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VOLUME 4 NUMBER 2
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CONTENT

Original Research Papers

Review Papers

International Physiology

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Association of rs9939609 and rs1421085 with Obesity Risk in North Indian Population

Apurva Srivastava*,, Neena Srivastava*, Balraj Mittal**, Jai Prakash*, Pranjal Srivastava***, Nimisha Srivastava******

Abstract

Introduction: Obesity is progressively important health problem worldwide as well as in developing countries like India. Recent genetic studies have suggested that obesity associated FTO genetic variants are associated to obesity risk. *Aim:* To evaluate the association of FTO genetic variants towards obesity risk. *Subjects and Methods:* North Indian individuals categorized as non-obese (BMI<25 kg/m^2) and obese (BMI≥30 kg/m^2) were selected. FTO rs1421085, rs9939609 were genotyped by validated Taqman allelic discrimination. Their association with obesity was evaluated by means of single locus logistic regression by SPSS ver. 19. *Results:* In single locus analysis, significant association with obesity risk was revealed by FTO rs9939609 [CA (P=0.0001, OR=2.6(1.7-3.9); AA (P=0.0001, OR=3.0(1.7-5.3)], rs1421085 [TA (P=0.0001, OR=2.6(1.7-3.9); AA (P=0.0001, OR=2.8(1.6-5.2)]. *Conclusion:* This study to reveals that genetic variants of FTO are associated with obesity risk in North Indians.

Keywords: BMI; FTO; Obesity.

Introduction

The prevalence of obesity is increasing rapidly worldwide. The primary cause of the present outbreak is an unhealthy lifestyle, especially high calorie intake and poor physical activity. However, studies have established that the pathogenesis of obesity also includes a genetic component predisposing some individuals to gain more weight from a sedentary lifestyle (1–3). Fat mass and obesity-associated protein also known as alpha-ketoglutarate-dependent dioxygenase FTO is an enzyme that in humans is encoded by the FTO gene located on chromosome 16. Certain variants of the FTO gene are reported to be correlated with obesity risk in humans [1].

A study of 38,759 Europeans for variants of FTO identified an obesity risk allele [2]. Simultaneously, a study in 2,900 affected individuals and 5,100 controls of French descent, together with 500 trios (confirming an association independent of population stratification) found association of SNPs in the very same region of FTO (rs1421085) [3]. In addition, variants in the FTO gene were further confirmed to be associated with obesity in two very large genome wide association studies of body mass index (BMI) [4,5].

Owing to such promising results worldwide in context to FTO gene and its association with obesity risk we planned our study to look for association of two important genetic variants of FTO gene with obesity risk in our North Indian population.

Materials and Methods

Study Population and Ethics Statement

Individuals recruited in the study were of north Indian origin belonging to states of Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttar Pradesh, Punjab and Uttarakhand. Individuals other than North Indian origin were excluded. Informed written consent was obtained from each participant. The study was carried out after approval from local ethics committee of King George's Medical University, Lucknow, Uttar Pradesh, India. The study conforms to the code of ethics of the world medical association (64th WMA International Code of Medical

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Ethics General Assembly, Fortaleza, Brazil, October 2013).

The participants were recruited by organizing health awareness camps in the Lucknow city and its rural surroundings with the help of social service organizations. All study participants were subjected to a careful screening program including assessment of detailed personal and family history, physical examination, determination of anthropometric measurements and biochemical profiles.

Based on BMI, individuals were categorized as normal (BMI<25) and obese (BMI≥30). Overall 289 male subjects and 191 female subjects were enrolled in the study befitting the strict inclusion/exclusion criteria mentioned below.

Inclusion Criteria (Obese Subjects)

Subjects having BMI≥30 kg/m^2, age of 20-42 years at time of interview and place of birth North India.

Inclusion Criteria (Non-Obese Subjects)

Subjects having BMI from 18.5 to 24.99 kg/m^2, age of 20-42 years and Place of birth North India.

Exclusion Criteria

Subjects not fulfilling the above inclusion criteria for obese and non-obese subjects at time of interview and or with congenital disorders, mental disorders, endocrine disorders like Myxoedema, Cushing's syndrome and cardiovascular disease were excluded.

Measurements

Body weight in kilograms with weighing scale (Mfd. by Sunshine Instruments, Coimbatore and Product name- Omron) and height in centimeters by a stadiometer (Mfd. by Anand medical export, New Delhi and Product name- Stadio) was measured for individuals wearing light clothing. Waist circumference was measured midway between the iliac crest and the lower costal margin all along with hip circumference in centimeters with the help of waist tape (ATICO Medical Pvt. Ltd, Ambala and Product name- Atico) (Table 1). Blood samples were taken for lipid profile and genotyping. Serum lipid profile was estimated by commercial kit (ERBA diagnostics Mannheim GmbH, Germany). Genomic DNA from Blood was isolated using Qiagen DNA extraction kit (QIAamp® DNA Blood Kit)

Genotyping

Genotyping of the SNPs was carried out using the validated Taqman® allelic discrimination protocol (Applied Biosystems®).

Genotyping Quality Control

Genotype calling from real-time PCR data was performed using an algorithm called best cycle genotyping algorithm (BCGA). The quality of assignment of individual samples to clusters was determined on the basis of silhouette values [6] .

Statistical Analysis

Single Locus Logistic Regression Analysis

Genotype and allele distribution was compared between obese and non-obese subjects using *chi-square test*. The independent segregation of alleles was tested for the Hardy-Weinberg equilibrium (HWE), comparing the observed genotype frequencies with those expected (*chi-square test*). For case-control studies, differences in genotype distributions were calculated applying log additive logistic regression model adjusted for sex and age. A two-tailed p-value of less than 0.05 was considered a statistical significant result.

All statistical analyses were performed using SPSS software version 19.0 (SPSS, Chicago, IL, USA).

Table 1: Single Locus logistic regression Analysis of the investigated FTO SNPs

S. No.	Gene	SNP Id	Non-obese n(%) (n=240)	Obese n(%) (n=240)	P-value	OR (95%CI)
1	FTO	rs9939609				
		CC	159(66.3)	100(41.7)		
		CA	57(23.8)	94(39.2)	**0.0001**	**2.6(1.7-3.9)**
		AA	24(10)	46(19.2)	**0.0001**	**3.0(1.7-5.3)**
2	FTO	rs1421085				
		TT	162(67.5)	104(43.3)		
		TA	56(23.3)	94(49.2)	**0.0001**	**2.6(1.7-3.9)**
		AA	22(9.2)	42(17.5)	**0.0001**	**2.8(1.6-5.2)**

Results

Case-control study was performed in 240 obese and 240 non-obese healthy subjects. All the studied FTO polymorphisms followed Hardy Weinberg equilibrium in the control population.

Table 1 shows single locus logistic regression analysis of the investigated FTO SNPs with obesity risk. The analysis revealed the significant associations (P <0.05) of the 2 SNPs with obesity risk in Indian population.

Strong association was exposed in genetic variants of FTO rs9939609 [CA (P=0.0001, OR=2.6(1.7-3.9); AA (P=0.0001, OR=3.0(1.7-5.3)], rs1421085 [TA (P=0.0001, OR=2.6(1.7-3.9); AA (P=0.0001, OR=2.8(1.6-5.2)].

Discussion

In the present study, we report association of two important SNPs in FTO gene with obesity BMI≥30kg/m^2 in population of north India.

A cluster of single nucleotide polymorphism (SNPs) in the first intron of the FTO gene was found to correlate with an increase in body mass index (BMI) in both children and adults, regardless of gender in multiple cohorts spanning multiple ethnicities[7]. Recently a meta-analysis included 12 eligible studies consisting 5,000 cases and 9,853 controls revealed that FTO rs9939609 polymorphism was significantly associated with the increased risk of obesity in co-dominant model (AA vs. TT: OR = 1.91, 95% CI: 1.47-2.48, p < 0.01; AT vs. TT: OR = 1.18, 95% CI: 1.02-1.38, p = 0.03), dominant model (AA + AT vs. TT: OR = 1.47, 95% CI: 1.35-1.59, p < 0.01), recessive model (AA vs. AT + TT: OR = 1.79, 95% CI: 1.47-2.17, p < 0.01), and allelic model (A vs. T: OR = 1.39, 95% CI: 1.22-1.58, p < 0.01) which concluded that FTO rs9939609 polymorphism is associated with the increased risk of obesity among children and adolescents, especially the homozygous carriers [8]. Also, a study in Chinese Han children and adolescents found that the FTO rs9939609 variation is significantly associated with the risk of obesity and a meat-based dietary preference [9] which reveals that dietary preferences are also controlled by genes leading to obesity.

Many previous studies have also reported strong association between single nucleotide polymorphisms (SNPs) in the first intron of the fat mass and obesity-associated gene (FTO), on the chromosome 16q12.2 and risk to obesity, of which the rs9939609 is one of the most broadly studied, explaining on 1% of BMI heritability. The risk allele A of this genetic variant is responsible for 1.5 kg increase of body weight in human beings [2]. Significant increase in BMI was observed with rising numbers of A-alleles of rs9939609 in the COBRA study [0.52 kg/m^2 (95% CI 0.15–0.89); P = 0.006] and the UKADS/DGP study [0.42 kg/m^2 (95% CI 0.16–0.68); P = 0.002] along with combined meta-analysis of these two studies [0.45 kg/m^2 (95% CI 0.24–0.67); P = 3.0×10^{-5}] [10].

In a meta-analysis Significant associations were detected between obesity risk and the polymorphisms: rs9939609 (OR: 1.31, 95% CI: 1.26 to 1.36) and rs1421085 (OR: 1.43, 95% CI: 1.33 to 1.53) [11]. Evidences have also proved that the previously reported common polymorphisms rs9939609 and rs1421085 in FTO gene increase the risk of obesity in the Portuguese children [12]. In an association analysis between the FTO gene variant rs1421085 and risk of childhood obesity CC and CT/CC genotypes were associated with 59% and 71% increased risks of childhood obesity (adjusted OR = 1.59, 95%CI = 1.00-2.53 for CC; adjusted OR = 1.71, 95%CI = 1.10-2.65 for CT/CC) suggesting that variant rs1421085 in the FTO gene contributed to childhood obesity in Chinese children [13].

Recently, studies have reported that association of SNPs in FTO with obesity might be due to linkage between FTO intronic variations and some other genes. Ragvina et al. [14] reported that the obesity-associated SNPs rs8050136, rs1421085, rs9939609, and rs17817449 in FTO regulate IRX3 gene which is located several mega base away from FTO. Similarly, Smemo et al. [15] have also reported that variants within FTO interact through the promoters of IRX3 gene regulating its expression and determining obesity. In one of our recent studies we have also reported that genetic variants rs9939609, rs1421085 of FTO and rs3751723 of IRX3 genes are in high linkage disequilibrium (LD) and are associated with obesity risk in North Indians [16].

The studies carried out in background of FTO rs9939609 and rs1421085 have strongly established the role of these particular genetic variant to obesity risk and correspondingly in our present study consistent results were replicated for these genetic variants leading to high obesity risk in North Indian Individuals. Therefore, based on the present study we suggest that both the variants rs9939609 and rs1421085 in the FTO gene can be used as strong biomarkers to predispose obesity risk.

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Study of Serum MDA, Serum Vitamin C, Serum Vitamin E Levels in Patients with Diabetes and Diabetes with Hypertension

Kiran Buge*, Pradeep Nahar, N.V. Aundhakar***, Swati Shah****, Anupam Khare****, Pranali Sonawane*******

Abstract

Introduction: Diabetes mellitus is one of the most common systemic diseases in the world. Diabetic patients are exposed to increased oxidative stress. However very few studies have measured and compared oxidative stress, antioxidant status in patient of diabetes with hypertension. Hence present study was conducted, which was aimed to measure antioxidant levels (Vitamin C, vitamin E) and oxidative stress (Malondialdehyde-MDA level) in type 2 diabetic patients, in type 2 diabetic patients with hypertension and to compare them with age and gender matched healthy controls.

Male volunteers of 40-60 years were divided into

Group I - 30 normal healthy controls,

Group II - 30 patients having type II diabetes mellitus since 3 to 6 years,

Group III - 30 patients having type 2 diabetes mellitus along with hypertension since 3 to 6 years.

Serum levels of MDA were estimated by method described by Buege and Aust. serum levels of Vitamin C and vitamin E were estimated by method described by Ayekyaw and Baker respectively. Serum MDA levels, serum Vitamin C and vitamin E levels compared by applying appropriate statistical test. We found statistically highly significant increase (<0.001) in serum MDA levels and significant decrease (<0.05) in both serum Vitamin C levels and serum vitamin E levels in patients of diabetes with hypertension as compared to patients having only diabetes. *Conclusion:* Our study showed that patients having both diabetes and hypertension have increased oxidative stress than patients having only diabetes. So, these patients will be more susceptible for developing complication related to oxidative stress. So proper precaution in the form for antioxidant supplementation to these patients can help them to live better quality of life.

Keywords: Hypertension; Malondialdehyde; Type 2 Diabetes Mellitus; Vitamin C; Vitamin E.

Introduction

Diabetes mellitus is one of the most common chronic diseases globally and in many countries it is now considered as one of the leading cause of death [1]. The prevalence of diabetes for all age groups worldwide was 2.8% in 2000 and is expected to raise up to 4.4 % (360 million) by 2030 [2]. Prevalence of Type 2 diabetes mellitus (DM) has increased from 1.2% to 11% over last 3 decades [3]. Diabetes mellitus is metabolic diseases characterized by high levels of blood sugar and it results from defects of insulin production, defects in insulin action or both. Uncontrolled hyperglycemia in diabetes prone for various long-term diabetic complications. This long-term complication in diabetic patients can be due to increased oxidative stress which results from increased reactive oxygen species and reactive nitrogen species. It has been found that diabetic patients are exposed to increased oxidative stress [4].

Various mechanism that explain oxidative stress in diabetic patients are- autooxidation of glucose, shifts in redox balance, decreased tissue concentration of antioxidant (Vitamin E, reduced glutathione-GSH) and impaired activities of antioxidant defence enzymes (superoxide dismutase-SOD, catalase-CAT) [5,6].

It has been also found that Type 2 DM patients have increased prevalence of hypertension than those without DM and most common cause of death in

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diabetic patients are heart disease [7,8]. Occurrence of Diabetes and Hypertension (HTN) are increasing in developing countries because of western, unhealthy and stressful lifestyle. Type 2 DM and HTN among the most common chronic non-communicable Diseases in developing countries and in most of the patients both diseases occur together because they share common risk factors [9].

It has been thought that patients having both diseases will have greater oxidative stress than patients having only diabetes. Recent study showed that complication of diabetes and hypertension has common aetiology involving oxidative stress and endothelial damage. Thus it has also been observed that patients of diabetic with hypertension have more oxidative stress than patient having only diabetes

So in the present study, we have compared antioxidant levels (Vitamin C vitamin E) and oxidative stress (Malondialdehyde-MDA level) in patients having type 2 diabetes and patients having both type 2 diabetes and hypertension

Materials and Method

The present cross sectional study was conducted in type 2 diabetic and diabetic with hypertension patients selected from diabetic OPD of the B. J. Medical College Pune. Duration of study was August 2010 to July 2012. After approval from Institutional Ethics Committee, male Patients were selected from diabetic outpatient department (OPD) of the hospital.

Inclusion Criteria

1. Male patients (age 40 – 60 years)
2. Diagnosed type 2 DM patients and type 2 DM patients with hypertension having diabetes since 3 to 6 years and on regular oral hypoglycemic and antihypertensive medication respectively.
3. Normal Healthy controls with no history of diabetes and hypertension.

Exclusion Criteria

1. Patients with acute complications of diabetes and hypertension.
2. Patients with life threatening diseases like cancer.
3. Patients on antioxidant drug therapy.
4. Fasting blood Sugar Level > 130 mg% and Blood pressure >130/80

5) Smokers, alcoholic, tobacco chewers.

Normal healthy controls were selected from relatives of the patient. Blood glucose levels were estimated in controls, diabetic patients and patients of diabetes with hypertension. Blood glucose levels of all the three groups were within normal range.

Based on inclusion and exclusion criteria, a total of 90 subjects were finally selected for the present study and were subdivided as follows –

Group I	Normal controls.
Group II	Type 2 diabetes since 3 to 6 years and taking regular oral antidiabetics medication.
Group III	Type 2 diabetes mellitus with hypertension since 3-6 year taking regular oral antidiabetics and antihy pertensive medication.

The study protocol was explained in detail to all the subjects and informed written consent regarding participation in the study was obtained from them. Serum MDA, serum vitamin C and serum vitamin E levels were estimated in all subjects.

Estimation of Blood Glucose Levels

Fasting and postprandial blood samples were collected to measure blood sugar levels. Blood glucose levels were estimated by glucose oxidase- peroxidase method [10].

Normal range for fasting blood glucose is 70-110 mg/dl.

Measurement of serum MDA, serum vitamin C, and vitamin E levels

To assess the oxidative stress, serum MDA levels of all subjects and controls were analysed. Serum levels of vitamin C and vitamin E were measured to know the antioxidant status.

Serum separated from the venous blood specimens was used for estimation of the serum MDA, vitamin C and vitamin E levels. All samples were stored in refrigerator and the estimations were done within 24-48 hours of specimen collection.

Estimation of Serum Malondialdehyde (MDA)

(Buege and Aust) Thiobarbituturic acid method [11]

Malonyldialdehyde is major aldehyde product of lipid peroxidation; is highly reactive three carbon dialdehyde produced from lipid hydroperoxides. It can, however, also be derived by the hydrolysis of pentose, deoxyriboses, hexoses, from some amino

acids and from DNA. MDA has most frequently been measured by the thiobarbituric acid reaction.

Normal range of MDA is 2-5 nanomol/ml.

Estimation of Serum Vitamin C (Ascorbate)

Method: described by Kyaw A [12]

Normal range of vitamin C is 0.5-1.5 mg%.

Estimation of Serum Vitamin E (Á-Tocopherol):

Method: described by Baker and Frank [13]

Normal range of vitamin E is 0.5-0.8 mg%

Serum MDA levels and Vitamin C, Vitamin E levels of 3 groups were compared by applying ANOVA test.

*p<0.05 statistically significant **p<0.001 statistically highly significant

Results

Table 1 shows that difference in means of age, height, weight and body mass index were not statistically significant between three groups. Though the difference in mean values of fasting blood glucose level, post prandial blood glucose level as well as systolic and diastolic blood pressure were statistically significant in all three groups (p< 0.05), their values were within normal limits (Table 1)

Table 2 and Graph 1 show that serum level of MDA in diabetes patients (4.83±0.15) and patients having both diabetes and hypertension (5.07±0.25) were significantly higher than control group (3.72±0.34). Also we found that increase in serum MDA level in patients of DM with HTN was statistically significant as compared to diabetes patients (p<0.001).

Table 2 and Graph 2 show that the serum levels of vitamin C in diabetes patients (0.50±0.10) and patients having both diabetes and hypertension (0.39±0.16) were significantly lower than control group (0.87±0.22).

Similarly, Table 2 and Graph 2 shows that the serum levels of vitamin E in diabetes patients (0.48±0.14) and patients having both diabetes and hypertension (0.40±0.15) were significantly lower than control group (0.64±0.08).

Table 3 and Graph 3 show negative correlation between serum MDA (oxidative stress) and vitamin C, E (antioxidant status) in control group, which is statistically highly significant.

Table 1: Descriptive characteristics of baseline parameters in the three groups:

Parameters	Control (n=30) Mean ± SD	DM (n=30) Mean ± SD	DM with HTN (n=30) Mean ± SD	p value
Age (years)	53±5.55	54.0±4.32	54.7±4.43	p>0.05
Weight (Kg)	64.9±8.06	66.1±7.82	67.4±10.65	p>0.05
Height (Meters)	1.65±0.07	1.64±0.07	1.63±0.08	p>0.05
Body mass index (Kg/m^2)	23.9±1.49	24.5±1.13	25.4±4.69	p>0.05
Blood glucose level fasting (mg/dl)	95.2±3.61	106.0±9.40	108.4±8.76	p<0.05*
Blood glucose level post-prandial (mg/dl)	124.5±7.03	149.2±12.35	152.4±8.21	p<0.05*
Systolic blood pressure (mm Hg)	118.6±4.64	122.1±6.19	127.1±2.80	p<0.05*
Diastolic blood pressure (mm Hg)	78.3±2.39	79.2±1.63	80.1±1.36	p<0.05*

* p<0.05 statistically significant ** p<0.001 statistically highly significant DM – diabetes mellitus, HTN – Hypertension

Table 2: Comparison of serum MDA (oxidative stress) and serum vitamin C, vitamin E levels (Antioxidant Status) among three groups (By ANOVA test):

Parameters	Control n=30 Mean ± SD	DM n=30 Mean ± SD	DM with HTN n=30 Mean ± SD	p value
MDA	3.72±0.34	4.83±0.15	5.07±0.25	<0.001 **
Vitamin C	0.87±0.22	0.50 ± 0.10	0.39 ± 0.16	<0.001 **
Vitamin E	0.64±0.08	0.48 ± 0.14	0.40 ± 0.15	<0.001 **

* p<0.05 statistically significant ** p<0.001 statistically highly significant DM-Diabetes mellitus, HTN-Hypertension, MDA- Malondialdehyde

Table 3: Correlation of MDA and vitamin C, vitamin E levels in control group

Oxidative stress levels	Antioxidant status	Pearson's correlation coefficient r	p value
MDA	Vitamin C	-0.908	<0.001**
	Vitamin E	-0.883	<0.001**

* p<0.05 statistically significant ** p<0.001 statistically highly significant MDA- Malondialdehyde

Table 4: Correlation between MDA and vitamin C, vitamin E levels in diabetes patients

Oxidative Stress levels	Antioxidant Status	Pearson's Correlation Coefficient r	p Value
MDA	Vitamin C	-0.942	<0.001**
	Vitamin E	-0.982	<0.001**

* p<0.05 statistically significant ** p<0.001 statistically highly significant MDA- Malondialdehyde

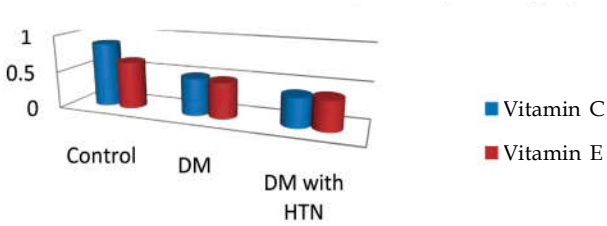
Table 5: Correlation between MDA and vitamin C, vitamin E levels in diabetes with hypertension patients

Oxidative stress levels	Antioxidant Status	Pearson's Correlation Coefficient r	p VALUE
MDA	Vitamin C	-0.9740	<0.001**
	Vitamin E	-0.9850	<0.001**

* p<0.05 statistically significant ** p<0.001 statistically highly significant MDA - Malondialdehyde

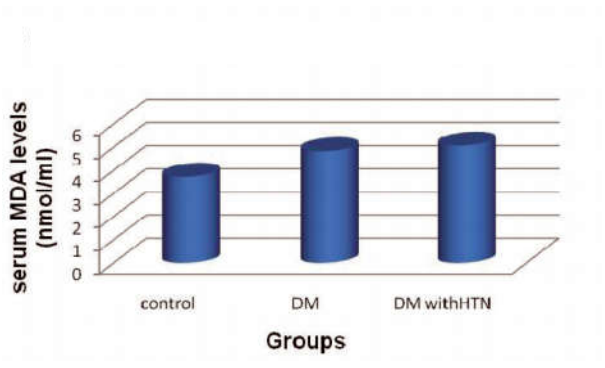
Table 4 and Graph 4 show negative correlation between serum MDA (oxidative stress) and vitamin C, E (antioxidant status) in diabetes group, which is statistically highly significant.

Table 5 and Graph 5 shows negative correlation between serum MDA (oxidative stress) and vitamin C, E (antioxidant status) in diabetes with hypertension group, which is statistically highly significant. Thus tables 3, 4, 5 and Graphs 3, 4, 5 show negative correlation between serum MDA (oxidative stress) and vitamin C, E (antioxidant status). The correlation analysis shows that higher the oxidative stress lowers are the levels of antioxidants



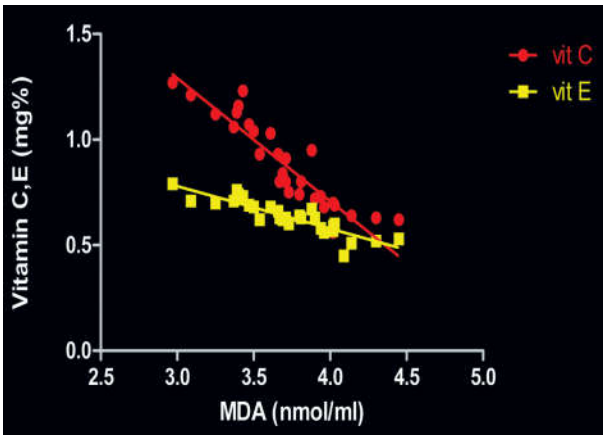
Graph 2: Serum vitamin C and Vitamin E levels (antioxidant) in three group

DM- Diabetes mellitus HTN- Hypertension



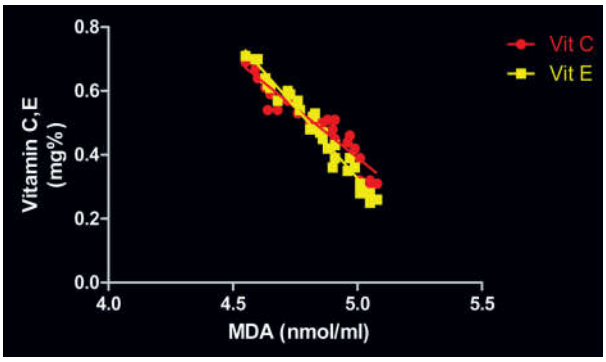
Graph. 1: Serum MDA levels (oxidative stress) in three groups

MDA- Malondialdehyde DM- Diabetes mellitus HTN- Hypertension



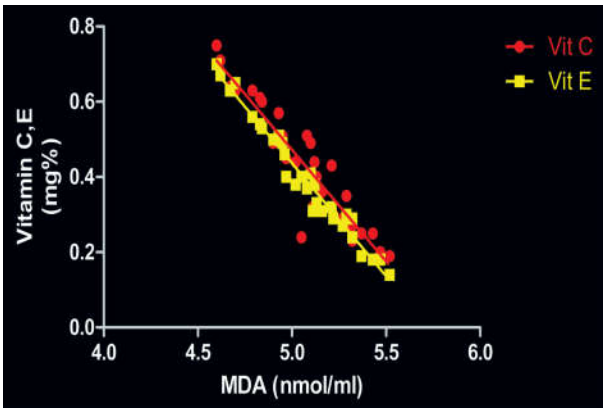
Graph 3: Correlation of MDA levels with vitamin C and vitamin E levels in Control group

MDA- Malondialdehyde



Graph 4: Correlation of MDA levels with vitamin C and vitamin E levels in diabetes patients

MDA- Malondialdehyde DM- Diabetes mellitus



Graph 5: Correlation of MDA levels with vitamin C and E levels in DM with HTN patients

MDA- Malondialdehyde DM- Diabetes mellitus HTN- Hypertension

Discussion

Various studies have shown that oxidative stress is increased in type 2 diabetes mellitus patients. However, patients having both diabetes and hypertension seem to have greater oxidative stress than patients having only diabetes. But there are very few published studies showing oxidative stress in type 2 diabetes mellitus patients with hypertension.

With this background, our present study was aimed to assess oxidative stress and antioxidant status in patients with type 2 diabetes mellitus and patients having type 2 diabetes mellitus with hypertension. We compared serum levels of malondialdehyde (MDA) - an index of oxidative stress, serum level of vitamin C and vitamin E -indices of antioxidant status, in patients with diabetes mellitus, in patients having diabetes mellitus with hypertension and normal healthy control subjects, each group having a sample size of 30.

Serum MDA Level: (Indicator of Oxidative Stress)

In present study we found that the serum levels of MDA in diabetic patients were statistically significant than control group (Table 2, Graph1)

Mehboob et al and other found higher serum MDA levels in diabetes patients as compared to control group due to oxidative damage to lipids [14,15].

Role of Oxidative Stress

In normal healthy individual there is balance between rate of free radical production and elimination and it is important for healthy life. Excess free radical can lead to oxidative stress either by increasing free radical generation or decrease in free radical elimination [16,17,18].

Oxidative stress results from increased reactive oxygen species and / or reactive nitrogen species.

Possible sources of oxidative stress in diabetes patients include

i. Increased non enzymatic glycosylation of proteins –in which chemical reaction between glucose and amino group of proteins take place and leads to formation of glycated protein. In turn, this glycated protein can give an electron to the molecular oxygen and form free radical [19].

ii. Auto-oxidation of glucose- when glucose reacts with trace amounts of transition metals like copper generating free radicals, (hydrogen peroxide, reactive ketoaldehydes) [20,21].

Other Mechanisms are- [6,16,22,23]

a. Metabolic stress resulting from changes in energy metabolism,

b. Alterations in sorbitol pathway

c. Changes in the level of inflammatory mediators,

d. Decrease tissue concentration of low molecular weight antioxidants –Vitamin E

e. Impaired activities of antioxidant defense system

In diabetes mellitus because of predominance of oxidative stress over antioxidant defense system there is damage to various biomolecules like lipid, protein and nucleic acid which prone for the diabetic complication like diabetic retinopathy, neuropathy, accelerated coronary artery disease. Oxidative stress also contributes to pancreatic â cell dysfunction and insulin resistance resulting in more prominent hyperglycemia. This vicious cycle leads to deterioration of diabetes.

Long term Oxidative stress in diabetes mellitus responsible for hypertension. Various mechanisms

postulated are [24]

1. Oxidative stress limits bioavailability of Nitric oxide (NO) in key tissues and organs involved in blood pressure regulation by several mechanism
   a. ROS (reactive oxygen species) avidly react and inactivate NO
   b. ROS reduce NO production by uncoupling endothelial NO synthesize

This reduction of NO in vascular tissue can raise systemic vascular resistance and hence blood pressure by lowering the NO-mediated vasodilator tone

2. ROS species can increase vascular smooth muscle tone by increasing cytoplasmic calcium concentration
3. ROS result in nonenzymatic oxidation of lipoproteins and cell membrane phospholipids, which leads to generation of vasoconstrictor proinflammatory products which in turn lead to endothelial injury and dysfunction which contributes to the rise in blood pressure

The hypertension in diabetes in turn can exaggerate the oxidative stress in diabetes. Thus the vicious cycle sets between oxidative stress and hypertension.

In our present study, we also found that serum levels of MDA were significantly higher in patients of diabetes with hypertension as compared to diabetes patients and controls. (Table 2, Graph1).

Gallou G et al and other found higher MDA levels in diabetes patients with complications such as hypertension, as compared to diabetes patients without complications [25,26,27].

Serum Levels of Vitamin C and Vitamin E

We found that the serum levels of vitamin C and vitamin E in diabetes patients were significantly lower than control group (Table 2, Graph 2).

Ford ES et al also found that there was a decrease in vitamin C and vitamin E in diabetic patients as compared to controls [28].

Our results are comparable with the results obtained by Pasupathi P et al [29] and Paramesha S et al [30].

In present study, we also observed that serum levels of vitamin C and vitamin E were significantly lower in patients having diabetes with hypertension as compared to diabetes patients and controls (Table 2, Graph 2,).

Gupta MM et al found that there was decreased level of vitamin C and vitamin E in diabetes patients with complication such as hypertension as compared to diabetes patient [31].

Oxidation reactions can produce free radicals. In turn these radicals can start chain reactions that damage cells and result in oxidative stress. Vitamin C and vitamin E terminate these chain reactions by removing free radical and inhibiting other oxidation reactions. They do this by getting oxidized themselves, so they are often reducing agents.

Vitamin C: (an essential water-soluble Vitamin), acts as a primary antioxidant in plasma and within cells that quenches ROS. Under physiological conditions, Vitamin-C predominantly exists in its reduced form Ascorbate; it also exists in trace quantities in the oxidized form, DHA (Dehydroascorbic Acid) transducers. Increased levels of Vitamin-C and DHA suppress the formation of ROS and induce the antioxidant defense mechanism [32,33].

Pasupathi P etal has shown that there is a significant decrease in the level of vitamin C in patients of diabetes and diabetes with hypertension because of utilization of vitamin C as an antioxidant defense against reactive oxygen species [29].

Vitamin E: Vitamin E is well known physiological antioxidant and membrane stabilizer. It breaks the chain reaction of lipid peroxidation by reacting with lipid peroxy radicals, thus prevent the cell membrane from damage [29]. Vitamin E can quench a variety of oxyradicals including superoxide anion radicals, singlet oxygen and hydroxyl radical. Vitamin E protects sulfhydryl groups in membrane proteins from peroxidation by quenching of $^1O_2$ (singlet oxygen). This activity depends upon a free hydroxyl group (OH) in position 6 of the chromane ring [32].

Vitamin E also acts as a potential immunoenhancing nutrient. It acts as a free radical scavenger and prevents free radicals from reacting with proteins in cell and thus protects against oxidation. It prevents formation of lipid peroxidation products. Vitamin E supplementation can prevent the development of abnormality of glucose metabolism and diabetes [28].

Table 3, 4 ,5, and Graph 3,4,5 show strong negative correlations between serum MDA and serum vitamin C and vitamin E levels in all the three groups.

Sureda A et al found negative correlation between oxidative stress and antioxidant status in normal subjects[34], While Ahmed RG and Cerilello A found negative correlation between oxidative stress and antioxidant status in diabetes patients and in diabetes with hypertension patients respectively [35,36].

Thus the correlation analysis showed that higher the oxidative stress lowers are the levels of antioxidants. This is mainly because antioxidants neutralize the oxidative stress i.e. free radicals, resulting in their consumption and decreased levels.

Conclusion

Thus the present study showed that patients having both diabetes and hypertension have much more oxidative stress as compared to those having only diabetes.

So, serum MDA and antioxidant levels can be good markers to find out the patients who are at increased risk of developing various complications along with other parameters of diabetes such as blood glucose, lipid profile and $HbA_{1C.}$

In addition to strict measures to control the blood glucose levels, Proper precaution in the form of antioxidant supplementation and yoga practices to these patients can help them to live better quality of life.

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Big Five Personality Traits and Gender Difference

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Abstract

The present study is the result of a scientific research in which the relationship between two important variables, namely Gender Differences in big five Personality Traits are determined in the research framework. Many statisticians have incorporated the five-factor model and the NEO Personality Inventory, both describing various aspects of personality including the five domains of personality—neuroticism, extraversion, openness, agreeableness, and conscientiousness—into determining whether there is gender difference in big five personality traits.. In this study, about 150 undergraduate medical students , were asked to rate various aspects of their personality by using personality inventory questionnaire of Buchanan (2001) based on Five-Factor Modality (FFM).then we calculated the gender difference for five personalities. In our study the Women were higher on Neuroticism ($p < .001$, $d = .54$) as compare to men and no significant gender difference has typically been found in Extraversion, Openness, Agreeableness, and Conscientiousness, (P<.05) at the Big Five trait level. So it is concluded that there is gender difference in big five personality traits. However, the study showed weakness such as small sample sizes , unequal sample size and we have not considered the sub-facetes of big five personalities. More accurate studies should be performed in the future to confirm or reject the results of this study.

Keywords: Personality Traits; Gender; Five-Factor Modality (FFM); Neuroticism.

Introduction

This paper studied the Gender differences in the big five personality traits.

Numerous research studies are performed with relation to the Gender differences based on the big five personality traits.

The study of personality is particularly useful in attempting to examine psychological differences between genders

Traits are the consistent patterns of thoughts, feelings, motives, and behaviors that a person exhibits across situations [1].

Gender differences in personality traits are often characterized in terms of which gender has higher scores on that trait, on average. For example, women are often found to be more agreeable than men [2,3].

The five-factor model and the NEO Personality Inventory -The five-factor model consists of five personality domains—Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness, often referred to as N, E, O, A, and C—and has become the most widely accepted model for personality [4,5].

Gender differences have been documented for a number of personality traits. Most meta-analyses and reviews examine gender differences in self-reports of personality on questionnaires that measure the Big Five, [2,3,6].

Women score higher on the Five Factor Model (FFM) traits of Neuroticism and Agreeableness [2] gender differences on Extraversion (encompassing gregariousness, excitement seeking, and positive affect) and Openness to Experience (encompassing interest in novel people, ideas, and aesthetics) have been either inconsistent or of negligible magnitude in large, statistically well-powered samples [1]. Neuroticism and Agreeableness are genetically based, species-invariant, and the result of adaptation to selection pressures which vary across men and women [7]. Budaev (1999) suggested an evolutionary hypothesis that Neuroticism and Agreeableness

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together represent a single dimension with low Neuroticism and low Agreeableness at one end and high Neuroticism and high Agreeableness at the other. His data suggested men and women fall at opposite ends of this dimension. Costa and colleagues concluded that gender differences on Neuroticism and Agreeableness stemmed from stable evolutionary and biological bases, but Social Role Theory [8], which articulates socialization processes leading to different roles and behaviors for men and women, also held potential usefulness for understanding gender differences in Neuroticism and Agreeableness [3, 9].

The goal of investigating gender differences in personality, therefore, is to find out the differences among general patterns of behavior in men and women on average, Gender differences in personality are often examined in terms of the Big Five [9] or by systematic sampling from the space defined by pairs of Big Five factors [11].

Biological and evolutionary approaches posit that gender differences are due to men and women's dimorphic ally evolved concerns with respect to reproductive issues, parental investment in offspring [12,7] According to these theories, women should be more concerned with successfully raising children and should therefore be more cautious, agreeable, nurturing, and emotionally involved. Men, on the other hand, should be more concerned with obtaining viable mating opportunities and should therefore exhibit more Assertiveness, risk-taking, and aggression. Other theories suggest that gender norms are shaped by socio-cultural influences, such that women and men are expected to serve different roles in society and are therefore socialized to behave differently from one another [13]., recent studies have shown that gender differences in personality tend to be larger in more developed, Western cultures with less traditional sex roles [3,14].

Neuroticism

Neuroticism describes the tendency to experience negative emotion and related processes in response to perceived threat and punishment; these include anxiety, depression, anger, self-consciousness, and emotional labiality. Women have been found to score higher than men on Neuroticism as measured at the Big Five trait level, as well as on most facets of Neuroticism included in a common measure of the Big Five, the NEO-PI-R [3].

Agreeableness

Agreeableness comprises traits relating to altruism, such as empathy and kindness. Agreeableness involves the tendency toward cooperation, maintenance of social harmony, and consideration of the concerns of others; Women consistently score higher than men on Agreeableness [2, 3].

Conscientiousness

Conscientiousness describes traits related to self-discipline, organization, and the control of impulses, and appears to reflect the ability to exert self-control in order to follow rules or maintain goal pursuit. no significant gender difference has typically been found in Conscientiousness at the Big Five trait level [3].

Extraversion

Extraversion reflects sociability, Assertiveness, and positive emotionality, all of which have been linked to sensitivity to rewards [15,16]. Women tend to score higher than men on Warmth, Gregariousness, and Positive Emotions, whereas men score higher than women on Assertiveness and Excitement Seeking [2,3].

Openness

Openness reflects imagination, creativity, intellectual curiosity, and appreciation of esthetic experiences. No significant gender differences are typically found on Openness at the domain level, likely due to the divergent content of the trait. For example, women have been found to score higher than men on the facets of Esthetics and Feelings [3], whereas men tend to score higher on the Ideas facet [2, 3].

Materials and Methods

This study was conducted in the people's medical college and research centre, Bhopal (mp). We collected data from 150 students of first MBBS 2011-2012 batch, of these individuals, 85% were males and 65% were females. Demographic information such as age, gender was collected, Ethical clearance was taken from institutional ethical committee and written consent was taken from the students of first MBBS those who are involved in the study.

At the start of the semester during classes a personality inventory was administered to the students. We used personality inventory questionnaire of Buchanan (2001) based on Five-Factor Modality (FFM). The students rated each item

on a 5-point Likert-type scale (1= strongly disagree, 5 = strongly agree). The FFM is based in a belief that people are rational beings and count for their own personality and behaving, can analyze their own actions and Reactions (McCrae & Costa, 1996).Then by using responses from the participants from the study, we calculated the average ratings for each of the five personality domains.

Results

Table 1 shows statistical analysis of personality ratings for each of gender that is for men and women. Latent mean differences are displayed, with positive numbers indicating higher latent means in women and negative in men.

Table 1: Statistical analysis of personality ratings for each of gender that is for men and women.

Sr. No	Domain models	MEN (n=85) Score M (SD)	WOMEN (n=65) Score M (SD)	Latent mean difference
1.	Neuroticism	11.30 (6.10)	19.30 (14.10)	0.54**
2.	Agreeableness	1.15 (0.10)	2.28 (1.18)	-0.05*
3.	Conscientiousness	11.30 (1.6)	11.48 (1.7)	-0.033*
4.	openness	16.23 (4.10)	14.30 (3.13)	-0.05*
5.	Extraversion	12.12 (1.11)	12.22 (1.12)	-0.050*

Latent mean differences are displayed, with positive numbers indicating higher latent means in women and negative in men. **= p < .001 –significant ,*(P <.05) -Non-significant

Women were higher on Neuroticism (p < .001, d =.54)

Gender differences on other five factor domains like Extraversion, Openness, Agreeableness, and Conscientiousness,(P<.05) were non-significant.

Discussion

In the present study the Women were higher on Neuroticism and no significant gender difference has typically been found in Extraversion, Openness, Agreeableness, and Conscientiousness,(P<.05) at the Big Five trait level the present study is consistent with the conclusions of previous reviews that have assessed general anxiety or neuroticism [2]. FFM traits have traditionally been considered to have strong biological bases, with heritability estimates on the order of .5 [19]. This would suggest relatively persistent gender differences across the lifespan as well as across culture. Gender Differences in Personality Traits Across Cultures: Robust and Surprising Findings by Paul T. Costa, Jr [20] suggest that gender differences are small relative to individual variation within genders; differences are replicated across cultures for both college-age and adult samples, and differences are broadly consistent with gender stereotypes: Women reported themselves to be higher in Neuroticism, Agreeableness, Warmth, and Openness to Feelings, whereas men were higher in Assertiveness and Openness to Ideas, It is also consistent with pan cultural gender serotype for example, Williams and Best in 1990 [21] reported M% scores across 14 cultures averaging 15 for *fearful* and 14 for *complaining*. These gender differences in susceptibility to negative affect are not attributable solely to differential sensitivity to emotional experience, because many of them remained significant even when Openness to Feelings was statistically controlled. Our results are congruent with reports by Barefoot and colleagues, 2001 [22] of higher levels of depression, and by Lowe and Reynolds, 2006 [23] of higher levels of anxiety in adult women.

As in previous studies and reviews [2], men were found to be higher in assertiveness and women higher in nurturance, with the net effect that women scored substantially higher than men on A. Both evolutionary and social role theory explanations have been proffered for the consistent finding that women tend to be more nurturing. Evolutionary explanations emphasize the adaptive advantage for reproduction and preservation of offspring conferred by sensitivity and nurturance [7], while social role theory attributes female nurturant behavior to feminine gender role socialization [8].These findings, again, are consistent with pan cultural gender stereotypes: mean M% scores for *adventurous* and *dominant* were 94 and 87, whereas mean M% scores for *affectionate* and *sentimental* were 10 and 12, respectively.

Because E combines aspects of dominance and nurturance [10], gender differences in E vary by facet, with men higher in E3: Assertiveness and E5: Excitement Seeking, and women higher in E1: Warmth, E2: Gregariousness, and E6:Positive Emotions. Because Extraversion scales vary in the ratio of dominant to nurturant content, the direction of gender differences may also vary. It seems likely

that women scored lower than men on Extraversion in Lynn and Martin's [18] review but higher here because the NEO-PI-R E factor emphasizes warmth more than assertiveness, whereas the opposite may be true for the Eysenck scale. At the facet level of Neuroticism, women have been found to show higher levels of anxiety, depression, self-consciousness, and vulnerability than men [3]. All of these facets load primarily on Withdrawal rather than Volatility [16]. This pattern is consistent with the fact that clinical diagnoses of depression and anxiety are considerably more common in women than men [26].

As in younger samples [3], men evinced more Intellectual Interests and women more Aesthetic Interests. In explanations of such differences among adults, Costa and colleagues have have noted that men favor more information-oriented occupations, while women prefer aesthetically oriented occupations. It remains unclear whether this is a cause or result of gender differentiation on these aspects of Openness, but a reasonable hypothesis would be that personality and vocation mutually influence one another: Gender differences in intellectual and aesthetic pursuits may emerge during schooling, leading to different educational and career trajectories. Spending one's work years in occupations congruent with one's basic tendencies may in turn strengthen those tendencies, entrenching gender differentiation in these aspects of Openness. Of course, there are many men who favor aesthetic pursuits and many women who favor intellectual activities, so gender differences are averages only about which individuals vary.

Our results must be considered in the context of a few qualifications. First, the present results are based primarily on self-report. McCrae et al. [9] replicated patterns of trait differences in observer reports of young adults. Many of the difficulties in interpreting cultural differences in gender differentiation are due to this mono-method approach a similar replication in older adults is required to rule out reporting bias. Second, we used the NEO-FFI rather than the NEO-PI R, so we were unable to thoroughly investigate the full complement of gender differences observed at the specific facet level of the latter instrument. Future work might examine NEO-PI R facet gender differences in older adults. Third, our sample size was very less also. Hence our results may not accurately reflect the trajectories of personality change in men and women.

Taken on balance, these results represent an important extension of prior findings to a young adulthood, women score higher than men on Neuroticism.

Finally, though this and other studies have shown the existence of gender differences in personality, the question remains as to why these differences exist. Although the general consistency of gender differences across cultures may suggest evolutionary reasons for the existence of gender differences in personality traits. Exactly how culture impacts personality is a complex question, worthy of future study.

Conclusions

As Women were higher on Neuroticism ($p < .001$, $d = .54$) and no significant gender difference has typically been found in Extraversion, Openness, Agreeableness, and Conscientiousness ($P<.05$) at the Big Five trait level .

So we conclude that gender differences emerged at the level of NEO-FFM domains.

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Effect of Smoking on PEFR: A Comparative Study among Smoker and Non-Smokers

Harkirat Kaur*, Sahiba Kaur**

Abstract

Background: Smoking is the most important factor contributing to the development of COPD and is one of the health risks in modern time. The purpose of the present study was to determine the relationship between cigarette/biri smoking and PEFR between various groups of smokers and non smokers. *Methods:* The study was carried out in 100 male subjects between 19-52 years of age. The subjects were drawn from the community such that they could be grouped as non smokers 25, mild smokers 25, moderate smokers 25, and chronic smokers 25 according to their questionnaire response. Equipment used computerized spirometer. *Results:* PEFR is decreased in cigarette smokers and magnitude of decline was higher in chronic smokers. *Conclusion:* The intensity of cigarette smoking [pack years] emerged as the main variable to influence airway obstruction in smokers that caused reduction in PEFR.

Keywords: Smoking; PEFR.

Smoking is apublic health problem and amajor cause of many preventable diseases premature deaths all over the world. It is now well established that cigarette smoking for only a few years causes early changes in peripheral airways of the lung. The primary objective of the study was to investigate whether PEFR differs between cigarette smokers compared to non smokers.

Cigarette smoking has been identified to be the most important determinant of ventilatory impairment.

Although it is known that smoking causes respiratory dysfunction, but very few works have been actually done on the dose and time dependent effect of smoking on lungs.

Objective is to know whether the chronic heavy smoking start deteriorating the pulmonary function test as early as 5years of smoking habit. Only parameter selected is PEFR as it can be monitored by smoker himself. PEFR asses the severity and variation of disease and evaluates the effects of treatment.

Soon after commencing the smoking habit, the body becomes used to absorbing so much nicotine regularly that it eventually demands more and more. To obtain the same stimulation more cigarettes are required as the body becomes incurred to the smaller amounts of nicotine. Also the effect does not last long even if a larger dose is taken in the form of either stronger cigarettes or more cigarettes in shorter time. Thus excessive smoking becomes vicious circle.

Tobacco is dried leaf of nicotianna tabacum, a plant indigenous to America but now grown in many parts of the world. The poisonous properties of tobacco are due mainly to the presence of nicotine, a heavy oil substance. The amount of nicotine in a pound of tobacco is estimated to be, on an average 377 grains and this alkaloid is so poisonous that of again given intra venously can kill a dog in three minutes. Cigarette tobacco contains, on an average 1.55 nicotine and thus an average cigarette of one gram may yield as much as quarter grain to even half grain of nicotine. When one smokes, heat liberates nicotine in varying degree into smoke, some of the alkaloid is burnt but appreciable quantities gain access to respiratory tract. Depending upon moisture of the tobacco filtration, heat, rapidity of smoking the depth of inhalation.

Bhinde studied the chemical analysis of smoke of Indian cigarettes, bidis and other ingenious forms of smoking levels of steam volatile phenol, hydrogen cyanide and benzopyrene [3]. Besides nicotine, some

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other specific components of total particulate matter TPM like steam volatile phenol, HCN and benzopyrene are known to be hazardous to health. It has been well established that cigarette smoking is a major risk factor for lung cancer and COPD.

Cigarette smoking is the most important factor contributing to the development of COPD. It is now well established that cigarette smoking for only a few years causes early changes in the peripheral airways of lung [4]. The single best thing a smoker can do to improve their lung functions and live a longer life is to stop smoking. Or to monitor the severity of disease by peak flow meter. And can decrease the smoking and see the response to treatment.the single best thing asmoker can do to improve their lung functions and live alonger life is to stop smoking. It was evident from a recent study that smokers who had their lung functions measured and explained to them in a specific way, were more likely to have quit smoking ayear later [5]. The present study has been undertaken to compare between smokers and non smokers the PEFR using a medspiror acomputerized spirometer.the spirometer is an effective and easy method for detection of copd in risk group population like smokers and thus promotes smoking cessation efforts to reduce the burden of copd and lung cancers in the community [6]. The single best thing asmoker can do to improve their lung function and live a longer life is to stop smoking and to monitor the severity of disease by measuring PEFR [5].

Material and Methods

This study included 100 male subjects between 19-58 years of age. They were further subdivided into following groups:-

Group I (Non-Smokers)

25, Non-Smokers, the subjects having no history of smoking, no current or past history of any Cardio respiratory disorders, exertion dyspnoea, general debility, malnutrition or skeleton deformity were grouped as Controls.

Group II (Smokers)

25, Mild Smokers (< 5 pack years) (Group lla); 25, Moderate Smokers (5-10 pack years) (Group llb); 25 chronic smokers,(.10 pack years) (Group llc).

1 Pack years =20 cigarettes/day for one years was considered. A detailed history of smoking was taken; (1) Type of smoking inhaled, bidi/cigarette; (2) Time since smoking; (3) Number of bidis, cigarettes smoked per day.

The protocol of the study was approved by the ethics committee of our institute. Person having asthma or chromic of our infection of lungs, having persistent cough treated recently for any respiratory illness were excluded. The subjects were drawn from amongst the staff and students of the institute and residence of the city. Written consent was taken from the study and a written bio-data was obtained from them to group them into various groups. A detailed history and physical examination of each subjects was carried out. All testes were carried out in the morning during the post absorptive phase. The ventilator tests were carried out with a computerized spirometer ''Med-spiror''. It reads the amount of air and the rate of the air that is breathed in and out over a specified period of time. Testing procedures were quite simple, non-invasive and harmless to the patent. The subjects were familiarized with instrument and technique used.

The regarding was taken in standing position. Age, height (without shoes), body weight were recorded. Body surface Area (BSA) was read from "Nomogram" The terminology and abbreviations used for different lung function tests carried out are as suggested by cotes.

Each subject was given two trials and three test runs for each test and best three test reading was taken. Once the were subject were include in the study, none were subsequently rejected except when they were unable to give the desired co-operation in the experimental procedure.

The parameters studies from the records were; The Anthropometric variable - Age, Height, Weight, Body surface Are (BSA) peak Expiratory Flow Rate (PEFR)

Statistical analysis was carried 'P' value was determined. $p > 0.05$ considered as non-significance. Independent student test was used for between groups comparison.

Result

The mean, standard deviation, t-value and p-value of PEFR and Anthropometric values have been shown in the observation tables.

Mean values of physical characteristics in non-smokers (Group I) were: - age (34.56 + 10.64yrs), height (168.68 + 9.96 cms), weight (65.04 + 11.80 Kg) and Body Surface Area (BSA) (1.74 + .175sqm). Mean

values in smokers (Group II) were age (37.16 + 10.86), height (164.95 + 11.72), weight (60.48 + 10.86), height (164.95 + 11.72), weight (60.48 + 12.35), BSA (1.66 + 0.20) Table 1).

Table 2 depicts the comparison of mean values of respiratory parameters with standard deviation, t-value and p-value in Group I and Group II.

Table 3 compares the mean, standard deviation, t-value and p-value of physical characteristics in Group I and Group IIa, II b and Group II c.

The comparison of mean age, height, weight and BSA of non-smokers (Group I), mild smokers (Group IIa) were found to be statistically insignificant. The value of mean age in Group IIc in comparison with Group I was found to be statically significant.

Comparison of Group I and Group IIa revealed non-significant changes in most of the spirometric values. Comparison of Group I and Group IIb revealed significantly higher values of PEFR (P<0.01).

Comparison of Group I and Group IIc revealed PEFR (P<0.001).

Table 1: Anthropometric values

	Non-Smoker (Group I) 25	Smoker (Group II) 75	p-value
Age (years)	34.56 + 10.64	37.16 + 1.86	N.S.
Height (cm)	168.68 + 9.96	164.95 + 11.72	N.S.
Weight(kg)	65.04 + 11.80	60.48 + 12.35	N.S.
BSA (mt2)	1.74 + 0.17	0.66 + 0.20	N.S.

Table 2: Spirometric values

	Non-Smoker (Group I) 25	Smoker (Group II) 75	p-value
PEFR	7.48 + 1.67	5.71 + 2.71	<0.001

Table 3: Anthropometric values

	No.	Non-Smokers (GROUP I)	No	Smokers (GROUP II)	p-value
Age (years)	25	34.56 + 10.64	25	31.36 + 8.31	N.S.
			25	37.56 + 7.24	N.S.
			25	42.56 + 13.01	<0.05
Height (cms)	25	168.68 + 9.96	25	163.84 + 13.38	N.S.
			25	163.84 + 9.44	N.S.
			25	163.52 + 11.58	N.S.
Weight (kg)	25	65.04 + 11.80	25	63.08 + 13.02	N.S.
			25	59.28 + 10.29	N.S.
			25	59.08 + 13.12	N.S.
BSA (mt2)	25	1.74 + 0.17	25	1.68 + 0.22	N.S.
			25	1.64 + 0.16	<0.05
			25	1.66 + 0.19	N.S.

Table 4: Depicts the mean values, standard deviation, t-value and p-value of six spirometric values for Group I and Group IIa, Group IIb and Group IIc

	No.	Non-Smokers (GROUP I)	No	Smokers (GROUP II)	p-value
PEFR	25	7.48 + 1.67	25	7.08 + 1.63	N.S.
			25	5.66 + 2.23	<0.05
			25	4.38 + 1.68	<0.001

Comparison of Group I and Group II revealed in PEFR (p<0.001).

Discussion

Comparison between various groups of smokers, mild/ moderate / chronic was undertaken to assess the lung function tests using a computerized spirometer. Comparisons were also drawn between non smokers and smokers in relation to lung functions. The study observed that spirometry was an effective and easy method for detection of copd in risk group population like smokers.

Pulmonary function data in smokers indicate narrowing of smaller airways chiefly bronchioles which lead to slowly copd. It is inflammatory response of lungs to noxious gases or particles. Oxidative stress induced by smoking also induces copd.

In the present study the results of lung function were recorded and compared amongst the various groups. The results were also compared with the studies carried out previously.

The physical parameters of the present study showed insignificant results though body surface area value was significant [p,<0.01] amongst the non smokers and smokers [table 1]. The above finding is in agreement with the findings of Rai and Nancy [9]. There is also comparative reduction in weight of chronic smokers though statistically insignificant [Table 3], the findings are in agreement with Dand and Malik [10]. The decrease in the body weight in chronic smokers may be due to the fact that absorbed nicotine interferes with the appetite and food intake and it also alters the balance between body protein and body fat.

In the present study it was reported that the value of PEFR in smokers is lower than that in non smokers as shown in Table 2 and pvalue is statistically significant. The above study is not in agreement with an earlier study by Nag and Dey because the study undertook the comparison study between equal number of smokers and non smokers and the age group was different 45-49 [11]. The present study comprises of 75 mild, moderate and chronic smokers. Intensity wise analysis showed that the values PEFR in moderate and chronic smokers is lower than the control group and the p-value is statistically significant [p,<0.001]. The results of the present study are comparable to earlier studies which reported decreasing trends in the valuesas we proceeded from non smokers to heavy smokers [11,18].

One possible reason for decrease in PEFR could be inflammation which is common and constant pathological finding in cigarette smokers [22].

Inflammation either directly or by increasing smooth muscle tones indirectly may cause airway fibroses. All these changes provide wall thickness leading to air way narrowing and flow limitation. In addition inflammation causes destruction of the alveolar walls attached to the airway contributing further to airflow limitation by deforming and narrowing the airway lumen [21].

Overall our findings are consistent with others that the intensity of cigarette smoking [pack years] emerged as the main variable to INFLUENCE air way obstruction in smokers.

Constituents of tobacco smoke cause damage throughout the respiratory tree from the main airways [bronchi] to the peripheral airways [bronchioles] right down to the terminal alveoli [air pockets] as well as to immune system.

Loss of cilia and mucus glands hypertrophy occur in the upper airways, inflammation, epithelial changes fibross secretory congestion occur in the peripheral airways and alveoli are destroyed with loss of gas exchange area and airway flexibility.

Conclusion

Study concludes smokers can be considered one of major risk factors for COPD and lungs diseases. Which can be prevented by avoiding smoking habits and secondly chronic smokers may benefits from regular peak flow monitoring. PEFR is useful parameter to monitor airway obstruction, assess the severity and variation of diseases of also to evaluate the effects of treatment.

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Effect of Pranava Yoga on Acute Stress Induced Changes in Cardiovascular Parameters in Healthy Young Adults

Sharad Jain

Abstract

Stress is major problem faced by most of the people in the present environment. This phenomenon is more pronounced in young adults. Stress adversely affects the learning capacity of the student and stress induced headache is most commonly seen as immediate adverse effect of stress. Persistent stress also harms almost all the systems of the body including cardiovascular system predisposing the individual at higher risk for development of hypertension and other cardiovascular diseases. Pranava Yoga is one of the most popular techniques of yoga which involves Aum chanting. Pranava yoga is very simple yogic exercise and might be beneficial in relieving stress. One hundred asymptomatic healthy male medical students, aged 17-25 years, participated voluntarily. Acute stress was produced experimentally by using cold water of 8^0C as per protocol of cold pressor test which is autonomic function test and produces marked stimulation sympathetic nervous system. Subjects were exposed to acute stress by standard procedure of CPT. Cardiovascular parameters were recorded using Impedance Cardiovasograph (Nivomon) and automatic digital sphygmomanometer. All the parameters were recorded before CPT, immediately after CPT and finally 5 minutes after CPT. All the above steps were repeated with a modification that subjects performed Pranava Yoga during cold pressor test and continued performing Pranava Yoga for next 5 minutes. All the parameters were recorded before CPT, immediately after CPT and 5 minutes after CPT. Statistical analysis was done by One-Way ANOVA and Tukey post Hoc tests using the window SPSS Statistics 17.0 version. Results showed that there was significant increase in all cardiovascular parameters immediately after exposure to cold stress for two minutes while all the cardiovascular parameters returned back to normal baseline after 5 minutes. In second stage subjects were performing Pranava Yoga during CPT and in recovery phase after CPT. All cardiovascular parameters increased significantly immediately after CPT nullifying the effect of Pranava Yoga but all the cardiovascular parameters recorded 5 minutes after CPT was significantly lower in comparison to parameters recorded before CPT nullifying the effect of cold stress. These results suggest that Pranava Yoga might not prevent appearance of stress induced adverse changes in the cardiovascular system and other parts of body but Pranava Yoga not only abolishes the stress induced changes but also produces marked relaxation even more than basal state before exposure to stress.

Keywords: Pranava Yoga; Acute Stress; Impedance Cardiovasograph.

Introduction

Stress is a common phenomenon and major problem in the present scenario as people find unfavorable or adverse conditions or stressors in their life which generate stress. Ability to cope up with stressor is declining in people as with advancement of technology; they are more self centered and more confined to television, computers and mobiles etc. In student life, they are having a tendency to remain in a

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well protected environment given by their parents and this feature is more commonly seen in people of high socioeconomic status. Young students specially are less involved in sharing their problem with their friends and parents and also do not try to get solution of a problem by combined efforts. This might be one of the reasons of their less ability to cope up with the problems and generation of stress with subsequent behavior changes including depression, anxiety and related disorders. Prolonged stress or repeated stress also makes the people more prone for generation of hypertension and other cardiovascular diseases [1,2].

Stress leads to release of stress mediators in brain which act via receptor on specific neurons and lead to unique downstream effects. Nature and intensity of the stressor and the response of the person varies. It has been demonstrated in many researches that responses to experimentally induced same stress are varied widely from person to person. However all types of stressors stimulate sympathetic nervous system . Problems are inevitable in our life but facing them properly, avoidance of generation of stress or quickly get relieved from stress is more important to remain healthy [3].

Various yoga techniques have been advocated and have been proved as stress reducer in many research studies. Yoga and meditation are practiced from Vedic period in ancient India. Yogic exercises have been proved to be very effective in relaxing the mind and body and advocated as adjuvant therapy in patients of hypertension, migraine and cardiovascular disease [4,5]. Pranava yoga is a very simple exercise among various yogic exercises. Pranava yoga (Aum yoga) is simple chanting of word Aum and focus the mind on the sound and vibrations produced during Aum Chanting. Many researchers have shown that yogic exercises shift the sympatho-vagal balance towards vagal side by decreasing the sympathetic activity and increasing the vagal activity [6-8]. Cold stress test or cold pressor test (CPT) is an autonomic function test and produces acute stress [9]. Cold stimuli cause intense stimulation of sympathetic nervous system with release of nor- epinephrine and epinephrine. Immersion in cold water activates afferent pain and temperature neurons which results in stimulation of sympathetic efferent neurons. Cold pressor test represents a wide spread neurogenic stimulation of multiple components of cardiovascular system [10]. Change in cardiac output and peripheral resistance is very good indicator of change in autonomic status. As they tend to increase with sympathetic stimulation and tend to decrease with increase in parasympathetic activity [11].

Cardiac output and peripheral resistance can be measured non-invasively by using Impedance Cardiovasograph (Nivomon, L&T Medical's). It is a Non Invasive vasography monitoring system. It measures the Cardiac Output (CO) and Blood Flow Index (BFI) of the patient non-invasively. It computes various other cardiovascular parameters [12,13].

As stress produces harmful effects on cardiovascular system and yoga may be helpful in reducing stress therefore this study aims to explore the effect of Pranava Yoga on acute stress induced changes in cardiovascular parameters in healthy young adults.

Material and Methods

The present study was conducted in Saraswathi Institute of Medical Sciences, Hapur. One hundred asymptomatic healthy male medical students, aged 17-25 years, participated voluntarily in this study. Experiment procedures were in accordance with the ethical committee on human experimentation. Study was carried out at ambient temperature with minimal external or internal sound disturbances in the room. Subjects reported to laboratory 2 hours after light lunch. They were explained in detail about the experimental procedure. After getting informed consent from all subjects, procedure was conducted in 2 steps. In first step, subjects were asked to lie down supine and to take rest for 10 minutes. Blood pressure and heart rate were recorded by using automatic digital sphygmomanometer. Subjects were connected to impendance Cardiovasograph (Nivomon) via color coded 8 leads of NICO patient cable. Leads were connected at their respective locations as given below:

1. Red leads (I1 and I1′) -Behind the ears (Top pair)
2. Yellow leads (V1 and V1′) -Roof of the neck (Second pair)
3. Violet leads (V2 and V2′) -Level of xiphisternum (Third pair)
4. Green leads (I2 and I2′) End of ribcage or >5 cm from third pair (Bottom pair)

Cardiac output, peripheral resistance and other parameters were recorded using Impedance Cardiovasograph (Nivomon).

Subjects dip their left hand in water of 8^{O}c for two minutes. Above mentioned parameters were recorded again immediately and at 5 minutes after removal of hand from cold water.

In next step, subjects took rest of 10 minutes again in supine position. All the above steps were repeated

with a modification that subjects performed Pranava Yoga during cold pressor test and continued performing Pranava Yoga for next 5 minute. All the parameters were recorded before CPT, immediately after CPT and 5 minutes after CPT.

All data were collected and statistical analysis was done by One-Way ANOVA and Tukey post Hoc tests using the window SPSS Statistics 17.0 version.

Result

Table 2 shows comparison of parameters before and after CPT. There was significant increase in all cardiovascular parameters immediately after exposure to cold stress for two minutes. Increase in heart rate (HR) , Systemic Peripheral Resistance (SPR), Systemic Vascular Resistance Index (SVRI) and Diastolic blood pressure (DBP), were highly significant ($p<0.01$). while increase in Stroke volume (SV), Stroke volume Index (SVI), Cardiac Output (CO), Cardiac Index (CI), Systolic blood pressure (SBP), were less significant ($p<0.05$). However, all the cardiovascular parameters returned back to normal after 5 minutes and there was no significant difference in parameters before CPT and 5 minutes after CPT.

Table 3 shows the comparison of parameters before and after cold pressor test with subjects performing Pranava Yoga during CPT and in recovery phase after CPT. All cardiovascular parameters increased significantly immediately after CPT even subject was performing Pranava yoga. Increase in HR, SPR, SVRI and DBP were highly significant ($p<0.01$); while increase in SV, SVI, CO, CI and SBP were less significant ($p<0.05$).

Table 1: Baseline characteristics of all subjects

S. N.		
1	Age (in years)	21.2±4.2
2	Height (cms)	168.5±5.1
3	Weight (Kg)	61.5±4.3
4	BSA (m^2)	1.67±0.15

Data are expressed as Mean±SD

Table 2: Comparison of cardiovascular parameters before & after CPT

S. N.		Before CPT	Immediately after CPT	5 minutes after CPT
1	SBP (Systolic blood pressure; mm Hg)	115.82±2.5	137.2±5.2*	115.2±2.5#
2	DBP (Diastolic blood pressure ;mm Hg)	72.92±2.2	87.32±2.5**	73.12±3.6#
3	HR (Heart rate; per minute)	70.80±1.13	82.4±2.9**	71.18±0.23#
4	CO (Cardiac Output; L/min)	5.21±0.28	6.44±0.17*	5.22±0.28#
5	SV (Stroke volume ;ml/ beat)	72.04±0.6	76.21±1.5*	72.84±0.16#
6	SVR (Systemic Peripheral Resistance ;dyne.sec/cm^5)	1355.1±9.4	1399±15.4**	1357.2±5.24#
7	CI (Cardiac Index) (L/min/m^2)	3.01±0.06	3.66±0.66*	3.02±0.07#
8	SVI (Stroke volume Index ;ml/ beat/m^2)	43.81±0.02	45.46±0.13*	44.02±0.12#
9	SVRI (Systemic Vascular Resistance Index; dyne.sec/cm^5/m^2)	767.5±12.5	793.5±12.1**	769.2±12.5#

Data presented are Mean±SD. *$p<0.05$, **$p<0.01$, #$p>0.05$ (non-significant)
*comparison between before CPT and Immediately after CPT, #comparison between before CPT and 5 minutes after CPT

Table 3: Comparison of cardiovascular parameters before and after Cold Pressor Test while subjects performing Pranava Yoga during and after CPT

S. N.		Before CPT	Immediately after CPT (with Pranava Yoga)	5 minutes after CPT (With Pranava Yoga)
1	SBP (Systolic blood pressure; mm Hg)	115.02±3.4	136.8±6.2*	105.6±2.1^^
2	DBP (Diastolic blood pressure ;mm Hg)	73.26±2.8	86.8±1.4**	64.12±1.3^
3	HR (Heart rate; per minute)	71.02±1.20	80.3±3.6**	65.2±0.14^^
4	CO (Cardiac Output; L/min)	5.26±0.20	6.18±0.06*	4.72±0.06^^
5	SV (Stroke volume ;ml/ beat)	71.84±0.8	74.22±1.4*	69.22±0.14^^
6	SVR (Systemic Peripheral Resistance ;dyne.sec/cm^5)	1357.1±8.6	1388±18.4**	1324.2±5.34^
7	CI (Cardiac Index) (L/min/m^2)	2.92±0.18	3.72±0.16*	2.61±0.04^^
8	SVI (Stroke volume Index ;ml/ beat/m^2)	44.12±0.02	44.16±0.24*	40.53±0.03^^
9	SVRI (Systemic Vascular Resistance Index; dyne.sec/cm^5/m^2)	765.5±12.44	796.98±14.8**	751.2±2.6^

Data presented are Mean±SD. *$p<0.05$, **$p<0.01$, ^$p<0.05$, ^^$p<0.01$, *comparison between before CPT and Immediately after CPT (with Pranava Yoga), ^comparison between before CPT and 5minutes after CPT (with Pranava Yoga)

During next 5 minute subjects were performing Pranava Yoga and all the cardiovascular parameters recorded 5 minutes after CPT were significantly lower in comparison to parameters recorded before CPT. Decrease in HR, SV, SVI, CO , CI and SBP were highly significant ($p<0.01$) while decrease in SPR, SVRI and DBP were less significant ($p<0.05$).

Discussion

Acute stress as well as prolonged stress increases sympathetic activity of autonomic nervous system. Prolonged sympathetic hyperactivity has been found to be associated with generation of hypertension. Cold stress produces intense stimulation of sympathetic nervous system with almost complete withdrawal of parasympathetic activity [9].Increased sympathetic discharge produces arteriolar constriction which leads to increased systemic peripheral resistance, systemic vascular resistance Index and diastolic blood pressure. In addition, increased activity of sympathetic nerves increases heart rate, stroke volume, cardiac output and systolic blood pressure. Release of nor-epinephrine from postganglionic sympathetic neurons and epinephrine from adrenal medulla are responsible for these changes. By the action of cold stress, parasympathetic activity is abolished and heart rate increases to unopposed increased sympathetic activity. Stroke volume is also increased significantly due to increased myocardial contractility. Increased heart rate and increased stroke volume significantly increase the cardiac output. Regular yoga exercises improve quality of life, reduces morbidity and mortality. It gives sense of subjective well being in normal people as well as in patients suffering from diseases [13]. It can be used as powerful tool to combat stress. Aum chanting is very easy exercise and can be done any time in any posture [8]. Results in the present study show that intense sympathetic stimulation produced by acute stress of cold pressor test is washed out by Pranava Yoga. These finding suggest that Pranava Yoga practice leads to decrease in sympathetic activity and increases parasympathetic activity. This is thing which is required to combat stress in day to day life. So Pranava yoga is beneficial as quick stress reliever technique. As it reduces stress and quickly vanish adverse effects of stress, regular practicing of Pranava Yoga is very beneficial for normal person and patients suffering from hypertension and other cardiovascular diseases.

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Chemotherapy Induced Peripheral Neuropathy; Mechanism and Treatment

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Abstract

The use of chemotherapeutic agents to treat cancersis associated with several adverse effects, one of the debilitating and often dose-limiting side effect is peripheral neuropathy, manifested with different clinical signs and symptoms. Most common being sensory neuropathy, followed by motor; presenting with loss of sensation, paraesthesia in the limbs, motor symptoms like weakness in the limbs, difficulty in walking, difficulty in carrying out fine motor movements; the effect on autonomic nerves have not been studied in detail. Numerous mechanisms are proposed by different researchers to explain the basis of neuropathy associated with the use of anti-cancer drugs. The chemotherapy induced peripheral neuropathy (CIPN) often requires dose-reduction and drug withdrawal, hampering the effectiveness of the drug and compromising survival outcomes. Various life modification strategies like mindfulness, exercise, occupational therapy etc. are being used to reduce the intensity of side effects and to tolerate the drugs better. In addition, various neuroprotective agents have been tried as adjunct therapy but according to published systematic reviews and meta-analysis, none of these agents have robustly proven their efficacy in treating CIPN. Anti-oxidants, anti-convulsants, anti-depressants, calcium and magnesium etc. are some of the drugs being used for reducing the intensity of CIPN. Out of these, topical pain relievers and duloxetine are considered as the first line of treatment for CIPN. Well planned clinical trials are required to establish the clinical utility of others.

The current review briefly focusses on the mechanisms involved in the genesis of CIPN and treatment strategies available for the same.

Keywords: Anti-Neoplastic Agents; Chemotherapy; Neuroprotective Agents; Peripheral Neuropathy.

Introduction

Chemotherapy induced peripheral neuropathy (CIPN) is a frequently observed and dose-limiting adverse effect of many chemotherapeutic (antineoplastic drugs) agents including taxanes (paclitaxel, nab-paclitaxel, ordocetaxel), platinum based drugs etc [1-5]. The incidence of CIPN ranges from 2% to 100% depending on the patient medical history and clinical condition and also on the chemotherapeutic agent being used [6]. This complication is one of the cause of significant disability in cancer patients leading to further deterioration of the quality of life. The anti-neoplastic drugs may affect the sensory and motor nerves and peripheral autonomic nerves to some extent. The involvement of autonomic nerves has not been studied extensively. The symptoms may vary from sensory loss (glove-and-stocking distribution), dysesthesia, and paraesthesia to shooting pain (features of nerve hyper excitability) and decreased muscle tone [7]. CIPN can be evaluated using a patient-based instrument, the Patient Neurotoxicity Questionnaire (PNQ) and a physician-based instrument, the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) in patients with cancer on chemotherapy [9,10]. Neurophysiological tests beneficial in diagnosis of CIPN include measurement of sensory and motor nerve conduction velocity (NCV), sensory nerve action potential (SNAP), and compound muscle action potential (CMAP) together with needle electromyography (EMG). EORTC QLQ-CIPN20 instrument, N06CA, developed by the European Organization for Research and Treatment of Cancer is a another widely used questionnaire for the assessment of CIPN [11]. In this review, we would briefly discuss the mechanism leading to the genesis

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of CIPN and current treatment strategies available for the same.

Chemotherapy Induced Peripheral Neuropathy

CIPN is a debilitating side effect associated with the use of various chemotherapeutic agents. The imperative antineoplastic agents responsible for CIPN are taxanes like paclitaxel (Taxol), docetaxel and newer cabazitaxel; platinum derivatives, such as cisplatin and carboplatin; vinca alkaloids and two old drugs with new applications- suramin and thalidomide etc [1-4].

Sensory neuropathies are more common chemotherapy-induced neuropathy. Early signs include tingling or numbness in the feet or fingers. Sensory symptoms including paresthesia; dysesthesia; tingling; itching; and burning, tight, stabbing, sharp (lightning like), or aching pain are often reported by patients [12]. Sensory loss in the feet and legs can cause sensory ataxia and gait disorders. Platinum compounds in addition alter smell and taste sensations; cause vestibular dysfunction and hearing loss. Motor neuropathy is manifested as absence of Ankle reflexes. Vinca alkaloids may cause distal weakness, including foot drop. Autonomic signs are rare but can be seen in vinca alkaloids, taxanes, and platinum compounds. Several drugs cause muscle cramps or weakness [13,14]. Raynaud's syndrome is observed in long-term survivors of testicular cancer [15].

Severity of CIPN depends on various factors; age and dose being the primary factor. In addition, cumulative dose, delivery method, prior and concomitant use of other anti-cancer drugs (synergistic neuro-toxicity), pre-existing neuropathy of any aetiology (hereditary or inflammatory) also add to the manifestations of CIPN [7,16,17]. In a study by Pereira S, no significant differences was reported in the variation of breast cancer patient-reported outcomes between the baseline and 1-year follow-up evaluations. Alcohol consumption and diabetes were shown not to be significantly associated with CIPN [10]. Chemotherapy induced sensory neuropathy in patients on Paclitexal, was reportedly increased during active treatment in terms of both the PNQ and NCI-CTC assessments. Contrary to this, increase in motor neuropathy symptoms were reported only by the PNQ [9].

Polymorphisms in several genes, for example the in the ones coding for voltage-gated sodium channel or genes affecting the activity of pivotal metal transporters, can also impact drug neurotoxicity [18].

Mechanism of CIPN

Various mechanisms have been proposed to explain the basis of CIPN, some are specific and others non-specific. Taxanes are the most common culprit leading to CIPN, manifested as symmetric, axonal sensory distal neuropathy, there is less of motor involvement. They primarily act by degenerating Schwann cells, neuronal body and also bring about changes in axonal transport and cytoplasmic flow in the affected neurons. Molecular mechanism bringing about degenerative changes in the peripheral nerves are DNA damage, alterations in cellular system repairs, mitochondria changes, oxidative stress [19] and various ion channelopathies [8]. Sensory symptoms have been implicated to structural deficits in dorsal root ganglia and sensory nerves [19,20].

Platinum derivatives, such as cisplatin and carboplatin, affect mainly the peripheral nerves and dorsal root ganglia neurons, possibly by progressive DNA-adduct accumulation and inhibition of DNA repair pathways. Oxaliplatin causes acute neurotoxicity by altering calcium sensitive voltage gated sodium channels [18].

Treatment of CIPN

Treatment options for CIPN include dose adjustments, drug withdrawal, altering the chemotherapy, and handling CIPN with adjunct therapy or any neuroprotective agents. Adoption of management strategies focussing on exercise, mindfulness, occupational therapy etc. is recommended [4,21,22].

Neuroprotective Agents

According to the systematic review and meta-analysis by Albers [23,24], the data on the benefits of neuroprotective agents are insufficient to conclude their protective role in chemotherapy induced neurotoxicity, as determined using quantitative, objective measures of neuropathy. Till date, numerous chemo protective agents viz. thiols, neurotrophic factors, anticonvulsants (oxcarbazepine), acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, antioxidants like glutathione, retinoic acid, and vitamin E have been proposed to be useful in preventing or limiting the neurotoxicity of chemotherapeutic drugs and have been tested in pre-clinical models and clinical trials [25].

In a pre-clinical study on Wistar rats, erythropoietin given systemically has shown a wide range of

neuroprotective actions against central and peripheral nervous system damage [26]. Adjunct therapy with topical agents, tricyclic antidepressants, and anticonvulsants, such as pregabalin and gabapentin, have also shown limited efficacy. Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) was found to be more effective than placebo in treating oxaliplatin- or paclitaxel-induced CIPN, was well tolerated, and was proposed to be considered to be a first-line treatment option for CIPN [27,28].

Calcium and magnesium infusions have strongest preliminary data regarding their potential efficacy in preventing CIPN, venlafaxine, another SNPR is also effective in preventing CIPN but are not routinely used because of concerns related to decreased chemotherapy efficacy [28].

Though anti-convulsants and anti-depressants have been found to be useful in CIPN but none of the findings have been duplicated in an RCT with a large sample size [29].

In one of the study, patients with CIPN were treated with regulated dose of acetyl-L-carnitine for at least 10 days. Out of twenty-six patients evaluated after completion of 10 days of acetyl-L-carnitine therapy, at least one WHO grade improvement in the peripheral neuropathy severity was shown in 73% of the patients [30].

Literature search has revealed the effectiveness of vitamin E supplementation in decreasing the incidence and severity of peripheral neurotoxicity in patients receiving cisplatin chemotherapy [3,31].

Although several of these agents hold promise as possible neuroprotective factors, clinical data are still controversial and none have as yet robustly been proven effective against CIPN. Agents with the strongest supporting evidence for efficacy in the treatment of CIPN include topical pain relievers, such as baclofen/amitriptyline/ketamine gel, and serotonin and norepinephrine reuptakeinhibitors, such as venlafaxine and duloxetine. Cutaneous electrostimulation, a nonpharmacological therapy appears, from an early pilot trial, to be potentially effective in the treatment of CIPN [4]. Chu SH points towards the need and importance of conducting well-designed RCTs to generate evidence on CIPN symptom management [29].

Since data on the effect of chemotherapy on peripheral autonomic nervous system is scarce, we are working on a project designed to evaluate the autonomic activity in patients receiving chemotherapy.

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The Mirror Neuron System: Basic Concepts

Bharati Mehta*, Bharti Bhandari**

Abstract

About two decades ago, it was discovered that some neurons in F5 area of ventral premotor cortex of the macaques monkeys discharged not only when the monkeys performed a motor act, but also when they saw the same act being done by another monkey. The accidental discovery of these fascinating neurons, named the *Mirror Neurons*, urged the scientists to think of presence of such kind of neurons in humans because the same area, the premotor cortex, exists in the human brain. In this article, we review first the basic properties of these neurons in monkeys. We then describe the Mirror Neuron System (MNS) in humans; we also compare the MNS of monkeys with that of humans. The aim of this review is to provide an account of the basic concepts &functionalproperties of the system formed by mirror neurons.

Keywords: Mirror Neurons; Imitation; Action Understanding.

In the mid-1990s, scientists studying the grasp response of macaques monkeys found that certain neurons in the area F5 of theirventral premotor cortex, sent out action potentials not only when the monkeys were moving their hands or mouths, but also when they were simply watching another animal or a human being who was making such a gesture [1-3].

These neurons were appropriately named mirror neurons because plausibly an observed movement was being 'mirrored' in the motor representation of the same movement in the observer.

Subsequent research elucidated the diverse regions, other than area F5, to be involved in the Mirror Neuron System (MNS) of monkeys as well as humans.

Basic Properties of Monkey Mirror Neurons

There are two classes of visuomotor neurons in monkey area F5:-

1. *Canonical neurons,* which respond to the presentation of an object [4]. Theybecome activated when the animal merely sees an object that can be grasped by the prehensile movement of the hand. The main property of canonical neurons is thus, to match the shape and size of the observed object with a specific type of prehension, as if the brain were foreseeing a possible interaction with this object and preparing itself accordingly.
2. *Mirror neurons*, which respond when the monkey sees object-directed action[5]i.e. which are activated both when they perform an action as well as when they see someone else performing it.In order to be triggered by visual stimuli, mirror neurons require an interaction between a biological effector (hand or mouth) and an object.

The characteristic property of mirror neurons is therefore, that of matching observation of hand and mouth motor acts with the execution of the same or similar motor acts. This matching mechanism enables the observing individual to achieve an automatic understanding—i.e. anunderstanding without inferential processing of others' goal-directed motor acts [6].

These mirror neurons are *not* activated with the mere sight of an object, of an agent mimicking an action, or of an individual making intransitive gestures that are non-object-directed. Also, the mirror-neuron response does not depend upon object significance for the monkey; grasping a piece of food

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or a piece of wood produces the responses of the same intensity.The discharge is of the similar intensity even if the experimenter grasps the food and gives it to the recorded monkey (reward)or to another monkey introduced in the experimental room.

Virtually all mirror neurons show compatibility between the visual actions they respond to and the motor responses they code [2]. The main feature of the visual properties of mirror neurons in both premotor and parietal cortices is the congruence between the executed and the observed motor act [1,2,7]. Although, the visual features of the observed actions are fundamental to trigger mirror neurons, their role is just that they allow the understanding of the observed actions. If action comprehension is possible on another basis (e.g., action sound), mirror neurons signal the action, even in the absence of visual stimuli.

Neurons responding to the observation of actions done by others are not restricted in area F5 in monkeys. Another region in which neurons with these attributes have been described is the superior temporal sulcus (STS) [8,9]. Another cortical area where there is presence of neurons that respond to the observation ofactions done by other individuals is area 7b formingthe rostral part of the inferior parietal lobule [10].

It is interesting to note that in contrast to F5, the mirror neurons of STS do not possess motor properties.

Functions of the Mirror Neurons in the Monkeys

The main function of mirror neurons in monkeys seem to be "Action Understanding". Every time an animal watches an action done by another animal, the neurons that represent that action are activated in the observer's premotor cortex. This unconsious motor representation of the observed action corresponds to that which is spontaneously generated during active action and whose outcome is known to the acting individual. It is thus postulated that the mirror system transforms visual information into knowledge [11].

It is now well established that these neurons code the 'goal' of the motor acts [12,13] i.e. they are directed towards goal and not the movement. Evidence supporting this point is provided by fact that the same neurons discharge when the monkey grasps an object (e.g. food) with its right hand, left hand and the mouth[14]. It is clear that this type of neural behavior cannot be explained in terms of movements because the movement differs in all the three mentioned acts, but the goal is same – eating food.

Basic Properties of Mirror Neurons in Humans

Brain imaging studies reveal that action observation in humans activates the inferior frontal gyrus (IFG), lower part of the precentral gyrus, the rostral part of the IPL and also the temporal, occipital and parietalvisual areas [2]. The frontal and the parietal mirror neuron regions are somatotopically organized. The activation of pars opercularis of the IFG reflects the observation of distal hand and mouth actions, whereas the activation of the premotor cortex reflects proximal arm and neck movements. Unlike those in monkeys, the mirror neurons in humans, fire even while observing meaningless (intransitive) movements. The observation of transitive actions causes the firing of the frontal and the temporal nodes ofthe MNS while that of intransitive actions result in the firing of the frontal node only [15,16]. Another important difference noted was that human mirror-neuron systems code also for the movements forming an action and not only for action (goal) as monkey mirror-neuron systems do. These properties of the human mirror-neuron system are proposed to play an important role in determining the humans' capacity to imitate others' action.

Functions of Mirror Neurons in Humans

Neurophysiological experiments like Electroencephalography (EEG), Functional Magnetic Resonance Imaging (fMRI), Transcranial magnetic stimulation (TMS) etc. demonstrate that when individuals observe an action done by another individual, their motor cortex becomes active even in the absence of any overt motor activity. A first evidence of this was provided in the 1950s by Gastaut et al [17,18]. They observed that the desynchronization of an EEG rhythm recorded from central derivations (the so-called mu rhythm) occurs not only during activemovements of studied subjects, but also when the subjects observed actions done by others.This observation was confirmed by Cochin et al. using EEG recordings [19,20].

Action Understanding

One of the first hypotheses forwarded about the plausible role of mirror neurons in humans was that they enable an individual to understand another's actions. We understand our own actions quite well, so it is logical to suppose that if the same neurons fire when we see someone else perform a similar action, the firing of these neurons tells us what this individual is doing. And this is indeed one of the most widespread interpretations of the function of

mirror neurons.

Action understanding is the fundamental function of the MNS in humans too. Each time the individual observes a certain action being performed by another, the mirror neurons representing the performance of that action are activated. The mirror neurons transform visual observation into knowledge [21]. One such possible function was proposed by Mahon and Caramazza (2008): that mirror neurons may provide a sensorimotor enrichment for certain abstract concepts, such as playing a saxophone or dancing a particular dance [22]. As a result of this enrichment mechanism, someone who plays this instrument or dances the dance in which he is adept, could more readily judge someone else's skill by watching them do so, whereas a non-musician or non-dancer would have more trouble in making this judgment.

Imitation

Imitation is the advanced skill seen in primates. The properties of the human mirror-neuron system of responding to not only the goal but the whole movement of the action (goal), are thought to play an important role in determining the humans' capacity to imitate others' action [23].

Basic circuit underlying imitation coincides with that which is active during action observation. Imitation requires a perfect matching of the performed action onto the observed one. Mirror neurons are able torecognize the actions of others and the intention associated with them. So they can code for likely future actions of others, thereby observers are able to anticipate the actions of others [1,23]. Children are thought to learn by imitating their elders. The data indicate that mirror system is adaptive and may start to function as early as 6 months post-birth, although at a rudimentary level [24].

Speech & Language

The mirror neurons are present in Broca's area of humans, which suggests that human language may have evolved from a gesture performance/ understanding system. Broca's area is considered to be a homologous region of ventral premotor cortex of monkeys [2]. The tasks like spontaneous speech and reading activate the hand motor area and the IFG, on the left side [25,26]. So language mirror neurons seem to be lateralized to the left side involving the categorical motor cortex and the higher levels of language network; the areas of which are supposedly located on the left cerebral cortex [27].

Empathy

Empathy is the experience of understanding another person's condition from their perspective, i. e. placing oneself in other's shoes and feel what they are feeling. Empathy is known to increase pro-social (helping) behaviors, affective sharing between self and others, adopting the perspective of others and the ability for self agency and self regulation [28].

Theory of mind, Social behavior, communication are other aspects where mirror neurons have a possible role.Social communication and identification involve imitation. The more the people tend to imitate each other, the more they are able to communicate, understand and develop an empathic relationship with each other [23].

Several of researchers in cognitive neuroscience consider that mirror system provides the physiological mechanism for the perception/action coupling, for understanding the actions of other people, and for learning new skills by imitation.Some researchers speculate that mirror systems contribute to understanding of theory of mind, language and empathy and even the intentions of other people [29].

However, in an article published in 2009, Gregory Hickok stirred up considerable controversy by showing that this theory of "action understanding" was poorly supported by the experimental data as most of the research on these neurons has been conducted in monkeys [30]. In a 2013 article for Wired Christian Jarrett also expressed skepticism about the theories being advanced to explain the function of mirror neurons.

To conclude, the fascinating discovery of MNS has generated tremendous enthusiasm among researchers in cognitive neuroscience, but there are mysteries yet to be resolved.

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