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Combined effects of varicocele and cell phones on semen and hormonal parameters

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Summary
Background The objective of this study was to evaluate if there is a combined effect of varicocele and cell phone storage in trousers pockets on semen and hormonal parameters.
Methods A retrospective analysis of 468 men attending an infertility clinic from 1993–2007 was performed. Varicoceles were determined by clinical examination and patients were questioned on cell phone usage and storage fashion. Semen samples were analyzed according to the World Health Organization (WHO) guidelines of 1999. Serum testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) were assessed.
Results There was a significant effect of cell phone storage in trousers pockets and varicocele in multivariate analysis (both $p < 0.001$). Varicocele showed an effect on sperm concentration ($p = 0.003$), LH ($p = 0.014$) and testosterone ($p = 0.003$). Compared to grade 1, grade 2 varicoceles showed a difference in sperm concentration ($p = 0.004$). Regarding testosterone differences were shown for grade 3 versus grade 1 ($p = 0.002$) and grade 3 compared to grade 2 ($p = 0.003$). Cell phone storage in trousers pockets showed an influence on the percentage of normal sperm morphology and LH (both $p < 0.001$). Varicocele and cell phone storage in trousers pockets did not show a combined effect ($p = 0.76$).
Conclusions This analysis showed an inverse relation between sperm concentration and degree of varicocele, with lower concentrations in higher grade varicoceles. Testosterone was significantly higher in higher grade varicoceles, which could reflect a compensatory mechanism to the impaired testicular function. Cell phone storage in trousers pockets showed an effect on LH and sperm morphology. A combined effect of varicocele and cell phone storage in trousers pockets was not detected.

Keywords Cell phone · Varicocele · Semen parameters · Hormonal parameters · Subfertility

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Introduction

Approximately 15% of couples suffer from infertility, which is defined as the inability to spontaneously conceive within 1 year of unprotected intercourse. A male factor is responsible in about 50% of cases [1]. The reasons for infertility are numerous and include amongst others genetic, hormonal, infectious and environmental factors or remain unknown. An established male factor is the presence of a varicocele. The possible negative effects of a varicocele on the male reproductive function have been thoroughly evaluated but not yet fully elucidated. Suggested pathophysiological mechanisms range from scrotal hyperthermia, reflux of toxic metabolites, venous hypertension, hormonal disturbances, testicular hypoperfusion and hypoxia to elevated oxidative stress [2–4]; however, almost two thirds of affected men are fertile [5]. Why most men with a varicocele retain their reproductive function has been intensively investigated. Recent research suggested that a variation in transcriptional response to oxidative stress might protect sperm from damage [6]. Moreover, numerous studies associated the presence of a varicocele with impaired sperm parameters [7, 8]. Furthermore, a varicocele can be detected in approximately 40–70% of men with primary and secondary infertility thus making varicocele the most common identifiable male infertility factor [9]. Other possible negative

factors, which may lead to secondary infertility, are environmental noxae, such as chemical substances, ionizing radiation and electromagnetic waves. Radiofrequency electromagnetic waves were attributed to have possible adverse effects on human health [10–13]. An important source of radiofrequency electromagnetic waves is the use of cell phones that has become more and more widespread within the last two decades. Mobile telephones use a wide range of frequency bands between 450 and 2000 MHz. Several studies reported potential unpleasant effects on different body organs, such as the brain, heart or endocrine organs [14, 15]. Extensive use of cell phones may lead to fatigue, headaches and sleep disturbances or difficulties in concentration [16]. A recent review published in 2015 reported an increased risk of glioma and meningioma and suggested that radiofrequency fields should be classified as probable human carcinogens under the criteria used by the International Agency for Research on Cancer [12, 13]. Additionally, animal studies showed damaging effects on the male reproductive functions by thermal and non-thermal mechanisms [17]. Significant negative effects on human sperm parameters have also been reported in recent years [18–20].

The objective of this study was to evaluate a possible combined effect of varicocele and cell phone storage in trousers pockets on sperm and hormonal parameters.

Materials and methods

A retrospective analysis was carried out on a database including 468 men who attended an infertility clinic between 1993 and 2007. Exclusion criteria consisted of hazardous alcohol consumption, defined by the World Health Organization (WHO) as daily alcohol intake over 60 g, systemic diseases and a previous history of orchitis. The presence of a varicocele was evaluated by clinical examination of the patient in a supine and standing position and classified as grade 1, 2 or 3. Patients were questioned on their cell phone use in a yes or no fashion. The analysis only comprised men who kept the cell phone in their trousers pocket. Men who used a cell phone but did not store it in the trousers pocket were not included in this analysis. In addition, smoking was evaluated as a yes or no covariate. Semen samples were obtained by masturbation after an abstinence period of 3–5 days. Semen analysis was carried out according to the WHO guidelines from 1999 (normal sperm concentration ≥20 million/ml, progressive motility ≥25%, percentage of pathologic sperm morphology <85%). Serum testosterone (T; 2.2–11 ng/ml), luteinizing hormone (LH; 0.8–8.5 IU/ml) and follicle stimulating hormone (FSH; 1.3–12 IU/ml) were assessed in all patients. All blood samples were drawn in the morning between 9 and 10 am.

Statistical analysis was carried out with IBM SPSS Statistics 22.0® by using multivariate analysis of variance (MANOVA). The seminal parameters semen volume, pathologic sperm morphology (in %), sperm concentration and sperm motility, as well as the hormone levels for LH, FSH and testosterone were treated as numerical dependent variables. The presence of a varicocele grades 1, 2 and 3 and cell phone storage in trousers pockets were analyzed as independent variables. Smoking status was evaluated as "yes/no" covariate. A p-value of <0.05 was considered statistically significant. Institutional review board approval was obtained.

Results

After application of exclusion criteria and omitting patients with missing values, 468 patients could be included in the analysis. The median patient age was 28.7 years. Age as an influencing factor on the results was eliminated. Further demographic statistics are presented in Table 1. A varicocele grades 1, 2 and 3 was present in 150, 182 and 136 patients, respectively. The cell phone group comprised 211 patients and 257 patients reported not using a cell phone.

Median sperm concentration was 39.1 million/ml (12.8; 78.5), 29.2 million/ml (10.0; 68.9) and 22.1 million/ml (7.8; 51.5) in varicocele grades 1, 2 and 3, respectively. Median LH values in varicocele patients were 3.4 IU/ml (2.4; 4.9), 3.8 IU/ml, (2.5; 5.3) and 3.9 IU/ml (2.8; 5.3), respectively. The corresponding testosterone values were 4.6 ng/ml (3.2; 5.9), 4.7 ng/ml (3.6; 6.3) and 5.6 ng/ml (4.3; 6.9), respectively (Fig. 1).

In cell phone users median LH levels were 3.4 IU/ml (2.4; 4.7) and 72.0% with pathologic sperm morphology (60.0; 82.0) and 4.0 IU/ml (2.9; 5.6) and 60.0% pathologic sperm morphology (46.0; 76.0) in men not using cell phones, respectively (Fig. 2).

Overall, there was a statistically significant effect of cell phone storage in trousers pockets and the presence of a varicocele in multivariate analysis (both $p <$ 0.001).

The presence of a varicocele showed a statistically significant effect on sperm concentration ($p = 0.003$), LH ($p = 0.014$) and testosterone ($p = 0.003$). There was no influence of varicocele on semen volume, sperm motility, sperm morphology or FSH level.

The influence of the grade of varicocele was confirmed by performing a Kruskall-Wallis test for the parameters sperm concentration ($p = 0.001$) and testosterone ($p < 0.001$) and was rejected for LH ($p = 0.057$). The presence of a varicocele showed an overall significant effect on LH values, but not for any varicocele grade in particular. Compared to grade 1 varicoceles grade 3 varicoceles showed a significant difference in sperm concentration ($p = 0.004$). Regarding testosterone values significant differences were shown for grade 3 versus grade 1 ($p = 0.002$) and grade 3 compared to grade 2 ($p = 0.003$). No differences could

Table 1 Characteristics of all patients

N	468
Age (years, median)	28.7
Sperm concentration (m/ml, median)	34.2
Sperm motility grade a (%, median)	25.0
Pathologic morphology (%, median)	64.0
FSH (IU/ml, median)	5.0
LH (IU/ml, median)	3.6
Testosterone (ng/ml, median)	5.0

SD standard deviation, *m/ml* million per ml, *IU/ml* international units per ml, *ng/ml* nanogram per ml

be detected regarding sperm motility and morphology between the varicocele grades.

Cell phone storage in trousers pockets showed a statistically significant influence on the percentage of normal sperm morphology ($p < 0.001$) and LH ($p < 0.001$). The Kruskall-Wallis test confirmed the statistical significance of cell phone storage in trousers pockets for both parameters ($p < 0.001$, respectively). There were no differences regarding semen volume, sperm concentration, sperm motility, testosterone and FSH level. The multivariate analysis did not detect any combined effect of varicocele and cell phone storage in trousers pockets, neither overall ($p = 0.76$) nor for any of the mentioned parameters in particular. Smoking did not show a significant effect on any of the parameters ($p = 0.40$).

Discussion

This study aimed to evaluate whether there is a combined effect of varicocele and cell phone storage in trousers pockets on semen or hormonal parameters. Additionally, smoking status was analyzed as covariate.

Limitations of our study are the lack of detailed information on the extent of cell phone storage in trousers pockets. Moreover, smoking status was analyzed as a yes or no covariate. Despite the relatively large study of group of 468 patients a grouping of smoking status was not reasonable due to resulting small group sizes. Moreover, there are many other factors known to have an influence on spermatogenesis, for example coffee consumption. Unfortunately, since this was a retrospective analysis, such information was not available to be taken into consideration. Also information on the duration of keeping the mobile phones in trousers pockets was not available.

Additionally, it has to be mentioned that during the time period of inclusion, cell phone technology and transmission frequencies have changed. Older types of cell phones only infrequently connected to the base station in standby mode, while smartphones show more active communication and signalling. The latter could therefore lead to a higher influence on spermatogenesis. Apart from the possible adverse effects of cell phone technology the simple reduction in space for the scrotum on the side of cell phone storage could lead to an increase in temperature and therefore disturbance of testicular functions. Because patients were included into a database between 1993 and 2007, the now outdated WHO guidelines of 1999 were used for sperm analysis, which represents another limiting factor of this study.

This analysis showed an inverse relation of sperm concentration and degree of varicocele. Patients with a varicocele grade 3 had a lower sperm concentration than those with a grade 2 or grade 1 varicocele. This difference was significant for the comparison of varicoceles with grade 3 and grade 1. Results of the few existing trials on sperm parameters in different grades of varicocele vary. These data join existing findings of other studies suggesting an increasing negative effect with higher grade of varicocele [21, 22]; however, the sperm parameters affected differ between these trials. One study found no significant impact on motility and morphology but detected the sperm concentration to suffer most in grade 3 varicoceles, while grade 1 and 2 showed similar results [21]. The other study reported a deterioration of sperm morphology with higher grade of varicocele but without impairment of sperm concentration and motility [22].

In this study, the effect on LH was detectable for all varicocele grades in multivariate analysis but was not assignable to any grade of varicocele. In contrast to testosterone, LH did not significantly change between the grades. Testosterone showed significant differences overall and between the grades 1 compared to 3 and 2 compared to 3, with higher values in higher grades. Nevertheless, values for testosterone and LH were still within the normal range. This supports findings published in 2010, which reported statistically significant higher serum testosterone levels with grade 3 varicoceles than with lower grades in a retrospective analysis of 716 patients presenting with varicocele and infertility; however, LH was not affected in this trial [21]. Another study by Cantatore et al. from 2010 also reported higher testosterone and also FSH levels in infertile patients with varicocele compared to infertile patients without varicocele [23]. On the other hand, other studies demonstrated low serum testosterone levels in patients with a varicocele [24, 25]. For example, in 2011 Tanrikut et al. reported lower testosterone levels in patients before undergoing varicocelectomy compared to vasectomy reversal patients, even after correcting for age [26]. After varicocelectomy for infertility, testosterone levels were shown to increase significantly [27], also independently of the varicocele grade [28]. Nevertheless, there are also trials which could not detect any overall impact of varicocele on testosterone [8, 29] nor between the grades of varicocele [29]. Pasqualotto et al. compared fertile and infertile men with varicoceles with fertile patients presenting for vasectomy and did not detect any difference in testosterone levels between the groups [8]. In summary, the results on serum testosterone in

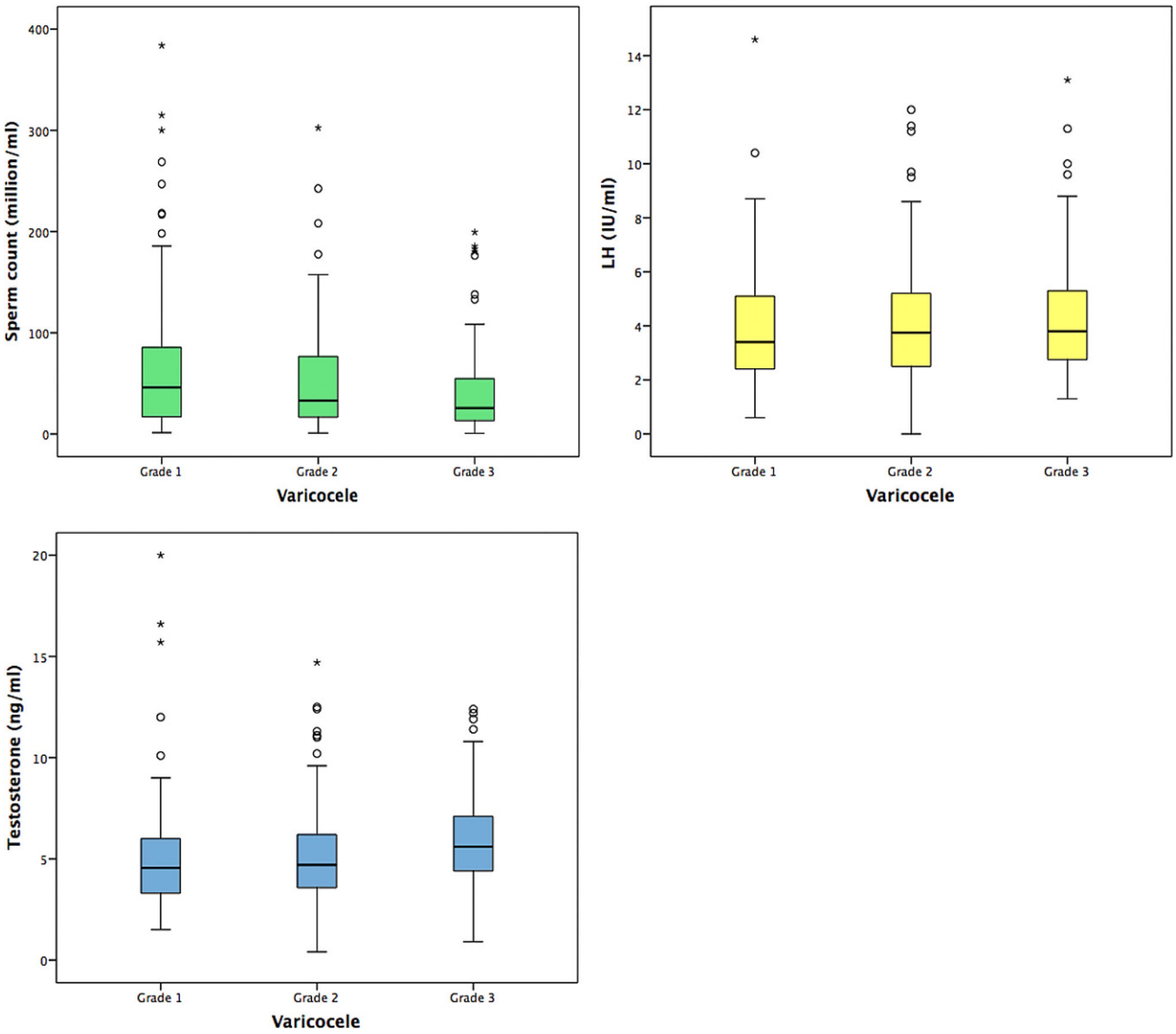


Fig. 1 Varicocele grades and sperm concentrations, LH levels and testosterone values

varicocele patients vary. This might be due to different stages of testicular dysfunction and in the case of this trial, the higher testosterone values in higher grades of varicocele, although still in the normal range, could reflect a compensatory mechanism of the testes to overcome impaired function. Interestingly, this analysis did not show any effect on sperm motility or sperm morphology, neither overall in multivariate analysis nor for any grade of varicocele in particular but only for sperm concentration. Also, there was no influence of varicocele on FSH, which could be expected to be above normal limits in patients with impaired spermatogenesis [8].

The relationship between cell phone storage in trousers pockets and male infertility remains unclear. In vitro, animal as well as human studies have tried to elucidate the effect of radiofrequency electromagnetic waves on semen parameters and fertility, coming to varying results and conclusions [30]. Adams et al. also published a meta-analysis in 2014 and used 10 in vivo and in vitro studies only on samples of human subjects from fertility clinics and research centers. The sperm quality outcome measures were concentration, motility, and viability. Experimental in vitro and observational in vivo studies led to consistent results. Cell phone exposure was associated with reduced sperm motility and viability, while the effects on sperm concentration were more equivocal [30] but the authors did state effects of cell phone use on sperm morphology. Moreover, in this trial it was the only seminal parameter affected by cell phone storage in trousers pockets. In contrary to the abovementioned study only few observational studies showed a negative effect of mobile phones on morphology [20, 31]. The pathophysiology leading to impaired spermatogenesis has not yet been fully elucidated but is thought to involve scrotal hyperthermia and sperm DNA damage through oxidative stress [32]. In this

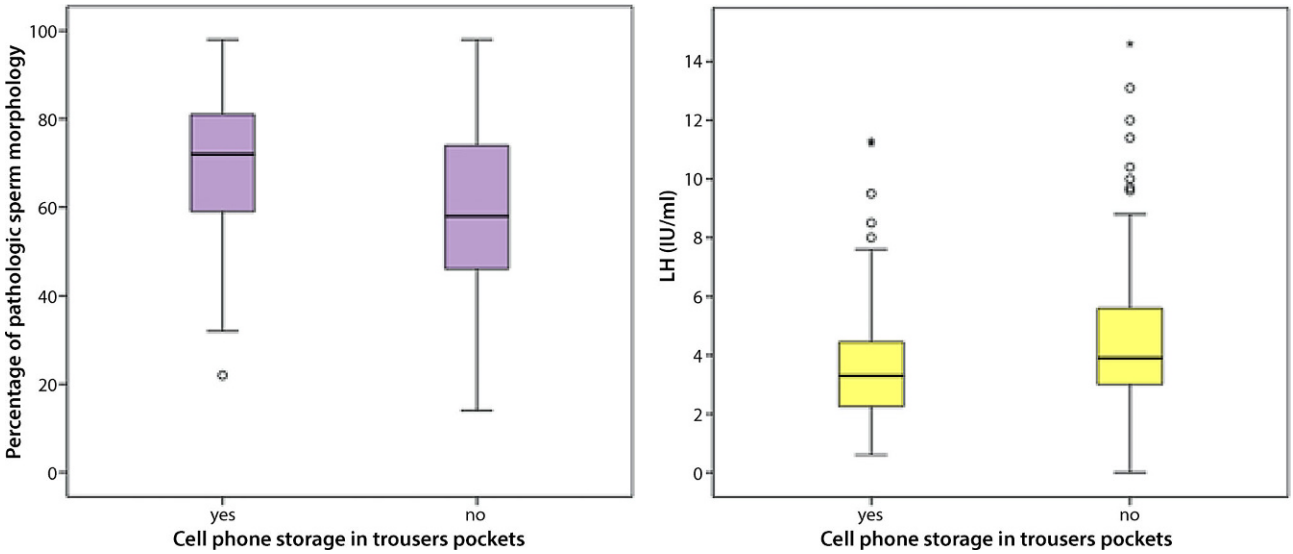


Fig. 2 Cell phone use and percentage of pathologic sperm morphology and LH levels

series, lower LH levels were detected in the group of cell phone users. This difference, however, was not reflected in the testosterone values. In 2008, Djeridane et al. reported no effects on hormonal functions by radiofrequency electromagnetic waves [33]. Gutschi et al. on the other hand reported significantly higher testosterone and lower LH levels in patients using cell phones [34]. In summary, inconsistent reports exist on radiofrequency electromagnetic waves and sperm and hormonal parameters, with the majority of trials reporting negative effects.

This trial did not detect a combined effect of varicocele and cell phone storage in trousers pockets. Nevertheless, as already mentioned as a limitation of this study, data on exact extent of use and the amount of time the cell phone is kept in the trousers pockets is lacking. This might have concealed the effect of radiofrequency electromagnetic waves. Further studies with more detailed history or measurement of exposure are recommended.

Smoking did not show a significant effect on any of the parameters examined in this trial. As explained in the limitations section, smoking could only be included as a "yes/no" covariate, which might have led to this result and maybe masked the negative effects of smoking on reproductive function, which have been extensively reported on in literature and recently confirmed by a meta-analysis [35].

To our knowledge this is the first study to analyze a possible combined effect of varicocele and cell phone storage in trousers pockets on seminal parameters.

Conclusion

This analysis showed an inverse relation of sperm concentration and degree of varicocele, with lower sperm concentrations in higher grade varicoceles. Interestingly, testosterone levels were significantly higher in higher grade varicoceles, which could reflect a compensatory mechanism to the impaired testicular function. Cell phone storage in trousers pockets showed an effect on LH levels and on the percentage of pathologic sperm morphology. A combined effect of varicocele and cell phone storage in trousers pockets could not be detected in this study. Also, smoking did not show a significant effect on any of the parameters analyzed.

Compliance with ethical guidelines

Conflict of interest I. Schauer and B. Mohamad Al-Ali declare that they have no competing interests.

Ethical standards All procedures reported in this study were carried out in accordance with national law and the Helsinki Declaration from 1964 (in its current revised form). Institutional ethics committee approval was obtained, all patient data were blinded. Informed consent statements were not obtained since this was a retrospective study.

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