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”Is stress and adrenal gland activity associated with semen quality and reproductive hormones in men”?

PhD thesis

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English Summary

Infertility is a major problem; approximately 8% of recent birth cohorts in Denmark are conceived by means of fertility treatment. Over the last five to six decades, semen quality appears to have decreased in many West-ern countries and some lifestyle factors and endocrine disrupting chemicals have been suspected to impair testicular function if the man is exposed prenatally or postnatally.

Psychological stress is also an increasingly common phenomenon as more than one fourth of young men have been reported to have 'high stress levels' in a large Danish survey. Several epidemiological studies have linked stress with impaired semen quality but the majority of these studies were conducted in small or selected pop-ulations, mostly infertile men, making it difficult to compare results and distinguish between stress as a cause or a consequence of infertility. In *Study I and Study II* a negative association between psychological stress and semen quality was detected in two cohorts of men from the general population comprising 1,215 and 1,362 young men, respectively. Unhealthy lifestyle factors in stressed men seemed to partly mediate the association. Also, the endocrine profile associated with increased stress indicated a primary adverse effect on the testicles, but additional hypothalamic-pituitary effects could not be excluded.

The biological background for the association between stress and semen quality is not fully understood, but a prevailing hypothesis is that excess glucocorticoids (GCs), secreted from the adrenal glands as part of the stress response, affect the hypothalamic-pituitary-gonadal (HPG) axis leading to impaired testicular function. However, insufficient glucocorticoid production may also exert adverse effects on testis function. Thus, it has been hypoth-esized that testicular function may require GC levels within a certain optimal range. In *Study III* investigations of human testicular biopsies revealed that GC receptors were indeed present in Leydig cells, peritubular cells, Sertoli cells, and spermatogonia. These findings support the notion that GCs could have a functional role for spermato-genesis, but may also indicate that GCs may be a potential mediator for the observed associations between stress and testis function. If so, single nucleotide polymorphisms (SNPs) in the GC-R gene (*NR3C1*) possibly affecting GC receptor sensitivity may also influence the associations. In S*tudy III*, genotyping of three well-known and common SNPs; *Bcl*I, 9β, and *Tth111*I, showed that the *Bcl*I polymorphism was associated with testis function with sperm motility showing the strongest association.

During the last decade, hair cortisol concentrations (HCC) measured in scalp hair has emerged as a potential ret-rospective biomarker of cortisol levels the previous months. The results from *Study IV* did not support the hy-pothesis that high levels of HCC would reflect prolonged psychological stress and be associated with reduced tes-ticular function. HCC was, however, associated with the *NR3C1* polymorphisms *Tth111*I and 9β; HCC increased with number of *Tth111*I minor alleles (T) and decreased with number of 9β minor alleles (G).

Taken together, the results obtained provide evidence for a negative association between psychological stress and semen quality. However, the effect of stress may partly be mediated by an unhealthy lifestyle in men with high stress levels. Lack of association between HCC and testicular function does not support the hypothesis that high levels of GCs mediated the detrimental effects of stress. The association between the *Bcl*I *NR3C1* polymorphism and semen quality along with the presence of GC receptors in the testis may support a function of GCs for spermatogenesis. The association between the *NR3C1* polymorphisms *Tth111*I and 9β and HCC may indicate that these SNPs may be co-regulators of the HPA axis and hence influence the systemic cortisol levels. However, for testicular function exposure at the tissue level may potentially be more important.

Future intervention studies might provide evidence that semen quality restores due to treatment aiming at lowering the stress levels. Additionally, as the results indicated a possible function of GCs for spermatogenesis, molecular studies will hopefully dig deeper into this new interesting area.