

## Effects of Smoking Cessation on Hormonal Levels in Men

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Received January 30, 2012

Accepted August 31, 2012

On-line November 22, 2012

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### Summary

Chronic smoking can cause imbalance in endocrine homeostasis and impairment of fertility in both sexes. The male reproductive system is more resilient, still the literature provides conflicting results about the influence of smoking on the steroid hormone levels. The data about smoking cessation are limited; there has not yet been a study primarily focused on changes in steroids levels. In our study, we analyzed levels of testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), cortisol and sex hormone-binding globulin (SHBG) in male smokers and during smoking cessation. Monitored analytes were determined by RIA. The free testosterone index was calculated. Basal samples of men successful and unsuccessful in smoking cessation did not differ and monitored hormones could hardly predict success of smoking cessation. After one year without smoking, a significant BMI increase and SHBG decrease in former smokers was observed. The decrease in total testosterone was non-significant. Changes in SHBG and testosterone did not correlate with BMI, presumably due to the direct effect of smoking cessation.

### Key words

Steroids • Smoking cessation • Prediction • Body mass index • Sex hormone-binding globulin

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### Introduction

Smoking still presents one of the most common addictions. Widespread and persistent abuse of cigarettes is determined by the nicotine's ability to induce addiction. Nicotine binds to acetylcholine receptors and causes the release of dopamine in the central nervous system (CNS). A number of studies point out nicotine's ability to alter hormonal homeostasis in both men and women. Smoking affects pituitary, thyroid, adrenal, testicular and ovarian functions, calcium metabolism as well as insulin effect (Stárka *et al.* 2005).

Chronic smoking can cause the impairment of fertility in both sexes. The male reproductive system is more resilient; mainly a negative shift in spermiogram parameters has been described in male smokers. However, only a small number of studies were dedicated to influence of smoking on levels of steroid hormones and similarly the effects of smoking cessation. These present conflicting results. The principal topic of these studies is semen quality (Istvan *et al.* 1994, Trummer *et al.* 2002, Patterson *et al.* 1990, Shaarawy and Mahmoud 1982) or an evaluation of the effect of smoking on erectile dysfunction (Natali *et al.* 2005, Corona *et al.* 2005).

In studies on sexual hormones in smokers, those describing an elevated testosterone level in male smokers, similarly as in female smokers, prevail. The increase

positively correlated with the number of smoked cigarettes (Svartberg and Jorde 2007). Studies frequently confirmed that an increase in total testosterone levels was accompanied by elevated SHBG in smokers (English *et al.* 2001, Field *et al.* 1994). However, both free and total serum testosterone levels were found to be increased in smokers (Trummer *et al.* 2002). Several studies also found reduced testosterone levels and demonstrated changes in enzyme expression in key tissues for androgen production (Meikle *et al.* 1988, Mittler *et al.* 1983, Olayaki *et al.* 2008, Mendelson *et al.* 2005). Very few studies observed levels of steroid hormones during smoking cessation. Testosterone levels were reported to be significantly lower in those who were able to stop or reduce smoking (Trummer *et al.* 2002).

Smoking activates hypothalamic-pituitary-adrenal axis (HPA), stimulates adrenocorticotropic hormone (ACTH) secretion and enhances ACTH effect on adrenal cortex which results in stimulation of cortisol production. Among other things, this activation is associated with the lower sensitivity of nicotine receptors in CNS. Prolonged discontinuation of smoking leads to changes in HPA activity and a steep decrease in serum cortisol (Kirschbaum *et al.* 1992, Frederick *et al.* 1998).

DHEA levels increased after one cigarette smoked (Mendelson *et al.* 2005, Schmidt *et al.* 2005) and some increase was also found in chronic smokers. This neuroactive steroid is considered to be an effective antidepressant and it was recommended as a suitable medication in smoking cessation (Marx *et al.* 2006). In Marx's study, the authors found that DHEA levels inversely correlated with negative effects and a desire for a cigarette.

In the literature, the prediction of smoking cessation success is described mainly in relation to body weight (Twardella *et al.* 2006, Osler *et al.* 1999, Godtfredsen *et al.* 2001). In addition to weight, relations to sex, nicotine amount per day, smoking of cigars and alcohol drinking are also discussed (Osler *et al.* 1999). In women, even a correlation between smoking cessation success and education was demonstrated (Osler *et al.* 1999).

Some studies showed that DHEA levels and decrease in cortisol levels after smoking cessation could predict the degree of nicotine addiction. A decrease in cortisol to DHEA ratio during the first eight days of smoking cessation was associated with a relapse in the weeks that followed (Rasmussen *et al.* 2006).

Our study had two aims. The first one was to search for a possible predictor of successful smoking cessation among selected steroids. We focused on searching for differences in levels of testosterone, DHEA, DHEAS, cortisol and SHBG among men successful and unsuccessful in smoking cessation from the first blood collection. These basic steroid hormones for neuroactive steroids are involved in mechanisms regulating CNS functions, modulating behavior and tendency toward addictions. So changes in basic steroids can indicate which concrete neurosteroids can influence the efficiency of smoking cessation.

Our second aim was to observe hormonal changes in men successful in smoking cessation after one year.

## Methods

The study involved 76 male smokers who decided to cease smoking and sought medical advice at the Tobacco Dependence Centre at the General University Hospital, Prague. The men included in the study did not suffer from any serious endocrinopathy and did not use any steroidogenesis affecting medication. Their average age was 39.3 ( $\pm 11.5$ ) years and possessed a mean Body Mass Index (BMI) of 26.5 ( $\pm 3.8$ ) kg/m<sup>2</sup>. The average smoker smoked 24 $\pm$ 10 cigarettes per day at the beginning of the study.

The men were monitored for one year during which their smoking cessation was medically observed. Nicotine patches were used. The reported decrease in smoking was checked by a cotinine analysis. As part of the study, the men underwent an examination before beginning smoking cessation and after one year without smoking. The examination involved blood collection to determine testosterone, DHEA, DHEAS and cortisol and the collection of basic anthropometric data. Sampling was performed in the morning hours with regard to the circadian rhythm of hormonal levels. Smokers were divided into three groups according to their success in smoking cessation. The first group consisted of 34 men who failed to stop smoking. The second group consisted of 16 men who managed to stop smoking for at least 6 weeks. The third group included 26 men successful in smoking cessation in that they did not smoke for one year.

The study was approved by the Ethical Board of the Institute of Endocrinology.

### Steroids analysis

Total testosterone (T), dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), sexual hormone binding globulin (SHBG) were determined and a free testosterone index was calculated ( $FAI = [(testosterone/SHBG) \times 100]$ ). Testosterone was determined by standard radioimmunoassay (RIA) using antiserum anti-testosterone-3-carboxymethyl-oxim: BSA and testosterone-3-carboxymethyl-oxim-tyrosylmethyl-ester-[125I] as a tracer. Intra-assay and inter-assay coefficients variants were 7.2 % and 10 %, respectively, and sensitivity was 0.21 nmol/l. SHBG was assayed by IRMA kit (Orion, Espoo Finland). Commercial kits Immunotech (Marseilles, France) were used to determine DHEA and DHEAS (RIA kit).

### Statistical analysis

The starting data were evaluated by using Kruskal-Wallis robust ANOVA followed by robust Dunn's multiple comparisons with Bonferroni correction. The data from successful smokers before and after smoking cessation were analyzed using a Wilcoxon paired robust test.

## Results

When searching for possible indicators of smoking cessation success prediction, basal samples

seemed to show higher testosterone levels in men successful in smoking cessation, but even these results were not statistically significant. Successful and unsuccessful men did not differ in other parameters as DHEA and cortisol; therefore monitored hormones did not apply in the smoking cessation prediction (Table 1).

After one year of abstinence, there was a statistically significant BMI increase in former smokers. Mean BMI in successful patients at the beginning of the study was 26.2 ( $\pm 3.3$ ) kg/m<sup>2</sup>; after one year without smoking it was 28.7 ( $\pm 3.7$ ) kg/m<sup>2</sup>. The average weight gain was 6.8 ( $\pm 3.5$ ) kg.

Furthermore, there was a statistically significant decrease in SHBG. We found no significant changes in testosterone levels; decrease in total testosterone, free testosterone index and DHEAS was non-significant. DHEA and cortisol levels did not change (Table 2).

Changes in SHBG and testosterone did not correlate with BMI increase. We assume that weight increase (in successful individuals, thus one year after the first check-up, 6.8 $\pm$ 3.5 kg, in average) and decrease in SHBG levels were associated with the smoking cessation since SHBG levels did not correlate with BMI. Therefore the smoking cessation probably had a significant effect on the SHBG level.

Thus, the study results confirmed several findings mentioned in the literature, which described the influence on male reproductive system as insignificant.

**Table 1.** Differences in steroid levels among a group of unsuccessful patients in smoking cessation, a group of patients who failed after 6 weeks and a group of successful patients.

Steroid	Unsuccessful (n=34)	Failed after 6 weeks (n=16)	Successful (n=25)	Between group differences***
Age	38 (30, 47.8)	41 (30, 49.8)	34 (32, 46.8)	p=0.74462
BMI [kg/m <sup>2</sup> ]	26.4 (24, 29.9)	24.6 (23.4, 26.9)	26.2 (23.8, 29.9)	p=0.419669
Testosterone [nM]	11.8 (9.95, 15.6)	12.1 (9.58, 13.5)	12.5 (9.85, 14.9)	p=0.719192
FAI*	0.499 (0.365, 0.738)	0.502 (0.347, 0.57)	0.448 (0.355, 0.688)	p=0.73723
fT**	0.292 (0.233, 0.376)	0.284 (0.195, 0.321)	0.274 (0.228, 0.312)	p=0.591776
DHEA [nM]	17.4 (12.2, 25.5)	21.4 (12.5, 27)	21.9 (14.9, 34.5)	p=0.381323
DHEAS [ $\mu$ M]	7.8 (5.58, 11)	7.85 (4.95, 14)	8.25 (6.08, 11.5)	p=0.846087
Cortisol [nM]	364 (289, 451)	337 (278, 492)	438 (364, 578)	p=0.09533
SHBG [nM]	25.8 (16.8, 32.7)	24.5 (18.3, 29.8)	26.2 (15.4, 36.2)	p=0.840684

\* free androgen index; \*\* free testosterone; \*\*\* Kruskal-Wallis robust ANOVA followed by robust Dunn's multiple comparisons with Bonferroni correction, only significant multiple comparisons are shown (p<0.05).

**Table 2.** Effect of smoking cessation on steroid levels.

Steroid	Before the initiation of smoking cessation	After a year of smoking cessation	Difference	Wilcoxon's paired test
SHBG	26.2 (15.4, 36.2)	20 (14.5, 30.6)	-4.02 (-8.57, 0.693)	p=0.0169631
Testosterone [nM]	12.5 (9.85, 14.9)	11.1 (8.9, 13.8)	-1.2 (-2.83, 0.2)	p=0.073306
DHEA [nM]	21.9 (14.9, 34.5)	20.1 (12.6, 30)	-1.25 (-6.98, 6.25)	p=0.542159
DHEAS [μM]	8.25 (6.08, 11.5)	7.5 (5.5, 9.9)	-0.35 (-1.35, 0.335)	p=0.112341
Cortisol [nM]	438 (364, 578)	487 (383, 620)	25.2 (-71.4, 150)	p=0.492839

## Discussion

Smoking affects testosterone levels; however, data in available studies differ. Both decreased and increased levels have been described. There are several reasons for the results not being strictly uniform, e.g. smoking characteristic of the patients, preanalytical and analytical errors etc. However, the majority of studies which also included SHBG levels confirmed that SHBG levels in smokers are higher, and both free and total testosterone are increased in smokers (English *et al.* 2001, Field *et al.* 1994, Kaapor and Jones 2005, Svartberg and Jorde 2007, Dai *et al.* 1988).

English *et al.* (2001) and Field *et al.* (1994) suggest that higher total testosterone in smokers was due to SHBG increase and that SHBG levels correlated with the serum nicotine level (English *et al.* 2001). Svartberg and Jorde (2007) found a positive association between testosterone levels and smoking even when adjusted to SHBG levels values. Field *et al.* (1994) demonstrated significant increase in SHBG levels but non-significant changes in testosterone levels bound to albumin.

The mechanism of how smoking increases testosterone levels remains unclear. Besides the opinion that it is a secondary elevation resulting from an SHBG increase in smokers, there are other theories.

Nicotine-mediated inhibition of aromatase can be one of the factors which decrease estrogen levels and cause higher androgen levels in women smokers. The study in which an aromatase inhibitor (anastrozole) was administered to older men with low testosterone demonstrated an increase in total and free testosterone (Leder *et al.* 2004).

There are also studies that conversely point to the reduction of testosterone due to smoking. The theories of smoking decreasing testosterone levels are usually based on the direct effect of smoking on steroidogenesis

with an influence on enzymatic functions. Some studies are based on experimental models. Meikle *et al.* (1988) studied the effects of nicotine and cotinine on canine prostate enzymes. It has been demonstrated that nicotine and cotinine acted as competitive inhibitors of 3 alpha-hydroxysteroid dehydrogenase (enzyme converting dihydrotestosterone to 3 alpha-androstandiol) and DHT cumulation occurred. As a result, it can alter androgen effect on tissues, e.g. skin and prostate (Meikle *et al.* 1988). The second study observed the effects of chronic smoking on androgen metabolism in dogs. It showed a decrease in 7 alpha-hydroxylase activity and stimulated activity of hepatic 6 beta-hydroxylase. Serum testosterone levels were decreased and LH levels were elevated compared to the controls. These results indicate that chronic smoking enhances intra-hepatic testosterone metabolism (Mittler *et al.* 1983).

Studies on male smokers confirm the above nicotine effect. Shaarawy and Mahmoud (1982) demonstrated significant decrease in total testosterone levels in smokers compared to non-smokers. Olayaki *et al.* (2008) found a reduced concentration of urinary testosterone in male smokers compared to non-smokers of corresponding age and BMI. Mendelson *et al.* (2003) studied the acute effect of a smoked cigarette and found only a non-significant decrease of testosterone levels.

It is known that nicotine increases energetic output and can also reduce appetite. That would explain why the weight of smokers tends to be lower compared to that of non-smokers and why smoking cessation leads to a weight gain. We observed a higher weight in heavy smokers in contrast to the smokers of a lower number of cigarettes; this was probably due to the predominance in heavy smokers of other types of risk behavior, e.g. low physical activity and poor diet. In addition, smoking increases insulin resistance and is associated with central fat accumulation, thus resulting in an increased risk of a

metabolic syndrome and diabetes (Chiolero *et al.* 2008).

As known from the literature, SHBG levels are decreased in obese men. Laaksonen *et al.* (2005) demonstrated a decrease of SHBG in men, in which metabolic syndrome developed in the future. Lower SHBG results in a decrease of total testosterone. Laaksonen *et al.* (2005) observed higher levels of total and free testosterone levels at baseline in smokers compared to non-smokers. During the subsequent 13-year observation, a reduced number of cigarettes was, however, associated with a greater decrease in testosterone, a higher risk of hypogonadism defined by levels of total and free testosterone and a greater increase in waistline compared to men who continued smoking without restrictions. The authors assume that the reduction of testosterone and increase in the risk of hypogonadism is related to weight gain in men who reduced the number of cigarettes per day or stopped smoking (Laaksonen *et al.* 2005).

In our study, individuals successful in smoking cessation gained 6.82 kg on average and the mean BMI was 28.7 kg/m<sup>2</sup>. We expected that a decrease in total testosterone and SHBG will correlate with BMI. Weight gain and BMI, however, surprisingly did not correlate with the SHBG value, which decreased without correlation to BMI. We believe that SHBG levels, which according to previous studies were enhanced in smokers, decreased during smoking cessation not correlated to weight gain. We assumed that this was due to the direct effect of smoking cessation on changes in hepatic production of SHBG.

An extensive cohort study showed that overweight men, unlike women, had a higher chance of successful smoking cessation compared to the men with normal weight. Another large cohort study observing over 10,000 smokers brought similar results. A positive association of BMI and successful smoking cessation was demonstrated (Twardella *et al.* 2006, Godtfredsen *et al.* 2001). The success rate was positively associated with male sex, with smoking cigarettes and negatively with the amount of smoked tobacco and alcohol drinking.

Smokers in our study who sought medical care in smoking cessation exhibited BMI above the norm in average at baseline. Mean BMI at baseline in unsuccessful patients was 26.4 kg/m<sup>2</sup> and it practically did not differ from the mean BMI 26.2 kg/m<sup>2</sup> in successful individuals. Therefore, we did not demonstrate

in our study that greater weight would predict success. However, it was the group of individuals already overweight who were certainly more strongly motivated to stop smoking than most smokers who did not seek medical surveillance.

Our study did not show changes in blood levels of serum cortisol levels following the discontinuation of smoking, as described in the literature. The predictor of successful smoking cessation, cortisol and DHEA ratio, described in the literature was not demonstrated in our study either. In smokers, both before the cessation and after one year, we demonstrated relatively higher cortisol levels compared to what we would expect with regard to the circadian rhythm, probably due to a stress reaction from the blood sampling.

## Conclusion

The results of our study concur with the opinion that the influence of smoking on male reproductive system, in terms of hormonal homeostasis, has little significance. When comparing hormone levels during smoking and after one year without smoking, we found no significant changes. Former smokers only differed significantly in decreasing SHBG levels which, however, did not correlate with increasing BMI. This finding suggests that smoking restrictions have an independent effect on the SHBG level. Changes in other parameters did not reach significant changes as well, as there was no significant correlation between androgen levels and success in smoking cessation. Therefore, basal testosterone levels are of no value in the smoking cessation prediction. It would be worth observing testosterone and SHBG levels after a longer period following the discontinuation of smoking, when the effects of chronic smoking could be eliminated.

## Conflict of Interest

There is no conflict of interest.

## Acknowledgements

We thank the study participants and our excellent research nurses. The study was supported by grant IGA MZ CR no NS 10125-3, by the project MZ CR for conceptual development of research organization 00023761 (Institute of Endocrinology, Prague, Czech Republic) and SVV UK 2012 no 264501.

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