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Original Research Paper

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Relationship between Basal Metabolic Rate and Body Fat Percentage in Obese and Non-obese Females: A Comparative Study

Nagashree V.[1], Nausheen Rumana[2], Revathi Devi M. L.[3]

Abstract

Background: Obesity and its associated disorders are a growing epidemic across the world. Many genetic, physiological, and behavioral factors play a role in the etiology of obesity which causes disturbance in energy equilibrium. Balance should be maintained between energy intake and its expenditure. This can be assessed by an individual's basal metabolic rate (BMR). *Aims & Objectives:* To measure and correlate variations in basal metabolic rate in obese and non obese individuals. *Materials and Method***:** 140 female subjects were grouped into 70 obese and 70 non obese categories. Anthropometric measurements like height, weight, BMI and waist circumference were recorded. Body fat percentage and BMR were measured using Omron HBF 306 body fat analyzer. *Results and Conclusions:* This study is done by random sampling with power > 80% and Level of significance being 5%. The present study shows statistically significant higher values of waist circumference, BMI and body fat percentage ($p< 0.000$) in obese. Basal metabolic rate (BMR) shows statistically significant higher values ($p< 0.000$) in obese. BMR showed positive correlation with body fat percentage and Body Mass Index (BMI).

This shows that the increased adiposity contributes for increased respiring cells thus resulting increased metabolism, resulting in higher BMR values in obese.

Keywords: Obesity; Body Fat Percentage; BMR; BMI; Lipid Profile; Fasting Blood Glucose.

Introduction

Obesity, a chronic non-communicable disorder is associated with abnormal, excessive body fat accumulation. Approximately 1.2 billion people in the world are overweight and at least 500 million of them are obese [1]. According to the World Health Organization, obesity is one of the 10 most preventable health risks. WHO estimates that approximately 58% of diabetes mellitus, 21% of ischemic heart disease, and 8-42% of certain cancers can be attributed to BMI above 21kg/m^2 [2]. Moreover, there is greater realization that both the amount of body fat and its distribution are important in determining health risks associated with overweight conditions. In many Asian populations, abdominal or central obesity (measured by waist circumference or the ratio of waist to hip circumference) is found to be more common than obesity defined by BMI [3]. A study in India observed that about 20% of adults who were not overweight or obese as per the BMI definition still had abdominal obesity [4].

Obesity is related to an imbalance between energy intake and expenditure. However, more recent research has suggested that genetic, physiological, and behavioral factors also play a significant role in the etiology of obesity. Body composition, i.e., the proportion of body fat and active protoplasmic tissue, has a great influence upon the basal metabolism. Basal metabolism of an individual is a function of the total mass of active protoplasmic tissue [5].

This study was designed to examine the associations of several measures of adiposity

like BMI and % BF and body fat distribution (waist circumference) with basal metabolic rate.

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Materials and Methods

In present study a total number of 140 female subjects were considered and grouped into 2 groups of 70 obese and 70 non obese medical and paramedical students of Mysore Medical College and Research Institute belonging to age group of 18-25 years. Females with BMI more than 25 are grouped as obese (Classification of weight by BMI in Asian and Euripides adults by WHO) and also with Body fat percentage more than 39% are considered as obese [6].

Subjects with history of diabetes mellitus, hypertension, cardiovascular diseases, drug intake, active sports training, yoga, aerobic exercise, and other metabolic disorders were excluded from the study. Study was conducted after obtaining ethical clearance from the ethical committee of MMC&RI. Informed consent was taken from all the participating subjects

Anthropometric measurements such as Height in meters, Weight in kilograms, Waist circumference in centimetres, Body Mass Index were recorded. Body fat percentage and Basal Metabolic Rate was recorded using bioelectric impedance body fat analyzer Omron Model HBF 306 which gives values of body fat % and BMR after feeding input of height, weight, age and gender details. For measurement of BMR, subjects were instructed to undergo 12 hours overnight fast and to reach the study centre without undue exertion. Subjects were then allowed to relax for half an hour before measurement. Recording was taken within the first ten days of menstrual cycle (the first day of menstruation taken as day 1) of the subjects. All measurements were carried out between 6am-8.30am, in a room, with temperature maintained between 23^0C-26^0C.

Results

This is a comparative study done by random sampling with power > 80% and Level of significance being 5%. Statistical analysis is done using SPSS software.

The distribution of age is not showing any statistically significant values between case and control. Maximum number of subjects belong to age group of 20 years (27.1% obese and 34.7% non-obese).

Graph 1: Age wise distribution of controls and obese cases

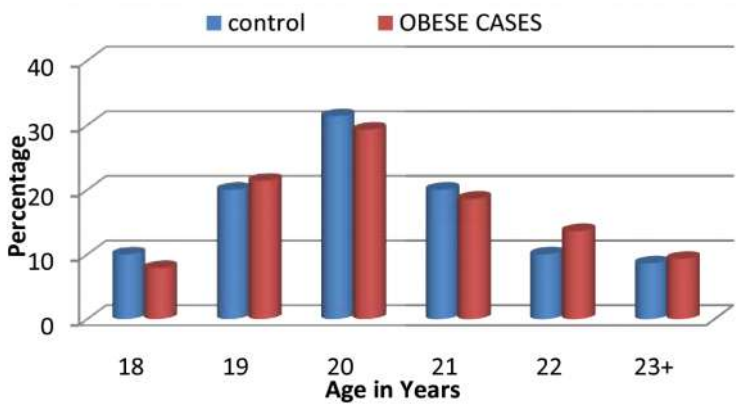
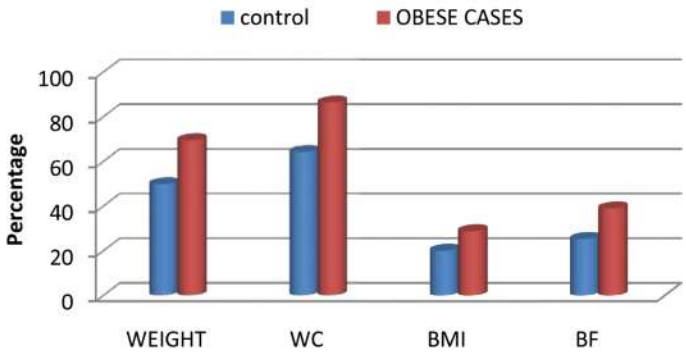


Table 1: Anthropometric measurements

Variables	Mean ± SD of Case	Mean ± SD of Control	P- Value
Height in cms	155.78 ± 5.38	157.41 ± 6.60	0. 112
Weight in kg	69.58 ± 6.17	49.88± 6.08	0.000*
Waist circumference in cms	86.41 ± 9.47	64.28± 4.05	0.000*
BMI	29.77 ± 2.27	20.05± 1.62	0.000*
Body Fat %	38.99± 2.66	25.29± 2.74	0.000*

*p-value (<0.05): considered as significant

Graph 2: Anthropometric measurements



The above table and graph shows statistically significant higher values of weight, waist circumference, BMI, Body fat % in obese (p- value = 0.000) . Height is not showing any significant variation (p-value = 0.115).

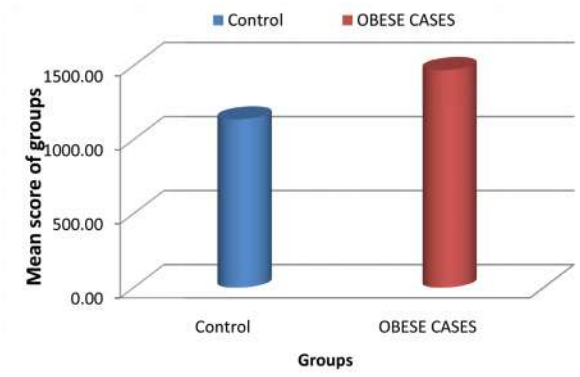
Table 2: Basal Metabolic Rate

Variables	case	control	p-value
Basal Metabolic Rate	1470.74±195.08	1137.42 ± 85.43	0.000*

*p-value (<0.05): considered as significant

The above table shows statistically significant higher values of BMR in Obese (p- value = 0.000)

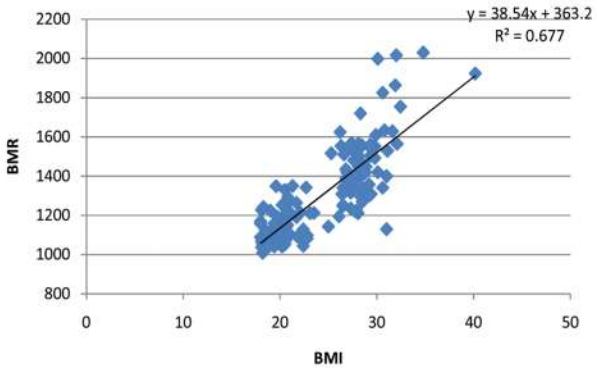
Graph 3: Comparison of basal metabolic rate between control and obese cases



Basal metabolic rate is higher in obese group compared to control group which is statistically highly significant with p value of 0.000.

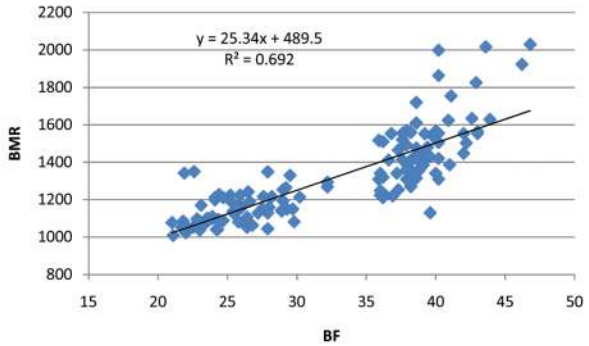
Correlations of BMR with BMI and Body Fat %

Graph 4: BMR with BMI



The above graph shows linear positive correlation between BMI and BMR

Graph 5: BMR with Body Fat %



The above graph shows linear positive correlation between BMR and Body fat per cent.

Discussion

Obesity is a major public health problem resulting in serious social, physical and psychological damages. The prevalence of obesity and overweight among adult and children is increasing in developed and developing countries including India.

During earlier studies done during 20th century obesity prevalence was higher in middle aged individuals, in contrast to present scenario where it is showing increasing trends in children and adolescents as a result of their genetic and environmental influences. Increasing prevalence of obesity in younger age groups is contributing its major share for global epidemic of obesity [7, 8, 9]. Several studies done in different parts of the world

have shown high prevalence of obesity in females. Girls with early menarche (age ≤ 11 years) are twice as likely to become obese adults as are late ones (age ≥14 years) [10]. The probable reasons for higher incidence of obesity in females might be due to hormonal influences and intensity of physical activities. In females, oestrogen causes increased deposition of fat in the subcutaneous tissues. This leads to particular pattern of fat distribution resulting in increased fat mass in them compared to males [11].

Basal metabolic rate (BMR) is the rate of energy expenditure by humans and other animals at rest, and is measured in kJ per hour per kg body mass. The results of the present study which shows significantly high values of BMR in obese, are in accordance with a study done on prediction of the basal metabolic rate in obese by Robert S Bernstein, John C Thornton, Mei Uih Yang, et al which showed significant correlation of basal metabolic rate with weight and fat mass in both sexes and also they reported that the adipose tissue has a high basal metabolic activity compared to other cells [12]. Another study done by Bray et al [13] also found a much greater effect of body fat on BMR than Fat Free Mass (FFM).

In contrast, studies by Ljunggren et al [14] and by Halliday et al [15] have concluded that FFM and not the body fat, is the sole predictor of BMR in obese individuals. A study done by James et al [16] found that body fat had no significant influence on BMR.

Age factor greatly influences basal metabolism. Studies done by Du Bois, on Basal Energy Requirement in June, 1916 shows that basal metabolic rate (BMR) varies greatly with age [17]. It is highest during growing period till 18- 20 years of age and till forty years shows little change and falls thereafter. This increased BMR in younger age group may be due to increased active protoplasmic tissue and greater cellular activity. As age advances this is replaced by atrophic protoplasmic tissue leading to decreased metabolism [5]. As this study group consists of subjects belonging to age group of 18-25 years, this may contribute for increased BMR values in both the groups. But, it is significantly higher in obese group because, body fat beyond its contribution to FFM also has a high basal metabolic activity compared to other cells. Studies have been done to assess the separate effects of fat cell size and number because it was possible that they would have separate influences on metabolic rate. Enlarged human fat cells in vitro have increased rates of lipolysis and basal glucose utilization. In addition, their increased surface area might require increased energy utilization through Na-K ATPase in order to maintain internal electrolyte balance. Regardless of cell size, the ratio of cell membrane surface area to cytoplasmic volume is higher in adipocytes than other cells, because most of the cell volume is occupied by the lipid. Similarly increase in fat cell number increases the number of actively respiring cells which utilises energy in the form of ATPs which are obtained as bi products of cellular metabolism and contributes for thermogenesis [6, 12, 13]. Hence there will be increased basal metabolic rate in obesity with increased adiposity which may be either in the form of increased adipocyte size or increased number or both. Adipocyte has generally been regarded as a storage depot for fat but it is also an endocrine cell that releases numerous molecules in a regulated fashion. These include the energy balance-regulating hormone leptin [18]. As obese individuals have increased adipose depots, there will be excessive leptin production and release which increases basal metabolic rate. This is in accordance to a study done by Ruffin M and Nicolaidis S, who inferred that the adipocytokine leptin is involved in the regulation of BMR by conducting several experiments on rats with leptin infusions which led to increase in their BMR [19].

Conclusion

The present study shows significant higher values of BMR in obese females than non obese group. This is attributed by increased respiring tissue in obese individuals compared to lean ones. Maintaining optimum energy balance in these obese individuals in the form of increased physical activity which burns extra calories and increases energy expenditure and dietary modification by increased intake of low calorie, highly nutritious food helps in reducing storage of extra calories as fat. All these measures help in preventing development and progression of obesity associated complications. Thus, assessment of BMR in obese individuals plays a key role in understanding their energy dynamics and to bring modifications in their lifestyles and lead them towards healthy life.

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Original Research Paper

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The Involvement of ANS in Neck Shoulder Pain and Low Back Pain

Aaditya Katyal[1], Rajesh K. Sharma[2], Abhay Elhence[3]

Abstract

A large number of people suffer from musculoskeletal disorders (MSDs), including regional pain in the neck-shoulder region and lower back, or more widespread pain, e.g., fibromyalgia [1]. Chronic MSDs are characterized by a localized, regional or widespread sensation of pain affecting muscles, joints, tendons or ligaments, accompanied by symptoms such as fatigue, tenderness at palpation and muscle stiffness. An autonomic imbalance may also reflect altered regulation of the entire stress response system and may have detrimental consequences in terms of pathological conditions as mentioned above [6].

In particular, this study paid attention to the involvement of the ANS in the initiation and maintenance of chronic muscle pain.

We had incorporated patients to study the Autonomic function imbalance in the Neck Shoulder Pain and Low Back Pain patients. We intended to include 15 patients in both the test groups and 15 normal subjects (Age and Sex matched) for comparative analysis. A detailed clinical history was taken from all the patients and subjects to exclude the presence of diabetes mellitus, hypertension, alcohol dependence and other diseases that can affect autonomic functions. Both the limbs of ANS were studied using standard battery of autonomic function tests:

• Deep Breathing Test • Lying to Standing Test • Valsalva Maneuver • Hand Grip Test • Cold Pressor Test

The results were recorded and carefully evaluated. It was found that Sympathetic over activity in low back pain patients can be the cause of this autonomic imbalance or it may be a predictor of prognostic evaluation in such patients.

We conclude that sympathetic overactivity plays a major role in the patients suffering from low back pain whereas the role of parasympathetic reactivity from the presence study is not clear.

The best way to arrive at investigative & prognostic evaluation of patients suffering from low back pain would be CPT and HGT as a standard marker of sympathetic reactivity.

Keywords: Musculoskeletal Disorders; Fibromyalgia; Palpation; Tendons; Ligaments.

Introduction

A large number of people suffer from musculoskeletal disorders (MSDs), including regional pain in the neck-shoulder region and lower back, or more widespread pain, e.g., fibromyalgia [1]. Chronic MSDs are characterized by a localized, regional or widespread sensation of pain affecting muscles, joints, tendons or ligaments, accompanied by symptoms such as fatigue, tenderness at palpation and muscle stiffness. Diagnoses are often based on self-reported symptoms, as adequate objective markers are difficult to obtain at an individual level [2].

The etiology of MSDs is multifactorial, involving the interactions of physiological, psychological, behavioral and external mechanical factors. Physical (e.g., mechanical) or psychological stressors can

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facilitate chronic pain by their effects on physiological stress systems [3].

At the central level there is a strong connection between autonomic activation and nociception [4]. The ANS does not function independently, but rather constitutes an important part of a multi-stress system involving sophisticated co-activation and interaction between different homeostatic processes, and the immune and endocrine systems, including the Hypothalamic-Pituitary-Adrenal Axis and the Sympatho-Adrenomedullary axis [5]. In this sense, an autonomic imbalance may also reflect altered regulation of the entire stress response system & may have detrimental consequences in terms of pathological conditions [6]. *In particular, this study paid attention to the involvement of the ANS in the initiation and maintenance of chronic muscle pain.*

A predominance of sympathetic activity, either due reduced parasympathetic tone or excessive sympathetic activation, reduces the dynamic flexibility of the ANS and results in poor adaptation to altered internal or external demands. Taken together, it is possible that chronic muscle pain could be maintained and intensified due to pain-induced alterations in ANS regulation, particularly through the sympathetic branch of the ANS. The other objective of this study was to explore this realm.

Furthering our understanding of core mechanisms could improve prevention, diagnostics and treatment of chronic MSDs. Both the limbs of the autonomic nervous system are important in maintaining and regulating visceral functions directly and other body systems indirectly.

We had hypothesized that since nociceptive pathways are also affected by autonomic control, the study was planned to evaluate the cardiovascular autonomic responses in patients suffering from low back pain and neck shoulder pain.

Objectives

1. Involvement of the ANS in the initiation and maintenance of chronic muscle pain in MSDs like Neck-Shoulder Pain & Low Back Pain.
2. To verify the dominant role of Sympathetic branch of ANS in sustenance and intensification of pain.

Methodology

We had incorporated patients to study the Autonomic function imbalance in the Neck Shoulder Pain and Low Back Pain patients.

We intended to include 15 patients in both the test groups and 15 normal subjects (Age and Sex matched) for comparative analysis.

Procedure of Recording Parameters

Clinical history

A detailed clinical history will be taken from all the patients and subjects to exclude the presence of diabetes mellitus, hypertension, alcohol dependence and other diseases that can affect autonomic functions. The vital signs of subjects, such as pulse and blood pressure will be checked. Subjects will be asked about the presence of any autonomic symptoms, like excessive sweating, loose motions, constipation, impotence, syncopal attacks and palpitation.

Prior instructions will be given before recording the physiological parameters. They will be:

- No use of medicine(s) 24 hrs before recording.
- No consumption of tea, coffee or any other caffeinated beverage at least two hours before the testing.

Pre-testing procedure

The subjects will be given proper instructions about the tests and recording procedure before starting the actual tests. The subjects will be made comfortable. Temperature of the laboratory will be comfortable (22 ± 1^{o} C) and the laboratory will be kept free of noise from any kind as far as possible. EKG electrodes will be applied for standard limb leads. The jack pins of electrodes will be connected to the connection board that will be connecting to amplifier.

Table 1: Amplifier setting for autonomic function tests

Signal	Sensitivity	½ Amplitude high frequency cut	Time constant	50 Hz filter
EKG	0.5mV/cm	35 Hz	0.1 sec	off

Lying to standing test (LST)

The subjects will be asked to stand up from supine position in 2 to 3 seconds. They will stand steady for 2 minutes. The EKG and respiration will be recorded continuously. Blood pressure measurement will be done serially at 0.5^{th}, 1^{st} and 2^{nd} minutes of standing. Then the patients will be asked to sit down comfortable. Rest of the tests will be performed in sitting position.

Deep breathing test (DBT)

The subjects will be given continuous signal in the form of raising the hand continuously up and then bringing the hand continuously down corresponding to inhalation and exhalation to their full capacity without breaking the breath during exhalation or inhalation. The frequency of the cycle will be 6 breaths per minutes for 1 minute. Phases of respiration will be marked manually on the chart paper. The average of 6 shortest inspiratory and 6 longest expiratory R-R intervals from EKG will be taken into account for the calculation of E:I ratio and heart rate difference between inspiration and expiration. The E:I ratio will be calculated by dividing the average of maximum expiratory R-R intervals by the average of minimum inspiratory R-R intervals.

Valsalva maneuver (VM)

In this test the subjects will be asked to raise the intra-thoracic pressure to 40mm of Hg through a mouthpiece connected to a mercury monometer and maintain at this level for 15 seconds. The subjects will be instructed prior to testing not to take deep breaths before and after VM. After 15 seconds as the mouthpiece will be removed the subjects will be instructed to sit quietly. The time event will be marked on the chart paper by a time marker. Artifacts arising from the movements of the limbs in EKG will be avoided by instructing the subjects to not to move their limbs. VR and latencies will be calculated from R-R interval changes in EKG.

Handgrip test (HGT)

Just before the test, baseline BP will be recorded in sitting posture. Then the subjects will be instructed to press the dynamometer with their dominant hands with maximum possible force. This gave the value of maximum voluntary contraction (MVC). The 30% of the MVC will be calculated and the subjects will be instructed to press the dynamometer continuously at 30% of their MVC for 4 minutes by their dominant hand. During the isometric contraction, BP will be recorded at 1st, 2nd, 4th and 6th minutes.

The EKG will be recorded continuously on Polyrite.

Cold presser test (CPT)

Prior to the test, the baseline blood pressure will be recorded. The subjects will be asked to immerse their hand up to the wrist in 10^{o}C cold water for 1 minute (Low, 1984). BP will be measured at 1st and 2.5th minute of hand immersion. The EKG will be continuously recorded on the Polyrite.

Statistical Analysis

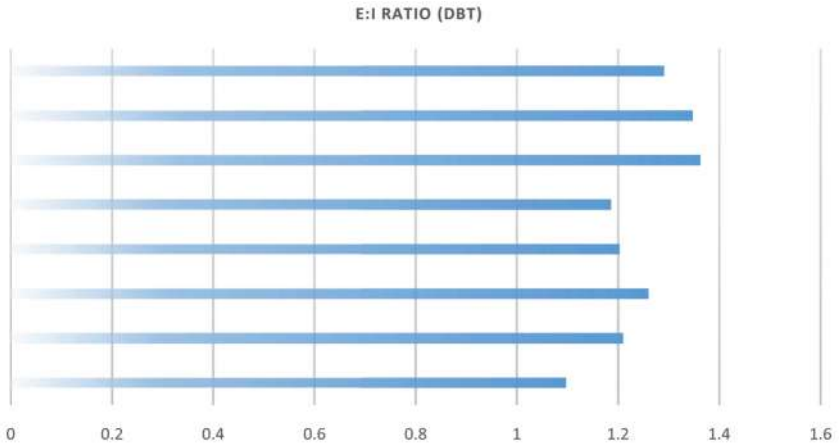
The data was supposed to be statistically analyzed by using unpaired t-Test between the two test groups and Anova among all the three groups. But because of a very few number of neck-shoulder pain patients, the results would have been skewed and statistically non-relevant. Since, it was an observational study; we feel that whatever result we got; though not statistically analyzed because of the paucity of data in one particular group, we could get a trend favoring our hypothesis.

Results

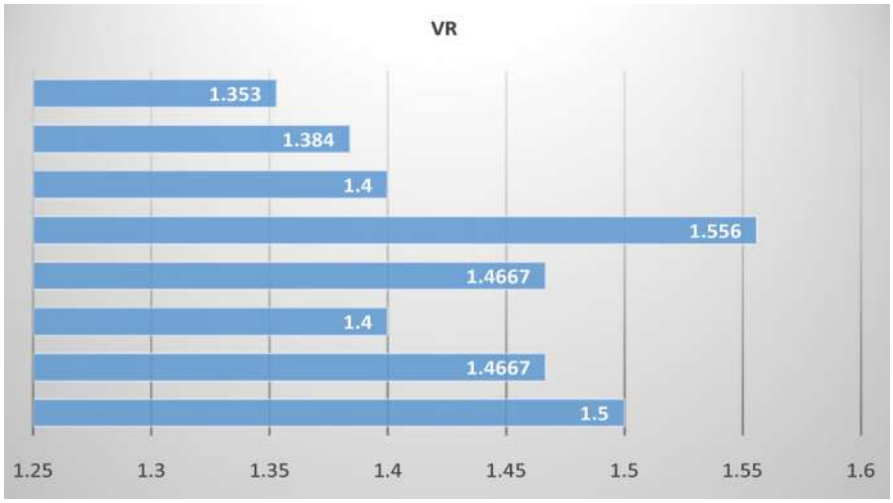
Sr. No.	Age	Sex	PSNS				SNS	
			DBT		VM	LST	LST	HGT	CPT
			E:I Ratio	ð HR	VR	30:15 Ratio	ð SBP	Rise in DBP	Rise in DBP
1	52	F	1.097	22	1.5	1.058	-6	12	2
2	36	F	1.21	16	1.4667	1.0625	-8	16	6
3	43	F	1.26	19	1.4	1.461	4	18	6
4	52	F	1.203	15	1.4667	1.105	-6	42	-14
5	36	F	1.186	3	1.556	1.02	-4	18	-2
6	29	M	1.363	7	1.4	1.217	14	8	-2
7	37	F	1.348	19	1.384	1.0625	4	14	-4
8	28	M	1.291	5	1.353	1.277	-2	38	40

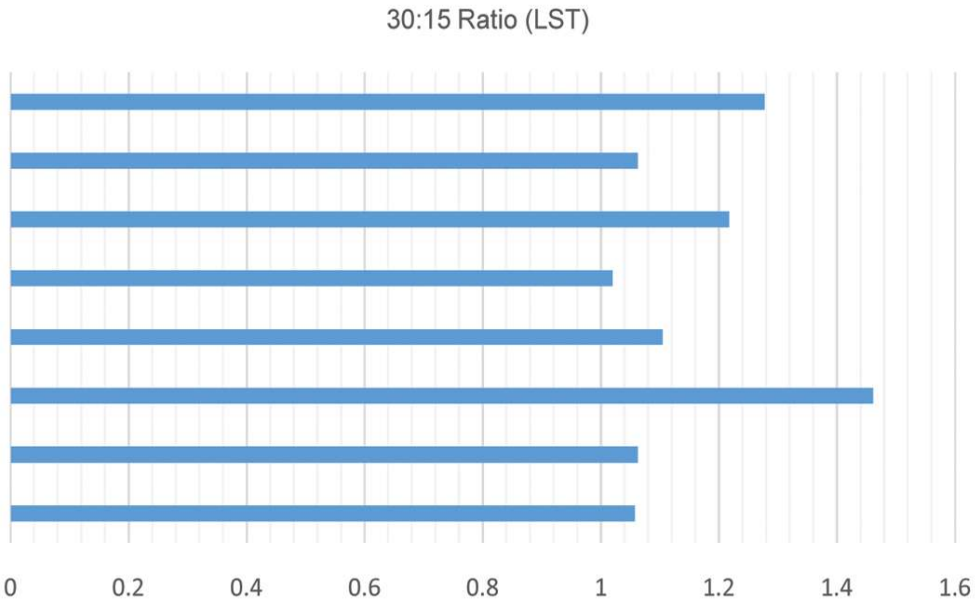
Both the limbs of ANS were studied using standard battery of autonomic function tests. The results are tabulated & graphically represented as follows.

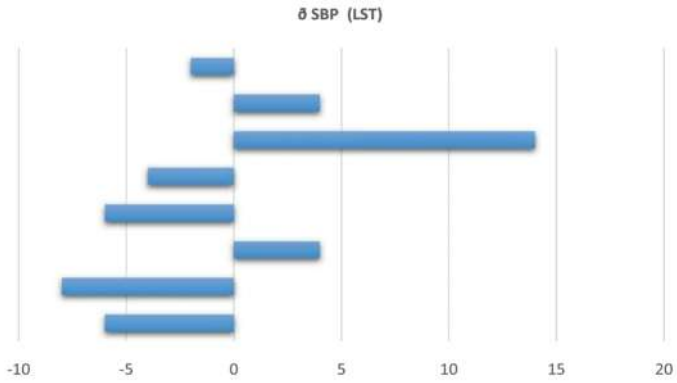
Graph 1: Autonomic Reactivity as measured by HR & BP changes in low back pain patients.



Graph 2: Autonomic Reactivity as measured by HR & BP changes in low back pain patients







Graph 3: Autonomic Reactivity as measured by HR & BP changes in low back pain patients

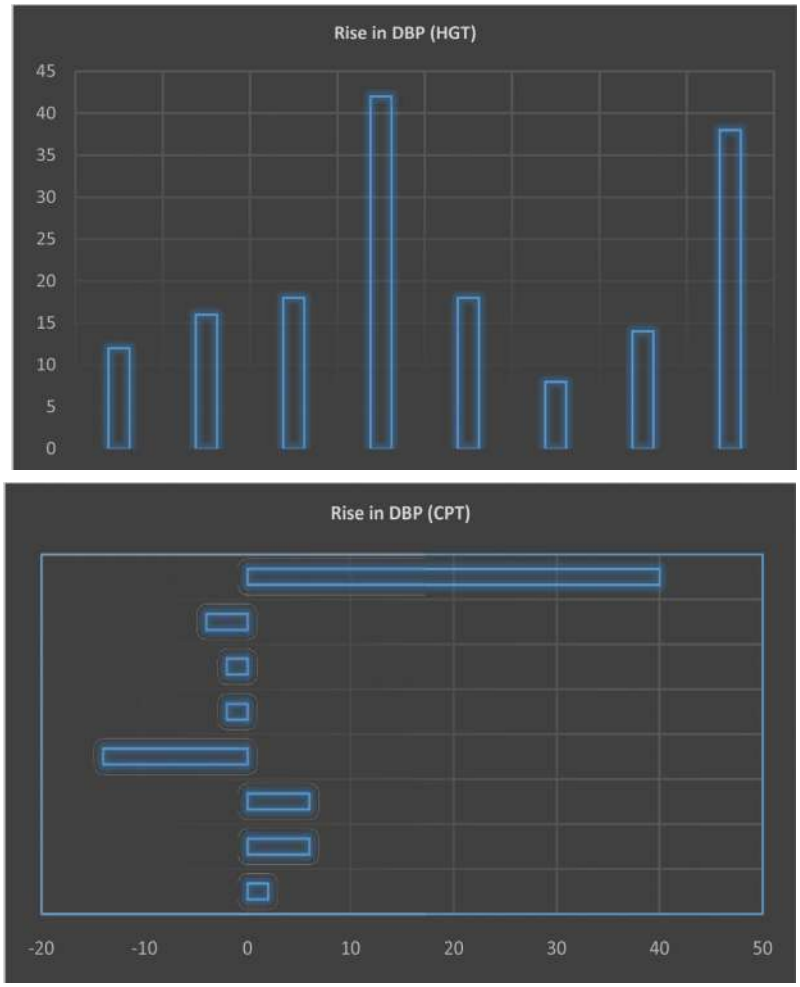
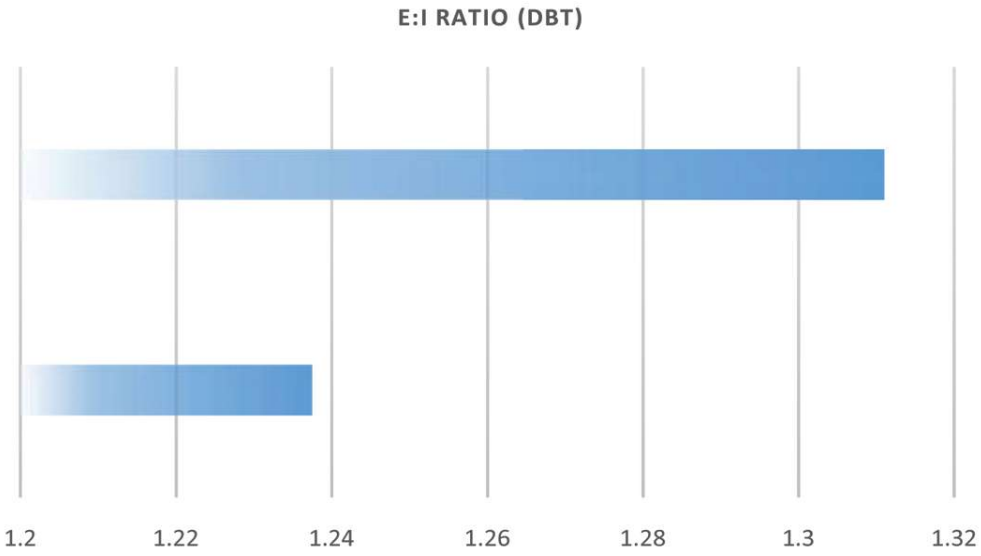


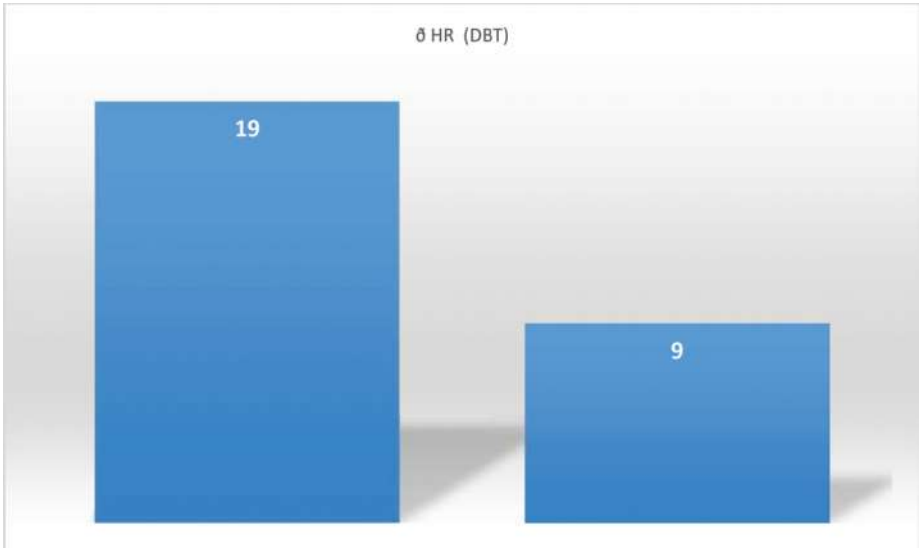
Table 2: Autonomic Reactivity as measured by HR & BP changes in low back pain patients.

Sr. No.	Age	Sex	PSNS				SNS		
			DBP		VM	LST	LST	HGT	CPT
			E:I Ratio	ð HR	VR	30:15 Ratio	ð SBP	Rise in DBP	Rise in DBP
1	38	F	1.2375	19	1.333	1	-2	8	2
2	50	F	1.311	9	1.375	1.285	-18	20	0

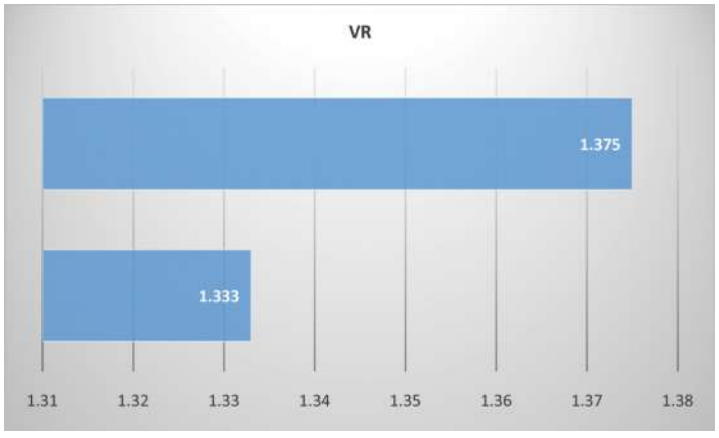
Autonomic Reactivity as measured by HR & BP changes in neck shoulder pain patients



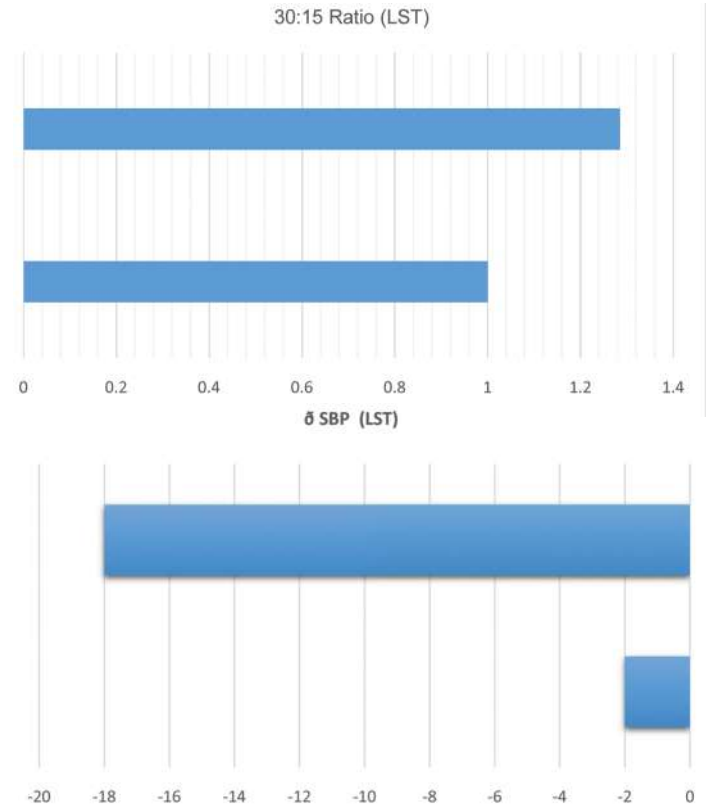
Autonomic Reactivity as measured by HR & BP changes in neck shoulder pain patients

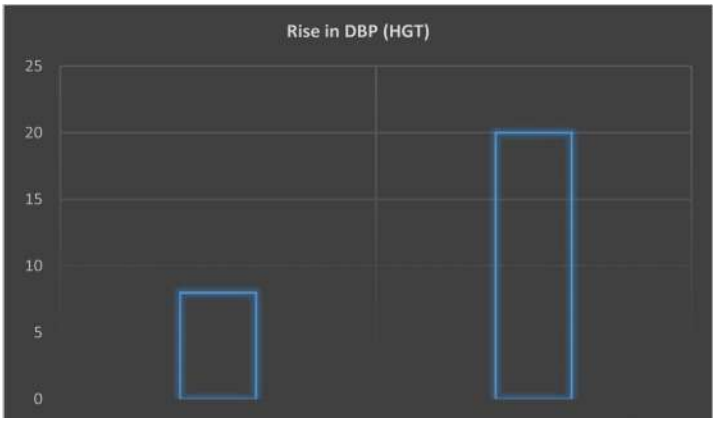


Autonomic Reactivity as measured by HR & BP changes in neck shoulder pain patients

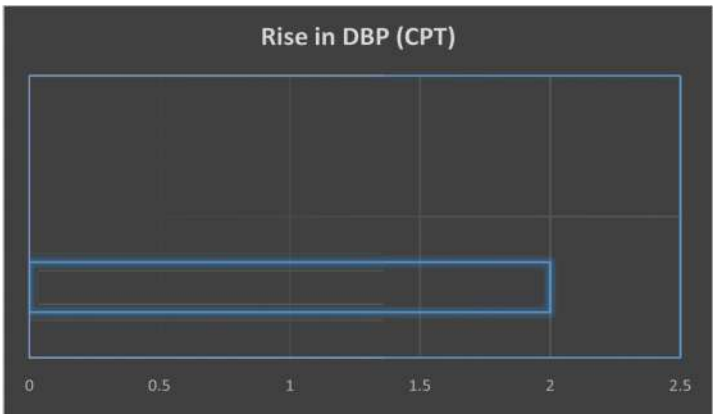


Autonomic Reactivity as measured by HR & BP changes in neck shoulder pain patients





Autonomic Reactivity as measured by HR & BP changes in neck shoulder pain patients



Discussion

To start with the study we had two primary objectives: One was to evaluate the autonomic imbalance, if any; in MSDs. The second was to look for any difference in autonomic control in low back pain & neck shoulder pain patients.

The prevalence of low back pain patients especially in older age is far more compared to neck shoulder pain patients. We couldn't analyze many neck shoulder pain patients because the study was designed to have a comparison between the two groups which are age & sex matched. The general trend of our study indicates that the parasympathetic reactivity was within normal range as compared with the normative data. But there was a significant trend of reduction in the rise in DBP in CPT & a trend of decreased SBP in LST. This trend indicates that Sympathetic overactivity in low back pain patients can be the cause of this autonomic imbalance or it may be a predictor of prognostic evaluation in such patients. We realize that the discrepancy between parasympathetic and sympathetic control of these patients were due to lack of normative to compare. Autonomic latency is a key factor in baroreflex mechanism as well as autonomic responses. We infer that such studies should be done on a population basis to concur on a conclusive decision.

Conclusion

We conclude that sympathetic overactivity plays a major role in the patients suffering from low back pain whereas the role of parasympathetic reactivity from the presence study is not clear. The best way to arrive at investigative & prognostic evaluation of patients suffering from low back pain would be CPT & HGT as a standard marker of sympathetic reactivity.

We intended to find out the correlation between the back pain patients and the autonomic imbalance which can manifest in terms of autonomic neuropathy, especially cardiovascular autonomic disturbance.

With a limited no. of patients at our hand, we can predict that autonomic evaluation of MSDs can be a useful tool to assess, evaluate & prognosticate them.

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Original Research Paper

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Effect of Pranava Yoga on Cardiac Output and Systemic Peripheral Resistance

Sharad Jain

Abstract

Pranava yoga is one of the most popular pranayama yogic exercises. The present study was done to find out direct effect of Pranava yoga on cardiac output and peripheral resistance by using Impedance Cardiovasograph (Nivomon, L&T Medical's). One hundred asymptomatic healthy male subjects, aged 17-23 years, participated voluntarily in the present study. Cardiac output, systemic peripheral resistance and other cardiovascular parameters were measured before and after Pranava yoga of 15 minutes. Statistically significant decrement was observed in all cardiovascular parameters after Pranava yoga but decrement was more pronounced in systolic blood pressure (SBP), heart rate (HR) , cardiac output (CO), stroke volume (SV), cardiac index (CI), stroke volume Index (SI) in comparison to decrement in diastolic blood pressure (DBP), Systemic Peripheral Resistance (SPR) and Systemic Vascular Resistance Index (SVRI).

Keywords: Pranava Yoga; Impedance Cardiovasograph; Cardiac Output; Systemic Peripheral Resistance .

Introduction

Human life is full of stress and tension. In the present scenario people have to face challenges at every step of life, which create a stressful life to a person. Failure to cope with stress leads to depression, anxiety and related disorders. Some studies have shown that people having spiritual life style are able to face the day to day stress more efficiently. Yoga and meditation are practiced from Vedic period in ancient India. Various methods of yoga and meditation are described in Upnishads and Yoga Sutras of Patanjali. These also consist of chanting of various mantras and performing Hawan etc. These meditation and yoga practices were performed daily as part of religious act in ancient India, but not common in present days in majority of population [1]. However now again practice of yoga and meditation is becoming popular throughout the world including India for improving the quality of life [2,3]. Many researches have proven multiple beneficial effects of yoga and meditation. Awareness and control over breathing is the key feature of yogic exercises. Yoga is claimed to be very effective in relaxing the mind and body. It has been found to reduce life stress [4,5]. It may alter cardio respiratory and autonomic parameters. Several investigations have been conducted to determine the long-term effects of pranayama and meditation techniques on the cardiovascular and autonomic nervous systems in healthy and clinical populations like hypothyroidism and rheumatoid arthritis[6-8]. Many of these studies have suggested that yoga leads to a shift in sympathovagal balance towards parasympathetic dominance [9,10]. Yoga has been advocated as adjunct therapy in hypertension and to reduce the dose of antihypertensive drug to control blood pressure in hypertensive patients[11,12]. These beneficial effects might be brought by altering the autonomic status of the body. Pranava yoga is a very simple exercise among various yogic exercises. According to Hindu philosophy, Aum is sound of power and whole universe is formed by this power of Aum. Pranava yoga (Aum yoga) is simple chanting of word Aum and focus the mind on the sound and vibrations produced during Aum Chanting.

Studies have shown that Pranava pranayama produces an immediate decrease in heart rate and systolic blood pressure in hypertensive patients and

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advocated for management of hypertensive patients in addition to the regular medical management and suggested the need of further studies to enable a deeper understanding of the mechanisms involved and its usefulness in the long term management of hypertension [13].

Therefore, the present study aims to study the effect of Pranava yoga on cardiac output and systemic peripheral resistance. Since any maneuver which may decrease cardiac output or peripheral resistance or both may be helpful for the patients suffering from hypertension and other cardiovascular diseases.

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 the Cardiac Output (CO), Stroke Volume (SV), Systemic Vascular Resistance (SVR), Cardiac Index (CI), Stroke volume Index (SI), Systemic Vascular Resistance Index (SVRI), Pulse Rate (PR) and various other cardiovascular parameters [14].

Material and Methods

The present study was conducted in the department of physiology, Saraswathi Institute of Medical Sciences, Hapur. One hundred asymptomatic healthy male subjects, aged 17-23 years, participated voluntarily in the present study, undertaken, to assess the effect of Pranava yoga on cardiac output and peripheral resistance and other cardiovascular parameters. 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 and little light in the room. Subjects reported to laboratory 2 hours after light lunch. They were explained in detail about the experimental procedure. Informed consent was taken from all subjects. Subjects were asked to lie in supine position. The color coded 8 leads of NICO patient cable 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)

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded by using mercury sphygmomanometer. Cardiac output , peripheral resistance and other parameters were recorded using Impedance Cardiovasograph (Nivomon). Subjects were asked to sit in comfortable position with back support.

Then they practiced Pranava yoga for 15 minutes as per instructions mentioned below.

1. Sit up with back rest in comfortable position taking care of the cables remain attached.
2. Close the eyes and relax all parts of body completely.
3. Keep breathing slowly and deeply without any jerky movements.
4. After slow deep inspiration, start chanting Aum during slow expiration phase.
5. At the end of expiration, repeat the procedure of slow deep inspiration followed by Aum chanting in expiration phase.
6. Focus the mind on the vibrations produced by Aum chanting.
7. After 15 minutes of Aum chanting subjects were asked lie down slowly in supine position.

After 15 minutes Pranava yoga, again all parameters were recorded.

All data were collected and statistical analysis was done by paired t-test using the window SPSS Statistics 20.0 version.

Result

Table 2 shows comparison of parameters before and after Pranava yoga. There was significant decrease in all cardiovascular parameters after performing 15 minutes Pranava yoga.

Table 1: Baseline characteristics of all subjects

S.N.		
1	Age (in years)	21.1±1.1
2	Height (cms)	172.5±2.3
3	Weight (Kg)	64.4±4.4
4	BSA (m^2)	1.75±0.06

Table 2: Comparison of cardiac output and peripheral resistance and other cardiovascular parameters before and after Pranava yoga

S.N.		Before Pranava yoga	After Pranava yoga
1	Systolic blood pressure (SBP) (mm Hg)	116.4±1.5	104.4±1.1**
2	Diastolic blood pressure (DBP) (mm Hg)	74.12±1.6	65.32±1.4*
3	Heart rate (HR) (per minute)	73.08±0.9	66.2±0.4**
4	Cardiac Output (CO) (L/min)	5.16±0.12	4.74±0.16**
5	Stroke volume (SV) (ml/ beat)	72.26±0.6	70.22±0.4**
6	Systemic Peripheral Resistance (SPR) (dyne.sec/cm^5)	1358.1±7.3	1328.2±5.4*
7	Cardiac Index (CI) (L/min/m^2)	2.94±0.06	2.61±0.04**
8	Stroke volume Index (SI) (ml/ beat/m^2)	41.31±0.13	40.53±0.03**
9	Systemic Vascular Resistance Index (SVRI) ((dyne.sec/cm^5/m^2)	770.1±4.2	753.25±3.8*

*$p<0.05$ (significant), **$p<0.001$(highly significant)*

Decrease in Systolic blood pressure (SBP), heart rate (HR), Cardiac Output (CO), Stroke volume (SV), Cardiac Index (CI), Stroke volume Index (SI) were highly significant ($p<0.001$). while decrease in Diastolic blood pressure (DBP), Systemic Peripheral Resistance (SPR) and Systemic Vascular Resistance Index (SVRI) were less significant ($p<0.05$).

Discussion

It is a proven fact that regular yoga exercises improve the life and give sense of subjective well being in normal people as well as in patients suffering from diseases. It can be used as powerful tool to combat stress. Aum chanting is very easy exercise and can be done any time in sitting posture. Previous studies have shown a significant decrease in heart rate during Aum chanting, insignificant reduction in oxygen consumption and significant decrease in finger plethysmogram amplitude (i.e. increased peripheral vascular resistance) indicating that chanting "Aum" mentally causes increased alertness (reduced finger plethysmogram amplitude), along with simultaneous relaxation of body (reduced heart rate) [15]. In contrast to this, present study showed significant decrease both in heart rate and systemic vascular resistance; however decrease in heart rate was more pronounced. Aum chanting shifted the symapatho vagal balance towards vagal side and resulted in a decrease in sympathetic activity.

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. Cardiac output and peripheral resistance are the key determinant of blood pressure. Blood pressure and heart rate are important cardiovascular parameters. Both are controlled by autonomic nervous system mediated via baroreceptor reflex mechanism. Cardiac output is product of stroke volume and heart rate. Stroke volume decreases with decrease in venous return & decrease force of contraction of heart and vice-versa. Increase in parasympathetic activity decreases venous return by producing venodialtion in splanchnic circulation and other parts of body and also decrease force of contraction of heart leading to less pumping of blood in each cardiac cycle leading to decreased systolic blood pressure. Decreased sympathetic activity also produces vasodilatation of arterioles and decreases total peripheral resistance leading to decrease in diastolic blood pressure. Impulses of Buffer nerves from arterial baroreceptors reach the medulla and affect the heart rate via vagal discharge to the heart. The neurons from which the vagal fibers arise are in the dorsal motor nucleus of the vagus and the nucleus ambiguous[16]. So, decreased sympathetic activity is responsible for decreased cardiac output and heart rate and vice versa. Any maneuver which can decrease the sympathetic activity or increase parasymapethetic activity will decrease blood pressure, cardiac output, total peripheral resistance and heart rate.

Pranava yoga results in decrease in sympathetic activity and increase in parasympathetic activity. As a result of this decrease in sympathetic activity there is vasodilatation which causes decrease in peripheral resistance. It also decreases heart rate and myocardial contractility leading to decreased cardiac output. Decrease in cardiac output and peripheral resistance both result in decrease in systolic as well as diastolic blood pressure. So Pranava yoga can be a useful exercise for the patients suffering from hypertension

and other cardiac disease and other stress related problems.

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Original Research Paper

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Relationship between Big Five Personality Traits and Total Peripheral Lymphocyte Count (TPLC)

Sunita Nighute[1], Sadavarte Sahebrao[2]

Abstract

It is often argued that a blend of personality characteristics is known to affect the immune system. It has been identified that The Limbic Hypothalamic Pituitary Adrenal (LHPA) axis acts as the principal path of the communication between the immune system and the central nervous system. so this study was done to find out the relationship between Big Five personality traits and Total Peripheral Lymphocyte Count (TPLC) as a parameter of immunity in an undergraduate medical students (n=150). We calculated the correlation between personality variables and Total Peripheral Lymphocyte Count (TPLC). Further regression analyses were performed using personality variables as predictors and Total Peripheral Lymphocyte Count (TPLC) as criteria by using various statistical measures.

The results demonstrated that the Agreeableness and the Conscientiousness are the strongest predictors of lymphocyte count of all the personality traits. The results offer support for the hypothesis that stressed the essential links between personality and immune regulation.

Keywords: Big five; Personality Traits; Total Peripheral Lymphocyte Count (TPLC); Medical Students.

Introduction

Today it is well known that psychological stress has effects on the immune system, which can result in increased susceptibility to various infections, latent virus reactivation, and also influence immune-regulatory circuits [1]. A group of seven researchers, each of whom has uncovered a particular personality trait associated with psychological and physical well-being, since each trait has been directly or indirectly linked to a vigorous immune system, called as Immune Power traits [2]. The principal path of the communication between the immune system and the central nervous system has been linked to the HPA axis, which can also be influenced by psychological factors [3].

Our own psychological resources can be activated to prevent and to heal diseases affecting every organ and system of the body. Studies associated personality characteristics such as aggression and hostility as some of the variables that can affect the activity and number of lymphocyte populations [4, 5].

Now mind-body scientists are demonstrating the role of healthy traits in maintaining a healthy state of body. However, up until now less research has been conducted in regard to the possible connections of personality dimensions and the parameters of the immune system. The purpose of this study is, therefore, to examine the impact of personality type on the immune system with the help of Total Peripheral Lymphocyte Count (TPLC) of the students in the medical college using five-factor model of personality.

Aims and Objectives

- To investigate the relationship between Five Factor Model of Personality (FFM) and immunity with the help of Total Peripheral Lymphocyte Count (TPLC) in medical college Students.
- To find out which personality traits predict immune power personality in medical students.

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Segerstrom, Castaneda & Spencer (2003) [6] used the five factor model of personality to evaluate effects of optimism on immunity. The five factor model (FFM) is widely accepted as the most salient taxonomy of the basic personality structure [7]. The Big-5 are commonly used because they combine the best of Cattell's (1970) [8]. Authors' comprehensive list of personality traits with the best of Eysenck's (1991) [9] concise lists. They are:

Extroversion	—	Introversion
Neuroticism	—	Stability
Agreeableness	—	Antagonism
Conscientiousness	—	Un-directedness
Openness	—	Non-openness

Extroversion

Extraverts are usually sociable, talkative and communicative, and friendly. They are described as active, bold, assertive, exciting, and stimulating. Introverts on the other hand tend to be reserved, even-paced and independent.

Conscientiousness

They are predisposed to be organized, exacting, disciplined, diligent, dependable, methodical, and purposeful. They have an intrinsic motivation and a positive attitude. Students low in conscientiousness tends to be less careful, less focused and more likely to be distracted from tasks.

Agreeableness

Agreeableness or likeability refers to such traits as selflessness, good-natured, gentle, co-operative, flexible, tolerance, generous, sympathetic, courteous, striving for common understanding, and maintaining social affiliations.

Students low in agreeableness tends to be more aggressive and less cooperative.

Neuroticism

The individuals who score high on neuroticism tend to experience effects such as fear, sadness, embarrassment, disgust and anger. Those who score low in this area are usually calm, even-tempered and relaxed at work and in their personal lives.

Openness to experience

These individuals feel both the good and the bad deeply, rendering its directional influence on affective reactions like subjective well-being or performance satisfaction unclear.

The past ten years have seen a growing number of studies on the personality correlate of immune system. Segerstrom, Castaneda & Spencer (2003) [6] found that only Conscientiousness had an effect on the parameters of the immune system, measured by the DTH (delayed-type hypersensitivity) response. Although the associations between WBCs and broad personality traits tend to be mixed [10], narrower traits, such as impulsivity, may share stronger relations with health related variables than the broad domains [11].

A study by Miller, Cohen, Rabin, Skoner & Doyle (1999) [10] examined three dimensions of the five factor model (Extraversion, Agreeableness and Neuroticism) and found no differences in leukocyte subsets for any of the dimensions. The current study focuses on the relationship between the Big Five and Total Peripheral Lymphocyte Count (TPLC) as the measures of the immune system function.

Neutrophils and lymphocytes account for most WBCs. Neutrophils, as part of the innate immune system, respond to acute injuries, whereas lymphocytes, as part of the adaptive immune system, determine the specificity of immune response. Neutrophils have a short lifespan, ranging from hours up to a few days, whereas lymphocytes may remain in the blood stream for years. at least some of the Big Five could be connected with the Total Peripheral lymphocyte Count (TPLC) as the measures of the immune system, we could predict substantial correlations with immune system measures for Conscientiousness on the basis of the Segerstrom et al. (2003) [6] study, and for Neuroticism because of its known relatedness to distress and coping [12]. It can also be expected that there is the connections between Agreeableness and lymphocyte measures, due to the role of this personality factor in risk, stress, and burnout management [13] and in the activation of the autonomous nervous system. Consequently we can also assume that the Big Five could have an essential predictive function in relation to immune system parameters.

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, Inclusion criteria was 150 healthy medical students of first MBBS batch 2011-2012, Exclusion criteria- Students who are having any major illness were excluded from the study.

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).

Immunological Assessment

Peripheral human blood leucocytes were collected by the finger prick method by taking all aseptic precautions in the haematology lab of department of physiology. Then Total Leukocyte Count (TLC) using Turk's fluid was performed on the improved Neubauer's chamber. While the differential count from peripheral blood smear was done by using Leishmans stain and from total 100 different white blood cells percentage distribution of lymphocytes were counted. Both Total and Differential white cell count was done by using Electron microscope and by following all the standard criterias.

By using above readings Total Peripheral Lymphocyte Count (TPLC) was calculated by the formula: TPLC = TLC X percentage of lymphocytes in differential count. Then correlation between big five personality traits and Total Peripheral Lymphocyte Count (TPLC) was calculated by using various statistical methods.

Table 1: Statistic of personality scale and Total Peripheral Lymphocyte Count (TPLC)

Personality traits	Mean	SD	Total Peripheral Lymphocyte Count(TPLC)
Agree	3.43	0.50	.840
Cons	22.78	4.36	.737
Open	30.53	6.62	.252
Extra	24.34	6.5	.095
Neuro	30.60	5.37	.080

Table 2: Regression analysis of personality traits and Total Peripheral Lymphocyte Count (TPLC)

Personality traits	Total Peripheral Lymphocyte Count(TPLC)	Significance level
Agree	0.840	0.003*
Cons	0.737	0.004*
Open	- 0.252	0.179
Extra	0.095	0.633
Neuro	0.080	0.530

Result

Table 1 presents the results of statistics of personality scales and lymphocyte count. The table shows the mean of lymphocyte count and the means of their personality traits (agreeableness, conscientiousness, openness, extroversion, and neuroticism) According to the findings there is higher lymphocyte count with Agreeableness as well as Conscientiousness personality traits than other personality traits.

Table 2 shows Relationships between Personality Traits and lymphocyte count. Regression analysis was done to find out the influence of the students personality traits as predictor and Lymphocyte count as criteria. All five personality factors show substantial percentages of variance of Lymphocyte count.

The Agreeableness and Conscientiousness factor was the only significant predictors of Lymphocyte count.

Agreeableness (0.840) and Conscientiousness (0.737) are the strongest predictors among

personality variables. The Openness, (- 0.252), Extraversion (o.095), and Neuroticism (0.080) these personality traits are not significant statically.

It is thus conclude that the students high on Agreeableness and Conscientiousness traits had higher Total Peripheral Lymphocyte Count (TPLC) in our study.

Discussion

In this study we focused on the connection between personality factors and lymphocyte count. The results of the study suggest that the Big five factors can predict immune status of the body with the help of Total Peripheral Lymphocyte Count (TPLC).

results of this study shows that Agreeableness and Conscientiousness are the most important predictive factors of immunity, This is consistence with the study by Ana Ožura, et al, 2012 and Cohen et al,1997 [14, 15]. The possible link between Agreeableness and immune function may be elucidated by the fact that both are associated with the quality of social relationships. More agreeable persons enjoy more social support which in turn increases their immunological effectiveness. Individuals high on Agreeableness are altruistic, emphatic, cooperative, and moral and trusting [16], those who are low on this trait might experience more stress and less support from colleagues and superiors. In stress research, Agreeableness was found to be the main protective factor (when highly expressed) and main risk factor (when it is low) for burnout [17]. Furthermore it is possible that Agreeableness is connected with sympathetic nervous system activity. Miller (1999) [1] found that individuals with low Agreeableness tended to have higher blood pressure and epinephrine due to increased catecholamine production and which in turn suppresses the immune functions, since it is hypothesized that chronic secretion of catecholamine's down regulates glucocorticoid receptor expression [1].

While individuals with high level of Conscientiousness demonstrate greater self discipline, greater adherence to ethical and moral standards and strong sense of order. Further they strive for achievement and are cautious in their action. Conscientiousness is most likely to influence immunity through its relationship with better health practice and adherence to medication regimen. The association between Conscientiousness and immunity has been addressed in four studies [15]. Study addressing the connection of the conscientiousness trait with immune parameters found that conscientiousness has an effect on DTH (delayed-type hypersensitivity) response due to the association of this trait to optimism [6]. A number of other studies suggested that optimism is related to immune parameters [6, 15] depending on the type of the stressors involved.

In this study there are no correlations between Neuroticism and Lymphocyte counts. Although Miller [1] (1999) did find higher cortisol levels he did not obtain any differences in white blood counts in individuals with high Neuroticism. He concluded that individuals with high Neuroticism often report somatic complaints but have no physiological, objective basis for them. One could speculate that, although Neuroticism is connected with higher distress [12]. It is more an indicator of heightened sensibility than a predictor of objective differences in health status. Also there is no positive correlation between openness and Extraversion type of personality with the immunity in this study.

The results of regression analyses revealed a possible role of the Big five factors in predicting Total Peripheral Lymphocyte Count (TPLC).

Reports show that reduction of T lymphocyte is connected with an increased risk of inflammation [18] while the reduction in B lymphocyte counts affects humoral immunity and reduces the protective function of antibodies [19].

It is therefore interesting to note that certain personality factors can be associated with increased Lymphocyte count. The association between these traits and higher lymphocyte counts may reflect the tendency of these individuals to get in to situations that expose their immune systems to more pathogens. The relation between lymphocytes and immune function is complex; some types of lymphocytes promote good immune function, whereas others contribute to chronic inflammation [20]. In the present research, although we did not distinguish between different types of lymphocytes, these associations suggest that the total lymphocyte count may predominantly reflect the types of cells that contribute to pathological states.

There are several possible interpretations of how personality factors and Lymphocyte counts could be related. As already mentioned, the personality dimensions have influence on stress behaviour, and may consequently affect the functioning of the immune system (and vice versa) in its entire neuro-endocrine context. Solomon and Moos (1964) [21] wrote about the influence of stress and emotions on adrenal cortical steroid hormones 40 years ago.

However, it is questionable whether the general explanatory model linking psychological factors to neuroendocrine responses to stress by HPA (Hypothalamo-pitutory axis) axis activation could explain all the variance in blood cell count associated with personality factors [14].

In addition the possibility of the vice versa effect (the immune system factors influencing personality) should be considered similarly to the process seen in long-term sickness behaviour [22]. Both personality and immune system factors are genetically determined [23, 24, 7] a possible genetic relation between them seems possible [23].

Both personality dimensions and immune function are related to the activity of the most investigated neurotransmitter systems in the brain, especially noradrenergic, cholinergic, serotonergic, and dopaminergic systems [25].

Differences in affect and optimism are related both with personality dimensions and immunological regulation and can therefore contribute to the general relationship between personality and the immune system, Personal relationships, especially social support, are also linked with immune function [26].

On the whole, the results of our study offer some support for the hypothesis that stressed the role of personality factors in the activity of the immune system but further research is needed [27, 6, 14]. This research has implications for how we understand the connection between psychological processes and physical health. Our findings suggest that characteristic ways of thinking, feeling, and behaving share relations with immune response.

Our study has several limitations the most important of them is the small number of participants and also we have not considered the different types of lymphocytes.

And quantitative measures of the immune system parameters (such as Lymphocyte counts) might not be the best way of assessing the immune status. Qualitative measures (such as DTH response) are clinically more relevant [6].

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Circadian Oscillations of Oxidative Stress Affects Nociception Sensitivity and Opioid Induced Antinociception: A Hypothetical Preview

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Abstract

Circadian rhythms are physical, mental, and behavioral changes that follow 24 hr cycle. The production of antioxidants and protective enzymes, have been reported to be regulated or expressed in rhythmic fashions. Thus, oxidative stress seems to have a circadian rhythm connection. Oxidative stress has been implicated in aging and neurodegenerative diseases. Reactive oxygen species have role in pain associated with peripheral nerve injury. Increase in oxidative stress as in aging cause profound decline in opioid system at supraspinal level than at spinal level and also the nociceptive threshold. Oxidative stress decreases the nociceptive threshold and also opioid receptor function leading to decreased opioid induced antinociceptive effects. Thus it is hypothesised that the circadian pattern of nociception is due to oxidative stress level in the brain areas.

Keywords: Circadian Rhythm; Nociception; Oxidative Stress.

Introduction

Circadian rhythms are intimately involved in living systems at environmental, organismal, and cellular levels. Circadian rhythms, by definition, are physical, mental, and behavioral changes that follow a 24 hr cycle. This cycle is generally slightly longer than 24 h (an average of 24.2 h in sighted humans, and 24.5 h in blind humans), but can vary from person to person [1, 2]. It is believed that the development of circadian rhythms is a response to the earth's rotation, both around its axis and around the sun, which dictates daily light and temperature changes [3]. The production of antioxidants and protective enzymes, have been reported to be regulated or expressed in rhythmic fashions. Thus, oxidative stress seems to have a circadian rhythm connection.

Oxidative Stress and Circadian Pattern

Reactive Oxygen Species (ROS), such as superoxide radicals (O_2^-), peroxides (ROOR), and hydroxyl radicals (OH^-), are by products of normal cellular metabolism, mainly in the mitochondria. These molecules can benefit the cell by playing critical roles in cellular defense and other important cellular processes [4, 5]. One such role that many of the ROS have, especially O_2^- and hydrogen peroxide (H_2O_2), is in cellular signalling controlling a variety of biological processes. The ROS have many features that make them excellent signalling molecules, and have been shown to be involved in many pathways, from kinase activation to insulin action [6, 7].

However, a tight regulation of ROS is needed, as they may inflict serious detrimental effects if left unchecked. To place checks and balances on ROS, the cellular machinery has a sophisticated system to neutralize them before they become problematic. This includes producing protective enzymes (e.g., catalases [CATs], superoxide dismutase [SODs], and glutathione peroxidases [GPxs]) and physiologically generated small molecule antioxidants (e.g., Vitamins C and E, glutathione [GSH], and uric acid) [8, 9]. If these protective measures are not enough, due to exposure to environmental stresses (such as

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ultraviolet [UV] light, chemical pollutants, or heat) or due to other physiological reasons (poor or inappropriate diet, life style, etc.), the cell enters a state of oxidative stress. When this happens, it can be disastrous for the cells, causing DNA damage, lipid peroxidation, oxidation of amino acids, and ultimately death of the cell or disease in the host [5].

Reactive nitrogen species (RNS), including nitric oxide (NO) and peroxynitrite (ONOO-), also play an important role in oxidative stress. NO is produced in normal cells as an integral part of cellular signalling and is a mediator of cellular damage [10]. NO can diffuse easily through cells, which makes it especially useful as a biological messenger, and although it is only mildly reactive, its chemical properties make it a very potent intermediate messenger for production of more reactive RNS [11, 12], as well as other biological processes such as vasodilation [10]. Excess NO is normally inactivated by various cellular responses, including in the blood by a reaction with oxyhemoglobin to form nitrate [12]. However, since NO is poorly reactive, it has been suggested that much of the cellular damage that occurs during oxidative stress comes from the oxidation products of NO, especially peroxynitrite [13, 5]. This compound is formed from the reaction of O_2 - and NO, is a particularly active oxidative molecule, and has been implicated in several diseases and disorders, including hypertension, arthritis, and cancer [12, 5].

As mentioned above, these reactive species can be produced in the mitochondria as a by product of metabolism or by environmental stressors such as exposure to UV light or exposure to chemical pollutants. Since it is difficult to directly measure the very short-lived ROS, much research has focused on studying the presence of the antioxidants and other enzymes produced by the body that work against the oxidant radicals [8]. Interestingly, the cellular concentrations or activity levels of many of these antioxidants and protective mall molecules (such as SOD, GPx, melatonin, and several others discussed in the next section) have been found to have circadian rhythmicity [14, 15, 16]. This suggests an importance of both oxidative stress and the circadian rhythm in human diseases.

The cyclic pattern in the expression of circadian proteins and other rhythmic elements is dependent on a number of external cues or melatonin, including light exposure, feeding patterns, exercise, and temperature change [17, 18]. The strongest zeitgeber, light, initiates synchronization of rhythms when the retinorecipient cells within the suprachiasmatic nucleus (SCN) in the hypothalamus region of the brain receive the light impulses from the retina [17]. The SCN has been found to be the main regulator of circadian rhythms, which then sends signals to peripheral cells throughout the body, causing that rhythm to be passed on to the proper cells and tissues [19]. However, the SCN can be stimulated by zeitgebers other than light, especially by serotonin and melatonin, although these are thought to be internal feedback regulators as opposed to primary circadian rhythm initiators [20, 21, 22]. Melatonin has also been found to be one of the signalling molecules used by the body to synchronize certain peripheral cells. However, it is believed that many more molecules and hormones, including insulin and glucocorticoids, may be involved in this process [23, 24].

Rhythmicity of the Cellular Antioxidant System

Data from various studies suggest that the circadian regulation of protein expression plays a significant role in the cellular response to oxidative stress. Several studies have shown evidence of differences in DNA damage, lipid peroxidation, and protein oxidation at different times of the day, thus indicating circadian oscillations of oxidative stress responses [25, 26, 27, 28, 29]. These oscillations relate directly to the daily rhythm of antioxidant expression and protective enzyme activity levels. This rhythmicity in antioxidant levels may be exploited for a more precise targeting of the ROS, thereby offering better protection for the cells.

One of the biggest causes of oxidative damage in the cell is the O_2- molecule, many of the enzymes used to transform it into less-reactive species are rhythmically expressed. One key group of antioxidant enzymes that oscillate with circadian rhythmicity is SODs. These enzymes protect against oxidative damage by catalyzing the dismutation of O_2 – into O_2 and H_2O_2. In eukaryotes, there are two main types of SODs: copper/zinc (Cu/Zn), found cytoplasmically and extracellularly, and manganese (Mn), found mitochondrially (30). Mn SOD is thought to be especially important in maintaining and influencing the redox status of the cell, since it is the form present in the mitochondria where most ROS are produced. Also, it can directly influence the flux of certain ROS in some instances [31]. Daily rhythmicity in SOD activity was first reported by Diaz-Munoz et al. in 1985. They found that in the rat cerebral cortex, SOD activity peaks in the dark phase, coinciding with the peak level of malondialdehyde, which is a product of lipid peroxidation [32]. SOD

converts O_2 - into O_2 and H_2O_2, CAT is one enzyme that offers further protection by catalyzing the decomposition of H_2O_2 to H_2O and O_2 [33].

The rhythmicity of CAT activity was established over 25 years ago, and has been studied in many model organisms, as well as in humans [34, 33]. CAT activity oscillation has been shown to peak in the middle of the dark phase in the liver and kidneys of nocturnal mice [33]. However, in diurnal humans, the peak occurs in the beginning of the light phase as detected in plasma samples [35], illustrating the difference in circadian oscillation between nocturnal and diurnal species that would be expected due to their opposing patterns of sleep/wake cycles and the differences in their feeding patterns and light exposure.

Circadian rhythms and oxidative stress components oscillate in humans. Many antioxidants and enzymes that protect the cell from oxidative stress exhibit daily cycles in their expression or activity levels. Levels of by products of oxidative stress, such as those indicating DNA damage, protein damage, or lipid peroxidation, also oscillate with circadian rhythmicity. In addition, the peak time of expression for the circadian period and CRY proteins are listed for comparison. Those that peak in the morning include glutathione peroxidise (GPx) [36], glutathione reductase (GR) [36], catalase [36], superoxide dismutase (SOD) [36], uric acid [36], and peroxiredoxins (Prxs) [38]. Peaks in the evening have been observed in melatonin [39], plasma thiols [40], lipid peroxidation [40, 36], ascorbic acid [36], Period 1 and 2 [37], and the CRYs [37].

Another group of enzymes that regulate the effects of oxidative stress on the cell by removing peroxides is the Prxs. In Syrian hamsters, Prxs have been shown to oscillate with circadian rhythmicity in both the SCN region of the brain, as well as in the peripheral tissue of the liver, although the two rhythms are not in sync with each other [29]. As mentioned earlier, Prxs have also been studied in mature red blood cells (as they do not have a nucleus or most other organelles, including mitochondria), and O'Neill and Reddy found that there was still rhythmicity of the Prxs, in the absence of external cues [38].

Finally, circadian oscillation is highly involved in the regulation of the GSH system. GSH is a powerful antioxidant that neutralizes ROS in a process catalyzed by one of the 4 selenium-dependant GPx proteins, thereby converting GSH to the oxidized state of glutathione disulfide (GSSG). Glutathione reductase (GR) then catalyzes the reaction in which GSSG is reduced to GSH, allowing for additional neutralization of ROS (41). An additional component of the GSH system, the glutathione S-transferases (GSTs), is a group of enzymes separated into three major classes in mammals (cytosolic, mitochondrial, and microsomal), with at least 18 different isoforms expressed in humans. They play important roles in oxidative stress defense through the inactivation of cytotoxic and mutagenic byproducts of the process, including a,b-unsaturated aldehydes, quinones, epoxides, and hydroperoxides [42, 43).

Oxidative Stress: Nociception Sensitivity and Opiod Antinociception

Oxidative stress has been implicated in aging and neurodegenerative diseases [44, 45, 46, 47]. The aging process is associated with cellular damage caused by reactive oxygen species. There was a significant increase in protein oxidation in aged mice brain regions such as the cortex, hippocampus, striatum, and midbrain [48, 49, 50]. The cortex, striatum, hippocampus, and midbrain express opioid receptors [51, 52, 53, 54] and contribute to pain processing [55], therefore age-related oxidative damage in these regions increase pain sensitivity and decrease opioid analgesia. Recent studies suggested a mediatory role of reactive oxygen species in pain associated with peripheral nerve injury [56, 57].

As per Raut and Ratka [58] due to increase in oxidative stress as in aging the protein carbonyl content which is the marker for protein oxidation and TBARS content a marker for lipid peroxidation showed a gradual increase in cerebral cortex, hippocampus, striatum, and midbrain. Further there was a significant negative correlation between the antinociceptive effect of morphine (15 mg/kg at 60 minutes) and protein oxidation and lipid peroxidation in the cortex, striatum, midbrain and hippocampus also a significant negative correlation was observed between fentanyl-induced antinociception at 30 minutes after 50 mg/kg, and protein oxidation and lipid peroxidation in the cortex, striatum, midbrain and in the hippocampus. Oxidation of opioid receptor proteins can result in decreased opioid receptor function. One study reported significantly reduced binding density of mu opioid receptors (MOR) in the striatum. Increase in oxidative stress as in aging may cause profound decline in opioid system at supraspinal level than at spinal level and also the nociceptive threshold.

Conclusion and Hypothesis

As evident by these studies it is concluded that oxidative stress decreases the nociceptive threshold and also opioid receptor function leading to decreased opioid induced antinociceptive effects. Further, there is circadian oscillation of oxidative stress level. Thus it is hypothesised that the circadian pattern of nociception is due to oxidative stress level in the brain areas.

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Original Research Article

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Memory and Physiological Basis of Gender Variations

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Abstract

Memory is our ability to encode, store, retain and subsequently recall information and past experiences in the human brain. In order to process and store memory, first it has to be 'fed' with bits and pieces of information, most of which are sourced from auditory and visual bodily facilities. Memory is of two types: short term memory and long term memory. Hippocampus is responsible for immediate memory and for selecting the experiences which need to be transferred to the long term memory.

Keywords: Memory; Short term Memory; Long Term Memory; Hippocampus.

Introduction

Memory is our ability to encode, store, retain and subsequently recall information and past experiences in the human brain [1]. In order to process and store memory, first it has to be 'fed' with bits and pieces of information, most of which are sourced from auditory and visual bodily facilities [2]. Memory is of two types: short term memory and long term memory. Hippocampus is responsible for immediate memory and for selecting the experiences which need to be transferred to the long- term memory [3].

Short term and Long term Memory

Short term memory can be defined as an initial memory buffer that allows us to hold a few units of information for a short period of time while we determine their importance [4]. Short term memory is limited in capacity which could vary in time from seconds to minutes and readily available to conscious awareness. Because of the limited capacity of short term memory, it may work better to rapidly combine the related pieces of information into larger units based on similarities, differences or other patterns this combining process is called chunking and it is important to make short term memory work more effectively [5].

The fundamental difference between short term and long term memory is that, short term memory involves merely modulation of synaptic transmission by modification of pre-existing proteins. On the other hand, long term memory involves formation of new synaptic connection and synthesis of new protein. The link between short term memory and long term memory, at least in some cases, is cyclic AMP, which can induce only modification of existing proteins in a short time, but if elevation of cyclic AMP is persistent, it can phosphorylate transcriptional regulator proteins, and thereby influence synthesis of new proteins [3].

Short memory is an example of how the brain processes information differently when it is either received through visual stimuli or through auditory stimuli, which are both sensory processes [6]. What we hear and see enters our consciousness and are either accepted or disregarded. Thus accepted information is processed in the brain and stored as memory. Disregarded information is soon forgotten. There are also certain factors that affect auditory and visual memory such as hearing and visual

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impairments, emotional and physical conditions. To ensure that the brain is effective in processing information, it is important that it has the capability to hold specific pieces of data and information and view it as a whole. It must do this by arranging the information into a particular order. Once this order is established, the brain can then form associations between certain elements, piece them together and form a complete memory out of the auditory and visual memories it processes [2].

Short term memory is formed by both auditory and visual information but cortex can process more auditory than visual information at one time, especially when broken into manageable "chunks" thus in the short term memory, auditory information plays a more important role than visual information. Although we usually remember only about seven items in the short term, we can remember longer strings of information, such as telephone or social security numbers, by breaking them into chunks. The way that different sensations are recorded in the brain makes the most difference in how short term memories are formed. Visual data, sensed by the eyes, must be processed by the visual cortex before it is stored in memory and auditory data sensed by the ears and processed by the auditory cortex. Short term memories form largely in the prefrontal cerebral cortex, an area of the brain that continues to process information such as image and speech [7].

Gender and Memory

On the basis of various theories to determine which gender has better short term memory or better capacity to retain recent events; many conclusions are being contemplated. Intellectually, genders seem to be fairly equal; however, cognitive abilities differ greatly among males and females. Because thought processes occur in the brain, it is not surprising that males and females could differ how they process information. The men have better short term memory for certain instances such as logical manoeuvres like direction, electronic circuitry, mathematical reasoning and navigation etc [8].

Women, on average, excel on tests that measure recall of words and on tests that challenge the person to find words that begin with a specific letter or fulfil some other constraint. They also tend to be better than men at rapidly identifying matching items and performing certain precision manual tasks, such as placing pegs in designated holes on a board. Whereas women perform better than men in both verbal memory and verbal fluency we find a large difference in memory [9].

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Insulin Resistance in Type 2 Diabetes Mellitus & Scope of Triglyceride / High Density Lipoprotein-C Ratio as a Marker of Insulin Resistance in Patients with Metabolic Syndrome

Zingade

Insulin resistance is a hallmark of Metabolic Syndrome. It is important to identify insulin resistance at an early stage of Diabetes mellitus. There are many indicators used traditionally for measurement of insulin resistance like HOMA-IR (Homeostasis Model Assessment of Insulin Resistance); QUICKI (Quantitative Insulin Sensitivity Check Index) and ratio of Triglyceride / High density Lipoprotein–C. There is a positive correlation between HOMR-IR and TG/HDL-C ratio and negative correlation between QUICKI and TG/HDL-C ratio. In following discussion; the pathophysiology of metabolic syndrome and it's relation with Insulin Resistance is discussed.

Pathophysiology of Insulin Resistance in Metabolic Syndrome

Patients with type 2 DM share a pathophysiology that involves pancreatic β cells, liver and peripheral target tissues namely skeletal muscles, adipose tissue. Both β cell dysfunction and insulin insensitivity result in hyperglycemia. Glucose uptake in skeletal muscles requires insulin binding to cell receptors; which facilitates movement of glucose across cell membrane. The glucose is then utilized as a source of energy via glycolysis to produce lactate or mitochondrial oxidation or is stored as glycogen in the cell. Hormones and/or cytokines produced by adipose tissue also plays an important role in glucose and fat metabolism and are likely to contribute in pathophysiology of DM. Free Fatty acids play an essential role in Type 2 DM by inducing insulin resistance and facilitating excessive glucose production by liver.

Normal Physiology of Glucose Homeostasis

Maintenance of glucose levels depends on feedback between blood cells and pancreatic hormones i.e., glucose and insulin levels. Glucose is produced by liver by glycogenolysis and neoglucogenesis. Approximately 70-80% of the glucose produced by liver is utilized by brain (Insulin independent tissue) and other insulin sensitive tissues i.e. intestinal mucosa and RBCs, Retina, Skeletal muscles and Fat require insulin for utilization of glucose. Thus at the hepatic level, Hepatic glucose output (HGO) is regulated by:

(i) Insulin, glucagon, catecholamine, glucose level itself on short term basis (minutes-hours).

(ii) GH, T3, T4, Glucocorticoids on long term basis (hours to days).

Insulin exerts an inhibitory effect on HGO. Thus decrease in insulin levels causes slow rise in HGO. If the feedback loop is intact, as serum glucose level rises, insulin secretion also rises and glucagon level decreases. If insulin resistance develops, a new steady-state higher glucose level is reached.

At the Cellular level

Insulin binds with cell receptor which activates receptor's tyrosine kinase activity. This activation triggers a molecular phosphorylation signaling a cascade reaction. Insulin receptor substrate 1 & 2 activation causes activation of:

(i) PI 3 kinase (phosphatidyl inositol 3 kinase),

(ii) CAP / cbl / Tc 10 pathway (CAP- cCbl associated protein),

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(iii) ERK pathway (extracellular signal regulated kinase).

Ultimate result of the activation is translocation of the GLUT 4 protein from cytoplasm to cell membrane which facilitates influx of glucose into the cell for subsequent metabolism.

Natural History and Epidemiology of Insulin Resistance

Insulin resistance is present in approximately 90% of patients with type 2 diabetes. IR is often associated with metabolic abnormalities (known as metabolic syndrome, dysmetabolic syndrome, insulin resistance syndrome, Syndrome X, Reaven's syndrome). This syndrome is identified by hypertension, hyperglycemia, glucose intolerance, dyslipidemia, abdominal (central) obesity, endothelial dysfunction, impaired vascular reactivity, vascular inflammation and impaired fibrinolysis. Some or all of these components may be present in any given patient.

Even though associated with Metabolic Syndrome insulin resistance also occurs in a person who is not diabetic (up to 25% of non-diabetic patients. have lower degree of insulin sensitivity).

Although more common in older people, there is an increasing number of children and teenagers having insulin resistance. Generally Insulin resistance progresses and worsens over a period of years. With worsening of insulin resistance, insulin is less able to dispose of glucose from blood. In order to maintain euglycemia, there is compensatory hyperinsulinemia. However β cells gradually decrease functionally resulting in prediabetes and then type 2 Diabetes.

For clinicians, it is challenge to identify persons who are at risk as early as possible where interventions are likely to be more effective.

Insulin Resistance

Insulin resistance is defined as a condition of low insulin sensitivity in which the ability of insulin to lower circulating glucose is impaired. Along with genetic determinants other factors like obesity, aging, elevated FFA and hyperglycemia contribute to insulin resistant state. Biochemical defects that provoke insulin resistance involve impaired insulin signaling and reduction of glucose transport in insulin sensitive tissue.

Hepatic Insulin Resistance

We have seen that basal rate of Hepatic glucose output (HGO) depend on insulin levels which suppresses HGO levels. So the levels of HGO are increased in type 2 DM. The degree of HGO is positively and strongly related to degree of fasting hyperglycemia. This suggests that HGO has a major role in maintaining morning glucose levels. However, if given enough insulin, HGO can be completely suppressed. This is consistent with a decrease in hepatic insulin receptor number.

After meals glucose and insulin enter the liver via the portal circulation and change liver function from glucose producing organ in fasting state to that of storage. Glucose is stored in the form of glycogen but because liver is insensitive to glucose and insulin, there is delayed suppression of HGO suppression in type 2 DM. This is a major contributor to post-prandial hyperglycemia observed in prediabetic and insulin resistance cases.

Peripheral Insulin Resistance

In type 2 DM peripheral insulin resistance is also exhibited in target tissues like skeletal muscles. It is observed that glucose disposal rate is reduced by at least 50% in DM. There is decreased number of insulin receptors, as well as a post binding defect of insulin action.

In normal subjects after cellular uptake, glucose undergoes both oxidative and non-oxidative metabolism. At low insulin levels the pathway of glucose utilization is glucose oxidation (using glucose as a metabolic fuel). At higher insulin conc. glucose is disposed by glycogen synthesis (i.e. glucose is stored). Glycogen synthesis is a major pathway of non-oxidative glucose metabolism. In type 2 DM the efficiency of glucose disposal is reduced by both these processes but primarily by non-oxidative pathway.

Non-Insulin mediated Glucose Uptake

Apart from oxidative and non-oxidative pathways of glucose utilization by insulin independent glucose uptake non-insulin mediated glucose uptake (NIMGU) plays an important role in the rate of glucose disappearance. About 80% of tissue glucose uptake in fasting state occurs via insulin independent mechanisms primarily in CNS and to a much lesser degree in muscles and adipose tissues.

The efficiency of glucose disposal by NIMGU in both normal controls and type 2 DM has been observed to be equal; however the absolute basal rate of NIMGU is higher in type 2 DM which plays an essential role in pathogenesis of DM.

Adipose Tissue

Proteins secreted by adipocytes that act as signaling molecules. Previously adipose tissue was simply regarded as a simple site of fat deposition but now it is regarded as an endocrine gland concerned with release of adipokines or adipo-cytokines. These are potential insulin sensitizers.

(i) Adiponectin (one of the adipokines) acts on skeletal muscles, blood vessels, liver. It causes decreased IC fat and triglycerides. Its levels are decreased in type 2 DM. It positively and strongly correlates with HDL levels.

(ii) Leptin similarly improves glycemic control and is necessary to maintain normal metabolic state.

Obesity, Adipose tissue and Metabolic syndrome

Obesity is increasing in incidence due to imbalance of food intake and energy balance. As body weight increases insulin resistance increases. Dyslipidemia associated with Metabolic Syndrome is strongly related to the higher incidence of insulin resistance. These observations suggest that fat produces a chemical signal that acts on the muscle and liver to increase insulin resistance. Evidence for this includes blocking adipose tissue glucose transporters selectively (GLUT 2). It results in decreased glucose transport in muscles too. One possible signal in fat is FFA which is increased in many insulin resistant states Fat deposits act as endocrine tissues, secreting adipokines some of which decrease and some increase insulin resistance. Leptin and adipokines for example decrease insulin resistance whereas resistin increases insulin resistance.

Adipose tissue now is recognized as a 4^{th} musketeer along with muscles, liver and pancreas.

Causes of Insulin Resistance

(i) Abnormal insulin molecule.

(ii) An excessive amount of circulating antagonist.

(iii) Target tissue defect commonest in type 2 DM- Defects in insulin receptors.

(a) Mutations of receptor gene produce different syndromes associated with defective receptors like:

(i) *Rabson Mendenhall Syndrome*- including tooth, nail, and pineal growth abnormalities.

(ii) *Type A insulin resistance*- In young females with polycystic ovarian syndrome.

(iii) *Presence of antibodies against insulin*- Associated with acanthosis nigricans and other autoimmune phenomenon.

(b) Receptors are rarely abnormal but it is post receptor pathway that is more commonly defective:

(i) There is decreased capacity of GLUT 4 to translocate glucose.

(ii) Defective glycogen synthesis is likely to be present.

(iii) Defective signals- tyrosine kinase.

Intra-abdominal fat is more resistant to insulin than peripheral fat resulting in increased lipolysis and FFA levels, worsening the insulin resistance.

Measurement of Insulin Resistance

HOMA-IR (homeostasis Model Assessment of Insulin Resistance)

$$\text{HOMA-IR} = \frac{\text{Fasting serum insulin x Fasting serum glucose}}{405}$$

1. QUICKI (Quantitative Insulin Sensitivity Check Index)

$$\text{QUICKI} = \frac{1}{\text{Log (fasting serum insulin)} + \text{Log (fasting glucose)}}$$

2. TG/HDL Ratio- greater than 3 is incidence of insulin resistance.

To summarize, there is an increasing incidence of insulin resistance with increasing weight, obesity acting as a main culprit due to imbalance of food intake and energy output. Metabolic Syndrome is associated with dyslipidemia which plays an essential role in increasing insulin resistance especially in muscles and liver.

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New Teaching Methodologies

Harkirat Kaur

The system of medical education is changing over the years. The article discusses and compares the traditional method of teaching and newer trends to produce better doctors.

The lectures delivered to medical students have usually been to large classes of students on certain rigid topics which have not seen much change over the years. This is very passive form of teaching where the content of lecture is dependent on the extent of knowledge of Lecturer.

The main stay of medical teaching has been the lectures. This is very passive form of teaching. Students are actively participating by series of tutorial discussions and problem solving sessions.

Comprehensive knowledge of physiology is essential for grasping the principles of pathology and pharmacology adequately to avoid incorrect and inadequate practice of teaching. Medical schools are starting to put small groups and help them solve real problems they will face in treating patients. Trend of problem based learning in medical schools will have ripple effects throughout education. Teachers must relinquish lecturers and they must be proficient in answering questions, and helping students frame good questions, formulate problems, and make effective decisions [Aspy et al 1993].

The essence of problem cantered learning, Schmidt [1983] summarized PBL in terms of three essential principles:

1. Activation of prior learning via the problem.
2. Encoding specificity such that the resemblance of problem intended application domains facilitates.
3. Elaboration of knowledge via discussion and reflection to consolidate learning experience.

Problem based learning students seemed to have experienced a more flexible, meaningful and enjoyable education compared with their counterparts from the traditional program.

In this method, students would be divided into smaller groups and supervised by a tutor. Each group would be given a particular problem to solve, this would usually be in the form of a clinical problem, the form in which a patient would actually present to the clinician. The student would then be asked to study about problem and discuss among themselves. The role of the tutor would be that of a facilitator rather than imparting information.

More attention should be paid to comprehennd the subject than on his capacity to remember factual details.

Case based learning is a brief self contained exercise that is designated to introduce medical students and faculty to one of the methods which promote active self directed learning of pre clinical medical disciplines (Schwartz et al 1987).

Incorporating small groups into lectures can therefore be beneficial for promoting the discussion of ideas and concepts for examining issues and presenting alternatives for encouraging the application of new concepts and for fostering problem solving and communication skills. Group discussion can also give the teacher an additional way of assessing student attitude and beliefs.

Questioning the audience is probably one of the most frequently used interactive techniques.

Questions can stimulate interest arouse attention serve as an ice breaker and provide valuable feed back to the student and teacher alike (Knox 1986).

Format of medical education has changed over the years, whereas every opportunity should be taken to

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teach the student. More attention should be paid to his comprehension of the subject than on his capacity to remember factual details. The teacher's job would rather be to guide students to look for their own answers and solutions.

The role of the medical teacher has changed enormously from an active one sage in centre stage to a fountain of knowledge to a facilitator a mentor and guide.

As per new paradigm medical students manage their own learning that continues as lifelong self education process.

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Molecular Basis of Diabetic Peripheral Neuropathy: Role of Oxidative Stress

Nisha Rani Jamwal[1], Senthil P Kumar.[2]

Abstract

It is well known that hyperglycemia is the predominant manifestation in diabetes mellitus, and the most common complication of DM is diabetic peripheral neuropathy (DPN). The aim of this short communication was to provide an insightful overview of the molecular basis of DPN by assimilating evidence on the role of oxidative stress. Existing evidence indicated that oxidative stress might be a final common pathway in the development of diabetic neuropathy, and that antioxidants could prevent or reverse hyperglycemia-induced nerve dysfunction. The effects of antioxidants were hypothesized to be mediated by correction of nutritive blood flow, and endoneurial oxidative state; and antioxidant drugs such as alpha-lipoic acid and vitamin E were therapeutically indicated.

Keywords: Molecular Endocrinology; Molecular Neurology; Diabetic Neuropathy; Oxidative Stress.

It is well known that hyperglycemia is the predominant manifestation in diabetes mellitus, and the most common complication of DM is diabetic peripheral neuropathy (DPN). The aim of this short communication was to provide an insightful overview of the molecular basis of DPN by assimilating evidence on the role of oxidative stress.

Figueroa-Romero et al [1] explained that "excess glucose overloads the electron transport chain, leading to the production of super-oxides and subsequent mitochondrial and cytosolic oxidative stress. These changes include the production of advanced glycation end products, alterations in the sorbitol, hexosamine and protein kinase C pathways and activation of poly-ADP ribose polymerase".

Pop-Busui et al [2] reviewed the impact of hyperglycemia-induced oxidative stress in the development of diabetes-related neural dysfunction and explained, "Oxidative stress occurs when the balance between the production of reactive oxygen species (ROS) and the ability of cells or tissues to detoxify the free radicals produced during metabolic activity is tilted in the favor of the former. Although hyperglycemia plays a key role in inducing oxidative stress in the diabetic nerve, the contribution of other factors, such as endoneurial hypoxia, transition metal imbalances, and hyperlipidemia have been also suggested. The possible sources for the overproduction of ROS in diabetes are widespread and include enzymatic pathways, auto-oxidation of glucose, and mitochondrial superoxide production".

Greene et al [3] established that "glucose-derived oxidative stress played a central role, linking together with the aldose reductase and glycation pathways, vascular dysfunction, and impaired neurotrophic support.Vincent et al (2004) in their review explored the concept that diabetes overloaded glucose metabolic pathways, resulting in excess free radical production and oxidative stress. Proteins that were damaged by oxidative stress in turn bear decreased biological activity leading to loss of energy metabolism, cell signaling, transport, and, ultimately, to programmed cell death or apoptosis.

Negi et al [4] postulated that excessive production of reactive oxygen species was a key component in the development and progression of diabetic neuropathy. Therapeutic strategies utilizing a more targeted approach like focusing on Nrf2 (a transcription factor modulating oxidative stress)

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might provide an enthralling avenue to optimize neuroprotection in diabetes and diabetic neuropathy.

Nazýroðlu et al [5] reviewed the role of Ca (2+) signaling through cation channels and oxidative stress on diabetic neuropathic pain in sensory neurons, and found "the polyol pathway, advanced glycation end products, oxidative stress, protein kinase C activation, neurotrophism, and hypoxiaand deficits in insulin trigger alterations of sensory neurone phenotype".

Van Dam [6] emphasized that oxidative stress might be a final common pathway in the development of diabetic neuropathy, and that antioxidants could prevent or reverse hyperglycaemia-induced nerve dysfunction. The effects of antioxidants were hypothesized to be mediated by correction of nutritive blood flow, and endoneurial oxidative state; and antioxidant drugs such as alpha-lipoic acid and vitamin E were therapeutically indicated.

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