IMAGE: A MAP OF THE STARS OF THE ORION CONSTELLATION

JournalPreview

London Journal of Medical and Health Research

Volume 22 | Issue 3 | Compilation 1.0

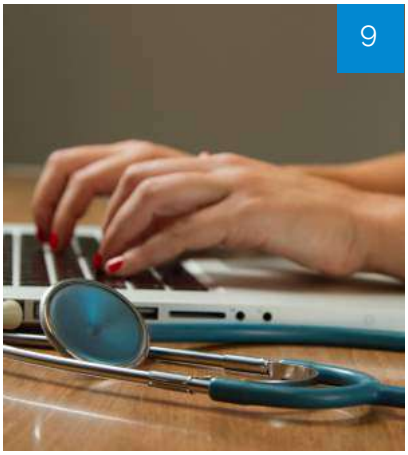
London Journals Press

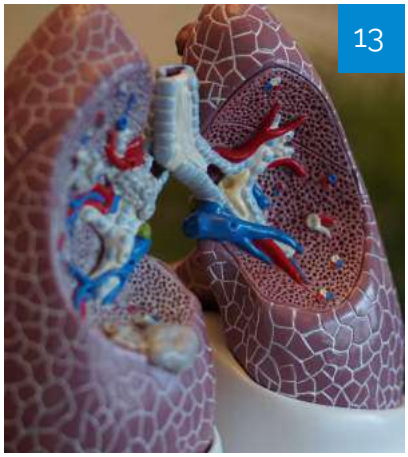
WWW.JOURNALSPRESS.COM

London Journal of Medical and Health Research

Journal Content
In this Issue

London Journals Press





Holistic Approach for Children with Cerebral Palsy Through Specialized Medical Care Clinics

Barrón-Garza, Fabiola; Arredondo-Garza, Pedro; Limón-Moya, Guadalupe; Velazco-Silva, Paulina; Contreras-Guevara Verónica; Alvarado-García, Fabiola; Ríos-Villarreal Jessicaχ; López-de León, Daniela & García-López, Andrea

ABSTRACT

Introduction: Cerebral palsy (CP) is a physically disabling condition affecting between 2 and 3 per 1000 live births and is believed to be the most common cause of severe physical disability in childhood. In addition to posture and movement disorders, these children have aggregate disorders such as limb use, communication, intellectual functioning, health, behavior, and social skills. The life of a family with a child with CP is transformed by obtaining a comprehensive diagnosis and treatment of their child's disorders.

Objective: To publicize the specialized medical approach promoted by the multidisciplinary team in caring for patients with CP through specialized care clinics.

Methodology: In these clinics, a coordinator shows to the consulting physician an average of 8 cases per month, offering clinical information and laboratory and cabinet studies of the patient, which the specialist physician assesses, and medical or surgical indications are offered according to the case. Between 1991 to 2020, care clinics were instituted; They have improved the health status of children with CP.

Keywords: cerebral palsy, malnutrition, orthopedic surgery, gastroesophageal reflux, pediatrics, primary care.

Classification: DDC Code: 303.4840973 LCC Code: HN57

Language: English

London Journal of Medical and Health Research

Volume 22 | Issue 3 | Compilation 1.0

Holistic Approach for Children with Cerebral Palsy Through Specialized Medical Care Clinics

Barrón-Garza, Fabiola[α]; Arredondo-Garza, Pedro[σ]; Limón-Moya, Guadalupe[ρ]; Velazco-Silva, Paulina[CD]; Contreras-Guevara Verónica[¥]; Alvarado-García, Fabiola[§]; Rodriguez-Hernández Ana M[χ]. , Ríos-Villarreal Jessica[ν]; López-de León, Daniela[Θ] & García-López, Andrea[ζ]

ABSTRACT

Introduction: Cerebral palsy (CP) is a physically disabling condition affecting between 2 and 3 per 1000 live births and is believed to be the most common cause of severe physical disability in childhood. In addition to posture and movement disorders, these children have aggregate disorders such as limb use, communication, intellectual functioning, health, behavior, and social skills. The life of a family with a child with CP is transformed by obtaining a comprehensive diagnosis and treatment of their child's disorders.

Objective: To share publicize the specialized medical approach promoted by the multidisciplinary team in caring for patients with CP through specialized care clinics.

Methodology: In these clinics, a coordinator shows to the consulting physician an average of 8 cases per month, offering clinical information and laboratory and cabinet studies of the patient, which the specialist physician assesses, and medical or surgical indications are offered according to the case. Between 1991 to 2020, care clinics were instituted; They have improved the health status of children with CP.

Result: Since the founding of the first clinic, more than 5000 evaluations and more than 32,600 medical visits have been offered to patients with Cerebral Palsy from newborn to 18 years of age in specialized medical and surgical clinics.

Keywords: cerebral palsy, malnutrition, orthopedic surgery, gastroesophageal reflux, pediatrics, primary care.

Author: Research and Development Department. Instituto Nuevo Amanecer ABP.

I. INTRODUCTION

Cerebral Palsy (CP) is a physically disabling condition, affecting between 2 to 3 per 1,000 live births, and is the most common cause of severe physical disability in childhood (1). In a study with an 8-year follow-up in children and adolescents with CP in Mexico, disorders of health integrity, muscle tone, structural state, use of limbs, communication, intellectual functioning, and mental health were found. Behavior and social skills in a range of 56 to 90% of cases (2). The life of a family with a child with CP is transformed by the challenge of obtaining a comprehensive diagnosis of their child's motor and related disorders. Spastic CP is the most common; In these children, hypertonic muscles and skeletal growth condition muscle-tendon and capsular contractures, bone deformities, conditioning more significant disability (3).

On the other hand, in this population, ocular mobility disorders occur in 66% (4). Gastrointestinal problems are a significant chronic problem in most children with CP, and a multidisciplinary approach can contribute to their well-being and quality of life (5); lack of appetite, hyper - salivation, eating dysfunction, and constipation are present in 25 to 38% of cases (6). Gastroesophageal reflux can influence its nutritional results (7), in which surgery offers nutritional and symptomatic improvement (8). Chronic pulmonary complications can include recurrent pneumonia, atelectasis, bronchiectasis, and chronic restrictive lung disease (9). The high prevalence of urinary tract infections in these

children supports effective physical therapy to achieve greater mobility and independence (10). Early provision of postural equipment plays a vital role in preventing hip subluxation/dislocation (11). The application of botulinum toxin has shown clinically significant, short-term improvements in the function of the upper extremities limbs (12).

The Institute Nuevo Amanecer A.B.P., a nonprofit organization with more than 43 years of experience dedicated to improving the quality of life of children and young people with cerebral palsy, has sought new ways to create prevention strategies and improve the care of these children and their families. For this reason, it has promoted and coordinated this clinical study, to continue promoting public policies and strategic alliances that promote the improvement of the quality of life of people with disabilities in the state of Nuevo Leon, Mexico.

II. OBJECTIVE

The objective of this manuscript is to share publicize the medical approach promoted by the multidisciplinary team in the care of patients with CP through specialized care clinics of different medical specialties.

III. METHODOLOGY

The Instituto Nuevo Amanecer A.B.P, is an outpatient care clinic. In 30 years, it has founded and offered systematized care through Specialized Care Clinics (SCC) to attend to this population's motor disorders and added problems; These services are offered within the same institution. The multidisciplinary team member refers the patient to the coordinator of a SCC, who offers a medical appointment to the mother or caregiver.

The team informs to parents the objectives of the respective clinic and the reason for the assessment to their son/daughter. The appointment includes detailed laboratory and X ray studies before their evaluation. The coordinator shows an average of 8 cases per month; she/he mentions the patient's symptoms in each clinic. The patient's medical history is reviewed, and interrogation and physical examination are carried out, and laboratory and cabinet studies results are analyzed. Finally, the pediatric neurologist offers the medical indications, requests complementary laboratory and X ray studies, and surgical if applicable. The social worker facilitates the performance of these procedures. There are agreements with different public and private hospitals to perform surgical procedures at no cost or minimal cost to the patient. In other cases, some foundations pay it directly to the hospital.

The clinics began in 1991, and from that date, others have been founded according to the needs of patients.

The clinics began in 1991, and from that date, others have been founded according to the needs of the patients.

These clinics began in 1991, and from that date, others have been founded according to the needs of the patients.

IV. RESULTS

Profile of families. Almost half of the families are married couples: 47%. 28% Free union, 11% Single mothers 8%, Separated 6%, Divorced or widowed. Socio-economic level: 70% Medium-low, 17% Low. Medical Service: 48%. Right holders of Federal Insurance for low-income families, 48%, 43% have Health Ministry Insurance for families with formal employment, and 9% have medical insurance for employees of the education sector.

The Institute offers medical care, physiotherapy, occupational therapy, nutrition, early stimulation, regular care for high risk children, vaccinations, dental care, imaging services, postural care, and locomotion equipment, among others.

The institute has provided care to 25,961 patients in 43 years. The medical department consists of a Family physician, physiatrist, pediatric neurologist, and orthopedist and has offered more than 272,000 highly specialized medical visits and 888 medical-surgical procedures in the SCC.

V. ORTHOPEDIC CLINIC

Participants: Pediatric orthopedist, physiatrist, social worker.

Objective: To provide patients with CP with a highly specialized diagnosis and treatment of orthopedic problems and musculoskeletal deformations through a medical visit with the pediatric orthopedic doctor and physiatrist, offering them a medical, therapeutic, postural, and surgical treatment.

Procedure: The multidisciplinary team refers the patient to the Orthopedic Clinic, together the patient is evaluated, their radiological studies are reviewed, and treatment is scheduled. If postural care is required, he is referred to the Postural Care Clinic and is provided with postural equipment. When Botulinum Toxin or orthopedic surgery is required in local hospitals, physicians explain to parents or caregivers the needs and objectives of this treatment, and the social worker advises them. The most frequently encountered problems in this clinic are hip dislocation and spine deviations (scoliosis and kyphosis, among others). The most frequently implemented treatments have been: postural management, application of Botulinum Toxin in the lower limbs, multilevel tenotomy of the lower limbs, (adductor hip, hamstring, and Achilles tendon tenotomy). If orthoses are needed, they are custom-designed, manufactured by an external vendor, and delivered to the institution.

Two thousand and eight hundred medical visits and 902 orthopedic surgeries such tenotomies and osteotomies among others, have been performed. There have been more than six hundred applications of botulinum toxin, and more than 1900 references to postural management.

VI. OPHTALMOLOGY CLINIC

Participants: Pediatric ophthalmologist, Family physician, nurse, and social worker.

Objective: Offer a systematic preventive, palliative, and surgical evaluation and intervention in ophthalmological problems to patients with CP.

Procedure: When visual disorders are clinically detected in patients, they are referred by psychologists, therapists or teachers to this clinic. The Family physician introduces patients to an ophthalmologist at the same institution, and they are referred to a specialized clinic. This requests specialized studies and prescribe a treatment such as ophthalmic patches, lenses, or surgery; all families are advised and supported by the social worker. The surgeries are performed through a collaboration agreement with a local clinic and foundation. The most frequent treatments are strabismus corrections and the prescription of lenses for refractive defects.

There have been one thousand, nine hundred and sixty medical visits, 300 strabismus correction surgeries, 1500 visual refraction evaluations, and many lenses have been awarded.

VII. NUTRITION AND GASTROESOPHAGEAL REFLUX CLINIC

Participants: Pediatric Gastroenterologist, Family physician, nutritionist, and Social worker.

Objective: Assess CP patients with undernutrition, digestive, and feeding disorders.

Procedures: Physicians analyze the clinical history, nutritional status, and reason for the patient & #39;s visit. Laboratory studies such as (Hematic biometry, Biochemical Profile, Albumin Globulin Ratio, and Guayaco in feces), among others, are analyzed. Video-fluoroscopy (swallowing mechanism and esophagogram), scintigraphy, and ph-metry are also analyzed, depending on the case. The most frequent diagnoses in this clinic have been: Feeding disorders gastroesophageal reflux disease, undernutrition, aspiration, and constipation, among others. Each patient is offered a treatment that includes oral-motor therapy, antacids, proton pump inhibitors, prokinetics and laxatives, a hypercaloric and hyper protein diet, (depending on the case).

This clinic has carried out more than two thousand and three hundred nutritional visits and has given indications for more than 2000 oral-motor therapy, and dietetic supplements have been prescribed, and references to pediatric surgery when apply.

VIII. PEDIATRIC SURGERY CLINIC

Participants: Pediatrician surgeon, Family physician, and social worker.
Objective: Assess patients with CP who are referred to evaluate surgical interventions. Mainly of the digestive and urinary system, or in case of requiring hernioplasty procedures or corrections of congenital malformations.

Procedure: Patients determined to require a surgical approach during the gastroenterology or urology evaluation are evaluated in this clinic. These are showed by the Family physician to the pediatric surgeon, describing the clinical manifestations and analyzing their laboratory and cabinet studies. If surgery is required, this is performed in local hospitals.

Frequent cases referred to this clinic are: Nissen Fundoplication, Gastrostomy, Hernioplasty procedures, Orchidopexies, or Circumcisions. Oromotor therapy is also offered to patients with gastrostomy due to an eating disorder, and indications to the primary caregiver for the use of gastrostomy and gastric button. When appropriate and linked to evolution, gastrostomy closure is also performed.

Since its foundation, more than one thousand and six hundred medical visits and 140 surgeries of different kinds have been performed (gastrostomy button, gastrostomy closure, Nissan surgery, and others).

IX. RESPIRATORY PROBLEMS CLINIC

Participants: Otolaryngologist, pediatric pneumonologist, Family physician, and social worker.

Objective: To offer patients with CP a highly specialized diagnosis and treatment in the case of chronic or recurrent respiratory diseases, as well as hearing loss.

Procedure: The multidisciplinary team detects and refers patients with recurrent respiratory problems for evaluation. The Family physician assesses the patient and requests the necessary studies. (Hematic Biometry, Paranasal Sinus Rx, Thorax Tele). The patient is referred to the otorhinolaryngologist, who assesses the patient, analyzes his clinical data, x-rays, and laboratory and office tests. After evaluation, some complementary studies are requested if necessary, such as scintigraphy, and ph-metry; after its analysis, treatment is prescribed. The most frequent diagnoses in this clinic have been: sinusitis, sinubronchial syndrome, bronchitis, pneumonia, otitis media, allergic rhinopharyngitis, bronchial aspiration, and adenoid hypertrophy. The most frequently prescribed medications have been antibiotics, antihistamines, anti-inflammatories,bronchodilators, and immuno-modulatory drugs.

The most frequent surgeries have been:

Tonsillectomy and myringotomy. In case of hearing loss, studies such as auditory evoked potentials and tympanometry, among others, are requested after evaluating the patient. Support are offered to carry out these studies, to obtain medications, hearing aids, and perform surgeries by the support of social worker.

The Family physician follows up and makes a new appointment at the clinic to see the results of studies and treatment.

This clinic has performed more than one thousand eight hundred medical visits, more than 100 surgical procedures as tonsillectomies and adenoid hypertrophy, myringotomies, more than 200 evaluations of hearing loss, and 150, auditory evoked potentials, among others.

X. CLINIC OF UPPER LIMBS

Participants: Plastic surgeon with a sub-specialty in the upper limb, occupational therapist, physiatrist, and social worker.

Objective: To evaluate patients with CP who have spasticity or hand/arm deformities.

Procedure: Cases with spastic upper limbs are referred by the multidisciplinary team to the department of family medicine. The patient is evaluated by the upper limb clinic coordinator occupational therapist and is classified according to his manual abilities and degree of spasticity, and radiological studies are carried out necessary for the assessment. During the visit, the participation in activities of daily living is analyzed to design functional goals in their treatment, including botulinum toxin application or surgery, with the social worker's support. After these procedures, a new evaluation of the manual abilities of the patients is carried out, and the necessary modifications are made to the occupational therapy treatment plan. In cases where splints are required; these are manufactured in a personalized way in the same institution.

This clinic has offered more than one thousand and two hundred medical visits, and also applied more than 6 hundred botulinum toxin specialy in hands and arms, and provided of more than 600 upper limb splints.

XI. POSTURAL MANAGEMENT CLINIC

Participants: Physiatrist, occupational therapist, an expert in postural management, biomedical engineer, and social worker.

Objective: To carry out a postural diagnosis to the patient and offer the design and manufacture of personalized postural aids.

Procedures: Patients with postural management disorders are referred to the Postural Care Clinic by the multidisciplinary team. Expert doctors and therapists evaluate them with the Chailey Approach Technique in prone and supine decubitus, sitting and standing, and a Chailey bed, modular or body contour seat, and stabilizer. The seats are inserted in conventional or power wheelchairs. Parents or caregivers receive the social worker's support from local organizations or foundations for their acquisition.

More than 3,000 postural management evaluations and the corresponding manufacture of the personalized postural management equipment have been carried out according to each patient needs, and more than 1200 equipments have been manufactured in the institution.

XII. UROLOGY CLINIC

Participants: Urologist, Family physician, nurse, and social worker.

Objective: To diagnose and take care of patients with CP and urological disorders.

Procedures: Patients with urination disorders, signs of urinary infection, and or at/the beginning of a sphincter control program are referred to this clinic by the multidisciplinary team. Before the examination, a general urine test is performed. The medical history and signs of urological disorders are analyzed during the evaluation, a physical examination focused on detecting urinary tract and genital malformations.

At the end of the evaluation, studies are requested, such as voiding cystourethrogram, urological ultrasound, and urine culture. As applicable, which are carried out with the social worker's support and medical or surgical treatment. A medical follow-up is carried out at the end of the procedure until the urinary problem is resolved. In the case of a urinary sphincter control program, nursing follow-up is offered to the patient once urological pathology has been ruled out. The most frequent diagnoses are urinary tract infection, cryptorchidism, phimosis, and congenital malformations.

This clinic is the most recent and has granted more than 500 urological visits.The most frequent pathologies detected have been chryptorchidism, and phymosis.

XIII. PNEUMOLOGY CLINIC

Participants: Pulmonologist, family doctor, and social worker.

Objective: Provide patients with a highly specialized diagnosis and treatment in chronic and recurrent respiratory diseases through a specialized medical consultation, thus increasing their quality of life of these children.

more than 100 urological visits.

Procedures: The multidisciplinary team detects and refers patients with respiratory problems to the Medical Department. They request laboratory studies such as blood counts and cabinet studies such as chest teleradiography and polysomnography.

The treatment plan may include medical or surgical treatment and, if required, referral to another specialty or hospital .In this CSS more than 500 medical visits have been made, Frequent diagnoses in this clinic are: recurrent pneumonia secondary to aspiration due to gastroesophageal reflux disease or allergies, bronchial hyperreactivity, laryngomalacia, and decreased ventilatory capacity secondary to scoliosis. Moreover, treatment includes antibiotic therapy, inhalation therapy, and percussive therapy.

XIV. SPASTICITY CLINIC

Participants: Pediatric neurologist, physical therapist, and social worker.

Objectives: To provide patients with a highly specialized diagnosis and treatment of spasticity problems and contribute to obtaining more satisfactory result in their rehabilitation.

Procedures: The patient level of spasticity and current weight are considered, and gross motor function classification system, (GMFCS).

They are evaluated with Modified Ashworth Scale, (MAS), and analyzing Reimer index.

The Coordinator presents the case to the consulting physician. The most frequently used studies are pelvic X rays to assess hip subluxation or dislocation.

The most frequent pathologies detected have been contractures of upper and lower limbs.

Treatment generally consists of administering muscle relaxants such as oral baclofen, the application of botulinum toxin, physical therapy, hydrotherapy, upper and lower limbs splints, and reference to postural management and/or orthopedic surgery. In this clinic, more than 340 patients have been assessed and more than 80 botulinum toxin have been applied with the support of social workers.

XV. DISCUSSION

In countries where few organizations provide highly specialized and rehabilitative care to children and young people, patients with CP and their families require multidisciplinary care coordinated with inter-institutional links that provide them with comprehensive care.

Laboratory and office studies, medications, postural aids, and surgeries necessary to provide this care can be facilitated through agreements with local hospitals and foundations. Therefore, we urge organizations that serve children and youth with CP to use this care methodology to provide greater well-being to these children and their families.

Some institutions in countries such as England (13) and the USA (14) use similar models of specialized care clinics for the comprehensive approach to patients with CP.

XV. CONCLUSIONS

The SCC have had a satisfactory result, for over 27 years, more than 15000 evaluations have been provided, and an average of 24 surgeries and procedures per year for children with CP from low-income families of northeastern Mexico. The results have been reflected in improving the patients' physical well-being attended.

THANKS

Dr. Adriana Bustamante Sáenz, Dr Alberto MorenoGonzález, Dr Arturo Garza Peña, Dr. Fernando de la Garza Salazar, Dr. Jorge Bernardo Elizondo Vázquez, Dr. José Alfredo Neira Garza, Dr. Juan Homar Páez Garza, Dr. María Esther Garza Montufar, Dr. Mario Riquelme Heras, Dr. Mauricio García Pérez, Dr. Ricardo de Hoyos Parra, Ms. Sarah Elizabeth Davies, Dr. Ulises Leal Quiroga. And MEDICT (Mexican Disabled Children's Trust) (England Foundation)

Hospitals: Universitario UANL, Shrinners, Clínica Santa María, and Foundations Santos y de la

Garza Evia, Adelaida Lafón, Zambrano Hellion, y TEC Salud.

BIBLIOGRAFÍA

1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007; 109(suppl 109): 8-14. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2007.tb12610.x/full
2. Barrón-Garza F, Riquelme-Heras HM, Ibarra-Rodríguez MC, et al. Functional assessment of patients with cerebral palsy by the abilities index. Rev Mex Pediatr. 2015;82(3):87-92. https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDREVISTA=30&IDARTICULO=61519&IDPUBLICACION=6105
3. Beguiristain, J. Clinical Logic in Orthopaedic surgery for cerebral palsy. Revista de Neurología 2003; 37(1): 51-54 https://europepmc.org/article/med/12861509.
4. Arroyo M; Benítez N A; Garrido E. Comportamiento del estrabismo en pacientes con parálisis cerebral infantil. Cir Ciruj 1999; 67(6): 208-211 https://www.imbiomed.com.mx/articulo.php?id=7592.
5. González Jiménez D1, Díaz Martin JJ, Bousoño García C, Jiménez Treviño S. Gastrointestinal disorders in children with cerebral palsy and neurodevelopmental disabilities. Anales de Pediatria 2010; 73 (6): 361.e1-6 https://europepmc.org/article/med/20817582.
6. Erkin, Gulten; Culha, Canan; Ozel, Sumru; Kirbiyik, Eylem Gulsen. Feeding and gastrointestinal problems in children with cerebral palsy. International Journal of Rehabilitation Research 2010; 33(3): 218-224 doi:10.1097/MRR.0b013e3283375e10https://journals.lww.com/intjrehabilres/Abstract/2010/09000/Feeding_and_gastrointestinal_problems_in_children.5.aspx.
7. Çaltepe G, Yüce Ö, Comba A, Özyürek H, Kalaycı AG, Taşdemir HA. Detection of gastroesophageal reflux in children with cerebral palsy using combined multichannel intraluminal impedance-ph procedure. Turk J Pediatr 2016; 58(5): 524-531. https://www.turkishjournalpediatrics.org/uploads/pdf_TJP_1639.pdf.
8. O'Loughlin EV1, Somerville H, Shun A, Gangemi R, La Hei E, Desphande A, O'Loughlin TF. Antireflux surgery in children with neurological impairment: caregiver perceptions and complications. J Pediatr Gastroenterol Nutr 2013; 56(1): 46-50. doi: 10.1097/MPG.0b013e318267c320https://journals.lww.com/jpgn/fulltext/2013/01000/Antireflux_Surgery_in_Children_With_Neurological.12.aspx
9. David W. Pruitt, MD, TobiasTsai, MD. Common Medical Comorbidities associated with Cerebral Palsy. Phys Med Rehabil Clin N Am 2009; 453–467 doi:10.1016/j.pmr.2009.06.002 https://www.pmr.theclinics.com/article/S1047-9651(09)00024-2/fulltext.
10. Emmanuel Adémólá Anígilájé and Terkaa Terrumun Bitto. Prevalence and Predictors of Urinary Tract Infections among Children with Cerebral Palsy in Makurdi, Nigeria. International Journal of Nephrology 2013e; Article ID 937268: 7 pages https://www.hindawi.com/journals/ijn/2013/937268/
11. Pountney TE1, Mandy A, Green E, Gard PRHip subluxation and dislocation in cerebral palsy - a prospective study on the effectiveness of postural management programs. Physiother Res Int 2009; 14 (2): 116-27 https://doi.org/10.1002/pri.434https://online library.wiley.com/doi/abs/10.1002/pri.434.
12. Koman LA1, Smith BP, Williams R, Richardson R, Naughton M, Griffin L, Evans P. Upper extremity spasticity in children with cerebral palsy: a randomized, double-blind, placebo-controlled study of the short-term outcomes of treatment with botulinum A toxin. J Hand Surg Am. 2013; 38(3): 435-46 https://doi.org/10.1016/j.jhsa.2012.12.019.
13. Pountney, A. Mandy, E. Green. Management of hip dislocation with postural management. Child Care Health and development 2002; 28(2):179-185 https://doi.org/10.1046 /j.1365-2214.2002.00254.x.
14. The Children Hospital San Antonio, Tx. Ortopedia: https://kidshealth.org/ChildrensHospitalSanAntonio/es/parents/scoliosis-brace.html.

This page is intentionally left blank

Syndrome of Inappropriate Anti Diuretic Hormone (SIADH) Presenting with Recurrent Hiccups in a Case of Small Cell Neuroendocrine Carcinoma of Lung with Concomitant Pulmonary Tuberculosis

Saurabh Puri

ABSTRACT

Tuberculosis (TB) and lung cancer are the leading cause of mortality and morbidity in the world. Burden of TB is significantly high in developing countries causing serious public health concern, and incidence of lung cancer is also increasing all around the world with high mortality. Pulmonary TB coexisting with lung cancer can mask the underlying disorder producing diagnostic dilemma resulting in delay in diagnosis leading to decreased survival of the patients. Here we report a rare case of a 66-year-old male diagnosed microbiologically confirmed TB along with coexisting small cell neuroendocrine carcinoma of lung presenting with SIADH.

Keywords: pulmonary tuberculosis, lung carcinoma, small cell neuroendocrine tumor, hiccups, SIADH.

Classification: DDC Code: 618.97689 LCC Code: RC451.4.A5

Language: English

London Journals Press

LJP Copyright ID: 392833

London Journal of Medical and Health Research

Volume 22 | Issue 3 | Compilation 1.0

Syndrome of Inappropriate Anti Diuretic Hormone (SIADH) Presenting with Recurrent Hiccups in a Case of Small Cell Neuroendocrine Carcinoma of Lung with Concomitant Pulmonary Tuberculosis

Saurabh Puri

ABSTRACT

Tuberculosis (TB) and lung cancer are the leading cause of mortality and morbidity in the world. Burden of TB is significantly high in developing countries causing serious public health concern, and incidence of lung cancer is also increasing all around the world with high mortality. Pulmonary TB coexisting with lung cancer can mask the underlying disorder producing diagnostic dilemma resulting in delay in diagnosis leading to decreased survival of the patients. Here we report a rare case of a 66-year-old male diagnosed microbiologically confirmed TB along with coexisting small cell neuroendocrine carcinoma of lung presenting with SIADH.

Keywords: pulmonary tuberculosis, lung carcinoma, small cell neuroendocrine tumor, hiccups, SIADH.

I. INTRODUCTION

One of the leading cause of cancer related mortality worldwide is lung carcinoma, whereas TB is major cause of morbidity and mortality in developing countries, despite availability of effective antibiotic therapy. Simultaneous or concomitant coexistence of both the disease is poorly understood and under reported but causes serious impact on outcome of patients along with public health. Due to similar clinical and radiological presentation of both TB and lung cancer, it is often overlooked and there is delay in diagnosis causing poor outcome of the patients. We present a case of an elderly male who was suffering from pulmonary TB and was diagnosed with coexistent small cell neuroendocrine lung carcinoma on further investigation in view of persistent hyponatremia not responding to IV normal saline.

II. CASE REPORT

A 66-year-old male presented with complaints of nausea, persistent vomiting, weight loss and loss of appetite from last 30 days followed by continuous hiccups since 14 days. He is a known case of diabetes mellitus, on regular treatment. He was diagnosed with pulmonary TB and anti-tubercular therapy (ATT) was initiated 21 days back. On examination, he was conscious, oriented to time, place and person. At admission, his vitals were pulse rate 118/min, blood pressure 110/80 mmHg, respiratory rate 24/min, oxygen saturation (Spo_2) 97% on room air, temperature 99°F, random blood sugar 96 mg/dl. General examination revealed dry tongue and systemic examination revealed decreased breath sound in left supra and infraclavicular region. Blood count revealed normal hemoglobin, leukocyte count and platelet count (Hb 12.0 gm/dl, TLC 6.54 x 10^9/L, Platelet 243 x 10^9/L). Liver function test revealed transaminitis (SGOT 194.8 U/L, SGPT 263.0 U/L, ALP 88 U/L, GGTP 51 U/L). Renal profile showed normal urea and creatinine with hyponatremia (sodium 114 mmol/L, potassium 4.4 mmol/L). Chest X ray PA view showed homogenous opacity in left upper and mid zone (figure 1). He was

London Journal of Medical and Health Research

managed with intravenous normal saline, proton pump inhibitor and anti emetic. His serum sodium was repeated next day which was further decreased to 112 mmol/L. Normal saline was stopped and intravenous 3% saline was initiated, however his serum sodium further dropped to 109 mmol/L. Workup for hyponatremia was done which revealed normal serum uric acid (4.8 mg/dl), low serum osmolality (224 mOsm/Kg), high urine osmolality (540 mOsm/Kg), spot urine sodium (120 mmol/L) suggestive of SIADH. His fluid intake was restricted to 1 litre/day.

Serial monitoring of serum sodium was done which revealed rising trend after fluid restriction was initiated. Contrast enhanced computed tomography (CECT) chest was done which showed .....(figure 2, 3) USG guided lung biopsy showed poorly differentiated carcinoma favoring small cell carcinoma with granulomatous inflammation in surrounding tissues with immunohistochemistry which was Tumor cells express Synaptophysin and CD56, Ki-67 proliferation index - 60%. (figure 4,5) PET/CT scan was done to rule out any metastasis, revealed a large FDG Avid heterogenous enhancing lobulated mass lesion involving anterior segment left lung upper lobe, extending to left suprahilar region encasing the left pulmonary artery and abutting arch of aorta suggestive of malignant etiology. (figure 6) Final diagnosis was made as SIADH induced by small cell neuroendocrine carcinoma lung with concomitant Pulmonary TB, and he was referred to oncologist for further management of lung carcinoma with continuation of ATT.

III. DISCUSSION

Since coexistence of Lung carcinoma and pulmonary TB was first reported by Bayle in 1810,[1] both lung carcinoma and TB, are important cause of morbidity and mortality, especially in poor and developing countries.[1,2] However, association between both the disease seldomly discussed, but it creates great impact over public health.[3] 0.7% cases of lung cancer have been found to have pulmonary TB, whereas Chandra et al found 17% cases of lung carcinoma were suffering from pulmonary TB.[4,5] Both diseases can occur in following patterns: 1) carcinoma over TB ground, reactivating old focus of TB. 2) carcinoma from previous TB scars (scar carcinoma). 3) carcinoma from epithelium metaplasia of TB cavities. 4) Independent and develop simultaneously. 5) Metastatic carcinoma in old TB lesion. 6) secondary TB in cancer patient.[6] Our case both the disease possibly occurred independently and develop simultaneously. Wu et al proposed theory of reverse causality explaining reactivation of latent TB due to weakened host immune system caused by occult lung cancer and diagnosed during the TB treatment.[7]

Clinically both pulmonary TB and lung cancer can present clinically with fever, loss of appetite, weight loss, fatigue, chest pain, hemoptysis along with similar radiological features leads to delay in diagnosis and management causing poor outcome.[8] Lung cancer is often overlooked and delayed due to masking by tubercular lesion in active TB cases.[9] Similar to our case, Ting et al. suggested radiographic features increasing suspicion of lung carcinoma in patients with preexisting pulmonary TB, foremost was progression of pulmonary infiltrates while on anti tuberculosis drugs.[10] Histologically, most common type was non small cell lung cancer, especially adenocarcinoma,[2] however in the case described above, he was found to have small cell neuroendocrine lung carcinoma.

Since SIADH in lung cancer was described in 1957 by Schwartz,[11] 10% patients of lung cancer present with paraneoplastic syndrome, with SIADH occurring in 7-16% patients of SCLC, linked with worst outcome.[12,13]

IV. CONCLUSION

Physicians should be aware of protean manifestations of both TB and cancer and simultaneous coexistence should be considered in high index of suspicion due to misleading clinical and radiological presentations. In patients who are non responsive to anti tubercular therapy and radiological worsening, physicians should look for other potential diagnostic clues and go for establishing additional diagnosis.

REFERENCES

1. C.H. Bayle, Recherches sur la phitisue pulmonaire, Galon, Paris, France, 1810.
2. Silva DR, Valentini DF Jr, Müller AM, de Almeida CP, Dalcin Pde T. Pulmonary tuberculosis and lung cancer: simultaneous and sequential occurrence. J Bras Pneumol. 2013 Jun-Aug;39(4):484-9.
3. Liang HY, Li XL, Yu XS, Guan P, Yin ZH, He QC, Zhou BS. Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review. Int J Cancer. 2009 Dec 15;125 (12):2936-44.
4. Tamura A, Hebisawa A, Tanaka G, Tatsuta H, Tsuboi T, Nagai H, Hayashi K, Sagara Y, Kawabe Y, Akagawa S, Nagayama N, Machida K, Kurashima A, Sato K, Fukushima K, Yotsumoto H, Mori M. [Active pulmonary tuberculosis in patients with lung cancer]. Kekkaku. 1999 Nov;74 (11):797-802. Japanese.
5. Chandra S, Mohan A, Guleria R, Singh V, Yadav P. Delays during the diagnostic evaluation and treatment of lung cancer. Asian Pac J Cancer Prev. 2009 Jul-Sep; 10(3):453-6.
6. Harikrishna, Janjam, V Sukaveni, D. Prabhath Kumar and Alladi Mohan. "Cancer and tuberculosis." (2012).
7. Wu CY, Hu HY, Pu CY, Huang N, Shen HC, Li CP, Chou YJ. Pulmonary tuberculosis increases the risk of lung cancer: a population-based cohort study. Cancer. 2011 Feb 1;117(3):618-24.
8. Kaur, A., Kajal, N. and Goyal, A., 2021. Lung cancer coexisting with pulmonary tuberculosis: A rare case report. *Indian Journal of Respiratory Care*, 10(1), p.126.
9. Singh SK, Ahmad Z, Bhargava R, Pandey DK, Gupta V, Garg PK. Coincidence of tuberculosis and malignancy: a diagnostic dilemma. South Med J. 2009 Jan; 102(1) :113.
10. Ting YM, Church WR, Ravikrishnan KP. Lung carcinoma superimposed on pulmonary tuberculosis. Radiology. 1976 May; 119(2): 307-12.
11. SCHWARTZ WB, BENNETT W, CURELOP S, BARTTER FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med. 1957 Oct; 23(4): 529-42.
12. Vanhees SL, Paridaens R, Vansteenkiste JF. Syndrome of inappropriate antidiuretic hormone associated with chemotherapy-induced tumour lysis in small-cell lung cancer: case report and literature review. Ann Oncol. 2000 Aug;11 (8): 1061-5.
13. Gross AJ, Steinberg SM, Reilly JG, Bliss DP Jr, Brennan J, Le PT, Simmons A, Phelps R, Mulshine JL, Ihde DC, et al. Atrial natriuretic factor and arginine vasopressin production in tumor cell lines from patients with lung cancer and their relationship to serum sodium. Cancer Res. 1993 Jan 1;53(1):67-74.

This page is intentionally left blank

Prevalence and Pattern of Aphrodisiac use among Adult Population in Sokoto Metropolis, Northwest Nigeria

Habibullah Adamu, Adamu Ahmed Adamu, Blessing Cletus, Lukman Marafa & Muhammad Abdulmalik

Usmanu Danfodiyo University

ABSTRACT

Aim: This study aims to determine the prevalence and pattern of aphrodisiacs use and associated side effects among adult population in Sokoto metropolis, Sokoto state Nigeria.

Methodology: It was a cross-sectional study carried out in Sokoto metropolis among 207 adults selected via a multistage sampling technique. Data was collected using semi- structured questionnaire and were analyzed using IBM SPSS version 23.

Results: The mean age of respondents was 35.23 years. The prevalence of aphrodisiacs use among adults in Sokoto metropolis was 138(67.6%) and up to 64(46.2%) of them have used it within the past one month. More than half (53.1%) of the respondents' partners knew they were using aphrodisiacs; 49 (66.3%) of their partners are in support of it and 101(73.2%) expressed satisfaction with the sexual performance of the respondents. Up to 61.6% of the aphrodisiacs consumed were local herbs and the major route of administration was oral route. Gender, marital status, level of education and occupational status were significantly associated with the use of aphrodisiacs ($p<0.05$).

Keywords: prevalence, pattern, aphrodisiacs, adult population, Sokoto.

Classification: DDC Code: 361.4 LCC Code: HV45

Language: English

London Journals Press

LJP Copyright ID: 392834

London Journal of Medical and Health Research

Volume 22 | Issue 3 | Compilation 1.0

Prevalence and Pattern of Aphrodisiac use among Adult Population in Sokoto Metropolis, Northwest Nigeria

Habibullah Adamu[α], Adamu Ahmed Adamu[σ], Blessing Cletus[ρ], Lukman Marafa[Ↄ] & Muhammad Abdulmalik[¥]

ABSTRACT

Aim: This study aims to determine the prevalence and pattern of aphrodisiacs use and associated side effects among adult population in Sokoto metropolis, Sokoto state Nigeria.

Methodology: It was a cross-sectional study carried out in Sokoto metropolis among 207 adults selected via a multistage sampling technique. Data was collected using semi-structured questionnaire and were analyzed using IBM SPSS version 23.

Results: The mean age of respondents was 35.23 years. The prevalence of aphrodisiacs use among adults in Sokoto metropolis was 138(67.6%) and up to 64(46.2%) of them have used it within the past one month. More than half (53.1%) of the respondents' partners knew they were using aphrodisiacs; 49(66.3%) of their partners are in support of it and 101(73.2%) expressed satisfaction with the sexual performance of the respondents. Up to 61.6% of the aphrodisiacs consumed were local herbs and the major route of administration was oral route. Gender, marital status, level of education and occupational status were significantly associated with the use of aphrodisiacs (p<0.05).

Conclusion: Prevalence of aphrodisiacs use is high among men and women in Sokoto metropolis and it is associated with gender, marital and education. Government and health workers at all levels should intensity efforts to educate the masses about the use and associated side effects through the media such as radio, television and the internet, also communication between couples should be encouraged rather than the use of the substances.

Keywords: prevalence, pattern, aphrodisiacs, adult population, sokoto.

Author α ρ Ↄ ¥: Department of Community Health, Usmanu Danfodiyo University, Sokoto, Nigeria.
σ: Department of Pharmacology and Therapeutics, Usmanu Danfodiyo University, Sokoto, Nigeria.

I. INTRODUCTION

The need to increase sexual arousal, sexual pleasure and sexual potency can be said to be as old as life itself. Men and women have for centuries sought different ways of gaining sexual fulfilment including the use of aphrodisiacs; this quest has been shown to increase rather than decline over the years.[1] An aphrodisiac can be described as any substance that enhances sex drive and or sexual pleasure.[1]The name comes from Aphrodite, the Greek goddess of sexuality and love; and substances used are derived from plants, animals or minerals.[1] Aphrodisiacs can be classified according to their mode of actions into three groups namely: substances that increase libido (i.e., sexual desire, arousal), substances that increase sexual potency (i.e., the effectiveness of erection) and substances that increase sexual pleasure.[2]

Makwana, and colleagues noted that the sale and use of these drugs often without medical prescriptions have been on the ascendency as they are now frequently advertised in both print and electronic media.[3] It is common to find sex enhancing drugs being sold in markets, bus stations, supermarkets and along the streets. Ironically, most of these drugs sold openly are not registered with the Food and Drugs Authority (FDA).[4] Globally, the use of either the orthodox

or non - orthodox form of aphrodisiacs is increasing, especially the herbal type aphrodisiacs. The World Health Organization (WHO) estimates that in many developed countries, 70% to 80% of the population have used some forms of alternative or complementary medicine including aphrodisiac substances.[5]

The use of sex enhancing drugs globally varies from country to country. For instance, in the United States, a study revealed that 4% of undergraduate men use erectile dysfunction medicines for recreational purposes,[6] in Buenos Aires, Argentina, a study among young men between 18 and 30 years of age in a public area showed that 21.5% of the men said they used sildenafil at least once in their lives.[7] In Saudi Arabia,[8] the use of sex enhancing medication among sexually active adults was found to be 39.9% and in Malaysia, use of traditional medicines for aphrodisiac purpose was found to be 38.26% among the general public in Penang.[9]

In Africa, studies have shown high prevalence of aphrodisiac use.[4,10] Ghanaians, especially men, are known to frequently use aphrodisiacs and are not keen on the type as long as it enhances their sexual function;[4] a study conducted in a municipal district of Ghana showed that up to 66.4% of the sampled men use aphrodisiac.[10] Another study in Ghana also reported the prevalence of sexual stimulants use to be 61%.[11] In Nigeria, the use of herbal substances to enhance sexual performance is quite high in many communities. In a study carried out in Calabar, Nigeria, the prevalence of sexual stimulants use was found to be 98%[12] and in Kano State Nigeria, more than half of the respondents (53.9%) in a study have used sexual stimulants.[1]

Regarding the pattern of aphrodisiac use among adult population, various forms are reported to be in use in many communities in Nigeria. In a study conducted in Kwara State on the pattern of aphrodisiac drug use among married adults, it was reported that most of the aphrodisiacs used are mainly the oral types (drinks, chewable herb, licks) and ointment to rub the private part to increase sexual energy, flavor and etc.[13] In Kaduna State, Nigeria, not less than 20 varieties of oral forms of herbal preparations were mentioned during interviews in a study. These include; tiger nut (Aya in Hausa language) which is thought to be good for both men and women in improving sexual performance.' Dates mixed with sugarcane watermelon and grapes are also believed to be useful.[14] Moringa seeds, 'Garin Tarmu' (a powdered formulation which tightens the vaginal mucosa) and '*Garda*lli' (herb that looks like small white onions) are believed to increase sexual urge. Some women use 'Tsimi', a herbal drink or brew that is said to be very effective in lubricating the vagina and therefore useful for women that naturally have dry vagina. 'Sabuzu kuma', a red powder drank with yoghurt is believed to drive a man crazy with sexual desire. Some herbal preparations are also mixed with roasted chicken (popularly called 'Kazan mata' in Hausa language); this is specially prepared for newly married couples.[14] Other preparations are known to cause tightness of the vaginal mucosa and are called '*y*an matsi' in Hausa language.[14] Examples of 'Yan matsi' currently in use especially in northern Nigeria include 'ruwan zakarin ayu' (the seminal fluid gotten from the genitals of an aquatic animal called '*A*yu') and 'Bagaruwa' (*Acacia spp*) (an edible fruit that women boil and use for sit bath after delivery, to tighten the vagina).[14]

In many communities, there is a wrong perception that natural substances are safer alternative to orthodox medicines with no side effects. These drugs are also readily accessible even without prescription in the open markets and on the Internet. Consequently, the free access to these drugs to enhance sexual drive has become increasingly popular, more than 300,000 intoxications were reported to poison control centers over the last 20 years.[15,16] Aphrodisiacs have been shown to have a number of effects especially on male sexual pattern.[17] Use of aphrodisiacs, whether the herbal or the orthodox preparations is associated with side effects such as headache, painful sexual intercourse, vaginal discharge, vaginal tightness, prolong painful erection, nausea, vomiting and urinary tract infection.[4]

Several factors have been reported to be associated with the use of aphrodisiacs; a study conducted among 352 Ghanaians revealed that

the main factors associated with the use of aphrodisiacs are presence of sexual problems, lower educational attainment, number of sexual partners, advertisement, and knowledge of side effects of aphrodisiacs.[4] In Kaduna State Nigeria, the use of aphrodisiacs was shown to be associated with pleasure seeking behavior (46%), competitions amongst co-wives in a polygamous family setting and seeking for vaginal tightness following childbirth or preparation of a woman for marriage after having several sexual intercourse outside of wedluck.[14]

Despite the side effects associated with use of aphrodisiacs, it is a common finding especially on the streets of Sokoto metropolis and other major towns in northwest Nigeria to see adults buying various types of aphrodisiac substances from local vendors. Studies conducted on aphrodisiacs especially in the northwest of Nigeria including Sokoto have concentrated mainly on the prevalence of its usage among married women; this study looked at the prevalence, pattern, self-reported side effects as well as factors associated with the use of aphrodisiacs among adult population in Sokoto metropolis.

II. MATERIALS AND METHOD

The study was conducted in Sokoto metropolis, in the North-western part of Nigeria. Sokoto state has 23 Local Government Area (LGAs) of which 4 are metropolitan (Sokoto North, Sokoto South, Wamakko and Dange-Shuni LGAs). There are 44 political wards in the metropolitan LGAs with each of the LGAs having 11 wards. As at 2021, Sokoto metropolis had a population of 662,000 inhabitants, based on projection from the 2006 general census;[18] its indigenous inhabitants are predominantly Muslims of the Hausa and Fulani ethnic group.

It was a cross-sectional study involving adult males and females in Sokoto Metropolis, Sokoto state. All consenting males and females aged 18 years and above were included irrespective their marital status; however, all temporary visitors to the study area were excluded.

A sample size of 206 was calculated using the Cochran formula for determining sample size in descriptive studies;[19] $n=Z^2pq/d^2$

The study participants were selected using multi-stage sampling technique. In stage I, one LGA was selected from the four metropolitan LGAs in the state using simple random sampling by balloting procedure; Sokoto South LGA was selected. This was followed line listing of all the political wards in the selected study LGA.

In stage II, one of political ward was selected using simple random sampling using balloting procedure; Gagi ward was selected.

Data were collected using a set of validated structured questionnaire uploaded on Open Data Kit (ODK) software App installed on android devices. The Questionnaire had four sections with a total of 26 items: Section A: Socio-demographic characteristics of the respondents; Section B: Prevalence and pattern of aphrodisiac use by the respondents; Section C: Forms of aphrodisiac used by the respondents and associated factors; Section D: Side effects experienced following aphrodisiac use. The questionnaire was pretested on 20 purposively sampled adults selected from Sokoto North LGA ward; necessary amendments were made thereafter to validate the questionnaire. Five research assistants comprising of 300 level medical students were trained and recruited as research assistants.

Data from the completed questionnaires were downloaded from the ODK server in Ms Excel format and then exported to IBM SPSS version 20 for analysis. Descriptive statistical analysis was done and continuous variables were presented as mean ± standard deviation (SD) while categorical variables were presented as frequencies and percent. Chi-square test was used to test for the existence of association between categorical variables. Level of statistical significance was set at 5% ($p<0.05$).

Ethical approval for the study was sought from the Ministry of Health of Sokoto state. Further permission to carry out the study was sought from the respective LGA authorities where the study was conducted; written informed consent was sought from each of the participants.

III. RESULT

Two hundred and seven questionnaires were administered to respondents and all were analyzed giving 100% response rate.

Table 1: Socio-demographic profile of the respondents

Variable	Frequency (n=207)	Percentage (%)
Age group (years)		
15-30	91	44.6
31-45	80	39.2
46-60	25	12.3
Above 60	8	3.9
Sex		
Male	130	63.6
Female	75	36.4
Religion		
Islam	200	96.6
Christianity	7	3.4
Marital status		
Single	59	28.5
Divorced	8	3.9
Widowed	10	4.8
Married	130	62.8
Tribe		
Hausa	171	82.6
Fulani	24	11.6
Yoruba	7	3.8
Igbo	2	1.0
Others	2	1.0
Level of Education		
None	1	0.5
Qur'anic only	45	22.0
Primary	9	4.4
Secondary	76	37.1
Tertiary	74	36.1
Occupational Status		
Full-term housewife	20	9.8
Student	39	19.0
Farmer	10	4.9
Business	81	39.5
Civil Servant	49	23.9
Vocational	6	2.9
Type of family setting (n=148)		
Monogamous	93	62.8
Polygamous	55	37.2

Those within 15-30 years age group constitute the highest proportion of respondents (44.6%) and majority were males (63.6%). Up to 96.9% of the respondents were Muslims, 82.6% were Hausa tribe and 62.8% were married. The highest educational attainment of most of the respondents is secondary school education (37.1%), 39.3% were business men/women, 9.7%

are full term housewives and 46.6% are married in a monogamous setting (table 1).

Table 2: Prevalence and pattern of aphrodisiac use among the respondents

Variable	Frequency (n=206)	Percent (%)
Have you ever used aphrodisiac before?		
Yes	138	67.6
No	66	32.4
How often		
Always	18	13.0
Very often	30	21.7
Occasionally	90	65.3
Did you use aphrodisiac within the past one month?		
Yes	64	46.2
No	74	53.8
How the aphrodisiac is obtained? (multiple responses considered)		
Doctors' prescription	3	2.2
From chemists	57	41.3
Mobile drug vendors	13	9.4
Traditional drug sellers	93	67.4
Source of information		
Friends	125	90.2
Health facility	2	1.4
Local street sellers	29	20.9
My partner	5	3.6
Duration of using aphrodisiac(months)		
<6	91	65.8
6-12	18	12.7
13-24	24	17.7
>24	5	3.8
Partners' awareness of respondents' use of aphrodisiacs (n=138)		
Yes	74	53.6
No	64	46.4
Partners' support for use of aphrodisiac by respondents (n=74)		
Yes	49	66.3
No	25	33.7
Partners' satisfaction with respondents' sexual performance (n=138)		
Yes	101	73.2
No	37	26.8
Would you recommend aphrodisiacs to others?		
Yes	72	52.2
No	66	47.8

Lifetime prevalence of aphrodisiac use was 67.6% (n=138) while the current prevalence (within the last one month) was 64(46.2%). Majority of respondents who use aphrodisiacs said they only use it occasionally [90(65.3%)] and the major source of the aphrodisiacs was traditional drug sellers [93(67.4%)]. Up to 125(90.2%) of the users said they got the information about aphrodisiacs from their friends, majority [91(65.8%)] have used it only for less than 6 months; more than half said their partners are aware they are using aphrodisiacs and [72(52.2%)] said they would recommend aphrodisiacs to others (table 2).

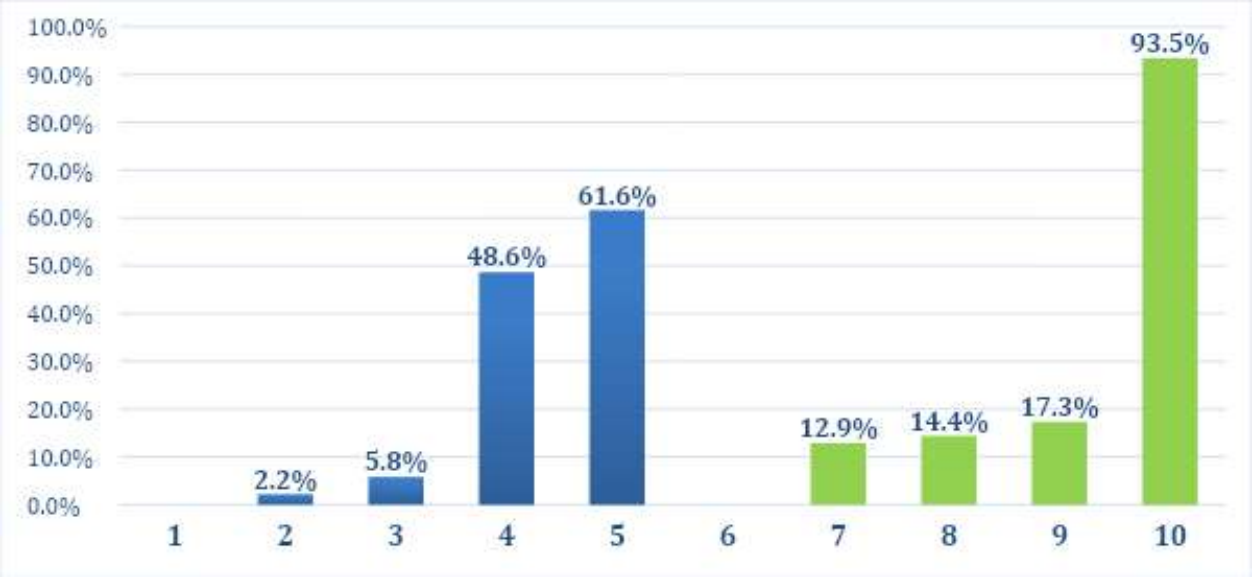


Figure 1: Types and routes of administration of aphrodisiacs used by respondents (multiple responses considered)

Local herbs were the most common types of aphrodisiacs used by the respondents followed by tablets/capsules. Regarding route of administration, up to 93.5% of the respondents said they administered the aphrodisiacs via the oral route (figure 1).

Table 3: Respondents' reasons for using aphrodisiacs

Variable	Frequency (n=138)	Percentage (%)
Reasons for use of aphrodisiac		
For sexual satisfaction	113	81.9
To keep my partner to myself	40	30.0
To satisfy my partner	89	64.5
For marital harmony	44	31.9
To increase my partner's love	36	26.1
Medical reason	4	2.9
Others	3	2.2
Reasons for choice of aphrodisiac		
Less side effects	52	37.7
Give more urge for sex	93	67.4
Cheaper	56	40.6
Availability	66	47.8

*Multiple responses considered

Up to 81.9% of the respondents said they use aphrodisiacs to derive sexual satisfaction, 64.5% said they use it in order to satisfy their partners; only 2.9% said it was for medical reason. Among the various reasons given by respondents for their choice of aphrodisiacs, the most mentioned reason was that it gives them more urge for sexual intercourse (67.4%); 47.8% said it was because of the availability of the drugs (table 3).

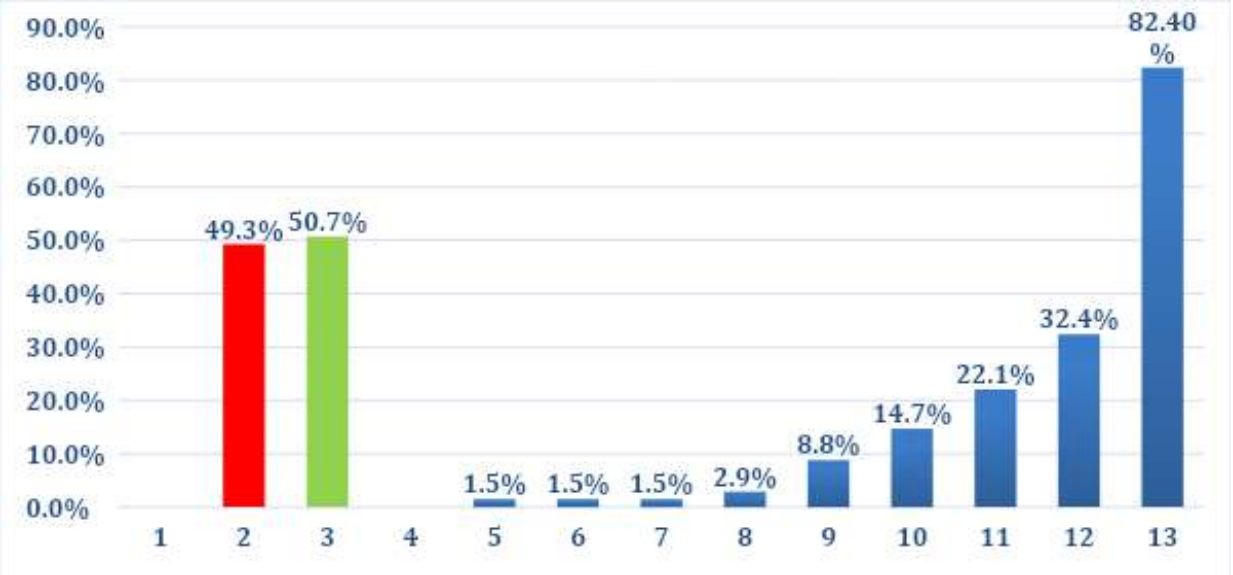


Figure 2: Side effects experienced by respondents following use of aphrodisiacs (multiple responses considered)

About half (49.3%) of the respondents said they experienced some side effects following their use of aphrodisiacs and the most common side effect experienced was headache (82.4%). Other side effects experienced were body weakness (22.1%), sustained erection (8.8%) and dryness of the vagina (1.5%) [figure 2]

Variable	Use of Aphrodisiacs Frequency (%)		p-value
	Yes	No	
Age (years)			
15-30	59(64.8%)	32(35.2%)	
31-45	52(66.7%)	26(33.3%)	
46-60	19(76.0%)	6(24.0%)	
Above 60	6(75%)	2(25%)	P=0.730
Sex			
Male	75(58.1%)	54(41.9%)	
Female	63(84%)	12(16%)	P<0.001
Religion			
Islam	136(68.7%)	62(31.3%)	
Christianity	2(33.3%)	4(66.7%)	P=0.088
Marital status			
Single	25(43.1%)	33(56.9%)	
Divorced	7(87.5%)	1(12.5%)	
Widowed	8(80%)	2(20%)	
Married	98(73.6%)	30(23.4%)	P<0.001
Tribe			
Hausa	116(68.6%)	53(31.4%)	
Fulani	18(75%)	6(25%)	
Yoruba	2(28.6%)	5(71.4%)	
Igbo	1(50%)	1(50%)	
Others	1(50%)	1(50%)	P=0.129
Level of Education			
None	1(100%)		
Qur'anic only	38(84.4%)	7(15.6%)	

Primary	8(88.9%)	1(11.1%)	
Secondary	49(64.5%)	27(35.5%)	
Tertiary	41(56.9%)	31(43.1%)	P=0.009
Occupational Status			
Full term housewife	19(95%)	1(5%)	
Student	13(34.2%)	25(65.8%)	
Farmer	9(90%)	1(10%)	
Business	58(71.6%)	23(28.4%)	
Civil Servant	33(67.3%)	16(32.7%)	
Vocational	6(100%)		P<0.001
Type of family setting			
Monogamous	68(70.9%)	28(25.1%)	
Polygamous	45(78.9%)	12(21.21%)	P=0.342

In table 4, factors significantly associated with use of aphrodisiacs include sex (p<0.001), marital status (p<0.001), level of education (p<0.009) and occupation (p<0.001). Factors such as age, religion, tribe and type of marriage were not significantly associated with use of aphrodisiacs (p>0.05)

IV. DISCUSSION

In this study, the majority of the respondents were relatively young considering their mean age and the fact that close to half of them were aged between 16-30 years. Studies conducted on the use of sexual stimulants in Sokoto and Kano, Nigeria also made a similar observation regarding the age distribution of the respondents where close to half of the respondents were between the ages of 16-25 years. This finding is not unexpected because according to the Nigeria Demographic and Health Survey (NDHS) 2018, those between the age of 15-29 years constitute close to half of the general population of Nigeria.[20] The possible implication is that a significant proportion of this age group (15-30 years) may be exposed to the use of sexual stimulants for a much longer time given their relatively young age, thus they are more likely to manifest long term side effects of the drugs. Similar study conducted in Ghana on indiscriminate use of sex enhancing products also showed that most of the respondents were aged below 36 years.[4] The fact that this study observed majority of the respondents to be Muslims from Hausa ethnic group could be because Sokoto state is largely dominated by Hausa Muslim communities.[20] In this study more than half of the respondents had attained up to secondary level of education and this is probably because the study was conducted in the metropolis where level of education of the inhabitants expected to be reasonably high. A study conducted in Kano, Nigeria lower proportion of the respondents were observed to have attained up to secondary level of education.[21]

In this study, lifetime prevalence of aphrodisiac use was quite high because up to two-third of the respondents have used aphrodisiacs at least once and among them, 46.2% have used it within the past one month prior to this study. Studies conducted in Ghana, Malawi and Nigeria also observed high prevalence aphrodisiacs use among men and women.[10,11,21,22] In all these studies, larger proportion of the respondents were relatively young and this could explain the high prevalence observed in these studies because young adults are likely to be engaged in sexual activities. Majority of the respondents ever used aphrodisiacs in this study said they got the information about the drugs from their friends and this further suggests that peer influence may have a significant association with the use of aphrodisiacs; Lampiao et al., also made similar observation in Malawi where majority of the respondents said aphrodisiacs were introduced to them by their friends.[22] In terms of duration of use of aphrodisiacs by the respondents, about two-third of them said they have only used it for less than 6 months and this may likely be as a result of the relatively young nature of most of the respondents. It is interesting to note that, in this study, more than half of the respondents said their partners were aware they were using aphrodisiacs and a significant proportion of them

said they would recommend aphrodisiacs to others. In a study conducted among women by Ango et al in Sokoto, more than two-thirds of the respondents said their husbands were aware and were in support of their use of aphrodisiacs, moreover, up to 83.4% of the women said their husbands reported increased sexual pleasure following their use of aphrodisiacs.[23] These may be responsible for the continued use of aphrodisiacs by the respondents, as their partners are pleased with their sexual performance.

Local herbs were the most common types of aphrodisiacs used by the respondents in this study, followed by tablets/capsules. Several studies have also reported similar observations where herbal preparations happened to be the commonest aphrodisiacs used by respondents.[10,14,24] This finding is not surprising because various types of herbal preparation with aphrodisiac properties are sold freely on the streets at relatively cheap price and without any consultation or prescription. Furthermore, traditional medicine sellers usually advertise and promote their drugs openly on the street and in radio stations, thus people find it much easier to access the herbal types of aphrodisiacs as against the conventional types that are sold in chemists/pharmacies in form of tablets/capsules. Incessant consumption of herbal aphrodisiacs may pose a great danger to public health due to the fact that most of the drugs have not been widely researched to know their safety profiles in terms of their optimal dose, toxicities and long term side effects. Regarding route of administration, up to 93.5% of the respondents said they administered the aphrodisiacs via the oral route. This finding is much higher than what was reported in studies conducted in Kano and Sokoto where 50.9% and 51.9% of the respondents respectively said they use the oral route.[1,23] The possible reason for this disparity is probably because in the Kano and Sokoto studies, the study population involved only women, thus a large proportion of them would be expected to use other topical agents that can be applied to the vagina; in this study, up to 63.6% of the respondents were males.

Among the reasons for using aphrodisiacs were the desire of the respondents to satisfy their own sexual needs and that of their partners; only 2.9% use aphrodisiac because of a medical condition. Similar observation was made in a study conducted in Kano State, where close to half of the respondents said they use aphrodisiac substances for better sexual satisfaction and a quarter to gain husband's favors.[8] These findings correlate with the findings of several studies where significant proportion of the respondents said they use sexual stimulants to get husband's favors and prevent marital disharmony.[1,21,25] Women who hawk these substances can always be heard telling their prospective women customers that the use of these substances could make their husbands buy cars, houses and other valuables for them.

The reason for the similarity could be due to the similar cultural setting of the study area (Sokoto and Kano). However, the above findings contradict that of a study carried out in Malawi where 37.2% of the respondents said they were using aphrodisiacs in order to enlarge their penis.[22] A study conducted in Ghana also reported that those with small penis were found to be nine times more likely to use aphrodisiacs.[10] This difference may be attributed to difference in the characteristics of the study population and their socio-cultural background.

This study also found that about half (49.3%) of the respondents have experienced side effects following the use of aphrodisiacs and the most common side effect experienced was headache (82.4%). Other side effects experienced were general body weakness, nausea and vomiting (14.9%), sustained erection (9.0%) and vaginal discharge/dryness (1.5%). As part of their mechanism of action, aphrodisiacs are known to cause dilatation of blood vessels of various parts of the body including brain[26] and this probably explains the high rate of headache experienced by most users of aphrodisiacs.

In this study, sex of respondents was found to be significantly associated with use of aphrodisiacs; higher proportion (84%) of the female respondents were found to be users of aphrodisiacs as against the male respondents (58.5%). The higher prevalence among women could be due to some cultural and religious factors

in the study area because polygamy is widely practiced, women may therefore use aphrodisiacs in order to gain more attention of the husband ahead of other co-wives. It has been reported in several studies including this study that a large proportion of people use aphrodisiacs in order to satisfy their partners.[1,21,23,25] A study conducted in Kwara state, Nigeria, however, did not find any association between gender and use of aphrodisiacs; this is probably because the study was conducted among people with sexual dysfunction.[13] Significantly higher proportion of those who were either married or divorced were found to have used aphrodisiacs compared to those who were single. The fact that this study observed significant association between aphrodisiac use and marital status is probably because of the influence of religion and culture in the study area; having sexual intercourse out of wedluck is something that is generally seen to be morally wrong in Sokoto, thus those who are married are more likely to have sexual intercourse than those who are single. This study also found significant association between level of education and use of aphrodisiacs; more than 84% of those with lower educational attainment have used aphrodisiacs, perhaps the higher the educational attainment the less likely the use aphrodisiacs. This relationship is probably because those who are educated are more likely to have access to adequate information about aphrodisiacs, including their adverse effects, thereby becoming discouraged from using it.[4,13]

V. CONCLUSION

Prevalence of aphrodisiacs use is high among men and women in Sokoto metropolis and it is associated with gender, marital and level of education. Government and health workers at all levels should intensity efforts to educate the masses about the use and associated side effects through the media such as radio, television and the internet.

ACKNOWLEDGEMENT

The researchers fully conducted and funded the research.

Conflict of interest

The researchers declare no conflict of interest in the course of the research.

REFERENCES

1. Abdullahi H, Tukur J. Sexual stimulants and their effect on women of reproductive age in Kano, Northern Nigeria. Department of Obstetrics and Gynaecology Bayero University Kano, Kano state Nigeria. Journal of Basic and Clinical Sciences. 2013; 10(1):13-16.
2. P Sandroni . Aphrodisiacs past and present: a historical review. Clin Auton Res 2001 Oct;11(5):303-7. doi: 10.1007/BF02332975.
3. Makwana, S., Solanki, M., Raloti, S., & Dikshit, R. (2013). Evaluation of Recreational Use of Aphrodisiac Drugs And Its Consequences : An Online Questionnaire Based Study, 2(1), 51–59.
4. Manortey, S, Mensah PA, & Acheampong GK. Evaluating Factors Associated with the Use of Aphrodisiacs among Adult Male Residents in Ashaiman Municipality, Ghana, Open Access Library Journal, 2018; 5: 1–13. Available at. https://doi.org/10.4236/oalib.1104876.
5. WHO. Traditional Medicine Strategy 2002–2005. 2014:12:05. Available: whqlibdoc.who.int /hq/2002/who.
6. Harte CB, Meston CM. Recreational Use of Erectile Dysfunction Medications in Undergraduate Men in the United States: Characteristics and Associated Risk Factors. *Arch Sex Behav* 2011; 40**:** 597–606. https://doi.org/10.1007/s10508-010-9619-y.
7. Bechara A, Casabé A, De Bonis W , Helien A, Bertolino MV. Recreational Use of Phosphodiesterase Type 5 Inhibitors by Healthy Young Men. The Journal of Sexual Medicine 2010; 7(11): 3736-3742 .
8. Ahmed A, Alshahrani S, Morgan A, Gabr AH, Abdel-Razik M, Daoud A. Demographics and sexual characteristics of sex-enhancing medication users: Study of a web-based cross-sectional sample of sexually active men. Arab Journal of Urology 2017; 15(4): 366-371 .
9. Hassali MA, Saleem F, Shafie AA, Al-Qazaz HK, Farooqui M, Aljadhey H, et al. Assessment of general public perceptions toward traditional medicines used for

aphrodisiac purpose in state of Penang, Malaysia. Complementary Therapies in Clinical Practice, 2012; 18(4): 257-260. https: //doi.org/10.1016/j.ctcp.2012.06.001.

10. Yidana A, Shamsu-Deen Z, Abdul- Manan S. Bio-Psychosocial Determinants of Aphrodisiacs use among men in the Sagnarigu Municipality. International Journal of Health Sciences & Research 2019; 9(12): 133-142
11. Danquah CA, Koffuor GA, Anto BP & Nimako KA. Pelagia Research Library The indiscriminate use of sex enhancing products among Ghanaians: Prevalence, and potential risk. Advances in Applied Science Research, 2011; 2(5): 350–359. Retrieved from http://www.imedpub.com/articles/the-indiscriminate -use-of-sex-enhancing-products-among-ghanaians-prevalence-and-potential-risk.pdf.
12. Nna VU, Ofutet EO, Ofem OE, Okpokam DC, Osim EE. The quest for an increased genital size drives sex stimulant abuse among male subjects in Calabar, Cross River State, Nigeria. Asian Pacific Journal of Reproduction 2016; 5(4): 311-316
13. Abdulrazaq Olayinka Oniye, Aminat Adeola Odebode, Shola Abdullahi Ajape. Patterns of aphrodisiac herbs usage as expressed by married adults in Kwara State, Nigeria. Nigerian J. of Guidance and Counselling 2016; 21(1). Available at https://www.ajol.info/index .php/njgc/article/view/152817.
14. Mohammed-Durosinlorun, A. (2008) Kayan Mata: The Secret World of Aphrodisiacs in Northern Nigeria. Project Submitted to the ARSRC. Sexuality in Africa Magazine and Monographs, 5, 12-13.
15. Corazza O., Martinotti G., Santacroce R., Chillemi E., Di Giannantonio M., Schifano F., Cellek S. Sexual enhancement products for sale online: Raising awareness of the psychoactive effects of yohimbine, maca, horny goat weed, and ginkgo biloba. *BioMed Res. Int.* 2014; 2014:1–13. doi: 10.1155/2014/841798.
16. Rao N, Spiller HA, Hodges NL., Chounthirath T, Casavant MJ, Kamboj AK, et al. An Increase in Dietary Supplement Exposures Reported to US Poison Control Centers. *J. Med. Toxicol.* 2017;13:227–237.doi: 10.1007/s13181-017-0623-7.
17. Pratap SA, & Singh R. Potent Natural Aphrodisiacs For The Management Of Erectile Dysfunction And Male Sexual Debilities, Frontiers in Biosciences 2012 1(4): 167-180 https://www.macrotrends.net/cities/22021/sokoto/population.
18. Ibrahim, T. Research Methodology and Dissertation writing for the health and allied professionals. Cress Global Links limited, Abuja. 2009
19. National Population Commission (NPC) [Nigeria] and ICF. 2019. *Nigeria Demographic and Health Survey 2018 Key Indicators Report*. Abuja, Nigeria, and Rockville, Maryland, USA: NPC and ICF.
20. Umar LB, Jibrin I. Use of Herbal medicines and aphrodisiac substances amongwomen in Kano State, Nigeria. IOSR Journal of Nursing and Health Science.2015;4(4):41- 50
21. Lampiao F, Miyango S, Simkoza H. Herbal aphrodisiac use among male adolescents and teenagers in a rural area of Blantyre district, Malawi. International Journal of Reproduction, Contraception, Obstetrics and Gynecology Lampiao F et al. Int J Reprod Contracept Obstet Gynecol. 2015 Jun;4(3): 581-583.
22. Ango U M, Oche MO, Bello MM, Yunusa EU, Umar MT, Adamu A, et al. Sexual Stimulants: Prevalence and Associated Factors Amongst Married Women in Sokoto Metropolis, Sokoto State, Nigeria. Archives of Current Research International 2021; 21(1): 24-33.
23. Bhagavathula AS, Elnor AA, & Shehab A. Pharmacovigilance on sexual enhancing herbal supplements. Saudi Pharmaceutical Journal 2015; 24(1): 115-118. Available at https://doi.org/10.1016/j.jsps.2015.01.018Accessed 24/09/21.
24. Sohil M, Manish S, Sandip R, Ramkumar Devaluation of recreational use of aphrodisiac drugs and its consequences, Int J Res Med. 2013;2(1);51-59.
25. Kotta S, Ansari SH, Ali J. Exploring scientifically proven herbal aphrodisiacs Pharmacogn Rev. 2013 Jan-Jun; 7(13): 1–10. doi: 10.4103/0973-7847.112832.

This page is intentionally left blank

Impact of Hyperglycaemia on the Length of Stay in Critically ill Non-Diabetic Patients Admitted in a Tertiary Care Hospital

Madiha Iqbal, Aysha Almas & Soomal Rafique

Aga Khan University

ABSTRACT

Hyperglycemia in hospitalized patients is associated with prolonged hospital stay, increased morbidity and mortality. Various degrees of glycemic control have been studied and guidelines recommend a target glucose range of 140-180mg/dl in most hospitalized patients. This study was done to evaluate and compare mean hospital stay among critically ill patients with hyperglycemia as compared with normoglycemia. A descriptive cross-sectional study was conducted in the Aga Khan University Hospital, Department of Internal Medicine from 10-May- 2019 to 09-Nov-2019. Critically ill patients admitted in hospital having age 18-75 years were enrolled using non-probability consecutive sampling. Patient with diabetes mellitus and those on medications causing hyperglycemia were excluded. Length of hospital stay was higher in critically ill patients with hyperglycemia. Hyperglycemia can be used as a predictor of increased hospital stay in critically ill non-diabetic patients.

Keywords: hyperglycemia, normoglycemia, hospital stay.

Classification: DDC Code: 616.462 LCC Code: RC660.7

Language: English

London Journals Press

LJP Copyright ID: 392835

London Journal of Medical and Health Research

Volume 22 | Issue 3 | Compilation 1.0

Impact of Hyperglycaemia on the Length of Stay in Critically ill Non-Diabetic Patients Admitted in a Tertiary Care Hospital

Madiha Iqbal[α], Aysha Almas[σ] & Soomal Rafique[ρ]

ABSTRACT

Hyperglycemia in hospitalized patients is associated with prolonged hospital stay, increased morbidity and mortality. Various degrees of glycemic control have been studied and guidelines recommend a target glucose range of 140-180mg/dl in most hospitalized patients. This study was done to evaluate and compare mean hospital stay among critically ill patients with hyperglycemia as compared with normoglycemia. A descriptive cross-sectional study was conducted in the Aga Khan University Hospital, Department of Internal Medicine from 10-May-2019 to 09-Nov-2019. Critically ill patients admitted in hospital having age 18-75 years were enrolled using non-probability consecutive sampling. Patient with diabetes mellitus and those on medications causing hyperglycemia were excluded. Length of hospital stay was higher in critically ill patients with hyperglycemia. Hyperglycemia can be used as a predictor of increased hospital stay in critically ill non-diabetic patients.

Keywords: hyperglycemia, normoglycemia, hospital stay.

Author α σ: Internal Medicine Department, Aga Khan University Hospital, Karachi.

I. INTRODUCTION

Hyperglycaemia in the hospitalized patients has gained attention due to its association with prolonged hospital stay, increased morbidity and mortality in inpatient.[1] This association has been established for acute conditions like myocardial infarction, Stroke, pneumonia acute trauma or burn.[2] In the last 14 years glycemic goals have changed within the hospital setting. Various degrees of glycemic control have been studied and a recent consensus statement from ADA/AACE recommends a target glucose range of 140-180mg/dl in most hospitalized patients.[3] Stress hyperglycemia historically was felt to be part of the natural course of acute illness and defined as a blood glucose level>140 mg/dL without a previous history of diabetes or glycated hemoglobin (HbA1c) >6.5%.[4] In the largest review of Hospital glucose data of more than 126 U.S hospitals, 46% of all Blood sugars in the ICU setting and 31.7% of all blood sugars in non ICU patients were in the hyperglycemic range.[5] Several studies including large trials, have shown that admission hyperglycemia is a risk factor for poor outcome following focal and global cerebral ischemia.[6]

The prevalence of admission hyperglycemia (glucose levels of>140 mg/dL) in different epidemiological studies ranges from 51% to >58% of patients admitted with acute myocardial infarction. A study reported hyperglycemia in up to 50% of patients with acute MI whereas previously diagnosed Diabetes was found only in 20% to 25% of patients.[7] The relationship between glycemic control and the severity of sepsis was analyzed in a cohort of 191 patients concluded that patients with hyperglycemia has longer length of stay as compared to those with normal blood sugars.[8] A meta-analysis of over 26 studies, including the largest, Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR), showed decreased morbidity and mortality in patients with moderately controlled hyperglycemia.[9] Impaired glycemic control are associated with increased rates of infections, morbidity, and mortality, and increases hospital length of stay (LOS).[10] [11] All prior studies have worked on

hyperglycemia and its impact on morbidity and mortality, less work has been done to evaluate effect of hyperglycemia on average length of stay.

All prior studies have worked on hyperglycemia and its impact on morbidity and mortality, less work has been done to evaluate effect of hyperglycemia on average length of stay. Purpose of this study will be to assess how glycemic control impacts on length of stay of patients in tertiary care hospital. Additionally we want to see if non-diabetics who have hyperglycemia differ in outcomes at the end on length of inpatient stay.

Despite advances in the management of patients with diabetes mellitus (DM), this population still has a poorer prognosis after ischemic events compared with nondiabetic patients. Stress hyperglycemia can be defined as a blood glucose level >140 mg/dL without a previous history of diabetes or glycated hemoglobin (HbA1c) >6.5%.[13] Although the Diabetes Insulin Glucose in Acute Myocardial Infarction (DIGAMI) trial and studies conducted in Leuven demonstrated the benefit of intensive glucose control in critically ill patients, later studies failed to replicate these findings.[14,15] It is difficult to define the incidence of acute hyperglycemia, which may vary from 40-90%, depending on the threshold used to define abnormal levels of glucose.[12,16] Hyperglycemia in the critical care setting is associated with a poor prognosis in patients with no history of DM. This association is well documented for both admissions and the mean glucose level during the hospital stay. In a prospective cohort study that evaluated patients with community-acquired pneumonia, increased blood glucose levels on admission were associated with increased mortality in patients with no history of diabetes.[17] The worldwide prevalence of diabetes is 2.8%. This rate increases to approximately 15-30% among critically ill patients.[12,13] In patients with pre-existing DM, the presence of hyperglycemia has not been consistently associated with a worse prognosis. Patients with diabetes exhibited increased mortality in a cohort of patients with community-acquired pneumonia, but this outcome was not influenced by the levels of glucose on admission.[17]

Hyperglycemia can be seen in various settings, Postoperative period, in a study of 263 patients undergoing vascular surgery, intensive glucose control was associated with a reduction in the composite endpoint of all-cause death, myocardial infarction, and acute heart failure. Moderately strict blood glucose control (target range 110-150mg/dl) throughout the hospital stay, added to the usual standard of care in patients undergoing heart surgery, was associated with a 6% reduction in infection rates and a 12% reduction in atrial fibrillation, with no between-group differences in mortality. However, other studies have failed to show any benefit, even in this subgroup of patients.[18]

Neuro-critical patients, in a study of 933 patients with an admission diagnosis of stroke, strict glucose control was not beneficial in reducing mortality or improving neurological outcomes.

However, this study was ended prematurely due to difficulties in enrollment, thus limiting its statistical power. These findings were replicated in a later study, which compared aggressive blood glucose control (target range <130mg/dL) with conventional control (target <200mg/dL) in 46 patients with ischemic stroke. However, in another study of acute ischemic stroke patients who developed hyperglycemia and did not have a previous history of diabetes, intensive glucose control was associated with improved 30-day neurological performance, as measured by the National Institutes of Health Stroke Scale (NIHSS) score, compared with performance following conventional blood glucose control.[19] In a meta-analysis that included studies on only neurocritical patients, strict glycemic control had no impact in mortality, although a less strict glycemic target (140-180mg/dL) was associated with fewer unfavorable neurological outcomes.[20]

Myocardial infarction, it is not known whether intensive blood glucose control is associated with better outcomes in patients with acute myocardial infarction (AMI). In the DIGAMI trial, patients were randomized to receive either an insulin/glucose infusion during the first 24 hours after admission, followed by subcutaneous administration of intermediate- and short-acting insulin four times daily for at least 3 months, or standard DM treatment at the discretion of their care providers. High cardiac risk was defined as

meeting two or more of the following criteria: age ≥70 years, a history of previous AMI, a history of congestive heart failure, and ongoing digitalis treatment. The patients were classified into four predefined strata according to their history of insulin use and their cardiac risk: 1, no insulin and low risk; 2, insulin and low risk; 3, no insulin and high-risk; and 4, insulin and high risk. All other aspects of AMI management were similar between the two groups. Although patients in the intervention group (who received the insulin/glucose infusion) had a slight reduction in in-hospital mortality (9.1% versus 11.1%; non-significant) and 3-month mortality (12.4% versus 15.6%; nonsignificant), only 1-year mortality was significantly lower in the intervention group (18.6% versus 26.1%; relative mortality reduction, 28%; 95% CI, 8-45%), questioning whether the benefit was due to acute management in the ICU or to later intensive control. An analysis of mortality in the pre-stratified risk groups showed that the greatest reduction occurred among patients with no prior insulin treatment. In this group, the relative reduction in mortality was 51% (19-70%; p=0.004) at the 1-year follow-up. [21]A meta- analysis of 11 randomized clinical trials including over 23,000 AMI patients showed no benefit for the use of intensive glucose control protocols.[22]

In sepsis, the relationship between glycemic control and the severity of sepsis was analyzed in a cohort of 191 patients treated with intensive glucose control (target of 80-140mg/dl). The researchers concluded that among patients with severe sepsis or septic shock, the risk of hypoglycemia and hyperglycemia was higher. In a multicenter randomized trial (the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP study), conventional therapy was compared with intensive insulin therapy, and fluids for resuscitation (10% pentastarch versus modified Ringer's lactate) were also compared. There was no benefit for strict glucose control in patients with severe sepsis, and the trial was stopped early for safety reasons, given the high rate of hypoglycemia. In the NICE-SUGAR trial, an analysis of subgroups did not show any improvement in mortality in patients with severe sepsis. The Surviving Sepsis Campaign Guidelines recommend starting insulin therapy after two consecutive blood glucose measurements above 180mg/dl and an upper target level ≤180mg/dL.[23]

The administration of vasopressors, corti-costeroids, and enteral and parenteral nutrition, as well as the discontinuation of this therapy due to a variety of procedures, leads to significant variability in blood glucose levels. Retrospective studies have shown a relationship between increased blood glucose variability and increase mortality. A retrospective analysis of the Leuven dataset showed that patients with the greatest blood glucose fluctuations had the worst outcomes, regardless of allocation within the study.[24] The optimal method to measure the amplitude of blood glucose levels is not defined. In a systematic review, 13 different indicators were reported, without a clear definition of the best method for the assessment of glycemic variability. However, a prospective cohort study evaluated the standard deviation and mean amplitude of the glycemic index, the absolute glucose change per hour, and the glycemic lability index. The standard deviation was the only measure that was consistently associated with hospital mortality.[25] Further clinical trials are required to determine whether the use of indices of glucose control variability in critically ill patients can reduce morbidity and mortality.

A need for an assessment of baseline blood glucose prior to ICU admission by HbA1c measurement has been suggested, particularly in patients with no history of DM. In hospitalized patients with random admission, hyperglycemia with HbA1c >6% had a specificity of 100% for the diagnosis of diabetes and a sensibility of 57%.[26] Acute hyperglycemia does not appear to be a marker of mortality in critically ill patients with pre-existing DM.

II. PATHOGENESIS OF THE STRESS HYPERGLYCEMIA

Severe sepsis, systemic inflammatory response syndrome (SIRS), and traumatic brain injury (TBI) are conditions associated with significant morbidity and mortality. Hyperglycemia is often a consequence of these three related conditions. Although the first steps in response to severe infections (sepsis), severe tissue damage (SIRS),

and brain injury subsequent to trauma (TBI) vary, the later steps, which lead to morbidity, multi-organ failure and death, seem to be very similar.[27]

In the initial phases of these three conditions, there is a very strong inflammatory response, with high levels of IL-1β, TNFα, and IL-6, among other cytokines and chemokines, being secreted by M1-type macrophages and others. In this initial pro-inflammatory stage of these critical illnesses, very high levels of blood glucose (hyperglycemia) are often observed in these Patients.

Hyperglycemia, even in non-diabetic patients, is a hallmark of these conditions in their initial phase but is also a prognostic indicator, with a general correlation between glucose blood levels and the outcomes of morbidity and death. Glycemic control in the critically ill also affects the immune system with general attenuation of immune function which might avoid unnecessary inflammation in TBI but could prove disastrous in sepsis. Here we discuss molecular mechanisms leading to hyperglycemia in critically ill patients.[28]

III. METABOLIC CHANGES IN HYPERGLYCEMIA

If hyperglycemia is at least partially consequent to a shift in glucose metabolism and insulin resistance, then what does that imply for the treatment of hyperglycemia in critically ill patients? Although insulin treatment may constitute part of the therapy, is it not better to try insulin treatment in combination with new therapies that could possibly redirect the altered glucose metabolism in these cells? Recent advances in understanding the role of aerobic glycolysis in critically ill patients suggest novel mechanisms contributing to hyperglycemia and, as a result, novel approaches to therapy. One of the first important recent findings was the identification of increased succinate in macrophages stimulated by the pro-inflammatory compound lipopolysaccharide (LPS). These authors conducted a thorough metabolomic study of this inflammatory pathway and confirmed the stimulation of glycolysis and inhibition of oxidative phosphorylation. Succinate was elevated some 30-fold during LPS stimulation. Succinate is transported from the mitochondria (where most of the excess is formed through anaplerosis via stimulation of glutamine transformation to α-ketoglutarate, the precursor to succinate in the TCA cycle) to the cytoplasm, where it inhibits prolyl hydroxylase, the enzyme that acts on HIF-1α and leads to its normal fast protein turnover. Inhibiting prolyl hydroxylase stabilizes HIF-1α and leads to aerobic glycolysis (the Warburg Effect).[36]

Before we investigate more deeply into the hyperglycemia and hyperlactatemia observed in critically ill patients, we ask whether it is justifiable to treat hyperglycemia (and hyperlactatemia) as one entity in sepsis, SIRS, and TBI. The literature is somewhat confusing on this point. We have already mentioned that the original correlation of hyperglycemia and increased mortality came from patients treated in a surgical ICU and were often cardiac or thoracic surgical patients. When the same group reported on patients treated in a medical ICU, they found that intense insulin therapy to lower glucose levels decreased morbidity but not mortality. A meta-analysis of patients from five different ICUs (medical, cardiothoracic surgery, cardiac, surgical, and neurosurgical) in one large medical center showed differences in mortality when patients were very hyperglycemic among the five units. Laird and colleagues found that early hyperglycemia ([glucose] >200 mg/dL) in trauma patients led to increased mortality rates independent of the type of injury sustained.[37] TBI patients also have worse outcomes, including increased mortality, when they are severely hyperglycemic ([glucose] >200 mg/dL) on admission to an ICU. A more recent study not only confirmed this relationship but also related the prognostic capacity of initial glucose levels to the prognostic capacities of both the initial Glasgow Coma Scale (GCS) score and the Apache II score. Interestingly, initial mean glucose concentration was a better prognostic indicator for survival than either GCS or Apache II scores. Nonetheless, there are some unique properties of glucose metabolism in the brain. The glucose transporter GLUT-1 is the major transporter of glucose for non-neuronal cells (astrocytes, microglia, and oligodendroglia) and is also part of the endothelial blood-brain barrier. The GLUT-3

transporter seems to be the major source of glucose transport into brain neuronal cells. During glycolysis, accumulated lactate is shuttled between non-neuronal cells and neurons, using two different monocarboxylate transporters (MCTs) to effect this: MCT1 in endothelial and non-neuronal cells and MCT2 in neurons. Although the precise metabolism of lactate in the brain is still somewhat controversial, it is not important for further consideration here. The contribution of increased lactate to poor outcomes in TBI and the consideration of the biochemical targets that might overcome such outcomes seem to be no different than for sepsis and SIRS.[38]

IV. DIAGNOSIS

Stress hyperglycemia generally refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes. For the purpose of this Seminar, we will discuss physical—rather than psychological—stress. However, the identifi- cation of such patients is complex. No guidelines specifically define stress hypergly- cemia. In a technical review written by the Diabetes in Hospitals Writing Committee of the American Diabetes Association (ADA), patients are classified into one of three groups—known diabetes, newly diagnosed diabetes, and hospital-related hyperglycemia (panel). This classification needs information from hospital follow-up that is not usually available. Change in glucose from baseline and not the absolute glucose concentration might be of value, irrespective of whether a patient has pre- existing diabetes. Thus, we propose two diagnostic categories of stress hyperglycemia—hospital- related hyperglycemia according to the ADA consensus definition (fasting glucose >6·9 mmol/L or random glucose >11·1 mmol/L without evidence of previous diabetes), and pre-existing diabetes with deterioration of preillness glycemic control. The most appropriate cutoff point for stress hyperglycemia in patients with pre-existing diabetes needs to be established, but certainly a patient with a well-controlled (<7%) glycosylated hemoglobin (HbA_{1c}) whose glucose concentration is consistently higher than the threshold defined for hospital-related hyperglycemia would qualify.[45] 30% of people who have diabetes in the USA are unaware of their status and, therefore, many hospitals in patients with apparent stress hyperglycemia have underlying diabetes or prediabetes. In an undifferentiated hospital population, results from a small study showed that 60% of patients with admission hyper-glycemia had confirmed diabetes at 1 year. Another study showed that nearly one in five adult inpatients had probable unrecognized diabetes—identified by an admission HbA_{1c} higher than 6·1%. In this study, random glucose concentrations poorly predicted elevated HbA_{1c}, indicating the need for more sophisticated diagnostic criteria than are available.[46,47]

Poor Outcomes related to Stress Hyper-glycaemia: One retrospective review of 1886 unselected hospital inpatients were stratified according to whether patients had normogly-cemia, pre-existing diabetes, or newly diagnosed hyperglycemia (fasting glucose >7 mmol/L or random glucose >11·1 mmol/L on two separate occasions). Compared with patients with normoglycemia, after adjustment for age, body-mass index, sex, hyper tension, coronary artery disease, infection, renal failure, and ICU admission, mortality was 18·3 times higher in patients with newly diagnosed hyperglycemia ($p<0·05$), but only 2·7 times higher in those with known diabetes ($p<0·05$). This study did not distinguish between a new diagnosis of diabetes and transient stress hyperglycemia.

However, a relation between short-term glycemic control and hospital outcomes has been identified. Patients with hyperglycemia without known diabetes who were critically ill or had acute coronary or cerebro-vascular events were shown to have increased risk of mortality, although patients who were hyperglycemic with known diabetes did not.

In post analysis, data from a large randomized controlled trial of intensive insulin therapy in a surgical ICU suggest that patients with a previous diagnosis of diabetes were at lower risk of mortality than were those without or newly diagnosed with diabetes (odds ratio [OR] 0·356, 95% CI 0·158–0·803, p=0·01). Posthoc analysis of the counterpart to this study in a medical ICU showed a reduction in mortality only in patients

needing an ICU stay of 3 days or longer, and seemingly only in patients with newly discovered hyperglycaemia (11·5% reduction in mortality in patients with new hyperglycaemia *vs* 1·8% increase in mortality with those with known diabetes).[2] In a pooled analysis of both trials, patients with diabetes achieved no survival benefit, although the number of patients with known diabetes was small.[49]

In other randomized studies, results were stratified according to the presence of pre-existing diabetes. Investigators of a small (n=523) single-center study reported no benefit of intensive intravenous insulin therapy with a mean glucose target of 4·4–6·1 mmol/L compared with a target of 10–11·1 mmol/L. This study was powered to detect an 8% absolute risk reduction. No difference in outcomes between patients with or without diabetes was identified. Investigators of a multicenter randomized controlled study of patients with sepsis noted outcomes did not differ between those with or without diabetes treated with intensive insulin therapy. However, this study was stopped before enrolment was completed largely because of frequent hypoglycaemia.[50]

A pivotal, large, multicenter randomized controlled trial (NICE-SUGAR) comparing conventional (<10 mmol/L) versus tight (4·5–6·0 mmol/L) glycemic control using intravenous insulin infusions in ICU patients showed increased mortality for patients in the intensive arm (OR 1·14, 95% CI 1·02–1·28, p=0·02). The treatment effect did not differ between surgical and non-surgical patients, nor was a difference observed between patients with or without known diabetes.[51]

Other non-randomized or observational studies provide less robust data than does the NICE-SUGAR trial but deserve mention because they attempt to identify patients with stress hyperglycemic. In a mixed surgical (n=676), medical (n=1856), and trauma (n=134) ICU, outcomes in patients with diabetes (n=532) were compared with those in patients without known diabetes after implementation of a moderately tight glycemic control protocol (target blood glucose concentrations 6·9 mmol/L). Mortality was significantly reduced in non-diabetic patients but not in those with known diabetes. Furthermore, in patients without diabetes, mortality began to rise when mean glucose concentration exceeded 7·8 mmol/L in patients without diabetes, whereas in patients with diabetes this threshold was 10 mmol/L.[52]

Several observational studies have assessed whether patients with stress hyperglycemia have a high risk of poor outcomes. A large observational study of 728 patients with diabetes and 4218 patients without diabetes established that at any mean ICU glucose concentration, ICU (but not hospital) mortality is greater (up to nearly four times) in patients without diabetes than in those with the disorder, even after adjustment for disease severity (Acute Physiology and Chronic Health Evaluation II score). In a mixed ICU sample of 2826 patients, those without diabetes who needed treatment for hyperglycemia had higher sequential organ failure assessment (SOFA) scores, greater hospital length of stay (8·0 *vs* 6·7 days, p<0·001), and higher mortality rates (10% *vs* 6%, p<0·01) than did patients with known diabetes, despite lower median glucose and adjustment for severity of illness and other covariates. By contrast, patients with the disorder had the same death rate as normoglycemic non-diabetic patients (6% *vs* 5%), despite higher SOFA scores and median glucose values. The high mortality rate in hyperglycemic patients without known diabetes and absence of relation of hyperglycemia to mortality in patients with diabetes was also reported in mixed ICU populations and in those with severe sepsis. However, not all results from ICU studies show a high risk of mortality related to acute hyperglycaemia.[53]

The relation between newly discovered hyperglycemia and mortality in patients presenting with acute myocardial infarction or acute coronary syndrome has been investigated. Unfortunately, most studies rely on glucose concentrations at admission to identify stress hyperglycemia. In a meta-analysis, the pooled unadjusted relative risk (RR) of in-hospital mortality after myocardial infarction in 1856 patients without diabetes who had stress hyperglycemia at admission was 3·9 (95% CI 2·9–5·4) compared with normoglycemic non-

diabetic patients. By comparison, the risk of death in 688 hyper glycemic patients with diabetes was 1·7 (95% CI 1·2–2·4) relative to normoglycemic patient with diabetes.[54]

Other studies support these findings. In more than 160 000 patients admitted with acute myocardial infarction, glucose concentration at admission was associated with a steep rise in 30-day mortality for those without known diabetes: for glucose concentrations of 6·1–7·8 mmol/L on admission, OR 1·17, (95% CI 1·11–1·24); 13·3 mmol/L or more, OR 1·87, (95% CI 1·75– 2·00). However, for patients with established diabetes, mortality rose only at the highest glucose concentration (>13·3 mmol/L OR 1·32, 95% CI 1·17–1·50). Discrepancies between studies might be explained in part by the length of follow-up—the association between diabetes status and mortality strengthened as the length of follow-up increased. With longer follow-up, the association between diabetes and mortality was significant, but the association with stress hyperglycemia became non-significant.

Another study investigated the role of acute and chronic hyperglycemia in 827 patients with diabetes, 324 of whom had at least two HbA_{1c} measurements in the previous 2 years. Glucose concentrations at admission in the third (2·84 mmol/L, 95% CI 1·04–7·76, p=0·04) or fourth (5·03 mmol/L, 95% CI 1·90–13·26, p=0·001) quartiles independently predicted in hospital mortality after acute myocardial infarction. However, mortality did not differ much between quartiles of HbA_{1c}. Results of another study confirmed no association between mortality and HbA_{1c}, thus drawing attention to the potential importance of acute hyperglycemia over chronic hyperglycemia in hospital in patients with acute myocardial infarction.[55]

A retrospective analysis of 433 patients after stroke established that blood glucose concentrations higher than 10 mmol/L at admission (OR=2·1, 95% CI 1·1–4·6, p=0·02), but not diabetes itself, was an independent predictor of dependency 1 year after first-ever stroke. A meta-analysis showed that in patients without diabetes, stress hyperglycemia (definition varied by study) was associated with a high risk of mortality after stroke (pooled RR 3·07, 95% CI 2·50–3·79). However, this was not true for patients with diabetes (pooled RR 1·30, 95% CI 0·49–3·43). In further studies, Glucose concentration on admission was associated with higher mortality rates in patients without a history of diabetes than in those with a history of diabetes both for ischemic stroke and intracranial hemorrhage. This finding was not confirmed in another study.[56]

In a prospective observational analysis of 262 patients with stroke, researchers used a normal fructosamine and to identify those with transient hyperglycemia. HbA_{1c} Patients with transient hyperglycemia had worse stroke severity scores than did those with either known diabetes or normoglycemia. Furthermore, 30-day mortality was higher in patients with transient hyperglycemia than in those with normoglycemia (27·4% *vs* 12·7%, p=0·01), but no significant difference between patients with diabetes (16·2%) and normoglycemia was reported.[57]

The first Leuven study consisted largely of postsurgical patients, two-thirds of whom had cardio thoracic surgery. Because patients with no history of diabetes benefited most from intensive insulin therapy, the same could be true for the subset of post cardiothoracic surgery patients.

However, a prospective study with historical controls showed reductions in mortality, hospital length of stay, and surgical site infections after cardiothoracic surgery in patients with diabetes who received intensive insulin therapy. By contrast with the Leuven study, in the Furnary study patients with transient hyperglycemia were excluded, indicating that patients with diabetes also benefit from glycemic control. This finding seems to be in agreement with another study.[58]

Chronic hyperglycemia in the perioperative setting also seems to be harmful, affecting the rate of postoperative infections and neurological outcomes. A meta-analysis of 34 trials showed that perioperative insulin infusion reduces mortality but increases rates of hypoglycemia. However, researchers calculated that the available mortality data were too few to reliably detect a plausible treatment effect, and that the presence of diabetes did not affect outcomes. Thus, hyperglycemia in patients with or without

diabetes could adversely affect outcomes after surgery.[59]

Stress hyperglycemia is linked to poor outcomes and the association seems to be stronger for patients without diabetes than for those with pre-existing diabetes. However, studies were not prospectively designed to compare patients with stress hyperglycemia and pre-existing diabetes, creating some limitations. Despite data from interventional studies and controlling for severity of illness, residual confounding could be difficult to eliminate. For example, patients with pre-existing diabetes might be more likely to undergo glycemic monitoring and receive insulin treatment or other life-saving drugs in the hospital than would undiagnosed patients.

Additionally, studies lack a consistent or strict definition of stress hyperglycaemia.[60]

Many studies do not have enough comparator groups because they are observational. For example, direct comparisons of glycemic control in non-diabetic patients who have stress hyperglycemia with diabetic patients are often unable to account for the change in glucose from baseline in the latter. Non-diabetic patients with stress hyperglycemia should ideally be compared with those who have been diagnosed and who have deterioration of pre-illness glycemic control to enable assessment of whether outcomes differ. However, results of a few studies show poor outcomes that persist in patients with newly discovered hyperglycemia, after accounting for glycemic control. Despite these limitations, results of controlled studies seem to show that treatment of hyperglycemia in patients improves outcomes, although new data indicate that the quest for strict normoglycemia is harmful.[55]

In a retrospective study, pre-existing hyperglycemia affected the relationship between acute blood glucose levels and mortality, suggesting a significant interaction between chronic and acute glycemic control.

HbA1c levels were shown to be predictive of mortality in a study of diabetic patients with sepsis. This finding was not replicated in a later study conducted in the ICU of *Hospital de Clinicals de Porto Alegre, Porto Alegre* (RS), Brazil.[62]

V. Relationship Between Glycemic Control in the Critically Ill and Mortality

The relationship between mean glycemia during ICU stay and mortality is distinctly different when comparing patients with and without diabetes. A number of observational cohort studies have demonstrated that for patients without diabetes the lowest mortality is seen in patients with mean blood glucose in the 80–110mg/dl range during ICU stay, with a modest increase associated with mean blood glucose 110 –140mg/dl and progressively higher mortality rates observed with mean blood glucose 140–180mg/dl and higher. In contrast, for patients with diabetes, there is a 'blunted', or even absent, relationship between mean blood glucose above 80–110mg/dl and mortality.

The relationship between diabetes status and outcome in patients with sepsis or acute bacteremia was evaluated in a retrospective cohort study of 128 222 patients admitted with sepsis over a 5- year period to 83 Dutch ICU's. Among patients with diabetes, only hypoglycemia in the absence of severe hyperglycemia was independently associated with risk of death. In contrast, for patients without diabetes, hyperglycemia and hypoglycemia were independently associated with increased risk of death, as was their combination. In a cohort of 317 patients with Acinetobacter baumannii complex bacteremia, the lowest mortality among patients without and with diabetes the lowest mortality was seen with mean blood glucose 70–100 mg/dl and 100–140 mg/dl, respectively.

The studies describing the relationship between mean glycemia and mortality also confirmed the strong association of hypoglycemia with death in critically ill patients with and without diabetes; those with mean blood glucose during ICU stay less than 80 mg/dl sustained the highest mortality. Recently published work suggests that the independent association of hypoglycemia with death may even be stronger in patients with diabetes than in those without.[65]

Several observational cohort studies have demonstrated that high glucose variability is independently associated with risk of death in patients without diabetes, in contrast, there was no association between increasing glucose variability and risk of death for patients with insulintreated diabetes.[66] A recently published multicenter observational cohort study included 90 644 septic patients, 5127 with insulin treated diabetes evaluated glucose metrics in the first 24 h of ICU admission. Patients with insulin-treated diabetes had lower adjusted hospital mortality with higher peak blood glucose levels whereas those without diabetes had increased mortality.

VI. DURING CRITICAL ILLNESSES ACUTE HYPERGLYCEMIA IS MORE TOXIC THAN IN DIABETIC PATIENTS

Different theories regarding acute toxicity of hyperglycemia:

Some theories suggest that subtle molecular differences, patients' genetic background and differences between the acute and chronic status of hyperglycemia are interfering factors. Others point out that intracellular glucose overload during critically illnesses is involved in this scenario. [67]*Glucose transporters & intracellular glucotoxicity***:** It is known that glucose itself influences the regulation and expression of its cellular transporters. Downregulation of GLUTs during moderate hyperglycemia in normal cells is a protective mechanism against glucotoxicity.

Enhanced concentration of cytokines, such as TNFα, angiotensin II and endothelin 1, during the stress response stimulate the translocation and upregulation of glucose transport in different cells. Likewise, hypoxia has the same effect on GLUTs. Therefore, upregulated glucose transporters that are working without the influence of insulin cause extra influx of glucose into the cell. This leads to enhanced intercellular glucose levels in different cell types, including endothelial and epithelial cells, as well as immune cells.[69] Hyperglycemia has been associated with enhanced mitochondrial superoxide production.

Mitochondrial dysfunction, with a failure to produce energy for efficient metabolisms, is the major cause of cellular abnormalities and organ dysfunction leading to multiple syndromes among CIPs who die. Mitochondrial dysfunction is also attributed to insulin resistance. As a result of decreased oxidation of mitochondrial fatty acids, intracellular fatty acyl coenzyme A and diacyl glycerol levels are enhanced. Thus, atypical protein kinase C, JNK and IKKβ are activated to block IRS-1 tyrosine phosphorylation causing insulin resistance. 70

VII. MANAGEMENT OF HYPERGLYCEMIA

Glycemic Targets: The literature is fairly consistent in recommendation values for optimal glycemic control however debates arise over how strict the recommended glucose range should be set and whether there is any discernable advantage of adopting tight glycemic control versus having a more conservative approach. Due to variations in hospitalized patients' nutritional status and other factors contributing to their comorbidities, higher than normal glucose targets can be advised for these patients opposed to those who are in outpatient care. Therapy should be initiated in the majority of critically ill and non-critically ill patients who have consistent levels of hyperglycemia once they have crossed a threshold of >180 mg/dL (10.0 mmol/L) and maintained in a target glucose range of 140-180 mg/dL (7.8-10.0 mmol/L).71 These glucose ranges are maneuverable however and are not a set standard for all hospitalized patients. Certain patients may be given more aggressive goals of < 140 mg/dL (7.8 mmol/L) though glucose levels must be monitored appropriately to prevent hypoglycemia. On the other hand, if patients are in a position where strict glucose monitoring is simply not possible or glucose control is perhaps second to other more significant issues in their medical care such as palliation or severe comorbidities, then a higher target glucose range may be explored. Because of these outliers, an individualized approach to target glucose values may be worth the extra effort as treatment can be tailored to each individual patient to decrease hyperglycemia risk and avoid hypoglycemia due to overaggressive therapy.72

Management of Hyperglycemia in Non-Critically Ill Inpatients: The use of insulin has

become the mainstay of hyperglycemia in the hospital setting. The traditional use of sliding scale insulin was once considered an essential treatment method of high blood glucose levels but has now been considered inappropriate for safe management in hospitalized patients due to the risk of inadequately treated hyperglycemia and severe hypoglycemia. In general medicine and surgery patients who are not in critical care, subcutaneous short-acting insulin before meals or every 4-6 hours if NPO, has become the mainstay of treatment to adequately control hyperglycemia in diabetics and non-diabetics. The basal bolus (prandial) insulin regimen is effective because it follows the physiological response by covering the basal, nutritional and supplemental requirements of insulin production. A study by Korytkowski et al. found increased baseline glucose levels, greater insulin requirements, increased adverse outcomes, and a greater incidence of hypoglycemia in patients treated with sliding-scale regular insulin versus a basal dose of insulin glargine with SSRI. In patients being treated solely with SSRI therapy, they had a three times greater chance of having blood glucose levels >300mg/dL compared to those given basal-bolus insulin. A prospective randomized multicenter trial found 14% of patients being treated with sliding-scale insulin therapy had a blood glucose >240mg/dL despite administering higher insulin doses compared to patients treated with insulin glargine and glulisine, though no differences in length of hospital stay or incidence of hypoglycemia were noted.[73] A sliding - scale regimen can be of use for initial therapy in non-diabetic patients with moderate hyperglycemia, however these patients should be transitioned to a scheduled insulin regimen once insulin requirement is determined. The issue with treating patients with SSRI therapy is that the underlying mechanism acts to correct hyperglycemia only when it occurs and has no beneficial effect of preventing or decreasing recurrences of hyperglycemia, something which a basal-bolus regimen can achieve.[74]

The use of a constant intravenous insulin infusion has the benefit of a very rapid achievement of glycemic control however it is not recommended in non-critical care patients in many hospitals, especially when feeding protocols are subject to change, requiring insulin dosage to be adjusted accordingly. If patients are being weaned off of intravenous insulin during their hospital care, a proper transition protocol to subcutaneous insulin can lower costs and prevent morbidity and is thus recommended. Consideration about the patient's age, comorbidities, renal function, and nutritional intake should all influence the clinician's decision about the amount of total daily insulin required for patients. Most patients should be started with a starting total daily dose of insulin between 0.3 and 0.5 units/kg as higher doses greater than 0.6 to 0.8 units/kg/day have been associated with hypoglycemia. The seemingly increased safety profile of basal bolus (prandial) insulin regimen as well as its success rate of achieving and maintaining appropriate glucose levels in treated patients should lead to its uniform implementation in hospitalized non-critical care patients.[75]

Noninsulin antihyperglycemic treatments are currently not recommended in the treatment of hospitalized patients as evidence regarding safety and efficacy is lacking. Many inpatients in the hospital have clear contraindications for the use of certain oral antihyperglycemic agents.

Metformin is generally not prescribed for patients with renal insufficiency, hepatic and cardio-vascular disease due to concerns over lactic acidosis though its use in the hospital is still common despite these concerns. Sulfonylureas act as long-acting insulin secretagogues and are very commonly used in patients with type 2 diabetes however their side effect profile includes a high risk of hypoglycemia, limiting its use for inpatients. A nested case-control study showed 19% of hospitalized patients taking a sulfonylurea developed hypoglycemia, with the majority of cases occurring in patients older than 65 years, those with decreased GFR of 30ml/minute /1.73m2 and those who were receiving concurrent intermediate or long-acting insulin while being treated with a sulfonylurea. Patients being treated with a sulfonylurea have the increased risk of prolonged hypoglycemia due to the pharma-codynamics of the agent, and require further monitoring and strict management with glucose preparations. Other oral antihyperglycemic

agents such as thiazolidines, Sodium glucose co - transporter 2 inhibitors, α - glucosidase inhibitors and incretin based therapies generally have side effect profiles and contraindications in hospitalized patients that substantially limit their use for inpatient treatment.[76]

Management of Hyperglycemia in Critically Ill Inpatients: Insulin is indisputably the gold standard for treating critically ill patients in the hospital setting, as agreed upon by most of the literature. Intravenously administered insulin is preferred due to its rapid delivery which allows for quick correction of deteriorating glucose levels with greater predictability and effectiveness compared to subcutaneously administered insulin. However, infusing insulin intravenously is quite labor intensive and in a majority of health centers requires ICU admission for proper administration and monitoring. In the critical care setting, predetermined written or computer protocols factoring glycemic fluctuations and insulin dose may be used for adjustments of the infusion rate when considering infusing patients with insulin. Obvious fluctuations in the patients' clinical status and glucose targets should be accounted for when adjusting insulin infusion rates. Traditionally a blood glucose target was achieved by using a drip which was mathematically calculated by the medical staff using an established algorithm. Unfortunately, errors in dosing can be common due to human errors which is why computer protocols have set the stage to replace simple predicting on the physicians part. Computer based algorithms proved to deliver tighter glycemic control with less risk of hypoglycemia when compared to the traditional paper protocol.[77]

VIII. HYPERGLYCEMIA IN HIGH RISK PATIENTS

Certain subsets of patients are deemed high risk due to their underlying comorbidities, concurrent medications and procedures in the hospital which can contribute to hyperglycemia. Corticosteroids, which are commonly used in the hospital as a single therapy or in combination therapies, can contribute to hyperglycemia more commonly by late morning when it is prescribed, but can have a prolonged effect throughout the course of the day if daily doses are required. It is essential to monitor capillary blood glucose values in patients on high dose corticosteroids, especially during the period 4 to 8 hours after oral administration and sooner after intravenous administration. A basal dose of intermediate or long acting insulin may be able to offset the increased glucose levels of early morning corticosteroid therapy, however care should be taken to avoid episodes of hypoglycemia when long acting insulin preparations are used in these cases. The COIITSS study hypothesized that patients being treated for septic shock in the ICU with corticosteroids may benefit with intensive insulin therapy versus a conservative therapy, even though general ICU patients may not. Prolonged bed rest for as little as seven days in hospitalized patients may also contribute to insulin resistance in skeletal muscle and decreased glucose uptake. Severe hyperglycemia (minimum 9.99 mmol/L) has been shown to increase the likelihood of developing graft versus host disease in nondiabetic patients after allogenic stem - cell transplantation, though the researchers' results were found in non-obese patients only.[81] One study analyzing cardiac surgery patients found that while glucose concentrations were lower at the end of surgery with intensive insulin treatment, there was no decrease in perioperative death and mortality between this group and the conventional treatment group, in fact showing more deaths and strokes in the intensively treated group. Intensive glycemic control in the range of 80- 180 mg/dL (4.4-10 mmol/L) was not shown to benefit perioperative patients with diabetes undergoing surgical procedures and showed a higher incidence of hypoglycemia in these patients, advising against practicing tight glycemic control in surgical patients. A multicenter randomized trial found improved glycemic control in general surgery patients with a basal plus regimen with glargine once daily and corrective glulisine before meals compared to a standard basal-bolus regimen.[82]

IX. TARGET OF GLUCOSE CONTROL IN CRITICALLY-ILL PATIENTS

In the clinical studies on intensive insulin therapy, it is impossible to completely distinguish

the impact of insulin infusion from that of blood glucose control as both are done concomitantly.

Therefore, a four-arm design study was set up in a rabbit model of prolonged critical illness. Two norm insulinemic and two hyperinsulinemia groups were each controlled to either normal or elevated glucose levels. The study revealed that glycemic control mediated the survival benefit of intensive insulin therapy, independent of insulin.

Indeed, mortality was 41.4% in hyperglycemic versus 11.1% in normoglycemic rabbits, whereas insulin levels did not contribute to the survival benefit.[85] The clinical data are in agreement with this experimental observation. In the Leuven surgical study, the risk of death appeared to be linearly correlated with the degree of hyperglycemia, with no clear cut-off level below which there was no further benefit.

Conventionally treated patients who developed severe hyperglycemia (150–200 mg/dl) carried the highest risk of death, this risk was intermediate for patients who received conventional insulin therapy and who developed only moderate hyperglycemia (110–150 mg/dl), whereas the lowest risk was present in the patients whose blood glucose levels were controlled to strict normoglycemia below 110 mg/dl with intensive insulin therapy. This relation of risk of death with strata of glucose control was confirmed in the mixed medical/surgical patient population, with most benefit gained when glycemia was controlled below 110 mg/dl. Patients with diabetes appeared to behave differently though, with an inverse pattern for the 3 strata of glucose control, although no significant differences were noted among these 3 levels.[86,87]

Glycemic control also accounted for most effects of intensive insulin therapy on morbidity of critical illness. Tight glycemic control below 110 mg/dl appeared to be of crucial importance for the prevention of bacteremia, anemia, and acute renal failure[86,87] and for reducing the risk of critical illness polyneuropathy, for which a positive linear correlation was observed with glycemia.[88] The superior clinical benefit with glucose control below 110 mg/dl underscores the importance of achieving the normoglycemic target range. Seventy percent of the patients allocated to intensive insulin therapy in the Leuven studies achieved a mean daily blood glucose level below 110 mg/dl. At the time of interim analysis of the GLUCONTROL study, median (interquartile range) levels of glucose were 147 (127–163) mg/dl in the conventional and 118 (109–131) mg/dl in the intensive insulin group (Preiser JC, data presented at the 19th European Symposium on Intensive Care Medicine, Barcelona, Spain, September 2006).

This means that tight glycemic control was achieved in only approximately 25% of the patients on intensive insulin therapy.[89,90]

Communication and Discharge of Hyperglycemic Patients: Generally, a patient with an HbA1C of less than 6.5% can be discharged with no antidiabetic treatment, and those with elevated HbA1C levels should be prescribed insulin, oral antihyperglycemic agents or combination therapies for the outpatient setting. Proper communication is imperative to ensure the patient administers their treatment correctly and at the appropriate times in order to prevent aberrations in their glucose levels. Due to the complexity of insulin treatment regimens, it is recommended that written orders be given to the patient as oral communication can lead to errors and complications in management. To prevent these types of errors, several organizations have implemented strategies that incorporate clear, formal discharge instructions about medications and follow up appointments, however evidence is still lacking regarding the ideal method of providing a safe transition to the outpatient setting. A systematic review found that patients who have been treated for stress hyperglycemia in the hospital are at increased risk for developing subsequent diabetes and should be followed up accordingly. Another study determined a prevalence of new-onset diabetes of 8% in stress hyperglycemia patients during follow up and noted a positive correlation between the degree of in-hospital hyperglycemia and risk of subsequent diabetes development. Hospitalized in patients with severe hyperglycemia showed a striking 28% increased risk of developed new-onset diabetes after discharge. This perceived link necessitates

further research into the development of new-onset diabetes in stress-hyperglycemia patients and reiterates the importance of proper discharge orders and follow up appointments in such patients as research on the pathophysiology of such events is still lacking.[98]

Objective:

- To determine mean hospital, stay in critically ill patients admitted in hospital.
- To compare mean hospital, stay mong critically ill patients with hyperglycemic versus normoglycemic.

X. PATIENTS AND METHODS

This descriptive study of 7 months was conducted in the setting of Department of Internal Medicine, The Aga Khan University Hospital.The sample size for this study is 151 patients as calculated by using WHO sample size calculator. Mean length hospital stay = 5.4±1.0 (12), margin of error = 0.16. Nonprobability consecutive sampling was done Patients' age varied between 18- 75 years, blood sugar of >140mg/dl on admission to SCU/ICU was marked as cases and blood sugar of <140mg/dl on admission to SCU/ICU was labelled as control. Those with known diabetes or taking medications causing hyperglycemia (Steroids) were excluded from the study.

Patients fulfilling the mentioned-above inclusion criteria were included in the study. Mean hospital stay was seen in critically ill patients and comparison between hyperglycemic versus normoglycemic were done among those patients. Detailed patient demographics e.g. Age, gender, HBA1c levels were recorded. The first blood glucose level from a peripheral blood draw on the day of admission was used as the admission blood glucose value. Data was also recorded for reasons for admissions e.g. HTN, CKD, Stroke, IHD, sepsis and MI. Hospital stay was measured in all patients. All the gathered information was a pre-designed Proforma. All the collected data was entered and analyzed by using the SPSS (version-23). Variables were recorded include continuous variables such as age, blood sugar levels, length of hospital stay were reported as mean ± standard deviation. Frequency and percentage were calculated gender, reasons of hospital admission e.g. HTN. CKD, STROKE, IHD, sepsis and MI. stratification of effect modifiers e.g. age, gender, reasons of hospital admission was done. Post-stratification independent sample t-test was applied. P-value of <0.005 was taken as statistically significant difference. Comparison of mean hospital stay between hyperglycemic versus normoglycemic was done using independent sample t-test.

XI. RESULT

Mean age of patients included in this study was 55.40±17.20 years. Minimum age was 20 years and maximum age was 75 years.

Mean hospital stay was 6.45±5.82 days. Minimum hospital stay was 01 day and maximum stay was 35 days (Table 1).

Table 1

Hospital stay (Days)	
Mean	6.45
S.D.	5.82
Minimum	01
Maximum	35

Mean blood sugar level was 179.36±69.21 mg/dl. Minimum blood sugar level was 60.00 mg/dl and maximum stay was 560.00 mg/dl (Table 2).

There were more males as compared to females. There were 79 (52.32%) male and 72 (47.68%) female patients (Figure 1).

Table 2

Blood Sugar level (mg/dl)	
Mean	179.36
S.D.	69.21
Minimum	60.00
Maximum	560.00

On frequency of reason for admission, 19 (12.58%) patients were having MI/heart failure, 01 (0.68%) road traffic accidents, 13 (8.61%) acute kidney injury, 83 (54.97%) sepsis/ infections, 2 (1.32%) hypertensive emergency, 15 (9.93%) stroke and 18 (11.92%) patients were having COPD/Asthma/interstitial lung disease (ILD) (Figure 2).

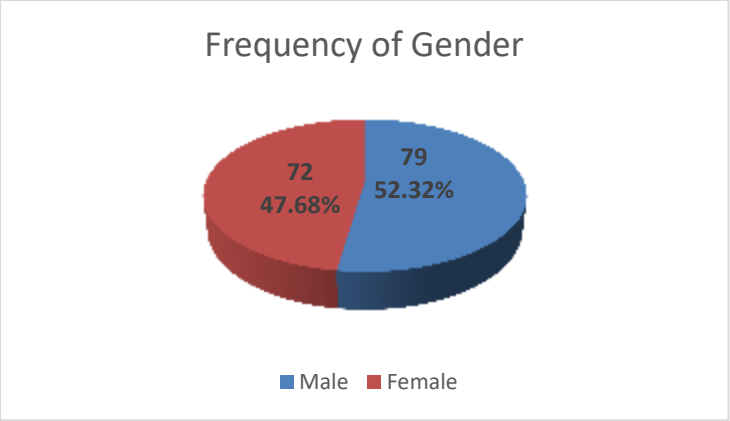


Figure 1

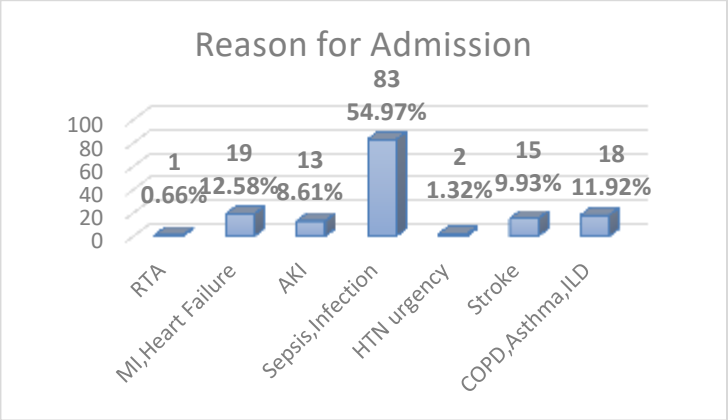


Figure 2

Hyperglycemia was diagnosed in 134 (88.74%) patients.

On comparison of mean hospital stay between the groups, mean hospital stay in hyperglycemia group was 6.70±6.09 days versus 4.52±2.03 days in normoglycemia group. This difference was statistically insignificant with p-value of 0.004.

Stratification of age was performed, in age group of 18-50 years, mean hospital stay in hyperglycemia group was 8.06±7.50 days and 5.14± 2.54 days in normoglycemia group. This difference was statistically significant with p-value of 0.05. In age group of 51-75 years, mean hospital stay in hyperglycemia group was 5.97 ±4.10 days and 5.08±1.59 days in normoglycemia group. This difference was also statistically significant with p-value of 0.01 (Table 4).

Table 4: Stratification of age to determine the association of age with mean hospital stay between the groups

Age Group	Hospital Stay	Groups		P- value
		Hyperglycemia	Normoglycemia	
18-50 Years	Mean	8.06	5.14	0.05
	S.D.	7.50	2.54	
51-75 Years	Mean	5.97	5.08	0.01

Table 5: Stratification of gender to determine the association of gender with mean hospital stay between the groups

Gender	Hospital Stay	Groups		P- value
		Hyperglycemia	Normoglycemia	
Male	Mean	6.21	4.40	0.04
	S.D.	5.63	1.83	
Female	Mean	7.23	4.71	0.05
	S.D.	6.55	2.42	

Stratification of gender was also performed, in males, mean hospital stay in hyperglycemia group was 6.21±5.63 days and 4.40±1.83 days in normoglycemia group. This difference was statistically significant with p-value of 0.04. In females, mean hospital stay in hyperglycemia group was 7.23±6.55 days versus 4.71±2.42 days in normoglycemia group. This difference was also statistically significant with p-value of 0.05 (Table 5).

Stratification was also performed on the basis of reason for admission. There is no significant association was found of its with hospital stay between the groups.

XII. DISCUSSION

Hyperglycemia is a condition frequently encountered in daily practice with hospitalized patients. It is estimated that nearly 25–35 % of admitted patients are hyperglycemic. [99] Several studies have shown that hyperglycemia is associated with poor outcomes and extended hospital stay in patients hospitalized for various conditions and in different settings (i.e. coronary care and intensive care units, post-operatively).[100-102]. In present study, we determined the association of hyperglycemia with hospital stay in critically ill non-diabetic patients. In our study, hospital stay was significantly higher in patients with hyperglycemia. Lipton reported that patients admitted to the intensive cardiac care unit had a longer length of stay and increased mortality if they were in the upper tertile of admission glucose levels.[103] In addition, these investigators noted that hypoglycemia was associated with an increased mortality rate and that an increase in the average glucose level during the ICU stay was associated with increased mortality. Williams et al. have reported that stroke patients complicated with hyperglycemia had longer hospital stay (7 vs. 6 d, p-value 0.015) and higher inpatient hospital charges ($6611 vs. $5262; p < 0.001).104 Karetnikova et al. studied 529 patients admitted with an ST-segment elevation myocardial infarction. They found a linear association between the blood glucose level and in-hospital mortality in nondiabetic patients.[105] Kasirye et al. studied 209 patients admitted to the hospital with an acute exacerbation of COPD. They did not find any correlation between hyperglycemia and adverse outcomes, including increased length of stay, 30-day readmission rates, and 90-day all-cause mortality.[106]

Van Vught did an extensive study of the relationship between the admission glucose levels and outcomes in critically ill patients with sepsis. This study included 987 patients, including 201 patients with severe hyperglycemia defined by glucose levels greater than 200 mg/dL. Multivariable regression analysis demonstrated that patients with severe hyperglycemia had an increased risk of mortality by day 30. This occurred in patients both with diabetes and without diabetes. This association between severe hyperglycemia and mortality persisted in patients after adjustment for lactic levels in patients with diabetes but not in patients without diabetes.[107]

Sung and colleagues prospectively collected data on 1,003 consecutive trauma patients admitted to an intensive care unit over 2 years. Twenty-five percent of these patients had severe hyperglycemia defined by glucose levels>200 mg/dl. These patients with severe hyperglycemia

had an increased risk of infection, longer hospital lengths of stay, and higher mortality after adjustment for age and the injury severity score. These five studies demonstrate that admission levels of glucose have important associations with outcomes in patients presenting to emergency departments, in patients admitted to intensive care units, and in patients admitted with trauma.[108]

In summary, hyperglycemia is a frequent condition occurring in critically ill patients. Patients with stress hyperglycemia have a longer average hospital stay, although it remains unresolved whether stress hyperglycemia is a determinant rather than a marker of increased morbidity and mortality in critically ill patients. Furthermore, identifying previously unknown diabetes has relevant therapeutic implications and represents a great opportunity for prevention of diabetes related acute and chronic complications.

XIII. CONCLUSION

Our study showed a positive association between hyperglycemia and length of stay in critically ill patients. Therefore, hyperglycemia can be used as a predictor of increased hospital stay in critically ill non-diabetic patients.

REFERENCES

1. Deane AM, Horowitz M. Dysglycaemia in the critically ill–significance and management. Diabetes Obes Metab. 2013;15(9):792-801.
2. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004;27 (2) :553-91.
3. Taylor JH, Beilman GJ. Hyperglycemia in the intensive care unit: no longer just a marker of illness severity. Surg Infect. 2005;6(2):233-45.
4. Razzaque S, Ghauri MI. Stress induced hyperglycemia in stroke patients. Pak J Neurol Sci.2015;10(2):9-12.
5. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalized with acute myocardial infarction. Circulation. 2008;117(8):1018-27.
6. Clark ME, Payton JE, Pittiglio LI. Acute ischemic stroke and hyperglycemia. Crit Care Nurs Q. 2014;37(2):182-7.
7. Wahab NN, Cowden EA, Pearce NJ, Gardner MJ, Merry H, Cox JL, et al. Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era?. J Am Coll Cardiol. 2002;40(10):1748-54.
8. Grossman AN, Opie LH, Beshansky JR, Ingwall JS, Rackley CE, Selker HP. Glucose-insulin-potassium revived. Circulation. 2013;127(9):1040-8.
9. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359-67.
10. Gholap NN, Achana FA, Davies MJ, Ray KK, Gray L, Khunti K. Long-term mortality after acute myocardial infarction among individuals with and without diabetes: A systematic review and meta-analysis of studies in the post- reperfusion era. Diabetes Obes Metab. 2017; 19(3):364-74.
11. Garg R, Bhutani H, Alyea E, Pendergrass M. Hyperglycemia and length of stay in patients hospitalized for bone marrow transplantation. Diabetes Care. 2007;30(4):993-4.
12. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med. 2008; 36(8):2249-55.
13. Smith FG, Sheehy AM, Vincent JL, Coursin DB. Critical illness-induced dysglycaemia: diabetes and beyond. Crit Care. 2010;14(6): 327.
14. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2011; 154(4):260-7.
15. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. Best Pract Res Clin Endocrinol Metab. 2001;15(4):533-51.

16. Inzucchi SE. Clinical practice. Management of hyperglycemia in the hospital setting. N Engl J Med. 2006;355(18):1903-11.
17. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359-67.
18. Kansagara D, Fu R, Freeman M, Wolf F, Helfand M. Intensive insulin therapy in hospitalized patients: a systematic review. Ann Intern Med. 2011;154(4):268-82.
19. Staszewski J, Brodacki B, Kotowicz J, Stepien A. Intravenous insulin therapy in the maintenance of strict glycemic control in nondiabetic acute stroke patients with mild hyperglycemia. J Stroke Cerebrovasc Dis. 2011; 20(2):150-4.
20. Kramer AH, Roberts DJ, Zygun DA. Optimal glycemic control in neurocritical care patients: a systematic review and meta- analysis. Crit Care. 2012;16(5):R203.
21. Malmberg K, Norhammar A, Wedel H, Rydén L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation. 1999; 99(20):2626-32.
22. Zhao YT, Weng CL, Chen ML, Li KB, Ge YG, Lin XM, et al. Comparison of glucose -insulin-potassium and insulin-glucose as adjunctive therapy in acute myocardial infarction: a contemporary meta-analysis of randomised controlled trials. Heart. 2010;96(20):1622-6.
23. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580 -637.
24. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. Crit Care Med. 201 10;38(4): 1021-9.
25. Meynaar IA, Eslami S, Abu-Hanna A, van der Voort P, de Lange DW, de Keizer N. Blood glucose amplitude variability as predictor for mortality in surgical and medical intensive care unit patients: a multicenter cohort study. J Crit Care. 2012;27(2):119-24.
26. Greci LS, Kailasam M, Malkani S, Katz DL, Hulinsky I, Ahmadi R, et al. Utility of HbA(1c) levels for diabetes case finding in hospitalized patients with hyperglycemia. Diabetes Care. 2003;26(4):1064-8.
27. Osterbur K, Mann FA, Kuroki K, DeClue A. Multiple organ dysfunction syndrome in humans and animals. J Vet Intern Med.20 14:28(10):1141-51.
28. Van Niekerk G, Davis T, Engelbrecht AM. Hyperglycaemia in critically ill patients: the immune system's sweet tooth. Crit Care. 2017:21(1):202.
29. Sperry JL, Frankel HL, Vanek SL, Nathens AB, Moore EE, Maier RV, et al. Early hyperglycemia predicts multiple organ failure and mortality but not infection. J Trauma. 2007: 63(3):487-94.
30. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(1):125-39.
31. Investigators TN-SS. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009; 360(1): 1283 -97.
32. Stapleton RD, Heyland DK. Glycemic Control and Intensive Insulin Therapy in Critical Illness-UpToDate. Available online at:https://www.ptodate.com/contents/glycemic-control.and-intensive-insulin-therapy-incritical-illness.
33. Kelly B, O'Neill LAJ. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell Res. 2015:25(6):771-84.
34. Douzinas EE, Tsidemiadou PD, Pitaridis MT, Andrianakis I, BobotaChloraki A, Katsouyanni K, et al. The regional production of cytokines and lactate in sepsis - related multiple organ failure. Am J Respir Crit Care Med. 1997: 155 (4):53-9.

35. Choi CS, Kim Y-B, Lee FN, Zabolotny JM, Kahn BB, Youn JH. Lactate induces insulin resistance in skeletal muscle by suppressing glycolysis and impairing insulin signaling. Am J Physiol Endocrinol Metab. 2002;283 (2): E233-40.
36. Selak MA, Armour SM, MacKenzie ED, Boulahbel H, Watson DG, Mansfield KD, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-α prolyl hydroxylase. Cancer Cell. 2005;7(6):77- 85.
37. Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma. 2004;56(9):1058-62.
38. Dienel GA. Brain lactate metabolism: the discoveries and the controversies. J Cereb Blood Flow Metab. 2012;32(1):1107-38.
39. Chen J, Xie J, Jiang Z, Wang B, Wang Y, Hu X. Shikonin and its analogs inhibit cancer cell glycolysis by targeting tumor pyruvate kinase-M2. Oncogene. 2011;30(3):4297-306.
40. Nemoto E, Sugawara S, Takada H, Shoji S, Horiuch H. Increase of CD26/dipeptidyl peptidase IV expression on human gingival fibroblasts upon stimulation with cytokines and bacterial components. Infect Immun. 1999;67(5):6225-33.
41. Kim SC, Schneeweiss S, Glynn RJ, Doherty M, Goldfine AB, Solomon DH. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes may reduce the risk of autoimmune diseases: a population-based cohort study. Ann Rheum Dis. 2015; 74(1):1968-75.
42. Miyoshi H, Shulman GI, Peters EJ, Wolfe MH, Elahi D, Wolfe RR: Hormonal control of substrate cycling in humans. J Clin Invest. 1988;81(5):1545-55.
43. Van den Berghe G, de Zegher F, Bouillon R: Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab. 1998;83(6):1827-34.
44. Smith TR, Elmendorf JS, David TS, Turinsky J:Growth hormone-induced insulin resistance :role of the insulin receptor, IRS-1, GLUT-1, and GLUT-4. Am J Physiol. 1997;272(6 Pt 1):E1071-E9.
45. lement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004;27(4):553-91.
46. Gray CS, Scott JF, French JM, Alberti KG, O'Connell JE. Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke. Age Ageing. 2004;33(6):71-7.
47. Greci LS, Kailasam M, Malkani S, Katz DL, Hulinsky I, Ahmadi R, et al. Utility of HbA(1c) levels for diabetes case finding in hospitalized patients with hyperglycemia. Diabetes Care. 2003;26(9):1064-8.
48. Nordin C, Amiruddin R, Rucker L, Choi J, Kohli A, Marantz PR. Diabetes and stress hyperglycemia associated with myocardial infarctions at an urban municipal hospital: prevalence and effect on mortality. Cardiol Rev. 2005;13(1):223-30.
49. Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, et al. Intensive insulin therapy in mixed medical/ surgical intensive care units: benefit versus harm. Diabetes. 2006;55(2):3151-9.
50. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(1):125-39.
51. Finfer S, Chittock DR, Su SY. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(11):1283-97.
52. Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years' experience at a university-affiliated community hospital. Semin Thorac Cardiovasc Surg. 2006;18(2):317-25.
53. Freire AX, Bridges L, Umpierrez GE, Kuhl D, Kitabchi AE. Admission hyperglycemia and other risk factors as predictors of hospital mortality in a medical ICU population. Chest. 2005;128(2):3109-16.
54. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355(6):773-8.

55. Hadjadj S, Coisne D, Mauco G, Ragot S, Duengler F, Sosner P, et al. Prognostic value of admission plasma glucose and HbA1c in acute myocardial infarction. Diabetic Med. 2004;21(2):305-10.
56. Stöllberger C, Exner I, Finsterer J, Slany J, Steger C. Stroke in diabetic and non-diabetic patients: course and prognostic value of admission serum glucose. Ann Med. 2005;37 (2):357-64.
57. Freire AX, Bridges L, Umpierrez GE, Kuhl D, Kitabchi AE. Admission hyperglycemia and other risk factors as predictors of hospital mortality in a medical ICU population. Chest. 2005;128(2):3109-16.
58. Jones KW, Cain AS, Mitchell JH, Millar RC, Rimmasch HL, French TK, et al. Hyperglycemia predicts mortality after CABG: postoperative hyperglycemia predicts dramatic increases in mortality after coronary artery bypass graft surgery. J Diabet Complicat. 2008 ;22(2):365-70.
59. Gandhi GY, Murad MH, Flynn DN, Erwin PJ, Cavalcante AB, Nielsen HB, et al. Effect of perioperative insulin infusion on surgical morbidity and mortality: systematic review and meta-analysis of randomized trials. Mayo Clin Proc. 2008;83(3):418-30.
60. Kosuge M, Kimura K, Kojima S. for the; Japanese Acute Coronary Syndrome Study (JACSS) Investigators. Effects of glucose abnormalities on in-hospital outcome after coronary intervention for acute myocardial infarction. Circ J. 2005;69(2):375-9.
61. Fogelholm R, Murros K, Rissanen A, Avikainen S. Admission blood glucose and short term survival in primary intracerebral haemorrhage: a population based study. J Neurol Neurosurg Psychiatry. 2005;76(2): 349-53.
62. Agwunobi AO, Reid C, Maycock P, Little RA, Carlson GL. Insulin resistance and substrate utilization in human endotoxemia. J Clin Encrinol Metab. 2000;85(2):3770-8.
63. Sechterberger MK, Bosman RJ, Oudemans-van Straaten HM. The effect of diabetes mellitus on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study. Crit Care. 2013;17(4):R52.
64. Van Vught LA, Holman R, de Jonge E, de Keizer NF, Van der Poll T. Diabetes is not associated with increased 90-day mortality risk in critically ill patients with sepsis. Crit Care Med. 2017;45(9):e1026-35.
65. Egi M, Krinsley JS, Maurer P, Amin DN, Kanazawa T, Ghandi S, et al. Premorbid glycemic control modifies the interaction between acute hypoglycemia and mortality. Int Care Med. 2016;42(4):562-71.
66. Magee F, Bailey M, Pilcher DV. Early glycemia and mortality in critically ill septic patients: Interaction with insulin-treated diabetes. J Crit Care. 2018;45(1):170-7.
67. Vanhorebeek I, Langouche L, Van den Berghe G: Glycemic and nonglycemic effects of insulin: how do they contribute to a better outcome of critical illness? Curr Opin Crit Care. 2005;11(4):30411.
68. Kono T, Nishida M, Nishiki Y, Seki Y, Sato K, Akiba Y: Characterisation of glucose transporter (GLUT) gene expression in broiler chickens. Br Poult Sci. 2005;46(4):510-5.
69. Clerici C, Matthay MA: Hypoxia regulates gene expression of alveolar epithelial transport proteins. J Appl Physiol. 2000;88 (5):1890-6.
70. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al.: Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002:360(9328):219-23.
71. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32(6):1119-31.
72. Care H, Standards D. Diabetes Care in the Hospital. Diabetes Care. 2017;40 (Supplement 1):S120-7.
73. Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, Ceron M, et al. RABBIT 2: Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes. Diabetes Care. 2007;30(9):2181-6.

74. Korytkowski MT, Salata RJ, Koerbel GL, Selzer F, Karslioglu E, Idriss AM, et al. Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: A randomized controlled clinical trial. Diabetes Care. 2009;32(4):594-6.
75. Schmeltz LR, DeSantis AJ, Thiyagarajan V, Schmidt K, O'Shea-Mahler E, Johnson D, et al. Reduction of surgical mortality and morbidity in diabetic patients undergoing cardiac surgery with a combined intravenous and subcutaneous insulin glucose management strategy. Diabetes Care. 2007;30(4): 823-8.
76. Deusenberry CM, Coley KC, Korytkowski MT, Donihi AC. Hypoglycemia in hospitalized patients treated with sulfonylureas. Pharmacotherapy. 2012;32(7):613-7.
77. Newton CA, Smiley D, Bode BW, Kitabchi AE, Davidson PC, Jacobs S, et al. A 22 comparison study of continuous insulin infusion protocols in the medical intensive care unit: Computer-guided vs. standard column-based algorithms. J Hosp Med. 2010;5(8):432-7.
78. Preiser J-C, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intens care med. 2009;35 (10):1738-48.
79. Finfer S, Chittock DR, Su SY-S, Blair D, Foster D, Dhingra V, et al. Intensive versus Conventional Glucose Control in Critically Ill Patients. Nejm. 2009;360(13):1283-97.
80. Zoungas, S., Patel, A., Chalmers, J., de Galen, B.E., Li, Q., Billot, L., et al. Severe hypoglycemia and risks of vascular events and death. Nejm. 2010;363(13):1410-8.
81. Gebremedhin E, Behrendt CE, Nakamura R, Parker P, Salehian B. Severe hyperglycemia immediately after allogeneic hematopoietic stem-cell transplantation is predictive of acute graft-versus-host disease. Inflammation. 2013; 36(1):177-85.
82. Buchleitner A, Hernández M, Solà I, Mauricio D, Buchleitner AM, Hernández M, et al. Perioperative glycaemic control for diabetic patients undergoing surgery. Perioperative glycaemic control for diabetic patients undergoing surgery. 2012;(9):9-12.
83. McMahon MM, Rizza R. Nutrition support in hospitalized patients with diabetes mellitus. Mayo Clin proc. 1996;71(6):587-94.
84. Curll M, Dinardo M, Noschese M, Korytkowski MT. Menu selection, glycaemic control and satisfaction with standard and patient- controlled consistent carbohydrate meal plans in hospitalised patients with diabetes. Qual Saf *Health Care*. 2010;19 (4): 355-9.
85. Ellger B, Debaveye Y, Vanhorebeek I, Langouche L, Giulietti A, Van Etten E, et al. Survival benefits of intensive insulin therapy in critical illness. Impact of normoglycemia versus glycemia-independent actions of insulin. Diabetes. 2006;55(9):1096-105.
86. Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med. 2003; 31(2): 359-66.
87. An den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, et al. Intensive insulin therapy in mixed medical/ surgical ICU: benefit versus harm. Diabet. 2006;55(2):315 1-9.
88. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ, et al. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005;64(8):1348-53.
89. An den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345 (19):1359-67.
90. An den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in medical intensive care patients. N Engl J Med. 2006;354(5): 449-61.
91. Boord JB, Graber AL, Christman JW, Powers AC. Practical management of diabetes in critically ill patients. Am J Respir Crit Care Med. 2001;164(1):1763-7.
92. Vriesendorp TM, DeVries JH, van Santen S, Moeniralam HS, de Jonge E, Roos YB, et al. Evaluation of short-term consequences of

92. Vriesendorp TM, DeVries JH, van Santen S, Moeniralam HS, de Jonge E, Roos YB, et al. hypoglycemia in an intensive care unit. Crit Care Med. 2006;34(11):26714-18.
93. Mackenzie I, Ingle S, Zaidi S, Buczaski S. Hypoglycemia? So what! Intensive Care Med. 2006;32(5):620- 1.
94. Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. J Clin Invest. 2007;117(4):910-8.
95. Dungan K, Chapman J, Braithwaite SS, Buse J. Glucose measurement: confounding issues in setting targets for inpatient management. Diabetes Care. 2007;30(3):403-9.
96. Vlasselaers D, Schaupp L, van den Heuvel I, Mader J, Bodenlenz M, Suppan M, et al. Monitoring blood glucose with microdialysis of interstitial fluid in critically ill children. Clin Chem. 2007;53(4):536-7.
97. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79(8):992-1000.
98. Jivanji CJ, Asrani VM, Windsor JA, Petrov MS. New-Onset Diabetes After Acute and Critical Illness: A Systematic Review. Mayo Clin Proc. 2016;92(5):762-73.
99. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32(6) :1119-31.
100. Chen PC, Chua SK, Hung HF, Huang CY, Lin CM, Lai SM, et al. Admission hyperglycemia predicts poorer short-and long-term outcomes after primary percutaneous coronary intervention for ST-elevation myocardial infarction. J Diabetes Investig. 2014;5(1): 80-6.
101. Deedwania P, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T, Raskin P. Hyper glycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2008; 117 (12):1610- 9.
102. Lazzeri C, Valente S, Gensini GF. Hyperglycemia in acute heart failure: an opportunity to intervene? Curr Heart Failure Rep. 2014;11(3):241-5.
103. Lipton JA, Barendse RJ, Van Domburg RT. Hyperglycemia at admission and during hospital stay are independent risk factors for mortality in high risk cardiac patients admitted to an intensive cardiac care unit. Eur Heart J Acute Cardiovasc Care. 2013; 2(3): 306-13.
104. Williams LS, Rotich J, Qi R. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. Neurology. 2002;59(1):67–71.
105. Karetnikova V, Gruzdeva O, Uchasova E, Osokina A, Barbarash O. Glucose levels as a prognostic marker in patients with ST-segment elevation myocardial infarction: a case–control study. BMC Endocrine Disord. 2016;16(1):31.
106. Kasirye Y, Simpson M, Mamillapalli CK, Epperla N, Liang H, Yale SH. Association between blood glucose level and outcomes in patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease. WMJ. 2013;112(6):244-9.
107. Van Vught LA, Wiewel MA, Klein Klouwenberg PM, et al. Admission hyperglycemia in critically ill sepsis patients: association with outcome and host response. Crit Care Med. 2016;44 (7):1338-46.
108. Sung J, Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma Acute Care Surg. 2005;59(1):80-3.