Correlation between smoking, serum serotonin level, and peripheral fatigue of back extensors: cross-sectional study

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Background
Smoking is a negative behavior pattern that is harmful to our life .When the spinal muscles are fatigued, their capacity to create a quick extensor movement is compromised, and serotonin is the master regulating hormone in the body that controls distinctive body works for instance.
Purpose
This study was conducted to investigate the relation of serum cotinine level (the metabolite of nicotine), serum serotonin level, and peripheral fatigue of back extensors.
Patients and methods
A total of 60 (40 smokers and 20 nonactive smokers) normal men were assigned into three groups: 20 nonsmokers (control group), 20 moderate smokers, and 20 heavy smokers. Blood samples were taken from all patients to analyze cotinine and serotonin levels by laboratory tests. Isokinetic dynamometer was used to measure fatigue susceptibility by calculating the fatigue index.
Results
There was a statistically significant correlation among serum cotinine level, fatigue index, and serum serotonin level in heavy smokers ($P<0.05$) and in moderate smokers ($P<0.05$). In addition, there was a significant correlation between serum cotinine and serotonin levels in the nonsmoker group ($P<0.05$).
Conclusion
An increase in the serum cotinine level increases the fatigability of back extensors in smokers. Further, cotinine has an inverse relationship with serum serotonin level in smokers and nonsmokers. In addition, serum serotonin level had an inverse relation with peripheral fatigue of back extensors in smokers.

Keywords:
back extensors, fatigue, serotonin, smoking

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Introduction

Smoking is a bad habit that is destructive to our life; it is a noteworthy problem regarding general well-being that has a huge financial and additionally heath sway [1]. Worldwide, tobacco use causes nearly six million deaths per year, and current trends show that tobacco use will cause more than eight million deaths annually by 2030, and on average smokers die 10 years earlier than nonsmokers [2,3].

Cotinine is a metabolite of nicotine and, therefore, can be used as an objective surrogate marker for smoking status, and it is generally used to recognize smokers from nonsmokers in epidemiologic studies. Serum cotinine levels less than 10 ng/ml are thought to be steady with nonsmokers. Values of 10–100 ng/ml are connected with light or moderate smoking, and levels above 300 ng/ml are found in heavy smokers (>20 cigarettes a day). In any case, there are racial contrasts in cotinine levels [4,5].

It has been accounted for that, in youthful male smokers coordinated for physical movement with controls, smoking causes a significant decrease in skeletal muscle fatigue resistance [6]. At the point when the spinal muscles are exhausted, their capacity to create a quick extensor movement is compromised, alongside their capacity to control trunk steadiness [7]. Similarly, lumbar extensor weakness influences paraspinal muscle reflex and influences trunk proprioception [8].

Serotonin different body functions, such as change in mood and behavior, the event of depression the ability to sleep, the level of appetite, learning and memory, and direction of body temperature; some endocrinal regulation and muscle contraction are also controlled

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by serotonin. Serum serotonin level ranged from 101 to 283 ng/ml [9,10].

There was a contradiction about the relation between cotinine and serotonin; some studies reported that cigarette smoking stimulates serotonin release [11], and others reported that nicotine exhausts serotonin production levels in the mind. It is believed that smoking cigarettes can decrease our serotonin generation level by as much as half. In addition, there is receptor desensitization and receptor inhibition by nicotine [12].

However, the inter-relationships between cotinine level, serotonin level, and fatigue of back extensors have not been reported. In addition, there is absence of a significant correlation between cotinine levels and fatigability of the muscle [13]. The present study was directed to correlate serum cotinine level, serum serotonin level, and peripheral fatigue of back extensors.

Patients and methods

This study was conducted at the isokinetic laboratory in the Faculty of Physical Therapy, Cairo University, from September 2015 to March 2016. To study the relationship between serum cotinine level, serum serotonin level, and peripheral fatigue of back extensors, blood samples were taken and fatigue susceptibility was measured by calculating the fatigue index of back extensors.

Design of the study

This is an observational study. Its cross-sectional design was used to study the relation between serum cotinine level, serum serotonin level, and peripheral fatigue of back extensors.

Patients

Sixty normal employees at the faculty of physical therapy participated in this study. Patients were recruited using publically distributed posters, online social media, and by verbal invitation after approval from the Ethical Committee of the Faculty of Physical Therapy, Cairo University, and all patients signed a written informed consent.

G*Power 3.1 software (Universities, Dusseldorf, Germany) was used for calculation of sample size with 80% power, 0.05 type I error (2 tailed) and effect size of 0.99; so 20 subjects was recruited in each group and total number recruited was 60.

After taking blood samples and performing laboratory tests, the participants were assigned into three equal groups according to their serum cotinine level: (a) nonsmokers (control group) with serum cotinine levels less than 10 ng/ml; (b) light, moderate smokers with serum cotinine levels of 10–100 ng/ml; and (c) heavy smokers with serum cotinine levels above 300 ng/ml [3]. Each group consisted of 20 patients. The demographic data of patients were as follows: their age ranged from 20 to 40 years and their BMI ranged from18.5 to 24.9 kg/m^2. Smokers smoked at least 5–6 cigarettes a day in the past 5 years. Smoking was restricted to cigarettes. The exclusion criteria for participants were athletic patients, patients who receive antidepressants, patients with a history of lower back pain, spine-related dysfunction, cardiopulmonary or cardiovascular problems, diabetes, a recent history of vestibular disorder, inner ear infection with associated balance, and coordination problems.

Instrumentation

Biodex System 3 Pro Isokinetic Dynamometer (Biodex Medical Inc., Shirley, New York, USA) was used to objectively assess the parameters of muscle performance (torque, peak torque, angle specific torque, work, power, and angle acceleration energy) that would be difficult to obtain using manual testing techniques [14]. The biodex isokinetic dynamometer equipped with a special forward reclined back attachment was used to measure prefatigue and postfatigue peak torques of back extensors. It is one of the most comprehensive, computer-driven, biomechanical systems used for musculoskeletal rehabilitation and conditioning [15].

Procedure

The study procedure was explained to all patients, and blood samples were taken from all patients to analyze cotinine and serotonin levels by laboratory tests. We used Neogen Cotinine Human Forensic Drug detection ELISA for the determination of trace quantities of cotinine undiluted human serum (Neogen Corporation, Lexington, Kentucky, USA). In addition, we used Serotonin ELISA (RE59121) enzyme immunoassay for the in-vivo diagnostic quantitative determination of serotonin in human serum (IBL International GmbH, Hamburg, Germany).

Every patient was positioned in the upright neutral sitting position (the actual 0° starting position) so that the anterior superior iliac spine and the posterior superior iliac spine were aligned in the horizontal

plane [16]. The predetermined spinal range of motion, which was chosen to be 'the target angle' to measure peak torque for the patients during the prefatigue and postfatigue testing protocol, is the angle of the spinal flexion at 30° of spinal flexion angle from the actual starting position (neutral starting position) [17].

Each patient was asked to move into flexion as much as he can to set the maximum available trunk range of motion to determine whether he was able to perform the experimental task. The dynamometer was locked in the 0° position to ensure the same starting position in all the tests.

Prefatigue test

The testing protocol was explained to each patient, the test was started with the patient in 30° of spinal flexion, and then the patient was instructed to extend his back with maximal force against the tension in his back muscles over 2–3 s and holding this maximal isometric effort for 2 s before relaxing. Three trials were performed [18], and it was a part of the standardized testing protocol established by isokinetic dynamometer. The session was terminated when the patient completed the series of isometric back extension contractions, and maximum isometric torques were measured at this angle.

Fatigue challenge

The patients were asked to complete successive repetitions of full spinal range of motion, with a weight load equal to 50% of their peak torque of prefatigue test. Each repetition was performed in a slow controlled manner. Each patient was encouraged to complete as many repetitions as possible before signaling that they could not perform further repetitions because of fatigue [7].

Postfatigue test

Immediately after the indication of fatigue, the patients were instructed to perform the postfatigue test in the same manner and sequence as the prefatigue test. The torques generated from prefatigue and postfatigue tests were collected to calculate the fatigue index.

Fatigue index

It is the percentage change in maximum torque after the fatigue challenge [5].

$$\text{Fatigue index} = \frac{\sum \text{Prefatigue torques} - \sum \text{postfatigue torques}}{\sum \text{Prefatigue torques}} \times 100.$$

Data analysis and statistical design

All statistical measures were performed through the statistical package for the social sciences (SPSS), version 20 for Windows. One-way analysis of variance was used for comparison of the mean age and BMI among groups, and Pearson's correlation test was used to correlate serum cotinine level and serum serotonin level, serum cotinine level and fatigue index, and serum serotonin level and fatigue index. The level of significance for all statistical tests was set at P value less than 0.05.

Results

General characteristics of the patients

Analysis of variance test among three different groups (A, B, and C) for patient's age and BMI revealed that there were no statistically significant differences ($P>0.05$) among the three groups, as shown in Table 1.

Correlation between cotinine level, serotonin level, and fatigue of back extensor muscle

Pearson's correlation coefficient (r) was used to find out the relationship between variables. For group A, there were significant negative moderate correlations between cotinine level and serotonin level. There was no significant correlation between the level of fatigue of back extensors and neither cotinine nor serotonin levels. For group B, there were significant negative strong correlations between cotinine level and serotonin level. There was a significant positive strong correlation between cotinine level and fatigue of back extensor muscle. There was a significant negative strong correlation between serotonin level and fatigue of back extensors muscle, and for group C there were significant negative strong correlations between cotinine level and serotonin level. There was a significant positive strong correlation between cotinine level and fatigue of back extensor muscle. There was significant negative strong correlation between serotonin level and fatigue of back extensor muscle, as shown in Table 2.

Discussion

The purpose of this study was to investigate the relationship of serum cotinine levels (the metabolite of cigarette nicotine), serum serotonin levels

Table 1 Mean values of patient's age and BMI among groups A, B, and C

Items	Age (years)	BMI (kg/m^2)
Group A	25.2±3.83	22.25±1.83
Group B	27.95±7.57	22.74±1.81
Group C	26.8±7.41	22.09±1.84
F-value	0.900	0.671
P-value	0.412	0.515

Table 2 Correlation between serum cotinine level and serum serotonin level and fatigue index for 3 groups

	Serotonin level		Fatigue of back extensors	
	r	*P*-value	*r*	*P*-value
Group A				
Cotinine level	–0.510	0.022	0.352	0.128
Serotonin level	–	–	–0.402	0.079
Group B				
Cotinine level	–0.677	0.001	0.660	0.002
Serotonin level			–0.815	0.000
Group C				
Cotinine level	–0.843	0.000	0.785	0.000
Serotonin level			–0.844	0.000

(as neurotransmitter), and fatigability (fatigue index) of back extensors.

In the current study, the results indicated that there was a significant association between the smokers groups for the fatigue index of back extensors. The higher fatigue index was recorded in the heavy smokers group, as with increasing cotinine level the fatigue index increased.

In addition, the results indicated that there was a significant association among the three groups for serum serotonin level. Higher serum serotonin level was recorded in nonsmokers group, as with increasing serum cotinine level the serum serotonin level decreased.

In addition, the results indicated that there was a significant association between the smokers groups for serum serotonin level and fatigue index. Serum serotonin level had an inverse relation with peripheral fatigue of back extensors in smokers.

The results of the current study come in agreement with those of Al Obaidi *et al.* [7], who expressed that the hazard for creating LBP because of disc prolapse increased by 20% for each 10 cigarettes smoked every day in 1 year. The relevance of back pain was expanded by the amount of cigarette smoking annually. With the heaviest smoking levels, biopsies obtained from patients with herniated lumbar disc have more type IIa than type IIb filaments in the longissimus and multifidus muscle.

Orlander *et al.* [19] attributed the lower rate of high oxidative type I and higher rate of low oxidative type II fibers in vastus laterlaris muscle of sedentary male smokers compared with nonsmokers to the reduction of blood and O_2 supply on exposure to tobacco smoke, which causes a type shift of fibers from high oxidative to low oxidative in skeletal muscle.

Another explanation was given by Wüst *et al.* [20] who found that smokers frequently have a sensation of general fatigue and the effect would increased by increasing the smoking volume, this general fatigue could be brought on by (a) oxidative capacity of the muscle that smokers have a lower activity of mitochondrial enzymes, (b) smokers have decreased oxygen deliverd to the muscles because of diminishing of the blood flow or the oxygen content of the blood is lower than normal because of nicotine in the cigarette.

In addition, Nakatani *et al.* [21] suggested that increasing blood carbon monoxide (HbCO) because of tobacco smoke induce hypoxia, and nicotine in tobacco smoke causes capillary contraction, resulting in diminished blood and O_2 supplies, which in turn lead to muscle fatigability in smokers compared with nonsmokers.

This study is supported by the work of Price *et al.* [22], who investigated that exposure to the nicotine in cigarettes cause insulin resistance, making nutrient transport into muscles and different tissues more difficult, which affect energy generation and in this manner decreasing fatigue resistance and sports performance.

In addition, our finding is consistent with that of Rinaldi [23], who studied skeletal muscle contractile and fatigue properties in smoking mice, and presumed that smokers were more at risk for muscle fatigue than nonsmokers. They hypothesized that because of neuromuscular transmission failer and in addition carboxyhemoglobin (COHb) that decreasing amount of oxygen delivered to muscles. This conclusion based on the result of the study of Morse *et al.* [24] whom determined that inhalation of carbon monoxide (CO) bringing about COHb levels found in smokers, acuty affected the capacity of the muscle to resist reduced fatigue because when oxygen binding sites on haemoglobin (Hb) become occupied with (CO), resulting in hypoxemia, and COHb may achieve level of 9% in smokers prevent the arrival of oxygen from Hb to muscle diminishing oxygen supply to the muscles.

Breitinger *et al.* [12] reported that nicotine is binding with nicotinic acetylcholine receptors, and nicotine expands the level of neurotransmitters; it is believed that expanded levels of dopamine in the reward circuits of the mind are responsible for euphoria and relaxation.

However, nicotine exhausts serotonin creation levels in the cerebrum, and smoking cigarettes can drain serotonin generation level by as much as half.

The findings of this study are in concurrence with those of Awtry and Werling [25], who found that nicotine reaches the cerebrum in 8 s, instantly stimulating the neurotransmitters (norepinephrine, dopamine, and serotonin). Smoking rapidly stimulate serotonin generation, however, just in the short term, as expanded serotonin levels continue increasing as the length of the cigarette is being smoked, and then smoking seems to cause a physical change in the mind that represses serotonin creation, and thus it clarifies the inverse relation between serum serotonin levels and serum cotinine levels.

In addition, Wüst *et al.* [13] attempted to infer that smoking causes neuromuscular transmission deficiency using direct muscle deficiency superimposed on nerve, and thus it clarifies the inverse relationship between muscle exhaustion and serotonin level.

On account of the fact that smoking is a notable hazard that causes numerous infections and on account of its financial effect, our study attempted to reveal an insight and include more dangers about smoking habit.

Limitation

This study had a few constraints; to begin with, it was possible that smokers may be asymptomatic for vascular problems during testing. In addition, the impact of smoking on the vascular system may affect physical performance levels and, therefore, hid the true effect of smoking on muscle fatigue. Besides, the outcomes may be that were connected affected by different factors with smoking status and were not controlled in this study – for example, depression, nervousness, and lower financial status.

Conclusion

Serum cotinine levels (the metabolite of nicotine) had a direct relation with the peripheral fatigue of back extensors in smokers, as increased serum cotinine level in the back extensors made smokers more susceptible to fatigue; also, cotinine had an inverse relation with serum serotonin level in smokers and nonsmokers. In addition, serum serotonin level had an inverse relation with peripheral fatigue of back extensors in smokers.

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Conflicts of interest

There are no conflicts of interest.

References

1 Goldberg MS, Mayo NE, Scott S. A review of the association between cigarette smoking and the development of nonspecific back pain and related outcomes. Spine 2000; 25:995–1014.

2 World Health Organization. WHO report on the global tobacco epidemic. Geneva, Switzerland: World Health Organization; 2011.

3 Jha P, Ramasundarahettige C, Landsman V. 21st Century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013; 368:341–350.

4 Benowitz NL, Bernert JT, Caraballo RS, Holiday DB, Wang J. Optimal serum cotinine levels for distinguishing cigarette smokers and nonsmokers within different racial ethnic groups in the United States between 1999 and 2004. Am J Epidemiol 2009; 169:236–248.

5 Auer M, Hegen H, Luft T, Bsteh G, Fogdell-Hahn A, Loercher A, Deisenhammer F. Serum cotinine does not predict neutralizing antibodies against interferon beta in an Austrian MS Cohort. J Interferon Cytokine Res 2016; 36:667–670.

6 Morse CI, Wust RC, Jones DA, Haan A, Degens H. Muscle fatigue resistance during stimulated contractions is reduced in young male smokers. Acta Physiologica 2007; 191:123–129.

7 Al Obaidi S, Al-Zoabi BA, Chowdhury RI, AL-Shuwai N. Fatigue suspectability of the lumbar extensor muscles among smokers. Phys Ther 2003; 89:238-248.

8 Herrmann C, Madigan M, Davidson B, Granata K. Effect of lumbar extensor fatigue on paraspinal muscle reflexes. J Electromyogr Kinesiol 2007; 16:637–641.

9 Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington W, *et al.* Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003; 301:386–389.

10 Lee GS, Simpson C, Sun BH, Yao C, Foer D, Sullivan B, *et al.* Measurement of plasma, serum, and platelet serotonin in individuals with high bone mass and mutations in LRP5. J Bone Miner Res 2014; 29:976–981.

11 Bach H, Arango V, Kassir SA, Dwork AJ, Mann JJ, Underwood MD. Cigarette smoking and tryptophan hydroxylase 2 mRNA in the dorsal raphe nucleus in suicides. Arch Suicide Res 2016; 20: 451–462.

12 Breitringer HG, Geetha N, Hess GP. Inhibition of the serotonin 5-HT3 receptor by nicotine, cocaine and fluoxetine. Biochemistry 2001; 40:8419–8429.

13 Wüst RC, Morse CI, de Haan A, Rittweger J, Jones DA, Degens H. Skeletal muscle properties and fatigue resistance in relation to smoking history. Eur J Appl Physiol 2008; 104:103–110.

14 Rochconger P. Isokinetic thigh muscles strength in sports. A review Ann Readapt Med Phys 2004; 47:274–281.

15 Drouin JM, Valovich-mcLeod TC, Shultz SJ, Gansneder BM, Perrin DH. Reliability and validity of the Biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements. Eur J Appl Physiol 2004; 91:22–29.

16 Maffey-Ward L, Jull G, Wellington L. Toward a clinical test of lumbar spine kinesthesia. J Orthop Sports Phys Ther 1996; 24:354–358.

17 Keller TS, Roy AL. Posture-dependent isometric trunk extension and flexion strength in normal male and female subjects. J Spinal Disord Tech 2002; 15:312–318.

18 Al-Obaidi MS, Antony J, Al-Shuwai N, Dean E. Differences in back extensor strength between smokers and non-smokers with and without back pain. J Orthop Sports Phys Ther 2004; 34: 254–260.

19 Orlander J, Kiessling KH, Larsson L. Skeletal metabolism, morphology and function in sedentary smokers and nonsmokers. Acta Physiol Scand 1979; 107:39–46.

20 Wüst RC, Jaspers RT, van der Laarse WJ, Degens H. Skeletal muscle capillarization and oxidative metabolism in healthy smokers. Appl Physiol Nutr Metab 2008; 33:1240–1245.

21 Nakatani T, Nakashima T, Kita T, Ishihara A. Effects of exposure to cigarette smoke at different dose levels on extensor digitorum longus muscle fibers in wister-kyoto and spontaneously hypertensive rates. Clin Exp Pharmacol Physiol 2003; 30:671–677.

22 Price T, Karishnan-sarin S, Rothman D. Smoking impairs muscle recovery from exercise. Am J Physiol Endocrinol Metab 2003; 285:116–122.

23 Rinaldi R. Skeletal muscle contractile and fatigue properties in smoking mice. Am J Respir Crit Care Med 2011; 183:24–56.

24 Morse CI, Pritchard LJ, Jones DA, Wust RC, Degens H. Carbon monoxide inhalation reduces skeletal muscle fatigue resistance. Acta Physiologica 2008; 192:379–401.

25 Awtry TL, Werling LL. Acute and chronic effects of nicotine on serotonin uptake in prefrontal cortex and hippocampus of rates. Synaps 2003; 50:206–211.