples from buffalo, yak, canine, and ovine increased IGF-1 levels associated with spermatozoa motility, mitochondrial membrane potential, and the oocytes cleavage rate.^{2–4}

Oligoasthenoteratozoospermia (OAT) is a multifaceted condition, which consists of a lower sperm count (oligozoospermia), poor sperm movement (asthenozoospermia), and abnormal sperm shape (teratozoospermia). IGF-1 stimulates the maturation of spermatozoa, the increase in sperm motility, and also correlated significantly with total sperm count,⁵ which suggests that treatment of IGF-1 could improve sperm quality. Here, we evaluated the effect of IGF-1 on

semen parameters in a patient with primary infertility and severe OAT.

Case presentation

A couple was referred to the Ingenes Institute for a male infertility issue. Both originate from Mexico City. They have been together for 15 years, and for the last 10 years, they

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Table 1. Semen characteristics of a 47-year male, before and after treatment with IGF-1 for 2 months.

Category	Before treatment	After treatment
Volume (mL)	0.7	1.2
Concentration (10 ⁶ per mL)	1.1	18.3
Progressive mobility (%)	2	43
Morphology	0	0
TPM (%)	0	23.6
TPMN (%)	0	0

TPM: total progressive motility; TPMN: total progressive motility with normal morphology.

have been trying to get pregnant. The intervention protocol has been approved by the Ethics Committee of the Ingenes Institute. Both patients provided written consent to participate in this study, in accordance with the Declaration of Helsinki.

The 47-year-old male, with a 10-year history of primary infertility, was diagnosed with varicocele in 2014, with normal secondary sexual development characteristics; however, the testicular volume was determined to be between 6 and 12 mL (Grade 3, Prader orchidometer). He had no other significant medical problems. He was of average Mexican height (1.74 m) but was overweight (84.2 kg, body mass index: 28.0 kg/m²). His hormonal profile was normal: serum follicle-stimulating hormone (FSH: 3.4 mIU/mL, normal range: 1.27–19.26 mIU/mL), luteinizing hormone (LH: 1.7 IU/L, normal range: 1.0–9.0 IU/L), total testosterone (T: 10.3 nmol/L, normal range: 10.4–41.6 nmol/L), prolactin (10.4 nmol/L, normal range: 0.17–1.00 nmol/L), thyroid-stimulating hormone (TSH: 1.5 mIU/L, normal range: 0.5–5.0 mIU/L), free thyroxine (FT4: 9.2 pmol/L, normal range: 10.30–23.17 pmol/L), and free triiodothyronine (FT3: 4.2 pmol/L, normal range: 3.53–6.45 pmol/L). Karyotype analysis indicates the patient was 46, XY.

His 39-year-old partner presented a normal weight (body mass index: 24.6 kg/m²). She had no significant medical history concerning assisted reproduction. She has a normal menstrual history. Since 2003, she has had two spontaneous pregnancies that resulted in one birth and one late-term abortion. The cause was determined to be that the heart stopped beating. She has undergone one in vitro fertilization attempt, which resulted in one embryo transferred but with no biochemical pregnancy. For this cycle, her hormonal profile was normal: FSH (6.2 IU/L, normal range: 4.7–21.5 IU/L), LH (4.3 IU/L, normal range: 1.0–18.0 IU/L), progesterone (0.9 nmol/L on day 21 of the menstrual cycle, normal range: (≤3.2 nmol nmol/L), prolactin (1.2 nmol/L, normal range: 0.17–1.30 nmol/L), TSH (1.6 mIU/L, normal range: 0.5–5.0 mIU/L), FT4 (6.2 pmol/L, normal range: 10.30–23.17 pmol/L), and FT3 (3.5 pmol/L, normal range: 3.53–6.45 pmol/L) and her karyotype analysis indicates 46, XX.

The patient reported been previously treated (in other facilities and the previous years) with antioxidants, L-carnitine, clomiphene citrate, and recombinant human chorionic gonadotropin (hCG), yielding no improvement in semen parameters. Since then, the patient has discontinued any previous treatments for in vitro fertilization or antioxidants for 24 months. Here, a semen sample was collected by masturbation after 3-day abstinence. Seminogram analysis indicated that the patient suffered from OAT. Characteristics are presented in Table 1. The patient was administered once a day 1.5 IU of human growth hormone (hGH)/IGF-1 (Saizen 5.83 mg/mL, 1.33 mg equivalent to 4IU) by intradermal injection for 2 months, typically at 10:00 pm. The dose and method of delivery were chosen because multiple reports have shown that at this concentration, IGF-1 can elicit a response.⁶ During the in vitro fertilization procedure, the patient did not indicate any adverse side-effects during treatment, post-treatment, and at his partner's final appointment. After 60 days of daily treatment, a subsequent semen sample was collected and the specimen was evaluated within 1 h after collection. To note, the patient was still under treatment at the time of the second seminogram. Marked improvement in semen parameters was noted as determined for concentration, progressive mobility, and total progressive motility (TPM; Table 1). Due to the improvement in the quality of the semen sample, and because the partner's controlled-ovarian stimulation concluded successfully, the sperm was used for in vitro fertilization, and the patient was instructed to stop taking the IGF-1.

The female partner underwent a standard ovarian stimulation protocol with a daily dose of gonadotropin-releasing hormone (GnRH) antagonists with total dosage of FSH 2700 UI and hCG 10,000 UI. A total of 12 M-II ovules were captured and were fertilized by intracytoplasmic sperm injection (fertilization rate=75%). Of the nine embryos, three had <10% fragmentation at day 3, 6–8 cells at day 3, and were symmetrical. At day 5, three blastocysts were of Grade 2. Three embryos were transferred, and pregnancy was confirmed 14 days after transfer measuring hCG (288 mIU/L) and the presence of two gestational sacs and fetal heartbeats at week 20. She has given birth to twins, one male and one female.

Discussion

IGF-1 has been shown to affect sperm quality and reproduction outcomes in numerous species, including humans. Low levels of IGF-1 are associated with poor sperm morphology and motility. Therefore, we postulated that if IGF-1 was administered daily, this would improve sperm quality parameters. Indeed, after using IGF-1 for 2 months, the patient's semen sample had increased volume, improved total sperm concentration, and improved motility. Ultimately, the couple had two healthy babies.

In knockout mice and mice with reduced growth hormone expression, injection of IGF-1 improved sperm quality parameters, thus providing the basis for this study.⁷ IGF-1 is mainly produced in the liver, which is believed to be the primary source affecting spermatogenesis. However, Leydig and Sertoli cells also produce IGF-1, which can significantly affect spermatogenesis. Here, the male patient received intradermal injections, thus suggesting we were mimicking hepatic production of IGF-1. This does suggest that the patient's infertility could be caused by alterations in liver function, such as insulin resistance. However, we cannot rule out the indirect effects of intradermally injected IGF-1 has on Leydig and Sertoli cells. Moreover, IGF-1 biosynthesis is not solely controlled by growth hormone and significant biological amount of IGF-1 can be produced by LH, fibroblast growth factor, or FSH (for review, see Gnnessi et al.⁸).

Here, treatment with IGF-1 for 2 months led to a 15.5-fold increase in sperm production. This was expected, because, in mice and humans,⁹ growth hormone and IGF-1 were shown to affect Sertoli cell proliferation and testicular volume, both associated with sperm output. Moreover, it has been proposed that IGF-1 is an important factor for spermatogenesis because the IGF-I receptors were numerous found at the secondary spermatocytes and early spermatids.¹⁰ Therefore, we postulated that increases in sperm production are due to the autocrine action of IGF-1; however, more studies are required to determine the actual mechanism.

Sperm motility develops in the epididymis, and Miao et al.¹¹ demonstrated that IGF-1 impairs human sperm motility in vitro. We should note that in their study, the sperm samples came from healthy volunteers and optimal sperm were selected using the "swim-up" technique. However, in males suffering from infertility, oligoasthenospermia or asthenozoospermia,¹² treatment with growth hormone augmented seminal plasma IGF-I simultaneously with sperm motility. It was proposed that growth hormone stimulates IGF-I production from Leydig and Sertoli cells and this stimulated maturation of spermatozoa, which ultimately promoted increased sperm motility. Conditional inactivation of the IGF-I receptor in cultured Sertoli cells decreased the number of viable Sertoli cells, diminished Sertoli cell proliferation, and increased Sertoli cell death.¹³ IGF-I production in a paracrine/autocrine manner stimulates the maturation of spermatozoa, with a subsequent increase in sperm motility and IGF-I levels correlating linearly and significantly with total sperm count. IGF-I might function as a differentiation marker in the male germ cells and have a role in the maturation of spermatozoa (reviewed in the study of Moss et al.⁵). Our results are in agreement with these observations; however, our patient suffered from OAT.

Age-related decline in sperm production could be another factor to be taken into consideration. By the age of 40, most men demonstrate diminished semen volume, number of sperm, and sperm motility.¹⁴ Here, our patient was 47 years, which would suggest that age-related decline in sperm production could also be a factor. However, the patient was not

suffering from other age-related complications, such as diabetes and metabolic syndrome. Therefore, we can only assume that these age-related factors minimally affected our results. Moreover, a more extensive study has to be performed to statistically determine whether age is a factor when considering IGF-1 treatment to improve semen quality.

In conclusion, we demonstrate that administering IGF-1 daily for 2 months improves sperm quality parameters in a patient suffering from OAT and infertility. The sperm collected did produce viable embryos by intracytoplasmic sperm injection, suggesting a minimal effect on the in vitro fertilization protocol. We provide evidence of using an alternative hormone to improve semen quality in a patient who suffers from OAT; however, larger studies are required to determine its practicality for male infertility.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

The intervention protocol has been approved by the Ethics Committee of the Ingenes Institute.

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Informed consent

Written informed consent was obtained from the patient(s), in accordance with the Declaration of Helsinki, for their anonymized information to be published in this article.

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References

1. Hull KL and Harvey S. Growth hormone: a reproductive endocrine-paracrine regulator. *Rev Reprod* 2000; 5(3): 175–182.
2. Padilha RT, Magalhaes-Padilha DM, Cavalcante MM, et al. Effect of insulin-like growth factor-I on some quality traits and fertility of cryopreserved ovine semen. *Theriogenology* 2012; 78(4): 907–913.
3. Pan Y, Cui Y, Baloch AR, et al. Insulin-like growth factor I improves yak (*Bos grunniens*) spermatozoa motility and the oocyte cleavage rate by modulating the expression of Bax and Bcl-2. *Theriogenology* 2015; 84(5): 756–762.
4. Shin SM, Kim S, Hong JG, et al. IGF-I improves mitochondrial membrane potential during hypothermic storage of canine spermatozoa. *J Vet Med Sci* 2014; 76(7): 1065–1067.
5. Moss JL, Crosnoe LE and Kim ED. Effect of rejuvenation hormones on spermatogenesis. *Fertil Steril* 2013; 99(7): 1814–1820.

6. Kalra S, Kalra B and Sharma A. Growth hormone improves semen volume, sperm count and motility in men with idiopathic normogonadotropic infertility. *Endocr Abstr* 2008; 16: P613.
7. Baker J, Hardy MP, Zhou J, et al. Effects of an Igf1 gene null mutation on mouse reproduction. *Mol Endocrinol* 1996; 10(7): 903–918.
8. Gnessi L, Fabbri A and Spera G. Gonadal peptides as mediators of development and functional control of the testis: an integrated system with hormones and local environment. *Endocr Rev* 1997; 18(4): 541–609.
9. Bartke A. Effects of growth hormone on male reproductive functions. *J Androl* 2000; 21(2): 181–188.
10. Vannelli BG, Barni T, Orlando C, et al. Insulin-like growth factor-I (IGF-I) and IGF-I receptor in human testis: an immunohistochemical study. *Fertil Steril* 1988; 49(4): 666–669.
11. Miao ZR, Lin TK, Bongso TA, et al. Effect of insulin-like growth factors (IGFs) and IGF-binding proteins on in vitro sperm motility. *Clin Endocrinol (Oxf)* 1998; 49(2): 235–239.
12. Ovesen PG, Jorgensen JO, Ingerslev J, et al. Growth hormone treatment of men with reduced sperm quality. *Ugeskr Laeger* 1998; 160(2): 176–180.
13. Froment P, Vigier M, Negre D, et al. Inactivation of the IGF-I receptor gene in primary Sertoli cells highlights the autocrine effects of IGF-I. *J Endocrinol* 2007; 194(3): 557–568.
14. Kidd SA, Eskenazi B and Wyrobek AJ. Effects of male age on semen quality and fertility: a review of the literature. *Fertil Steril* 2001; 75(2): 237–248.