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ABOUT THE JOURNAL

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AIMS & SCOPE:

The Green Life Medical College Journal is an english language scientific papers dealing with clinical medicine, basic sciences, epidemiology, diagnostic, therapeutics, public helath and healthcare in relation to concerned specialities. It is an official journal of Green Life Medical College and is published bi-annually.

This Joural is recognized by Bangladesh Medical & Dental Council (BM&DC).

The Green Life Medical College Journal of Bangladesh intends to publish the highest quality material on all aspects of medical science. It includes articles related to original research findings, technical evaluations and reviews. In addition, it provides readers opinion regarding the articles published in the journal.

INSTRUCTION TO AUTHORS:

Papers:

The Green Life Medical College Journal (published bi-annually) accepts contributions from all branches of medical science which include original articles, review articles, case reports, and letter to the Editor.

The articles submitted are accepted on the condition that they must not have been published in whole or in part in any other journal and are subject to editorial revision. The editor preserves the right to make literary or other alterations which do not affect the substance of the contribution. It is a condition of acceptance that the copyright becomes vested in the journal and permission to republish must be obtained from the publisher. Authors must conform to the uniform requirements for manuscripts submitted to biomedical journals (JAMA 1997; 277: 927-34).

Legal considerations:

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Preparation of manuscript:

Each manuscript should indicate the title of the paper, and the name(s) and full address(es) of the author(s). Contributors should retain a copy in order to check proofs and in case of loss. Two hard copies of each manuscript (double-spaced) should be submitted. If a manuscript is accepted for publication in the GMCJ, the editor responsible for it and may request a soft copy (a CD or via internet) for the revision. Each paper will be reviewed for possible publication. The Editor may wish to see the raw data (electronic form) if necessary.

In preparing the manuscript, use double spacing throughout, including title, abstract, text, acknowledgement, references, table and legends for illustrations and font type and size 'Times New Roman 12'. Begin each of the following sections on a separate paper. Number pages consecutively.

The standard layout of a manuscript:

- Title page
- Abstract, including Keywords
- Introduction
- Methods
- Results
- Discussion
- Acknowledgements
- Funding
- List of references
- Tables & Figures
- Illustrations

The pages should be numbered in the bottom right-hand corner and the title page being page one, etc. Start each section on a separate page.

Title page:

A separate page which includes the title of the paper. Titles should be as short and concise as possible (containing not more than 50 characters). Titles should provide a

reasonable indication of the contents of the paper. This is important as some search engines use the title for searches. Titles in the form of a question, such as 'Is drinking frequent coffee a cause of pancreatic carcinoma?" may be acceptable.

The title page should include the name(s) and address(es) of all author(s). Details of the authors' qualifications and post (e.g., professor, consultant) are also required. An author's present address, if it differs from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers ([1, 2, 3] etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

Abstract:

The 'Abstract' will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Introduction/Background; Methods; Results; and Conclusions) for all Clinical Investigations and Laboratory Investigations. For Reviews and Case Reports, the abstract should not be structured. The Abstract should give a succinct account of the study or contents within 350 words. The results section should contain data. It is important that the results and conclusion given in the 'Abstract' are the same as in the whole article. References are not included in this section.

Keywords:

Three to six keywords should be included on the summary page under the heading Keywords. They should appear in alphabetical order and must be written in United Kingdom English spelling.

Introduction:

The recommended structures for this section are:

- Background to the study/Introduction
- What is known/unknown about it
- What research question / hypothesis you are interested in
- What objective(s) you are going to address

The introduction to a paper should not require more than about 300 words and have a maximum of 1.5 pages double-spaced. The introduction should give a concise account of the background of the problem and the object of the investigation. It should state what is known of the problem to be studied at the time the study was started. Previous work should be quoted here but only if it has direct bearing on the present problem. The final paragraph should clearly state the primary and, if applicable, secondary aims of the study.

Methods:

The title of this section should be 'Methods' - neither 'Materials and methods' nor Patients and methods'. The Methods section should give a clear but concise description of the process of the study. Subjects covered in this section should include:

- Ethics approval/license
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- Inclusion/exclusion criteria
- Conduct of the study
- Data handling
- Statistics
- Cognitive Task Analysis (CTA)

Ethical clearance:

Regardless of the country of origin, all clinical investigators describing human research must abide by the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association. This document can be found at: http://ohsr.od.nih.gov/guidelines/helsinki.html. Investigators are encouraged to read and follow the Declaration of Helsinki. Clinical studies that do not meet the Declaration of Helsinki criteria will be denied peer review. If any published research is subsequently found to be non-compliant to Declaration of Helsinki, it will be withdrawn or retracted. On the basis of the Declaration of Helsinki, the Green Life Medical Journal requires that all manuscripts reporting clinical research state in the first paragraph of the 'Methods' section that:

- The study was approved by the appropriate Ethical Authority or Committee.
- Written informed consent was obtained from all subjects, a legal surrogate, or the parents or legal guardians for minor subjects.

Human subjects should not be identifiable. Do not disclose patients' names, initials, hospital numbers, dates of birth or other protected healthcare information. If photographs of persons are to be used, either take permission from the person concerned or make the picture unidentifiable. Each figure should have a label pasted on its back indicating name of the author at the top of the figure. Keep copies of ethics approval and written informed consents. In unusual

circumstances the editors may request blinded copies of these documents to address questions about ethics approval and study conduct.

The methods must be described in sufficient detail to allow the investigation to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be stated in detail, but appropriate reference to the original should be cited. However, any modification of previously published methods should be described and reference given. Where the programme of research is complex such as might occur in a neurological study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation. In longitudinal studies (case-control and cohort) exposure and outcome should be defined in measurable terms. Any variables, used in the study, which do not have universal definition should be operationalised (described in such terms so that it lends itself to uniform measurement). Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Keyence VHX-6000 digital microscope). The manufacturer's town and country must be provided, in the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

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Single case reports of outstanding interest or clinical relevance, short technical notes and brief investigative studies are welcomed. However, length must not exceed 1500 words including an unstructured abstract of less than 200 words. The number of figures/tables must not be more than 4 and references more than 25.

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In the case of animal studies, it is the responsibility of the author to satisfy the board that no unnecessary suffering has been inflicted on the animal concerned. Therefore, studies that involve the use of animals must clearly indicate that ethical approval was obtained and state the Home Office License number or local equivalent.

Drugs:
When a drug is first mentioned, it should be given by the international non-proprietary name, followed by the chemical formula in parentheses if the structure is not-well known, and, if relevant, by the proprietary name with an initial capital letter. Dose and duration of the drug should be mentioned in sufficient details. If the drug is already in use (licensed by appropriate licensing authority), generic name of the drugs should preferably be used followed by proprietary name in brackets.

Present the result in sequence in the text, table and figures. Do not repeat all the data in the tables and/or figures in the text. Summarize the salient points. Mention the statistics used for statistical analysis as footnote under the tables or figures. Figures should be professionally drawn. Illustration can be photographed (Black and White glossy prints) and numbered.

Discussion:
Do not repeat the data in detail, already given in the results. Give implications of the findings, their strengths and limitations in comparison to other relevant studies. Avoid un-qualified statements and conclusions which are not supported by the data. Avoid claiming priority.

Conclusion:
Comments on the observation of the study and the conclusion derived from it. New hypothesis or implications of the study may be labeled as recommendations.

References:
References should be written in Vancouver style, numbered with arabic numerals in the order they appear in the text. The reference list should include all information, except for references with more than six authors, in which case give the first six names followed by et al.

Examples of correct forms of references:
Dorababu M, Prabha T, Priyambada S, Agrawal VK, Aryaa NC, Goel RK. Effect of Azadirachta indica on gastric ulceration and healing of bacopa monnierang in experimental NIDDM rats. *Indian J Exp. Biol 2004; 42: 389-397.*

Chapter in a book:
Hull CJ. Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. Acute Pain. London: Butterworths. 1985,1 55-79.

All manuscripts for publication should be addressed to the executive editor.

LETTER TO THE EDITOR:
Any reader can provide feedback regarding published articles by writing letter to editor. The reader can also share any opinion in relation to medical science.

Prof. Dr. ABM Bayezid Hossain
Editor-in-chief
Green Life Medical College Journal and
Principal
Green Life Medical College

ABOUT THE COLLEGE

INTRODUCTION

In 2005, about fifty distinguished physicians of the country started a hospital to give specialized care in the private sector. They named it Green Life Hospital and it turned out to be a great success. So in 2009, they decided to establish a medical college which will be a non-government, non-profit, self-financing project and will serve the humanity.

This College came into existence in 2009. The college commences its activities with the enrollment of 51 students in the 1st batch in 2010. Since inception, the college has undergone tremendous development and became a splendid centre for learning and development. At present we are enrolling 110 students each year. Among them, numbers of seats are reserved for overseas students.

We continue to evaluate and improve our programme to ensure the best medical education for the students. Our educational strategy is to create a conducive learning environment and to steer our students to acquire adequate knowledge, skills and temperament to practice medicine and be a competent health care professional group.

Green Life Medical College (GMC) is approved by the Ministry of Health and Family Welfare (MOHFW), Government of Bangladesh and Bangladesh Medical and Dental Council (BMDC) and affiliated to the University of Dhaka.

AIMS AND OBJECTIVES OF THE COLLEGE

Aims:

To create a diverse and vibrant graduate scholars in medical discipline and to create highly competent and committed physicians for the country.

Objectives:

- To provide an appropriate learning environment where medical students can acquire a sound theoretical knowledge and practical skills with empathetic attitude to the people.
- To carry out research in medical sciences to scale up the standard of medical education in the country.

LOCATION

The campus is located at 31 and 32, Bir Uttom K. M. Shafiullah Sarak (Green Road), Dhanmondi, Dhaka. The location is at the heart of the mega city Dhaka and is facilitated with very good communication networks.

The Medical College and the Hospital complexes have been raised in a multistoried fully air-conditioned building with an arrangement of approximately 500 patients. The building is equipped with state-of-the-art infrastructure, excellent with an out-patient department and adequate in-patient facilities.

EDITORIAL

Pain Management: Educational Overview in Bangladesh

Pain is the oldest and complex clinical condition which is assessed by the verbal reports, physical perceptions. Irrespective of the nature, origin or intensity, pain has become an issue of the major public health concern. There is a relation between the pain reduction and the level of satisfaction in patients. The poorly managed pain influences the mental, physical and emotional status of the patient. As long as human have exploited pain, they have given clarifications for its extant and attemped to find something to reduce or erase the painfull sensation.

In the context of Bangladesh, the burden of acute pain increased due to change in socioeconomic background, especially urbanization. Most of the patients present with acute pain in emergency department due to road traffic accident, injuries, history of fall from height, burn or physical assault. At present, the emergency physicians provide the required care empirically that varies from one facility to another. The management and selection of medicine primarily depends on the education that was provided during their undergraduate medical course. The key objective of pharmacology teaching-learning is to make a graduate knowledgeable about risks and benefits of medicines, so that they can select medicines appropriately. The Pharmacology curriculum, textbooks, teaching and evaluation supposed to influence the medicine selection and therefore needs evaluation. The education provided by medical school at undergraduate level appears inadequate to select pain medication in emergency situation, which later addressed at postgraduate levels in different programs.[1]

The emergency services are mostly urban centered, semi-urban cares are inadequate and facility at rural level is virtually absent. The burden of patient attending the emergency department of any hospital primarily depends on the density of the population of the catchment area. One government medical college hospital situated in any metropolitan city handles more than 1000 patients per day. The emergency physicians manage pain on the basis of their pre-existing knowledge acquired during their undergraduate course (MBBS) as postgraduate course for emergency medicine has not started yet in Bangladesh. The emergency physicians primarily depend on their perception and they assess pain according to the patients' expression. So there is possibility to inadequate pain management either due to physicians' lack of knowledge about pain management or lack of evidence based guideline in the hospital. In addition, diversity in facial expression of the patients at emergency and no use of pain scale such as visual analogue scale (VAS) during assessment might also have contributed adversely. There is a chance of failure to meet patients' expectations during discharge without reassessment of patients' conditions. About 80% of patients who enter in the ED present with pain of which, the pain is intense in 54% of cases.[2]

In our country, emergency physicians use intramuscular analgesics to manage moderate to severe acute pain though oral formulations of analgesics are available. The route of drug administration is one of the major decisions regarding management of pain. The intramuscular (IM) route is often the easiest, but IM pain medication administration can be characterized by pain especially if multiple injections are required and needs others help, uncertainty with respect to onset times, and difficulty with titration.[3] Oral pain medications are self-medicated process. Inadequate assessment and inappropriate treatment is the main factors of inadequate management of pain. There is evidence that appropriate use of analgesics can provide good pain relief for the majority of the patients.[4] In Bangladesh, the physicians are also concerned about pain. Bangladesh Society for Study of Pain (BSSP) was formed in 1997 to improve knowledge about pain, the education of the health-care providers and the care of patients.[5]Though, enough recommendation has not yet been formulated in acute pain management in ED. Bangladesh society for Emergency Medicine (BSEM) also concerned about the decrepit condition of emergency cares.[6] In order to improve situation of prescribing and dispensing in Bangladesh, couple of educational and managerial interventions like 'Audit and feedback', 'Monitoring-Training-Planning (MTP)', were found to be effective in other fields of healthcare.[7,8,9]

The Bangladesh Society for Study of Pain (BSSP) is one of the organizations that is working on support for "pain medicine". They have been delivering "Essential Pain Management (EPM)" courses in Bangladesh since 2013.[10] The BSSP initiated the formation of the South Asian

Regional Pain Society(SARPS) during the conference held in Dhaka with representatives from all SAARC members.[11] There are a total of 18 EPM workshops have been conducted in Bangladesh providing training to over 400 participants. EPM is the first course of its kind in Bangladesh that trains and provides doctors and nurses with the basic knowledge of pain management. Currently, there is no national guideline for pain management. The coordinators noted that BSSP is currently formulating a policy regarding this.[10]Educating and providing proper training to future clinicians is of utmost importance to meet the challenge of sub optimal management of pain.

In this present pain management situation in our country, it has been manifested that the formulation of a consensus document on pain management and implementation of that recommendation has become an immense necessity.

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ORIGINAL ARTICLE

Factors Responsible for Low Vitamin D Status in Healthy Medical Students

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Abstract

Introduction: *Vitamin D deficiency is a common and important medical problem worldwide, which may precipitate or exacerbate musculoskeletal pain, fibromyalgia, osteopenia, osteoporosis, and fractures in adults. It has been associated with increased risk of common cancers, autoimmune diseases, hypertension, infectious diseases and even depression. This study was carried out to assess the vitamin D status and factors responsible for low vitamin D status among healthy medical students.*

Methods: *It was a cross sectional study, conducted from July 2020 to June 2021 among the healthy medical students of Green Life Medical College. Total 132 healthy medical students were selected as random sample from the study population and vitamin D level was estimated. A semi structured questionnaire prepared by the researcher about the environmental and nutritional factors of the participants. Data was processed and analyzed by using computer aided statistical software SPSS Version 22. Presentation was done by tables and graphs.*

Results: *Among all the respondents 48(36.36%) had insufficient vitamin D level in blood while 38(28.79%) had deficient vitamin D and rest 46(34.85%) had sufficient vitamin D level. Mean vitamin D level among 40 male was 31.61±11.98 and mean vitamin level in 92 female was 26.83±10.62. Regarding food habit 41% took egg daily, 21% took fish 1-3 times monthly, 55% took 1-6 times weekly and 24% took fish 1-2 times daily. Among the respondence 52(39%) did exercise daily, 18(14%) walked outdoor daily for sufficient sun exposure, 28(21%) exposed to sun light in between 9 am to 3 pm, 35(53%) used umbrella, 56(42%) used cap, 46(35%) used sun screen to avoid severe sun exposure. For sufficient exposure to sunlight majority (85%) were not engaged in outdoor physical activities. Among 132 students only 24(18%) students took one multivitamin daily and 34(26%) took vitamin D supplement daily in last 6 months. Among the respondents vitamin D deficiency was significantly related with egg and milk consumption and use of sun screen ($p<0.05$). Vitamin D deficiency was significantly related with daily exercise ($p<0.05$).*

Conclusion: *This study shows that large number of medical students is deficient of vitamin D. Lack of physical activity, exercise, insufficient exposure to sunlight, inadequate egg and milk consumption may be responsible for low vitamin D among healthy medical students.*

Keywords: *Factors, Low Vitamin D Status, Healthy Medical Students*

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Introduction:

Vitamin D is increasingly being recognized as an important indicator of health.[1] Vitamin D deficiency has become a worldwide problem among all age groups. Data emerging from North America, Europe and Australia show that vitamin D insufficiency is common among children and adults.[2-5]

Vitamin D has received considerable interest from the medical community and the public at large because of recent evidence for the non-skeletal effects of vitamin D combined with the finding of widespread global deficiency. Vitamin D deficiency is more common than previously

thought. It has been estimated that almost 1 billion people in the world suffer from vitamin D deficiency or insufficiency.[6]

In Bangladesh malnutrition is extremely prevalent among women and children.[7] Malnutrition occurs mainly due to the micronutrient deficiencies. Although various factors contribute to micronutrient deficiencies, poor socio-economic condition of Bangladesh is considered to be the major cause. Among various micronutrients, vitamin D and calcium are two important micronutrients for our body. Vitamin D plays crucial role on bone mineralization and other metabolic processes in the human body such as calcium and phosphate homeostasis and skeletal growth. Vitamin D is synthesized in our body upon the exposure to sun light but in some sunny countries such as Bangladesh, Nigeria and South Africa rickets is prevalent although there is adequate exposure of ultra-violet (UV) light.[8]

Vitamin D deficiency causes rickets in children and may precipitate or exacerbate musculoskeletal pain, fibromyalgia, osteopenia, osteoporosis and fractures in adults. It has been associated with increased risk of common cancers, autoimmune diseases, hypertension, infectious diseases, and even depression.[9-14]

The consumption of foods that contain vitamin D and adequate sun exposure are important to prevent vitamin D deficiency. Sunlight fulfills about 50–90% of body requirement of Vitamin D while dietary source of Vitamin D provides only 20% of the total requirement. Some factors are important for the optimum vitamin D synthesis in the skin through sun exposure, such as the angle of the sunlight, duration of sun exposure, the exposed skin surface, sunscreen use, clothing style and air pollution.[15] Decreased vitamin D synthesis, insufficient consumption of vitamin D, poor absorption from the intestine (malabsorption syndromes), liver or kidney disease, certain medications (such as corticosteroids, phenytoin, phenobarbital), advanced age, obesity and extreme weakness can be considered as the main causes of vitamin D deficiency.[16-19] In addition, sedentary lifestyle and inadequate physical activity are also risk factors for vitamin D deficiency [20]. Very few study is found regarding vitamin D status and low vitamin D among health professionals. So this study was carried out to assess the vitamin D status and factors responsible for low vitamin D status among healthy medical students.

Methods:

It was a cross sectional study, conducted from July 2020 to June 2021 among the healthy medical students of Green Life Medical College. Total 132 healthy medical students were selected as random sample from the study population and vitamin D level was estimated. A semi structured questionnaire prepared by the researcher about the socio and demographic characteristics and food habit, physical activity and sun exposure of the participants. After taking informed consent, predesigned questionnaire were administered to these medical students. After explaining the study, the questionnaire was distributed to the students. The students were asked to tick appropriate option and questionnaires were collected immediately. Height and weight were measured and body mass index (BMI) was calculated. Blood sample for 25(OH) D vitamin level was drawn. For vitamin D level, >20-100 ng/ml was considered sufficient, 12-20 ng/ml was insufficient and <12 ng/ml as vitamin D deficiency. Descriptive statistics were applied. After collection of data, each questionnaire was checked for consistency. Data was processed and analyzed using computer aided statistical software SPSS (Statistical Package for Social Sciences) Version 22. Continuous data were expressed as mean and standard deviation. Categorical data were analyzed with chi square test. P value <0.05 was considered significant.

Result:

Among 132 respondents 48(36.36%) had insufficient vitamin D level in blood while 38(28.79%) had deficient vitamin D and rest 46(34.85%) has sufficient vitamin D level in blood (Figure 1).

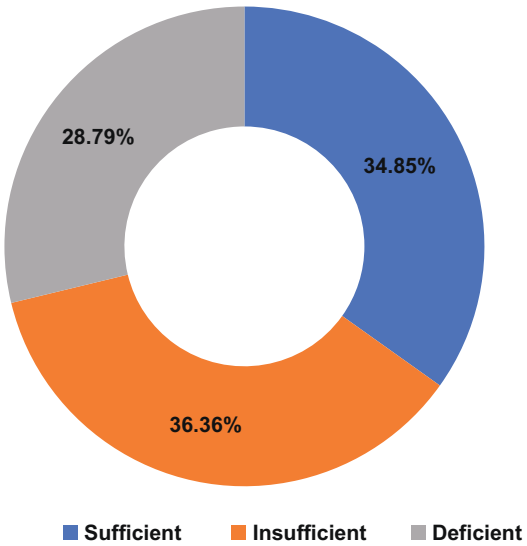

Figure 1: *Distribution of the respondent according to level of vitamin D (N=132)*

Among 132 students 42(31.82%) were in 22 years age group, 34(25.76%) were in 23 years age group, 24(18.18%) in 21 years, 32(24.24%) were in 24 years of age (Figure 2). The mean age of the students was 22.67±2 years.

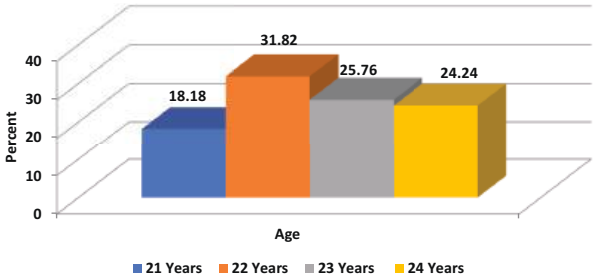

Figure 2: *Distribution of the respondents according to Age (n=132)*

Mean vitamin D level among 40 male was 31.61±11.98 ng/mL and mean vitamin level in 92 female was 26.83±10.62 ng/mL (Table I).

Table I

Distribution of the respondent according to gender and level of vitamin D (n=132)

Gender	Frequency	Mean ± SD	p-value
Male	40	31.61±31.98	0.13
Female	92	26.83±10.62	

Among the 132 respondents all were non-vegetarian among them 54(40.9%) took egg daily and 78(59.1%) did not eat egg daily, 28(21.21%) took fish 1-3 times monthly, 72(54.55%) took 1-6 times weekly and only 32(24.24%) took fish 1-2 times daily (Table II).

Table II

Distribution of the respondent according to vitamin D containing food consumption (N=132)

vitamin D containing food consumption		Frequency	Total (%)
Egg consumption	Yes	54	40.90
	No	78	59.10
Fish consumption	1-3 times monthly	28	21.21
	1-6 times weekly	72	54.55
	1-2 times daily	32	24.24
Milk consumption	Consume milk daily	54	40.90
	Did not consume milk daily	78	59.10
Fruit consumption	Took any fruit daily	40	30.30
	Took a fruit sometime	60	45.46
	Did not take any fruit	32	24.24

Among the respondents 108(81.82%) did not take any multivitamins in last 6 months. Only 24(18.18%) students took one multivitamin daily in last 6 months (Figure 3).

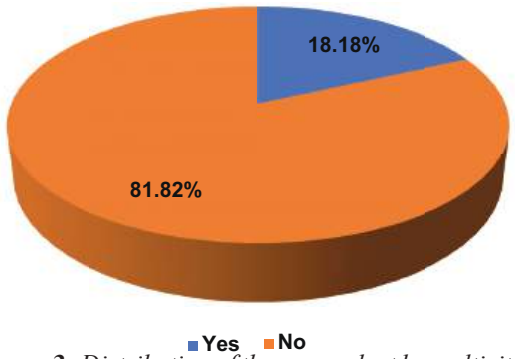

Figure -3: *Distribution of the respondent by multivitamin intake during last 6 months (n=132)*

Among the respondents only 42(31.82%) took vitamin D supplement daily in last 6 months and 90(68.18%) did not take any (Table III).

Table III

Distribution of the respondent by intake of Vitamin D supplement in last 6 months

Vitamin D supplement	Frequency	Percentage
No	90	68.18
Yes	42	32.32
Total	132	100

Among 132 students 52(39.39%) did exercise daily but 80(60.61%) did not exercise regularly, 18(13.64%) walked outdoor daily for sufficient sun exposure and 114(86.36%)

did not, 104(78.79%) did not expose to sunlight between 9 am to 3 pm, 35 (53%) students used umbrella, 56(42.42%) used cap, 6(4.55%) used hat and 46(34.85%) used sun screen >15 SPE to avoid severe sun exposure. For sufficient exposure to sunlight majority 112(84.85%) were not engaged in outdoor physical activities. Among 92 female students only 34(36.96%) used veil and rest 58(63.04%) did not use any veil (Table IV).

Among respondents 54(40.91%) consumed egg every day and vitamin D was deficient in 20(37.04%). Among the respondents 78 did not consumed egg every day and vitamin D was deficient in 22(28.21%). The difference was not statistically significant (p>0.05). Among respondents 54(40.91%) consumed milk every day and vitamin D was deficient in 6(11.11%). Among the respondents 78 did not consumed milk every day and vitamin D was deficient in 36(46.15%). The difference was statistically significant (p<0.05). Among respondents 46 used sun screen for protection from sunburn and vitamin D was deficient in 18(39.13%). Among the respondents 86 did not use any sun screen and vitamin D was deficient in 24(27.91%). The difference was statistically significant (p<0.05). Among respondents 52 did exercise every day and vitamin D was deficient in 6(11.54%). Among the respondents 80 did not do any exercise and vitamin D was deficient in 36(45%). The difference was statistically significant (p<0.05) (Table V).

Table IV

Distribution of the respondent to increase vitamin D production from sunlight (N=132)

Vitamin D production from sunlight		Frequency	Percentage
Daily Exercise	Yes	52	39.39
	No	80	60.61
Walk outdoor for sunlight	Yes	18	13.64
	No	114	86.36
Exposure to sunlight between 9am to 3pm	Yes	28	21.21
	No	104	78.79
To avoid sun exposure use	Hat	6	4.55
	Cap	56	42.42
	Umbrella	70	53.03
Using sun screen >15 SPE	Yes	46	34.85
	No	86	65.15
Outdoor physical activities	Yes	20	15.15
	No	112	84.85
Used veil	Yes	34	36.96
	No	58	63.04

Table V

Distribution of the respondent according to egg and milk consumption, use of sun screen, exercise and level of vitamin D (n=132)

		Deficient	Not deficient	Total	P-value
Egg consumption	Yes	20(37.04%)	34(62.96%)	54	0.59
	No	22(28.21%)	56(71.79%)	78	
Milk consumption	Yes	6(11.11%)	48(88.89%)	54	0.003
	No	36(46.15%)	42(53.85%)	78	
Use of sun screen	Yes	18(39.13%)	28(60.87%)	46	0.003
	No	24(27.91%)	62(72.09%)	86	
Exercise	Yes	6(11.54%)	46(88.46%)	52	0.000
	No	36(45%)	44(55%)	80	

Among the respondents BMI was normal in 62%, 1% were underweight, 23% overweight and 14% were obese (Figure 4).

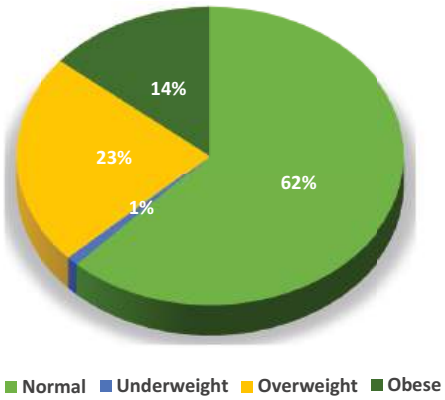

Figure-4: *Distribution of the respondent according to Body Mass Index (n=132)*

Discussion:

Vitamin D belongs to the group of fat soluble vitamins. Diet is a poor source as very few foods contains vitamin D; hence dermal synthesis is the major natural source of this vitamin. The dermal 7-dehydrocholesterol gets converted in to pre-vitamin D on absorbing UVB radiation from sunlight.[21] Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. The central role of hormonal 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] is to regulate calcium and phosphorus homeostasis via actions in intestine, kidney and bone.[22]

In this study, insufficiency was found to be present in 36.36% respondents, deficiency was found in 28.79% and adequate serum vitamin D level in 34.85% in spite of the fact that they were apparently young and healthy medical students and were living in a country with abundant sunlight. Hasanato et al[23] in Saudi Arabia found vitamin D deficiency in 70.8%, insufficient vitamin D in 16.3% and normal in 12.9% among medical students. Vitamin D deficiency is much higher in their study. Similarly Chauhan et al[24] in India found much higher incidence of insufficiency and deficiency of vitamin D in their study. This variation may be due to the fact that these two studies were done among female medical students. Female medical students are particularly vulnerable to Vitamin D deficiency due to maximum indoor stay and their lifestyle. Mean vitamin D level among female students were also low in the present study.

The frequency of milk consumption was significantly related to vitamin D status. Consuming milk every day was associated with a high level of vitamin D. In this study 54(40.91%) consumed milk every day and vitamin D was deficient in 6(11.11%) and 78(59.09%) did not consumed milk every day and vitamin D was deficient in 36(46.15%). The difference was statistically significant ($p<0.05$). A study in central Saudi Arabia showed that only 23.8% consumed milk every day. In comparison between vitamin D deficient and non-deficient groups, daily milk consumption were significantly higher in the non-deficient group.[23]

Several factors are postulated for low Vitamin D levels in females including dietary habits, lack of sun exposure, sunscreen use, skin hyperpigmentation, poor dietary intake, breast feeding, pregnancy, and lactation, their longer indoor stay in the college as well as at home.[25] The majority of this study group avoided sun exposure as they remained at home due to covid-19 pandemic situation and busy in their academic activities and that might a possible reason for their vitamin D deficiency during this time. A similar attitude like busy in academic activities of avoiding sun exposure had been reported in university students in the United Arab Emirates.[26] Hasanato et al[23] in Saudi Arabia found sun exposure for e"5 days/week were significantly higher in the nondeficient group.

Sunblock usage is stated to decrease the absorption of vitamin D, as it blocks UV-B rays which when absorbed are converted to vitamin D.[27] Only few (35%) in this study claimed to use sunblock. Similarly, veiling is considered to be risk factor for vitamin D deficiency[28] and studies conducted on veiled girls showed low levels.[29] Only 36% of respondents in this study were veiled.

Conclusion:

This study shows that large number of medical students is deficient of vitamin D. Lack of physical activity, exercise, insufficient exposure to sunlight, inadequate egg and milk consumption may be responsible for low vitamin D among healthy medical students. Added to few available results on vitamin D status in medical students worldwide, this study more clarified a pitfall. In fact, the future doctors who should provide medical care to the general population in the near future are not really aware of the common, but latent health matter they suffer from, themselves.

Further studies are required to confirm these findings and plan interventions to prevent Vitamin D deficiency in asymptomatic population. To improve the community vitamin D status, in addition to population based food fortification programs, more education activities seem to be essential.

Limitation:

The potential limitation of this study was that it was cross-sectional rather than longitudinal. Besides, information on consumption of milk and exposure to sunlight was

collected by means of a validated questionnaire rather than data collection sheet. Dual-energy X-ray absorptiometry scan is suggested to evaluate bone mineral density which was not done for economic limitation.

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ORIGINAL ARTICLE

Inflammatory Markers in Different Obesity Phenotypes of Non-Diabetic Adult Bangladeshi

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Abstract

Introduction: *Obesity is a global problem and it antedates inflammation. Recently, low-grade inflammation has been suggested to be associated with obesity. As CRP and ferritin usually respond to any inflammatory condition, they are expected to be raised in obesity. Assessment of inflammatory markers (CRP & Ferritin) can help in prediction of severity of obesity induced health risks.*

Methods: *A cross sectional analytical study was conducted in the Department of Biochemistry and Molecular Biology, BSMMU from March 2022 to February 2023. 512 non-diabetic adult respondents were taken according to inclusion and exclusion criteria and were divided into two groups, 149 non obese respondents and 363 obese respondents on the basis of BMI and WC.Obese individuals were further classified into three phenotypes named as phenotype A (obese BMI, non-obese WC), phenotype B (non-obese BMI, obese WC) and phenotype C (obese BMI, obese WC). After taking informed written consent from each subject, a structured questionnaire was filled up for necessary information. Serum ferritin and plasma CRP were measured. Then inflammatory markers were assessed and compared among different obesity phenotypes. We used Mann Whitney U test and Kruskal-Wallis test followed by Dunn-Bonferroni pairwise comparison test. All the statistical tests were considered at 5% level of significance at SPSS.*

Results: *Obesity phenotype C was found to dominate with lowest frequency in phenotype A. All inflammatory markers were significantly higher in obese individuals compaired to non-obese individuals. Plasma CRP and ferritin significantly elevated in phenotype C with statistically identical phenotype A and phenotype B.*

Conclusion: *Phenotype C showed high risk of increased CRP and ferritin in relation to phenotype A and phenotype B. Phenotype A and phenotype B were found statistically identical.*

Keywords: *Inflammatory markers, Obesity phenotypes, Non-diabetic adult*

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Introduction:

Obesity is an alarming issue for public health worldwide. It is assumed that 51 % of the total population will be obese by the year, 2030.[1] Obesity is a complex disease defining abnormal distribution of fat containing adipose tissue that usually causes metabolic, endocrine alterations resulting in lower life expectancy.[2] Obesity introduces inflammation which ultimately increases the risk of different cardiovascular adverse outcomes.[3,4] In obese individuals ectopic fat deposition in different organs causes excess production of reactive oxygen species and pro-inflammation.[5]

C reactive protein (CRP) is one of the earliest markers of any inflammatory conditions.[6,7] In blood, the normal concentration of CRP is less than or equal to 5 mg/L.[8] Obesity causes activation of certain inflammatory mechanisms and increases cytokine secretion from adipose tissue, which increases the hepatic secretion of CRP.[9] Normal ferritin level is usually 30 to 300 ng/ml are considered normal for men, and 10–200 ng/ml for women.[10] Some recent studies suggested that obesity induced

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chronic inflammatory reaction causes increased serum ferritin level which is not just because of an increased in iron stores.[11] So serum ferritin seems to be related to obesity as an inflammatory marker. There are two types of obesity, named as general obesity (measured by Body Mass Index or BMI) and central obesity (measured by Waist Circumference or WC). According to WHO criteria for Asia-Pacific region (WHO, 2000) individuals with BMI e"25.0kg/m^2 are considered as generally obese and WC e"90 cm (men) and e"80cm (women) are considered as centrally obese. Some recent studies have suggested that BMI may vary in different obesity phenotypes.[12,13] Waist circumference (WC) is a good surrogate marker of abdominal obesity.[14] Studies suggested that WC, coupled with BMI, predicts health risk better than BMI alone.[15] Therefore in this study obesity phenotypes are classified based on both BMI and WC. This study aims to evaluate inflammatory markers (CRP and Ferritin) in different phenotypes of obesity.

Methods:

A cross sectional analytical study was conducted in the Department of Biochemistry and Molecular Biology, BSMMU from March 2022 to February 2023. 512 non-diabetic, healthy adult aged between 25 to 75 years old (non-obese and obese individuals) from the outpatient department of BSMMU, were enrolled in the study by non-probability sampling (convenient sampling) technique by taking history. Individuals with chronic diseases, diabetes, malignancy, pregnancy, cardiovascular diseases and taking lipid lowering drugs, steroids, NSAIDs were excluded from the study. The respondents were divided into two groups, 149 non obese (reference) respondents and 363 obese respondents on the basis of BMI and WC. Individuals with both non-obese BMI and non-obese WC were included into non-obese (reference) group. On the other hand, individuals with either obese BMI or obese WC or both were included into obese group. Obese individuals were classified into three phenotypes which were determined as phenotype A (obese BMI ,non-obese WC), phenotype B (non-obese BMI, obese WC) and phenotype C (obese BMI, obese WC) considering BMI e"25.0 kg/m^2 as obese and waist circumference (WC) e"90 cm as obese in men and e"80 cm as obese in women. A written informed consent was taken from all who agreed to participate in the study after explaining them the blood sample collection procedure. All relevant information were collected and recorded in a data collection sheet. After giving proper instruction fasting blood sample and another blood sample at 2 hours after 75gm glucose were collected for estimation of fasting lipid profile, fasting plasma glucose, serum creatinine, SGPT and post load blood glucose to exclude diabetes and chronic diseases. Serum ferritin and plasma CRP were estimated. Finally inflammatory markers were compared among different obesity phenotypes.

Data were cleaned, entered and analyzed by Statistical Package for the Social Sciences (SPSS) software version 26.0. Mann-Whitney U-test and Kruskal-Wallis test were performed. According to data as needed to achieve level of significance. P-value d" 0.05 was considered statistically significant.

Results:

This was a cross-sectional analytical study. 512 nondiabetic, otherwise apparently healthy adult individuals were selected from outpatient department (OPD) of Bangabandhu Sheikh Mujib Medical University (BSMMU) dividing them into non obese (reference) group and obese group. Obese group were further divided into three groups named as phenotype A, phenotype B and phenotype C.

Table I

Distribution of subjects with respect to obesity

Total subjects	Non-obese group (reference group)	Obese Group			Total Obese
		Phenotype A	Phenotype B	Phenotype C	
512	149	49	92	222	363 (71%)

Table II

Comparison of CRP between non-obese (reference) and obese group

Parameter	Non-obese (n= 149) [Median (IQR)]	Obese (n = 363) [Median (IQR)]	p-value
CRP	1.6 (0.6-2.9)	2.9 (1.2- 5.7)	**0.000**

Mann Whitney U test was done

Mann Whitney U test among obese and non-obese individuals showed plasma CRP was significantly elevated in obese group, in comparison to non-obese (reference) group.

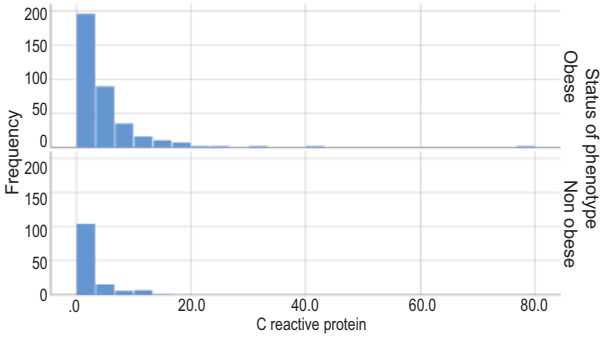

Figure 1: *Comparison of CRP between non obese and obese group*

Table III

Comparison of CRP between different obesity phenotypes

Obesity phenotypes	Mean Rank	p- value
Phenotype A (n= 49)	142.6	**0.000**
Phenotype B (n= 92)	154.1	
Phenotype C (n= 222)	202.3	

Kruskal-Wallis test was done followed by Dunn-Bonferroni pairwise comparison test

Kruskal-Wallis test followed by Dunn-Bonferroni pairwise comparison test among obesity phenotypes showed that plasma CRP was significantly elevated in phenotype C, compared to phenotype A and phenotype B. Phenotype A and phenotype B found statistically identical with respect to CRP.

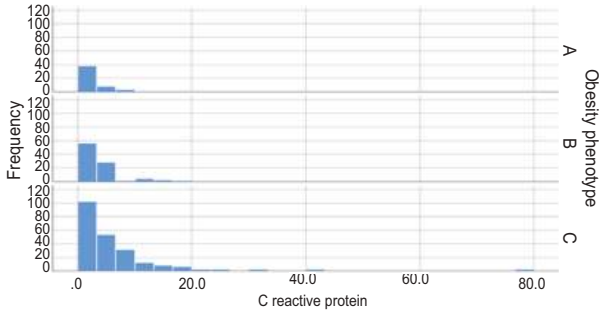

Figure 2: *Comparison of CRP between different obesity phenotypes*

Table IV

Comparison of ferritin between non-obese (reference) and obese group

Parameter	Non-obese (n= 149) [Median (IQR)]	Obese (n = 363) [Median (IQR)]	p-value
Ferritin	66.5 (32.9 – 102.7)	79.3(37.6- 140.9)	**0.012**

Mann Whitney U test was done

Mann Whitney U test showed that serum ferritin was found significantly elevated in obese group, in comparison to non-obese (reference) group.

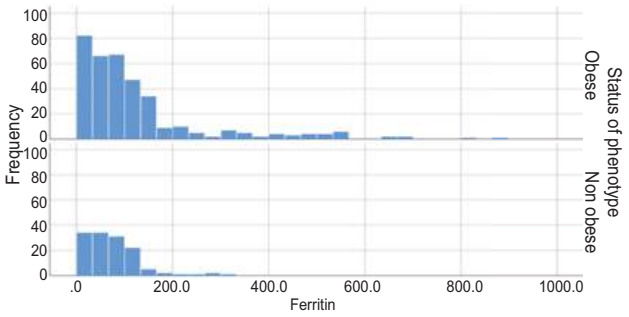

Figure 3: *Comparison of ferritin between non obese and obese individuals*

Table V

Comparison of ferritin between different obesity phenotypes

Obesity phenotypes	Mean Rank	p- value
Phenotype A (n= 49)	158.6	
Phenotype B (n= 92)	163.3	**0.013**
Phenotype C (n= 222)	194.9	

Kruskal-Wallis test was done followed by Dunn-Bonferroni pairwise comparison test

Kruskal-Wallis test followed by Dunn-bonferroni pairwise comparison test showed that serum

ferritin significantly elevated in phenotype C, compared to phenotype A and phenotype B.

Phenotype A and phenotype B found statistically identical with respect to ferritin.

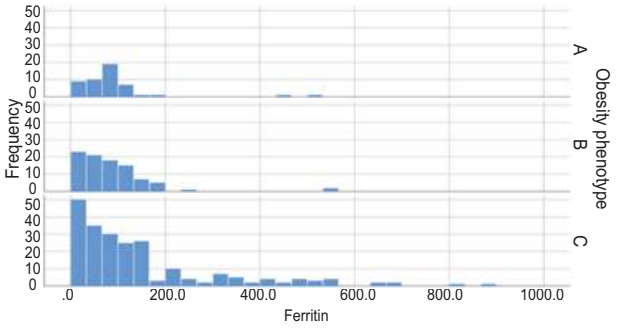

Figure 4: *Comparison of ferritin between different obesity phenotypes*

Discussion:

According to the record of World Health Organization, more than 650 million adults were obese worldwide in 2016, which have almost tripled since 1975.[3] Once obesity was considered to be a problem of high income countries but now it is threatening to overwhelm both developed and developing countries. The World Health Organization

(WHO) Expert Consultation on Obesity has already warned about the escalation of obesity prevalence in developing countries.[16]

Individuals with different obesity phenotypes are at different metabolic risk. Certain phenotypes are at higher risk than other phenotypes because of variation in obesity induced inflammation. The main purpose of this study was to determine the status of inflammatory markers (CRP and Ferritin) in different obesity phenotypes. With this aim, 512 nondiabetic, normotensive and otherwise apparently healthy individuals were selected from outpatient department of BSMMU. Among 512 total study subjects 363 (71%) were obese possessing an obese BMI or an obese WC or both together. This indicates a very high proportion of obese individuals among our study subjects. This might be due to enrollment of subjects from hospital outpatient department (not from general population) where people with obesity related medical problems frequently attend. In this study, the obese individuals (363) were further classified into three obesity phenotypes. Among them, obesity phenotype C (obese BMI and obese WC) showed the highest prevalence, followed by obesity phenotype B (non-obese BMI and obese WC). Obesity phenotype A (obese BMI and non-obese WC) showed the lowest frequency. It was observed higher prevalence of phenotype C over other obesity phenotypes on Korean population.[17] So, we have got higher proportion of central obesity (obese WC) in comparison to general obesity (obese BMI). Excessive intake of high calorie food and sedentary life style may be responsible for the increasing prevalence of both general and central obesity altogether regardless of gender.[18]

We observed inflammatory markers (CRP and ferritin) to be significantly elevated in obese individuals in comparison to non-obese group. Obesity increases the size of adipocytes . The enlarged adipocytes and adipose tissues further release FFAs, reactive oxygen species (ROS), and pro-inflammatory cytokines which initiates low grade systemic inflammation[19] and ultimately CRP level increase significantly in obese individuals compared to non-obese. In this study, we observed significantly high level of serum ferritin among the obese individuals and non-obese individuals. It was also observed that obese individuals show a unique picture of high ferritin , low serum iron and transferrin saturation.[20] In this study, we observed that among all the obesity phenotypes, individuals with phenotype C showed higher level of inflammatory markers (CRP and ferritin). Plasma CRP and serum ferritin were found significantly elevated in phenotype C, compared to phenotype A and phenotype B. Phenotype A and phenotype B found statistically identical with respect to both plasma CRP and serum ferritin. In subjects of phenotype B, the accumulation of visceral adipose tissue is responsible for the up-regulation of low-grade chronic inflammation[21] and increases plasma CRP and ferritin. Subcutaneous adipose tissue in contrast to visceral adipose tissue shows saturation of adipose tissue expansion. Beyond the saturation point, subcutaneous adipose tissue cannot expand anymore and spillover fat to be deposited in undesirable non adipose tissue ectopic sites (eg: liver, pancreas etc). This ectopic fat depots are associated with adverse metabolic and inflammatory profile.[22] Individual of obesity phenotype A probably have ectopic fat depots because of which plasma CRP and ferritin of phenotype A did not differ from that of obesity phenotype B. Ferritin and CRP found to be highest in phenotype C in comparison to other phenotypes because of combined effect of both general and abdominal obesity.

Conclusion:

Inflammatory markers (CRP and ferritin) were significantly elevated in obese individuals in comparison to non obese individuals. Among obese people, obesity phenotype C showed high risk in relation to phenotype A and phenotype B with respect to plasma CRP and serum ferritin .With respect to CRP and ferritin, phenotype A and phenotype B were found to be statistically identical.

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ORIGINAL ARTICLE

Relation Between Connecting Peptide and Duration of Type 2 Diabetes Mellitus to Develop Diabetic Nephropathy

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Abstract

Introduction: *The treatment of Diabetic Nephropathy (DN) is mainly to prevent or delay disease progression. Latest studies suggest that connecting peptide may have a beneficial biological role on DN. The relationship between connecting peptide and duration of DM in diabetic nephropathy is poorly known. The aim of the study is to observe the relation between connecting peptide with duration of DM to develop diabetic nephropathy.*

Methods: *An observational cross sectional study was conducted in the Department of Pharmacology and Therapeutics of Dhaka Medical College, Dhaka from July 2019 to June 2020. Total 63 randomly selected type 2 diabetic patients were included according to selection criteria. Complete history was taken including disease duration. Urine for microalbumin, serum creatinine, connecting peptide were collected, recorded and analyzed by SPSS.*

Results: *Among 63 study participants, 40 (63.5%) were female and 23 (36.5%) were male. Mean age of patients was 50.30±10.55 years. Mean duration of DM of total study subjects was 6.29±3.15 years. Out of total study subjects, 17.5% (11) had low connecting peptide, 74.6% (47) had normal connecting peptide and 7.9% (5) had high serum Connecting peptide. An inverse relationship between connecting peptide levels and the duration of diabetes mellitus (DM) has been observed, and a similar pattern is observed with microalbumin levels. The duration of DM of study subjects are significantly associated with connecting peptide.*

Conclusion: *This study revealed that duration of type 2 diabetes mellitus significantly related with low connecting peptide level to develop diabetic nephropathy.*

Keywords: *Connecting peptide, Diabetic Nephropathy (DN), Diabetes Mellitus (DM)*

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Introduction:

Diabetes mellitus is a chronic metabolic disease which is associated with a state of high blood glucose level due to inability of the pancreas to produce enough insulin or when the body is unable to utilize the insulin it produces effectively or both.[1] Diabetes is one of the most prevalent and serious non communicable disease all over the world. It is the leading cause of death, disability and economic loss. It is identified as a major threat to global development.[2] According to World Health Organization (WHO) diabetes will be the 7th leading cause of death by the year 2030.[3] Diabetes Mellitus can be classified into general categories as (a) Type 1; (b) Type 2; (c) Gestational diabetes mellitus; (d) Specific types of diabetes due to other causes. In type 1 diabetes, there is autoimmune destruction of beta cell of pancreas leading to absolute insulin deficiency.[4] In type 2 DM glycaemia is either due to impaired insulin secretion, insulin resistant or in combination of both.[5] The aim of optimum glycemic control (HbA1c<7.0%, FBG: 4.4-7.2 mmol/L, 2hr after meal: 10 mmol/L) of type 2 DM is to reduce the risk of long-term microvascular and macrovascular complications.[6] Recent studies have revealed that a deficit of â-cell function is an important component of the pathophysiology of type 2 DM. â-cell dysfunction is present at the diagnosis of type 2 DM and gradually worsens with the disease duration, if it is not treated properly.[7] The chronic hyperglycemia in diabetes mellitus causes damage, dysfunction and failure of different organs specially eye, kidney, nerve, heart and

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blood vessels.[8] Diabetic nephropathy is one of the most dangerous diabetic microvascular complications, affecting 30% to 45% patients with either type 1 or type 2 DM.[9] Diabetic nephropathy is the damage to kidneys because of diabetes.[10] Pathologically it is often characterized by glomerular basement membrane thickening, glomerular mesangial matrix expansion and formation of glomerular nodular sclerosis in its advanced stages.[11] Clinically it is usually defined by proteinuria occurrence or declines renal function.[12] According to Latif, et al approximately 34.64% DM patients in Bangladesh had been screened for renal complications. The most commonly encountered renal complication was microalbuminuria (10.0%) followed by gross proteinuria (4.0%).[13] The prevalence of diabetes and nephropathy is high in the world as well as in Bangladesh. Connecting peptide is a polypeptide with a molecular weight of 3021 Daltons.[14] It contains 35 amino acids.[15] It connects A chain and B chain in pro-insulin.[16] Connecting peptide is a natural cleavage product of proinsulin. It is released from pancreatic beta cell in equi-molar amounts with insulin.[17] Insulin and connecting peptide is stored together and co-secreted into the blood stream from secretory granules in the beta cells.[16] Kidney has been suggested as the main organ for the degradation of connecting peptide. Half-life of connecting peptide in the circulation is 2-5 times longer than insulin. It is the more reliable indicator of insulin secretion than insulin itself.[18] Recent studies have exposed that a deficit of â-cell functional mass is an vital component of the pathophysiology of type 2 DM. â-cell dysfunction is present at the diagnosis of type 2 DM and progressively deteriorates with disease duration.[7] It is now assumed that â-cell failure occurs much earlier and is more severe that insulin resistance in type 2 diabetes. DeFronzo, Eldor and Abdul have shown that â-cell function is reduced by 80% in patients with impaired glucose tolerance and even less in patients with type 2 diabetes.[19] A deficit of â-cell functional mass is not only present in patients with type 2 DM but it also progressively declines with the duration of disease. In the UK Prospective Diabetes Study found that in type 2 DM patients, â-cell function was already reduced by 50% at the time of diagnosis. The function is gradually decayed by 5% per year if it is not treated properly.[7] The purpose of this study is to determine whether or not there is a relation between the connecting peptide and the duration of type 2 diabetes mellitus to develop diabetic nephropathy.

Methods:

This study was observational cross-sectional of 63 randomly selected individuals with type 2 DM. Assessment of the demographic and laboratory profiles of patients with type 2 diabetes mellitus, including newly diagnosed cases. Data was collected and study was conducted in the department of pharmacology and therapeutics at Dhaka Medical College. From July 2019 to June 2020, there was a one-year study term in total. All clinical trials were authorized by the Institutional Ethics Committee, and informed written consent was obtained from each patient during evaluation. Every patient had a comprehensive physical checkup. In addition, information regarding anti diabetic medication, duration of disease and associated disorders was collected. FBG, 2hrsABF, HbA1c, urine for micro albumin, serum creatinine, and connecting peptide were measured by using appropriate methods.Qualitative data were expressed as frequency distribution and percentage. Quantitative data were expressed as mean±SD (standard deviation). The p value ≤0.05 was considered as statistically significant at 95% CI (confidence interval). The data were analyzed by using statistical software SPSS (version 26.0).

Results:

Based on the predefined criteria, 63 participants were selected to participate in the study. Among these participants, 40 were female, constituting 63.5% of the total, while 23 were male, making up 36.5% of the participant pool. The average age (Mean±SD) of all study subjects was 50.30±10.55 years. Specifically, the mean age of male participants was 52.39±11.34 years, and the mean age of female participants was 49.10±10.01 years. For further demographic details of the patients, please refer to Table I.

Table I

Demographic characteristics of the patients

Variables	Value
Age (Years)	50.30±10.55
Males (%)	52.39±11.34
Females (%)	49.10±10.01
Duration of diseases (Years)	6.29±3.15
Creatinine (mg/dl)	0.83±0.12
Microalbumin (mg/L)	26.93±13.97
Connecting peptide	2.39±0.99

The study reveals a pattern in the connecting peptide levels based on the duration of diabetes mellitus (DM) among the study subjects. Specifically, 74.6% (47 patients) exhibited normal connecting peptide levels. This distribution can be further assorted by DM duration: 31.7% (20 patients) had duration of less than 5 years, 41.3% (26 patients) had duration of 5 to 10 years, and only 1.6% (1 patient) had duration of more than 10 years. Additionally, 17.5% (11 patients) displayed low levels of S. Connecting peptide, with the distribution as follows: 1.6% in the group with less than 5 years of DM duration, 7.9% in the 5 to 10 years group, and another 7.9% in the group with more than 10 years of DM duration. Furthermore, 7.9% (5 patients) exhibited high S. Connecting peptide levels, and notably, all of these patients were within the group with duration of less than 5 years of DM (Table-II).

Table II

Pattern of connecting peptide according to duration of DM

Connecting peptide	Duration of DM (in years)				pvalue
	Total	<5	5-10	>10	
	n (%)	n (%)	n (%)	n (%)	0.001
High	5 (7.9%)	5 (7.9%)	0	0	
Normal	47 (74.6%)	20 (31.7%)	26 (41.3%)	1 (1.6%)	
Low	11 (17.5%)	1 (1.6%)	5 (7.9%)	5 (7.9%)	

Normal range of connecting peptide: 1.1 – 4.4 ng/ml

Table III

Urine microalbumin level according to connecting peptide

Characteristics	Connecting peptide			
	High (n-5) Mean±SD Range (Min-Max)	Normal (n-47) Mean±SD Range (Min-Max)	Low (n-11) Mean±SD Range (Min-Max)	p value
Microalbumin	15.72±2.81	25.57±13.54	37.87±12.63	
	12.0-19.20	12.0-81.90	23.0-57.0	0.004

Normal range of connecting peptide: 1.1 – 4.4 ng/ml

The relationship between microalbumin levels and serum Connecting peptide reveals an interesting pattern. The mean microalbumin level varies across different serum connecting peptide groups. In the high serum connecting peptide group, the mean microalbumin level was 15.72±2.81. In the normal serum connecting peptide group, the mean microalbumin level was higher at 25.57±13.54. However, in the low serum connecting peptide group, the mean microalbumin level was even higher at 37.87±12.63. This suggests a potential inverse relationship between serum Connecting peptide and microalbumin levels, with lower Connecting peptide associated with higher microalbumin levels (Table-III).

The correlations among clinical and biochemical variables in all study subjects reveal a consistent negative association with serum connecting peptide levels. Notably, both the duration of diabetes mellitus (DM) among study subjects and microalbumin levels were found to be significantly correlated with serum connecting peptide. This negative association suggests that as serum connecting peptide decrease, the duration of DM and microalbumin levels tend to increase, indicating a potential relationship between lower Connecting peptide and the progression of DM as well as increased microalbumin levels.

Table IV

Correlation's of clinical & biochemical variables among participants

Characteristics	Connecting peptide	
	r	p value
DM Duration	-0.483	0.001**
Creatinine	-0.024	0.854
Micro-albumin	-0.268	0 .034**

Discussion:

This cross sectional study was carried to observe the relation between connecting peptide with duration of type 2 diabetes mellitus to develop diabetic nephropathy. Connecting peptide measurement is beneficial when there is uncertainty about the treatment. Connecting peptide can induce definite intracellular process and influence the nerve and renal function in connecting peptide deficient type diabetes patients. Diabetic nephropathy is one of the most dangerous micro vascular complications of DM patients. With increasingly common clinical perspective, connecting peptide is highly useful in providing appropriate treatment and reduces the complications in diabetes mellitus patients.

This study showed majority of patients were female. The demographic profile showed that female (63.5%) patients

were higher than male (36.5%). It may indicate those females were predominantly coming for consultation than male. This finding is similar with previous study conducted by Safita, et al., 2016[20], on diabetes patients of Bangladesh . But another study conducted by Bhuyan & Fardus, 2019[21] on diabetes patients of Bangladesh showed male patients were more than female patients.

In this study the mean duration of type 2 diabetes in total study subjects was 6.29±3.15 years. Here, mean duration of type 2 diabetes in male respondents was 7.35±3.57 years and in female respondents was 5.68±2.74 years. Masoom and Albiladi, 2017[10], in their study showed the mean duration type 2 DM was 8.59±0.5 years.

Here 71.4% (45) patients had microalbuminuria where male 28.6% (18) and female 42.9% (27). 28.6% (18) patients had normal microalbumin where male 7.9% (5) and female 20.6% (13).

In this study baseline main parameter was connecting peptide. The mean connecting peptide level of total study subjects was 2.39±0.99 where mean connecting peptide level of male respondents were 2.33±0.92 and female respondents were 2.42±1.03. p value was 0.727. Here, serum connecting peptide level was normal in 47 patients (74.6%), above normal in 5 patients (7.9%) and below normal in 11 patients (17.5%). Near similar was seen in the study conducted by Chowta, et al., 2010.[18]

In the aspect of duration of DM and connecting peptide level, in this study normal connecting peptide level was found in 47 patients where duration of DM 5-10 years in 26 patients. That is 41.3% patients suffering from DM for 5-10 years and their Connecting peptide level in normal range. In 5-10 years and more than 10 years group there was no high connecting peptide patients seen. In 5-10 years and more than 10 years group there were same percentages (7.9%) of low serum connecting peptide level. Here, p value was 0.001 that is duration of DM was more in patients with lower serum connecting peptide level. Similar result has seen in the study by Chowta, et al., 2010.[18] A study conducted by Masoom and Albiladi, 2017[10] also shown a negative correlation between Connecting peptide and DM duration.

In this study the pattern of microalbumin level showed according to high, normal and low serum connecting peptide level. Here the mean microalbumin in high serum connecting peptide group was 15.72±2.81, normal connecting peptide group was 25.57±13.54 and low connecting peptide group was 37.87±12.63. Here, p value was 0.004.

The study found significant correlations between connecting peptide levels and the duration of diabetes mellitus (DM) as well as microalbumin levels. Other variables such as fasting blood glucose (FBG), 2-hour postprandial blood glucose (2hr ABF), HbA1c, and creatinine also showed negative correlations with connecting peptide levels, although these were not statistically significant. Microalbumin emerged as the most important variable, exhibiting a significant negative correlation with connecting peptide levels. This finding is consistent with previous studies by Masoom and Albiladi (2017)[10] and Chowta et al. (2010)[18], which also reported negative associations between connecting peptide and microalbumin. Additionally, Mohammad and Aghbari (2018)[22] found that a significant proportion of patients with low connecting peptide levels had a higher prevalence of diabetic nephropathy, emphasizing the potential clinical relevance of this biomarker. From the above discussion, it is observed that, the duration of DM of study subjects are significantly associated with connecting peptide and diabetic nephropathy.

Conclusion:

The study aimed to investigate the relationship between connecting peptide and the duration of type 2 diabetes mellitus for the development of diabetic nephropathy. It revealed that most patients had uncontrolled diabetes mellitus and exhibited microalbuminuria. Correlations between clinical and biochemical variables among participants indicated a significant association between connecting peptide levels and the duration of diabetes mellitus, as well as between serum connecting peptide and microalbumin. Notably, connecting peptide showed a negative correlation with the duration of diabetes mellitus, which was statistically significant. Based on these findings, it can be concluded that connecting peptide levels are linked to the duration of diabetes mellitus and its potential role in the development of diabetic nephropathy.

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ORIGINAL ARTICLE

Clinical, Echocardiographic & Angiographic Profile of Chronic Coronary Syndrome (CCS) Patients with Depressive Features

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Abstract

Introduction: The link between depression and coronary artery disease (CAD) is well-established. Many research revealed its detrimental impact on cardiovascular health, potentially leading to coronary artery disease. Depression alters the nervous system and hypothalamic-pituitary-adrenal axis. This disruption triggers catecholamine and corticosteroid release. These hormonal changes inflict significant damage on coronary arteries, compromising vascular integrity, resulting in coronary artery disease, in the form of myocardial infarction or chronic coronary syndrome. This study sort to find out the clinical, echocardiographic & angiographic profile of chronic coronary syndrome (CCS) patients with depressive features.

Methods: This cross sectional study was conducted in Bangabandhu Sheikh Mujib Medical University, Dhaka. This study included 372 patients of chronic coronary syndrome suffering from depressive features, according to inclusion and exclusion criteria; who visited cardiology out patient department. Informed written consent was taken from patients and data were collected in semi structured data sheet by personal interview. After assessment of pre test probability (PTP) for coronary artery disease (CAD), patients who had pre test probability (PTP) <5% were marked as having no coronary artery disease (CAD) and patients who had pre test probability (PTP) >15% were sent directly for coronary angiogram (CAG) test to diagnose coronary artery disease (CAD). Patients, who had pre test probability (PTP) of 5-15%, underwent risk stratification by exercise testing. Patient with high risk in exercise test were sent for coronary angiogram (CAG), and low risk on exercise test were sent for assessment of clinical likelihood by presence of multiple risk factors, abnormal findings in ECG, resting Echocardiography. When there was high clinical likelihood of coronary artery disease (CAD), patients were sent for coronary angiogram (CAG).

Results: Chronic coronary syndrome was more common in females with depressive features (54.96%). Diabetes, hypertension, dyslipidemia, and family history significantly correlated with its development. Patients in our study population presented with atypical (44.2%) and typical (42.7%) chest pain, rarely dyspnea (2.8%). ECG findings varied: normal (53%), non-specific ST-T changes (14.3%), inferior ischemia (14.5%), sinus tachycardia (11.5%), inferolateral ischemia (5.2%), anteroseptal ischemia (4.9%), and sinus bradycardia (1.2%). Echocardiograms were mostly normal (70.8%), with some regional wall motion abnormalities: inferior-lateral (7.9%), antero-septal (5.2%), anterior (2.7%). Minor valve issues included mild mitral regurgitation (5.8%), aortic sclerosis (4.02%), and mild tricuspid regurgitation (1.44%). Coronary angiography revealed coronary artery disease (CAD) in 67% of subjects: LAD (28.76%), RCA (23.88%), and LCX (16.71%) involvement

Conclusion: Chronic coronary syndrome and coronary artery disease are common in patients with depressive features. These patients present with diverse clinical, echocardiographic & angiographic charecteristics. Our study highlights the need of further research in this field, which will potentially open new avenues for diagnosis and treatment in this population.

Keywords: Chronic Coronary Syndrome (CCS), Depression, Echocardiogram, Coronary Angiogram (CAG), Major Depressive Disorder (MDD)

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Introduction:

Depression severity directly correlates with the risk of developing coronary artery disease (CAD) .[1] Major Depressive Disorder increases the mortality risk by 180% in patients with comorbid CAD .[2] After a heart attack, Major Depressive Disorder becomes a dire prognostic factor, boosting cardiac mortality by 500% within six months .[3] Psychophysiological research proves that depressed individuals face a higher risk of autonomic nervous system and hypothalamic–pituitary–adrenal axis dysregulation .[4] These dysregulations trigger the release of catecholamines and corticosteroids, affecting the cardiovascular system through hemodynamic changes ,[5] tachycardia, intima injuries, and metabolic changes. Chronic coronary syndrome remains a leading public health concern globally, causing widespread death and disability. Bangladesh has the highest rate of coronary artery disease in South East Asia .[6] Predicting the pattern of significant coronary artery disease in patients with depressive features can significantly reduce morbidity and mortality due to CAD. These patients typically present with chest discomfort, dyspnea, palpitation, syncope, and fatigue, with chest discomfort being the most common symptom. Our study aimed to determine the clinical, echocardiographic & angiographic profile of chronic coronary syndrome (CCS) patients with depressive features.

Chest discomfort is a common presentation in both outpatient and inpatient settings and is often suspected to be cardiac in origin. It however has a broad differential diagnosis involving many systems including gastrointestinal, musculoskeletal and psychiatric. Chest discomfort and depression commonly co-exist. Over 30% of patients with CAD suffer from depressive features, a rate three-fold higher than in the general population . Both pain and depression share common neurochemical pathways, and a few studies have suggested that patients with CAD and depression have greater incidence of persistent chest pain. Several studies have demonstrated that, incidence of CAD in patients with depressive features is higher in comparison to normal population. But in Bangladeshi population, no such study have been conducted yet

The purpose of our study was to find out the clinical, echocardiographic & angiographic profile of CCS patients with depressive features; characteristics and type of chest discomfort in CCS patients with depressive features; categorize CCS patients according to the percentage of pre-test-probability (PTP) for stress testing; to find out the evidence of chronic coronary syndrome either by dobutamine stress echocardiogram or coronary angiogram.

Methods:

This cross-sectional observational study was conducted in Bangabandhu Sheikh Mujib Medical University, Dhaka from July 2021 to June 2022. The study included 372 participants, selected using purposive sampling based on specific inclusion and exclusion criteria. Patients (age >30 years) with depressive features having chest discomfort for more than two months and has gtiven informed written consent for the study. Patients with depressive features with any of the following criteria were excluded: patients presented primarily for Acute Myocardial Infarction or Acute Coronary Syndrome, patients with cardiomyopathy, moderate to severe valvular heart disease, prosthetic valves & pacemakers, congenital heart disease, severe pulmonary disease, active infection, chronic debilitating illness, pregnancy and subjects unwilling to give interview & undergo investigative procedure. Data was collected in semi structured questionnaire by personal interview.

The study received clearance from the NICVD Ethical Review Committee and adhered to the Helsinki Declaration for Medical Research involving Human subjects (1964). Participants were thoroughly informed about the study's nature and purpose.

Patients with depressive features were was identified based on the DSM-5 criteria, and severity was evaluated using the PHQ-9 scoring system. 0 -4 was considered no depression; 5-9 was considered mild depression, 10-14 was moderate depression, 15-19 was moderately severe depression and 20-27 indicated severe depression (Kroenke et al., 2001). Patients with depressive features experiencing chest pain for over two months were selected as cases. A detailed medical history was taken, covering symptoms, severity, duration, onset, timing, precipitating, and relieving factors of chest discomfort. Additionally, risk factors like hypertension, diabetes, dyslipidemia, smoking status, and family history were assessed. Physical examinations, including general, precordial, and respiratory system evaluations, were performed. Routine laboratory tests, such as RBS/FBS/2HABF, HbA1C, and fasting lipid profiles, were conducted. A 12-lead surface ECG was recorded at 25 mm/s speed and 1.0 mV. Furthermore, 2D and M-mode echocardiography was used to evaluate anatomy, wall motion abnormality, and ejection fraction using the Teicholz method.

To determine the pre-test probability (PTP) of Coronary Artery Disease (CAD), patients were categorized into three groups: those with PTP <5% (no CAD), those with PTP

>15% (directly sent for coronary angiogram), and those with PTP of 5-15% ,underwent risk stratification by exercise testing. Patients with high-risk exercise test results were sent for CAG, while those with low-risk results were sent for assessment of clinical likelihood based on multiple risk factors, abnormal ECG findings, and resting echocardiography results. When clinical likelihood was high, patients underwent CAG.

Statistical analyses were performed using SPSS 29.0 for Windows. Continuous data were expressed as mean ±SD, and categorical data were presented as frequency and percentages. A significance level of p-value <0.05 was used for all cases.

Results:

The study revealed a significant association between chronic coronary syndrome (CCS) and depressive subjects. Specifically, the data showed that CCS was most common among depressive individuals aged 50-60 years, suggesting that this age group is particularly susceptible to the condition.

When examining the distribution of CCS by sex, the study found no significant association between gender and the presence of CCS in the depressive population. However, a notable trend emerged: a higher percentage of depressive female patients were diagnosed with CCS, indicating that depressive women may be more likely to develop CCS.

Further analysis revealed a strong connection between CCS and certain risk factors including depression. The study found that depression, diabetes mellitus, hypertension, dyslipidemia, and a positive family history of coronary artery disease (CAD) were all significantly associated with the development of CCS.

In terms of symptoms, the study showed that chest discomfort was a common complaint among the depressive subjects. A significant proportion of depressive patients (44.2%) presented with atypical chest pain, while 42.7% experienced typical chest pain. Additionally, 2.8% of patients reported shortness of breath.

Electrocardiogram (ECG) findings among the depressive subjects were varied, notably, non-specific ST-T changes (14.3%), sinus tachycardia (11.5%), inferior ischemia (14.5%), and inferolateral ischemia (5.2%). Other ECG findings included anteroseptal ischemia, sinus bradycardia, and various other abnormalities. This indicates that depressive population may suffer from ischemic heart disease in long term.

Echocardiogram results showed that the majority of depressive populations (70.8%) had a normal 2D, M-mode, and color Doppler echocardiogram. However, a significant proportion of patients displayed regional wall motion abnormalities, with 7.9% showing inferior-lateral wall abnormalities, 5.2% showing antero-septal wall abnormalities, and 2.7% showing anterior wall abnormalities. Additionally, mild mitral regurgitation (MR), mild tricuspid regurgitation (TR), and aortic sclerosis were present in 5.8%, 1.44%, and 4.02% of patients, respectively.

Coronary angiography (CAG) of depressive population with CCS revealed that 67% of subjects had coronary artery disease (CAD), while 33% had no significant CAD. Among those with CAD, the angiographic findings showed that 28.76% had left anterior descending (LAD) disease, 16.71% had left circumflex (LCX) disease, and 23.88% had right coronary artery (RCA) disease.

Above findings indicates that depressive population may suffer from ischemic heart disease in long term.

Table I

Distribution of ECG findings among the study subjects:

ECG	Frequency	Percentage
Normal	36	50.0%
Sinus Tachycardia	9	12.5%
Inferior ischemia	9	12.5%
Nonspecific ST-T changes	11	15.3%
Inferolateral ischemia	4.2%	3
Antero-septal ischemia	3	4.2%
Sinus bradycardia	1.4%	Total
	72	100.0%

The above table shows the ECG findings among the study subjects. The predominant pattern of the ECG was within the normal limit (50%) followed by Non-specific ST-T changes (15.3%), sinus tachycardia (12.5%), inferior ischemia (12.5%), inferolateral ischemia (4.2%), anteroseptal ischemia (4.2%) and sinus bradycardia (1.4%).

Table II

Distribution of Echocardiogram findings among the study subjects:

Echo		Frequency	Percentage
RWMA - Antero-septal wall		2	2.8%
RWMA - Anterior wall		2	2.8%
RWMA - Inferior lateral wall		5	6.9%
Normal		51	70.8%
EF	<40%	4	5.55%
	>40%	68	94.45%
Total		72	100.0%

The above table shows the echocardiogram finding among the study subjects. (70.8%) patients showed normal 2D, M- mode and color doppler echocardiogram. Baseline Regional wall motion abnormality was present as 6.9% in Inferior-lateral wall,4.2% in antero-septal wall,2.8% in anterior wall. Mild mitral regurgitation (MR), Mild tricuspid regurgitation (TR), aortic sclerosis were seen in 5.6%, 1.4%, 4.2% patients respectively.

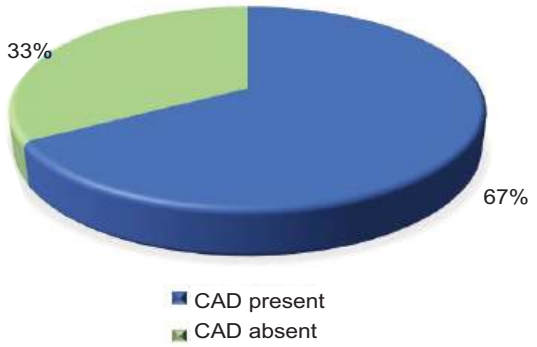

Figure 1: *Pie Diagram showing frequency of CAD among the subjects who undergone CAG*

The above pie chart shows the distribution of CAD among the subjects based on CAG. Total 9 patients were selected for CAG. Among them 6 patients (67%) were found to have CAD whether 3 patients (33%) were having no significant CAD.

Discussion:

In our study, the demographic variable that stood out was the age of the patients. The largest proportion of depressive patients fell within the 4th decade of life, which is consistent with previous findings that most people are diagnosed with depressive disorder in their 30s and 40s. In fact, a study conducted in Bangladesh in 2008 found that depressive Disorder was most prevalent among individuals between 20 and 40 years of age .[6]

When it comes to sex, our study revealed that depressive female patients were more likely to have coronary involvement than male patients. This finding is supported by another study published in 2013, which included 155 cardiac patients and found that the majority of them were female .[7,8] In our study, 54.96% of the patients were female, although the association between depressive patients with Chronic Coronary Syndrome and sex was not statistically significant. Nevertheless, our results showed that female patients were more likely to develop Chronic Coronary Syndrome than male patients.

Our study also explored the risk factors associated with the development of coronary artery disease in individuals with depression. We examined six specific risk factors: diabetes mellitus, hypertension, dyslipidemia, family history of coronary artery disease, smoking, and overweight/obesity. Our analysis revealed that diabetes mellitus, hypertension, dyslipidemia, and a positive family history of coronary artery disease were significantly associated with the development of Chronic Coronary Syndrome in our study subjects, with a p-value of less than 0.05, which correlates with other studies .[9, 10,11,12]

In our study, chest discomfort was prevalent among depressive subjects, with a notable proportion experiencing atypical (44.2%) and typical (42.7%) chest pain, alongside reports of shortness of breath (2.8%). This aligns with findings by Smith et al. (2019), who similarly noted high rates of atypical chest pain (47%) in their cohort of depressive cardiac patients.[13]

The most frequent ECG result in our study was a normal reading (53%), followed by non-specific ST-T changes (14.3%), sinus tachycardia (11.5%), and various ischemic patterns including inferior (14.5%) and inferolateral (5.2%) changes. This indicates that depressive patients are in risk of chronic ischemic heart disease in long term, rather than acute MI. These findings are consistent with the study conducted by Johnson and colleagues (2018).[14]

Based on the echocardiogram and coronary angiography results from our study, several key findings stand out. Firstly, the majority of patients (70.8%) exhibited normal findings on 2D, M-mode, and color Doppler echocardiography, which aligns with similar studies indicating a prevalence of normal echocardiograms in a significant portion of depressive CCS patient populations (Smith et al., 2019).[13] which again proves that chronic ischemic heart disease is more common in depressive population, rather than acute MI. However, notable deviations were observed, particularly in regional wall motion abnormalities, with significant proportions noted in the inferior-lateral (7.9%), antero-septal (5.2%), and anterior walls (2.7%). These findings underscore the presence of localized myocardial dysfunction, a common feature in coronary artery disease.[15]

Regarding coronary artery disease (CAD), our study found that 67% of depressive subjects had significant CAD, with specific distribution among the coronary arteries: 28.76% had left anterior descending (LAD) disease, 16.71% had left circumflex (LCX) disease, and 23.88% had right coronary artery (RCA) disease.

These findings are consistent with global trends in CAD distribution in depressive patients , reported in large-scale studies. (Yusuf et al., 2004 , Kotseva et al., 2016). [16,17]

Conclusion:

A substantial percentage of individuals afflicted with depressive disorders and experiencing chest discomfort suffer from chronic coronary syndrome. Furthermore, advanced age, the severity of major depressive disorder, diabetes mellitus, hypertension, a positive family history, and dyslipidemia are linked to the development of chronic coronary syndrome. This discovery holds significant implications for future research on interventions targeting concomitant depression in coronary artery disease patients. Therefore, it is recommended that patients with major depressive disorder undergo thorough screening to identify occult coronary artery disease. Additionally, a large-scale, multi-centered, long-term prospective cohort study should be conducted among patients with major depressive disorder to determine the natural progression of coronary artery disease development among this population.

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REVIEW ARTICLE

An Update on Clinical Profile, Diagnosis and Management of Childhood Febrile Seizure

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Abstract

Febrile seizure (FS) is the most common type of seizures in children, typically occurring between 6 months to 5 years of age. These seizures are associated with rapid rise of temperature, often due to either viral or bacterial infection without underlying neurological problem. Febrile seizures are classified into simple febrile seizure (SFS), complex febrile seizure (CFS), Febrile status epilepticus and febrile infection related epilepsy syndrome (FIRES). Majority of childhood FS are benign and self-limiting, most children recovering completely without any long-time sequelae. Complex febrile seizure is associated with increased risk of epilepsy in future. Diagnosis is done on basis of typical history of fever and seizure nature and investigations are warranted only when abnormal neurological signs are present or to detect cause of fever and infection. Treatment typically involves management of acute seizure episode and specific treatment of underlying cause of fever and infection. Parental counseling and reassurance are crucial aspect of treatment as FS are often distressful for parents. Only 2-4% children have the risk of developing subsequent epilepsy.

Keywords: Febrile seizure (FS), Simple febrile seizure (SFS), Complex febrile seizure (CFS), Febrile infection related epilepsy syndrome (FIRES), American Academy of Pediatrics (AAP), Association of child Neurology (AOCN), Anti-seizure medication (ASM)

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Introduction:

Febrile seizures (FSs) are the most common seizures among children between 6 months to 5 years of age, accompanied by fever (≥100.4°F or 38°C) without central nervous system infection.[1] Their prevalence among children ranges between 2% and 5% in Western countries and reaches 12% in some parts of Asia[2]. The cause of FS seems to be multifactorial, with both genetic and environmental factors involved.[3]These patients often have a family history of FS. Genetic factors may encompass genes related to neuronal excitability, such as ion channels, particularly sodium channels, as well as genes associated with the immune- inflammatory response.[4,5]FS is an utmost challenge in pediatric practice due to its high prevalence and tendency to recur. Updated guidelines for diagnosis and treatment of FS have been issued by the American Academy of Pediatrics (AAP) and the Japanese Society of Child Neurology in 2011 and 2015, respectively.[6]This review will give an overview & update on definition, epidemiology, evaluation & treatment outcomes of childhood febrile seizure.

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Definition and Classification of Febrile Seizure

The International League against Epilepsy (ILAE) defines FS as a seizure occurring in childhood after one month of age, associated with a febrile illness that is not caused by an infection of the central nervous system. A child with the diagnosis of FS cannot have a history of neonatal seizures, a previous unprovoked seizure or meet criteria

for other acute symptomatic seizures.[7] The Association of child Neurology (AOCN) guidelines published in 2021 defined FS as seizures accompanied by fever (temperature >38.4 C) without CNS infection or metabolic disturbances or a history of afebrile seizures or any acute neurological insult (severe electrolyte imbalance, meningitis, trauma) in children aged six months to six years.[2]The AAP guidelines defined FS as seizuresaccompanied by fever (temperature 380C) that occurs in neurologically healthy children aged six to 60 months, without CNS infection, metabolic disorders, or history of afebrile seizures.[8]

There are four types of febrile seizure ie. simple febrile seizure (SFs), complex febrile seizure (CFs), febrile status epilepticus, febrile infection related epilepsy syndrome (FIRES). Simple febrile seizure is a primary generalized, usually tonic-clonic, associated with fever, lasting for maximum of 15 minutes, not recurrent within 24-hour period.[9] CFS were defined as focal, prolonged (longer than 15 minutes), and/or recurrent within 24 hours and/or associated with postictal neurological abnormalities, more frequently postictal palsy, or occurring in children with previous neurological deficits.[2,9] Febrile status epilepticus defined as seizure lasting >30 minutes.[9]

Epidemiology

Febrile seizure is the most common cause of seizure in children. There is 2-5% incidence in European & American children. Some study gives a statement about the higher incidence in Japan & Guam 7-10% and 14% respectively.[10,11] The peak incidence of 1stfebrile seizure is 12-18 months. Most of the febrile seizure (90%) occur within 1st 3 year of life.[11] Some studies show, higher incidence of febrile seizure in male & other shows no significant difference between male & female.[12]

Etiology &Pathophysiology

FS is an age-dependent response of immature brain to fever.[12] Cytokines like interleukin 1 and tumor necrosis factor during a fever may alter normal brain physiology including certain temperature sensitive ion channels, triggering seizures.[13] The cause of febrile seizures is likely multifactorial. Viral illnesses, certain vaccinations, and genetic predisposition are common risk factors that may affect a vulnerable, developing nervous system under the stress of fever.[14]

Febrile seizures have been more strongly associated with certain virus then others.[15] Upper respiratory tract infections (URTIs) and the common viruses that cause URTIs, such as influenza viruses, respiratory syncytial virus, adenovirus, parainfluenza viruses 1, 2, 3, 4a, and 4b, rhinovirus, enterovirus, and human metapneumovirus and rotavirus have been related to FSs in numerous studies This association is supported by the fall/winter seasonality of these events.[15-18]

Vaccination was found to be the second cause of febrile seizure.[19] Some retrospective found first seizure occurred within 72 hours of vaccinations.[19,20] The relationship between vaccination and development of epilepsy during infancy has been controversial for a longtime. Many studies focused on vaccine-related adverse events.[21-23] There is no causal relationship between FS and vaccination. This relationship is complex by other factors, such as age, genetic inheritance, type of vaccine, combination of different types of vaccines and the timing of vaccination.[23] FS usually occur within 3 days after Diphtheria, tetanus toxoids and whole-cell pertussis vaccine, 2 days after Pneumococcal conjugate vaccine PCV(P3), and 24 hours after MMR vaccine & Hib vaccine.[23-25]

Febrile seizure tends to occur in families. Although clear evidence exists for a genetic basis of FS, the mode of inheritance is unclear.[26] Polygenic inheritance is likely a small number of families are identified with an autosomal dominant pattern of inheritance of FS.[27,28] FS may develop due to mutations in the gene that encodes for the ã-aminobutyric acid A receptor and sodium channels.[29] Mild loss of function or polymorphisms in SCN1A gene of NaV1.1 channels may cause a remarkable portion of FS.[30]

Risk factors of febrile seizure

There are several case-control studies found variable risk factors are associated with febrile seizure.

Box :1

Risk factors of FS [6,16,31-33]

I. 1st or 2nd degree relative with history of FS
II. Neonatal nursery stay of > 28 days
III. Presence of developmental delay
IV. Family history of afebrile seizure
V. High peak temperature
VI. Day care attendance
VII. Exposure to maternal smoking

Box 2
Risk factors for recurrence of FS [6,7,33]

I.	Family history of FS
II.	Age less than 18 months
III.	Temperature lower than 40.0°C at first convulsion and less than 1 hour between onset of febrile illness and first convulsion
IV.	Frequent febrile illnesses
V.	Multiple FSs during the same febrile illness
VI.	Neurodevelopmental delay

Iron, zinc, vitamin B12, Folic acid deficiency decrease the seizure threshold of a child and may be the risk factors for recurrent febrile seizure.[34-37]

The major concern for both parents and physicians whether the child with febrile seizure may develop epilepsy in future or not. Those children who are vulnerable for developing further epilepsy are.[14,33]

i. Shorter duration of fever (<1 h) before the seizure
ii. Onset of FS before 1 year or after3 years of age
iii. Neurodevelopmental abnormality
iv. Complex FS
v. Family history of epilepsy
vi. Low Apgar at 5 min at birth
vii. Epileptiform discharges on EEG

Evaluation of a child with Febrile Seizure

The evaluation of a child with febrile seizure should take a detailed history and do physical examination. Key features of the history include onset of the fever, duration of fever, seizure semiology, duration of seizure, post-ictal drowsiness, recent illness, antibiotic use, personal or family history of febrile seizure, epilepsy, recent vaccination and immunization status for Hib,streptococcus pneumonia, developmental milestone, CNS trauma.[4,11] Physical examination should search for signs of meningitis, such as depressed sensorium, irritability, bulging fontanelle, nuchal rigidity and decreased tone.

Investigations

Investigations should seek to identify the etiology when a patient presents with fever andseizures because there are many potential differential diagnoses. If there are no other symptoms, there should be no testing done for simple FSs. Diagnostic testing may not be as straight- forward in children with a complex febrile seizure, because complex febrile seizures are more heterogeneous.[6,14,16,38] The basic laboratory investigations should be individualized based on the history and physical examination.[6,38,39]

The role of lumbar puncture

All the published guidelines recommend performing LP if there are meningeal signs or if a CNS infection is suspected.[2]

The AAP consider a LP in child with FS in following situations:[3,6,40-42]

1. Less than 12 months of age who present with FS, especially if the vaccination status for Streptococcus pneumoniae and Hemophilus influenzae is deficient or unknown
2. Younger than 6 months with a simple FS
3. At any age: Altered alertness, lethargy, and/or meningeal symptoms or FSE
4. Occurrence of seizure after the 2nd day of fever, who have taken prior antimicrobial therapy

The role of EEG

Electroencephalograms (EEGs) have been variably recommended for investigating febrile seizures and to predict the risk of development of recurrent febrile and afebrile seizure.[5,6,43-45] A routine EEG is not recommended to evaluate neurologically healthy child with a simple FS.[6]

EEG should be considered in the presence of risk for epilepsy, abnormal neurological findings, delayed developmental milestone, positive family history of epilepsy, and initial febrile seizure before 12 months of age and atypical febrile seizure.[44] EEG carried out in the week after a febrile seizure will be abnormal in one third of casas, showing posterior slow wave activities which may be unilateral or bilateral and usually disappear by 7-14 day.[6,44,46]

Role of neuroimaging

Neuroimaging is not recommended in case of simple febrile seizure. MRI or CT scan are indicated in.[6,8,44]

1. Evidence of raised intracranial pressure or abnormally large heads
2. Suspected structural defect in the brain, focal neurologic abnormality, and severe head injury
3. Neurodevelopmental abnormality
4. Complex febrile seizure and febrile status epilepticus.

Management and prophylaxis

Parental counseling and assurance is an important mainstay of treatment of febrile seizure. Parents should be counseled about this seizure. It is a benign condition, do not lead to neurological disease or dysfunction, treatment is often unnecessary and rare association of simple febrile seizure with epilepsy.[6,47] Education and anticipatory guidance for pediatric caregivers are needed to help reduce fear and to empower caregivers with knowledge of appropriate practices in the event of a seizure. Lying the child on the floor in a side-lying position to prevent aspiration, noting the nature and duration of symptoms, not placing fingers inside the child mouth.[48-50]

Six hourly paracetamols should be advised for the first 48 hours in case of future episode of fever. Antipyretics administered round the clock for the duration of fever may not prevent occurrence or recurrence of seizures but will make the child less uncomfortable.[47] Parents must be educated and trained in the home management of seizures and use of antiseizure medication (per rectal diazepam). Antiseizure medication should be administered if febrile seizure last longer than 3-5 minutes recommended by several guidelines(UK, ILAE, AOCN).[2]

As per AAP recommendation, clinically stable children older than 18 months should not be hospitalized.[51] Hospital admission should only be considered for children in following conditions.[52]

1. Suspicion of any serious infection
2. Who have prolonged and/or focal seizures, particularly if there is residual neurological findings or delayed recovery to baseline
3. Less than 18 months of age, for observation and possible requirement for LP.

Almost all published guidelines state that neither intermittent nor continuous seizure prophylaxis is recommended in SFS except for few cases.[2,6,40,47,53] Intermittent prophylaxis among children with frequent recurrent SFS with parental anxiety, residence far from medical facilities, prolonged febrile seizure persists>15 minutes and the children with complex febrile seizure not require continuous prophylaxis.[2,6,47] Oral benzodiazepine or clobazam are used as intermittent prophylaxis.[54,55] Intermittent administration of diazepam (0.3–0.5 mg/kg/dose 8 hourly, maximum 10 mg) or oral clobazam (1 mg/kg once daily, maximum 20 mg) at the onset of fever for initial 3 days has been shown to be effective in recurrent FS prevention in 80% of cases[56,57] . Some studies recommended intermittent clobazam therapy is more beneficial to diazepam due to less side effects such as drowsiness, sedation, ataxia, and low cost.[2,6,47,55]

According to AOCN guideline continuous prophylaxis should be considered among children with febrile status epilepticus, febrile seizure plus, pre-existing neurodevelopmental disorders like CP, global developmental delay or autism spectrum disorder.[2,47] ILAE guidelines state that phenobarbital or valproic acid may be used as continuous prophylactic antiseizure medication.[2,45]

Prognosis

The prognosis is good in the majority cases as it is a benign and self-limiting condition[58]. About one-third of FS will have a recurrence during early childhood, wherein only<10% will have e”3 recurrences. Approximately, 90%recurrences occur within 2 years wherein 75% happen within1 year.[2,6,59] The risk of developing subsequent epilepsy is 2-4% of children with a history of febrile seizure and 57% risk in children with focal, prolong, recurrent febrile seizure.[7]

Conclusion:

Majority of childhood febrile seizures are benign in nature. Despite of several national & international guideline, diagnosis & management of childhood FS are heterogenous. Diagnosis is highly dependent on typical presentation with limited role of investigations. One third of child with FS have chance to recur within 5 years of age. Indications for use of prophylaxis whether intermittent or continuous is controversial. Reassurance of parents of a child of 1st attack of FS, educate them about home management of acute seizure episode, identification & notifying the risk factors for recurrent FS are important components of management.

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A Young Man with Bilateral Leg Edema due to Protein S Deficiency

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Abstract

Protein S deficiency is a rare hematological disorder due to inherited or acquired deficiency of a vitamin-K dependent plasma glycoprotein, protein S. This is formed in various body tissues and acts as an integral part of natural anticoagulation. Deficiency of protein S manifests as thromboembolic events, commonly causing deep vein thrombosis and pulmonary embolism, but may affect other venous systems including unusual sites as well. While multiple case reports have suggested protein S deficiency as a potential risk for arterial thrombosis, there is little data to support this theory. Here, we have described a case report of a young man presenting with bilateral leg swelling. His routine workups failed to reveal any identifiable cause until a doppler ultrasonogram of abdominal and lower limb vessels showed thrombosis involving lower part of inferior vena cava, both external iliac and femoral veins. A coagulation profile was then assessed revealing decreased level of protein S. This case illustrates the variable appearance of an uncommon hematological disease and the importance of consistent work-up to reach the underlying diagnosis.

Keywords: Protein S deficiency, Venous thromboembolism, Bilateral leg edema

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Introduction:

Hepatocytes are the main precursors of protein S. It is also produced by megakaryocytes, osteoblasts, endothelial, leydig, and vascular smooth muscle cells.[1] It serves as a cofactor for activated protein C, forming the protein C-protein S complex. The complex inhibits factor Va and factor VIII by binding to Ca^{2+} and phospholipids, thus prevents additional thrombin production.[2] Protein S regulates fibrinolysis in the early stages of clot formation by preventing independent thrombin production and consequently lowering the rate of activation of thrombin-activatable fibrinolysis inhibitors. In addition to its function in inhibiting the production of thrombin, protein S also amplifies the effects of activated protein C on fibrinolysis, which neutralizes plasminogen activator inhibitors, as evidenced by clot lysis tests. A deficit can be inherited or acquired. It is linked to a higher risk of thromboembolism.[3] The inherited Protein S deficiency is an autosomal dominant disorder caused by mutations in the PROS1 gene, located on chromosome 3. This condition may also be acquired as a result of vitamin K antagonist medication, oral contraception, pregnancy, and a variety of illnesses, including liver disease, nephrotic syndrome, disseminated intravascular coagulation, and persistent infections (e.g., HIV).[4] Protein S deficiency affects around 0.03% to 0.13% of healthy individuals and may affect any gender. However, clinical manifestations of venous thromboembolism and fetal loss are more common in women due to risk factors such as oral contraceptives, pregnancy, and hormone replacement treatment.[1]

Case Report:

Mr. Tulon, 35-year-old man hailing from Manikganj, was admitted to Dhaka Medical College Hospital through emergency department in June 2024 with the complaints

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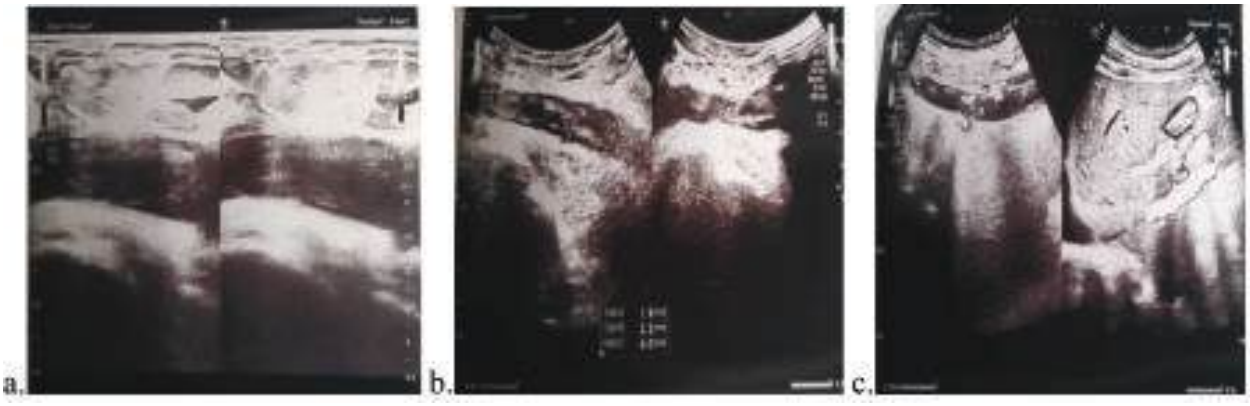

Figure 1. Soft echogenic thrombus with thickening of vein walls involving the dilated and noncompressible (a) common femoral veins, (b) external iliac veins, (c) inferior vena cava

of bilateral lower limb swelling for one month. The onset of this swelling was insidious, gradually progressive and slightly painful. It was not associated with any trauma, redness or increased local temperature. Any history of prolong immobilization or long travel, recent surgery, breathlessness, chest pain, abdominal distension, hematemesis, melaena, jaundice, abdominal pain, facial puffiness, scanty micturition, headache, visual difficulty, fever, any joint pain, and recurrent genital or oral ulceration were not associated with bilateral leg edema. He had no such event earlier and also, did not give any positive family history related to his illness. On examination, patient was mildly anemic, blood pressure was 100/70 mmHg with no postural drop, all the peripheral pulses were palpable with a rate of 72 beats/min, regular rhythm and normal volume. Bilateral pitting leg edema was present with a grading of +++. Bedside urine dipstick test revealed no proteinuria or hematuria. There was no organomegaly or lymphadenopathy, no abdominal mass was found. Examination of other systems revealed no abnormality.

His complete blood count (CBC) was normal except for thrombocytopenia with a platelet count of 94,000/mm^3. Peripheral blood film (PBF) showed microcytic hypochromic anemia. Serum creatinine, electrolyte, albumin, OGTT, urine R/M/E, ECG and chest x-ray all were within normal limits. From suspicion on the clinical ground, color doppler study of abdominal vessels and lower extremities was advised accordingly. Doppler ultrasonography of abdominal vessels revealed reduced flow in the lower part of inferior vena cava along with bilateral external iliac and femoral veins as well as evidence of thickening of vein walls and soft echogenic structures within the lumen of the affected veins which was suggestive of venous thrombosis. Later on, a coagulation screening was done which showed increased D-dimer level (9.5 mg/L), prothrombin time (PT) with INR and activated partial thromboplastin time (APTT) were near to their upper limits. Protein C was within normal range but, protein S was 39.2% which was markedly below the normal limit. Antinuclear antibody (ANA) was negative and antiphospholipid syndrome (APS) panel was normal. Due to financial constraints, any further detailed evaluation of the patient could not be possible.

However, low molecular weight heparin (LMWH) was started immediately after diagnosis. It was given for 5 days followed by rivaroxaban daily, a direct oral anticoagulant (DOAC). Patient took discharge and was advised for follow-up after one month. Two months later, he reported that he was having improvement with bilateral leg swelling though it seems to be in recurrent manner which often hampers his daily life. But the patient did not mention any new complaint and was unable to afford investigations anymore. Therefore, he was advised to take the prescribed DOAC for indefinite period and emphasized to ensure further follow-up.

Discussion:

Protein S (PS) is primarily produced by hepatocytes or macrophages and is a vitamin K-dependent plasma glycoprotein. 60% of PS is bound to C4b and is inactive, while 40% of PS is unbound and possesses anticoagulant properties. PS primarily acts as a co-factor for activated protein C (APC) to help deactivate factor Va (FV) and VIIIa, resulting in an anticoagulant effect. Alternatively, PS also acts as a cofactor for tissue factor pathway inhibitor (TFPI), which hinders tissue factor activity by enhancing the binding between TFPI and factor Xa. Protein S deficiency (PSD) is a genetic disorder that can be inherited in an autosomal dominant manner, and can also be influenced by both genetic and acquired factors.[5] Three

forms of protein S deficits have been identified. Type I is the traditional form of hereditary deficiency where, protein S function deficiency occurs along with reduction in the level of both free and total protein S. One of the rarest types of this impairment is the type II variety, which exclusively affects protein S function (reduction in the cofactor activity of protein S) with normal antigenic levels and hence, is a qualitative abnormality. Type III is the selective reduction of functional protein S and deceased level of free protein S with normal values of total protein S.[6] Free protein S level is not affected by age. There is not a considerable distinction between the clinical manifestations of these three types, which can only be distinguished through laboratory tests. 95% of individuals with PSD will develop type I and type III PSD. More than 360 mutations in PSD-related genes have been recorded in the Human Gene Mutation Database (HGMD) as of September 6, 2021.[5] There are two types of protein S assays. Immunoassay is used to determine the level of total and free protein S, and clotting assay is used to measure activated protein C (APC) cofactor activity. The most frequent sign of this illness is deep venous thrombosis (DVT) in the lower limbs, accounting for 90% of cases. It is defined by the traditional triad of calf pain, oedema, and pain during dorsiflexion of the foot. Additionally, pulmonary embolism and/or thrombophlebitis may manifest as symptoms of this illness.[7] About 50% of thromboembolic episodes are unprovoked which means they don't have any transient risk factor prior to the occurrence of venous thromboembolism (VTE), and they usually happen repeatedly.[1] A venous duplex ultrasonography is an excellent diagnostic tool for DVTs. Clotting assays to determine the functional activity and laboratory testing to measure PS antigen are used to diagnose PSD abnormalities.[8] Anticoagulation is the principal treatment for acute presentations followed by prophylactic anticoagulation for long duration or for life depending on the severity & recurrence.[1] Anticoagulants such as warfarin with a heparin bridge should be started on patients with a VTE for preventing skin necrosis, that can happen in this group as a serious adverse effect.[4] Initial treatment consists of unfractionated heparin or low molecular weight heparin (LMWH) overlapped with warfarin until an international normalized ratio (INR) of 2.0-3.0 is reached on two consecutive days.[1] Heparin is required for at least 5 days, followed by vitamin K antagonist (VKA) or direct oral anticoagulant (DOAC). The choice between a DOAC and a VKA depends on patient preferences and convenience. VKA was conventionally used for the treatment of VTE, now DOACs are increasingly being used due to their equal efficacy and better safety profile.[9] Treatment should be continued for 2 years and may be considered for life-long with associated thrombophilia defects. Prophylactic anticoagulant therapy should be considered in all patients with protein S deficiency in conditions with high risk of recurrence of VTE, such as in case of surgery, trauma, immobilization, air travel for more than four hours and pregnancy or puerperium etc.[10]

Conclusion:

Despite being a rare hematological disorder, protein S deficiency implies patients at risk of significant morbidity and mortality due to recurrent venous thromboembolism resulting from the lacking of a natural anticoagulant activity. It is thereby important to identify this group of patients to prevent the recurrence and complications. Currently there is no definite cure for the inherent deficiency and therefore, long-term anticoagulation is the treatment of choice. Educating the patients on managing risk factors is crucial. Routine follow-up is highly encouraged for the patients on anticoagulation and also for those who have risk factors of developing venous thrombosis.

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