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Editorial

BREAST CANCER IN YOUNG WOMEN OF PAKISTAN: AN EMERGING THREAT

Atika Masood

Breast cancer is spreading like fire in a jungle in the world with approximately 2.3 million new cases annually, making it 11.7% of all cancer cases. According to recent cancer statistics in 2020, it has vanquished lung malignancies and now has become the leading cause of global cancer incidence in females. Breast cancer is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths annually. The most alarming situation is that breast malignancies account for 1 out of 4 cancer cases and 1 out of 6 cancer deaths among women. This makes it as an entity with the highest incidence in the majority of countries around the globe (159 of 185 countries) with cancer mortality in 110 countries, according to GLOBOCON statistics 2020.[1]

In Pakistan, the incidence of breast carcinoma is 14.5% with 25,928 cases in 2020 and mortality is 11.7% with 13,725 deaths.[2] The risk of breast malignancies is currently on the rise, as one in every 9 Pakistani women has a lifetime risk of being diagnosed with this fatal cancer.[3] Moreover, the age-standardized incidence rate for breast cancer is highest in Pakistan when compared to other Asian countries.[2]

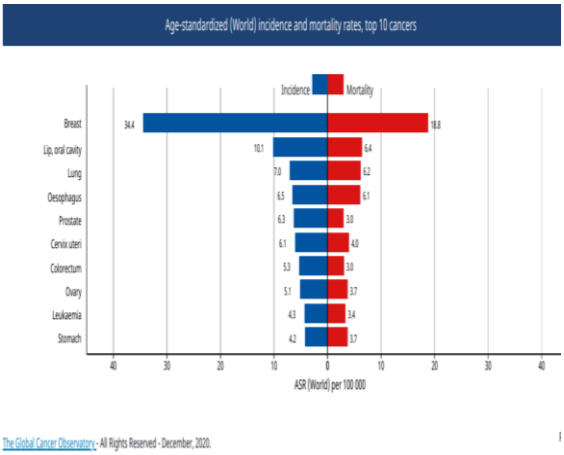

Figure-1: Age-standardized incidence and mortality rates[2]

The past and future time trends in age-specific breast cancer incidence among Pakistani women have predicted that the total number of this cancer will jump from 23.1% to 60.7% in 2025. Similarly, in relatively young Pakistan females, the number of diagnosed breast cancer is estimated to rise to 70.7% and 130.6% in the years 2020 and 2025, respectively.[4]

A Lahore-based study at the Institute of Nuclear Medicine & Oncology (INMOL) concluded that 64% of total breast malignancies were already in the late/advanced stage with an average age of 46.5 ± 13 years.[5] Another study conducted at a tertiary care hospital of Karachi shows that 28% and 7 % of breast cancer patients at the time of diagnosis are under the age of 40 and 30 years, respectively.[6]

The patients diagnosed in stage 2 were half in number (47%), stage 3 (36%), and stage 4 (1%). However, other local studies have reported stage 4 disease in 17% and 25%.[7,8] The diagnosis of breast cancer at an early stage would improve the treatment outcomes and hence survival rates.

When compared with developed countries, only few breast cancer cases (less than 1%) were diagnosed at stage 1 in developing countries such as Pakistan and India.[9] The delay in presentation to medical facilities is because of lack of awareness and health education, mistaken believes, and fears of side effects of the chemotherapy along with a strong belief in spiritual healing and traditional medicines. In addition to all of this, insufficient resources for diagnosis of breast cancer and free therapeutic services especially in rural areas as well as in small towns.[10] Detection of early-stage breast carcinoma would reduce morbidity as well as mortality and hence improved survival rates. It will also help to ease the burden on the health care system and economy of the

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country. So, health education for self-examination and regular screening in the form of ultrasonography and mammography is highly recommended. There is an increased risk for the development of systemic recurrence and eventually high mortality rates in breast carcinoma so it is the need of time that we should focus our energies on educating and sensitizing them. Government should work with private organizations, local influential and religious leaders to create awareness in this matter. This is upsetting the health resources of Pakistan and also creating psychological and financial disturbances in the family lives of affected young patients. Early diagnosis and treatment of breast cancer can improve the survival rate.[11] This can only be possible if we have an effective central registry system for exact incidence, the prevalence of cases, and the mortality rate of breast carcinoma. In Pakistan, a comprehensive database for breast cancer cases is still lacking and the only available data is mainly hospital-based.

The members from International Atomic Energy Agency (IAEA), WHO Cancer Coordinator, and the International Agency for Research on Cancer (IARC) visited several hospitals and organizations to develop the National Cancer Control Program. Member of Permanent Mission of Pakistan to the IAEA has also emphasized the importance of accurate data from Pakistan for plans to tackle this alarming situation.[12] This information, in turn, will aid evidence-based decisions and comprehensive policy-making regarding cancer control interventions and treatment facilities. This will be possible with strong commitment from the medical community, the administration, civil society, and international health agencies. In Pakistan, only a small percentage of the annual budget is specified for health care.

Unlike the GDP of Afghanistan (11.78%), Pakistan spends a meager percentage of GDP (2.90%) on health care provision. In 2019, Pakistan is placed among 93rd rank out of 117 countries with a poor score of 28/100 on the Open Budget Index on health.[13] There is a need at the government level to re-prioritize health spending by having a health-sensitive budget and special emphasis should be made on allocation of health budget on cancer awareness and treatment programs. In Pakistan, the alarming rise in breast cancer incidence, calls for an integrated approach, and the focus should be on research in the demographic, therapeutics, and genetics of breast cancer in Pakistan. The precise evaluation of age-specific breast cancer incidence will augment proper planning and execution of screening and awareness programs in the community and provision of therapeutic services at district levels.

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Original Article

OUTCOME OF LOWER EXTREMITY SALVAGE WITH IPSILATERAL VASCULARIZED FIBULA AFTER TIBIAL BONE TUMOR RESECTION IN PEDIATRIC AGE GROUP

Sobia Manzoor[1], Ahmad Faraz Bhatti[2], Sami Ullah[3], Ilyas Rafi[4], Saima Tabassum[5], Ehsan Ahmed Khan[6]

ABSTRACT

Background: Malignant bone tumors are difficult to diagnose at every level of pubertal growth in children and such defects are challenging to reconstruct. The purpose of this study was to report clinical characteristics and outcomes of limb-sparing surgeries in a series of pediatric patients after resection of tibia sarcoma using the TESS questionnaire.

Material and methods: In this study, we retrospectively reviewed data of patients having tibial sarcoma, who underwent salvage of lower extremity with ipsilateral vascularized fibula after tibia tumor resection from July 2016 to July 2017 with follow up till July 2019, retrieved from hospital database software. We collected demographic, oncological data, reconstructive data, complications, and outcome during a 2-years follow-up. Morbidity was assessed by the number of hospital visits during the follow-up period.

Results: Single staged tribalization of the fibula was done in all 7 pediatric patients who had the age of 12±2.4 years and among them 5(71.4%) were male. Out of 7 patients, 5(71.4%) had Osteosarcoma with the mean ± SD size of the defect after tumor resection being 13±2.6 cm. Weight-bearing in 5(71.4%) patients, was started at 6 months. Mean ± SD TESS at 3 months, 6 months, 1 year, and at 2 years showed gradual improvement in daily routine activities of the patient ($p<0.001$). Mild hypertrophy was observed in 4(57.2%) patients who had no complications after 2 years.

Conclusion: Single-stage pedicled ipsilateral fibula transposition for tibial segmental defect has fewer complications with better outcome making it the procedure of choice for tibia reconstruction.

Key Words: Lower Extremity, Fibula, Morbidity

INTRODUCTION

Marked variation in the incidence of pediatric bone tumors has been observed all over the world. In children, various benign and malignant tumors such as fibrous dysplasia, osteoblastoma, histiocytosis x, lymphoma, adamantinoma, and Ewing's sarcoma involve diaphysis of long bones.[1] Malignant bone tumors account for 3-5 percent of neoplasms among children aged 0-14 years and 57% of those tumors occur in bones of the lower extremities.[2] Also, these tumors are difficult to diagnose at every level of pubertal growth in children and such long bone defect reconstructions affect children physically, socially, and psychologically.

Limb sparing resections of tibial tumors have evolved with advances in reconstructive surgery, orthopedic oncologic surgery, medical oncology, and radiation oncology and it has become the treatment of choice for >80% of children without increase in mortality.[3,4] Various options for reconstruction of such defects are in use including endoprosthetic replacement, non-vascularized bone graft, ipsilateral transposition of the fibula, free fibula bone graft, distraction osteogenesis by Ilizarov ring fixator, and reimplantation of recycled

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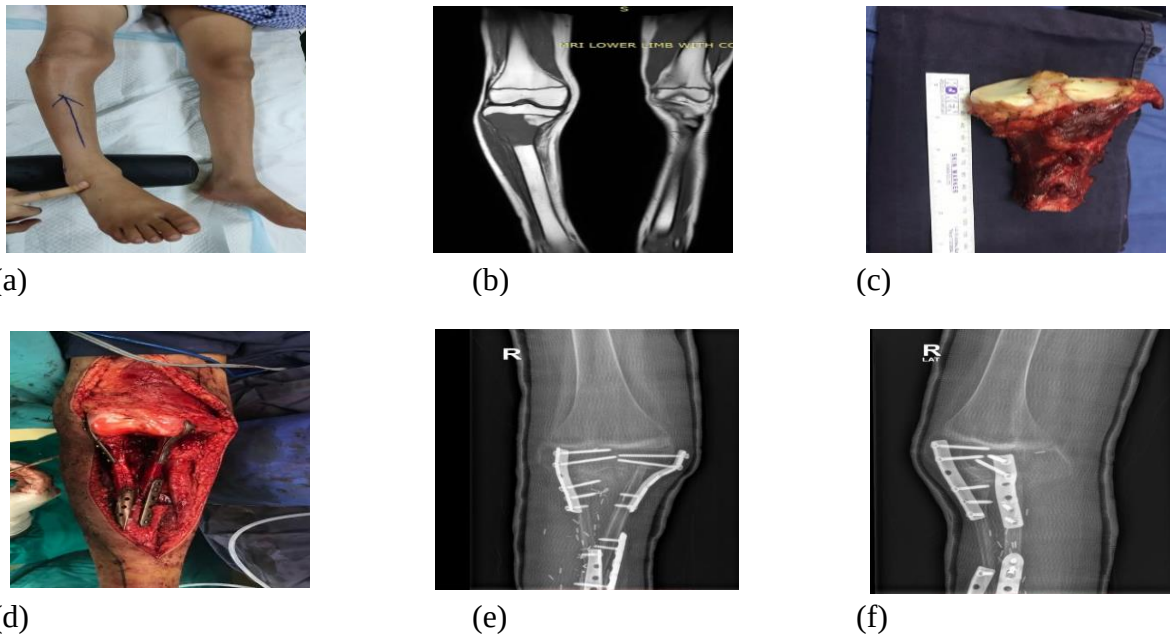
bone after autoclavization, pasteurization, or liquid nitrogen treatment.[5,6] Neoadjuvant or adjuvant chemotherapy and radiotherapy are applied for systemic and local effects to the patient pre-and post-operatively to reduce surgical morbidity.

Transposition of the ipsilateral fibula to the tibia (fibula pro tibia) was suggested by Hahn in 1884 and was first used successfully by Huntington in 1903, to fill a 12.7 cm tibial defect in a 7-year-old boy in a staged manner.[7,8] Various modifications were suggested using ipsilateral fibula with or without allograft to reconstruct segmental tibial defect with good long-term functional results.[9] Functional outcome was most frequently measured by Toronto Extremity Salvage Score (TESS) or Musculoskeletal tumor society (MSTS) 1993 questionnaire.[10] However, there is a scarcity of studies showing outcomes in terms of functional, social, and psychological wellbeing of the patient after such reconstruction by analyzing daily activities using TESS questionnaire in pediatric age group during follow up. The purpose of this study was to report clinical characteristics and outcomes of lower extremity limb-sparing surgeries in a series of pediatric patients after resection of tibia sarcoma using the TESS questionnaire.

MATERIAL AND METHODS

In this retrospective cohort study, data of pediatric patients who underwent salvage of lower extremity with ipsilateral vascularized fibula after tibia tumor resection from July 2016 to July 2017 with follow-up till July 2019, were retrieved from hospital database software. This study was conducted in the Plastic and Reconstructive surgery department of Shaukat Khanum memorial cancer hospital and research center (SKMCH & RC), Lahore, Pakistan. Approval was taken from the Institutional review board (EX-30-09-19-01). Patients with age < 15 years, having biopsy-proven tibial sarcoma on presentation, completed neoadjuvant chemotherapy, showing at least posterior tibial and peroneal vessels not involved by a tumor on MRI and underwent lower limb salvage for tibial defect ≥6 cm with ipsilateral vascularized fibula bone graft were included in the study using non-probability consecutive sampling technique (Data of all the patients fulfilling inclusion criteria at presentation were continuously included in the study). Patients, with age > 15 years and tibial defect <6 cm, requiring only soft tissue coverage for reconstruction, had posterior tibial and peroneal vessels involved in tumor mass, underwent previous flap surgery as a result of initial wound-related complications or pre-existing vascular limb disease were excluded from the study. Patients who had previous tumor excision outside our hospital or presented with distant metastasis or recurrent disease were also excluded.

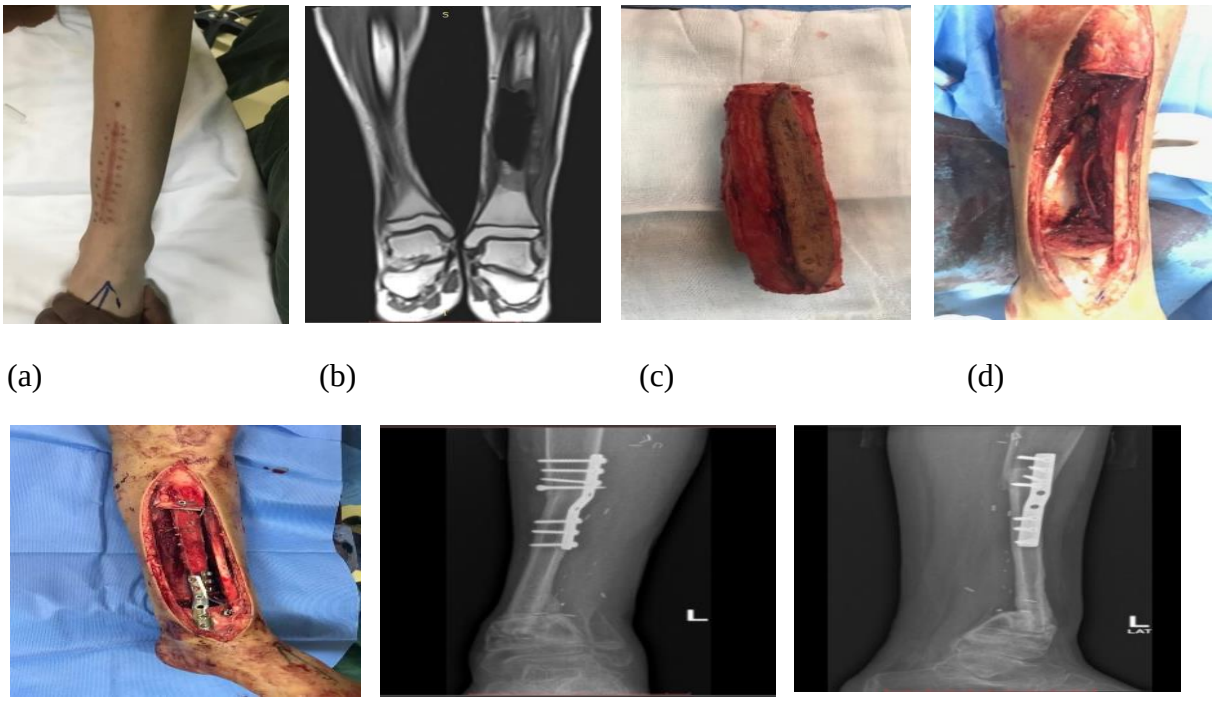
All the study patients were admitted to the hospital one day before surgery. Informed consent was taken by all patient's guardians after explaining the procedure, its complications, and possible future outcomes. The pre-operative assessment was done by routine investigations for surgery, the decision about incisions for tumor resection and fibula flap elevation made, and perforator marking of fibula flap by handheld Doppler done. Prophylactic antibiotics were given before surgery. During surgery, tumor resection was done by the Orthopedic team under pneumatic tourniquet control. After achieving margin clearance by frozen section, the plastic surgery team measured the defect size, harvested fibula bone of the same leg based on peroneal vessels through a separate lateral incision. The fibula was harvested to have at least 2 cm extra length to overlap the tibia proximally and distally. Vascularity of the foot was confirmed by removing a pneumatic tourniquet followed by clamping of peroneal vessels before the division of the pedicle distally. The harvested fibula was transposed to tibia defect after osteotomies as per requirement and fixed in single or double barrel arrangement using K-wire, tension band wire, screws, or plates avoiding kinking, torsion, or tension on the pedicle. The drain was placed for 3-5 days. Final closure in all patients was done without the need for a soft tissue flap.



(a) (b) (c)

(d) (e) (f)

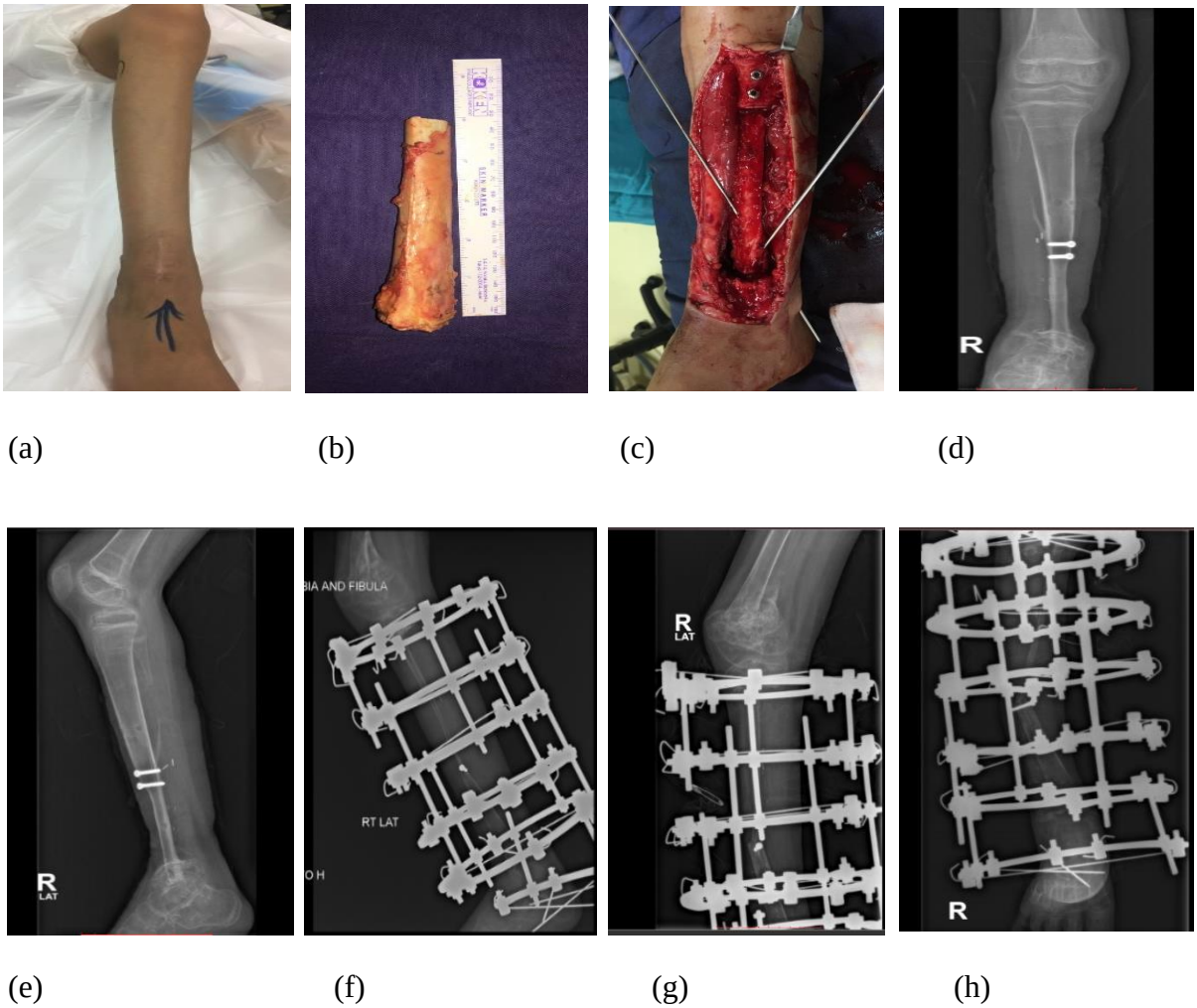
Figure 1: (a) 14 years old male with osteosarcoma of the right proximal tibia (b) MRI image showing tumor of the right proximal tibia (c) Gross picture of 8 cm excised tumor (d) Intraoperative image after fixation of the vascularized fibula as double-barrel with plates and screws (e) & (f) Anterior and Lateral view of X-ray right tibia after 14 months of reconstruction showing the union of bones.



(a) (b) (c) (d)

(e) (f) (g)

Figure 2: (a) 13 years old male with osteosarcoma of the left distal tibia (b) MRI image showing tumor of the left distal tibia (c) Gross picture of 14 cm excised tumor (d) Intraoperative image of the defect (e)Intraoperative image after fixation of the vascularized fibula as a single barrel with plates and screws (f) & (g) Anterior and lateral view of X-ray left tibia after 8 months of reconstruction showing the union of bones.



(a) (b) (c) (d)

(e) (f) (g) (h)

Figure 3: (a) 11 years old female with Ewing sarcoma of the right distal tibia (b) Gross picture of 12 cm excised tumor (c) Intraoperative image after fixation of the vascularized fibula as a single barrel with plates and screws (d) & (e) Anterior and Lateral view of X-ray left tibia after 2 months of reconstruction showing the union of bones (f), (g) & (h) Different X-ray views showing Ilizarov fixation after the fracturing of the fibula at 8 months postoperatively.

Assessment during follow up period was done by clinical examination of wounds, functional outcome by Toronto extremity severity score (at 3 months, 6 months, 1 year and 2 years), and radiological analysis by two views X-ray (at 2 weeks, 6 weeks, and as per the requirement of Orthopedic team) of the reconstructed site of the leg. Partial weight-bearing was started with a splint once bone healing was confirmed by radiograph.

We collected demographic, oncological data (primary disease, neoadjuvant, and adjuvant treatment), reconstructive data (location of defect in tibia, length of graft and osteosynthesis type), complications, and outcome data (limb growth and TESS at months, 6 months, 1 year and 2 years) during 2-years follow-up. Morbidity was assessed by the number of hospital visits during the follow-up period.

Descriptive variables were presented by proportions, mean or median values, and percentage as appropriate by data distribution. Data of categorical variables like age, gender, defect size, length of the graft, and outcome measures like TESS were analyzed using the chi-square test. Data of variables like tumor type, tumor size, type of bone arrangement, complications, and the number of days of hospital stay during the

follow-up period were analyzed by Student's T-test. Statistical analysis was performed using SPSS 21.0 statistical software. Statistical significance was defined as p value <0.05.

RESULTS

Single staged tribalization of the fibula was done in all 7 pediatric patients from July 2016 to July 2017 with follow-up till July 2019. The patients had mean ± SD age of 12 ± 2.4 years and among them 5 (71.4%) were male. All patients presented with biopsy-proven bone tumor and completed chemotherapy for the down staging of the tumor before surgery. Out of 7 patients, 5 (71.4%) had Osteosarcoma and 2 (28.6%) had Ewing sarcoma of tibia. The most common site of the tumor was proximal tibia in 3 (42.8%), distal tibia in 3 (42.8%), and Midshaft of the tibia in 1 (14.4%). The mean ± SD size of the defect after tumor resection was 13 ± 2.6 cm. One patient had a defect involving the knee joint due to removal of the proximal end of the tibia while another patient had medial malleolus removal as the tumor involved the distal end of the tibia. Margin clearance was achieved in all patients by frozen section with at least > 1 cm soft tissue and 1 cm bone margin clearance.

The mean ± SD length of vascularized fibula harvested was 19 ± 2.7 cm. It was used as a single barrel in 5 (71.2%) patients and as a double-barrel in 2 (28.8%). The proximal end of the fibula was fixed with tibia by plates and screws in 5 (71.2%), screws in 1 (14.4%), and tension band wiring in 1 (14.4%) while the distal end of the fibula was fixed with plates and screws in 4 (57.2%), cortical screws in 2 (28.6%), and K-wire in 1 (14.4%). Knee joint arthrodesis was done in 1 (14.4%) and ankle arthrodesis in 1 (14.4%) patient while joint movements in the rest of the patients 5 (71.2) was normal along with the axial alignment of fibula graft. Adjuvant chemotherapy was given in 4 (57.2%) patients and 3 (42.8%) patients who had margin clearance of > 2cm did not receive adjuvant chemotherapy (Table 1)**.** None of our patients received radiotherapy pre- or post-operatively. The mean follow-up period was 28.6 (Range: 25-39) months with mean ± SD hospital visits 13±(4.2) during the follow-up period. All the patients were assessed by clinical examination and radiologically (when needed) during the follow-up period. Weight-bearing in all patients was started at 6 months in 5 (71.2%) except for the first operated patient 1 (14.4%) who started weight bearing at 5 months. That patient developed a fracture of the proximal end of the fibula after an accidental fall followed by fibula graft resorption and was managed by applying an Ilizarov ring fixator. Another patient had a mal-union at the distal end of the graft and was managed by revision surgery by refreshing bone margins and adding bone graft with an additional 3-month period of non-weight bearing. The rest of the 4 (57.2%) patients had no complications. None of our patients developed recurrence or metastasis during 28.6 months follow-up period. Out of 7 patients, 6 (85.6%) are alive and disease-free to date while 1 (14.4%) patient died due to complications of postoperative chemotherapy.

Table 2 shows the Toronto extremity salvage score (TESS) in all patients measured at 3 months, 6 months, 1 year, and 2 years. Mean ± SD TESS at 3 months was 55.1 ± 4.9 for 7 patients, at 6 months 72.3 ± 7.2 for 6 patients (One patient died after 5 months), at 1 year 81 ± 8.7, and at 2 years it was 82.3 ± 7.4 showing gradual improvement in daily routine activities, socializing and psychological wellbeing of the patient (Statistically significant $p<0.001$). Mild hypertrophy was also observed in 4 (57.2%) patients who had no complications after 2 years.

Table-1: Showing demographic, oncological, reconstructive, and outcome data of study patients.

Sr. No.	Age/ Gen-der	Tumor type and site	Defect size	Graft length	Fixation type	Chemo-therapy	Follow Up		Complications	Outcome status
							Total period (Months)	Number of hospital visits in follow up period		
1.	9 y/ F	Ewing Sarcoma Right distal tibia near ankle joint	12 cm	16cm	Single barrel, Prox--2 screws, Distal--K-wire	Both Neo-adjuvant and Adjuvant	39	18	Fracture of the proximal end, resorption of the graft	Alive and disease-free
2.	14 y/ M	Osteosarcoma Right proximal tibia	17cm	21cm	Single barrel, Prox--TBW, Distal--Cortical screws	Both Neo-adjuvant and Adjuvant	38	20	Malunion at the distal end	Alive and disease-free
3.	14 y/ M	Osteosarcoma, Right proximal tibia near knee joint	9 cm	20cm	Double barrel, Plates with screws	Only Neo-adjuvant	26	12	Nil	Alive and disease-free
4.	14 y/ M	Osteosarcoma, Left proximal tibia	11 cm	24cm	Double barrel, Prox--DCP plate, Distal--Cortical screws	Both Neo-adjuvant and Adjuvant	5	7	---	Dead
5.	13 y/ M	Osteosarcoma, Left distal tibia	12 cm	16cm	Single barrel, Prox--Interfragmentary screws + tubular plate, Dostal--T shaped plate + 6 screws	Only Neo-adjuvant	25	11	Nil	Alive and disease-free
6.	11 y/ F	Osteosarcoma, Right tibial midshaft	14 cm	18 cm	Single barrel, Plates with screws	Only Neo-adjuvant	36	10	Nil	Alive and disease-free
7.	8 y/ M	Ewing Sarcoma, Left distal tibia	16 cm	20 cm	Single barrel, Prox--Interfragmentary screws + tubular plate, Dostal--T shaped plate + 6 screws	Both Neo-adjuvant and Adjuvant	31	12	Nil	Alive and disease-free

Table-2: Toronto extremity salvage score (Range 0-100)

Serial No.	At 3 months	At 6 months	At 1 year	At 2 years
1.	45	58	71	80
2.	54	76	68	70
3.	65	75	90	92
4.	56	0	0	0
5.	52	78	90	94
6.	63	75	86	90
7.	58	70	88	90

DISCUSSION

Autologous reconstruction is considered to be the gold standard for bony defect especially in the setting of lower limb salvage after tumor extirpation in children. It has replaced amputations in most of the primary bone tumors of the lower extremity in the pediatric age group. Various studies have shown the better outcome of limb-sparing surgeries compared to amputation in terms of functional, social, and psychological wellbeing.[11] Also, some review studies showed that there was no significant difference in recurrence rate, the disease-free period after surgery, and overall survival of patient after limb salvage and amputation.[12]

Among many approaches described for autologous reconstruction of tibial defect, we used single-stage tribalization of the ipsilateral fibula in our pediatric patients.[13] Pedicle ipsilateral vascularized fibula with preserved endosteal and periosteal circulation, is considered to be superior for tibial defects as compared to free vascularized fibula graft which has the risk of flap loss owing to microvascular anastomosis failure and donor site complications.[14] The advantages of using vascularized bone are their osteo-inductive, osteo-conductive, and osteo-progenitor properties along with its minimal donor site morbidity.[15] Limitations of non-vascularized bone graft include large bone defect size, presence of infection, resorption of bone graft, and potential need of soft tissue for closure.

In our study, we used fibula graft in a single barrel manner in most of our cases (71.2%) as the defect size was large (Range 12-17 cm) and one (14.4%) of these patients had a stress fracture and subsequent resorption of graft and later on developed major limb length discrepancy (>2cm). This was consistent with the findings of some studies showing a low rate of stress fracture (10-20%) when the graft was used in a double-barrel manner.[16]

Studies have shown good long-term results and an overall low complication rate after single-stage transposition of the ipsilateral vascularized fibula for tibia defect reconstruction.[17] It was also seen that functional outcome like routine activities, socializing and psychological wellbeing of patients undergoing such reconstructions, is reliably measured by TESS questionnaire as compared to MSTS.[18] The TESS is superior to MSTS as this questionnaire is filled by the patient himself giving details of the patient's activity level, does not require a hospital visit, can be administered by email or electronically, and therefore is used for the long term follow up studies. In our patients, we found that the score improved significantly from 6 to 12-month duration. It was most likely associated with completion of chemotherapy, the start of weight-bearing, and overall improvement in activity of patient owing to painlessness. After 1 year follow-up, the score showed slight improvement which was consistent with many retrospective studies.[19]

The fibula is known to hypertrophy in response to functional loading when it is transferred to a weight-bearing location. Initially, hypertrophy can be appreciated after 4-6 months of bone healing and in 2-3 years its size becomes comparable to the size of the tibia.[20] Variable hypertrophy of fibula was observed in our patients with the achievement of diameter comparable to the tibia in two patients while the rest of the patients are still on follow-up.

Although, our study patient number was relatively small, yet their outcome measures showed that single-stage tribalization of the fibula can replace lower extremity

amputations especially in pediatric patients. Also, even a shortened lower limb with limited movement at the knee or ankle and extensive scarring can have acceptable function for many patients.

CONCLUSION

Single-stage pedicled ipsilateral fibula transposition to fill tibial segmental defect after sarcoma excision is a reliable option in children. Good bone union, fewer complications, hypertrophy comparable to the tibial diameter, and resuming to early weight bearing along with daily activities make it the procedure of choice for tibia reconstruction.

AUTHOR'S CONTRIBUTION

SM: Conception of idea
AFB: Article writing
SU: Data Collection
IR: Review critically
ST: Data Analysis
EAK: Editing

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Original Article

COMPARISON OF ACADEMIC PERFORMANCE OF STUDENTS OF DIFFERENT BLOOD GROUPS AND GENDER

Shumaela Kanwal[1], Maryam Rao[2], Qanita Mahmood[3], Hamid Javaid Qureshi[4]

ABSTRACT

Background: There has been increasing concerns that personality characteristics including knowledge, behavior, skill, and intelligence can be predicted by a person's blood group. This study was conducted to compare the academic performance of students of different blood groups and gender

Material and methods: Cross-sectional study was conducted at Akhtar Saeed Medical and Dental College. The study included 181 participants. General characteristics and academic scores were recorded on a structured Performa and the blood group of each participant was determined by the glass slide method. Comparison of academic scores of students in different ABO blood groups was done by one-way ANOVA. Academic scores of males and females students were compared by independent t-test. Comparison of academic scores in Rh-positive and negative groups was done by independent t-test.

Results: Academic scores were significantly higher in blood group O (p-value=0.02). There was no significant association in academic scores among genders and Rh blood groups.

Conclusion: Students with blood group O have high academic performance.

Key Words: Blood Groups, Academic Performance, Gender

INTRODUCTION

Blood groups are determined by antigens present in the red cell membrane. Two antigens A and B are responsible for four blood group types; A, B, AB, and O in ABO blood group system.[1] In Rh system of blood grouping, the blood type is either positive or negative based on the presence or absence of Rh antigen in the red blood cell membrane respectively.[2] The importance of blood groups cannot be denied. The blood group of a person is very important in blood transfusion and forensic medicine.[3] Researches have also proved the importance of blood groups in the development of cardiovascular diseases, cancers, and other disorders.[4] There has been increasing evidence that personality characteristics like intelligence, knowledge, skills, and behavior can also be predicted by the blood group of a person.[5] Studies have been conducted to find out the association of emotional intelligence and behavior with blood groups.[6]

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Academic performance is the evaluation of knowledge developed by a student over a specific period through marks obtained in tests/examinations.[7] Academic performance is a very important parameter to assess intelligence as well as knowledge of a person.[8] Studies have been conducted to determine the influence of gender on academic performance and variation in academic performance of different blood groups.[9,10] There is less data available about the comparison of academic performance in different blood groups and gender in our part of the world. This study was conducted to compare the academic performance of students of different blood groups and to find the gender differences in academic performance

MATERIAL AND METHODS

This was a cross-sectional study, conducted in the Physiology department at Akhtar Saeed Medical and Dental College, Lahore. A total of 181 students of MBBS I and II participated in this study. After taking informed consent, general characteristics including age, gender, parent's blood group and academic performance were recorded on

a standardized proforma. Matric/O-level and F.Sc/A-level marks were recorded and an aggregate of the matric/O level and F.Sc/A was calculated to assess academic performance.

The blood group of each participant was determined by the glass slide method. Blood was obtained with aseptic techniques on three separate glass slides marked as A, B, and D. The blood was mixed with antisera A, B, and D at A, B, and D respectively. Agglutination was observed with the naked eye and under the microscope in case of the doubt after 10 minutes.

The data was entered and analyzed in SPSS version 21. Mean and standard deviation was determined for quantitative parameters while qualitative parameters were presented as percentages. On the basis of presence or absence of agglutination, the subjects were divided into four groups in the ABO system (A, B, AB, and O groups) and for Rh blood groups; the subjects were divided into two groups (Rh-positive and Rh-negative). Comparison of academic scores of the students of different ABO blood groups was determined by one-way ANOVA. Comparison of academic scores in gender and Rh blood group was determined by independent t-test. A p value ≤ 0.05 was considered significant.

RESULTS

A total of 181 students participated in this study. Of these, 105 were female and 72 were males. Mean ± SD of the age of male and female students is given in Table-1. In the ABO system, blood group B was the most frequent blood group (Table-2) while 88% of subjects were Rh positive (Table-3). It was found that subjects with blood group O had significantly high mean academic scores as compared to other blood groups (Table-4). No significant difference in academic scores was found between Rh positive and Rh negative the students (Table-5). There was no significant difference between the academic scores of male and female students (Table-6).

Table-1: Mean age and standard deviation of the students (n=181)

Gender	Age of the students (Year)
	Mean ±Standard Deviation
Male	19±0.765
Female	19±0.818

Table-2: Percentages of ABO blood groups in students (n=181)

Blood group	Percentage of students (%)		
	Male	Female	Total
A	17	14	16
AB	9	15	12
B	43	37	40
O	30	33	32

Table-3: Percentage of Rh factor in students (n=181)

Rh blood group	Gender		
	Male (%)	Female (%)	Total (%)
Rh Positive	79	97	88
Rh Negative	21	3	12

Table-4: Comparison of academic scores in students with different ABO blood groups

Blood group	Academic score Mean ±SD	p-value
A	1893±146	0.028*
AB	1871±138	
B	1884±131	
O	1914±102	

**p<0.05 significant*

Table-5: Comparison of academic scores in students with Rh positive and Rh negative blood groups

Blood group	Academic score Mean ±SD	p-value
Rh Positive	1895±125.73	0.63
Rh-Negative	1877±126.37	

p>0.05 non-significant

Table-6: Comparison of Academic scores in male and female students

Gender	Academic scores Mean ±SD	p-value
Male	1888±119.1	0.6
Female	1897±130.47	

p>0.05 non-significant

DISCUSSION

Different clinical conditions have been established to have been associated with blood groups like carcinomas, clotting, and bleeding disorders.[4] In the recent year the concern is growing to find association of blood groups and biological characteristics.[11] Researches have been investigating the relation of intelligent quotient and personality traits with blood groups. Studies have also been conducted to find the relation of blood groups with academic performance. It was found in a study, that the eligibility to appear in examinations of universities and academic achievements were associated with blood groups. The students having blood group A had high academic scores but these differences were not statistically significant.[12] Niraj and Asha compared the academic achievement of medical students with ABO blood groups and found that there was no relation between blood groups and high academic performance.[4] In another study conducted by Anandarajan et al, students having blood group O scored high.[13] The present study found significantly high academic scores in students having blood group O ($p \leq 0.5$). Kumar Sarvottam et al also found that students with blood group O obtained highest percentage in first year examination[14] while in another study, a significant association was found between blood group O and proficiency in computer gaming.[1] Saif Ullah Sheikh et al conducted a study to find the association of emotional intelligence with blood groups and found that emotional intelligence was significantly high in students having blood group O.[15] Academic performance was not associated with Rh factor ($p=0.6$) in the present study. Similar findings were reported by Barun et al. in their study.[16] Mankumari and Ajay found that the academic performance of females was significantly higher than males. Similarly, Kumar Sarvottam et al also reported that females have statistically significant high scores in academics as compared to male students.[14] In contrast, the present study did not find the difference of academic performance among gender. Similar results were also determined by Ritu Chandara in his study.[17] Other studies also did not find differences of academic scores between males and females.[18,19]

CONCLUSION

The present study concludes that high academic performance varies in ABO blood groups while Rh blood group and gender have no impact on academic performance.

AUTHOR'S CONTRIBUTION

SK: Principal author, complete write-up
MR: Data Collection, data analysis
QM: Discussion write up
HJQ: Helped write up, introduction, literature review, results and discussion

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Original Article

INSULIN SELF-ADMINISTRATION PRACTICES AMONG DIABETICS ATTENDING DIABETES MANAGEMENT CENTRE OF A TERTIARY CARE HOSPITAL IN LAHORE

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ABSTRACT

Background: More than 30% of all diabetic patients administer insulin as a sole therapy or together with oral hypoglycemic medications. This study was conducted to assess insulin self-administration practices among diabetic patients visiting Diabetes Management Center of tertiary care hospital in Lahore.

Material and methods: A cross-sectional study was conducted, using a convenient sampling technique, on 210 patients. A questionnaire developed, by using WHO guidelines regarding Insulin Self Administration, was filled by interviewing 210 patients attending the Diabetes Management Center, Services Hospital, Lahore. SPSS version 23 was used for data analysis.

Results: Out of 210 patients, 99.5% of the patients took care of temperature regulation, 83.9% practiced hand hygiene, merely 16.2% of the patients changed needle every time before use and 52.9% of the patients disposed of the needle properly. About 91.4% of patients rotated the injection site with 31.9% developing an injection scar. There is a significant relationship between educational status and checking of expiry date on vial (p= .016) and between gender of the patients and their knowledge of the proper site of administration (p= .014).

Conclusion: Health educational videos emphasizing storage, preparation of the solution and application as well as handling of syringes along with pictorial pamphlets, guidance from hospital staff and monitoring patient compliance with these practices can further improve these competencies.

Key Words: Insulin, Syringes, Temperature, Educational status

INTRODUCTION

Diabetes mellitus is a metabolic derangement, characterized by hyperglycemia primarily occurring as a consequence of partial or total insulin insufficiency.[1] The "diabesity" is considered as the largest epidemic of mankind history. Diabetes mellitus has been utterly belittled as an inclusive public health problem and it can no longer be ignored by the world.[2] Afflicting greater than 171 million people throughout the world and the calculation is anticipated to increase to 366 million by 2030.[3]

National Diabetes Statistics Report showed that approximately 9.3% of the United States residents have diabetes equivalent to 21.9 million people living in the United States.

A 2012 study calculating the number of patients who take diabetes medications speculated that 2.9 million diabetics (14%) use insulin solitarily, while 3.1 million (14.7%) take insulin and oral hypoglycemic drugs in combination.[4] About 7.5 million population of Pakistan is suffering from diabetes that is about 13.14% of the total population[5], of which type1 diabetes constitutes about 2% of the diabetic population of our country. The calculated incidence in Pakistan is about 1.02 per 100000 per year.[6]

Insulin is an essential component of the management of Diabetes Mellitus.[7] Figures from the developed world show that greater than 30% of all diabetic patients administer insulin either as the sole therapy or together with oral anti-diabetic medications.[8]

Despite consistent expert multidisciplinary care, concerns for glucose monitoring along with insulin injection administration is the

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responsibility of the diabetic patients or their attendant. Providing efficient self-management of diabetes is quite critical towards glycemic control, minimizing hypoglycemic attacks and improving health.[9] Insulin administration can be done subcutaneously through a variety of methods for example vial and syringe, devices like insulin pens, and continuous subcutaneous insulin infusion pumps.[10] These new devices, like insulin pens, are becoming more popular and provide easy and appropriate insulin administration. These devices are equipped to provide accurate dose adjustment, therefore minimizing the side effects like hypo- or hyperglycemia.[11]

According to research carried out in 5 tertiary care hospitals of Pakistan; of 375 patients, the majority of the patients used syringes (88.3%) for insulin administration, while fewer patients used pen devices (11.7%).[12]

Insulin self-administration demands for the best of expertise developed by learning of various practices, such as proper storage, carriage, formation of the solution and its administration, along with usage of syringes, needles, or injectable pens. Therefore, proper insulin administration at home necessitates training, an urge for learning along with devotion and attention to self-care.[13]

Proper management and education provide consequential perfections in knowledge, attitudes, and skills which results in better glycemic control and is vastly acknowledged to be a fundamental element of inclusive diabetes care. Patient education proved to be an effective way in controlling the main health problem.[14]

Studies conducted throughout various parts of the world showed inadequate knowledge and poor practices regarding self-administration of insulin among diabetics. It was evident that the education of patients is crucial to decrease the side effects of diabetes mellitus and its proper management.[15]

In a developing country like Pakistan which is ranked 7th by WHO in diabetic prevalence, it is mandatory to assess the knowledge gap and the practices regarding insulin self-administration among patients suffering from diabetes mellitus.

The objective of study was to assess insulin self-administration competencies among diabetic patients visiting Diabetic Management Center of Services Hospital Lahore.

MATERIAL AND METHODS

It was a cross-sectional study conducted in Professor Faisal Masud's Diabetes Management Center of Services Hospital Lahore. The study duration was 6 months (April-September 2019). The sample size was estimated by WHO statistical software S-size by using the formula of estimating a proportion with specific relative precision. At a confidence level of 95%, anticipated population 0.9[12] and relative precision of 0.05, the estimated sample size of 210 patients was taken. The non-probability convenience sampling method was used for this study. Diabetic patients, visiting the Diabetes Management Center of Services Hospital Lahore, using insulin for the last 6 months falling between the ages of 18-70 years, were included in this study. Patients who were diabetics but using oral hypoglycemic drugs were excluded from this study design. A detailed structured questionnaire was prepared to collect the data. Face-to-face interviews were conducted, by using the checklist for standard operational procedures, for insulin self-administration.[16] SPSS version 23.0 was used for entry, compilation, and analysis of data. For quantitative variables, mean and standard deviation were calculated. For qualitative variables, frequency and percentage distribution tables were generated and Chi-square test was applied to see the significant difference between variables.

RESULTS

The data was collected from the Diabetes Management Centre of Services Hospital Lahore. A total of 210 patients fulfilling the inclusion and exclusion criteria were interviewed. Most of the respondents were

between 40-70 years with mean age of 51.3 years and SD±12.8.
According to sociodemographic data collected 119(56.7%) were female and 91(43.3%) were male of which 15(7.1%) were unmarried and the remaining 195(92.9) were married. Among them 74(35.2%) were illiterate, 40(19%) had primary education, 69(32.9%) had secondary education and 27(12.9%) had higher education.

Table-1: Sociodemographic characteristics of respondents

Demographic Characteristics	Frequency (n)	Percentage (%)
Gender		
Male	91	43.3
Female	118	56.2
Marital status		
Married	195	92.9
Unmarried	15	7.1
Educational status		
Illiterate	74	35.2
Primary	40	19
Secondary	69	32.9
Higher education	27	12.9

201(95.7%) had proper knowledge about insulin self-administration and 173(82.4%) had knowledge of proper sites. When inquired about the practices regarding insulin self-administration results showed that 208(99.5%) patients took care of temperature regulation, 160(76.2%) checked expiry date before use, 174(82.9%) of patients maintained a proper blood sugar monitoring chart,176(83.9%) practiced hand hygiene, whereas 34(16.2%) patients changed the needle every time before use. Only 78(37.1%) of the respondents used to clean injection site with spirit swab before use, 192(91.4%) patients rotated the injection site, which is why only 67(31.9%) patients felt a scar mark. About 171(80%) of the respondents used to inject at 90-degree angle. Only 111(52.9%) of the patients disposed of the needle properly. Only a few respondents 42(20%) immediately consulted a doctor in case of hypoglycemic attack.

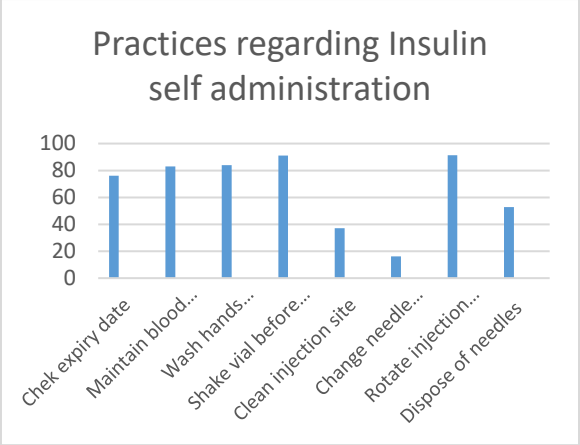

Figure-1: Practices related to insulin self-administration

This shows that there are significant practice gaps in the areas of disposal of needles and cleaning injection sites.

Table-2: Relationship of gender with knowledge about suitable site of insulin self-administration.

Gender	**Do you know what the suitable sites for self-administration are?**		
	No	**Yes**	**Total**
Female	13 (6.2%)	105 (50%)	118 (56.2 %)
Male	24 (11.4%)	68 (32.4%)	92 (43.8%)
Total	37 (17.6 %)	173 (82.4%)	210 (100%)

(p=0.014)

There is a significant relationship between gender and patient knowledge about proper sites of self-administration.

Table-3: Relationship between checking of the expiry date and educational status of respondents

Educational Status	**Do you check the expiry date on the vial before use?**		
	No	**Yes**	**Total**
Illiterate	25 (11.9%)	49 (23.3%)	74 (35.2%)
Primary	9 (4.3)	31 (14.8%)	40 (19.1%)
Secondary	15 (7.1%)	54 (25.7%)	69 (32.8%)
Higher education	1 (0.5%)	26 (12.4%)	27 (12.9%)
Total	50 (23.8%)	160 (76.2%)	210 (100%)

(p=0.014)

The above results show that there is a significant relationship between educational status and checking the expiry date on the vial before use.

DISCUSSION

Diabetes Mellitus is a chronic, non-communicable disease, associated with impaired blood glucose levels either due to defective insulin production or increased insulin resistance. Insulin administration is one of the mainstay therapies for Diabetes Mellitus. The treatment of Diabetes Mellitus requires the proper practice of self-administration of insulin in users.

Our study revealed that only 4.3% of subjects had insufficient knowledge regarding the self-administration of insulin, whereas 95.7% of participants were well aware of the proper method. However, in another study conducted in the diabetic clinic of Primary Health Centre, Alnamas only 60% had knowledge regarding the proper technique of insulin self-administration.[17] Another study conducted in the Out-Patient Department of a Multispecialty hospital in Kolkata, West Bengal, showed that 48% of patients possessed adequate knowledge about storing the insulin.[18] Hand washing is a very important measure to prevent the transmission of harmful microorganisms. About three fourth (83.9%) of participants had a satisfactory idea regarding washing hands properly before administration however, 37.1% of subjects in our study adopted the recommended practice of using spirit swab to disinfect the area before injecting. This was analogous to an earlier study carried out at Kolkata which had laid stress on the practice of washing hands before self-administration. It generated quite appreciative results revealing about 88% of patients following the practice.[19]

A similar study at Sri Devraraj Urs University, Tamaka, Kolar indicated 68% of the subjects had inadequate knowledge regarding insulin self-administration.[15] The reason for this high level of knowledge among patients is the provision of a proper classroom by the Diabetes Management Center for the patients where they are taught the proper method of insulin self-administration via videos.

A very small proportion of diabetic patients were admitted to changing the injection site. These findings correspond to similar research carried out in Finland, which revealed only a fraction of patients rotated the injection sites on the body. The most common site selected for injection was the abdomen.[10] However, in our study 91.4% of patients used to rotate the site on the abdomen itself. Injection administration at the same site repeatedly is related to the high incidence of lipohypertrophy and scar formation which in our study was positive for almost 31.9% of patients. Majority of patients 68.1% did not experience any scar formation since they avoided injecting the same area of the skin routinely. A study conducted in Spain showed that, of the patients who correctly rotated sites, only 5% had lipohypertrophy while, of the patients with lipohypertrophy, 98% either did not rotate sites or rotated incorrectly.[20]

Keeping insulin in a constantly cool environment at a stable temperature is imperative for its effectiveness. Around 99.5% of the patients admitted to keeping the insulin in a refrigerator to preserve the cold chain, as the diabetes center providing free insulin emphasized on bringing ice-filled thermos to take insulin from the Centre which inculcated the habit of storing insulin in refrigerators. This is in contrast to the findings from another study at Chitwan Medical College Teaching Hospital, Bharatpur, Nepal, which revealed that the majority of patients had denied maintaining the cold chain required for keeping the insulin injection.[15]

Used needles and syringes are dangerous for people if not disposed of properly. These can cause needle stick injuries and infections. Almost half (47.1%) of patients in our study disposed of the syringe by directly discarding it into the waste bin. However, 52.9% damaged the needle prior to discarding it. A study in Nepal conducted on the disposal of needles disclosed that the most common

method was disposal directly into the waste bin.[15] The United States Food and Drug Administration (USFDA) recommends syringes to be used for once only but due to financial constraints patients reuse needles and syringes often.[21]

The few shortcomings faced while conducting this study include the lack of diversity as only patients from a single hospital were involved in the study, which made it difficult to generalize the results. Another important factor was the lack of time for data collection which had a great impact on the findings of the study.

CONCLUSION

In our study almost all the patients had been provided with the information regarding self-administration of insulin while only a few changed the injection site leading to greater chances of lipohypertrophy. The majority of patients stored the insulin at an adequate temperature. On the other hand, a significant practice gap was observed in disposing of needles, washing hands, and cleaning the injection area before insulin administration.

Recommendations

Diabetes Mellitus can have long-term and fatal effects on the health of an individual. Proper health educational videos in the clinic emphasizing on different techniques including storage, transportation, preparation of the solution and application of insulin as well as handling of syringes or injection pens, and guidance from hospital staff as well as monitoring patient's compliance with these practices on each visit can further improve these competencies. Secondly, the provision of needles free of cost should be ensured as many of the patients belonging to low and middle-class backgrounds cannot afford to purchase syringes and needles frequently enough. Furthermore, the disposal of needles after use is an equally important issue and patients should be properly guided about the types of containers that could be used, proper labeling, and securing the lid of containers. Last, of all, the government must bring into existence legislation, national guidelines, or local municipality rules concerning the disposal of used needles and syringes.

AUTHOR'S CONTRIBUTION

MQ: Objectives, introduction, discussion & data collection
RM: Result analysis & interpretation
AS: Topic selection methodology & critical review
MC: Data collection, SPSS entry & abstract
MM: Data collection, SPSS entry & conclusion
MA: Data collection, SPSS entry & recommendations

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Original Article

KNOWLEDGE AND PRACTICES REGARDING SELF-CARE MANAGEMENT AMONG DIABETICS VISITING MEDICAL OUTPATIENT DEPARTMENT OF FATIMA MEMORIAL HOSPITAL, LAHORE

Seema Hasnain

ABSTRACT

Background: Diabetes Mellitus is one of the major chronic diseases which has become a public health problem worldwide. The complications of diabetes can be reduced by proper self-care knowledge and practices among diabetics. The objectives of this study are to assess the knowledge and self-care practices among patients having diabetes type 2 and its relationship with sociodemographic factors in of medical outpatient department of Fatima Memorial Hospital, Lahore.

Material and methods: This was a cross-sectional survey**.** The study was conducted in the Medical Outpatient Department of Fatima Memorial Hospital, Lahore from 12th February 2019 to 26th September 2019.

By using non-probability purposive sampling, 220 patients having type 2 diabetes fulfilling the inclusion criteria were selected. A pre-tested questionnaire was filled after taking written consent from them and data were analyzed in SPSS version 20.

Results: Out of 220 respondents, 55.7% have belonged to the age group 40-54 having 64% females. The overall knowledge about self-care among diabetics was good in 44%, satisfactory in 49%, and poor in 7% of the respondents. Whereas the overall practices among the diabetics were good at 24.5%, satisfactory at 60%, and poor at 15.4%. There was a significant association between self-care knowledge and self-care practices (p-value=0.032) and only income has shown a statistically significant association with the overall knowledge (P-value: 0.000). Regarding knowledge about physical activity, 87.7% were aware of its importance and about 95.9% had the knowledge that anti-diabetic medicines are to be taken regularly. However, only 27% participated in thirty minutes of physical activity and 85.5% took the anti-diabetes medicine over the past seven days before the interview

Conclusion: About half of the respondents have satisfactory self-care knowledge and one-fourth have poor self-care practices. Among the sociodemographic factors, only income has a statistically significant association with self-care knowledge.

Key Words: Knowledge, Self-care, Diabetes mellitus

INTRODUCTION

Diabetes Mellitus is one of the major chronic diseases which has become a public health problem worldwide. Globally about 425 million people (8.8% of adults) between 20-79 years are estimated to have diabetes and out of which about 79% are citizens of low and middle-income population. By the year 2045, it is estimated that 629 million people of 20-79 years will suffer from diabetes if this trend continues. The major upsurge will occur in countries where economies are moving from low-income to middle-income levels.[1]

The increase in diabetes prevalence is going to be more in developing countries and the reasons for this will be high population rate, increase in the number of elderly, inappropriate diets, obesity, and unhealthy lifestyles. The age group to be affected in these countries by the year 2025 will be 45-64 years in contrast to the developed countries where mainly people aged 65years or more will have diabetes.[2] Though diabetes is widespread globally but a major threat for Eastern Mediterranean countries where out of ten, six countries have the highest prevalence rate throughout the world.[3] In Pakistan, it has been reported that the prevalence rate of diabetes is 16.8% as 35.3 million adults are having diabetes.[4]

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The inception of diabetes and its related complications can be prevented or delayed by certain lifestyle behaviors facilitated by favorable environments. Diabetes inflicts a substantial economic effect on the health care systems of countries and above all, for diabetics and their families as a result of premature deaths and lower quality of life due to various complications of diabetes.[1] Continuous self-care education and support are important to prevent acute and long-term complications of diabetes.[5]

Self-care activities in people with diabetes comprise having an appropriate diet, being physically active, self-monitoring of blood glucose, and regular intake of medicines.[6] Day-to-day self-care measures are very vital for attaining diabetes-related good health results and several studies have reported a significant association between glycemic control and self-care activities.[7] There are standard self-care measures that can help in preventing and/or delaying the complications related to diabetes type 2 which includes regular self-monitoring of the blood sugar level, healthy diet, proper physical exercise, regular intake of antidiabetic medicines, and appropriate foot care. However, diabetics of developing countries have very little knowledge about self-care.[8] A consistent and strong compliance of the patients is needed for the effective management of diabetes. In developing countries like Pakistan where there is a high prevalence of diabetes, measures should be taken to improve self-care education and management among diabetics to delay and reduce the complications of diabetes.

MATERIAL AND METHODS

A cross-sectional study was conducted in the Medical Outpatient Department (OPD) of Fatima Memorial Hospital, Lahore. The inclusion criteria were known cases of type 2 diabetes of both genders for at least one year and had no complications to diabetes. The sample size was calculated by using the standard formula based on prevalence which is 17% with a 95% confidence level with a 5% margin of error, the minimum number of samples was 216.7 which was rounded off to 220 respondents. The respondents were selected by non-probability purposive sampling technique and were interviewed by using pretested structured questionnaire after taking written consent from them and approval by the Institutional Review Board (IRB No. FMII-07-2020-IRB-770). The study was conducted from 12th February 2019 to 26th September 2019. The dependent variables were self-care knowledge and practices whereas independent variables were age, sex, educational status, marital status, income, occupation, duration of diabetes, and family history. Information regarding self-care knowledge and practices among the diabetics was collected by using a validated Diabetes Self Care Knowledge -30 item questionnaire (DSCK-30) and a revised version of the validated Summary Diabetes Self Care Activities questionnaire (SDSCA) respectively. Data was entered and analyzed by using SPSS version 20. Simple frequency distribution tables were created for dependent and independent variables. To find out a significant association between sociodemographic factors and knowledge/practices regarding self-care management, a Chi-square test/Fisher's exact test (wherever applicable) was applied. Statistical significance was set at a p-value of less than 0.05. Twelve questions were asked regarding self-care knowledge and fourteen questions regarding self-care practices. Each correct answer was given one mark. Following grading was used.

Good knowledge/ practices: If the diabetics answered 70 % or more knowledge /practice items correctly individually.

Satisfactory knowledge/ practices: If the participants answered 50-70% of knowledge/practice items correctly individually

Poor knowledge/ Practices: If the diabetics answered less than 50% of knowledge /practice items correctly.

RESULTS

The mean age of the respondents was 50.60±8.357 years. Out of 220 respondents,

64% were females and 40% were males with a mean duration of diabetes 7.40 ±5.96 years. Almost 41 (18.6%) were illiterate, the qualification of 48 (21.8%) was matriculation and 40 (18.2%) were graduates and only 13 (5.9%) were masters and above. The majority of the patients had household income ranged from Rs.10000-60000 per month.

Regarding knowledge about self-care among diabetics, about 193 (87.7%) were of the view that physical activity for 20-30 minutes three days per week is essential and 158(71.8%%) knew that cigarette smoking could worsen diabetes. However, 203(92.3%) and 211(95.9%) respondents had the knowledge about the importance of extra care of feet and regular intake of anti-diabetic medicines respectively (Table-1). About half of the respondents (49%) had satisfactory self-care knowledge about diabetes (Table-3) Regarding diet respondents who followed a healthy eating plan for all days in the week were 71 (32.3%). People who did not participate in any physical activity for at least 30 minutes per day were 65 (30%). People who tested their blood sugar for seven days in the last week were 41 (18.6%). People who took medication for seven days in the last week were 188 (85.5%). People who checked feet for seven days in the last week were 107 (48.6%). (Table-2). The practices of 133 (60.5%) respondents were satisfactory (Table-3).

There was a significant statistical association between self-care knowledge and practices among the diabetics (Fisher's exact test=10.091 and p-value=0.032) (Table-3). The effect of age of respondents had no significant statistical association (Fisher's exact test=6.087 and p-value=0.372 and Fisher's exact test=5.890 and p-value=2.61) with the self-care knowledge and practices respectively. The income per month of the family has a statistically significant association with the overall knowledge of the respondents (Fisher's exact test: 19.631 and p-value=0.000) but no significant statistical association with the overall practice of the respondents (Chi-square test=2.871 and p-value=0.238). Effect of education on self-care knowledge and practices had no significant statistical association (Fisher's exact test=5.237 and p-value=0.257 and Fisher's exact test=6.08 and p-value=0.1940 respectively) as shown in Table-3.

Table-1: Knowledge regarding self-care among the respondents

Sr. No.	Questions related to knowledge	Response options *	Frequency & Percentage of correct answers
1.	Fasting blood sugar can be used to monitor 2-3 months blood sugar control	Yes **No**	101 (45.9%)
2.	Only doctors should make plans on how a person with diabetes can achieve his/her target goals	Yes **No**	67 (30.53%)
3.	Self-monitoring of blood glucose allows doctor and other health care team to gather data for clinical decision making	**Yes** No	197 (89.5%)
4.	Having Physical activity for 20-30minutes 3 days per week is essential	**Yes** No	193 (87.7%)
5.	Regular exercise does not reduce the need for insulin	Yes **No**	121 (55%)
6.	Maintaining a healthy weight is not imp. For management of diabetes	Yes **No**	135 (61.4%)
7.	A person with diabetes should only ask for help when he/she feels sick from his/her doctor	Yes **No**	66 (30%)
8.	Cigarette smoking can worsen the diabetes disease	**Yes** No	158 (71.8%)
9.	Appropriate advice on Self Blood Glucose monitoring and diet should be given to the diabetics	**Yes** No	211 (95.9%)
10.	A person with diabetes should take extra care of his/her feet	**Yes** No	203 (92.3%)
11.	Diet and exercise are not as important as medication in control of diabetes	Yes **No**	128 (58.2%)
12	Anti-diabetic medicines are to be taken regularly	**Yes** No	211 (95.9%)

***Correct answers shown in bold letters**

Table-2: Self-care practices among the respondents

Diet	Days							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Following a healthy eating plan on all days of the week	33 (15%)	12 (5.5%)	17 (7.7%)	23 (10.5%)	26 (11.8%)	22 (10%)	16 (7.3%)	71 (32.3%)
On average, over the past, how may days per week have you followed eating plan	52 (23.6%)	10 (4.5%)	18 (8.2%)	24 (10.9%)	23 (10.5%)	30 (13.6%)	15 (6.8%)	48 (21.8%)
Incorporating fruit/vegetables in the diet on the all days of the week	3 (1%)	4 (6%)	21 (10%)	43 (20%)	37 (17%)	34 (16%)	15 (7%)	53 (24%)
Consumption of high fat diet on all days of the week	8 (3.6%)	7 (3.2%)	6 (2.7%)	12 (5.5%)	38 (17.3%)	56 (25.5%)	53 (24.1%)	40 (18.2%)
Exercise:								
For the last SEVEN DAYS, how many days did you participate in physical activity for at least 30 minutes? (Total minutes of continuous activity, including walking)	65 (30%)	16 (7%)	24 (11%)	16 (7.3%)	14 (6%)	13 (6%)	13 (6%)	59 (27%)
Specific exercise session apart from the routine physical activity on a daily basis	147 (67)	18 (8)	14 (6%)	8 (4)	6 (3%)	5 (2%)	2 (1%)	20 (9%)
Blood sugar testing:								
For the last SEVEN DAYS how many times did you test your blood sugar?	24 (10.9%)	38 (17.3)	39 (17.7%)	43 (19.5%)	19 (8.6%)	12 (5.5%)	4 (1.8%)	41 (18.6%)
On how many of the last seven days did you test your blood sugar the number of times recommended by your health care provider	43 (19.5%)	31 (14.1%)	25 (11.4%)	34 (15.5%)	18 (8.2%)	10 (4.5%)	8 (3.6%)	51 (23.2%)
Medication								
On how many days of the last seven days, did you take your recommended diabetes medication		2 (0.9%)	5 (2.3%)	6 (2.7%)	4 (1.8%	10 (4.5%)	5 (2.3%)	188 (85.5%)
Foot care:								
On how many of the last seven days did you check your feet	40 (18.2%)	9 (4.1)	12 (5.5%)	13 (5.9%	14 (6.4%0	12 (5.5%0	13 (5.9%)	107 (48.6%)
On how many of the last seven days did you inspect the inside of your shoes	77 (35%)	9 (4.1%)	19 (8.6%)	9 (4.1%)	9 (4.1%)	8 (3.6%)	11 (5%)	78 (35.5%)
On how many of the last seven days did you wash your feet	6 (2.7%)	3 (1.4%)	8 (3.6%)	9 (4.1%)	6 (2.7%)	15 (6.8%)	13 (5.9%)	160 (72.7%)
On how many of the last seven days did you soak your feet	30 (13.6%)	7 (3.2%)	6 (2.7%)	6 (2.7%)	7 (3.2)	12 (5.5%)	23 (10.5)	129 (58.6%)
On how many of the last seven days did you dry between your toes after washing	84 (38.2%)	9 (4.1%)	21 (9.5%)	8 (3.6%)	8 (3.6%)	7 (3.2%)	13 (5.9%)	70 (31.8%)

Table-3: Overall knowledge and practices regarding self-care and its relationship with socioeconomic factors among the respondents

Overall knowledge regarding self-care				**Overall practices regarding self-care**		
	Good	Satisfactory	Poor	Good	Satisfactory	Poor
	97 (44%)	108 (49%)	15 (7%)	55 (25%)	133 (60.5%)	32 (14.5%)
Impact of self-care knowledge on the self-care practices in diabetics						
Self-care knowledge among the diabetics				**Self-care practices among the diabetics**		
				Good	Satisfactory	Poor
Good (71% and above)				19	54	24
Satisfactory (50-70%)				13	72	23
Poor (Less than 50%)				0	7	8
Fisher's exact test=10.091 & p-value=0.032						
Association of self-care knowledge and practices with socioeconomic factors and diabetic profile						
Self-care knowledge				**Self-care practices**		
Age in years	**Good**	**Satisfactory**	**Poor**	**Good**	**Satisfactory**	**Poor**
40-54	54	63	10	21	74	32
55-69	37	31	3	10	46	15
70-84	2	30	0	1	3	1
Fisher's exact test=6.087 & p-value=0.372				**Fisher's exact test=5.890 & p-value=2.61**		
Self-care knowledge				**Self-care practices**		
Gender	**Good**	**Satisfactory**	**Poor**	**Good**	**Satisfactory**	**Poor**
Males	33	39	7	10	48	21
Females	69	64	8	22	85	34
Chi-square test: 0.906 and p-value=0.636				**Chi-square value=0.427 and p-value=0.808**		
Self-care knowledge				**Self-care practices**		
Educational status	**Good**	**Satisfactory**	**Poor**	**Good**	**Satisfactory**	**Poor**
Illiterate-middle	33	53	6	9	55	28
Matric-FSc/FA	53	33	22	13	43	35
Graduation& above	6	6	3	28	19	8
Fisher's Exact test: 5.237 and p-value=0.257				**Chi-square test=6.08 and p-value=0.194**		
Self-care knowledge				**Self-care practices**		
Income of family (Rs.)	**Good**	**Satisfactory**	**Poor**	**Good**	**Satisfactory**	**Poor**
10000-60000	58	89	15	24	93	45
More than Rs.60000	39	19	0	8	40	10
Fisher's Exact test: 19.631 and p-value=0.000				**Chi-square test=2.871 & p-value= 0.238**		
Self-care knowledge				**Self-care practices**		
Family history of diabetes	**Good**	**Satisfactory**	**Poor**	**Good**	**Satisfactory**	**Poor**
Yes	65	73	10	20	92	36
No	32	35	5	12	41	19
Fisher's exact test=0.067 and p-value=0.995				**Chi-square test=0.0632 and p-value=0.0729**		
Self-care knowledge				**Self-care practices**		
Duration of diabetes	**Good**	**Satisfactory**	**Poor**	**Good**	**Satisfactory**	**Poor**
1-10 years	76	85	13	23	105	46
11-20 years	18	20	01	6	25	8
21-30 years	3	3	1	3	3	1
Fisher's exact test 2.236 and p-value=0.659				**Fisher's exact test =4.451 and p-value=0.314**		

DISCUSSION

The purpose of this study was to find out the self-care knowledge and practices among the type 2 diabetics so that results obtained from this study can help in identification of areas for improvement of self-care programs in the public and private sector hospitals/clinics so that morbidity and complications related to diabetes can be reduced.

In this study, 55.7% of patients suffering from diabetes type 2(DM type 2) were 40-54 years old with a mean age of 50.60±8.357 years. This indicates that in Pakistan the onset of adult type 2 diabetes is in earlier age groups which may be due to increased prevalence of obesity, lack of physical activity, and unhealthy diet as reported by International Diabetes federation 2018.[9] About 64.1% were females in the present study which is comparable to study of India which reported 60% of females having diabetes thus indicating that females are more prone to type 2 diabetes.[10] The same fact was reported by the Diabetes prevalence survey in which 17.85% were females and16.22% were males.[4] Thus indicating that females are more prone to suffer from diabetes type 2 as compared to females.

The overall self-care knowledge, 44% had good knowledge whereas only 25% had good self-care practices which indicates that though they had knowledge they have not utilized this knowledge for changing it into practices. The reason may be that diabetes is a slowly progressive disease and its complications occur after a long period and that is why they do not take the disease seriously. A study from Islamabad reported that 33.7% of patients showed adequate knowledge about the disease,[11] however in contrast to the study conducted in Iraq which showed 82.5% had good knowledge about self-care.[12] Whereas, the study of India reported that 77% of diabetics had good knowledge and 63% had good self–care practices.[13] A study conducted in Iran using the SDSCA tool only 4.7% of diabetics had good and 63.6% had poor self-care activities.[14] However, the study conducted in Bangladesh reported that levels of practice of participants were found to be poor in 12%, moderate in 72%, and good in 16% of the subjects.[15] This variation in numerous studies is due to the use of different validated and self-developed questionnaires, level of education of the participants, and standard of educational programs.

In the present study, two-thirds of DM type 2 patients had good knowledge regarding antidiabetic drugs to be taken regularly and the benefits of physical activity, harmful effects of cigarette smoking, and importance of extra care of feet. Whereas the study conducted in Jordan, only 42.5% of the respondents had knowledge about the benefits of exercise and 57.4% had knowledge about the importance of foot care and 49.30% had the knowledge about taking antidiabetics medicine regularly.[16] This discrepancy with the current study could be that Jordan's study had been conducted in rural areas where probably the physicians were not well trained in imparting self-care education and because of illiteracy and poverty. However, another study reported that 87.5% population knew that physical activity like exercise, walking, and swimming was essential for proper control of blood sugar levels which is consistent with the present study.[17] Similarly Islamabad study stated that 70% of the respondent had knowledge about cigarette smoking as a risk factor and 75% knew that exercise could help in blood sugar control.[18] A study by Rawanda reported that around 2/3rd of patients knew about the role of exercise in diabetes and 68.8% had the knowledge about the checking of shoes before being worn.[19]

In the current study, 71% followed the dietary plan, 59% practiced exercise, 85.5% were taking the medication regularly and 72.5% washed their feet regularly. Whereas, in a study of Addissababa, most respondents did not follow properly the advice regarding diet and physical activity which is contrary to this study but most patients took their

medications regularly.[8] However in another study, the majority of the subjects had a good level of self-practices regarding regular checking of blood glucose level, proper diet plan, taking regular medication, and proper foot care.[13]

Most of the researches has been conducted to evaluate the self-care knowledge and practices among diabetics but very few studies have been done in Pakistan about the evaluation of health care providers about Diabetes Self-Care Management (DSCM). In a qualitative study conducted in Karachi, it was reported that for starting a successful program of DSCM it is essential to have proper knowledge and expectations of people with diabetes.[20] Another study of Pakistan stated that the awareness level of physicians and patients was low on diabetes self–care management.[21] Thus self-management practices and their assessment is essential for diabetics.

There is a significant association between the self-care knowledge and practices among the diabetics (p-value=0.032) reported in this study. Whereas a similar type of study reported that knowledge was significantly associated with practice (p-value=0.001).[18] Same results are stated in another study showing a positive relationship (r=0.09) between the level of knowledge and practices.[13] Contrary to this, however, another study reported no significant correlation between the diabetic self-care knowledge and activities ((r=0.190, p=0.187) thus specifying that self-care practices do not relate to the level of knowledge.[22] In a study conducted in Peshawar, 45% of the patients had ever been educated about diabetes care and the main source of information was a doctor (78%). Of those who had received diabetes education, 65% received only 5minutes from the doctor while only 4 received more than 15 minutes.[18] A single-blinded randomized controlled trial in China reported that there was remarkable progress in the self-care activities of diabetics who received health education programs as compared to the control groups ($p<0.01$).[23] In the current study no association of knowledge and practices was reported with the sociodemographic profile. However, there is a significant association of knowledge with monthly income (p-value=0.000). The study conducted in Nigeria also indicated a significant association between occupation and knowledge (p-value=0.000).[24] Patients having higher monthly incomes are expected to have frequent visits to their physicians, regular checkups of blood sugar levels, and able to purchase their drugs. Whereas, a study conducted regarding Jordan, self-care knowledge had reported association with age, education, and antidiabetic medicines.[16] However, this study did not report the relationship between gender and self-care knowledge which is comparable to our study.[16] Similar results are mentioned in another study showing significant association with the education of the respondents. Respondents older than 50 years, those who were educated, and those earning 5000 Riyals had practiced self-care activities with p-value less than 0.05.[25] However, a study of Karachi observed that higher education of diabetic patients is a definite predictor regarding self-care practices which is in contradiction to our study but is consistent with patients' gender, age, type of job and duration of diabetes were found to be insignificant predictors for patients' self-care activities.[26]

CONCLUSION

Regarding the knowledge and practices of patients suffering from type 2 diabetes, 44% of respondents has good self-care knowledge but only 25% follow good self-care practices. There is a significant association between knowledge and self-care practices among diabetics. Only the monthly income of the respondents has a significant association with the self-care knowledge.

LIMITATIONS OF THE STUDY

It is not a population-based study so its results cannot be generalized and also the practices of the diabetics are not observed.

RECOMMENDATIONS

- The government should prepare guidelines for Diabetes Self-care Management and it is to be implemented in all private and government sector hospitals/ clinics
- Health care providers should be properly trained and should motivate diabetics to understand the importance of self-care in diabetes.
- Mass media must be involved to spread public awareness about the importance of self-care.

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Original Article

EFFECTIVENESS OF ORAL GLUTAMINE CHALLENGE TEST IN DIAGNOSING MINIMAL HEPATIC ENCEPHALOPATHY IN LIVER CIRRHOSIS PATIENTS

Raja Omer Fiaz[1], Farooq Hanif[2], Shahzad Latif[3], Usman Chaudhary[4], Tariq Waseem[5]

ABSTRACT

Background: Due to the lack of a gold standard test, it is difficult to diagnose minimal hepatic encephalopathy. Oral glutamine challenge has been found to increase blood ammonia in patients with cirrhosis. This study was aimed to investigate the accuracy of the oral glutamine challenge test in diagnosing minimal hepatic encephalopathy

Material and Methods: This validation **s**tudy was performed at the gastroenterology unit, East Medical Ward, Mayo Hospital, Lahore, from September 2016 to November 2018 by using the non-probability convenience sampling technique. All patients included in the study had undergone a baseline blood ammonia measurement and were administered Trail Making Test-A and B; those having an abnormal test were diagnosed to have minimal hepatic encephalopathy (MHE). Arterial blood samples were collected for ammonia measurement. After that, patients were given oral glutamine challenge and blood ammonia levels were again determined after 60 minutes, together with psychometric tests.

Results: The mean age of study participants was 46.22±10.04 years. Psychometric Test-A showed positive findings in 50 patients. Psychometric Test-B showed the same findings as that of Psychometric Test A. Mean ammonia level before Oral glutamine challenge (OGC) was 88.71±45.20 mg/dL. After the OGC test, the mean ammonia level was 145.16±69.02 mg/dL. The sensitivity and Specificity of OGC to diagnose MHE was 86% and 93.26% respectively. While 87.75% value represents positive prediction and a value of 92.22% suggests negative prediction. Overall diagnostic accuracy of OGC for detecting MHE was 90.65%.

Conclusion: In liver cirrhosis patients, the oral glutamine challenge test is as effective as a psychometric test for the diagnosis of the MHE.

Key Words: **A**mmonia, Hepatic encephalopathy, Glutamine

INTRODUCTION

Liver diseases are one of the major causes of mortality worldwide.[1] Hepatic encephalopathy (HE) is a neuropsychiatric dysfunction that can ensue in patients with liver disease, excluding other primary neurological disorders. The minimal hepatic encephalopathy (MHE) presents with the neurocognitive disorder of mild intensity and is present in patients having liver cirrhosis with or without porto-systemic shunts.[2,3]

MHE is often prevalent in patients having liver cirrhosis. The prevalence of MHE has been estimated between 20% to 74% in patients with liver cirrhosis, but the gold standard test for diagnosis has not been yet established.[4,5] Diagnosis of MHE is very important as it may affect daily life.[6,7] Oral administration of an amino acid solution categorically prepared to be similar to the amino acid composition of hemoglobin in cirrhotic patients leading to an incrimination in brain glutamine and dihydrogen monoxide levels. This process results in the deterioration of neuropsychological attainment. Altered glucose metabolism and cerebral perfusion caused by changes in ammonia concentration are associated with decreased utilization of glucose by sundry

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cortical areas concerned with cognitive functions.[8,9] MHE diagnosis reposes on the substantiation of illness responsible for MHE, like cirrhosis and portosystemic shunt, omission of normal brain functions as per clinical assessment, presence of un-coordination and neurophysiological variables, and omission of concurrent neurological dysfunctions. The objective of the OGC test is to quantitatively assess any increase in blood ammonia post glutamine oral intake, simulating oral protein intake during meals.[10] The assessment is carried out in the morning after at least 12 hours of fasting. An intravenous cannula is inserted followed by oral administration of either 10 or 20 g glutamine mixed in 100 ml of water. Twenty grams of glutamine contains 3.8 g nitrogen suggesting ingestion of approximately 24 grams of protein. A total of four blood samples are collected regularly each at half an hour interval after ingestion of glutamine to assess levels of ammonia in the blood.[11] It is anticipated that oral ingestion of glutamine will enhance blood ammonia in patients with the impending condition of liver cirrhosis but a healthy individual serving as control will not exhibit a similar upward trend of blood ammonia. The level of ammonia in blood after 1 hour of oral ingestion of glutamine is expressed as an ammonia response. The ammonia level appears to peak at between half an hour to one hour after ingestion, suggesting its association with the post-ingestion metabolism of glutamine in the small intestine. A less than 75 mg/dl level of blood ammonia is considered below the threshold for a positive test while higher than 128 mg/dl at one-hour post ingestion is typically established as pathological response.[12] Patients with disturbed OGC and MHE are appeared to be more vulnerable with the risk of developing overt HE (OHE) during follow-up compared to patients with typical OGC and having no MHE. This proposes that an altered value of OGC could function as a predictive factor for developing OHE in patients with MHE.[13-16] The current study aims to investigate the accuracy of the oral glutamine challenge test by measuring the ammonia levels in the blood of patients having liver cirrhosis due to viral hepatitis B and C.

MATERIAL AND METHODS

This validation study was conducted at the gastroenterology unit, East Medical Ward, Mayo Hospital, Lahore, from September 2016 to November 2018 using a non-probability convenience sampling technique. Keeping confidence level at 95% and margin of error at 9%, the sample size of 139 patients was determined by Rao soft sample size calculator. Informed consent was taken from study participants. All patients were enrolled after the diagnosis of compensated liver cirrhosis due to viral hepatitis B or C, confirmed by clinical and biochemical methods and radiological assessments.

Basic demographic characteristics like age, gender, etc. were recorded. Investigations including recent blood profiles i.e., complete blood count, renal function tests, liver function tests, activated partial thromboplastin time, international normalization ratio, ultrasound abdomen, and viral markers were also performed. The patients included in the study were invited to undergo a baseline blood ammonia measurement and were administered Trail Making Test-A and B, those with the abnormal test were diagnosed to have MHE. The arterial blood sample was drawn for ammonia measurement and samples were transported to the laboratory immediately in an ice bag. Measurement of ammonia levels was performed within one hour of sampling. Following this, patients were given oral glutamine challenge (20 grams of glutamine in 50 mL distilled water) and blood ammonia levels were again determined at 60 minutes, together with psychometric tests.

Data were analyzed using SPSS version 20 (IBM SPSS, 2016). Descriptive summary analyses were performed for calculating means and standard deviations for continuous variables and frequencies for categorical variables. Blood ammonia levels of patients with MHE were compared to

those without MHE. Results of the oral glutamine test were concluded by calculating positive and negative predictive values, sensitivity, and specificity of the test to determine the accuracy.

RESULTS

The mean age of participants was 46.22±10.04 years. The maximum and minimum ages of the patients were 70 and 19 respectively. Gender distribution of patients showed that there were 44(31.7%) female and 95(68.3%) male patients. The result of psychometric Test-A was positive in 50 patients while 89 patients exhibited negative results of the test. Psychometric Test-B showed similar findings as of Psychometric Test A with positive findings in 50 patients. The mean ammonia level before OGC was 88.71 mg/dl ranging between 47 and 177 mg/dl. After the OGC test, mean ammonia levels were 145.16±69.02 mg/dl. At this point, maximum and minimum ammonia levels seen in patients were 271 mg/dl and 88mg/dl respectively. The diagnostic accuracy of OGC was determined while keeping the Psychometric test-A as a gold standard test. Specificity and sensitivity of OGC for diagnosis of MHE were recorded as 93.26% and 86% respectively. While positive and negative predictive values of OGC were 87.75% and 92.22% respectively. Overall, the diagnostic accuracy of OGC for detecting MHE was 90.65%. (Table-1)

Table-1: Diagnostic accuracy of OGC test while taking psychometric test-A as the gold standard

		Test-A		Total
		Positive	Negative	
OGC	Positive	43	6	**49**
	Negative	7	83	**90**
Total		**50**	**89**	**139**

Sensitivity= 86%
Specificity= 93.26%
Positive Predictive value= 87.75%
Negative Predictive value= 92.22%
Diagnostic Accuracy= 90.65%

DISCUSSION

Hepatic encephalopathy is one of the signs of portal hypertension with spontaneously created high-grade portosystemic shunts. There are no specific clinical manifestations of minimal hepatic encephalopathy making it difficult to diagnose. Presently, the diagnosis of MHE is contentious, especially regarding establishing criteria and robust diagnostic assessment that is robust and readily applicable in clinical practice. Psychological and neurological assessments often do not present enough clinical evidence for MHE diagnosis. The present study attempted to assess the diagnostic accuracy of the OGC test compared to the psychometric test for MHE diagnosis. The results demonstrated that the diagnostic accuracy of OGC for the diagnosis of MHE was 90.65%. In addition, other diagnostic accuracy parameters like negative and positive predictive values, specificity, and sensitivity of OGC were 92.22%, 87.75%, 93.26%, and 86% respectively. There is no single gold standard test for diagnosis of MHE, a combination of two neuropsychological tests/psychometric hepatic encephalopathy score battery tests or neurophysiological tests is standard for diagnosis of MHE in liver cirrhosis in absence of overt encephalopathy.[15] Various combinations of psychometric tests with or without neurophysiological methods are required for the diagnosis of MHE in liver cirrhosis in absence of overt encephalopathy.[16]

Findings of this study showed that the mean ammonia level before OGC was 88.71 mg/dl ranging between 47 and 177 mg/dl. After the OGC test, mean ammonia levels were 145.16±69.02 mg/dl, indicating a significant rise in ammonia level. Ditisheim et al. in agreement with the present study, reported a rise in capillary ammonia levels comparing OGC induced ammonia with basal levels to rise from 0.541 to 0.727 in AUROC value after 60 minutes of glutamine ingestion.[17]

In this study, in all participants with liver cirrhosis, ammonia levels raised after the OGC test (145.16±69.02 mg/dl). Romero-Gómez et al assessed the usefulness of oral

glutamine challenge (OGC) and minimal hepatic encephalopathy in evaluating the risk of overt hepatic encephalopathy in cirrhotic patients. They revealed that patients with higher than 128 mg/dl of blood ammonia level measured for OGC indicate pathological condition. In healthy controls, ammonia concentrations remained unchanged but increased significantly in cirrhotic patients (127.43±78.6). In multiple logistic regression analysis, altered OGC was related to MHE (OR=5.45; 95% CI=1.17–25.4).[18]

Ampuero et al also described that oral glutamine challenge induces an increase in blood ammonia in patients with cirrhosis but not in healthy control or transplanted subjects. Oral glutamine challenge can predict minimal hepatic encephalopathy, as well as is associated with poor survival.[14]

According to the findings of this study, the diagnostic accuracy of the OGC test is 90.65% indicating the usefulness of this test in the diagnosis of MHE. Results of another study conducted by Irimia et al demonstrated that arterial ammonia levels significantly increased in post-glutamine ingestion (85.2±20.8μg/dL to 159.82±66.01μg/dL) compared to control where it remained unchanged. At baseline, 53.7 % of patients met the Psychometric Hepatic Encephalopathy Score (PHES) criteria for MHE diagnosis. After glutamine load, the percentage of patients diagnosed with MHE increased to 79.6 %. The values of PHES were significantly lower post-OGC compared to baseline, suggesting that OGC increased the diagnostic performance of PHES for MHE in cirrhotic patients, and it remained almost unchanged in healthy subjects.[10]

Some other researchers also emphasized the need for standard screening and diagnostic tests for MHE. In their opinion, the fact that MHE can affect daily life even though patients are asymptomatic signifies the need for screening tests. These tests should be easy to use, and quantifiable in a short time.[19] The oral glutamine challenge test is relatively simple and poses no adverse implications to the patients. The present study in conjuncture with previously published literature confirms that the OGC test can predict the MHE. Results of this study also suggest that future research looking into developing potential drug inhibiting activity of glutaminase enzyme could be promising to treat patients with MHE.

CONCLUSION

It is concluded that the diagnostic accuracy of OGC for the diagnosis of MHE is 90.65%. Negative and positive predictive values, specificity, and sensitivity of OGC are 92.22%, 87.76%, 93.26%, and 86% respectively. An oral glutamine challenge test is as effective as psychometric evaluations for the diagnosis of MHE in liver cirrhotic patients.

AUTHOR'S CONTRIBUTION

ROF: Primary topic idea
FH: Data analysis
SL: Critical review
UC: Helping data collection
TW: Peer and critical review

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Review Article

ROLE OF ANGIOTENSIN SYSTEM INHIBITION IN THE CARDIOVASCULAR MANIFESTATIONS OF COVID – 19

Muhammad Saeed Anwar[1], Mariyam Iftikhar Piracha[2]

ABSTRACT

The Association of the drugs inhibiting the angiotensin system with the severity of coronavirus disease has been studied intensively at different research centers of the world over the past year. It has been found that the admitted COVID-19 patients with co-existing cardiovascular diseases taking angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) develop less severe disease, and persistent ACEI /ARB therapy during their hospitalization lowers the risk of fatality as well. The current literature supports the use of ACEI/ARB therapy for corona patients with co-morbidities as it yields better clinical outcomes.

Key Words: COVID-19, Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor

INTRODUCTION

Corona Virus disease (COVID-19), a pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS-CoV-2) has emerged as the most striking medical challenge of the era and is associated with a notable rise in morbidity and mortality worldwide.[1] Basically, it is a pulmonary disease but affects the cardiovascular system as well. Advancing age, male sex, and comorbidities like cardiovascular diseases, chronic pulmonary diseases, diabetes, and cancer are the major risk factors for severe infection and mortality.[2]

As Angiotensin-Converting enzyme type 2 (ACE2) is the significant receptor for the entry of the virus into the host's pulmonary cells, it was speculated that drugs modifying Renin-Angiotensin System (RAS) may increase the risk for infection and severity.[3] Therefore, it was hypothesized that Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB); the major drugs prescribed for cardiovascular diseases make patients vulnerable to corona infection and also worsen the disease outcomes through upregulation of the functional receptor essential for the virus's entry: ACE2.[4]

Thus, a great conflict about their use in COVID-19 developed and is one of the major concerns for clinicians treating COVID patients with cardiovascular diseases.

In the current review, clinical and pathological features of COVID-19 mediated damage to the cardiovascular system, the potential pathogenic role of ACE2 in COVID, factors modifying ACE2 expression and activity in relation to COVID-19, and potential therapeutic options for COVID-19 will be discussed.

DISCUSSION

Pathological and Clinical characteristics of COVID-19 mediated cardiac complications

COVID-19 has the peculiar properties of high transmission, long incubation period, and varied clinical manifestations. Besides pulmonary insult; causing Acute Respiratory Distress Syndrome (ARDS), it also involves other systems, especially the cardiovascular system (CVS).[5] The most common cardiac complications include myocarditis, arrhythmia, disseminated intravascular coagulation, pulmonary embolism, and heart failure.[6] Based on limited knowledge of the disease, the proposed process of cardiac insult involves the direct entry of the virus and myocardial injury, hypoxia, cytokine storm, systemic inflammation, interferon-

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mediated immune response, and plaque destabilization.[7]

Cardiac biomarkers (D-dimer, troponin) rise frequently, particularly during the phase of systemic inflammation and ARDS, and are quantitatively associated with poor disease outcome.[8] Initially pulmonary infection may cause right ventricular dysfunction but as a consequence of cytokine storm, hypoxia, and systemic inflammation; heart failure may develop.[7] However, even mild COVID-19 infection in children can produce a multisystem inflammatory syndrome along with the cardiogenic shock.[8]

Current researches indicate that mortality from COVID-19 can be attributed to cardiovascular diseases and disease outcome worsens in patients with comorbidities like hypertension and diabetes mellitus probably due to overexpression of ACE2 receptors.[9]

Pathogenic Role of ACE2 in COVID-19:

Coronavirus enters the host cells by binding its spike proteins to ACE2 which is widely expressed in different tissues and plays a central part in disease pathogenesis.[10] ACE2 catalyses the conversion of angiotensin I (Ang I) to angiotensin II and has direct effects on the CVS and multiple organs via counter-regulation of RAS (Figure-1). The pulmonary insult by coronavirus affects both alveolar interstitium and capillaries, and is linked to functional downregulation of ACE2.[11] It is an essential enzyme for balancing the two arms of RAS: ACE/Angiotensin (Ang) II/Ang II type 1 Receptor Axis (classic RAS) and the ACE2/Ang (1-7)/ Mas- receptor axis (anti-RAS). Downregulation of ACE2 enhances the classic RAS and reduces the anti-RAS mediated attenuation leading to lung injury, leaky blood vessels, inflammation, and pulmonary fibrosis.[12] With the progression of the disease immune cells and coagulation pathways get activated leading to multiorgan failure and eventually death.[10]

Factors determining expression and activity of ACE2 in relation to COVID-19

Multiple factors have been linked to altered ACE2 expression and severity of COVID-19, including age, gender, ethnicity, comorbidities: cardiovascular diseases and metabolic syndrome, and medications.[13]

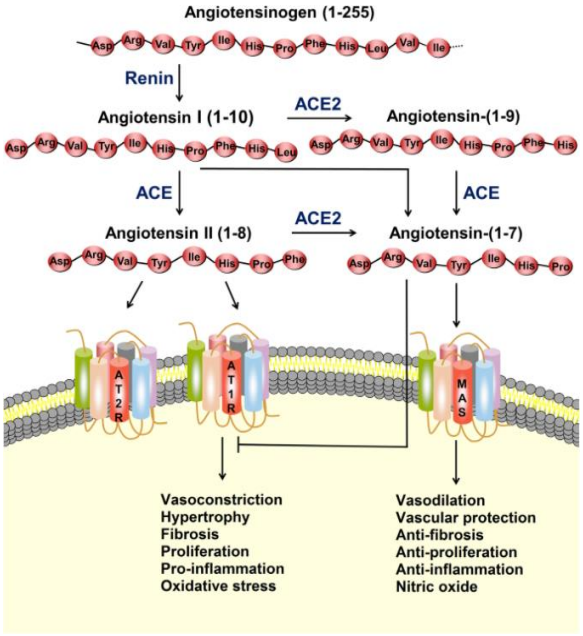

Figure-1: Renin Angiotensin System (RAS) and ACE2 / angiotensin-(1-7) MAS axis (https://ccforum.biomedcentral.com)

ACE inhibitors are a group of drugs primarily used in the management of hypertension and heart failure. They cause vasodilation and decrease blood volume, which lowers the blood pressure and reduces the cardiac oxygen demand.[14]

In vitro, both ACEIs and ARBs have been shown to upregulate the expression and activity of ACE2. Increasing ACE2 may be beneficial as it forms Ang (1-7), a vasodilator that possesses anti-oxidative and anti-inflammatory properties and thus might prevent multiorgan failure plus ACE2 blockade may disable viral entry into the heart and lungs.[15]

A study showed that ACEI or ARB therapy in comparison to other antihypertensives in COVID patients, lowered the disease severity, decreased IL-6, and increased CD3 and CD8 T cell counts in peripheral blood in addition to the reduction in peak viral load.[16] This evidence supports the usage of these drugs in COVID-19 patients with cardiovascular diseases.

Vitamin D, a fat-soluble vitamin, is a negative endocrine renin-angiotensin system modulator that induces anti-RAS axis and inhibits classic-RAS axis by increasing ACE2 and Ang-(1-7) concentration and expression and thus might prove beneficial in COVID-19 associated ARDS.[17]

CONCLUSION

The exact impact of Renin-Angiotensin System blockers on COVID-19 infection is currently unknown. There is no evidence of the detrimental effects of using angiotensin inhibitors during COVID-19 infection despite the theoretical concerns of probably increased expression of ACE2 by RAS blockade but in fact, their use has been proven favorable in some animal studies. Based on their anti-inflammatory effects and current data it can be concluded that treatment with RAS inhibitors in COVID may outweigh the risks and therefore, currently there is no reason to abort their use in COVID-19. Although for the ultimate decision, more clinical studies are mandatory to assess the safety of RAS blockers in COVID-19.

FUTURE RECOMMENDATIONS

Extensive knowledge of the cardiovascular effects of the corona virus is a prerequisite for the development of novel therapeutic strategies to target the virus-induced cardiac damage and hence reduce morbidity and mortality. ACE2 interaction with viral S protein and ACE2/Ang 1-7 axis could be potential targets for developing preventive and therapeutic regimens for COVID-19 and decreasing its severity.

AUTHOR'S CONTRIBUTION

MSA: Critical revision & final approval of article
MIP: Drafting & Editing

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Case Report

DIAGNOSIS OF AN UNUSUAL CASE OF PELLAGRA WITH HYPOTHYROIDISM

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ABSTRACT

Niacin deficiency, Pellagra or the 3D´S disease, is a disorder associated with either poor intake of niacin-containing food or secondarily decreased bioavailability of the same. Being an essential component in several co enzymes, its deficiency is also considered a multi-nutritional disorder involving the deficiency of tryptophan and consequently vitamin B2 and B6. The low clinical suspicion of this disease, which may be associated with hypothyroidism, made it a clinical challenge even with the classical triad of symptomatology. A case report of 38 years old woman presented with a 3-month history of progressive erythematous lesions on the dorsum of hands resembling photosensitivity eruptions but lacking the typical Casal necklace sign and preceded by multiple episodes of diarrhea, a paradoxical manifestation to its underlying hypothyroid state.

Key Words: Hypothyroidism, Pellagra, Vitamin B_6

INTRODUCTION

The name pellagra, derived from the Italian word pellagra, sharp, i.e. rough skin, is a disease characterized by dermatitis resembling the photosensitive type, diarrhea that may be present in 50% of the cases, and progressive neuropsychological disorders that may lead to dementia. Without prompt treatment, severe niacin deficiency may lead to death.[1,2] Pellagra was initially described by a Spanish physician Don Gaspar Casal in 1763, who recorded all the clinical features and attribute the disease to the unbalanced diets, based on maize, the reason why it is historically considered a maize-eater's disease.

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Pellagra is caused by deficiency of niacin and or its precursor tryptophan, which is essential for cellular metabolism such as redox reactions, DNA repair, and as a co enzymes in various processes. Thus, clinical manifestations are focused on highly metabolic tissues such as skin, gastrointestinal cells, and CNS. Symptoms of the later two are subtle and nonspecific, thus muco-cutaneous signs should provide diagnostic clues.[3] This case report unveils how a patient with severe niacin deficiency and subclinical hypothyroidism presented to us.

CASE REPORT

A 38 years old woman, came to Medicine I Outpatient department with a one-month history of symmetrical hyperpigmented leathery thickened plaques on the dorsal aspect of both hands that started on the knuckle area. Initially, they were confined to 2/3rd of the dorsum, later it spread up to the wrist joint leaving a sharply demarcated border between affected and unaffected skin. A month back, lesions on hands were erythematous itchy, painful but no treatment was taken for the same. There was no movement restriction or tenderness on hand

joints. The same pattern of lesion started appearing on the patient´s nose and both cheeks, symmetrical in the distribution along with angular stomatitis, glossitis, and vesicle formation in the lower lip causing difficulty in food intake along with odynophagia.

Before the onset of dermatological manifestations, the patient complained of diarrhea for three months, unrelated to food intake, associated with mild to moderate diffuse abdominal pain, with mucus but no blood. (Bristol classification 5-6) and indigestion, dyspepsia, occasional heartburn. She sought medical attention for the same complaint and took multiple medications including antibiotics but symptoms were not relieved. She also had dizziness, palpitations on exertion, and tingling sensation on hands and feet with no specific diurnal, nocturnal variation. Family members of the patient noted behavioral changes such as irritability, weakness, lassitude, and inability to perform normal house activities such as cooking or cleaning.

The patient was diagnosed with pulmonary Tuberculosis in Ghulab Devi Hospital 15 years back, for which she completed a 6-month treatment course. On asking, she was unable to verify the intake of Vitamin B6 during the treatment. She also had a history of 2 pregnancies where there was no vitamin supplementation during the prenatal period. There was no history of similar disease in the family, no history of drug addiction or alcohol intake.

On examination, there was bilateral symmetrical thickened skin on the dorsum of hands, hyperpigmented like leathery parchment, with fissuring and crackling of overlying skin. Same hyperpigmentation was noted over the nose and cheeks in a butterfly pattern. Oral cavity examination revealed multiple erosions on buccal mucosa along with superimposed candidal infection, glossitis with fissuring on the tip of the tongue and lower lip showed vesicles, erosions, and crusted papules. Another systemic examination was unremarkable except for myxedematous swelling on both feet, overall xerotic skin, and periorbital swelling. Neurological examination revealed delayed knee jerk and ankle reflex but power was preserved. The sensory system and autonomic nervous system were intact. Moreover, the patient showed neuropsychiatric symptoms such as apathy, low response, and confusion. Mini-mental examinations were done with a score of 22/30 showing a mild degree of cognitive impairment.

Before treatment:

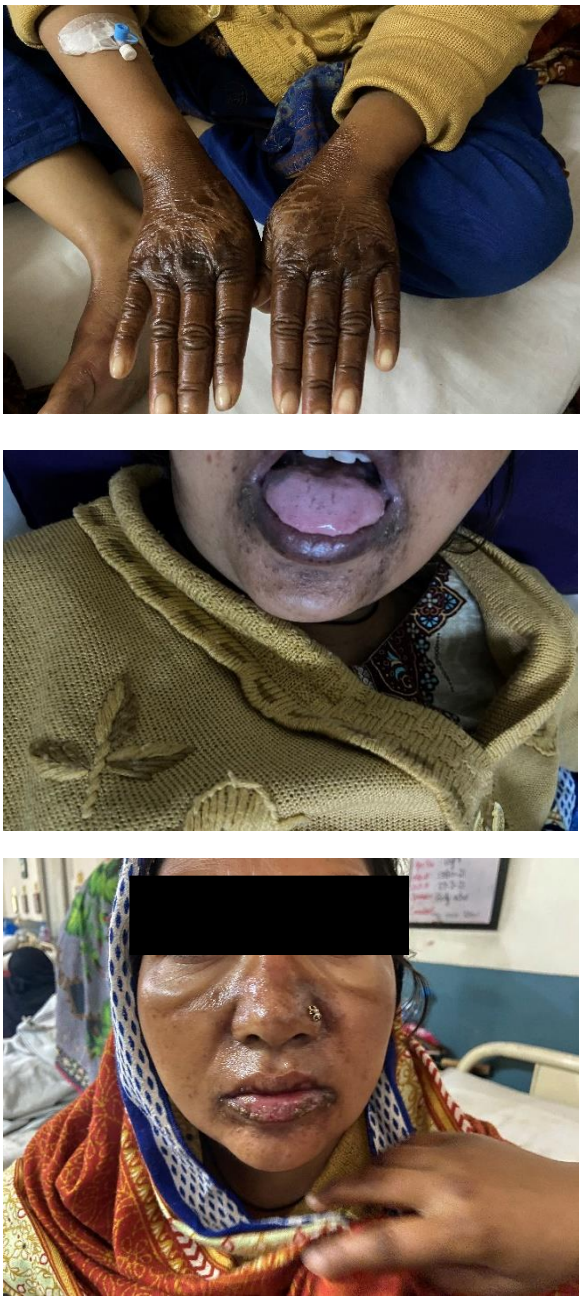
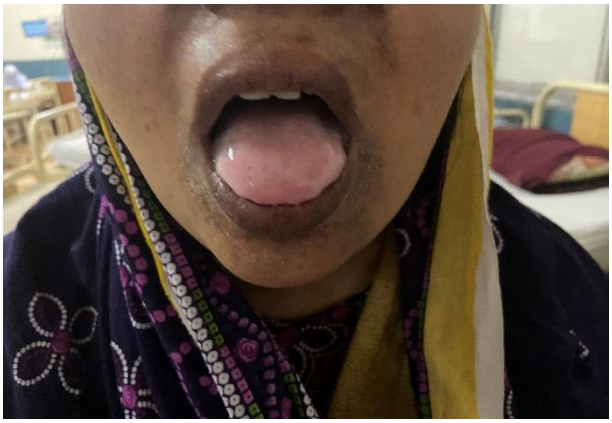


Figure-1: Clinical manifestations before the initiation of treatment

On Laboratory findings, hypochromic normocytic anemia with a Hb of 6.8g/dl, hypokalemia with a value of 2.7 mmol/L, hypocalcemia with 6.9 mg dl was found. CRP was positive and ESR was 102mm 1st hour. Fasting lipid profiles were borderline high with cholesterol 200mg dl and triglycerides 140 mg dl. Thyroid function tests were done and primary hypothyroidism was diagnosed with a TSH level of >100 microIU/ml and T4 levels 0f 0.81 microgram/dl. Serum iron and TIBC were normal. USG abdomen and pelvis showed fatty infiltration of the liver. ECG was low voltage, regular sinus rhythm and echocardiography showed good biventricular function with an ejection fraction of 55-60% and a thin rim of pericardial effusion with approximately 100ml of fluid. The remaining laboratory values were within the normal range.

Niacinamide 500mg in divided doses was started along with multivitamin supplementation, folic acid, and dietary management. She increases caloric intake up to 2400 kilocalories per day focusing on a Niacin-rich diet. The patient's dermatitis, glossitis, and angular stomatitis started improving within the third day of admission, facilitating food intake. By the 8th day of admission, MMSE was repeated and there was an improvement in score from 22 to 24/30 (taking into consideration patient education level) Thyroxine 200 micrograms were started on the 4th day of admission and one blood transfusion was done which brought Hb to 9.0g/dl. The patient´s gastrointestinal symptoms resolved by the time patient was discharged.

After Treatment:



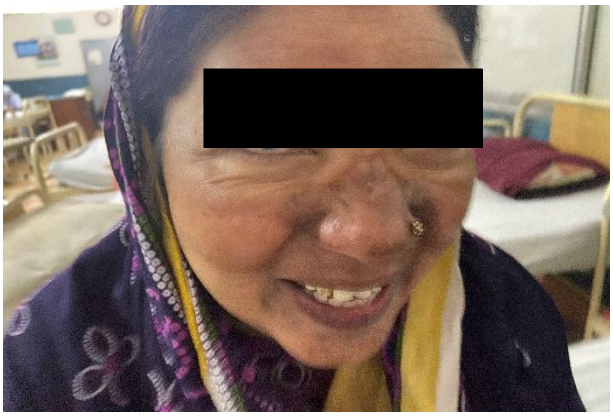


Figure-2: Improvement in clinical signs observed after initiation of treatment

Consent

The authors has produced written counsent of the patient for producing her pictures for academic purpose in Journal.

DISCUSSION

Pellagra is a disorder characterized by the deficiency of the water-soluble vitamin B_3, one of the vital components for various metabolic processes in the body. Pellagra reflects severe malnutrition, as for it to have happened, various other vitamins and amino acids, especially tryptophan, had to be deficient to get a florid manifestation of the disease. Albeit niacinamide can be obtained by tryptophan, the main source of B3 is dietary and storage within the body is minimal, thus a poor suboptimal caloric intake is necessary to cause pellagra. Hence metabolically active cells are the most affected, explaining why the CNS, GIT

system, and skin are the primary target of the disorder resulting in the cardinal features of the disease.[3] Primary pellagra is mainly caused by dietary deficiency, corn-based diets, or eating disorders while secondary pellagra etiology is based on either poor metabolism or poor ability to use niacin within the diet such as in malabsorption syndromes, bypass surgery or subtotal gastrectomy, alcoholism, carcinoid syndrome, Hartnup disease and deficiency of micronutrients use to convert tryptophan to niacin such as riboflavin and pyridoxine.[4] Niacin structural analogs such as isoniazid, 5 fluorouracil, 6 mercaptopurine, and drugs such as anticonvulsants, sulfonamides, chloramphenicol, azathioprine may also lead to pellagra.[5] Nowadays, sporadic cases are reported in rural areas during times of drought and food shortage as well as in food-aid dependent populations during food emergency and refugee programs. Cutaneous findings of pellagra resemble sunburn with papules and occasionally vesicles formation that may exfoliate or may form hyperkeratotic darkly pigmented patches. Facial dermatitis mostly follows the trigeminal nerve distribution and is manifested in a butterfly pattern over the nose and cheeks. Similarly, dermatitis on the neck follows C3 and C4 distribution giving the well-known Cassal´s necklace of Pellagra.[6] In one-third of patients, mucosal surfaces of lips tongue, and oral cavity are involved in the form of glossitis, angular stomatitis, cheilosis, and thrush are seen in niacin deficiency, although these may, in part, be a result of a simultaneous riboflavin deficiency. Inflammation spreads through the gastrointestinal tract, with chronic gastritis and diarrhea typically watery, but it can be mucoid.[3] Neurological symptoms include headache, irritability, poor concentration, anxiety, delusions, hallucinations, fatigue, depression that may progress to confusion, memory loss, and psychosis.[1]

Diagnosis requires a high index of suspicion and is usually done by improvement of symptomatology with the administration of niacinamide. The findings of anemia, low potassium and phosphorus, and higher levels of calcium along with hypoproteinemia may contribute to the diagnosis. Specific tests include Serum niacin levels, tryptophan, NAD, NADP levels, and lower urinary levels of N-methyl nicotinamide and pyridine.[3,4]

A daily average intake of 15–20 mg of niacin prevents pellagra for all age groups. The daily recommended dose is 300 mg of nicotinamide in divided doses, and treatment should be continued for 3–4 weeks.[3] Nicotinamide form is preferable over nicotinic acid because of the side effects such as hot flushing, tachycardia, and itching.[4] Moreover, vitamin B complex preparation, bed rest, and strict dietary management along with photo-protection and emollients should be emphasized during treatment.[3]

CONCLUSION

Our patient presented with the classical symptoms of vitamin B_3 deficiency and primary hypothyroidism. Severe niacin deficiency appeared to unmask the hypothyroid state in our patient. Very few cases have been reported with both concomitant diseases and even though thyroxine may have a role in riboflavin regulation as some case reports showed, there is no evidence of hypothyroid-induced pellagra or pellagra-induced hypothyroidism.[7] Our patient´s dermatitis, diarrhea and neuropsychological symptoms started improving as soon as niacin was administered and diet was improved, however, the complaints attributable to thyroid deficiency, ankle and knee jerk reflexes, and hoarse voice started improving after 2 weeks of thyroxine therapy.

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ML: Conception of Idea
MIH: Data Collection
ROF: Data Analysis
IUR: Review Critically
ZIC: Literature review
MS: Drafting the article

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