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## EDITORIAL

# Multidrug Resistant Tuberculosis and Importance of DOTS

Iqbal Ahmad Khan

Globally millions of people become sick each year with tuberculosis and it is one of the top 10 causes of death worldwide.<sup>1</sup> According to World Health Organization (WHO), the incidence of tuberculosis was 10 million in 2017 and reported TB mortality was 1.6 million globally.<sup>2</sup> Pakistan is one of the 30 high burden countries for tuberculosis worldwide with 61% of TB burden in Eastern Mediterranean Region of WHO. In Pakistan, 510,000 new cases of TB emerge each year and around 15000 cases develop drug resistant tuberculosis annually.<sup>1</sup>

In recent years, prevalence of drug-resistant TB has increased and became a continued public health crisis worldwide. There are three forms of drug resistant cases of tuberculosis: RR-TB, (Rifampicin Resistant-Tuberculosis), MDR-TB (Multidrug Resistant-Tuberculosis) and XDR-TB (Extensively Drug Resistant-Tuberculosis). According to WHO, 160684 cases of MDR/RR-TB (Multidrug Resistant/Rifampicin Resistant) were reported in 2017 all over the world. Pakistan has fourth highest prevalence of multidrug resistant TB (MDR-TB) globally.<sup>2</sup>

Drug resistant tuberculosis is a potentially devastating threat to TB control as it gives emergence to the strains that cannot be cured by standard first line anti-tuberculosis treatment.<sup>3</sup> MDR-TB cases are resistant to isoniazid and rifampicin. After developing resistant to first line therapy, patient is treated with prolonged and extensive therapy of second line injectable drugs. If patient develops resistance to second line injectable drugs then it is termed as extensively drug resistant-tuberculosis (XDR-TB). At this level disease becomes virtually untreatable.<sup>3</sup>

As treatment success remains low, at 55% globally, there is an urgent need to improve the quality of diagnosis, treatment and care for people with drug resistant tuberculosis. Key reasons for developing drug resistance among TB cases are: Delayed

diagnosis, unsupervised treatment, inappropriate drug regimens, lack of social support in the communities and lack of timely follow-ups. To close these gaps, much work is required for: drug susceptibility testing among diagnosed cases of TB, reducing under-diagnosis of TB cases, improving access and supervised continuous treatment, designing new diagnostics, new medicines and treatment regimens with higher efficacy and better safety.<sup>2</sup>

Progress is being made in diagnostic test technologies but still there is need to overcome questions related to validation and assessment of these technologies to make ideal diagnostic test available with high sensitivity and specificity levels.<sup>4</sup>

As previously reliance on passive case finding has not helped to stop TB pandemic. So active case finding and screening strategies instead of passive case finding of infectious cases are also needed to eradicate the disease. TB has been declared as global epidemic. The UN's first high-level meeting in 2018 on TB, was given the title as "United to End TB: An Urgent Global Response to a Global Epidemic".<sup>1</sup>

TB DOTS (Directly observed treatment, short course) has been recommended by WHO since 1994, as a strategy to treat TB cases and to get control over its prevalence. TB DOTS had five components for effective treatment and control of disease as following:

1. Sustained political and financial commitment by the government
2. TB diagnosis with sputum smear microscopy
3. Standardized short course treatment given under direct observation for 6-9 months
4. Uninterrupted and regular supply of anti TB drugs
5. Standardized recording and reporting of disease.<sup>4</sup>

In 1999, WHO launched "TB DOTS-Plus" as a strategy to control TB resistance by adding second line drug into already adopted DOTS components because DOTS did not account for TB resistance cases rather caused MDR-TB when treatment was repeated among untreated cases for prolonged duration.

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DOTS-Plus ended in 2006 due to resource constraints and subsequently WHO decided to expand TB DOTS again, by redefining the TB DOTS with focus on TB diagnosis, treatment and care of patients. The global plan to stop TB by 2015 included TB control targets that were covered under the targets of Millennium development goals (MDGs).<sup>1</sup>

After 2015, another global plan to end TB by 2020 was “WHO End TB strategy” which emphasized on a need of paradigm shift for radical change in TB surveillance and to set targets to be met in coming years. The focus of End TB strategy is to improve tools for case finding among high risk population, treatment of new cases and detection of drug resistance among TB cases. It is also to be understood that only improving diagnostic technologies will not reduce disease transmission unless early detection of infection and treatment of cases will not be carried out.<sup>1</sup>

DOTS are still considered effective for treatment of new cases of TB and prevention of RR-TB/MDR-TB. Failure to adapt DOTS in its true spirit is the leading cause of increased drug resistance cases of tuberculosis globally. The most important part of TB

DOTS is the role of treatment supporter. Treatment supporter ensures that patient has taken right drugs in appropriate doses and enters its record in patient's treatment card. In stop TB strategy, patient supervision and support to complete treatment course without skipping any dose is the cornerstone of DOTS for achieving TB control with maximum treatment success rate globally.<sup>5</sup>

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## ORIGINAL ARTICLE

# Treatment Outcomes of Tuberculosis Patients Under Directly Observed Treatment Short Course Program at a Tertiary Care Hospital of Rawalpindi

Farhan Hassan<sup>1</sup>, Sidra Tul Muntaha<sup>2</sup>, Fazal Mahmood<sup>3</sup>

## ABSTRACT

**Objective:** To determine the treatment outcomes of tuberculosis patients registered under directly observed treatment short course (DOTS) program at Holy Family Hospital, Rawalpindi.

**Study Design:** Descriptive Case Series.

**Place and Duration of Study:** TB DOTS Clinic, Holy Family Hospital, Rawalpindi from September 2015 to March 2016.

**Materials and Methods:** A total of 75 tuberculosis patients were enrolled by consecutive sampling. Data was collected by means of structured proforma in which demographic details of patients were entered along with information regarding site of TB and treatment outcomes and success of outcomes. "Cured" was labeled for those patients who finished six months treatment with negative sputum microscopy result for Acid Fast Bacillus (AFB) at the end of treatment. "Treatment Completed" was labeled for those patients who finished six months treatment, but no sputum microscopy result for AFB at the end of treatment. Data was analyzed using SPSS version 17.

**Results:** Majority (61.3%) of patients coming to TB center were females showing increased frequency of women having tuberculosis in the setting. Most of the patients belonged to urban area i.e. 65.3%. In our study, a healthy finding was observed that the commonest treatment outcome was treatment completed (65.3%) followed by 21.3% of cured ones and treatment failure was very low (2.7%).

**Conclusion:** Majority of the tuberculosis patients registered under directly observed treatment short course program at Holy Family Hospital, Rawalpindi had successful treatment outcomes. It is recommended that patients with unsuccessful treatment outcomes should be followed up for health education as well as treatment accordingly.

**Key Words:** DOTS, Tuberculosis, Outcomes.

## Introduction

World Health Organization (WHO) announced Tuberculosis (TB) as a worldwide "public health emergency" in 1993.<sup>1</sup> Tuberculosis (TB) is one of the most debilitating diseases of the world.<sup>2</sup> Global Health Report of WHO, 2010 shows 9.4 million patients of Tuberculosis in overall world. MDGs target set for TB control is to "halt and reverse the

incidence of TB by 2015". The most important & effective measure to control TB is early detection of TB and completing treatment of those who get diagnosed of disease and get cured. Most of TB mortality and morbidity (95%) is reported in low and middle-income countries.<sup>3</sup> Pakistan ranks fifth amongst "22 high burden countries (HBCs)", contributing around 63% of disease burden in Eastern Mediterranean Region (EMRO). Government of Pakistan initiated "DOTS strategy (Directly Observed Treatment Short course)" recommended by WHO for effective control of this menace in 1995 and declared TB a national health emergency in 2001.<sup>4</sup> Lot of researches have been carried out globally on the TB treatment outcomes, as evident by a study conducted in Ethiopia which has evaluated pattern of Tuberculosis and its "treatment outcomes" over past few years. 64.6% were declared as treatment completed, 18% as cured, 5.1% defaulted, 5.4% transferred out.<sup>3</sup> A study

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of India showed that with DOTS, the cure rate was 94.6%.<sup>2</sup> A similar study has been carried out in Karachi on TB treatment outcomes which showed successful outcome in 47.2% patients and 47.2% were lost to follow up and defaulted, 5.6% were treatment failure.<sup>5</sup> A study done in Kohat showed 32.6% cure rate, 41.3% treatment completed and 25% default rate.<sup>6</sup>

The key to control of TB includes case finding as early as possible and its prompt treatment. Monitoring of treatment outcomes is important to evaluate DOTS programme which in turn prevents development of resistant TB.<sup>7</sup> The present study was aimed to evaluate the DOTS program in a tertiary care setup in terms of assessment of treatment outcomes of TB patients registered under DOTS programme at Holy Family Hospital, Rawalpindi. This will add to the current knowledge about DOTS program efficiency in study setting in terms of treating TB patients to achieve successful treatment outcomes. This study will be helpful for public health authorities to take action accordingly as per WHO standards.

## Materials and Methods

It was a Descriptive Case Series conducted at TB DOTS clinic, Holy Family Hospital, which is a tertiary care teaching hospital attached with Rawalpindi Medical University, Rawalpindi, Pakistan. Duration of study was six months (from September 2015 to March 2016). Non Probability Consecutive Sampling was used and sample size was 75. All newly diagnosed cases of pulmonary as well as extra-pulmonary tuberculosis of both male as well as female gender aged 18-65 years were included in study. Cases transferred-in from other health facilities were excluded from the study. Data was entered in proforma. Age, sex, place of residence and site of tuberculosis were entered in proforma. All the patients underwent six months treatment for tuberculosis using Anti-tuberculosis therapy (ATT). During initial two months (Intensive Phase), four drugs namely Isoniazid, Rifampicin, Ethambutol and Pyrazinamide were given. Only two drugs Isoniazid and Rifampicin were given in next four months treatment (Continuation Phase). Patients were followed till the end of the treatment course and relevant information was entered in proforma. Finally "treatment outcomes" were entered by the conclusion of treatment course. Treatment

outcomes were labeled as "Successful" if it came out to be either "Cured" or "Treatment Completed"; and as "Unsuccessful" if came out to be as "Treatment Failure", "Defaulted", "Died" or "Transferred Out". "Cured" was labeled for those patients who finished six months treatment with negative sputum microscopy result for Acid Fast Bacillus (AFB) at the end of treatment. "Treatment Completed" was labeled for those patients who finished six months treatment, but no sputum microscopy result for AFB at the end of treatment. "Treatment Failure" was labeled for those patients who remained sputum positive for AFB at five months despite correct intake of medication. "Defaulted" was labeled for those patients who interrupted their treatment for two consecutive months or more after registration. "Died" was labeled for those patients who died during the course of treatment. "Transferred out" was labeled for those patients whose treatment outcomes are unknown due to transfer to another health facility. The data was entered and analyzed in Statistical Package for Social Sciences (SPSS) version 17. Frequency and percentages were calculated for variables like gender, age categories, treatment outcomes and success of outcomes.

## Results

Total of 75 patients participated in the present study, out of them 29 were males and 46 were females. Out of 75 patients, 34 patients were aged between 18-25 years as shown in Table no. I. 26 were from rural areas and 49 from urban areas. 27 patients were pulmonary sputum positive and 12 were pulmonary sputum negative and 36 were extra pulmonary cases. Frequency of treatment outcome and success of outcome is shown in Table II and III respectively. Cross tabulations of success of outcome with age category and gender is shown in Table IV and V respectively.

**Table I: Age Distribution**

Age Category (years)	Frequency	Percent	Cumulative Percent
18-25	34	45.3	45.3
26-35	16	21.3	66.7
36-45	12	16.0	82.7
46-55	8	10.7	93.3
56-65	5	6.7	100.0
Total	75	100.0	

**Table II: Frequency of Treatment Outcomes**

Treatment outcome	Frequency	Percent	Cumulative Percent
Cured	16	21.3	21.3
Treatment completed	49	65.3	86.7
Died	2	2.7	89.3
Treatment failure	2	2.7	92.0
Defaulted	3	4.0	96.0
Transferred out	3	4.0	100.0
Total	75	100.0	

**Table III: Frequency of Success of Outcome**

Success of Outcome	Frequency	Percent	Cumulative Percent
Successful	65	86.7	86.7
Unsuccessful	10	13.3	100.0
Total	75	100.0	

**Table IV: Cross Tabulation of Success of Outcome with Age**

Age Category (years)	Success of Outcome		Total
	Successful	Unsuccessful	
18-25	30	04	34 (45.3%)
26-35	15	01	16 (21.3%)
36-45	10	02	12 (16.0%)
46-55	07	01	8 (10.7%)
56-65	03	02	5 (6.7%)
Total	65	10	75 (100.0%)

**Table V: Cross Tabulation of Success of Outcome with Gender**

Gender	Success of Outcome		Total
	Successful	Unsuccessful	
Male	26	03	29 (38.7%)
Female	39	07	46 (61.3%)
Total	65	10	75 (100.0%)

## Discussion

In our study, majority (61.3%) of patients coming to TB centers were females showing increased

incidence of women having tuberculosis in the settings. Risk of tuberculosis in females may be clarified by the difference in exposure to mycobacterium tuberculosis which in turn may be related to gender specific differentiation of labor, traditional seclusion practices and socialization arrangements. Higher frequency of advanced disease might be observed due to poorer quality of health of females compared to males with respect to nourishment. According to World Health Organization (WHO), at few places, for example Iran, Afghanistan and areas of Pakistan bordering Afghanistan, higher number of females in comparison to males are diagnosed as TB patients, however worldwide, considerably higher number of males in comparison to females develop the disease and expire due to TB per annum.<sup>8</sup> Similar results were seen in the province of Yazd, in Iran, where average yearly rate of TB was higher in females being 31.0 per 100,000.<sup>9</sup> Demographics of tuberculosis in district Mansehra also showed that most of the patients registered at the District Tuberculosis Control Office (DTO) were females (57%) as compared to males (43%).<sup>10</sup>

In our research work, most of the study population belonged to urban area i.e. 65.3%. This portrayal is alike to most countries with low-incidence and selected high-incidence countries.<sup>11</sup> Certain social conditions may have an effect on urban localities, for instance, homelessness or those conditions that make other residents prone to tuberculosis, like high population density and deteriorating public health infrastructures. Health facilities in city localities may be in somewhat easy range. In rural localities, patients have to move from far flung areas every so often. Another positive result was found in a study conducted in USA where frequency in big metropolises stayed greater than double, compared to what was stated for other areas of USA. Insistently, more frequency of TB in big cities was linked to presence of risk factors in people, for advancement to tuberculosis.<sup>12</sup>

Another finding portrayed by our investigation was site of tuberculosis where the most common site was extra pulmonary tuberculosis (48%). This is line with another research conducted in USA on extra pulmonary tuberculosis (EPTB) depicting that though there is a decline reported in the occurrence

of pulmonary tuberculosis in the U.S.A. but it has not been supplemented by a drop in prevalence rate of extra pulmonary tuberculosis.<sup>13</sup> So EPTB is contributing to the burden of infection and does not obtain explicit responsiveness in global control strategies resulting in certain diagnostic challenges. In Australia, EPTB counts for more than forty percent of cases and it turns to greater than 50%, if co-existing Pulmonary TB is also taken into consideration. These figures have been purportedly cumulating in Western countries & Australia. Moreover extra pulmonary tuberculosis manifests different presentations that renders it perplexing as far as diagnosis is concerned, quite often connected to delay in diagnosis, leading to higher possibility of severe disease and death, predominantly "TB meningitis".<sup>14</sup> From a public health standpoint, there is thus a necessity to address this set of patients, as they do add to the total problem of disease and they do have a substantial influence on available resources of national health systems.

In our study, a healthy finding was observed that the commonest treatment outcome was treatment completed (65.3%) followed by 21.3% of cured ones and treatment failure was very low (2.7%). It shows that national government is trying to fulfill its obligation for treating TB patients and to control the spread of the disease. Other contributory factors are political commitment by government, better-quality laboratory facilities, an uninterrupted provision of medicines, and a monitoring system for documentation & evaluation. Finally, the direct observation of treatment has resulted in effective treatment completion and cure rates. Similar results were found in a research conducted in Northwest Ethiopia where the outcomes were categorized as cured 19.9%, treatment completed 50.3%, lost to follow up 05%, treatment failure in 1.7% and died 0.6%.<sup>15</sup> Likely outcomes were seen in researches conducted at Bangalore with cure rate of 65.7%, and Tamil Nadu with cure rate of 75%. For purpose of understanding, WHO recommends to achieve "85% cure rate".<sup>16</sup> In contrast to our results, a study conducted at South Africa reported 30% of failed treatment, died and lost to follow up in their patients.<sup>17</sup> The core reason for the high failed treatment may be the non-compliance of the cases in the study settings. Therefore, frequency of failed

treatment in TB cases having pulmonary disease, getting treatment at DOTS clinics differs from one place to another and reveals the level of threat posed to close contacts of the patients as well as development of multidrug-resistant TB.

It is clear in our findings that the overall success rate of outcome was 86.7% in the study participants which is quite satisfactory, though room for improvement is still there. The reason for reasonable success rate might be "Directly Observed Treatment Short Course (DOTS) strategy" that makes TB cases to ingest anti-TB medicines under the surveillance of liaison persons. Improved compliance to the treatment leads to better TB cure rate. Such outcomes were observed in a research conducted at Southern Ethiopia, where 85.2% "treatment success rate" was documented. The main reason behind this improved success rate may be the improved compliance of TB patients to the treatment in the study setting under "DOTS" which highlights the significance of the strategy.<sup>18</sup>

As this study has been conducted in a limited context of only one hospital setting so the results of this study are not generalizable.

## Conclusion

Majority of the tuberculosis patients registered under directly observed treatment short course program at Holy Family Hospital, Rawalpindi had successful treatment outcomes. It is recommended that patients with unsuccessful treatment outcomes should be followed up for health education as well as treatment accordingly.

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## ORIGINAL ARTICLE

## Nephroprotective Effect of Aqueous Extract of Carica Papaya Seeds

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## ABSTRACT

**Objective:** To determine the nephroprotective effect of aqueous extract of *Carica papaya* seeds in Aminoglycoside induced acute nephrotoxicity in rats.

**Study Design:** Quasi Experimental study.

**Place and Duration of Study:** The study was conducted from April 2016 to March 2017 at “Department of Pharmacology and Therapeutics” and “Multidisciplinary Laboratory of Islamic International Medical College, Riphah International University”, Islamabad in collaboration with National Institute of Health (NIH), Islamabad.

**Materials and Methods:** Thirty Sprague Dawley rats were divided into 3 groups i.e., A, B and C with 10 rats in each group. Group B and C were given Aminoglycoside; Gentamycin in 80 mg/kg) via intraperitoneal route once daily for 5 consecutive days to induce acute nephrotoxicity. At day 6<sup>th</sup>, nephrotoxicity was confirmed by measuring serum urea and creatinine. Aqueous extract of *Carica papaya* seeds (1000 mg/kg) was started once daily through oral route in group C for 5 consecutive days. All animals were given standard diet pellets manufactured at NIH.

**Results:** Mean serum urea and creatinine for Group A (Control Group) at day 0 was 24.70 mg/dL 5.16 and 0.750 mg/dL 0.1958 respectively. Mean serum urea and creatinine for Group B (Disease Control Group) was 78.60 mg/dL 3.921 and 1.920 0.1229 at day 6<sup>th</sup>. This suggested induction of nephrotoxicity by gentamycin. Mean serum urea and creatinine for Group C (Aqueous Extract Treated Group) at 11<sup>th</sup> day was 50.60 mg/dL 5.910 and 1.380 mg/dL 0.1932 after 5 days treatment with aqueous extract of *Carica papaya* seeds.

**Conclusion:** Aqueous extract of *Carica papaya* seeds has significant nephroprotective effects on aminoglycoside induced acute nephrotoxicity in rats.

**Key Words:** Aminoglycoside, *Carica papaya*, Gentamycin, Nephrotoxicity.

## Introduction

A total of 25% of cardiac output is received by kidneys. They serve as main organs for maintenance of homeostasis of circulatory fluid. Kidneys also serve as primary organs for elimination and detoxification of xenobiotic elimination and detoxification.<sup>1</sup> Direct or indirect exposure of drugs and different chemicals to kidneys result in nephrotoxicity. Many drugs may result in acute or

chronic renal failure.<sup>2</sup> Adverse reactions to drugs occur in approximately 6 % of admitted patients in hospitals and amongst these approximately 7 % patients suffer drug-related toxicities.<sup>3</sup> Nephrotoxic drugs may be responsible for 19% – 25% of acute kidney injury in critically ill patients receiving them.<sup>4</sup> Due to the intrinsic functions of kidneys for drug metabolism, concentration and excretion, they are vulnerable to toxicity due to drugs and their metabolites. Many patients suffer from drug-induced nephrotoxicity that can cause either acute injury to kidneys or chronic damage. Many widely used marketed drugs including anti-cancer drugs, antibiotics, immunosuppressants and radio contrast agents are nephrotoxic.<sup>5</sup> Nephrotoxicity is characterized by raised serum urea and creatinine levels.<sup>6</sup> Aminoglycosides used for the treatment of Gram-negative bacteria have been a vital component of antibiotic armamentarium. This is peculiar to their cost effectiveness and efficacy.<sup>7</sup> Aminoglycosides are not metabolized in the body and eliminated unchanged in the urine by glomerular filtration.<sup>8</sup> Due

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to their potent ability to cause nephrotoxicity and ototoxicity, dosage limitations of Aminoglycosides pertain.<sup>9</sup> Gentamycin, an important aminoglycoside antibiotic, is used widely due to its potent antibiotic activity against various gram-negative microorganisms.<sup>10</sup> However, its use is greatly limited by nephrotoxicity, accounting for 10 – 15 % of all cases of acute renal failure.<sup>10</sup> Aminoglycoside-induced nephrotoxicity is confirmed by rise in serum creatinine, serum urea, and marked decrease in glomerular filtration rate.<sup>11</sup> Drug induced nephrotoxicity at renal tubular level more commonly affects proximal tubular cells due to high exposure to drug and its metabolites during processes of drug concentration and reabsorption through the glomerulus. Mitochondria are damaged in tubular cells, tubular transport system is disturbed and there is increased oxidative stress due to generation of free radicals leading to cytotoxicity. Nephrotoxic drugs fiberize the kidney due to inflammation in glomerulus and proximal tubular cells and damage to surrounding renal cellular matrix.<sup>12</sup> Current research was aimed to see the effect of *Carica papaya* seeds on acute Drug-induced nephrotoxicity and to support it biochemically. Present study aims to find out the effect of extract of *Carica papaya* seeds in Aminoglycoside induced acute nephrotoxicity.

## Materials and Methods

A quasi experimental study including 30 Sprague Dawley rats was performed in the “Department of Pharmacology and Therapeutics” and “Multidisciplinary Laboratory of Islamic International Medical College, Riphah International University”, Islamabad in collaboration with National Institute of Health (NIH), Islamabad for duration of one year.

A total of 30 Sprague Dawley rats were acquired and divided into 3 groups; A, B and C with 10 rats each through random selection via balloting method. Authorization of the study was made by the Ethics Review Committee of Islamic International Medical College (Riphah International University) and was implemented within the frame of rules specified by the National Institute of Health for animal experiments. Rats weighing more than 300 grams and with normal baseline serum urea and creatinine levels were included in the experiment. All rats were served with standard food pellets manufactured at

the Animal house of NIH, Islamabad according to the recommendations agreed by the universities federation for animal welfare, alongside fresh water supply of 250 mL in inverted water bottles anchored on the enclosures in a particular inclined position.

Group A was taken as control group throughout the experiment. Group B and C (10 rats each) were given Aminoglycoside drug Gentamycin (80 mg/kg) via intraperitoneal route for 5 consecutive days for induction of acute nephrotoxicity.<sup>11</sup> Blood samples were collected via tail vein and serum urea and serum creatinine were measured at day 6 to see that nephrotoxicity has developed.<sup>13</sup> After the confirmation of nephrotoxicity on day 6, Group C was started with administration of Aqueous Extract of *Carica papaya* seeds (1000 mg/kg) dissolved in distilled water for 5 consecutive days.<sup>14</sup> After terminal sampling through cardiac puncture serum urea and creatinine were measured again at Day 11 to see the effect of aqueous extract of *Carica papaya* seeds on renal function.

*Carica papaya* plants were grown locally. Seeds were collected from ripened fruits of papaya. Seeds were air dried. The dried seeds of *Carica papaya* were identified and authenticated by herbarium section of National Agricultural Research Centre (NARC) Islamabad. Coarse powder was made. In 1.0 L of distilled water, approximately 200 g powder was soaked. The mixture was kept for 48 hours with intermittent shaking. After 48 hours, the extract was filtered using Whatman filter paper no.1. The filtrate was dried via rotary evaporator through evaporation. The extraction yielded 5.61 w/w dry matter. The extract was then stored in a refrigerator at 4°C till usage.<sup>15</sup>

The data was analyzed using Microsoft Excel 2010 and SPSS 20. Multiple comparisons were done through Tuckey test and group mean differences were observed. A p-value of <0.05 was considered as statistically significant.

## Results

At day 6 mean value of serum urea for Group A (Control Group) was 24.70 mg/dL  $\pm$  1.633. Mean serum urea for Group B (Disease Control Group) and Group C were 81.00 mg/dl  $\pm$  1.247 and 82.70 mg/dl  $\pm$  2.587. There was significant difference (p Value less than 0.05). This suggested induction of acute nephrotoxicity by aminoglycoside drug gentamycin.

Mean serum urea for Group C (Aqueous Extract Treated Group) at day 11 was 50.60 mg/dL $\pm$ 1.869 after 5 days treatment by aqueous extract of *Carica papaya* seeds. There was significant difference (p Value <0.05) which supported the nephroprotection by the herb.

**Table I: Mean Values of Serum Urea of All Groups at Day 0, 6 And 11**

Study Groups	Serum Urea on Day 0 Means $\pm$ SD	Serum Urea on Day 6 Means $\pm$ SD	Serum Urea on Day 11 Means $\pm$ SD
Group A (control group)	24.90 $\pm$ 1.633	24.70 $\pm$ 1.633	24.70 $\pm$ 1.633
Group B (Disease Control)	24.70 $\pm$ 1.760	81.00 $\pm$ 1.247***	78.60 $\pm$ 1.240
Group C (Aqueous Extract Treated Group)	24.50 $\pm$ 1.821	82.70 $\pm$ 2.587***	50.60 $\pm$ 1.869***
p-value	0.924	< 0.05	< 0.05

Mean value of serum creatinine for Group A (Control Group) was 0.750 mg/dL 0.0619. Mean value of serum creatinine for Group B (Disease Control Group) and Group C were 1.980  $\pm$  .0467 and 2.030  $\pm$  .0667 respectively. There was significant difference (p Value .000). This suggested induction of nephrotoxicity by aminoglycoside drug gentamycin. Mean serum Creatinine for Group C (Aqueous Extract Treated Group) was 1.380  $\pm$  .0611 after 5 days treatment by aqueous extract of *Carica papaya* seeds.

**Table II: Mean Values of Serum Creatinine of All Groups at Day 0, 6 And 11**

Study Groups	Serum Creatinine on Day 0 Means $\pm$ SD	Serum Creatinine on Day 6 Means $\pm$ SD	Serum Creatinine on Day 11 Means $\pm$ SD
Group A(control group)	0.750 $\pm$ .0619	0.750 $\pm$ .0619	0.750 $\pm$ .0619
Group B(Disease Control)	0.780 $\pm$ .0611	1.980 $\pm$ .0467***	1.920 $\pm$ .0389
Group C(Aqueous Extract Treated Group)	0.770 $\pm$ .0559	2.030 $\pm$ .0667***	1.380 $\pm$ .0611***
p-value	0.988	< 0.05	< 0.05

## Discussion

Kidneys function as main organ to detoxify and eliminate xenobiotics. Xenobiotics which accumulate in renal tubular cells can damage the kidneys acutely.<sup>1</sup> Acute kidney injury (AKI) being a common clinical complication possesses high mortality and morbidity. According to the statistics, the incidence rate of chronic Kidney Disease followed by an episode of AKI is 7.8 per 100 patients per year. The rate of End Stage Renal Disease (ESRD) is 4.9 per 100 patients per year. Gentamycin, an important aminoglycoside antibiotic, has potent antibiotic spectrum but its clinical use has been greatly reduced due to nephrotoxicity that accounts for 10 to 15 % of all cases of acute renal failure in drug induced kidney damage.<sup>10</sup> Gentamycin due to its cost effectiveness and high potency and more liability to cause toxicity in kidneys is widely used for inducing nephrotoxicity in experimental models.<sup>13</sup> Baseline serum urea and serum creatinine were measured at Day 0 i.e., beginning of the experiment. Gentamycin was administered intraperitoneally to Group B and Group C for five consecutive days. At day 6 Mean serum urea and serum creatinine were again measured. Mean serum urea and creatinine of Group B (Disease Control Group) and Group C were significantly raised when compared with the Control Group A suggesting that gentamycin produced acute nephrotoxic changes in the kidney and altered the renal function. After measuring the serum markers; Group C was started with administration of aqueous extract of *Carica papaya* seeds dissolved in distilled water via oral route. The aqueous extract was administered for five consecutive days. At Day 11, again serum markers were measured and the values of serum urea and serum creatinine were found to have been reduced than Day 6 in Group C which received aqueous extract of *Carica papaya* seeds. There was significant difference statistically between the Disease Control Group i.e., Group B and the Aqueous Extract treated Group i.e., Group C (p Value less than 0.05). The difference in serum markers showed nephroprotection by *Carica papaya* seed extract.

Gentamycin resulted in increased levels of serum markers i.e serum urea and creatinine in Group B and Group C after five days intraperitoneal administration of Drug in dose of 80 mg/kg when

compared to Group A i.e., Control Group. These findings were found to be in accordance with findings of a study by (Ajami M et al; 2010), in which nephrotoxicity was induced in male Wister rats via Gentamycin in same dose and there was resultant increase in levels of serum markers i.e., serum urea and creatinine.<sup>13</sup> After the induction of nephrotoxicity, the protective effect of aqueous extract of *Carica papaya* seeds was observed when 1000 mg/kg dose of Aqueous extract of *Carica papaya* seeds was administered to Group C. This was consistent with the study performed by umana et al., (2013) in which same dose of Chloroform extract of *Carica papaya* seeds was utilized in rats for toxicity studies.<sup>16</sup> In current study aqueous extract preparation of *Carica papaya* seeds was utilized which revealed improvement in levels of serum urea and serum creatinine in Group C after previous induction of nephrotoxicity by Gentamycin. The results indicated that Aqueous extract of *Carica papaya* seeds possess the potential of nephroprotection in Gentamycin induced acute nephrotoxicity. However, the cost of experiment limited the study of phytochemical constituents of the extract preparation. The duration of experiment can however be prolonged in further studies to assess complete reversal of nephrotoxicity and to study other extract preparations of *Carica papaya* too.

## Conclusion

Aqueous extract of *Carica Papaya* seeds have significant protective effect as shown by the improvement of kidney function after Gentamycin induced acute renal injury.

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## ORIGINAL ARTICLE

**Obesity an Emerging Epidemic: Effects and Consequences of Loneliness and Perceived Parental Neglect**Rabia Zonash<sup>1</sup>, Kehkashan Arouj<sup>2</sup>**ABSTRACT****Objective:** To explore the effect of loneliness and perceived neglect on obesity among university students.**Study Design:** Cross sectional research design.**Place and Duration of Study:** The study was conducted at Air University, Foundation University Rawalpindi Campus, International Islamic University, National Defence University, Riphah International University and National University of Modern Languages from August 2016 to May 2017.**Materials and Methods:** The study comprised of 200 respondents (males=102, females=98), selected through purposive sampling technique. Three self-reported assessments tools were used in present study namely De Jong Gierveld Loneliness Scale, Childhood Trauma Questionnaire, The Weight Self-Stigmatization Questionnaire to measure the variables of loneliness, perceived neglect and obesity among the student. To determine the reliability of measures, Cronbach's alpha co-efficient Pearson correlations, T-test, ANOVA analysis were used.**Results:** Results showed that emotional loneliness and social loneliness have a negative relation with obesity (e.g., self-devaluation and enacted stigma). Perceived parental neglect has a positive relation with obesity. Gender means differences indicated that female (49.0%) experience more loneliness and obesity whereas boys (51.0%) are higher on perceived parental neglect subscales. Age differences indicated that adolescents (16.5%) experienced more obesity than adult's students (83.5%).**Conclusion:** The higher level of loneliness feelings and perceived neglect by parents are significant predictors of obesity in university student.**Key Words:** BMI, Loneliness, Neglect, Obesity, Students, Trauma, Weight.**Introduction**

In this world, man is viewed as a social creature. It is an essential need of individuals to connect so they can't be left alone. Parental figures or guardians are initial ones with whom one associates, they either satisfy or dissatisfy the child need of association. Sometimes these dissatisfying relation and harsh relation with parents can foster emotional difficulties in children that often lead to dissatisfied body image.<sup>1</sup>

Loneliness is an emotional component of social separation in which individual wants to be alone to avoid social confrontation.<sup>2</sup> It is unique in relation to

disengagement (being distant from everyone else). It is a subjective affair of the disparity between the individual's present actual and desired social relations that one wishes.<sup>2</sup> Loneliness can be knowledgeable about two different ways as social loneliness and emotional loneliness. Social loneliness is described by encountering the absence of social relations and emotional loneliness is linked to still feel lonely in presence of abundant of people including mistrust trust in others.<sup>3</sup> There are several factors that link the feeling of loneliness and perceived loneliness with multiple factors like obesity, higher mortality rates, and smoking habits.<sup>4</sup> Obesity is a rising epidemic in Pakistan which is still un-recognized in indigenous culture. Obesity and overweight are a global epidemic that is affecting about 1 billion in the general population, out of which 300 million are obese and 2.6 million die due to obesity and over-weight issues.<sup>5</sup> Obesity is a medical condition that is caused by increased fat deposition in the body due to less physical activity and more caloric intake.<sup>8</sup>

According to World Health Organization (WHO) categorize the overweight and obesity on the basis of

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body mass index (BMI), and is recognized as one of the independent risk factors that is linked with other serious non-communicable diseases such as hypertension, cardiovascular diseases, type-II diabetes mellitus, osteoarthritis, obstructive sleep, and cancers.<sup>8,9</sup> In 2008, according to global estimates 1.46 billion adults are overweight, 502 million are obese, and 170 million of the children are obese and overweight.<sup>10,11,12</sup> Hence, obesity is a global phenomenon affecting a large number of individuals across the globe. According to the new survey, country wise obesity is highest in Papua New Guinea almost 79–80 percent population is obese, in Qatar 34–45 percent population is obese, Lebanon have 36–38 % population and the United States have 32–35 % of obese population.<sup>6,7,11</sup>

A recent survey by National Health Survey of Pakistan (NHSP) in duration of (2004-05) in city of Karachi Reported that the prevalence of overweight population is 3% and 5.7% urban school-aged children also were found to be obese and overweight.<sup>13</sup> In indigenous culture, obesity disease is changing pattern of expression that is affecting all age groups of Pakistan. Urban population especially females experience more obesity than rural males and females. Age is another factor girls of all ages experienced more obesity as compared to boys.<sup>10</sup>

Researchers have recognized that individuals who experience the negative effects of loneliness demonstrate expanded utilization of sugar or glucose-rich junk food and drinks which consequently influence body mass index (BMI).<sup>14</sup> Another examination demonstrated that the individuals who are socially avoidant in nature display high basal glucose levels in their blood.<sup>15</sup> In gentle to extremely large people it was seen that higher amount of food is consumed by females when encountering pessimistic feelings, for example, outrage, gloom, fatigue, and loneliness.<sup>16</sup> Several factors play its role in the development of obesity in adults. Early past experiences develop habits to deal with life stresses in different manners either in the positive manner or negative.<sup>17</sup> For that, child maltreatment incorporates both physical abuse and neglect which is most common while deliberate neglect is uncommon.<sup>18,19</sup> Child neglect is very different from child physical, sexual or emotional abuse endured. Neglect is tenacious, non-physical

hurtful collaborations between a child and parental figure. Neglect is characterized as the sort of maltreatment in which guardian neglects to fulfill a child physical, emotional, educational or emotional needs.<sup>20</sup>

A study from Denmark in educational sector found that childhood neglect anticipated obesity in youthful adulthood.<sup>34</sup> Further, numerous studies found the relationship between child maltreatment and obesity which demonstrated that the chances of obesity expanded in children who had encountered neglect in early long periods of life.<sup>20</sup> A longitudinal study on emotional wellbeing on 8471 individuals indicated that children who have encountered neglect in childhood have higher BMI development rates in adult age.<sup>21,22</sup> A meta-examination of 41 studies including 190,285 participants revealed that childhood maltreatment was related to the higher risk factor for prolonging obesity over lifetime.<sup>22</sup>

University students experience diverse psychological issues but the variables being explored in the present study have been understudied and most of the researches have been carried out in the western researches. Numbers of western, medical researches have done experimental researches with obese individuals but none of the indigenous researches have explored the link between different psychological variables with BMI and obesity among university students. There are a few kinds of research that have examined the relationship between loneliness and neglect; and the relationship of both with obesity. Regardless of the purpose of the study none of the indigenous researches have explored the effect of neglect and loneliness on obesity among university students. Loneliness and neglect have been studied with a number of independent variables e.g., psychiatric disorders, physical health, attachment styles, and personality disorders with sexual and physical abuse.<sup>23,24,25</sup> Hence, for that the present study was aimed to explore the predictive effect of loneliness, neglect on obesity among university students.

## Materials and Method

The cross-sectional research design was used in present study at Air University, Foundation University Rawalpindi Campus, International Islamic University, National Defence University, Riphah International University, National University of

Modern Languages from August 2016 to May 2017. After the approval of the ethical committee of Foundation University Rawalpindi Campus, the study was started. Purposive sampling technique was utilized in the present study to include students after receiving written informed consent. Initially, BMI scores of the students were obtained before they were included in the study sample; students having low BMI were excluded from the sample. Total of 280 students was taken after fulfilling the inclusion criterion only 200 were selected for the present study. Three standardized measures were used in the present study the first questionnaire utilized in the present study was The Gierveld Loneliness Scale was developed by Gierveld and Kamphuis in 1985. The scale consists of 11-item and it's a 5-point Likert scale. The overall Cronbach alpha coefficient range for emotional and social loneliness scale respectively was 0.81-0.73. The second scale used in the present study was The Childhood Trauma Questionnaire was developed by Bernstein and Fink in 1998. The scale comprised of 23 items and its 5 points Likert scale. Overall Cronbach alpha coefficient range for parental neglect was in the range of  $\alpha = 0.83-0.91$ . The third scale utilized in the present study was "The Weight Self-Stigmatization Questionnaire" is a 12 item scale (5-point Likert scale) containing two subscales namely self-stigmatization and fear of enacted stigmatization with overall Cronbach alpha coefficient range of (0.88-0.87).

After data collection, the data was analyzed using SPSS-21 version. Means standard deviation mean differences were calculated for demographic variables for numeric variables like gender, family structure, BMI, levels of education, and SES on study variables. The correlation matrix was calculated to explore the relationship between loneliness and perceived neglect and obesity among university students. The reliability of the table was determined by Cronbach Alpha reliability. The reliability estimate of  $p \leq .05$  was considered significant.

## Results

For purpose of present study a total of 200 students were selected out of which 102 were males (51.0%) and 98 were females (49.0%). 33 adolescents in the age range of 17-27 years (16.5%) were taken whereas, 167 adults in the age range of 28-40 years (83.5%) were selected. Only 4 students were in

category of (underweight) with BMI of 17.75 (2.0 %), 39 students were in (healthy) category with BMI range from 17.76-23 (19.5 %), 40 students were in (overweight category) in BMI range of 24-25 (20.0%), 117 students were (obese) with 25 BMI or above (58.5%). The result of the study indicated that most of the participants were obese and indicated the prevalence of obesity in our society in relatively high. Cronbach's alpha reliability was also determined for the present sample.

Table II indicates that emotional loneliness has negative whereas social loneliness has a positive relation with obesity. Overall emotional abuse, physical abuse, sexual abuse, emotional neglect, parental neglect has a positive relation with obesity (self-devaluation and fear of enacted stigma). Table III indicates gender differences on the study variables. The table showed that females mean scores were higher on emotional and social loneliness as compared to male students. Female means were higher on emotional abuse and emotional neglect. Male students were higher on physical, sexual abuse, and parental neglect as compare to female students. Females were also higher on obesity as compare to the male students. The gender means differences were also in accordance with previous researches which showed that parental neglect was higher in female as compared to male counterparts. Table IV indicated that students in the age range of 17- 27 years were higher on social loneliness as compared to students in the age range of 28- 40 years. Students in the age range of 17- 27 years were higher on emotional abuse, emotional neglect, and parental neglect; whereas, students in the age range of 28- 40 years were higher on physical abuse and sexual abuse. Students in the age range of 17- 27 years were higher on obesity as compared to students in the age range of 28- 40 years. Table V shows that emotional loneliness means was higher in underweight and obese students, whereas social loneliness was higher in underweight students. Physical and sexual abuse was significantly higher in overweight individuals. Emotional abuse, emotional neglect and parental neglect was higher in underweight students, physical abuse and sexual abuse mean was higher in overweight students. Obesity is highest in overweight and obese students above the BMI of

>27 or above. The result findings indicated that loneliness and parental neglect can lead to fluctuations of increasing or decreasing BMI in students.

**Table I: Demographic Variables Frequency and Percentages (n=200)**

Variables		Frequency	(% age)
<b>Gender</b>	Male	102	51.0%
	Female	98	49.0%
<b>Age</b>	17-29 years	33	16.5%
	27-40 years	167	83.5%
<b>BMI</b>	Less than 17.75 (underweight)	4	2.0%
	17.76-23 (healthy)	39	19.5%
	24-25 (overweight)	40	20.0%
	25 or above (obese)	117	58.5%

**Table II: Correlation Between Loneliness, Neglect, and Obesity (n= 200)**

	11	2	E3	4	5	6	7	8	9	.
1.Emotional Loneliness	--	.22**	.28**	.23**	.20**	.22**	-.17*	-.17*	-.030	.80
2.Social Loneliness		--	.13	.18*	.23**	.27**	.15*	.06	.10	.67
3.Emotional Abuse			--	.44**	.24**	.15*	.06	.28**	.20**	.77
4.Physical Abuse				-	.27**	.20**	.17*	.04	.18*	.63
5.Sexual Abuse					--	.15*	.15*	.07	.108	.50
6.Emotional Neglect						-	.50**	.01	-.021	.83
7.Parental Neglect							-	-.06	.13	.56
8.Self-Devaluation								-	.26**	.38
9.Fear of Enacted Stigma									-	.75

\*p <0.05, \*\*p <0.01

**Table III: Mean, Standard Deviation, t Value of Gender on Loneliness, Neglect, and Obesity (N= 200)**

	Male (n=102)		Female (n=98)				95% CI	
Variables	M	SD	M	SD	t	p	LL	UL
Emotional Loneliness	117.95	5.45	19.67	5.60	-2.15	.034	-3.31	-.14
Social Loneliness	111.17	4.09	12.34	3.83	-2.04	.044	-2.31	-.03
Emotional Abuse	8.91	3.95	9.12	4.43	-0.36	.720	-1.4	.97
Physical Abuse	8.43	5.01	7.44	3.70	1.55	.08	-0.27	.24
Sexual Abuse	8.10	6.84	7.33	3.51	0.98	.33	-0.78	.33
Emotional Neglect	3.23	5.92	14.16	6.01	-1.05	.303	-2.67	.81
Parental Neglect	8.42	3.78	7.50	3.15	1.83	.073	-0.06	.89
Self-Devaluation	14.37	6.09	15.58	7.49	-1.22	.28	-3.17	.74
Fear of Enacted Stigma	12.6	4.65	13.00	4.44	-0.61	.54	-1.67	.88

**Table IV: Mean, Standard Deviation, t value of age on Loneliness, Neglect, and Obesity (N= 200)**

	17- 27 years (n=33)		28-40 years (n= 167)				95%CI	
Variables	M	SD	M	SD	t	p	LL	UL
Emotional Loneliness	18.97	.60	18.77	5.59	0.18	0.81	-1.92	2.31
Social Loneliness	12.07	.27	11.69	3.96	0.48	0.42	-1.19	1.95
Emotional Abuse	9.94	.96	8.83	.40	1.37	0.03	-0.48	2.70
Physical Abuse	6.78	3.12	8.18	4.63	-1.64	0.02	-3.09	.28
Sexual Abuse	6.55	2.86	7.94	5.8	-1.31	0.1	-3.5	.71
Emotional Neglect	15.6	5.37	13.34	6.02	1.82	0.45	-0.18	4.69
Parental Neglect	8.03	3.24	7.95	3.56	0.11	0.15	-1.25	1.39
Self-Devaluation	16.06	11.27	14.76	5.57	0.97	0.09	-1.32	3.92
Fear Of Enacted Stigma	13.00	5.12	12.76	4.43	0.16	0.72	-1.57	1.85

**Table V: Mean, Standard Deviation, t value of BMI on Loneliness, Neglect, and Obesity (N= 200)**

Variables	BMI	N	M	SD	F (df)	P	.
Emotional Loneliness	Underweight	4	19.00	1.41	2.153	.1	.21
	Healthy	36	17.47	4.80	[3, 186]		
	Overweight	38	17.60	5.24			
	Obese	112	19.64	5.89			
Social Loneliness	Underweight	4	14.75	3.3	5.350	.001	.12
	Healthy	37	12.75	2.9	[3, 186]		
	Overweight	39	13.10	4.75			
	Obese	110	10.81	3.82			
Emotional Abuse	Underweight	4	12.50	3.31	1.062	.37	.10
	Healthy	38	8.95	3.81	[3, 190]		
	Overweight	40	9.27	4.89			
	Obese	112	8.82	4.04			
Physical Abuse	Underweight	4	7.50	3.78	1.798	.15	.11
	Healthy	38	7.84	3.09	[3, 189]		
	Overweight	38	9.42	5.22			
	Obese	113	7.51	4.5			
Sexual Abuse	Underweight	4	6.25	2.5	1.677	.17	.06
	Healthy	36	7.83	4.34	[3, 187]		
	Overweight	40	9.32	9.54			
	Obese	111	7.15	3.38			
Emotional Neglect	Underweight	4	16.50	6.60	2.000	.116	.11
	Healthy	38	14.31	5.47	[3, 180]		
	Overweight	40	15.07	6.05			
	Obese	102	12.76	6			
Parental Neglect	Underweight	4	8.25	3.30	.362	.781	.08
	Healthy	38	8.47	3.55	[3, 193]		
	Overweight	38	7.71	3.59			
	Obese	117	7.88	3.49			
Self-devaluation	Underweight	4	13.50	1.29	.262	.853	.12
	Healthy	37	15.54	10.39	[3,186]		
	Overweight	37	14.32	8.29			
	Obese	112	15.07	4.69			
Fear of Enacted Stigma	Underweight	4	12	1.63	.775	.510	.06
	Healthy	39	12.38	3.70	[3,193]		
	Overweight	39	12.07	4.47			
	Obese	115	13.2	4.86			

## Discussion

The aim of the study was to see the relationship between loneliness (e.g., emotional and social loneliness), parental neglect (e.g., emotional abuse, physical abuse, sexual abuse, emotional neglect, parental neglect), and obesity (e.g., self-devaluation and fear of enacted stigma) among university students. The study also aimed to explore the effect of different social factors e.g., gender, age, and BMI on loneliness, neglect and obesity among university students. The result indicates that felling of loneliness tend to increase/ add up obesity. Similarly parental neglect is another variable that increased obesity issues among students. Previous researches have indicated that neglectful families have children that have more probability of being lonely or inaccessible. Chronic loneliness is significantly related to neglect.<sup>26</sup> Emotional loneliness in past writing has a significant negative correlation with childhood abuse and neglect, the fundamental rationale behind neglect is that the families neglect to satisfy the emotional needs of their kids when neglected these youngsters tend to concentrate more on subjective based cognitive biases.<sup>27</sup> At the point, when youngsters learn set examples or limits/governs for good exercises then social outcomes are normal. Specialists have demonstrated that such kids show great execution in school and professions while having clear standards for working for<sup>28,29</sup> such families monetarily advantage from neglecting young children that positively influence the existence working performance. Emotional abuse has a significant positive correlation ( $r= 0.281^{**}$ ) with self-downgrading. Past research has featured that childhood abuse is found to foresee low confidence, more mistreatment, melancholy and sadness in grown-ups.<sup>30</sup>

Gender differences in the present study showed that females significantly suffer more emotional and social loneliness, emotional neglect and obesity (e.g., self-devaluation and fear of enacted stigma). Thus, it proves our hypothesis that loneliness and neglect are suffered more by women. Though, physical abuse and parental neglect are endured more by males when contrasted with females. Results portraying that physical abuse is experienced more by men is as per another study demonstrating

the same outcomes. A UK-based study reports that females are more helpless against physical abuse and emotional abuse as young men are less inclined to get great supervision which is inverse to the findings of the present study.<sup>30</sup> Cross-sectional literature has suggested UK, Afro-Caribbean, and Pakistani girls were at high risk of developing obesity. Obesity was also considered with other variables of height and weight.<sup>30</sup> Result of the study also showed that students with more BMI are also higher on loneliness, neglect and obesity. Mean of BMI was higher in Afro-Caribbean girls and boys, whereas, Indian, Bangladeshi, and Chinese boys and girls had low BMI, in comparison of overall general population BMI.<sup>31,32</sup> Age differences indicated that students in age range of 17- 27 years were higher on social loneliness as compared to students in age range of 28- 40 years. Students in an age range of 17- 27 years mean were higher on emotional abuse, emotional neglect, parental neglect, whereas; students in the age range of 28- 40 years were higher on physical abuse and sexual abuse. Students in the age range of 17- 27 years mean were higher on obesity as compared to students in an age range of 28- 40 years. Previous researches have indicated that loneliness is a higher in adolescents than adults which are consistent with the researches that most elevated amounts of loneliness are experienced under age 25 years and over age 65 years.<sup>33</sup> Emotional loneliness is significantly higher in both underweight and obese individuals, physical and sexual abuse is significantly higher in overweight individuals. Obesity e.g., self-devaluation and fear of enacted stigma are more in obese as compared to others. Researches have indicated that lower socioeconomic status is the predictor of higher emotional neglect and higher loneliness among student that lead to higher obesity. Multiple types of research have also indicated similar research findings, as being neglected and feeling lonely are risk factors for increasing obesity and overweight among students.<sup>30,32,33</sup> The results of the study have supported the previous literature findings. The present study is cross-sectional study that assessed study variables through self-report measures for that the comprehensive information source of abuse are unknown for that qualitative research with interview technique in future research would help to highlight the sources and forms of



abuse with severity of loneliness. As neglect is sensitive issue, it's important in future researches to distinguish between abuse and neglect and their resulting consequences for future using longitudinal research method would enable to highlight the consequences and associated variables causes linked with study variables. The study focused only on relationship between study variables in future it would be appropriate to use higher analysis such as multinomial logistic and hierarchal regression to determine the cause and effect and direction of relationship that exists between study variables. The study only explore the effect of different demographics variable effect it is recommended that future researches should device and suggest interventions specifically for neglect as neglect is a strong variable that is major factor behind impairing personal functioning.

## Conclusion

The study aimed to explore the relation between loneliness, neglect and obesity. The study has concluded that loneliness and parental neglect tend to increase obesity. The study findings suggested that decreasing feeling of loneliness and working on parental neglect can help to minimize risk of obesity among the students. There are many factors that affect to help in minimizing feeling of loneliness when social factors are supportive and when parent provide protective environment to offspring it can help to foster feeling of better healthy habits among the participant.

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## ORIGINAL ARTICLE

# Hepatoprotective Effect of Aqueous Extract of *Cichorium Intybus* (Kasni) on Pyrazinamide Induced Hepatotoxicity in Male Mice

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## ABSTRACT

**Objective:** To determine the hepatoprotective effect of aqueous extract of *Cichorium intybus* (kasni) roots on Pyrazinamide induced hepatotoxicity in male mice.

**Study Design:** Experimental randomized control study.

**Place and Duration of Study:** The study was conducted in the department of pharmacology at Islamic International Medical College Trust (IIMCT), Rawalpindi in collaboration with Riphah Institute of Pharmaceutical Sciences (RIPS), Islamabad and National Institute of Health (NIH), Islamabad. The duration of study was from 14<sup>th</sup> March, 2015 to 14<sup>th</sup> March, 2016.

**Materials and Methods:** The experimental randomized control study was carried out on fifty six male albino Balb/C mice which were divided into four groups each having 14 mice. Group A (control) received normal diet with no medication. Group B was given pyrazinamide in dose of 500mg/kg while group C and D were given pyrazinamide along with low dose (200mg/kg) and high dose (400mg/kg) of *Cichorium intybus* roots (aqueous extract) via gavage tube. At day 0, baseline blood samples were taken and normal values of serum alanine aminotransferase (ALT) were obtained. Mid cycle samples were obtained to ensure the progress of study. Final sampling was done at day 30 through cardiac puncture. Serum was separated in sterile tubes and biochemical estimation was done on the same day. Mean and standard error of mean was calculated. Data was analyzed through SPSS 20 and p value of <0.05 was considered statistically significant.

**Results:** The extract of *Cichorium intybus* roots showed improvement in serum alanine aminotransferase (ALT) values in group C and D. ALT value of 5-50UL was considered normal. Group A showed normal value of 24.5 UL. Group B showed severe hepatotoxicity as indicated by the raised value of 143.5UL. The value of ALT in Group C was 86.5 UL and it was 59.9UL in Group D.

**Conclusion:** Aqueous extract of *Cichorium intybus* roots has significant hepatoprotective activity in high doses as compared to low doses.

**Key Words:** Alanine Aminotransferase (ALT), *Cichorium Intybus*, Hepatoprotective, Pyrazinamide.

## Introduction

Now a days, across the world, tuberculosis (TB) is major health issue.<sup>1</sup> Yearly 2 million deaths are reported from this disease.<sup>2</sup> Pakistan has been ranked in the top six countries who are bearing the major brunt of TB.<sup>3</sup> Pyrazinamide is one of the first line anti tuberculosis drug.<sup>4</sup> Liver toxicity due to

pyrazinamide is being reported worldwide.<sup>5</sup> First line anti TB drugs i.e, Isoniazid and Rifampicin show hepatotoxicity but the liver toxicity caused by pyrazinamide is more commonly reported.<sup>6</sup> The exact mechanism of pyrazinamide induced hepatotoxicity is unknown.<sup>7</sup> Drug induced hepatotoxicity (DIH) clinically manifests by raised liver function tests (LFTs).<sup>8</sup> *Cichorium intybus* has been commonly used in Asia and China to improve the liver function.<sup>9</sup> It is an erect perennial plant commonly known as chichory and kasni.<sup>10</sup> *Cichorium Intybus* inhibits free radical mediated injury which accounts for its hepatoprotective effect.<sup>11</sup> Aqueous extract of *Cichorium intybus* roots has hepatoprotective,<sup>12, 13</sup> anti-hyperglycemic,<sup>14</sup> antiinflammatory,<sup>15</sup> antimicrobial,<sup>16</sup> antidyslipidemic,<sup>17</sup> neuroprotective,<sup>18</sup> immunomodulatory<sup>19</sup> and gastroprotective effects.<sup>20</sup>

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The rationale of the present research was to provide cheap and easily available hepatoprotective drug to general population. Our study was intended to explore the hepatoprotective activity of aqueous extract of *Cichorium intybus* roots in pyrazinamide induced hepatotoxicity in male mice.

## Materials and Methods

Experimental randomized control study was conducted at Pharmacology department, Islamic International Medical College (IIMC) in collaboration with Riphah Institute of Pharmaceutical Sciences (RIPS) and animal house of National Institute of Health (NIH), Islamabad from 14th March, 2015 to 14th March, 2016. Research proposal was approved from Institutional Review Committee. A total of fifty six healthy male albino Balb/C mice weighing 30-50g and aged of 8 weeks, having normal ALT were included in study. Mice having weight less than 30 g, age less than 8 weeks and female mice were excluded from the study. Mice were kept under room temperature of  $22 \pm 2$  degree Celsius and 12 hour light dull cycle for 1 week. The mice were randomly divided into four groups each containing 14 mice (n=14). Group A, control group was given normal diet and tap water. Group B, drug treated group was given pyrazinamide in dose of 500mg/kg<sup>21</sup> Group C was given aqueous extract of *Chichorium intybus* roots in dose of 200mg/kg<sup>22</sup> and Group D was given aqueous extract of *Chichorium intybus* roots in dose of 400mg/kg<sup>22</sup> along with pyrazinamide.

The roots of *Chichorium intybus* were collected from National Institute of Research and Agriculture and was identified by Herbarium department, Quaid-e-Azam University, Islamabad. The fine powder was obtained from the dried roots. After boiling this powder in water for 2 hours, aqueous concentrate was obtained, which is then passed through Whatman No.1 filter paper. Finally the concentrate was formed with a vacuum rotary evaporator and freeze-dried.<sup>23</sup> On day 0, baseline blood samples were taken from 2 mice belonging to each group. To evaluate the progress of study, samples of 2 mice from each group were taken on day 15. On day 30, blood samples from 10 mice of each group were collected. All the sampling was through cardiac puncture by using 3cc syringe. Samples were allowed to clot. Serum was separated by Bench top machine after centrifugation at 3000 rev/min for 5 minutes.<sup>24</sup>

Serum was separated in sterile tubes and serum ALT was estimated by using ALT kit (Merck) on Chemistry Analyzer, Micro lab 200 (Merck). This parametric data was statistically analyzed by using SPSS 20. Mean and standard error of mean was calculated for all the four groups and post-hoc test was done for comparison between the different groups. Results were considered significant at p value less than 0.05 (p<0.05).

## Results

There is significant increase (p<0.001) in serum ALT levels in mice of drug treated group (B) as compared to control group (A) due to pyrazinamide. The levels were significantly reduced in group D who received high dose of *Chichorium intybus* as compared to the group C who received low dose of *Chichorium intybus*. The results are summarized in the following table.

**Table I: Mean  $\pm$  SEM Values of ALT in All Groups**

Groups (n=10)	ALT (5-50 U/L)
Group A	24.50 $\pm$ 9.30
Group B	143.50 $\pm$ 51.866
Group C	86.50 $\pm$ 37.616
Group D	59.90 $\pm$ 34.323
p-value	< 0.001*

\* = Significant

ALT=Alanine Aminotransferase

**Table II: Post-Hoc Comparison of ALT Between the Groups**

Group Comparison	ALT (50-150 U/L)	
	Mean difference	p-value
Group A vs. Group B	- 119.0	0.000*
Group A vs. Group C	- 62.0	0.003*
Group A vs. Group D	- 35.4	0.154
Group B vs. Group C	57.0	0.007*
Group B vs. Group D	83.6	0.001*
Group C vs. Group D	26.6	0.379

\* = Significant

ALT=Alanine Aminotransferase

## Discussion

Many drugs adversely affect the liver function with their hepatotoxic effects.<sup>25</sup> Globally the drugs used for the treatment of tuberculosis are the sole largest cause of acute hepatic failure.<sup>26</sup> Amongst the drugs which are used as first line therapy for tuberculosis, incidence of liver toxicity is highest with pyrazinamide.<sup>27</sup> The fact that pyrazinamide or its metabolites produce toxic effects in liver is still not known.<sup>28</sup> *Chichorium intybus* roots have shown its hepatoprotective role in acute liver toxicity caused

by drugs.<sup>29</sup> The free radicle scavenging property of *Chichorium intybus* roots is proposed to be due to its inulin constituent.<sup>10</sup> Estimation of ALT is done based on its high sensitivity and specificity for the evaluation of hepatic functioning.<sup>30</sup> To evaluate the hepatoprotective effect of aqueous extract of *Chichorium intybus* roots, our study was conducted with sample size of 56 mice which were divided through random selection in four groups (n=14). Group A (control), group B (drug treated group), group C and D (experimental groups). Significant rise in serum ALT levels were seen in group B who were given pyrazinamide while reduction in serum ALT levels was observed in group C and D which were given *Chichorium intybus* along with pyrazinamide. Our results were in accordance with Li and his colleagues who observed hepatoprotective effect of *Chichorium intybus* on carbontetrachloride (CCL<sub>4</sub>) induced hepatotoxicity in rats by measuring serum ALT and ALP levels.<sup>9</sup> Chen also observed decrease in liver enzymes of mice after treatment with *Chichorium intybus* in tert-butyl hydroperoxide (t-BHP) induced hepatotoxicity.<sup>31</sup> El-Sayed observed antioxidant effect of chichory in CCL<sub>4</sub> induced hepatotoxicity in rats.<sup>32</sup> Study by Atta revealed beneficial hepatoprotective effect of *Chichorium intybus* when used in combination with Zingiber officinale.<sup>33</sup>

## Conclusion

Aqueous extract of *Chichorium intybus* roots has beneficial hepatoprotective potential both in low and high doses in pyrazinamide induced hepatotoxicity in male mice.

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## ORIGINAL ARTICLE

# Comparison of Direct Smear and Cell Block Preparation for the Evaluation of Thyroid Epithelial Lesions on Fine Needle Aspiration

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## ABSTRACT

**Objective:** To determine the effectiveness of cell block technique by comparing cytomorphological features on cell blocks and conventional fine needle aspiration smears and to assess the utility of combined approach for cytodiagnosis.

**Study Design:** Cross sectional study.

**Place and Duration of Study:** Pathology Department of Pakistan Railway Hospital Rawalpindi and Pakistan Institute of Medical Sciences from April 2017 to April 2018.

**Materials and Methods:** Sixty cases were included in the study through non- probability convenient sampling. All patients having palpable solitary or dominant thyroid nodules were included in the study. In addition to the routine cytological smears, cell blocks were prepared from the residual aspirates and cytomorphological criteria like cellularity, obscuring background material, morphological and architectural preservation were compared. Data was analyzed using SPSS software version 21. Wilcoxon signed rank test was used for significant difference.  $P$  value  $\leq 0.05$  was considered significant.

**Results:** Male to Female ratio was 1:6.5 (13%: 87%). Age ranged from 22 to 81 years with mean age of 44.9 and standard deviation of  $\pm 14.5$  years.

According to the Mair et al scoring system, the mean values for the cellularity and morphological preservation parameters of the cell block technique were 0.86 and 1.13, while that of the cytological smears were 0.95 and 0.86 simultaneously. And the mean values for the obscuring background material and architectural preservation of the cell block technique were 1.13 and 0.82 and that of the cytological smears were 0.86 and 0.54 simultaneously.

**Conclusion:** Cell block technique was found effective in decreasing obscuring background material and in preserving architectural preservation. Hence, this technique facilitated in the diagnosis when reviewed along with the cytological smears.

**Key Words:** FNAC, Cell Block, Mair et al criteria, Cytopathology.

## Introduction

Thyroid swellings are a common clinical presentation in our setup especially in endemic areas.<sup>1</sup> The prevalence of these thyroid nodules ranges from 4% to 7% in adult population and 0.2% to 1.2% in children.<sup>2</sup> The incidence of malignancy in the clinically solitary nodules is 14% compared to 10% for

the dominant nodules and the chances of malignancy in a cold solitary thyroid nodule is 15-20 %.<sup>3</sup>

Since imaging modalities cannot differentiate benign from malignant nodules; fine needle aspiration cytology becomes a valid procedure for the evaluation of these lesions.<sup>2</sup> FNAC is a rapid, simple and safe office procedure to evaluate thyroid nodules. It is the most accurate and cost-effective screening test. Its diagnostic accuracy is 94-96 % from different studies.<sup>4</sup> However this technique has its limitations i.e. limited availability of material for adjuvant diagnostic investigation and also there may be paucity of representative cells, overcrowding of cells, air drying artifacts or poor cellular architecture preservation.<sup>5</sup>

Cell block (CB) preparation has been resorted to make best use of the available material and to

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improve cellular yield and increase diagnostic accuracy.<sup>6</sup> These are micro biopsies prepared from residual tissue fluids and FNA, processed, embedded, sectioned and stained. Simultaneous use of both techniques increases the diagnostic accuracy up to 98.33%.<sup>7</sup> The main advantage of cell block is that it preserves cellular architecture which closely resembles that of surgical specimen on microscopy. Other benefits are that it provides several sections of the same material for special staining, immunocytochemistry, ultrastructural analysis and molecular testing.<sup>8</sup> However, cell block technique has some limitations such as sparse cellularity, distortion artifacts, increased cost and increased processing time.<sup>7</sup> Studies have shown that use of cell blocks has been increasingly advocated as they provide better architectural information and allow additional investigations which complement FNA smears, but its use is limited in thyroid lesions in our setup. The objective of our study is to determine the effectiveness of cell block technique by comparing cytomorphological features on cell blocks and conventional fine needle aspiration smears.

### Materials and Methods

A cross sectional study was carried out at Pathology Department of Pakistan Railway Hospital Rawalpindi and Pakistan Institute of Medical Sciences from April 2017 to April 2018. A total of sixty cases were included in the study. Non-Probability convenient sampling method was used. Approval for the study was taken from the Ethical Approval committee. The study included patients from all ages and from both genders that have palpable solitary or dominant thyroid nodules. Patients not willing for fine needle aspiration cytology of their thyroid lesions, after explaining the purpose and utility of the procedure were excluded.

Patients having thyroid lumps were referred from Surgical outpatient department to the Pathology department with a pre requisite FNAC form. Bio demographic data was collected on a data collection form. Verbal informed consent was taken from each patient.

A standard procedure of fine needle aspiration was followed and a 22-23 gauge needle with 5 ml syringe attached was used to aspirate. Minimum of two needle passes were made. First cytological smears were made and stained with hematoxylin & eosin

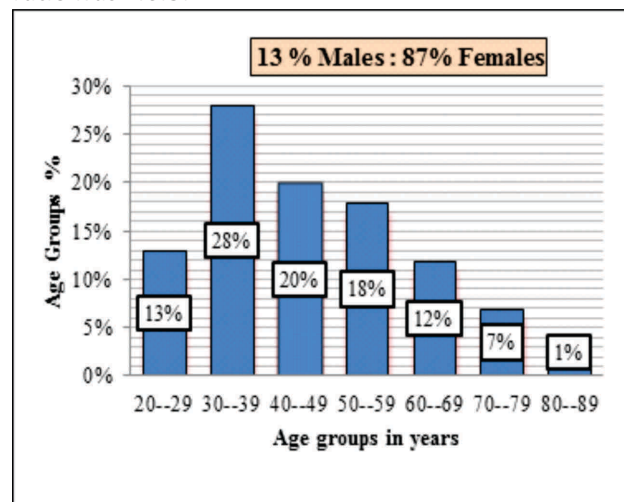
stain according to the standard procedure. Cell blocks were either made from an additional pass and/or remnant aspirate in the needle hub and syringe. Needle rinses in alcohol formalin fixative (50% of 95% ethyl alcohol and 10% formalin each) and then was centrifuged at 1500 rpm for 3-4 minutes. The supernatant was discarded and further 3 ml of fresh fixative added and kept for one day. The cell button was scooped out and processed as a routine surgical specimen and stained with hematoxylin and eosin stain. Both smears and blocks were reviewed by two consultant histopathologists independently.

Qualitative assessment of both slides was graded according to the Mair et al criteria<sup>9</sup> i.e. cellularity, obscuring background material, degree of cellular degeneration and architectural preservation. The data was analyzed by using SPSS version 21. Frequencies and percentages were calculated for the categorical variable data and mean and standard deviation for numerical data. Wilcoxon signed rank was used for test significant difference. P value  $\leq 0.05$  was considered significant.

### Results

The age range was from 22 to 81 years with mean age of 44.9 years and standard deviation of  $\pm 14.5$  years. The highest percentage of cases were in the third decade (28%) followed by the fourth decade (20%) of life. (Figure 1).

Majority of the cases were females, accounting for 87% (52/60) of total participants. The male to female ratio was 1:6.5.



**Fig 1: Bar Graph Showing Age Group Distribution (Percentages)**



The details of cytodiagnosis are given in Table I

**Table I: Frequency Table of Cytodiagnosis**

Cytodiagnosis	Frequency (%)
Unsatisfactory	4 (6.6%)
Colloid Cyst	8 (13.3%)
Colloid goiter	43 (71.6%)
Thyroiditis	3 (5%)
Malignant	2 (3.3%)
Total	60 (100%)

Four cases out of sixty showed no cellular material and were therefore not scored. Using Mair et al criteria, the cytomorphology of the two processing techniques was compared. The comprehensive cytomorphological details of both the processing techniques are given in the table II.

**Table II: Comparison of the Cytomorphological Parameters for both Cytological Smear and Cell Block (%)**

Mair et al Category	Cytological Smears	Cellblock
	Percentage (%) Frequency (n) /56	Percentage (%) Frequency (n)/56
CELLULARITY		
Minimal	35.7% (20)	37.5% (21)
Moderate	37.5% (21)	39.3% (22)
Abundant/Excellent	26.8% (15)	23.2% (13)
OBSCURING BACKGROUND MATERIAL		
Minimal	14.3% (8)	32.1% (18)
Moderate	57.1% (32)	48.2% (27)
Marked	28.6% (16)	19.6% (11)
DEGREE OF CELLULAR DEGENERATION		
Well preserved	75% (42)	58.9% (33)
Moderately preserved	19.6% (11)	30.4% (17)
Poorly preserved	5.4% (3)	10.7% (6)
ARCHITECTURE AND CELLULAR ARRANGEMENT		
Minimum	51.8% (29)	32.1% (18)
Moderate	42.8% (24)	53.6% (30)
Excellent/Marked	5.4% (3)	14.3% (8)

Descriptive statistics were calculated for both techniques using SPSS version 21, the details of which are given in the table.

**Table III: Comparison of Descriptive Statistics for Each of the Four Parameters of both the Techniques and the Statistical Significance of Difference**

	Conventional Smear		Cell Block		P value
	Mean	Standard Deviation	Mean	Standard Deviation	
Cellularity	0.95	± 0.793	0.86	± 0.777	0.699
Obscuring background	0.86	± 0.645	1.13	± 0.715	0.014
Cellular Degeneration	1.70	± 0.570	1.48	± 0.687	0.123
Architectural preservation	0.54	± 0.602	0.82	± 0.664	0.003
Total	1.01	± 0.65	1.07	± 0.710	0.21

No significant difference was found on cellularity and cellular degeneration, while significant difference was noted on obscuring background material and architectural preservation.

## Discussion

A total of 60 patients were recruited from the Pakistan Railway Hospital Rawalpindi and Pakistan Institute of Medical Sciences. The age of patients ranged from 22 to 81 years with mean of 44.9 years which is similar to the findings of Thanigaminai et al<sup>10</sup> and Revati et al.<sup>11</sup> This finding proves that thyroid lesions are present in wider age ranges. The majority of patients 28.3% were in their third decade of life followed by 20% of patients in their fourth decade. These findings are similar to Zariqa A. et al<sup>12</sup> and Basnet et al.<sup>13</sup> study results which show that majority of patients were in their third decade of life. The male to female ratio was 1:6.5, which is in correspondence to Chowhan et al.,<sup>14</sup> and Song et al.,<sup>15</sup> studies.

In our study 6.6% of the cases were reported as unsatisfactory for the cytodiagnosis. Majority of the studies show that the unsatisfactory rate ranges from 5 to 20%. 72% of cases were reported as benign, which is similar to the findings of Shipra A et al<sup>16</sup> study. Three cases were reported as chronic thyroiditis, two cases were malignant (anaplastic carcinoma). This findings is similar to Zariqa A. et al<sup>17</sup> study, which show 2.13% are malignant. The mean value of Mair et al., scores for the cellularity parameter was lower for the cell block technique (0.86) than that of the cytological smears (0.95). This finding agrees with the findings of Sanchez N. et al.,<sup>18</sup>

Raafat A Hegazy et al.,<sup>19</sup> and Michelle H et al.,<sup>20</sup> studies and contrary to the findings of Basnet et al.<sup>11</sup> and Thanigaimani et al.<sup>10</sup> studies. The reason of this low cellularity is that most of the times no special passes were done for the cell block, instead, the remnant in the needle hub was fixed in alcohol formalin fixative and then removed for tissue processing.

The mean value of Mair et al scores for the obscuring background material parameter was better for the cell block technique (1.13) than that of the cytological smears (0.86). This finding is similar to the findings of Raafat A et al.,<sup>19</sup> and Nithyananda et al.<sup>21</sup> studies. The reason for this decrease obscuring background material is that the cell block technique requires dilution and centrifugation of the aspirated fluid that allow the follicular cells to settle down.

The mean value of Mair et al., scores for the morphological preservation parameter was lower for the cell block technique (1.48) than that of the cytological smears (1.70). This finding is similar to the findings of Khan. S et al.,<sup>22</sup> and contrary to the Nithyananda. A et al.,<sup>21</sup> study results. The reason for this decrease morphological preservation can be pre-fixation lag time.

The mean value of Mair et al., scores for the architectural preservation parameter was higher for the cell block technique (1.0) than that of the cytological smears (0.54). This finding agrees with Basnet et al.,<sup>13</sup> and Shenaz K. et al.,<sup>18</sup> which conclude that cell block preserves better architecture pattern . Cell block also provide additional information in most cases which is similar to the studies of Rajib et al.,<sup>20</sup> and Katherine et al.<sup>23</sup>

## Conclusion

In our study, the cell block technique was found effective in decreasing obscuring background material and in preserving architectural preservation. Hence this technique facilitated in the diagnosis when reviewed along with the cytological smears.

## Limitations and Recommendations

Patients were recruited from two centers; a multicenter study should be carried out with increased sample size. A Prospective study can be carried out, comparing direct smear and cell block with histopathology as gold standard in thyroid lesions.

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## ORIGINAL ARTICLE

**Maitland's Mobilization versus Mulligan's Mobilization Technique to Treat Anterior / Posterior Innominate Dysfunctions**Shakeel Ahmad<sup>1</sup>, Shazia Ijaz<sup>2</sup>, Thamer Altaim<sup>3</sup>, Sadaf Shafique<sup>4</sup>**ABSTRACT**

**Objective:** The objective of the study was to compare the efficacy of Maitland's mobilization Technique with Mulligan's mobilization Technique to treat Anterior & posterior Innominate Dysfunctions.

**Study Design:** It was a Randomized Controlled Trial (RCT).

**Place and Duration of Study:** The study was conducted in Women Institute of Rehabilitation Sciences (WIRS) Abbottabad from July 15, 2016 to January 10, 2017.

**Materials and Methods:** Total 48 patients with sacroiliac joint (SIJ) dysfunction of both genders, from 20-60 years were placed into two groups. Patients with sacroiliac joint dysfunction and mechanical low back pain and having 3 out of 5 tests (Distraction test, Compression test, thigh thrust test, Gaenslen's Test and Sacral thrust test) positive for sacroiliac joint were included in the study. The study participants were divided into two groups, Group A received Maitland's Mobilization treatment while group B were treated with Mulligan's Mobilization technique. Three sets of 10 repetitions for each session, 3 sessions per week for 4 weeks were given to both the groups. Pain, disability and lumbar Range of motion (ROM) was assessed before and after treatment through Numeric Pain Rating Scale (NPRS), Modified Oswestry Disability Index (MODI) and Goniometry respectively. SPSS 20.00 was used for data analysis.

**Results:** At the completion of 4 weeks, patients in Group A who received treatment with Maitland's Mobilization technique showed slightly more ( $6.181 \pm 0.732$  to  $1.09 \pm 1.108$ ) reduction in pain, greater improvement in Modified Oswestry disability index ( $48.77 \pm 14.48$  to  $10.59 \pm 4.90$ ), increase in Lumbar Flexion ( $43.409 \pm 6.737$  to  $52.63 \pm 4.44$ ), and improvement in Lumbar side bending ( $12.40 \pm 4.82$  to  $18.54 \pm 3.93$ ,  $14.5 \pm 2.85$  to  $21.90 \pm 3.04$ ), increase in Lumbar Rotation ( Rt. Rotation:  $13.54 \pm 4.055$  to  $21.6 \pm 3.67$  , Lt. Rotation:  $14.27 \pm 3.50$  to  $20.22 \pm 4.04$  ) than group B. Analysis of pre and post treatment for Lumbar extension revealed that Group B had more improvement ( $16.76 \pm 4.194$  to  $21.76 \pm 2.50$ ) as compared to group A. Statistically there was no significant difference between two treatment regimens in the management of pain, to increase ROM, decrease functional disability in patients suffering with anterior and posterior innominate dysfunctions.

**Conclusion:** It is concluded that both the treatments are equally effective in decreasing pain, disability and increasing range of motion in patients with anterior and posterior innominate dysfunctions.

**Key Words:** Anterior Innominate, Mulligan's Mobilization, Maitland's Mobilization, Posterior Innominate, Sacroiliac joint dysfunctions.

**Introduction**

Sacroiliac joint dysfunction (SIJD) refers to any state that alter the range of movements of the sacroiliac

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joint either unilaterally or bilaterally that leads to changes in the structural connection between the ilium and the sacrum.<sup>1</sup> Till date, debates continuous to exist over the relationship between the presence of SIJD and the development of new episode of low back pain (LBP).<sup>2</sup> LBP is considered one of the health conditions that have a huge economic burden. For instance, Dagenais et al.<sup>3</sup> Conducted a systematic review that examined direct and indirect cost of LBP in different countries. The systematic review suggested that direct costs (healthcare services) in Switzerland were estimated at €2.6 billion. Indirect costs (productivity losses) reached to more than €4.1 billion. The systematic review suggested that

movement limitations due to LBP represented more than two-third of the overall economic burden of LBP. Approximately 70% of people will experience at least one incidence of LBP in their life at any point and high percentage of people who suffer from LBP due to SIJD will seek medical attention.<sup>4</sup> There are many treatment options for SIJD such as physical therapy, manipulation, laser and chiropractic.<sup>5</sup>

Physical therapy approaches helps in correcting sacroiliac joint dysfunctions manually by restoring the normal balance between muscles of lumbar spine and pelvic. This can be achieved using manual mobilization techniques such as Maitland and Mulligan's mobilization techniques, which are routinely used for SIJD.<sup>6,7</sup>

Despite the huge number of researches conducted to examine the effect of various manual therapy techniques in the treatment of SIJD, there is an urgent need to compare between various treatments techniques to enable clinicians selects the best available option for patients. Hence the purpose of this study was to compare and determine the effect of Maitland's mobilization techniques and the Mulligan's mobilization technique in individuals with SIJD.

## Materials and Methods

This randomized controlled Trial (RCT) was conducted in the clinical setting of Women Institute of Rehabilitation Sciences (WIRS) from July 15, 2016 to January 10, 2017. Ethical approval was taken from Research Ethical Committee of Riphah College of Rehabilitation Sciences. The inclusion criteria was age range from 20 to 60, participants with clinical diagnosis of sacroiliac joint dysfunction and mechanical low back pain, both male and females (except females having any gynecological issue), pain and tenderness at SIJ, participants having 3 out of 5 tests positive for sacroiliac joint dysfunction (Distraction test, Compression test, Posterior shear or thigh thrust test, Pelvic torsion test/ Gaenslen's Test and Sacral thrust test). Participants below 18 and above 60 years, those suffering from ankylosing spondylitis, vertebral fracture and nerve root irritation, inflammatory diseases of vertebral column, any systemic disease, and neoplasm, pregnancy, and bone tumors were excluded. Total 48 patients were screened as per inclusion criteria and randomly allocated to groups through lottery

method in to group A and group B. Group A received treatment with Maitland's mobilization technique in lying position and Group B received treatment with Mulligan's mobilization technique lying in prone position. Three sets of 10 repetitions for each session, 3 sessions per week for 4 weeks for both groups. Intensity of treatment increased as patient's tolerance level increased. Both groups received hot packs for 15 minutes prior to application of respective technique. Data was recorded at base line and after treatment by structured questionnaire which included demographics detail, duration of pain, radiation of pain, previous treatment or physiotherapy, investigations, pain radiation side or side involvement e.g. right/ left or bilateral. Modified Oswestry Disability Index, Numeric Pain Rating Scale and Goniometer were used as assessment tool for functional disability, pain and range of motion respectively. The data was analyzed by SPSS version 20 to draw the descriptive and statistical results. Mann-Whitney U test was applied for between the analyses of NPRS and MODI readings of both the groups and clinical results were made by subtracting the pre mean from post mean values of variables of respective groups.

## Results

Total 48 patients met the inclusion criteria, 24 patients in Group A and 24 in Group B. Two patients from group A and 3 patients from group B were dropped because they were not willing to continue their sessions due to personal issues. Twenty two patients in group A and 21 in group B were analyzed for further study. Demographics variables like age and gender are reported in Table-I.

**Table I: Participants' Demographic Data (N=43)**

Demographics	Group A Maitland's Mobilization	Group B Mulligan's Mobilization
Male	8	5
Female	14	16
Age(years) Means±SD	39.45 ± 9.44	35.66 ± 7.05

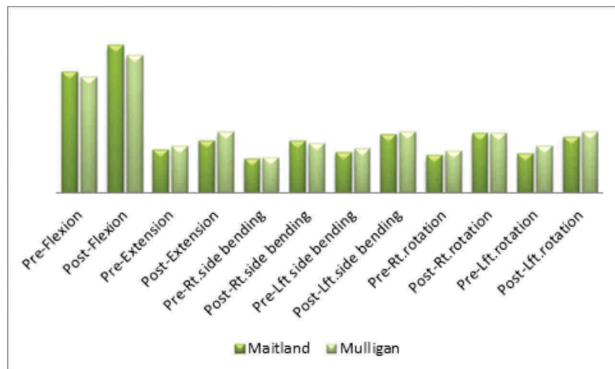
Within the group difference showed significant results but when across the group analysis was done, Group A showed slightly more ( $6.181 \pm 0.732$  to  $1.09 \pm 1.108$ ) reduction in pain than Group B Participants ( $6.047 \pm 0.804$  to  $1.61 \pm 1.160$ ). Statistically there was no significant difference ( $p=0.51$ ) between two

treatment protocols, both were equally effective in reducing pain as shown in Table II. The pre and post treatment interventional analysis showed that participants in group A showed greater improvement in modified Oswestry disability index ( $48.77 \pm 14.48$  to  $10.59 \pm 4.90$ ) as compared to Group B ( $45.523 \pm 14.225$  to  $8.85 \pm 3.66$ ), while there was no significant difference in both treatment regimens. Both were equally effective ( $p=0.27$ ) for lowering the level of disability as shown in Table II.

**Table II: Pre and Post Values of NPRS and MODI of both the Groups**

Study Variables	Group	Pre	Post	P value
NPRS Mean $\pm$ SD	Group A	6.18 $\pm$ 0.73	1.09 $\pm$ 1.108	0.51
	Group B	6.04 $\pm$ 0.80	1.61 $\pm$ 1.160	
MODI Mean $\pm$ SD	Group A	48.77 $\pm$ 14.48	10.59 $\pm$ 4.90	0.27
	Group B	45.52 $\pm$ 14.22	8.85 $\pm$ 3.66	

With regards to pain and disability, Lumbar ROM also showed within group improvement but on comparing the two treatment regimen there was no significant improvement as shown in Fig 1.



**Fig 1: Lumbar ROM pre and post values of both treatment Groups.**

## Discussion

The purpose of this study was to compare the efficacy of Maitland's mobilization and Mulligan's mobilization for the treatment of anterior and posterior innominate dysfunction.

In the current study both Maitland's mobilization and Mulligan's Mobilization techniques have been used as an intervention for 4 weeks treatment regime to treat the patients with sacroiliac joint dysfunction. Generally results showed that participants in both the groups improved markedly. NPRS and MODI scores decreased while Lumbar ROM increases in both treatment groups.

Furthermore, after the completion of 4 weeks of manual therapy sessions, it was found that clinically Maitland's mobilization was more effective in reducing pain, functional disability, lumbar flexion, side bending and rotation while Mulligan's mobilization was found to be more effective in increasing lumbar extension but statistically no significant difference was found hence both Maitland's and Mulligan's mobilization were equally effective in treatment of sacroiliac joint dysfunctions.

A study by Kenkamph et al., showed that Sacroiliac joint mobilization increases the lumbar range of motion and decreases the pain in patients of mechanical low back pain associated with sacroiliac joint dysfunction<sup>7</sup> and Kaushik Guha stated that Maitland's Mobilization was an effective treatment for increasing spinal flexibility, decreasing pain and disability in patients of sacroiliac joint dysfunction.<sup>8</sup> Both these studies favor the finding of this study.

Post treatment score of numeric pain rating scale of this study revealed that both Maitland's mobilization and Mulligan's mobilization were equally effective in reducing pain intensity and the results of this study are supported by the study carried out by Fernandes S.<sup>9</sup>

McCollam et al., in their study found that both Maitland and Mulligan's mobilization techniques were effective in increasing lumbar flexion and extension and similar results were reported in our study.<sup>10</sup>

The results of current study revealed that post treatment range of lumbar side bending and rotation for both groups showed that Maitland's mobilization and Mulligan's mobilizations techniques were equally effective in increasing lumbar spine ROM. Samir et al<sup>11</sup> in their study found that there was no difference in both treatment protocols and concluded that both the treatment techniques were equally effective in improving lumbar ROM and pain in patients of chronic low back pain however a study by Javaherian et al.<sup>12</sup> Compared the immediate effects of Maitland's mobilization and Mulligan's mobilization techniques on lumbar flexion and extension ROM and found that SNAGS improved flexion ROM while Maitland mobilization increased extension more. These results are consistent with the findings of this current study.

In a study Gautam et al compared the effects of Maitland's mobilization with Mulligan's mobilization in neck pain and they concluded that both the mobilization techniques were equally effective in reducing disability.<sup>13</sup> In the current study score of Modified Oswestry Disability Index for both groups after treatment showed that Maitland's mobilization and Mulligan's mobilization were equally effective in reducing disability.

A study by Khan S et al.,<sup>14</sup> suggested that both techniques SNAG and Maitland's mobilization improved the ROM, decreases the pain and disability of chronic low back pain. Based on these results SNAG and exercise should be the treatment of choice for chronic low back pain rather than Maitland's with exercise. These results are consistent with the findings of this current study.

Another study of Ganesh et al.,<sup>15</sup> in which they compared the Maitland's mobilization and Mulligan's mobilization in mechanical neck pain and found non-significant results and concluded that both techniques were equally effective in treating neck pain no one is superior to another. A study by Khan, et al., was conducted to compare the effects of Maitland's and Mulligan's mobilizations techniques in treating cervicogenic headache, concluded that both the techniques were effective in reducing pain and disability.<sup>16</sup>

## Conclusion

It is concluded that both the Maitland's mobilization and Mulligan's mobilization treatment techniques were equally effective in decreasing pain, disability and increasing range of motion in patients with anterior and posterior innominate dysfunctions.

## Limitations of Study

This study was conducted in a single setting with limited sample size due to non-availability of patients. Lumbar ROM was measured by Goniometer as Inclinator was not available. There was no literature found providing the standard treatment force and time of sacroiliac joint mobilization for increasing lumbar flexibility. Pain pressure threshold for sacroiliac joint dysfunction was not measured due to non-availability of algometer.

## Recommendations

Future studies on sacroiliac joint dysfunction should be conducted on larger scale and sample size and

ultimately will enhance the generalizability of results. Longitudinal cohort study design will be of great value as it provides more information about long-term effects of these interventions. Force and time of sacroiliac joint mobilization should be studied on the same population for more accurate findings.

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## ORIGINAL ARTICLE

# Immunomodulatory Effect of Betulinic Acid in Ovalbumin Induced Airway Inflammation in Male Mice

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## ABSTRACT

**Objective:** To compare the effects of Betulinic Acid and Dexamethasone on proinflammatory markers in ovalbumin induced airway inflammation in male mice.

**Study Design:** Experimental Randomized Control trial.

**Place and Duration of study:** This study was conducted in Pharmacology department at Islamic International Medical College, Rawalpindi, in collaboration with National Institute of Health (NIH), Islamabad over a period of one year from May 2017 to April 2018.

**Materials and Methods:** Forty (n=40) healthy BALB/c mice weighing between 30-50 grams were recruited in this study. They were divided into four groups, each group comprising of 10 healthy mice. Group I (Normal control), Group II (Asthmatic control), Group III (Ovalbumin + Betulinic Acid) and Group IV (Ovalbumin + Dexamethasone). Group I was kept under normal conditions for 10 days without giving medications. Asthma was induced in group II by sensitizing mice at day 0 by intraperitoneal injection of Ovalbumin 10µg and then challenged intranasally for one week. In-group III and IV same method was used for asthma induction. In-group III, Betulinic Acid was given orally at a dose of 5mg/kg for next 7 days. In-group IV Dexamethasone was given orally at a dose of 0.5-2.0 mg/kg for next 7 days.

IL-13, IL-18, TLC and DLC were estimated in all groups and compared after one week. The data was entered and analyzed using SPSS 22.0 (Statistical Package for Social Sciences). All data was shown as Mean ± S.E.M. One way ANOVA was applied to observe group mean differences. For the comparison of mean difference between groups, Post Hoc Tuckey test was applied. A p-value of ≤0.05 was considered as statistically significant.

**Results:** Our result showed a major ( $P < 0.001$ ) raise in proinflammatory markers in Asthmatic Control group as compared with Normal Control group. Treatment with Betulinic Acid and Dexamethasone considerably ( $P < 0.001$ ) reduced proinflammatory markers as compared with Asthmatic Control group respectively

**Conclusion:** Betulinic acid lowers pro-inflammatory mediators as compared to Dexamethasone in ovalbumin induced airway inflammation in mice.

**Key Words:** Asthma, Betulinic Acid, 1L-13, 1L-18.

## Introduction

Asthma is an allergic disease of the lungs associated with airway inflammation on and hyper responsiveness to broncho constricting agents. The cross-linking of high-affinity surface-bound IgE

receptors on mast cells initially drives the pathophysiology, which results in degranulation of mast cells and of inflammatory mediators like histamine. The pathogenesis of asthma reflects, in part, the activity of T cell cytokines. Murine models support participation of interleukin-13 (IL 13) and the IL 13 receptor in asthma. IL 18, a member of the Interleukin 1 (IL-1) family, a pro-inflammatory cytokine is known to play an important role in Th1/Tc1 polarization, but it also promotes Th2 cytokine (e.g. IL-4, IL-5, IL-9, and IL-13) production from T cells, NK cells, basophils, and mast cells.<sup>1,2</sup>

The prevalence of asthma showed variations globally with higher rates typically seen in developed and affluent societies. According to data collected by Global Initiative for Asthma (GINA), the estimated number of people affected with asthma was 300

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million worldwide and it is anticipated that this number would increase to 400 million by 2025, which is an alarming situation.<sup>3</sup>

According to the data shared by the Global Initiative for Asthma (GINA), prevalence of asthma in Pakistan is 4-5%.<sup>4,5</sup> Around 20 million of Pakistan's adult population is suffering from asthma. With an annual increase of 5%, the prevalence of asthma is increasing on a daily basis. Chronic Respiratory Diseases like asthma is among the non-communicable diseases, which are estimated to lead to over 36% to total deaths in Pakistan.<sup>6</sup> At present asthma cannot be restored totally and just be controlled and coped with the goal that patient can carry on with a usual routine life by avoiding potential risk and being vigilant about the sickness.<sup>7</sup>

According to the national and international guidelines on asthma management of adults and children, the inhaled corticosteroids (ICS) are the most operative and active medications, which may be used alone or associated with other controller therapies, in a stepwise, control-based approach. Although the most endorsed therapy based on inhaled corticosteroids may fail to reach control in more than one third of patients, especially adults and in these lung function and quality of life may gradually deteriorate leading to morbidity and eventually mortality. Novel biologic medications have been tried with patients of asthma which at first appear to guarantee in diminishing annual exacerbation rates and steroid use in glucocorticoid-dependent cases, yet when it comes to the long term management, there is still a room for discovery of such compounds which offer more benefits with less side effects.<sup>8</sup> Betulinic acid (BA) is a pentacyclitriterpene found in the stem bark of the plant white birch. BA and its derivatives have been subjected to intense research focusing on their anticancer properties, anti-HIV, anti-bacterial, anti-inflammatory, antimalarial, anti-helminthic, and other pharmaceutical activities.<sup>9</sup> As inflammation is the backbone of asthma, the focus of treatment must be a substance that tends to target the inflammation and its mediators. Betulinic acid is diverse in this aspect that it knocks out the inflammation and happens to reduce the pro inflammatory markers, thereby improving the disease condition of patient.<sup>10</sup>

Keeping in view the importance of IL-18 in terms of its association in airway inflammatory loop, we looked for the molecular aspect of IL-18 expression along with IL-13 when treated with BA. This uncovered area needs to be addressed. This experimental study was done to compare the effects of Betulinic Acid (BA) and Dexamethasone (Dex) on proinflammatory markers in ovalbumin (ova) induced airway inflammation in male mice.

## Materials and Methods

This randomized control trial was conducted at Pharmacology Department and Multidisciplinary research laboratory at Islamic International Medical College Trust (IIMCT), Rawalpindi with the collaboration of National Institute of Health (NIH), Islamabad. Before starting the study, a formal approval by the Ethics Review Committee of Islamic International Medical College, Riphah International University was taken. The duration of this study was 12 months (May 2017 to April 2018). A total of forty (n=40) healthy BALB/c male mice weighing 30-50 grams were recruited in this study. All the experimental mice were divided into four groups. Group I (Normal control), Group II (Asthmatic control), Group III (Ova + B A) and Group IV (Ova + Dex). Group I was kept under normal conditions for 10 days without giving medications. Asthma was induced in group II by sensitizing mice at day 0 by intraperitoneal injection of Ovalbumin 10µg and then challenged intranasally for one week. In-group III and IV same method was used for asthma induction. IL-13, IL-18 TLC and DLC were estimated in all groups and compared after one week. IL-13 and IL-18 were estimated by PCR technique in 10<sup>3</sup> copies/µL in all the groups. TLC and DLC were estimated by commercially available kits by Merck and 5 part Sysmex Automated Hematology Analyzer. The data was entered and analyzed using SPSS 22.0 (Statistical Package for Social Sciences). All data was shown as mean ± S.E.M. One way ANOVA was applied to observe group mean differences. A p-value of ≤ 0.05 was considered as statistically significant.

## Results

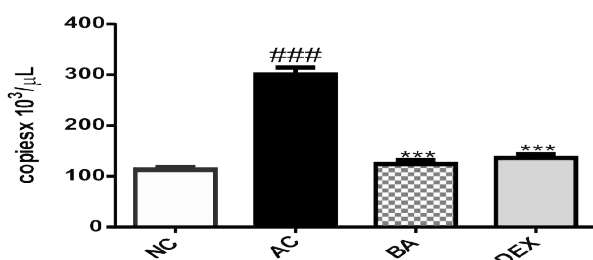
Our result showed a major (P < 0.001) raise in IL-13 and IL-18 in group II (Asthmatic Control) as compared with group I (Normal Control). Treatment with group III (Betulinic Acid) and Group IV (Dexamethasone)

considerably ( $P < 0.001$ ) reduced IL-13 and IL-18 levels as compared with Asthmatic Control i.e Group II, respectively. (Table I, II & figure 1, 2).

**Table I: Mean  $\pm$  SEM of IL-13 in All Four Groups**

Mean $\pm$ SEM	Group I NC	Group II AC	Group III BA	Group IV DEX
	113.3 $\pm$ 5.221	300.6 $\pm$ 13.93	124.3 $\pm$ 7.183	136.5 $\pm$ 7.042
P value	< 0.001			

#### IL-13



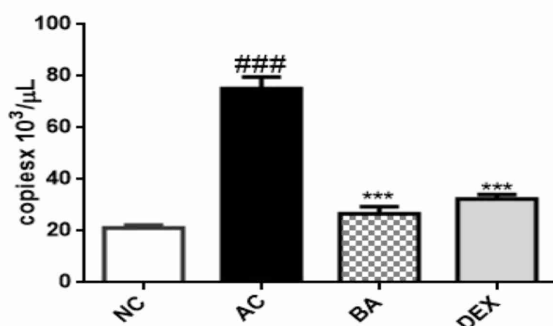
**Fig 1: Graphical Presentation of IL-13 in All Groups**

BA and DEX significantly decreased levels of IL-13 as compared with AC. Mean  $\pm$  SEM is shown to signify the data. ### denotes  $P$  value  $< 0.001$  when AC compared with NC whereas \*\*\* denotes  $P < 0.001$  when BA and DEX compared with AC.

**Table II: Mean  $\pm$  SEM of IL-18 in All Four Groups**

Mean $\pm$ SEM	Group I NC	Group II AC	Group III BA	Group IV DEX
	21.10 $\pm$ 1.170	75.16 $\pm$ 4.490	26.69 $\pm$ 2.648	32.40 $\pm$ 1.849
P value	< 0.001			

#### IL-18



**Fig 2: Graphical Presentation of IL-18 in All Groups**

Mean  $\pm$  SEM is shown to signify the data. ### denotes  $P$  value  $< 0.001$  when AC compared with NC whereas \*\*\* denotes  $P < 0.001$  when BA and DEX compared with AC.

## Discussion

The results of the present study confirm that the airway inflammation induced by ovalbumin, is ameliorated by the both experimental agents, yet the result of therapy with betulinic acid is very impressive, as compared to the traditional corticosteroids.

Several reports described the efficacy of oral (prednisone and prednisolone, methylprednisolone) and inhaled (triamcinolone, budesonide and fluticasone) corticosteroids in asthma management. The eosinopenic effect of corticosteroids helps in preventing the cytotoxic effect of the major basic proteins and other inflammatory mediators released from eosinophils. They prevent the increased airway reactivity associated with late bronchial reactions by blocking them.<sup>11</sup> BA is a recently discovered naturally occurring pentacyclic triterpenoid with anti-inflammatory and anticancer properties.<sup>12</sup> Current study results showed that BA can change the IL-13, IL-18, total and differential leukocytes counts when compared with the levels in mice sensitized with ovalbumin. BA reduced IL-13 levels comparable to the levels in normal controls (124.3 and 113.3  $\times 10^3$  copies/ $\mu\text{L}$  respectively). When compared to dexamethsone, IL-13 levels were slightly lower in BA group (136.5 and 124.3  $\times 10^3$  copies/ $\mu\text{L}$  respectively). BA also reduced IL-18 levels comparable to the levels in negative controls (26.69 and 21.10  $\times 10^3$  copies/ $\mu\text{L}$  respectively). When compared to dexamethsone, IL-18 levels were slightly lower in BA group (26.69 and 32.40  $\times 10^3$  copies/ $\mu\text{L}$  respectively). BA also reduced TLC comparable to the levels in negative controls (6417 and 6500  $\times 10^3 / \mu\text{L}$  respectively). When compared to dexamethsone, TLC levels were slightly lower in BA group (7033 and 6417  $\times 10^3 / \mu\text{L}$  respectively). BA also reduced mean eosinophils percent comparable to dexamethasone group (1.667% and 1.5% respectively). However, it did not reduce them to the levels in normal controls (0.833%). BA also reduced mean neutrophils percent comparable to dexamethasone group (19% and 22.17% respectively). However, it did not reduce them to the levels in negative controls (12.5%). BA also reduced mean lymphocytes percent comparable to normal control group (64.3% and 63.7% respectively). However, it did not reduce them



to the levels in dexamethasone group (55%). Several other studies reported less production of pro-inflammatory mediators in BA treated animals. In a recent study, Costa et al evaluated the effects of BA in a mouse model of endotoxic shock. They reported that pro-inflammatory mediators were produced in lesser amount by the macrophages obtained from mice treated with BA along with an increased production of IL-10 along with an increased production of IL-10 in comparison with non-stimulated macrophages from vehicle-treated mice.<sup>13</sup>

Authors concluded that BA has a powerful in vivo anti-inflammatory activity, which through a mechanism dependent on IL-10 protects the mice against LPS by modulating in vivo production of TNF- $\alpha$  by macrophages.<sup>13</sup>

In another study, authors determine the effects of oral administration of BA (50, 5, 0.5 mg/kg) five times at 24 hours intervals to red blood cells immunized (SRBC) and non-immunized mice. They found that, whatever the dose administered, five times administration of BA increased peripheral blood leukocyte count primarily by increasing the number of blood lymphocytes. While the administration of BA in a dose of 5 mg/kg administered 5 times at 24 hours intervals resulted in reduction of blood segmented neutrophils count on days 1 and 3 after drug administration.<sup>14</sup>

In another in-vitro study on human whole blood cell cultures highlighted that BA modulates the production of cytokine by Th1/Th2 cell subpopulations that results in enhancement of IL 10 formation and inhibits production of IFN- $\gamma$ , resulting in lower IFN- $\gamma$ /IL-10 ratio.<sup>15</sup>

Another study found the strongest immunomodulatory effect of BA with lowest investigated dose (0.5 mg/kg) when administered multiple times.<sup>16</sup>

## Conclusion

Betulinic acid has better anti-inflammatory effects in asthma induced by ovalbumin as compared to dexamethasone.

## Study Limitation

Study should also have involved the immunomodulatory effect of betulinic acid on other proinflammatory markers released in asthma but owing to the cost and availability issue, these

parameters could not be explored.

## Recommendation

- 1). Further research need to be directed on combined anti-inflammatory effect of corticosteroids and betulinic acid.
- 2). The comparison of betulinic acid with other antiasthmatic drugs should be studied.
- 3). The anti-inflammatory effect of other novel compounds by measuring levels of interleukin should also be explored.

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## ORIGINAL ARTICLE

**Glycated Hemoglobin: A Predictor of Cognitive Deficits in Type 1 Diabetes Patients**Amara Gul<sup>1</sup>, Memoona Sehar<sup>2</sup>**ABSTRACT**

**Objective:** To determine the association of Glycated Hemoglobin with frontal lobe cognitive dysfunction in type 1 diabetes patients.

**Study Design:** Case control study.

**Place and Duration of Study:** Bahawal Victoria Hospital, Bahawalpur, Pakistan from June 2016 until August 2017.

**Materials and Methods:** Fifty diabetic patients and fifty healthy adults were tested for fasting HbA<sub>1c</sub> levels. Following, they were administered Frontal assessment battery. Participants were given separate instructions for assessment of each frontal lobe function and they completed Frontal assessment battery in a single testing session. Data was analyzed for group differences on each frontal lobe function through ANOVA. Bivariate correlations were computed to assess the relationship between frontal lobe functions and HbA<sub>1c</sub>. Regression analysis was used to assess HbA<sub>1c</sub> as a predictor of frontal lobe cognitive functioning.

**Results:** Diabetic patients showed impaired performance on frontal lobe cognitive functions in contrast with healthy individuals. HbA<sub>1c</sub> and frontal lobe cognitive functions were negatively correlated. Deficient glycemic control was associated with frontal lobe cognitive deficits. HbA<sub>1c</sub> was found as a significant predictor of frontal lobe cognitive functioning.

**Conclusion:** Higher level of HbA<sub>1c</sub> is a predictor of frontal lobe cognitive functioning deficits in patients with Type 1 diabetes.

**Key Words:** *Cognition, Fasting Glucose, Glycemic Control, Glycemic Index, Type 1 Diabetes.*

**Introduction**

Diabetes Mellitus (DM) increases risk of cognitive decline.<sup>1</sup> Type 1 DM involves mental flexibility, visual perception and attention whereas Type 2 DM may cause memory deficits or reduced executive function.<sup>2</sup> Neurocognitive changes in Type 1 DM involve volume loss and atrophy of cerebral cortex.<sup>3,4</sup> Frontal lobes are involved in multiple cognitive processes i.e., executive functions, memory, attention, language etc. and constitute two-thirds of the human brain.<sup>5</sup> Temporal lobes have a role in memory and thinking processes and pathophysiology in this brain region leads to cognitive and neurodegenerative disorders.<sup>6</sup> Deficit in gray matter volume is also associated with higher glycated haemoglobin (HbA<sub>1c</sub>) levels.<sup>7,8</sup> DM

pathophysiology includes lesions of the subcortical white matter, cortical infarcts, density of neuritic plaques, hyperphosphorylated tau (i.e., group of neuronal microtubule-associated proteins) within axons, oxidative stress, and inflammation of nerve pathways.<sup>9,11</sup> Deregulation of major excitatory receptors of the central nervous system (i.e., glutamatergic receptors which control synaptic activity during learning and memory) accelerates cognitive deficits.<sup>12,13</sup> Cognitive impairments, brain aging and neurodegeneration are associated with molecular changes in protein kinases, second-messenger system and glutamate-receptors.<sup>14,15</sup> It was also found that DM prolongs peripheral as well as central conduction time (onset, peak latencies and velocity) in spinal cord structures. These changes are connected with demyelination along fibers needed to conduct nerve impulses through periphery and brain cortex.<sup>16,17</sup> Segmental demyelination, axonal degeneration and nerve loss involve peripheral nerves whereas velocities of sensory- motor nerve conduction are involved in deficits of the distal limbs.<sup>18,19</sup>

Previous research has shown that chronic hyperglycemia is associated with cognitive decline in

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non-demented elderly patients.<sup>20</sup> Increased glycated hemoglobin is associated with significant reduction in cognitive functioning in patients with diabetes.<sup>21</sup> This association has been observed in patients with metabolic syndromes and coronary heart disease.<sup>22</sup> High peaks of glucose over several years can even cause dementia.<sup>23</sup> To date, frontal lobe dysfunctions in relation with glycemic control have not been examined in Pakistani subjects. Given the brain structural and functional changes, it was hypothesized that diabetic patients would show weaker frontal lobe related functioning than healthy adults. Glycemic control as assessed through HbA<sub>1c</sub> would be associated with frontal lobe functioning and could therefore predict frontal lobe dysfunctions. HbA<sub>1c</sub> is an index of circulating glucose levels over 2-3 months. The objective of this study was to assess the association of glycated Hemoglobin with frontal lobe cognitive dysfunction in type 1 diabetic patients.

### Materials and Methods

This study had a case control design and was conducted at the endocrinology and diabetes department of Bahawal Victoria hospital Bahawalpur, Pakistan from June 2016 to August 2017. The study was ethically approved by The Islamia University of Bahawalpur and followed principles of Helsinki declaration. Purposive sampling was used. Fifty patients diagnosed with type 1 DM were included with criteria as (i) age range 35-55 years (ii) diagnosed with type 1 DM (iii) having no medication other than antidiabetics, whereas exclusion was done with reports of psychological disorder, neurological disorder, history of head trauma, cancer and diseases of the central nervous system. Fifty healthy demographically matched individuals took part in the study. Healthy individuals were included with age range 35-55 years and with no present use of any medication. The exclusion criterions were: (i) history /present complaints of diabetes. (ii) history/present illness of substance use, psychiatric disorder, neurological disorder, history of head trauma, cancer and diseases of the central nervous system.

All participants gave written informed consent. Participants had a fasting blood glucose test. Subsequently, they were administered Frontal Assessment Battery- F-A-B<sup>24</sup> to examine frontal lobe

functions. It is brief and easy to administer and has good psychometric properties. The total score consists of a cumulative score of six individual neuropsychological tasks (score range 0-18). In the "Similarities" (conceptualization) task, patient is required to indicate superordinate concept of objects from the same semantic category (score range 0-3 high score shows intact performance). Lexical verbal fluency (mental flexibility) examines semantic retrieval. Patient is required to say as many words as possible starting with S except nouns and surnames in 60 seconds (score range 0-3, more than nine correct responses=3). In motor series, patient executes a series of motor acts (score range=0-3; at least 6 consecutive series alone=3). Conflicting instructions assess self control by hitting the table one time fewer than the administrator hits. After the practice trial, patient has to follow an alternating numbered order (score 0-3, high score shows no error). Prehension behavior examines the activated behaviors. The administrator hints palms without uttering a word when subject placed their hands on knees. Subject is instructed not to take the administrator's hands. Doing so will be scored as three. Total score is cumulative of subscales of F-A-B which is 0 to 18; high score is intact cognition. SPSS (version 20) was used to analyze data. Descriptive statistics (mean, standard deviation and t-test) were used to analyze demographic and clinical characteristics of sample as shown in Table I. Interaction of group with subscales of F-A-B with factors as 6 F-A-B (within subject) x 2 Group (diabetic patients vs. healthy control subjects: between subject) was assessed using ANOVA. Bivariate correlations were computed to assess the relationship between Total FAB score, subscale scores and HbA<sub>1c</sub>. Regression analysis was conducted to assess HbA<sub>1c</sub> as predictor of FAB scores.

### Results

Results showed that the main effect of F-A-B  $F(1, 98) = 1.78, p = .11, \eta^2 = .01$  was non-significant whereas the main effect of Group was significant  $F(1, 98) = 1844.64, p = .001, \eta^2 = .95$ . The interaction between FAB and Group was significant  $F(1, 98) = 3.11, p = .01, \eta^2 = .03$ . Group differences on subscales are reported in Table II. Correlation between HbA<sub>1c</sub> and FAB scores on lexical verbal fluency  $(-.45, p = .001)$ , motor series  $(-.33, p = .01)$ , Go-NoGo  $(-.35, p = .01)$ ,

prehension behavior ( $-.36, p=.01$ ), and total FAB scores ( $-.81, p=.001$ ) were significant whereas correlations between glycemic control (blood glucose) and similarities ( $-.27, p=.055$ ), and conflicting instructions ( $-.16, p = .26$ ) were not significant. Regression analysis showed that HbA<sub>1c</sub> significantly predicted FAB total scores  $F(1, 49) = 95.99, p=.001, R^2 = .66, \beta = -.81, t = -9.79, p=.001$ . Odd ratio was 1.00,  $p < 0.001$ , 95%. Risk for cognitive deterioration was significantly different  $t(49) = 42.73, p = .001, M = 47.55, SD = 7.86$  between patients (50.34%) and healthy individuals (2.78%).

**Table I: Characteristics of Patients with Diabetes and Healthy Individuals**

	Diabetic Patients	Healthy Individuals		
	n	n		
	50	50		
Gender (Male/Female)	25/25	25/25		
	M $\pm$ SD	M $\pm$ SD	T	p
Age (Years)	46.36 $\pm$ 5.18	46.28 $\pm$ 5.43	t (49)=0.18	.85
Education (Years)	14.06 $\pm$ 1.49	14.28 $\pm$ 1.45	t (49)=0.67	.50
Duration of diabetes (Years)	2.00 $\pm$ 1.47	NA	-	-
HbA <sub>1c</sub> (%)	7.40 $\pm$ 0.60	5.2 $\pm$ 0.2	-	-
Glucose (mmol/l)	8.00 $\pm$ 0.70	5.1 $\pm$ 0.1		

Note. HbA<sub>1c</sub>= Glycated Hemoglobin (%)

**Table II: Group Differences on Subscale Scores of Frontal Assessment Battery (N= 100)**

	M $\pm$ SD	SE	Diabetic Patients Lower-upper bound	M $\pm$ SD	SE	Healthy controls Lower-upper bound
Similarities	1.58 $\pm$ .49	.05	1.49-1.69	2.90 $\pm$ .30	.05	2.78-3.01
Lexical verbal fluency	1.48 $\pm$ .50	.06	1.36-1.59	2.88 $\pm$ .32	.06	2.76-2.99
Motor series	1.60 $\pm$ .49	.05	1.48-1.71	2.92 $\pm$ .27	.05	2.80-3.03
Conflicting instructions	1.50 $\pm$ .50	.05	1.38-1.61	2.91 $\pm$ .26	.05	2.80-3.03
Go-Nogo	1.52 $\pm$ .50	.05	1.40-1.63	2.90 $\pm$ .27	.05	2.80-3.03
Prehension behavior	1.26 $\pm$ .44	.04	1.16-1.35	2.96 $\pm$ .19	.04	2.86-3.05

Note: Lower-Upper Bound Is Reported On 95% Confidence Interval

## Discussion

This study was designed to examine frontal lobe functions and glycemic control in Type 1 DM. Further objective was to determine whether any relationship

between these two variables exists in Type 1 DM. It was hypothesized that patients with Type 1 DM would show frontal lobe cognitive deficits and deficient glycemic control. In addition, impaired glycemic control was related with frontal lobe cognitive deficits. Neuropsychological measures of frontal-lobe-related functions were used to assess frontal lobe functions and glycemic control was assessed through HbA<sub>1c</sub>. There were few important findings: (i) Functioning of the frontal lobe was weaker in diabetics (ii) F-A-B subscales and glycemic control correlated (iii) glycemic control significantly predicted frontal lobe dysfunctions. Previous studies have illustrated that neurodegeneration in Alzheimer's disease and Diabetes is similar<sup>6-8</sup>, for instance lesions of the subcortical white matter, cortical infarcts, density of neuritic plaques, A $\beta$  plaques and NFTs-hyperphosphorylated tau within axons, oxidative stress, inflammation of pathways, deregulation of excitatory receptors in central nervous system, and long-term potentiation in hippocampus.<sup>9-11</sup> Furthermore, these changes extend to molecular changes in protein kinases, second-messenger systems, glutamate-receptors<sup>14,15</sup>, delay in nerve conduction times,<sup>16,17</sup> segmental demyelination and deficits of the distal limbs.<sup>18,19</sup> Results of this study are consistent with literature suggesting global cognitive deficits in type 1 diabetic patients<sup>2</sup> and neurocognitive changes in Type 1 DM such as reduced cerebral volumes and atrophy of frontal and temporal lobes<sup>3,4</sup>. Frontal lobes encompass two-thirds of the brain and are responsible for multiple cognitive processes<sup>6</sup> whereas temporal lobes are involved in memory and thinking processes. Degeneration in these brain areas are related with cognitive deficits.<sup>5</sup> The finding of the present study that glycemic control is associated with frontal lobe dysfunctions can be seen in the context of deficient gray matter volume and greater glycated hemoglobin as an index of reduced cognition in patients with DM.<sup>7,8,20,21</sup>

## Conclusion

Higher level of HbA<sub>1c</sub> is a predictor of frontal lobe cognitive functioning deficits in patients with Type 1 diabetes.

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## CASE REPORT

### Polypropylene Suture Loop as a Cause of Small Bowel Obstruction

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#### ABSTRACT

In this case report, we share our experience of complication with use of intra-abdominal polypropylene sutures. The patient presented with intestinal obstruction resulting from the herniation of small intestine through the polypropylene suture loop due to a knot placed on the uterine fundus around seven years prior during an uncomplicated low segment cesarean section with bilateral tubal ligation. An exploratory laparotomy was performed and suture material was cut to release the obstructed gut. Meticulous care needs to be taken when using suture material intra abdominally by either burying the suture material or keeping the suture short.

**Key Words:** *Intestinal Obstruction, Intraperitoneal Sutures, Prolene.*

#### Introduction

Polypropylene is a synthetic, monofilament, non-absorbable suture.<sup>1</sup> The suture is best suited for use on the skin, hernias, vascular anastomosis and closing rectus sheaths or linea alba. Its use intraperitoneally is very limited due to its propensity to erode through and into the surrounding tissue. Federal Drug Authority in America has issued several warnings regarding the use of prolene and prolene meshes due to an increase in the number of mesh driven tissue erosions reported by patients over the years, specifically in pelvic surgeries.<sup>2</sup> However, small bowel obstructions have previously been reported with intracorporeal suturing with barbed and V-lock sutures.<sup>3</sup> To our knowledge, no previous case of intestinal obstruction has been reported with polypropylene sutures used for previous intra-abdominal surgery.

This case highlights the potential problems that can arise from the use of this suture intra-abdominally.

#### Case Report

A 30 year old female presented with sudden severe colicky abdominal pain. Patient had associated greenish non bloody vomiting with obstipation. The abdomen was mildly distended and there was

significant tenderness or rebound on palpation. Bowel sounds were absent. X-ray of abdomen showed dilated small bowel loop with air fluid levels. Patient had no previous history of tuberculosis and no reported exposure to tuberculosis. Ultrasound of abdomen showed free fluid in pelvis and dilated small bowel. Patients findings were consistent with peritonitis due to intestinal obstruction, a suspicion of abdominal tuberculosis and adhesions couldn't be ruled out. A CT-scan abdomen was done to delineate the cause of obstruction, which showed significantly dilated ileum with few calcified mesenteric lymph nodes.

Patient was managed conservatively at first with nasogastric tube, fluids and nil per oral. Patient symptoms settled in a day and the X-ray of abdomen became normal. Patient was discharged after observing for any deterioration in starting oral fluids. However, patient returned to the hospital after a day with similar symptoms of pain, distention and similar X-ray abdomen.

An exploratory laparotomy was performed with lower midline abdominal incision. Dilated bowel loop was traced back to the transition point, a visible polypropylene suture was identified containing a herniated ileum passing through the suture loop. The suture was anchored on the fundus of the uterus running through the body in a continuous fashion and a single suture loop of the suture was free on the fundus. The free loop seemed to have eroded through the uterine wall. Two more polypropylene sutures were visible a distance away, used for bilateral tubal ligation. No comment on the type of previous surgery performed can be made because no history of any surgical procedure apart from cesarean section and bilateral tubal ligation seven

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years prior could be obtained. The free loop of suture had ileum in it and was compressing the lumen of the bowel causing obstructive symptoms. The suture was cut and removed, bowel checked for viability and abdomen closed in a layered fashion. Patient had a complete recovery after the surgery.

### Discussion

Intestinal obstruction is very commonly encountered in surgical practice. Although the cause of obstruction can be identified in majority of the cases based on history, examination and imaging studies, there are still dubious cases in which no definite cause is identifiable on initial studies. When no mechanical cause of obstruction is found on imaging, there is a high tendency of such patient being labelled as having chronic disease such as tuberculosis due to high prevalence of the disease in our setup and difficulty in diagnosing it.<sup>4</sup>

One needs to keep a high index of suspicion for rare causes of intestinal obstruction.

Although we have advances in imaging like multi slice scans, MSCT patient symptoms should never be overlooked. Multi slice CT scans have a diagnostic accuracy of about 91% to determine intestinal obstruction. These MSCT scans are less reliable for small bowel as compare to large bowel obstruction with a diagnostic accuracy of 98% for large and 78% for small bowel. To conclude, CT scans can't delineate all causes of intestinal obstruction and persistent or recurrent pain is an indication for prompt surgical intervention.<sup>5</sup>

Intraperitoneal sutures causing intestinal obstruction is very rare. Recently V-lock and barb suturing in laparoscopic surgery has been reported as a cause of intestinal obstruction either due to intestinal herniation through the loop or adhesions

post operatively.<sup>3</sup> However, as this case highlights, any non-absorbable suture has the ability to cause intestinal obstruction for an indefinite period of time if left intraperitoneally. Inadvertant loops can form after erosion in the tissue in which they are originally used. Although prolene is not commonly used intraperitoneally, its use in fixing meshes, especially in pelvic surgeries, is well known. Moreover, it is at times used to mark or hitch viscera to the abdominal wall. It should be kept in mind that its use in these situations is not completely risk free. Due to this reason, surgeons should be extra careful when using these sutures intraperitoneally. Meticulous use of sutures, keeping a short length of the suture intraperitoneally and burying them wherever possible are all suggested to decrease the risk of such complications.

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