

Effects of chronic cigarette and marijuana smoking on reproductive health

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ABSTRACT: The current study was aimed to analyze the ill effects of chronic cigarette, marijuana and marijuana plus cigarette smoking on the reproductive health of addicted men. The study was carried out in district Dir, Khyber Pakhtunkhwa (Pakistan). Four groups were made. These groups were control, cigarette smokers, marijuana smokers and marijuana plus cigarette smokers. Each group included 15 participants. Their age range was 30 to 40 years. A questionnaire was filled and blood samples were analyzed for serum total testosterone level by using Bio-check (USA) kit. A significantly reduced testosterone level was found in cigarette smokers (Mean \pm SEM 5.933 \pm 0.1801 ng/mL, P*** 0.0003), marijuana smokers (Mean \pm SEM 3.7 \pm 0.12 ng/mL, P**** < 0.0001) and marijuana plus cigarette smokers (Mean \pm SEM 3.2 \pm 0.15 ng/mL, P**** < 0.0001) when compared with control (Mean \pm SEM 7.293 \pm 0.2749 ng/mL). Reproductive health problems like decreased libido, erectile dysfunction, absent morning and nocturnal erection and infertility were more common in addicted groups as compared to control. In summary our findings support the role of cigarette and marijuana smoking in the negative regulation of testosterone and male reproduction.

KEYWORDS: Cigarette, marijuana, testosterone, reproductive health, District Lower Dir.

1 INTRODUCTION

Very complex cellular machinery is responsible for the regulation of reproduction, including three principal regulatory organs, hypothalamus [1], [2] pituitary [3] and gonads [4] that form reproductive axis. Luteinizing hormones (LH) and follicle stimulating hormones (FSH), also called gonadotropins, regulate the maturation and functions of gonads and are regulated by gonadotropins releasing hormones (GnRH) [5]. Many central and peripheral signals (both stimulatory and inhibitory) are responsible for the regulation of GnRH secretion and the reproductive axis [6], [7], [8], [9]. Nowadays one of the main health problems in public is the use of cocaine and cigarette smoking. It is very difficult to determine the exact sickness and death rates in the case of cocaine misuse but it is estimated that the death rate is 430,000 per year due to lung cancer, obstructive pulmonary disease and ischemic heart disease [10], [11]. There are important evidences that link smoking and coronary heart diseases. Several studies have shown that smoking causes reduction in androgen concentration in coronary heart disease patients when compared with disease free control individuals [12], proved by the measurement of biologically active androgens [13]. It has been documented that effects of i.v administration of nicotine are very similar physiologically to the effects of cocaine, introduced into the body by cigarette smoking [14]. Cocaine and nicotine have similar pharmacological mechanism of action regardless of route of administration [15], [16]. Cigarette smoking is an addictive problem like cocaine abuse [11], [17], [18]. It has been reported that nicotine stimulates mesolimbic dopamine system like cocaine that results in the increased concentration of extracellular dopamine level that in turn regulate the abusing effects of these chemicals [19], [20], [21], [22]. Dopamine negatively regulates GnRH secretion [23] suggesting the suppression of reproductive axis. Cocaine is also involved in the regulation of the pituitary, gonadal and adrenal hormone secretion [24].

Mammalian reproduction has been affected by marijuana and its neuroactive component delta-9-tetrahydrocannabinol (D-9-THC) but the results are controversial [25]. Marijuana has been shown to reduce circulating plasma testosterone levels in male rats [26]. There are several evidences that support the anti- estrogen functions of marijuana in female rats [27]. There are several findings in in vivo models, showing that D-9-THC positively regulate estrogens [28], [29], [30] but regulate androgens negatively [27], [31], [32]. The above variable effects suggest that different constituents of marijuana may have different effects on hormonal profiles. It has been reported that the receptors of the cannabinoid, have their important contribution in the regulation of hormonal profile via cannabinoid [23]. Low testosterone level in the body for long time due to either reason can causes cardiovascular problems, insulin resistance, obesity, osteoporosis, erectile dysfunction, hypoactive sexual desire, absent nocturnal and morning erection, disturb secondary sex characters, muscle weakness, fatigue and depression [33], [34].

The aim of current study was to determine whether chronic marijuana and cigarette smoking addiction is involved in the suppression of reproductive axis in the context of total testosterone levels separately and synergistically in human males. To test our hypothesis we have studied testosterone levels and reproductive problems in people addicted to cigarette, marijuana and both cigarette plus marijuana.

2 MATERIALS AND METHODS

2.1 INFORMED CONSENT

A written informed consent was taken from all the participants before starting the study. All the participants entered the study voluntarily and sufficient information was given to them about the purpose and outcomes of this study.

2.2 STUDY AREA

The present study was conducted in district Lower Dir, Khyber Pakhtunkhwa Pakistan.

2.3 QUESTIONNAIRE

A standard format questionnaire was designed by two experts. Questions about participant's age, profession, income, marital status, type of addiction, duration of addiction, dosage of abuse drugs as well as about their general health and reproductive health were asked from every participant.

2.4 STUDY DESIGN

Only married adult males were selected randomly from the community. Their age ranges from 30 to 40 years. Four groups were made such as, control, cigarettes smokers, marijuana smokers and cigarette plus marijuana smokers. Each group had 15 individuals. The control group participants were healthy and had no history of drug addiction or any other severe abnormalities. The details of socio-demographic characteristics, addiction type and history of drug addiction, dosage of drugs, occupational activities and clinical characteristics are summarized in Table 1.

2.5 BLOOD SAMPLING

A health technician collected 5 ml of the blood in vacutainers tube containing no anticoagulants. Blood was collected from the brachial vein of all participants aseptically between 9:00 A.M and 10:30 A.M. The collection tube and catheter site were covered so that smoke in air would not contaminate the samples. Immediately all samples were placed in ice. All the blood samples were centrifuged at 3000 rpm for 15 minutes at 4 °C and the resulting serums were frozen at -20 °C for latter analysis.

2.6 ASSAY

Testosterone enzyme immunoassay test kit, Bio-check (USA) was used for the determination of total serum testosterone level according to the manufacturer's protocol and procedures.

2.7 EXCLUSION CRITERIA

Individuals with a history of severe diseases like tuberculosis, hepatitis, typhoid, renal problems, pneumonia, heart problems and mental problems were excluded from the study.

2.8 STATISTICS

Analysis of data was done by using Graph Pad Prism (www.graphpad.com), version 6.03 (Graph Pad Software Inc., San Diego, CA, USA). Cigarette smokers, marijuana smokers and cigarette plus marijuana smokers were compared one by one with control group by using unpaired t test. All data were presented as Mean \pm SEM. A $P < 0.05$ indicated the significant difference.

3 RESULTS

3.1 HISTORY

The general and reproductive health problems found in all groups are summarized in Table 1.

3.2 TESTOSTERONE CONCENTRATION IN CIGARETTE SMOKERS

Statistically significant ($P^{***} 0.0003$) lower testosterone level (Mean \pm SEM 5.933 ± 0.1801 ng/mL) was observed in chronic cigarette smokers when compared with control (Mean \pm SEM 7.293 ± 0.2749 ng/mL) at 95% of confidence interval.

3.3 TESTOSTERONE CONCENTRATION IN MARIJUANA SMOKERS

Marijuana smoking has significant effect on testosterone level. Unpaired t-test has shown that marijuana smoking significantly ($P^{****} < 0.0001$) reduce testosterone level in marijuana addicted individuals (Mean \pm SEM 3.7 ± 0.12 ng/mL) as compared to control group (Mean \pm SEM 7.3 ± 0.27 ng/mL) at 95% confidence interval.

3.4 TESTOSTERONE CONCENTRATION IN MARIJUANA PLUS CIGARETTE SMOKERS

Marijuana plus cigarette smoking has more pronounced effect ($P^{****} < 0.0001$) on testosterone concentration (Mean \pm SEM 3.2 ± 0.15 ng/mL) than marijuana (Mean \pm SEM 3.7 ± 0.12 ng/mL) and cigarette smoking (Mean \pm SEM 5.933 ± 0.1801 ng/mL) alone at 95 % confidence interval when compared with control group (Mean \pm SEM 7.3 ± 0.27 ng/mL).

Table 1. Characteristics of study population

Groups	Economic status	Profession	Addiction	History Dose (per (Years) day)		General health problems	Reproductive health problems
Control	Middle	5 teachers 5 doctors 5 farmers	Nil	Nil	Nil	Absent	Absent
Cigarette smokers	Middle	All merchants	Capstan [®] , Red & White [®]	≥ 10	≥ 35	02 HT* 03 Cough 03 fatigue	06 DL*
Marijuana Smokers	Middle	8 drivers 7 tandoor occupants	Scorpion [®]	≥ 10	≥ 5 grams	04 HT* 03 A* 02 P*	04 AMN* 04 DL* 03 ED* 03 infertility
Marijuana plus cigarette smokers	Middle	5 drivers 5 farmers 5 barbers	Scorpion [®] Capstan [®] , Red & White [®]	≥ 10	≥ 5 gram plus ≥ 25	06 HT* 03 DM* 02 P* 04 CC*	04 infertility 04 DL* 05 ED*

DL*= Decreased Libido, ED*= Erection Dysfunction, AMN*= Absent Morning and Nocturnal erection, DM*= Diabetes Mellitus, HT*= Hypertension, A*= Asthma, RA*= Rheumatoid Arthritis, P*= Peptic ulcer, CC*= Chronic Cough.

4 DISCUSSION

In the current study we have analyzed the effects of marijuana and cigarette smoking on mean testosterone concentration. Our hypothesis was that, whether cigarette and marijuana smoking reduces testosterone level? To test our hypothesis we measured testosterone levels in cigarette and marijuana smokers. Hypothalamic stimulatory peptides act on pituitary gonadotrophs to release gonadotrophins that in turn act on testicular cells to produce testosterone which is the principal hormones responsible for male reproduction. In our results, cigarette, marijuana and marijuana plus cigarette smokers have shown significantly reduced testosterone levels than control group. A significant reduction has been reported in testosterone levels in cigarette smokers when compared with control individuals [35], [36] that support our findings. The concentration of biologically active testosterone does not vary in smokers versus nonsmokers but the total and free testosterone shows a significant increase in smokers suggesting that this difference is due to the high concentration of sex hormone binding globulin (SHBG) in smokers that give the speculation that smoking effects SHBG, not the hormones itself [37]. Key depression has been reported in smokers than in nonsmokers [38], [40]. Intra peritoneal, central administration and microinjection of nicotine in the catecholaminergic area of the brain has been shown the rapid increase in adrenocorticotrophic hormone (ACTH) secretion but these effects has been blocked by the injection of nicotine antagonist [41], [42], [43], [44] suggesting that nicotine is responsible for the release of ACTH. The concentration of corticotropin-releasing factor (CRF) can't be measured in blood plasma but we can predict its secretion by the concentration of ACTH and cortisol in rodents. RFRP-3(mammalian ortholog of GnIH) expression increases during chronic and acute stress [45]. Cortisol (glucocorticoids) receptors are present on RF-amide related peptide- 3 (RFRP-3) neurons, GnRH neurons and gonadotrophs and collectively regulate LH secretion negatively. Cortisol level increases in smokers that positively regulate RFRP-3 secretion while inhibit GnRH and LH secretion that ultimately results in the reduced testosterone concentration in smokers [45].

Acute injection of D-9-THC, principal constituent of the marijuana, has shown a rapid decrease in the secretion of gonadotropins [23] that supports our findings that marijuana addiction reduces testosterone levels. Cultural analysis of pituitary cells for D-9-THC has not shown to reduce the secretion of LH and FSH [46], [47] and the sensitivity of the pituitary cells to GnRH [46], [47], [48]. Exogenous GnRH stimulation [49], [50] or injection of endogenous GnRH [48], [51], [52], [53], [54], [55] has shown to recover D-9-THC induced inhibition of LH surge before ovulation and its basal level speculating the notion that marijuana centrally suppresses reproductive axis. Various studies have shown that D-9-THC is capable to activate gamma-amino butyric acid (GABA), dopamine, opioids and CRF activities that are responsible for the inhibition of GnRH secretion while it inhibits norepinephrine and glutamate function that positively regulate GnRH secretion that in turn result in the reduced release of LH [23]. As CRF is stimulated by D-9-THC [23] suggesting that it also activates adrenal axis that has the main contribution to the suppressed reproductive axis and thus testosterone. In the case of our results the decreased levels of testosterone in smoking, marijuana and marijuana plus smoking addiction males might be due to the increased concentration of cortisol, ACTH, CRF, GABA and opioids and the reduced concentration of norepinephrine and glutamate concentration that is the main regulator of the reproductive axis.

In the present study we have studied the combined effects of cigarette and marijuana smoking on total serum testosterone and found that, individuals addicted to both of cigarette and marijuana show a more reduced levels of testosterone than cigarette and marijuana addicted alone. This suggests that the combined addiction synergistically suppress testosterone secretion. The activation of some pathways that is responsible for the reduced testosterone shows overlapping in cigarette and marijuana addiction but some are specialized and are associated with cigarette or marijuana smoking alone. In the light of the above scenario, more pathways are activated in the combined addiction that are responsible for the reduced testosterone than those that become active in cigarette or marijuana addiction alone and this may be the cause for the highly reduced testosterone level in the combined addiction.

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DISCLOSURE

None of the authors is having any conflict of interest.

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